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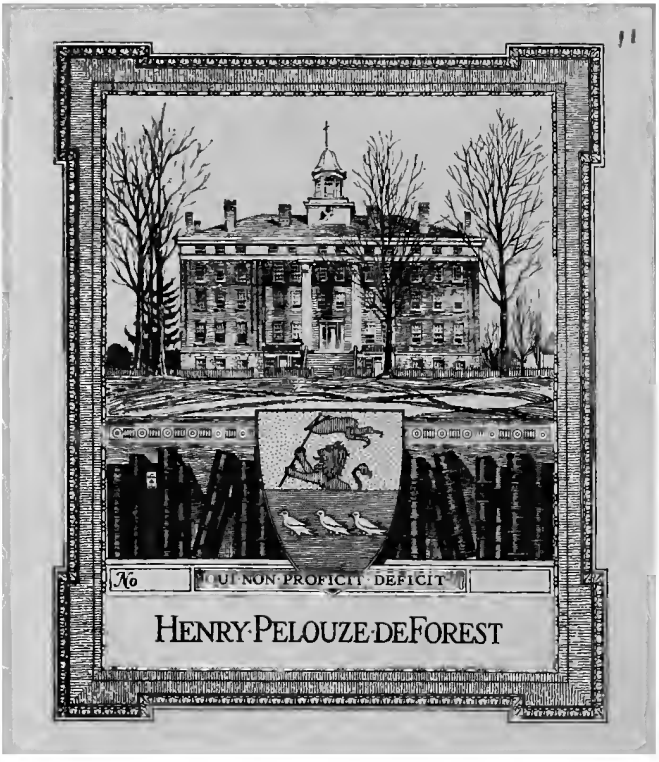

MANUAL

OF

HUMAN EMBRYOLOGY

WRITTEN BY

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PREFACE

THE second volume of this Manual makes its appearance almost half a year later than the editors had hoped. Explanations of the delay are hardly necessary; they are self-evident in the case of a book in which a large number of authors participate. The delay would, however, have been greater had not Professor Tandler and Dr. Evans undertaken the sections on the development of the heart and of the blood-vessels, which had originally been placed in other hands. To these two collaborators the editors are under special obligations. The account of the development of the sense-organs, for which also other plans were made, had to be undertaken by one of the editors, Keibel, an arrangement which precluded the treatment of the subject entirely on the basis of personal observation. A number of the contributions to the volume have been completed for a considerable time (some for more than a year), and consequently it has been impossible to include in them all the references to the most recent literature (since the beginning of 1910).

The editors regret that this second volume has considerably exceeded the limits originally set for it. If it had been written by a single hand, a greater condensation would certainly have resulted in many chapters, but under the circumstances this has not been possible, notwithstanding the earnest endeavors of the editors.

On the whole, however, the editors feel that they have reason both to congratulate themselves on the completion of the work, which, in spite of many minor defects, is undoubtedly an important one, and to hope that it will give further impetus to the study of human embryology.

In conclusion the editors wish to express their heartiest thanks to all those who have assisted in the completion of the work, to the collaborators, to Professor J. P. McMurrich for the excellent translation of the chapters by Zuckerkandl, Keibel, Tandler, and Felix, and, above all, to the publishers S. Hirzel and the J. B. Lippincott Company. They have done everything in their power to make the work a success, and, especially, have made possible the illustration of the text by so many and such excellent figures.

FRANZ KEIBEL. FRANKLIN P. MALL.

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HANDBOOK
of
HUMAN EMBRYOLOGY

XIV.

THE DEVELOPMENT OF THE NERVOUS SYSTEM.

By GEORGE L. STREETER, Ann Arbor, Mich.

The entire nervous system, as will presently be described, has a common origin. It is derived from an anlage that is very early differentiated from the ectoderm as the neural or medullary plate. The description of its development will be taken up under the following headings: 1, the histogenesis of the nervous tissues; 2, the development of the central nervous system; 3, the development of the peripheral nervous system; and, 4, the development of the sympathetic nervous system.

I. HISTOGENESIS OF NERVOUS TISSUE.

In Chapters III, IV, and V the segmentation of the ovum and the grouping of its cells in the form of three germ layers have already been described. It has also been described how a portion of the ectoderm becomes thickened and differentiated into the elongated axial neural plate and neural groove, and how eventually the elevated edges of this groove come together and fuse, thereby converting it into the neural tube. It is the anterior portion of this neural tube that is enlarged and converted by constrictions into the three primary cerebral vesicles from the thickened walls of which the brain is derived. The caudal portion of the neural tube remains nearly uniform in diameter and forms the spinal cord. The lumen of the caudal portion becomes converted into the central canal of the cord, and the enlarged cavities of the vesicles of the anterior part of the tube form the several ventricles of the brain. The nerves which serve to connect the central nervous system with the periphery either sprout out from the wall of the neural tube or from the ectodermal cellular crest that is attached along its dorsal seam. Thus, if we except the mesodermic

elements that subsequently penetrate the neural tube, accompanying the invasion of blood-vessels into its substance, we may say that all the essential nervous tissues of the body are derived from the thickening and differentiation of the walls of the neural tube and its ganglionic crest, and hence are ectodermal.

Development of the Walls of the Neural Tube.

In the absence of suitable human material our information regarding the changes that occur early in the differentiation of

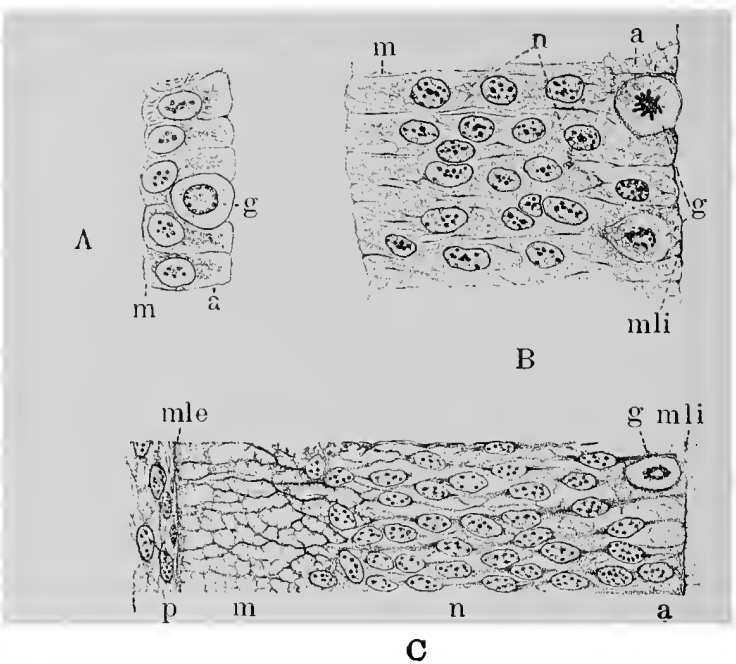

FIG. 1.—Three early stages in the development of the wall of the neural tube, showing the conversion of the single layer of discrete cells into a richly nucleated syncytial framework. A, medullary plate of embryo rabbit just before closure of neural tube; B, similar section of 5 mm. pig embryo just after closure of neural tube; C, wall of neural tube of 10 mm. pig embryo; *a*, ependymal layer; *g*, germinal cell; *m*, marginal layer; *mle* and *mli*, external and internal limiting membranes; *n*, mantle or nuclear layer; *p*, mesoderm. (After Hardesty.)

the wall of the neural tube is based on the chick, rabbit, and pig, notably through the investigations of His, Cajal, Schaper, and more recently Hardesty. The essential feature in this development, as can be seen in Fig. 1, consists in the conversion of the original single layer of cuboidal ectodermal cells into a thick wall whose elements are arranged in the form of three definite layers or zones. These three zones constitute respectively the anlages of the ependyma, the gray substance, and the white substance, the individual cells being accordingly differentiated into supporting cells and nerve-cells proper.

In Fig. 1, A, is shown the single layer of ectodermal cells which constitutes the original neural plate. It is to be noted that they consist of individual cells, distinctly outlined and definitely arranged. During the closure of the neural tube they proliferate and the cell boundaries partially disappear, and there thus results a thick wall of fused cells, a compact nucleated protoplasmic syncytium as seen in Fig. 1, B. As the growth continues the syncytium expands into a looser framework or myelospongium and its outer and inner margins are condensed in a continuous sheet to form the external and internal limiting membranes, as seen in Fig. 2, which is taken from a human embryo. In Fig. 1, C, which shows the appearance at the end of the first month, the myelospongium consists of radially arranged cellular strands still united in a

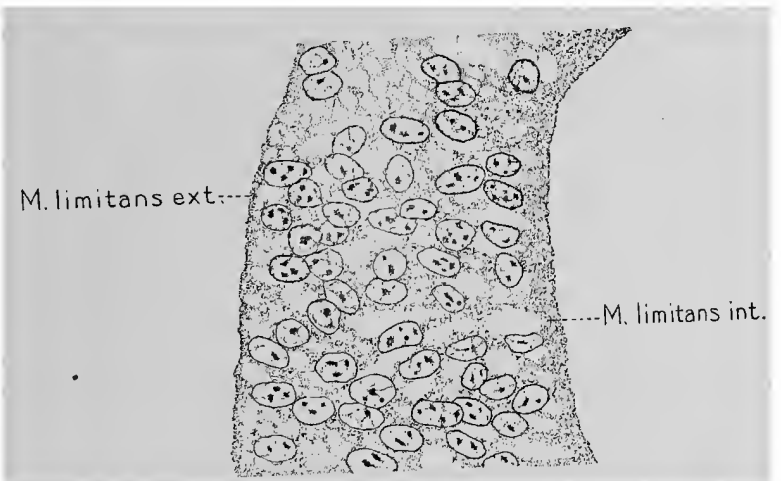

FIG. 2.—Wall of the neural tube in a human embryo about two weeks old, showing its syncytial character. This stage is between that of B and C, Fig. 1. (After His.)

syncytium by numerous branching processes. Further examination shows that, owing to the grouping of the nuclei, the wall may be subdivided into three primary zones or layers: (1) the ventricular or ependymal layer; (2) the intermediate or nuclear or mantle layer; and (3) the outer or non-nuclear or marginal layer (Randschleier). It may be added that the term nuclear layer is applied in the early stages, while the boundary between them is indistinct, both to the ependymal and mantle layers, thus contrasting them to the marginal or non-nuclear layer. In this sense one can say that the wall at first consists of two layers, nuclear layer and non-nuclear layer, and that later the former or nuclear layer becomes differentiated into the ependymal and mantle layers. Here the term nuclear layer is used as synonymous with mantle layer, which is its chief derivative. The ependymal layer consists of a single layer of elongated nuclei connected with the internal limiting

membrane by strong protoplasmic processes. Among these are seen prominent mitotic nuclei, the so-called germinal cells shown in Fig. 1, *g*, and Fig. 3. According to Hardesty, the germinal cells are found in greatest number in embryos (pig) between 10 and 20 mm. long, and gradually disappear, ceasing altogether at 40 mm. The nuclear or mantle layer consists of nucleated branching strands of the myelospongium forming a radially arranged protoplasmic framework. Rapidly proliferating nuclei are embedded in the strands and about them the protoplasm is becoming more condensed and granular. Mitotic nuclei are frequently found in this layer after the disappearance of the germinal cells of the ependymal layer, and it is suggested by Schaper

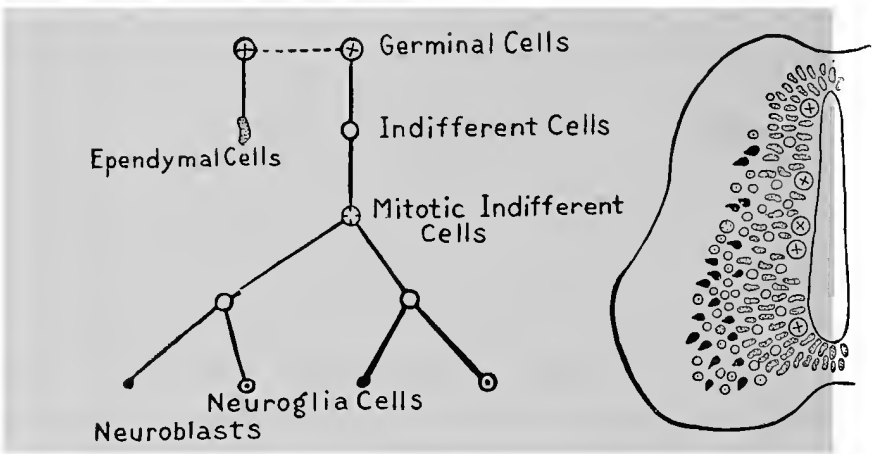

FIG. 3.—Diagram showing the differentiation of the cells of the wall of the neural tube and the theoretica derivation of the ependymal cells, neuroglia cells, and neuroblasts. (After Schaper.)

(1897) that they are a proliferation phenomenon. Those that persist until late stages are regarded by him as material for regeneration processes. Whether the proliferation of the nuclei of the mantle layer is always mitotic or whether it is to some extent amitotic remains to be determined. The mantle layer may be considered as the anlage of all gray substance. The marginal layer forms the anlage of the white substance, and through its meshes pass all the principal longitudinal fibre tracts of the cord and brain. For a considerable period it remains devoid of nuclei and consists simply of the network of the myelospongium.

The further steps by which this comparatively simple wall of three primary layers becomes subsequently converted into the complicated spinal cord and brain will be considered later. We will only consider at this time the histogenesis of its elements.

The cells, which in Fig. 1, C, are still fused in a common framework, gradually in their further differentiation undergo extensive change in form and position, and soon it is possible to class them

into two groups: (1) the *spongioblasts* which form the supporting framework or the neuroglia tissues; and (2) the *neuroblasts* or true ganglion-cells which come to lie within the meshes of the former. Up to the time the two groups can be distinguished from each other they are spoken of as *indifferent cells* (Schaper).

The differentiation into neuroblasts and spongioblasts does not occur in all cells simultaneously, some cells being more precocious than others; so that in a given section one may recognize well-defined neuroblasts, or spongioblasts, among other cells that are still in the indifferent stage, as is schematically shown in Fig. 3. In general, the spongioblasts develop somewhat in advance of the neuroblasts, and we find in some sections a fairly complete spongioblastic framework having as yet no differentiated nerve cells or fibres. In their further development the spongioblasts and neuroblasts will be treated separately.

Development of the Neuroglia Framework.

Embraced under the term neuroglia we must distinguish (a) ependymal cells, (b) neuroglia cells, and (c) neuroglia fibres, all of which elements serve as a supporting framework for the central nervous system, and all of which are differentiated products of the spongioblastic syncytium already referred to.

It was seen in Fig. 1, C, how the spongioblasts formed a radial framework traversing the entire wall of the neural tube. As the wall thickens the radial arrangement becomes still more marked and the spongioblastic strands become drawn out. These strands take the precipitate intensely in silver methods and form the characteristic Golgi picture seen in Fig. 4. From the radial strands numerous processes extend laterally and unite the whole in a complete framework. At the junction of the nuclear and marginal layers there exists a close felt-work of these lateral processes which is supposed to prevent temporarily the invasion of nuclei into the latter layer (Hardesty, 1904). A distinct group of spongioblasts maintain their radial arrangement near the ventricular border and eventually constitute the ependymal cells of the adult. In the remainder of the wall the radial arrangement is finally obliterated, which is due to the proliferation and growth of the neuroblasts, the spaces in the framework being determined by the shape of the elements that it supports. It is this portion of the framework that furnishes the neuroglia cells proper.

The *ependymal cells* represent the most primitive form of neuroglia, such as is found prevailing in certain lower forms. They are characterized by their radial arrangement and proximity to the lumen of the neural tube. Through their continuity with the general spongioblastic framework they extend through the whole thickness of the wall, from the internal to the external limiting

membrane, as shown in Fig. 1, C. As the ependymal cells proliferate and accumulate more body-protoplasm they come to form a compact mass of deeply staining columnar cells, constituting the lining membrane of the central canal of the cord and the ventricles of the brain. Their connection with the remainder of the neuroglia framework is maintained by processes which extend from the basal portion of the cells a variable distance into the underlying parts.

In the region of the anterior median fissure of the cord and the median raphe of the hind-brain, corresponding to the *Bodenplatte* of His, the neuroglia maintains its primitive ependymal type of simple radial fibres extending from the lumen to the sur-

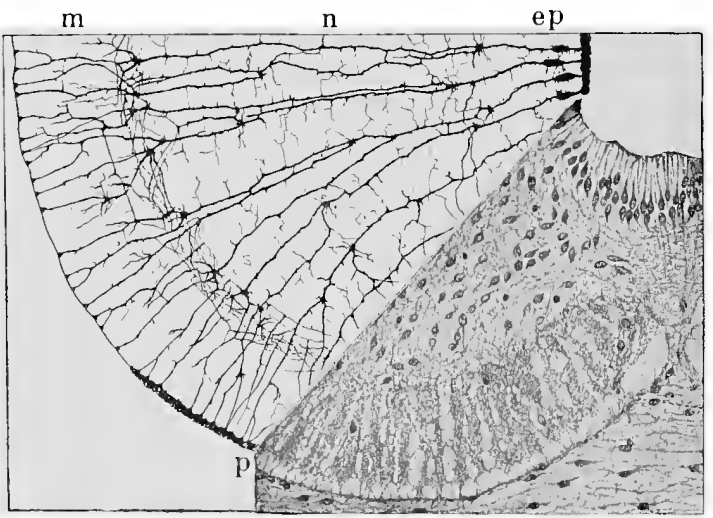

FIG. 4.—Development of neuroglia framework. Combined drawing, after Golgi and Benda methods, showing section of spinal cord of embryo pig 30 mm. long. It can be seen that the wealth of communicating processes of the neuroglia cells is not shown in the Golgi portion. *ep*, ependymal layer; *m*, marginal layer; *n* mantle or nuclear layer; *p* pia mater. (After Hardesty.)

face of the tube. It is this region that is traversed by the fibres of the anterior white commissure of the cord and the transverse arcuate fibres of the hind-brain. The persistence of this simple type of neuroglia may be explained by the absence of any mantle or nuclear layer with its consequent complications at this place. In a similar way in the posterior median region of the cord there is formed the posterior median septum, consisting of persistent radial neuroglia fibres extending from the lumen to the surface of the cord. Here, however, the conditions are modified by the partial fusion of the walls of the central canal and the fusion of the posterior funiculi, so that instead of a deep fissure we have in the end only a shallow groove. The development of the posterior median septum will be described in detail in the section on the development of the spinal cord.

Thus in the adult we find that the ependymal neuroglia is persistent only as septa in the anterior and posterior median planes of the nervous system and as a lining membrane for its central canal and ventricles. Otherwise the whole supporting framework of the nervous system consists of neuroglia cells proper and the neuroglia fibres developed in connection with them, that is if we do not regard the blood-vessels and the accompanying mesodermal tissue, which subsequently enter the neural tube, as a true supporting framework.

The *neuroglia cells* are differentiated somewhat later than the ependymal cells. They can be traced back to the time when they

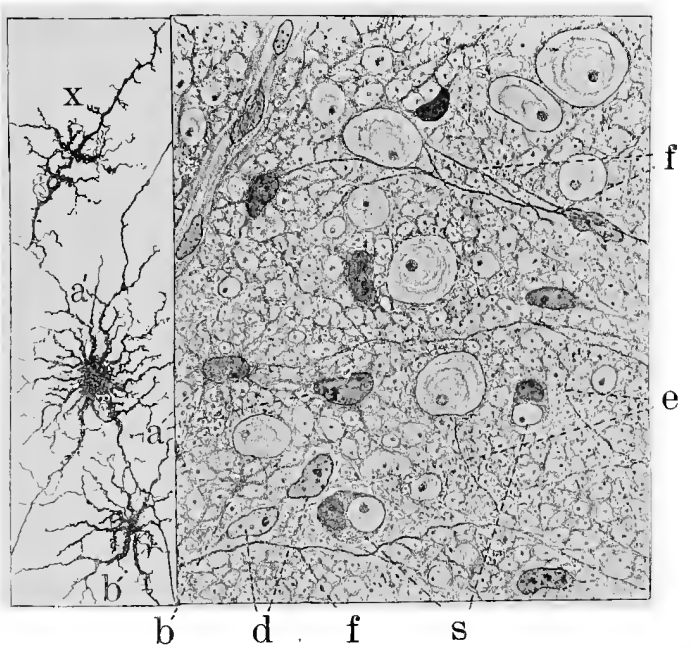

Fig. 5.—Combined drawings, after Golgi and Benda methods, of the spinal cord of fetal pig, 20 cm. long, showing syncytial character of neuroglia framework and the first appearance of neuroglia fibres. *a*, neuroglia cells after the Benda method; *a'*, similar cell after the Golgi method; *e* and *f*, neuroglia fibres beginning to take the neuroglia stain; *b*, pseudocell due to staining of a portion of the syncytium such as seen at *b*; *s*, seal-ring cells. (After Hardesty.)

constituted units in the primary spongioblastic syncytium. As the extension and branching of the latter continues, its component cells can be seen to proliferate and develop additional protoplasm. They at the same time become moulded into shape by the growing nerve cells and fibres which they enmesh. Due to this moulding process there result the characteristic much-branched cells that we know as spider-cells, glia-cells, astrocytes, or Deiters's cells, as shown in Fig. 5. Instead of the simple spongioblastic framework seen in the earlier stages, we now have a dense felt-work

produced by the anastomosing branches of these cells, intimately intertwining between the developing nerve-cells and their processes.

The variation in the shape of the individual neuroglia cells is determined by the nature of the nerve tissue supported, and consequently there are different types described for the cerebral cortex, the cerebellum, and the white and gray substance of the cord. Such variations involve the shape and size of the cell body as well as the character of their cell processes. The earlier concep-

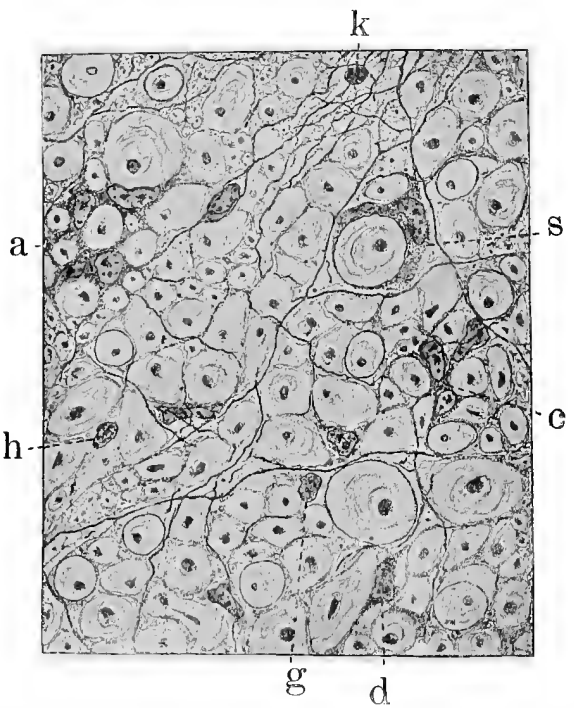

FIG. 6.—Section of spinal cord of suckling pig of two weeks, showing fully developed neuroglia fibre and fibres in the process of transformation. *a* and *c*, early stages of neuroglia cells, multinucleated protoplasmic masses; *d*, *g*, *h*, and *k*, stages of karyolysis which many of the free neuroglia cells undergo; *s*, sealring cell. (After Hardesty.)

tions of neuroglia cells were based on silver precipitation methods (Golgi) which failed to reveal the true wealth of their anastomosing branches, and there thus existed a false impression of neuroglia as consisting of scattered and independent cells.

The *neuroglia fibres* constitute the third element of the supporting tissue, and they resemble in their process of development the fibres in white fibrous connective tissue. They do not appear until late in uterine life. According to Hardesty (1904), they can first be recognized in pig embryos between 16 and 20 cm. long, and from then on gradually increase in number until after

birth. There is some evidence that the process of differentiation continues even into adult life.

It was formerly supposed (Golgi, v. Lenhossék, Erik Müller, and others) that neuroglia cells existed as separate units and that neuroglia fibres were simply the modified processes of these cells. With the development of the differential neuroglia stains it soon became apparent that this was not the case. From Weigert's studies (1895) on human tissues, followed by Huber's (1903) studies on several vertebrate classes, it was shown that neuroglia fibres are not to be regarded as processes of the neuroglia cells, but rather as fibres having specific physico-chemical properties which lie in close contact with or actually embedded in the peripheral layer of the protoplasm of the neuroglia cells from which they have become differentiated, as is shown in Fig. 7. The fibres are not

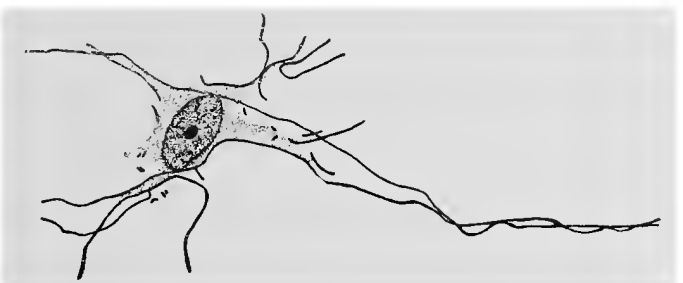

FIG. 7.—Neuroglia fibres in adult human spinal cord, showing their relation to the protoplasm of the neuroglia cell and its processes. (After Huber.)

interrupted by the protoplasm of the cells, and a single fibre may even be continuous from one cell to another.

To understand properly the manner in which these fibres form, one should keep in mind the syncytial character of the neuroglia framework. This has been especially emphasized by Hardesty (1904), on whose studies the description of this development is based. It has already been seen how the protoplasm of the syncytium in its development tends to accumulate about the nuclei and thus forms masses which we have described above as neuroglia cells. The separate nucleated masses or cells remain more or less continuous with each other by means of attenuated branching portions of the syncytium. In these attenuated portions at a certain period (pigs 16 to 20 cm. long) it can be seen that the protoplasm is becoming more condensed, stains less deeply, and is beginning to show fibrillation. The same process can be recognized in the peripheral portions of the nucleated masses or cells. The fibrillation continues to become more marked, and eventually distinctly outlined individual fibres of varying length can be recognized as lying in the attenuated portions of the syncytial proto-

plasm and passing through the "domain" of one or more nuclei, as shown in Fig. 5. Whether all the protoplasm in the attenuated portions is consumed in the process of fibrillation, or whether some remains as a partial coating of the fibre is not yet clearly determined.

The final step in their development is the chemical transformation that the fibres undergo, owing to which they exhibit a blue reaction when stained with special neuroglia stains. When that is attained they present the characteristic picture seen in Figs. 6 and 7. A portion of a fibre may give this reaction before the differentiation of the remainder of the fibre is complete. Sometimes a fibre ripens in interrupted areas along its course and hence temporarily appears as a row of fine dots. By the time the chemical transformation is completed the fibres have attained a size about the same as found in the adult. There is some variation in the distribution and form of the neuroglia fibres, depending on whether they are located in the region of gray matter or white matter or in the region of ependymal cells; the essential points in their development, however, are the same in all regions.

Those writers (*e.g.*, Rubaschkin, 1904) who consider neuroglia cells as separate and independent structures describe the neuroglia fibres as modified cell processes. A special cell is also distinguished from which they are derived (gliogenetic cells), which forms an intermediate stage between the spongioblast and neuroglia cell proper. Several fibres may be derived from one process, and eventually they detach themselves from the cell and lie free in the tissue.

Development of Neuroblasts and Motor Nerves.

We have seen above how the cells forming the wall of the neural tube in the early stages are fused in a common syncytial framework, and how the constituent cells of this framework gradually differentiate themselves into spongioblasts and neuroblasts. The former maintain their syncytial arrangement relatively late and continue even in the adult to show permanent traces of that condition. The neuroblasts, however, toward the end of the first month apparently detach themselves from the general framework and form separate clusters within its meshes. These clusters of proliferating neuroblasts form a prominent part of the nuclear or mantle layer, and it is from these that all the true nerve-cells of the brain and cord are derived.

The neuroblasts can be recognized by their characteristic shape (see Fig. 9). They possess a prominent nucleus and a tapering protoplasmic body which is continued into a slender primary process which is to become the future axis-cylinder of

the cell. There is always the tendency for the primary processes of adjacent neuroblasts to come together and form a common strand, in this way giving rise to the arrangement in clusters. It has not yet been shown whether the processes of these cells come together secondarily, or whether the arrangement is the result of the manner of cell cleavage, the processes being the last portion of the proliferating cells to split apart. The primary process may either extend to some other part of the neural tube or may leave the neural tube and extend through the mesoderm to some peripheral structure, as is shown in Fig. 8. The motor nerve roots are an example of the latter, and in Fig. 10 there is shown how clusters

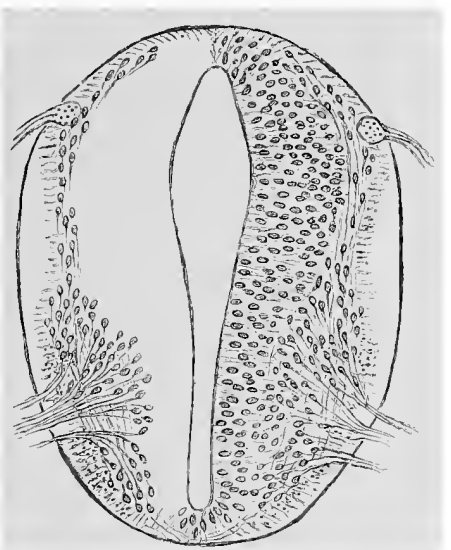

FIG. 8.—Diagram showing distribution of neuroblasts in human embryo of four weeks. On right side both neuroblasts and spongioblasts are shown; on left side neuroblasts only. The converging processes in the ventral part of cord unite to form the anterior nerve-roots. The processes forming the posterior roots enter the marginal layer and extend upward and downward as a longitudinal bundle, thus constituting the anlage of the posterior white column. (After His.)

of such motor neuroblasts form rootlets which pass through the marginal layer of the neural tube and enter the mesoderm and unite in a common nerve-trunk. A group of neuroblasts from the same section is shown under higher power in Fig. 9.

Later the original pear-shape of the neuroblast is altered by the increase in body protoplasm and the development of secondary processes which branch out into the neighboring spaces. With the increase in size the cell becomes moulded by the supporting framework and adjacent cells into its eventual shape, upon which the nucleus retires to the centre of the cell and enters upon the resting stage. The development of neurofibrils within the substance of the cell body and its processes occurs early; with special staining methods they can be demonstrated in embryo pigs 10 mm. long.

It was formerly thought (His) that the neuroblasts were derived directly and exclusively from the previously mentioned mitotic cells that are found during a brief period along the ventricular border of the wall of the neural tube, the so-called *germinal cells* (see Fig. 1, *g*). His pictures these germinal cells and shows them dividing and after assuming a pear-shape migrating out into the mantle or nuclear layer, being all the time sharply sepa-

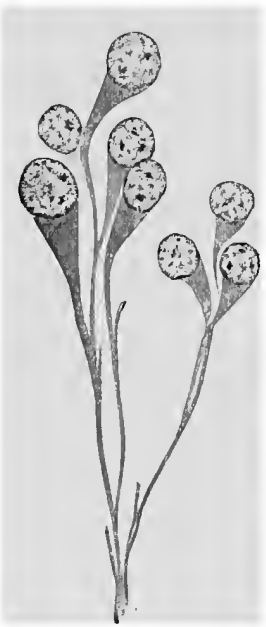

Fig. 9.—Cluster of neuroblasts from nucleus of origin of n. oculomotorius, showing characteristic shape and grouping of cells. Taken from same specimen shown in Fig. 10.

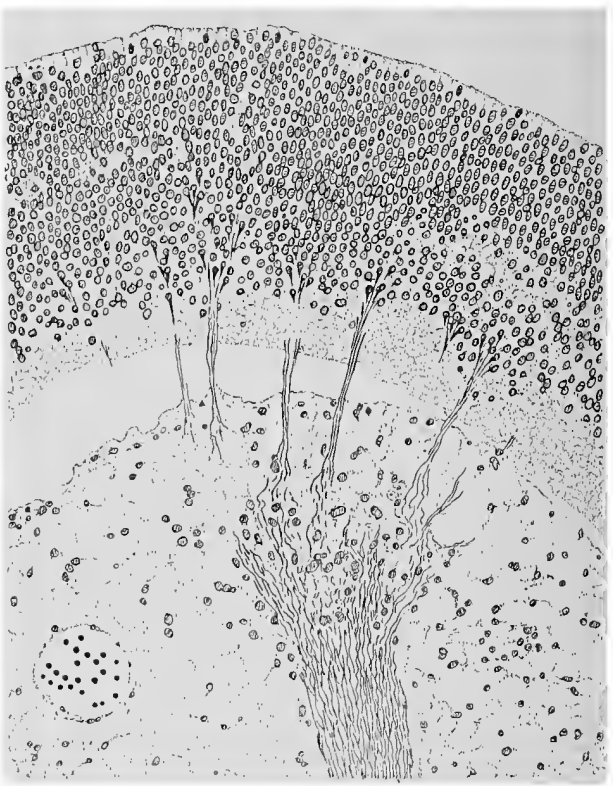

Fig. 10.—Section through floor of mid-brain of human embryo one month old (length 10 mm., Huber collection No. 3), showing the origin and formation of the trunk of a typical motor nerve (n. oculomotorius).

rated from the spongioblasts. This process has not been confirmed by the more recent investigators, and it is now generally thought that the germinal cells are only a sign of cell proliferation, and belong in common to the whole syncytial framework or myelospongium and thus are ancestors of the neuroblasts and spongioblasts alike.

The development of the neuroblast forms a problem that has been the subject of much investigation and discussion. Particular interest has been manifested in the growth of its attached nerve-fibre, both on account of the great length of the latter as compared with the size of the cell and on account of the intricate maze of

fibres through which it traces its way to reach the organ for which it is intended. Of the many interpretations that have been offered in explanation of this problem the one that seems now to be most generally accepted is the so-called *outgrowth theory* of His, according to which each nerve-trunk is the process of a single nerve-cell. The fibre is a simple elongation of the primary process produced by an actual outflow of substance from the ganglion-cell toward the periphery, and it thus makes its way through various tissues to reach its proper end organ with which it comes into relation secondarily. It is this theory that has been ably substantiated by the histological studies of Ramon y Cajal and conclusively established by the recent experimental studies of Harrison.

Among the other hypotheses that have been advocated regarding the development of the nerve-fibre the most prominent is the *cell-chain theory,* according to which each nerve-fibre is the product of a chain or pathway of ectodermal (according to some, mesodermal) cells extending from the neural tube to the periphery. From the protoplasm of these cells fibrillæ are differentiated which join to form a continuous fibre connecting secondarily the ganglion-cell with its end organ (Schwann, Balfour, Dohrn, Bethe). This theory was later modified by Apathy and O. Schultze, who conceived of a syncytium of anastomosing cells which from the beginning connects the neural tube with the peripheral end organs, somewhat like the older description of Hensen, according to which protoplasmic bridges persist between dividing cells everywhere in the embryo, and by fibrillar differentiation some of these protoplasmic connections become eventually converted into nerve-fibres and thus connect the ganglion-cells with the organs they supply. A further modification of this interpretation is that of Held (1907). Like Hensen, he conceives of a general syncytium connected everywhere by protoplasmic bridges, and later the nerve paths are formed by the transformation of these bridges; but, according to Held, the growth of these fibrillæ is from the nerve-cell outward, instead of simultaneously along the whole path, as maintained by his predecessors. In the protoplasm surrounding the nucleus of each neuroblast a plexus of neurofibrils forms, thus marking off neuroblasts from spongioblasts. From each of these a bundle of the fibrils extends out through the substance of the syncytial framework along a definite path and constitutes its axis-cylinder process. Subsequently, in addition to the primary bundle of fibrillæ, other fibrillæ extend out from the perinuclear network along other protoplasmic bridges and thus form the dendrites. In all these views the nerve-fibre is considered as a product of a group of cells instead of as an appendage of a single cell, as is postulated in the outgrowth theory.

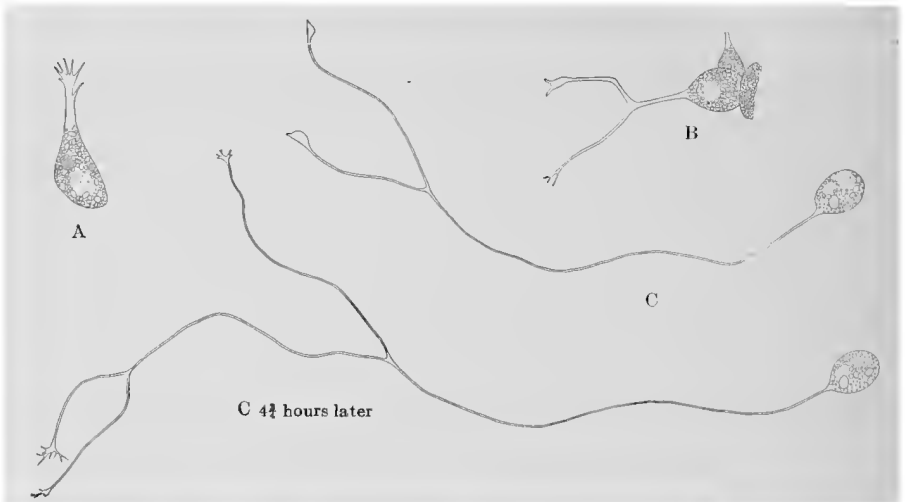

FIG. 11.—Isolated ganglion-cells, from embryonic spinal cord of frog, and growing in clotted lymph. B is an isolated cell from tissue taken from branchial sense organ. The drawings are made from live specimens; two views of C are shown, taken four and three-quarters hours apart, showing rate of outgrowth of the nerve-fibre and the manner of its branching. (After Harrison.)

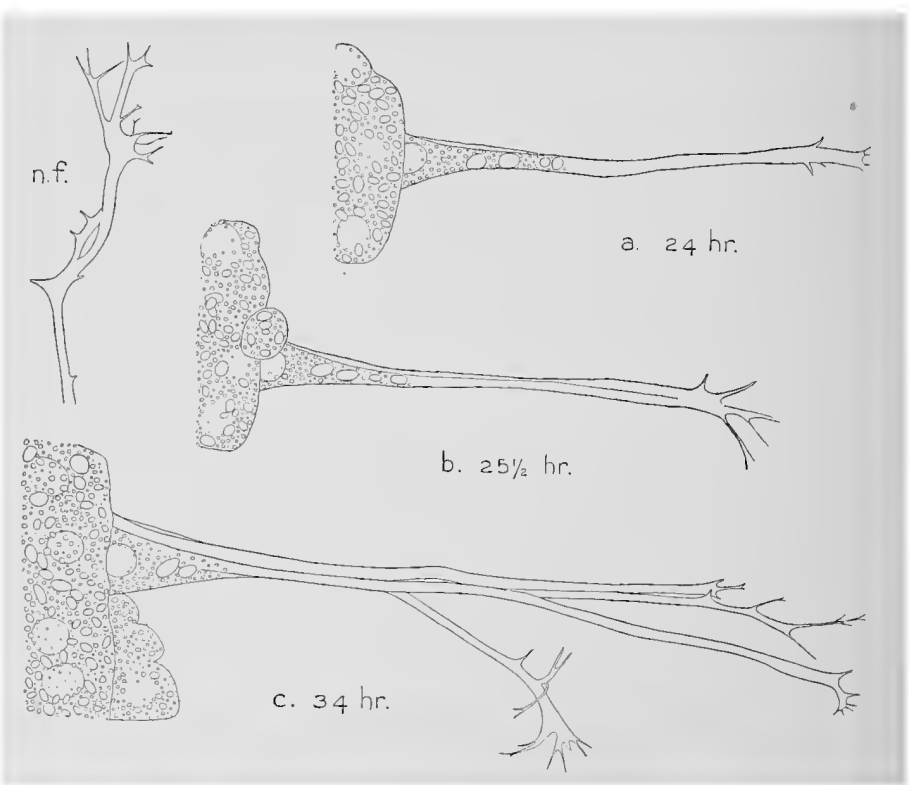

FIG. 12.—Three views, taken at intervals of 1½ and 8½ hours, of the same living nerve-fibres growing from a mass of spinal-cord tissue (frog embryo) out into clotted lymph. They show the rate of growth and the longitudinal splitting of fibres, and the characteristic growing ends, a larger example of which is represented by *n.f.* (After Harrison.)

In his experiments carried out on amphibian larvæ Harrison demonstrated four essential facts: In the first place he showed that no peripheral nerves would develop in an embryo from which the nerve-centres had been removed, thus establishing the fact that the ganglion-cells are an essential element in the development of the nerve-fibre. He next showed that the sheath cells of Schwann, upon the influence of which in the formation of the fibre many of the histologists had placed much emphasis, were not essential to the growth of the nerve-fibre, and that the axis-cylinders will develop and extend out in the surrounding tissues in the normal way and reach their normal length in specimens where the sheath cells have been eliminated. Thirdly, he showed, by modifying the environment of the developing nerve, that fibres will form in surroundings entirely different from their natural path and establish completely foreign connections. Finally, he succeeded in growing ganglion-cells outside of the body in an unorganized medium (clotted lymph), where all possibility of contributions on the part of other living tissues was eliminated, and he was able with this method to demonstrate directly under the eye the outgrowth of the nerve-fibre from the ganglion-cell as it developed hour by hour, proving conclusively the unity and continuity of the two.

Isolated ganglion-cells developing in an artificial medium are shown in Fig. 11, where A, B, and C represent three cells in different stages of growth. Two views of C are shown, one being taken four and three-quarters hours later than the other. The different cells shown in Fig. 11 are all represented under the same magnification, and on comparing them it is evident that the growth of the fibre is the result of a flowing out of the protoplasm of the cell into a thick primary process which as it elongates soon attains a uniformly slender width. The growing end of the process is characterized by an enlarged branched tip which continually undergoes amœboid changes in form. One of these characteristic much-branched growing ends is shown in Fig. 12 (*n.f.*) under higher magnification. Occasionally the growing tip completely bifurcates, which results in permanent bifurcation or branching of the nerve-fibre at intervals along its course.

In Fig. 12 there can be seen a further phenomenon in the growth of the nerve-cell consisting in the apparent longitudinal splitting of the cell and its main process, a form of retarded cell division that occurs subsequently to the formation of the primary process. In the figure *a, b,* and *c* represent the same nerve-cell mass as it appears at intervals of one and one-half and eight and one-half hours. It shows how that which is apparently a single cell and process becomes converted by this longitudinal cleavage into four individual cells with processes.

It is to be remembered that the forms shown in Figs. 11 and 12 represent the growth of ganglion-cells as it occurs in clotted lymph, and it is to be presumed that they depart in some details from that which occurs in living tissues; however, the structure of the fibres and the characteristic enlarged branching ends conform exactly to the appearances seen in sections of specimens where the fibres have developed under normal conditions, and they no longer leave room for doubt as to the essential validity of the His outgrowth theory.

Development of Spinal Ganglia and Sensory Nerve-Roots.

As the elevated borders of the neural plate come together and fuse to form the closed neural tube, it detaches itself from and becomes completely covered in by the general ectoderm. During

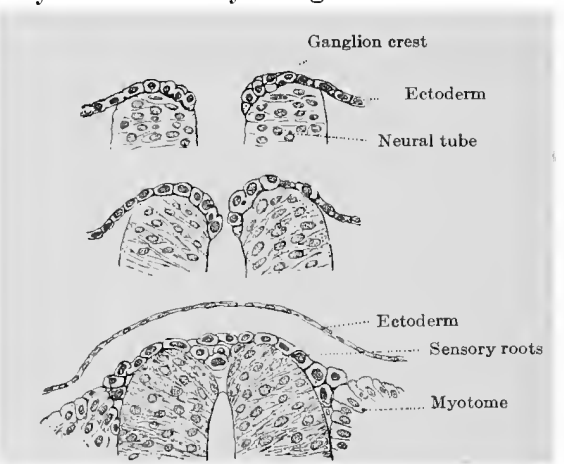

Fig. 13.—Transverse sections through dorsal region of human embryos showing three stages in the development of the ganglion crest and the anlage of the spinal ganglia. (After von Lenhossék and Kollmann.)

this process a row of ectodermal cells situated along the borders of the neural plate undergo special changes; they neither become incorporated in the neural tube nor do they become skin. It is these cells that form the so-called *ganglion crest* from which the cerebrospinal ganglia and sensory nerve roots are derived, in addition to the chromaffin cells and the sheath cells of Schwann.

The cells of the ganglion crest differentiate themselves from the cells of the neural tube during the closure of the latter. As shown in Fig. 13, they form a cellular ridge or crest along the line of closure. As they continue to develop they become apparently completely detached from the tube. Separating bilaterally into right and left crests, they migrate lateralward and ventralward in between the myotomes and neural tube. Here they continue to proliferate, and, as the constituent cells become differentiated into

ganglion-cells, rootlets appear along the dorsal border of the crest and attach it secondarily to the neural tube. The ganglion crest thus extends as a flattened cellular band on each side uninterruptedly from the caudal tip of the neural tube forward to the region of the ear vesicle (compare Fig. 83). In the spinal region it becomes notched with segmental incisures along its ventral border, producing a series of ganglionic masses which for a time remain connected with each other by a dorsal cellular bridge. Eventually the latter disappears and there results a complete segmentation of the crest into separate spinal ganglia.

In the head region the structures to be supplied lose their simple segmental character, and there are introduced the complications of the gill arches and the lateral line system. These factors

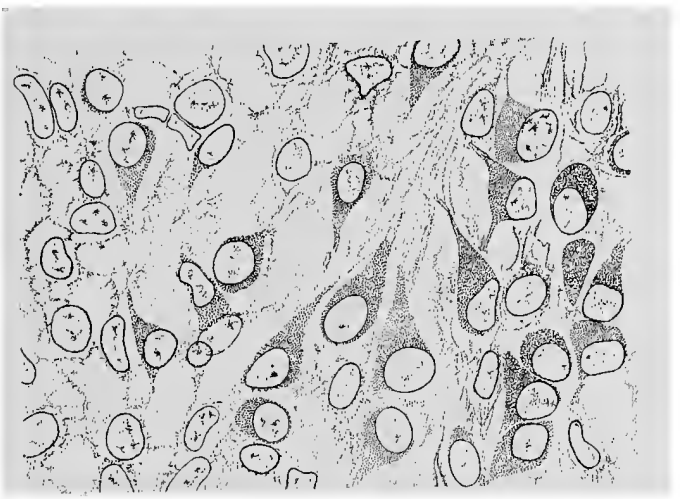

FIG. 14.—Section through spinal ganglion of human embryo 18 mm. long, about 6 weeks old (Huber collection No. 5). On the left the cells are mostly in the indifferent stage, and ganglion-cells and supporting cells look much alike; on the right the ganglion-cells stand out sharply, due to the accumulation of granular protoplasm around the nucleus.

modify the character of the ganglion crest, though in its derivation from the border of the neural tube it apparently follows the same process as described for the spinal region. In the region of the midbrain it is believed by some writers (Meyer, Johnston) that a portion of the ganglion crest becomes incorporated in the neural tube, and the cells derived from this portion never obtain a peripheral position. The gross features in the development of the ganglia of the head and spinal regions will be referred to again more in detail under the peripheral nervous system.

At the time the ganglion crest detaches itself from the neural tube and begins to spread ventralward (embryos 2–3 mm. long), examination of it reveals a moderately compact mass lying in the space between the neural tube and the myotomes. The constituent

cells possess oval or rounded nuclei with multiple small chromatin bodies such as are found in cells during active proliferation. The cell bodies possess ill-defined outlines and fuse with each other in a syncytial mass.

As the cells of the ganglion crest proliferate and become further differentiated it is possible to divide them into two different groups,—*i.e.*, ganglion-cells and supporting cells,—in the same way that neuroblasts and spongioblasts are developed in the neural tube. (Compare Figs. 3, 4, and 5.) The steps in this procedure are shown in Figs. 14, 15, and 16. On comparing these the most apparent difference between the ganglion-cell (ganglioblast) and the supporting cell (capsule and sheath cells) is that the ganglion-

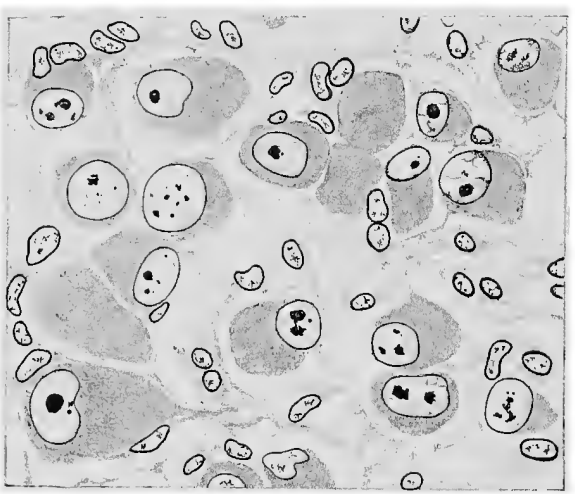

FIG. 15.—Section through cervical spinal ganglion of human fetus 8.5 cm. long, about 3 months old, showing large ganglion-cells with eccentric nuclei. Surrounding them are the much-branched supporting cells, some of which are to become capsule cells and the others sheath cells.

cells detach themselves more or less completely from each other and develop isolated large compact protoplasmic bodies, while the supporting cells consist almost entirely of branching processes which remain united in an extensive network or syncytium in the meshes of which lie the other cells.

By the end of the fourth month (Fig. 16) this differentiation is far advanced, and one can plainly recognize the supporting cells arranged in the form of capsules around the ganglion-cells proper. The next younger stage, at the end of the third month (Fig. 15), the supporting cells can be distinguished, but the capsule arrangement at that time is very incomplete. Going still further back, to the six-weeks embryo (Fig. 14), we find a portion of the ganglion mass consisting of undifferentiated neural crest cells, the ganglion-cells and supporting cells both having the same appearance. How-

ever, scattered in among these "indifferent cells" are some more advanced cells that can be recognized as ganglion-cells by their increased body protoplasm. As a rule, the ganglion-cells attain a characteristic appearance earlier than the supporting cells.

The differentiation of the ganglion-cell consists in the condensation of the body protoplasm and the development of fibrillar processes. As an indifferent cell of the ganglion crest syncytium it has no definite outline, and in a teased preparation it appears as a ragged granular mass around a nucleus. Later, as the protoplasm of the cell body accumulates, it detaches itself more or less

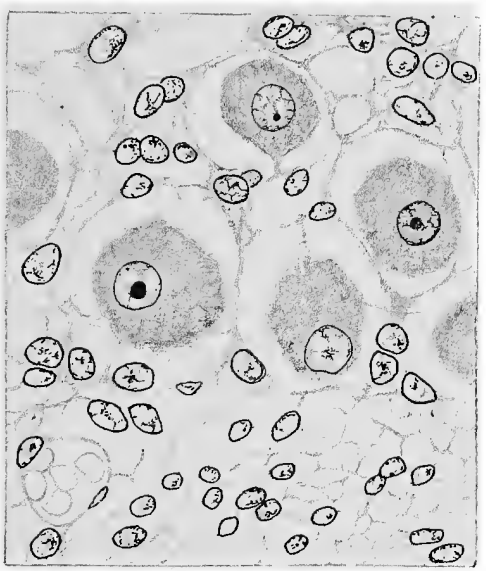

FIG. 16.—Section through sixth cervical ganglion of human fetus 16.5 cm. long, about 4 months old. Here the branched supporting cells are arranged in distinct capsules around the ganglion-cells, and in the lower part of the section they form a characteristic framework for the nerve-fibres. The ganglion-cells are nearing the completion of their development; the nuclei are retiring to the centre of the cell, and the basic stainable substance is appearing at the periphery of the cell bodies which later becomes clumped to form the Nissl bodies.

completely from the neighboring cells and attains discrete outlines. It is possible then to make teased preparations such as are shown in Fig. 17.

The earlier ganglion-cells usually have a simple fusiform shape with a process extending out at each pole, as is shown in Fig. 17, group A. These lie in clusters, like the neuroblasts in the spinal cord, and their processes are still fused so that in teasing them apart we get the appearances seen in group B. By Golgi methods it can be demonstrated that the central processes of such cell groups form rootlets which enter the dorsal part of the wall of the neural tube, where for the most part the fibres bifurcate and form a longitudinal bundle within the marginal layer, as seen

in Fig. 8, and after a longer or shorter course upward or downward they end in an arborization among the cells of the mantle layer. In the spinal region the sensory fibres thus entering form one continuous path, which eventually constitutes the dorsal funiculi of the cord. In the cranial region the entering fibres of the sensory nerves form separate paths, the vestibular tract, the trigemi-

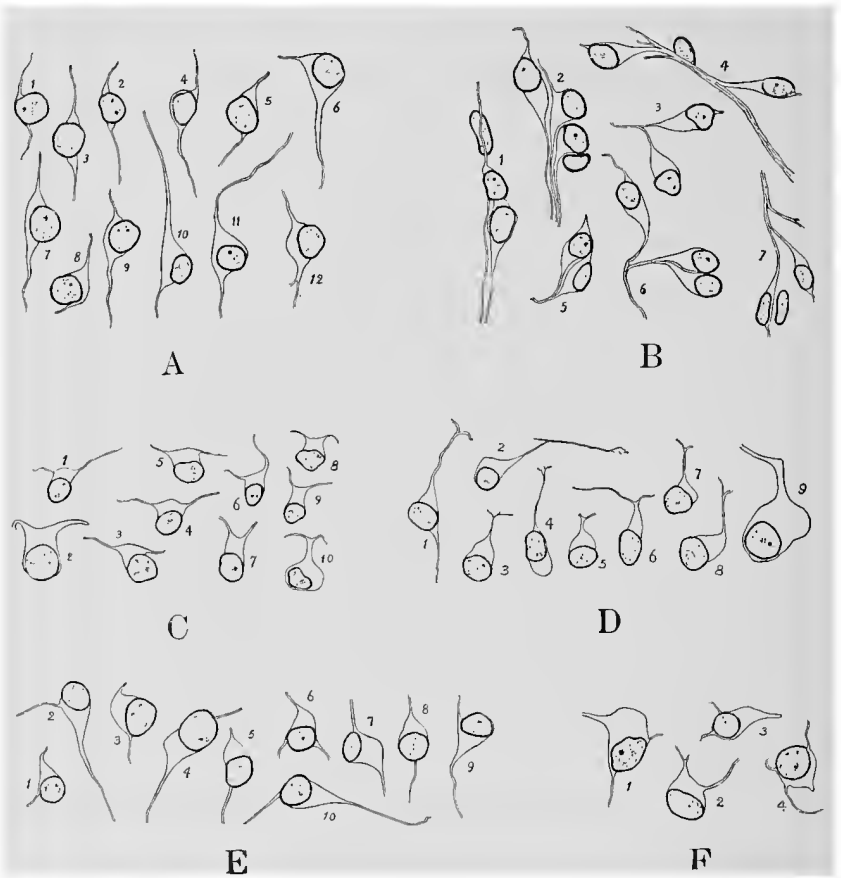

Fig. 17.—Isolated cells teased from spinal ganglia of embryo pigs 20–40 mm. long, showing the variation in the form of the early ganglion-cells. B shows the grouping of the cells; A, C, D, E, and F represent selected types arranged according to the form of the cell body and the character of the processes.

nal tract, and the tractus solitarius, to which are contributed fibres from the seventh, ninth, and tenth nerves. The peripheral processes unite into bundles, which join with the fibres of the anterior roots and with them form the main nerve-trunk, the further development of which will be referred to later in the section on the peripheral nervous system.

In examining a given ganglion in embryos about two months old it will be found that the cells are present in many different stages of growth, and that in addition to the simple bipolar earlier

cells there are younger cells that must make room for themselves in the intervening spaces. Such cells possess great irregularity in their shape. Their form and the manner in which the processes leave the cell body is apparently determined by the pressure that is exerted upon them by the adjoining cells. Some of the forms that are frequently seen in teased preparations are shown in groups C, D, E, and F, Fig. 17. The only feature common to all of them is the eccentric position of the nucleus, which is retained until the cell nearly reaches its full size, upon which the nucleus retires to the centre of the cell and assumes a resting appearance. (Compare Figs. 15 and 16.)

It will be seen that there is a great variety in the number, size, and situation of the cell processes. In group F there are multipolar forms, some of which persist as such in the adult forms. A very common form is shown in group E, which are technically bipolar cells, but in each case one of the processes is much better developed than the other, the small one having the appearance of undergoing retrogression. It suggests the possibility that these represent bipolar cells that are being converted into unipolar cells by absorption of the smaller process. All through the nervous system there is evidence of cell processes and nerve-fibres that grow out for a certain distance and then for some reason cease to develop any further and finally disappear, as in the case of the hypoglossal nerve. This phenomenon is not limited to the temporary existence of vestigial structures, but also represents what might be called a "tentative growth," under which we may understand that of the great number of processes and fibres which start out a certain number fail to establish adequate connections and subsequently disappear. On the other hand, in the present case of the ganglion-cell the smaller process may represent the slender axon that enters the cord, while the heavier process corresponds to the peripheral dendrite.

The conversion of bipolar cells into unipolar T-shaped cells of Ranvier is commonly supposed to be due to the unilateral growth of the cell body towards one side, which brings about an approximation of its two processes so that they fuse in a common extension from the cell. The cells shown in Fig. 17, C, are regarded as transitional cells undergoing this change, and cells 8, 9, and 10 would represent the successive steps in the process. But if this is the explanation, it should be expected that no cells would show the T division until they reach the stage of growth represented by cell 10. This, however, is not the case, for in group D we have cells in which the T division is already completed before that time, and moreover cell 1 in group D possesses the T division and the opposite process is still intact. Furthermore, as will be presently seen, the growth of the enmeshing capsule cells is already

well advanced while many of the cells are still of the simple bipolar type (*e.g.*, Fig. 18, *a* and *b*), and this would tend to prevent the approximation of opposite processes. There is therefore much reason to believe that the T division is simply the result of the bifurcation of the growing end of the main process of the cell in the manner so clearly demonstrated by Harrison's growing nerve-cells (Fig. 11), and that the so-called transitional cells are merely accidental forms due to the moulding influence of adjacent cells. Certainly a great many of the cells can never undergo the supposed transformation.

Concerning the migration of spinal ganglion cells and their relation to the formation of the sympathetic ganglia the reader

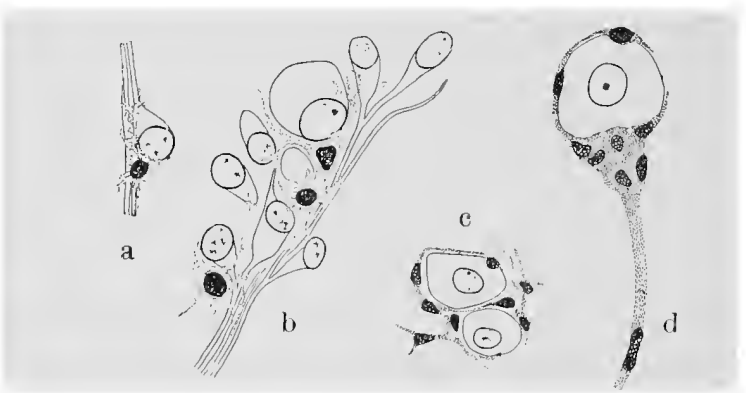

FIG. 18.—Teased preparations from spinal ganglia of pig, showing development of sheath and capsule cells. In *a* and *b* (pigs 3–4 cm. long) the supporting tissue consists of a loose syncytium enmeshing the ganglion-cells; in *c* and *d* (pigs 20 cm. long) the protoplasm is condensed and arranged in the form of distinct capsules. In *d* the capsule cells are directly continuous with the sheath coating the main process of the cell. Compare with Figs. 15 and 16.

is referred to the section on the development of the sympathetic system, and for the chromaffin or phæochrome cells and organs to Chapter XV which describes those structures.

The development of the supporting cells can be followed by comparing Figs. 14, 15, and 16, which show the appearance as seen in cross sections, and Fig. 18, which represents teased preparations. Like the ganglion-cell the supporting cell is derived from the indifferent cells of the ganglion crest, and also like the ganglion-cell the chief phenomenon of its differentiation consists in the condensation of the body protoplasm.

When first recognized the supporting cells form a loose poorly defined granular syncytium from which the ganglion-cells have become almost completely detached. The subsequent condensation takes the form of branching processes instead of full rounded bodies like the ganglion-cells, and there results a sharply outlined nucleated framework in the meshes of which lie the nerve elements proper (Fig. 18, *c*). In their derivation and behavior it will be

noticed that the supporting cells are directly analogous to neuroglia cells. Eventually they become subdivided into capsule cells and sheath cells, according to whether they form an envelope around some ganglion-cell or are situated along the course of a cell process. The two kinds are identical in character and are directly continuous with each other, as can be seen in Fig. 18, *d*. It is now believed, as will be referred to again under myelinization, that it is some of the supporting cells of the spinal ganglia that migrate outward along the course of the nerves and form all the sheath cells of the peripheral nerves.

Myelinization of Nerve-fibres.

The final development of the nerve-fibre is characterized by the formation of a fatty enveloping sheath. This process does not become apparent until about the fourth month, and it is not completed until after birth. Many details concerning the acquisition and structure of the nerve-sheath are still involved in dispute, and especially in human material there is no adequate description yet available. Our knowledge is mostly based on studies of the pig and sheep (Vignal 1883, Gurwitsch 1900, Bardeen 1903, and Hardesty 1904).

In the development of the nerve-sheath we have to distinguish between the formation of the non-nucleated myelin sheath and the nucleated membranous sheath which are its two subdivisions, the latter being synonymous with the *sheath of Schwann* or *neurolemma*. Either of these may make their appearance before the other. In the central nervous system the myelin sheath appears first, and until recently was supposed to be the only covering possessed by these fibres. In the case of the peripheral nerves, on the other hand, the axon is usually completely inclosed by the membranous sheath before the myelin appears, and in the case of some fibres, particularly in the sympathetic system, this remains the permanent condition. Such fibres are known as non-medullated fibres.

The cells that give rise to the membranous sheath of the peripheral fibres appear relatively early. They are easily distinguished toward the end of the third week as spindle-shaped cells (cells of Schwann or sheath cells) closely attached to the developing nerve-fibres. That these cells are ectodermal and are derived from the ganglion crest has been shown experimentally in amphibian larvæ by Harrison (1906). The experiments of this investigator show that the source of the sheath cells can be removed by early extirpation of the ganglion crest, and that in such cases there develop naked fibres which normally are found covered with sheath cells. It should, however, be remembered that this may not be the only source in all forms; in fact in elasmobranchii it is said that there are in addition a large number of sheath cells that wan-

der out somewhat later from the ventral part of the spinal cord along the motor roots (Neal, 1903). Up to the time of Harrison's experiments it was supposed that the sheath cells were derived from the mesenchyme and were foreign cells that invaded the nerve-trunks and ganglia very early (Vignal, Gurwitsch, and Bardeen).

In the human embryo during the transformation of the ganglion crest into spinal ganglia it is possible to trace step by step the differentiation of its constituent cells into ganglion-cells proper and supporting cells, as shown in Figs. 14, 15, and 16. It is these supporting cells that form the capsule cells and sheath cells. Of the latter some are for the spinal ganglia themselves while others

FIG. 19.—Isolated fibres showing development of medullary sheath. The specimens are taken from the intercostal nerve of pig fetuses about 15 cm. long and prepared by formalin and osmic acid. (After Bardeen.)

wander out along both the sensory and motor nerve-trunks, accompanying them in their growth forward, and eventually forming their membranous sheath.

The sheath cells are at first arranged so as to inclose a group of axons in a common trunk. By subsequent proliferation they invade the trunk and divide it into smaller bundles, until finally they close in around each axon and form individual sheaths. Each sheath cell corresponds to a segment of the sheath, and the interval between two adjacent cells corresponds to a node of Ranvier. The differentiation of the sheath cells and their conversion into the nerve-sheath is shown in Figs. 19 and 20. In the earlier stages they unite in the formation of a segmented thin-walled sheath, which in formalin specimens can be seen loosely enveloping the axis-cylinder, and apparently containing fluid (Bardeen, 1903); in osmic acid specimens it is found shrunken closely against the axis-cylinder (Fig. 20, A). Each nucleus maintains its position near the centre of a segment and continues to maintain a small quantity of granular protoplasm around itself. There then follows a deposit of myelin within the membranous sheath around the axis-cylinder. In the case of most peripheral fibres the axis-

cylinder becomes completely inclosed by the sheath of Schwann before the formation of the myelin sheath begins. As regards the origin of the myelin there have been three theories presented: first, that it is formed by the sheath of Schwann; second, that it is a differentiated portion of the outer part of the axis-cylinder (Kölliker, 1904); and according to the third it is precipitated from the fluid immediately surrounding the axon by some reaction between the two (Bardeen, 1903). At first the myelin is evenly distributed along the axis-cylinder, but later it accumulates more rapidly in some areas than in others, which produces the beaded appearance shown in Fig. 19, *c*. Eventually the sheath is completely filled out (Fig. 19, *d*). At the nodes of Ranvier the formation of myelin continues for some time after the completion of the myelin deposit in the remainder of the sheath (Fig. 19, *e*),

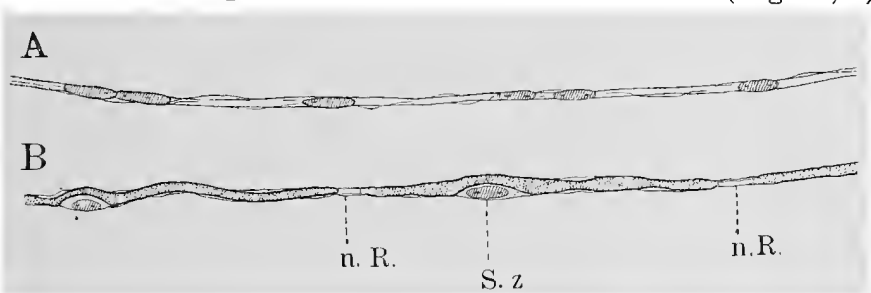

FIG. 20.—Isolated fibres of the sciatic nerve of sheep fetus 15 cm. long, treated with osmic acid and showing development of the nerve-sheath. A shows axon inclosed in membranous sheath with proliferating nuclei. In B the development is more advanced, and a deposit of myelin shown in dark stipple has formed within the membranous sheath: *n.R.*, node of Ranvier; *S.z.*, nucleus of membranous sheath. (After Vignal.)

apparently thus allowing for the lengthening of the fibre. During the later stages of development further provision is made for the lengthening of the fibre by the intercalation of new segments of the sheath of Schwann at the nodes of Ranvier.

In the central nervous system there seems to be no distinct separate membrane investing the fibres that exactly corresponds to the sheath of Schwann of the peripheral medullated fibres. There are, however, sheath cells present. They are apparently most numerous and possess most protoplasm during the active period of myelin development. On adult fibres they are relatively fewer in number and are less conspicuous since they then possess less body protoplasm. According to Hardesty (1904), these sheath cells of the central nervous system in the pig are derived from the indifferent supporting cells which we have already seen for the most part are converted into neuroglia tissue. Shortly after the beginning of myelin formation they become differentiated into typical sheath cells, and form around each nerve-fibre an extended lamellated reticulum, in the meshes of which the small globules of myelin are supported.

Myelin formation commences about the fourth month, but it does not make its appearance in all parts of the nervous system at the same time, nor simultaneously in all parts of an individual fibre. As a rule, it appears first in fibres that become functional first and in fibres that are phylogenetically the oldest. In an individual nerve the myelin is first seen at the central end and spreads from there toward the periphery. According to Westphal (1897), the medullation of the spinal nerves is completed between the second and third years, while the cranial nerves are completely medullated by the ninth or tenth post-embryonal week. Of the

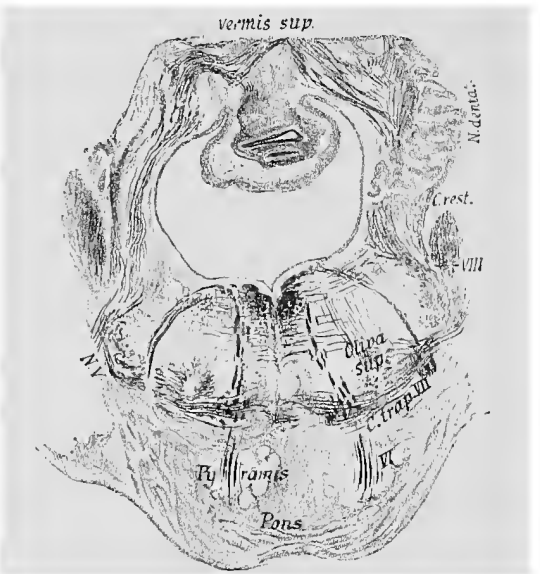

FIG. 21.—Section through hind-brain of new-born child, showing myelinization of fifth, sixth, seventh, and eighth cranial nerves and associated fibre tracts (fasciculus longitudinalis medialis and corpus trapezoides). The lemniscus medialis is also myelinated. These stand out in sharp contrast to the other fibres of the pontine region, including the pyramidal tract, which are still devoid of myelin. (After Edinger.)

cranial nerves the motor fibres are medullated first, and the sensory fibres a little later, excepting the acusticus, the vestibular division of which is medullated about as soon as the motor fibres. In premature births the medullation of the cranial nerves seems to be accelerated. Westphal states that there is a gradual increase in the size of the sheath with increasing age. He finds that on comparing the adult with the child the largest sheath in a given motor nerve in the adult is twice as large as the largest sheath in the same nerve in the child. He finds also that the sheaths are more uniformly large in the adult, while in the child there is a large proportion of small sheaths, so that the average of large sheaths in an adult nerve is four or five times greater than in the same nerve in a child. Regarding the time of myelinization of the different areas and fibre paths of the central nervous system

the reader is referred to Westphal's paper and the work of Flechsig (1896, 1904). As can be seen in Fig. 21, the relative time of appearance of the myelin is an important factor in the identification of the different fibre paths.

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II. DEVELOPMENT OF THE CENTRAL NERVOUS SYSTEM

The nervous systems of all vertebrates develop from the same ectodermal germ layer and within certain limits they always pass through the same series of developmental stages. The difference between the higher and lower forms consists only of a variation in size and degree of development of certain of the component structures, owing to the variation in the demand made upon those particular structures by the special life habits, size, and requirements of the respective animals. The nervous system is delicately responsive to the requirements of each individual animal and all of its parts are subject to a greater or lesser development in accordance with their functional necessity.

In this variability in the development of its different parts the nervous system does not adhere to a phylogenetic order. Hence it is impossible to definitely determine the relative position of two animals by the character of their nervous systems. With the exception of one portion the nervous system of the lower vertebrates possesses all the essential features and the same general grouping found in the highest vertebrates. In fact in certain instances they possess structures that are more complicated and presumably more efficient than the analogous structures in higher forms. Even the same structure may exhibit in closely related families a marked difference in the degree of its development, particularly in case of the higher co-ordinating apparatuses such as is represented by the cerebellum. One portion (pallium), however, contrary to the rest of the nervous system, varies in its development directly according to each animal's phylogenetic position. It follows a definite phylogenetic curve. It is present as a small rudiment in fish and amphibians and gradually increases in relative size and complexity as we ascend the vertebrate scale until it finally forms the prominent cerebral hemisphere of man.

In all vertebrates the central nervous system consists of a dorsally placed hollow tube, the walls of which are connected by the peripheral nerves with the different parts of the body. Where many nerves enter or arise the central apparatus is larger, as in the enlargements of the cord, the medulla oblongata, midbrain roof and thalamus. Further enlargement is produced by the establishment of fibres connecting different levels. A third group of enlargements is produced by the establishment of nuclear masses which serve as higher receptive and co-ordinating centres. In general, it may be said that the nervous system consists of afferent and efferent tracts, or peripheral system, and a central mass that serves to connect and co-ordinate them, or central system. Of the former, the afferent tracts are made up of receptor neurones and the efferent tracts of effector neurones. The latter, or central

nervous system, in addition to the central extension of peripheral neurones, consists of intersegmental neurones, uniting different levels, and suprasegmental neurones, that form the receptive and co-ordinating centres for control over the lower neurones. The location of the elaborated sense organs at the forward end of all vertebrates, to facilitate the gathering of food and the detection of enemies and mates, results in the highest development of the nervous system in the head region. We thus speak of cephalization of the central nervous system and distinguish the enlarged anterior end, with which the special sense organs are connected, as brain, and the remainder as spinal cord.

At the time of the closure of the neural tube that portion corresponding to the brain undergoes a threefold constriction, forming three primary brain vesicles which are constant in all vertebrates and form a definite morphological basis for the subdivision of the brain into three primary portions. These are known as the prosencephalon (the most oral one), the mesencephalon, and the rhombencephalon (the most caudal one). Subsequently the first of these (prosencephalon) becomes further subdivided into an end portion or telencephalon and an intermediate portion or diencephalon. The last, or rhombencephalon, is also often subdivided for descriptive purposes into the metencephalon, from which the pons and cerebellum are developed, and the myelencephalon, from which the medulla oblongata is developed. Owing to the tendency to metamerism of the mesencephalon and the rhombencephalon and their conformity with the type seen in the spinal cord, it has been suggested (Strong) that we recognize an epichordal system including all that portion of the central nervous system from which the true cerebrospinal nerves arise, and which lies dorsal to the chorda. The remainder is designated as prechordal, the boundary between the two being the primary ventral infolding of the brain wall (plica encephali ventralis). These terms of subdivision will be constantly made use of in the following pages.

We will first consider the anlage of the nervous system as it is found in the earliest stages, and will then follow its conversion into the medullary tube, and trace the development of the latter during the first four weeks. This will be followed by a description of the central nervous system as it is found at the end of the first month. Up to that time it is necessary to consider the different portions more or less in conjunction with each other. After the first month, however, the further development of the individual subdivisions will be described separately.

(a) Development of Central Nervous System during First Month.

The first evidence of the nervous system is the neural groove that forms as an axial furrow in the median line of the germinal plate, as can be seen in Fig. 22. The thickened ectoderm on each side of this groove forms the neural plate. In the Von Spee embryo Gle the borders of the neural plate are beginning to be indicated, and just a little later, in embryos about two weeks old, the elevated edges of the neural plate are clearly marked off from the rest of the ectoderm, as shown in Fig. 23, A.

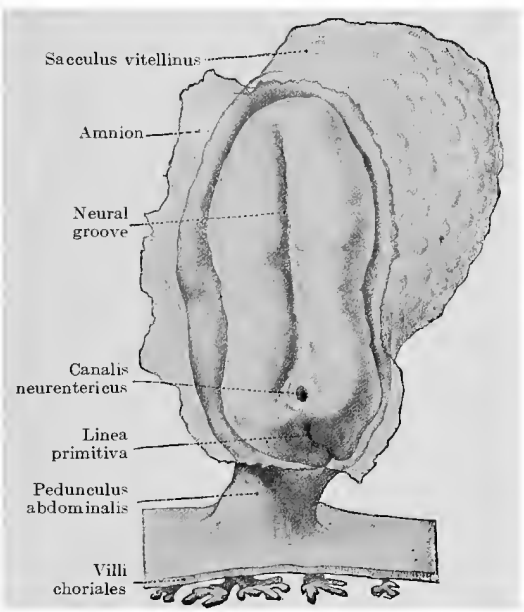


FIG. 22.—Dorsal view of human embryo in the neural-plate stage. The amnion is opened, exposing the germinal plate lying directly on the yolk-sac. (Graf Spee, from Kollmann.)

The further elevation of the edges and their approximation and fusion across the median line to form the neural tube is shown in four stages in Fig. 23. The comparison of these figures shows that the formation of the neural tube is most advanced in the middle of the germ plate corresponding to the junction of brain and spinal cord. From this region the differentiation and closure of the tube extends caudally and orally, the last portions to close being called the anterior and posterior neuropores (see Figs. 24 and 26). The process of closure, though it always begins in about the same region, shows some variation in the time of its occurrence. In Fig. 23, C, it is further advanced than in Fig. 23, D, which, judging from the number of somites, is the older embryo of the two.

The anterior neuropore is found closed in embryos of about 23 somites and the posterior neuropore a little later in embryos

of about 30 somites, the end of the third week. The neuropores do not exactly represent the anterior and posterior ends of the neural tube.[1] The anterior and posterior margins of the neural plate are rounded off laterally so that the extreme anterior and

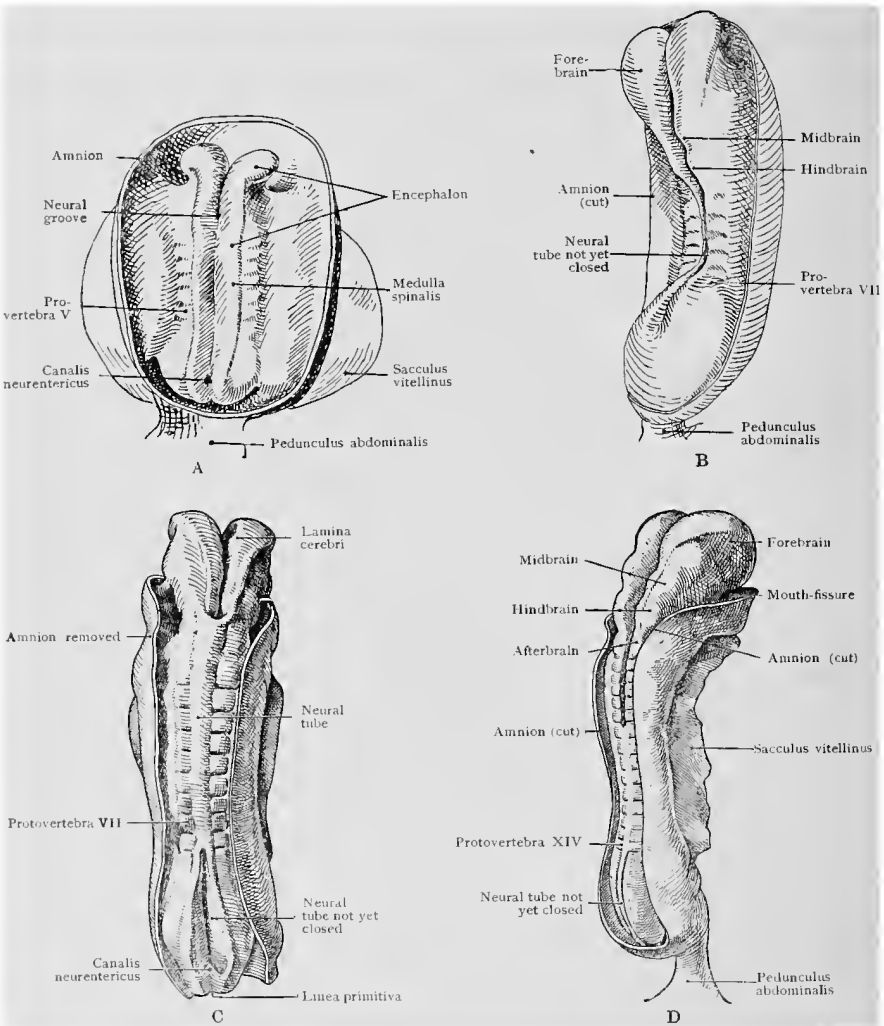


FIG. 23.—Four stages in the closure of the neural tube in human embryos possessing from 5 to 14 somites. A, embryo Klb, 5–6 somites, from Keibel u. Elze (Normentafeln); B, embryo No. 391, 7 somites, Mall collection, after Dandy; C, Eternod's embryo, 2.11 mm. long, 8 somites, after Kollmann; D, embryo 2.4 mm. long, 14 somites estimated age 14 to 16 days. (C and D after Kollmann.)

posterior ends of the neural plate are found in the median line. In the closure of the tube it is the lateral portions of the anterior and posterior margins that unite last, and so the neuropores are found dorsal to what was originally the extreme ends of the neural

[1] Compare also the chapter describing the development of the eye.

tube. This is particularly marked in case of the posterior neuropore (Fig. 24). The region in the adult brain corresponding to the anterior end of the neural plate was placed by His at the infundibulum. Johnston (1909) from comparative embryological studies places it at the optic chiasma. The anterior neuropore forms dorsal to this, and by its closure completes the lamina terminalis.

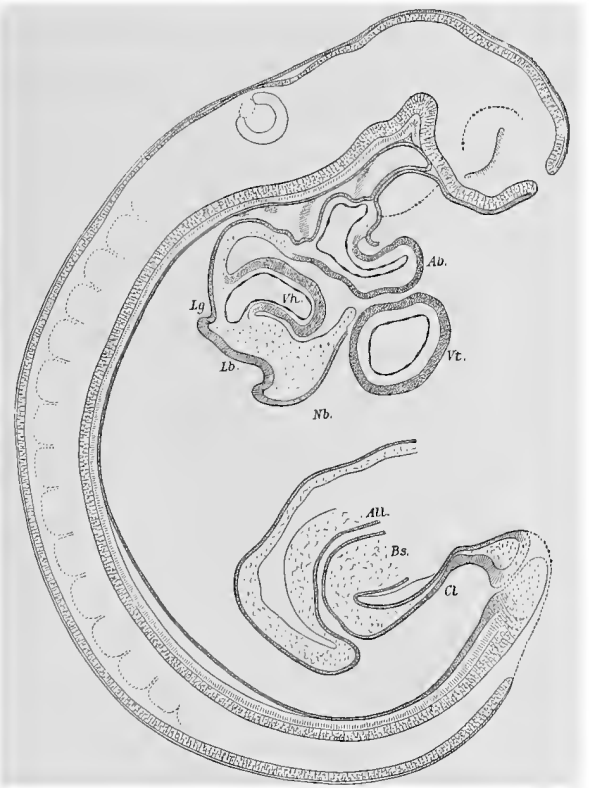


FIG. 24.—Profile reconstruction of human embryo 3.2 mm. long, showing neural tube closed except for anterior and posterior neuropores. The chorda lies closely against its ventral surface. The optic evagination is shown by a dotted line and is connected with the neural tube by a wide slit. The ear vesicle is indicated lateral to the hindbrain. In the area reuniens the neural tube, chorda, and foregut are still undifferentiated from one another. (After His, 1904.) *Ab.*, truncus arteriosus; *All.*, allantoic duct; *Bs.*, abdominal stalk; *Cl.*, cloake; *Lb.*, liver anlage; *Lg.*, lung anlage; *Nb.*, stalk of the umbilical vesicle; *Vh.*, atrium; *Vt.*, ventricle.

While still in the neural plate stage before its closure the central nervous system is differentiated into an anterior portion that is to form the brain and a posterior portion that is to form the spinal cord, as shown in Fig. 23, A. The brain portion is wider, more irregular, and projects beyond the yolk sac, bending forward nearly at a right angle. It forms about one-half of the neural plate. We cannot yet with any clearness recognize the subdivisions of the brain. The spinal cord portion is narrower and uniform in width. It extends caudally to the neurenteric canal, extending on each side a little beyond it. Most of the spinal por-

tion of the neural tube that is differentiated at this time is that which is to form the cervical cord. The lower cord is formed by the caudalward expansion of the neural plate. In embryos of seven somites, Fig. 23, B, where the neural tube is just beginning its closure, there appear two distinct constrictions in the brain

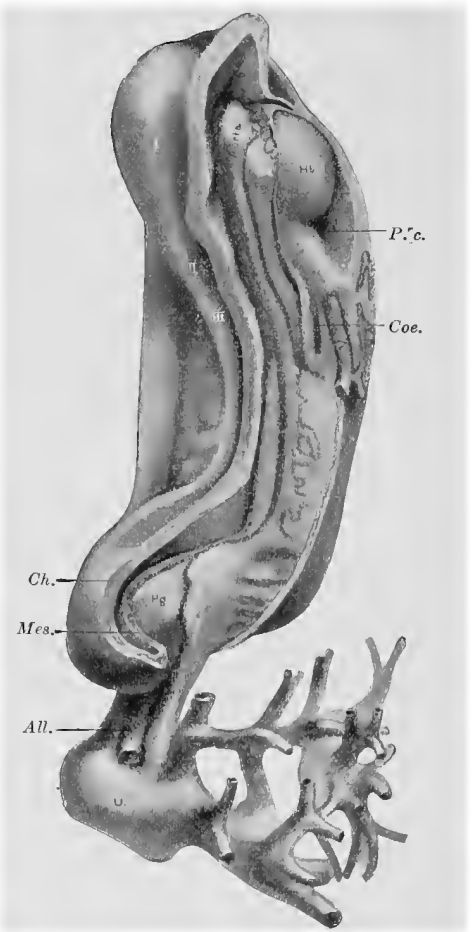


Fig. 25.—Dorsal view of model of human embryo possessing 7 somites, being the same embryo shown in Fig. 23, B. Portion of ectoderm of right neural plate is removed, showing thickness of wall and its relation to deeper structures. The three primary cerebral vesicles are indicated. (After Dandy.) *All.*, allantois; *Ch.*, chorda; *Coe.*, cœlom; *Fg.*, foregut; *Hg.*, hindgut; *Ht.*, heart; *Mes.*, mesoderm; *P. c.*, pericardial cœlom; *U.*, umbilical arterial sinus; *V.*, umbilical vein.

wall, subdividing it into a prosencephalon, mesencephalon, and rhombencephalon. These are best seen in Fig. 25, which is from the same embryo, but the ectoderm is partially removed, showing the cut edge of the right half of the neural plate. With the closure of the tube they become still more marked, as shown in Fig. 23, D. In these young stages the neural tube follows the flattened curve of the yolk sac, the only bending in the axial line being anteriorly

and posteriorly where it projects free beyond the surface. It is now supposed that the sharp ventral convexity sometimes found in the spinal region in these young specimens is artificially produced by the preserving medium.

The character of the neural tube at the beginning of the third week is shown in Figs. 24, 26, and 27. The age of embryo from which these reconstructions were made was estimated by His at two weeks, but on comparing it with other embryos we are probably safer in considering it as being in the third week. The

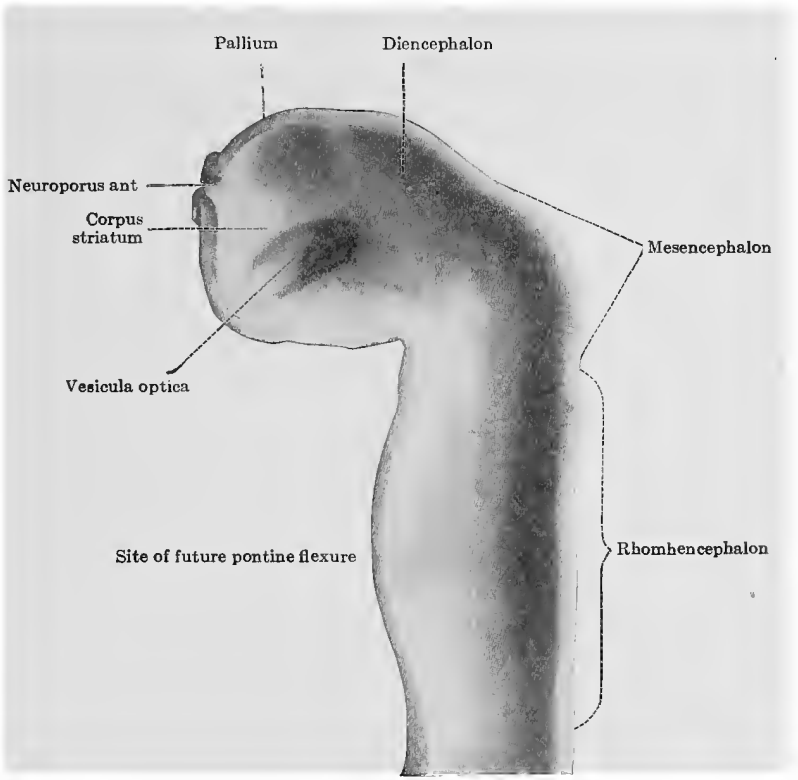


FIG. 26.—Median view of a model of the brain of a human embryo 3.2 mm. long, being the same specimen shown in Fig. 24. (After His.)

closure of the tube is now complete except for the small anterior neuropore and a small portion at the caudal end. The cranial portion of the tube is distinctly subdivided into the three primary vesicles. The most caudal one, or rhombencephalon, is much the largest. Its roof is not yet thinned out, the wall of the neural tube being everywhere of about the same thickness.

The first flexure to form in the neural tube is the cephalic flexure. It is well marked at this time, being a sharp bend in the neural tube in the region of the midbrain so that the axis of the forebrain forms approximately a right angle with that of the

hindbrain, the notch formed on the ventral surface being known as the ventral cephalic fold. The location of the future pontine flexure is marked by a ventral bulging of the floor of the tube. The anterior primary vesicle or forebrain at the completion of its closure is already marked off into its main subdivisions. The optic evagination exists as a depression in the lateral wall before the closure is complete, but at the time under consideration it forms a distinct pocket projecting lateralward and caudalward. Extending from its dorsal border is a fold (margo thalamicus) which marks the bound-

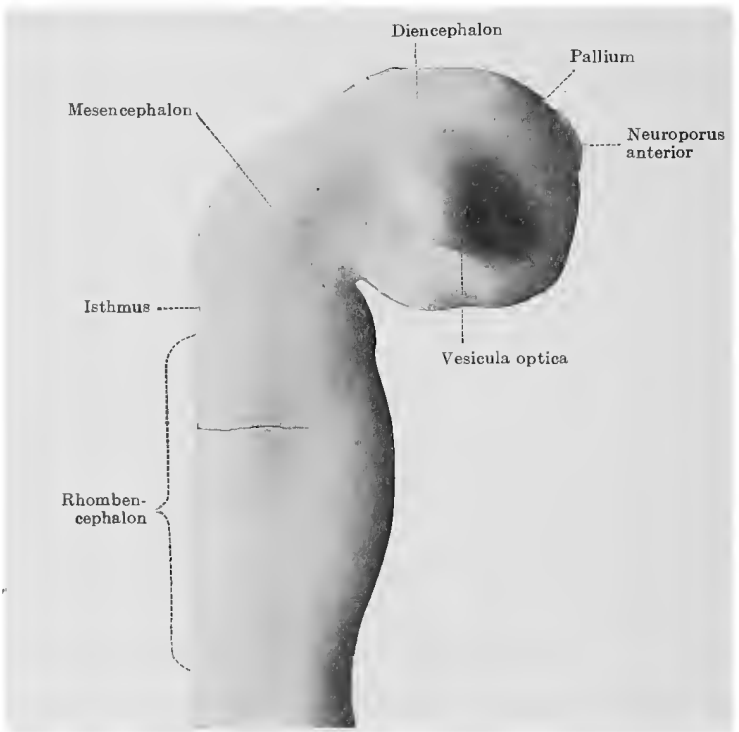


Fig. 27.—Lateral view of same model shown in Fig. 26.

ary between the telencephalon and diencephalon and separates the anlage of the thalamus from that of the pallium. The wall adjacent to and forming the anterior border of the evagination forms the anlage of the corpus striatum. The wall posterior to the evagination forms the ventral half of the diencephalon or hypothalamus.

The changes occurring in the central nervous system between the third and fourth weeks may be seen by comparing Figs. 28 and 29 with Figs. 26 and 27. The tube is now completely closed and the neuropores have disappeared. The walls due to their differentiation begin to show a variation in thickness. This is particularly marked in the thinning of the roof of the rhomben-

cephalon. The flexures of the tube are more marked. The cephalic flexure has increased from a right angle to an acute one,

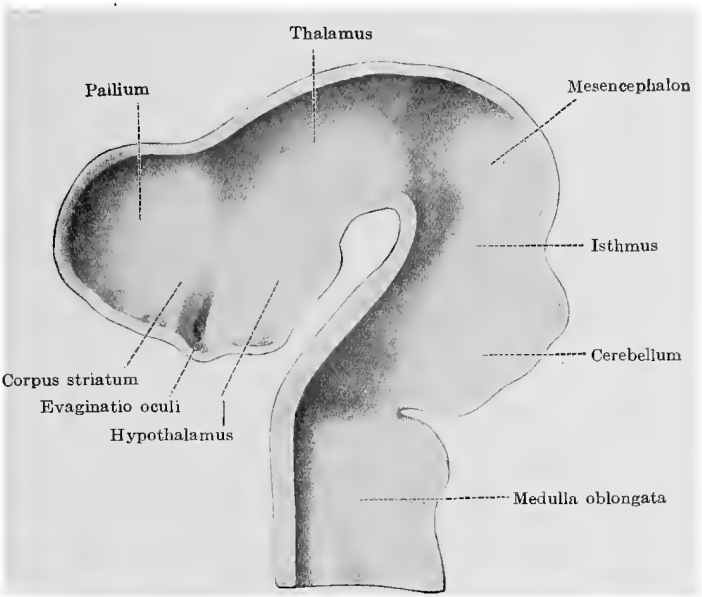


FIG. 28.—Median view of a model of the brain of a human embryo 6.9 mm. long. This figure should be compared with Fig. 26. (After His.)

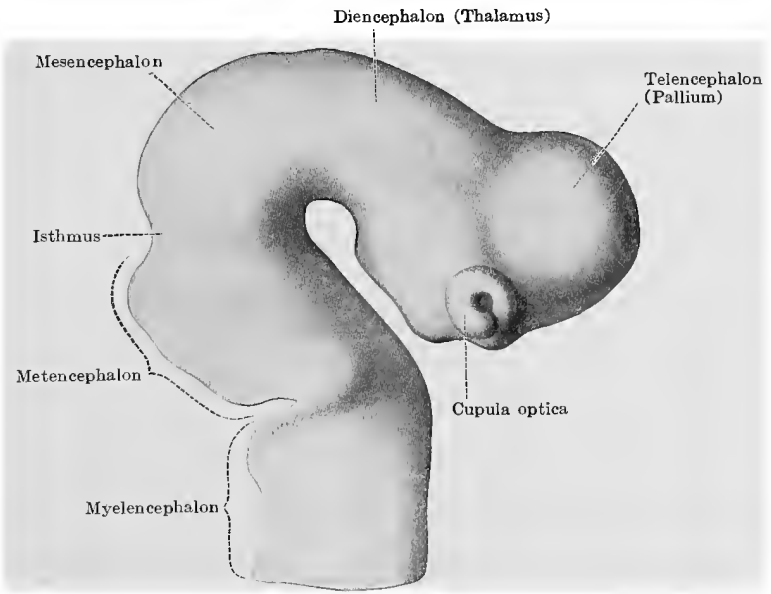


FIG. 29.—Lateral view of same model shown in Fig. 28. Compare with Fig. 27.

so that the axis of the forebrain is about parallel with that of the hindbrain. A distinct pontine flexure is now present in the rhombencephalon.

The formation of the flexures of the neural tube is shown in Fig. 30. It will be seen that there are three distinct flexures, cephalic, pontine and cervical. Two of them have already been

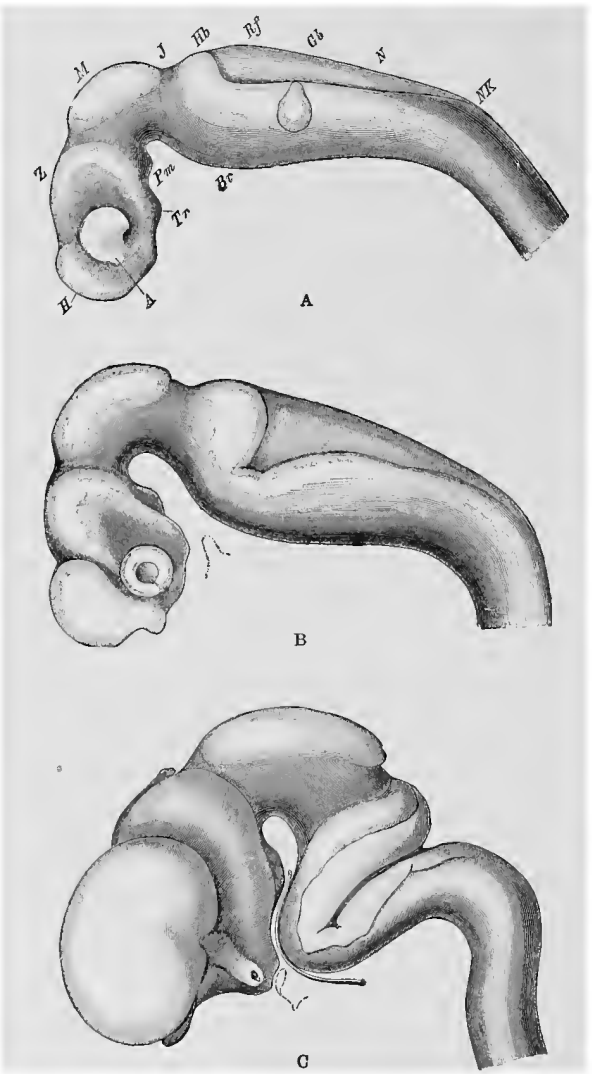


FIG. 30.—Profile views of the brains of human embryos as seen during the third (A), fourth (B), and eighth (C) weeks, showing the conversion of the three primary cerebral vesicles into their chief subdivisions and the formation of the flexures of the neural tube. *A*, optic vesicle; *Br*, pontine region; *Gb*, auditory vesicle; *H*, telencephalon; *Hb*, metencephalon; *J*, isthmus; *M*, mesencephalon; *N*, myelencephalon; *NK*, neck bend; *Pm*, mammillary recess; *Rf*, posterior medullary velum; *Tr*, infundibular recess; *Z*, diencephalon. (After His.)

mentioned. The third, or cervical flexure, marks the junction of brain and spinal cord and is formed about the same time as the pontine flexure. They are formed, in part at least, in consequence of unequal growth of different parts of the neural tube. They

probably influence and also are influenced by the growth of the surrounding structures. The cephalic and cervical flexures involve the surrounding structures to a considerable extent so that there is a corresponding bend of the axis of the whole head, and thus the presence of them can be recognized on the exterior of the embryo. The pontine flexure, however, is limited to the nervous system. The cephalic flexure persists into adult life. The pontine flexure finally disappears and the cervical flexure nearly does.

The formation of the pontine flexure marks a line dividing the rhombencephalon into an oral portion (metencephalon), from which the cerebellum and pons are developed, and a caudal portion (myelencephalon) which forms the medulla oblongata. The constricted portion separating the rhombencephalon from the mesencephalon (Fig. 28) is known as the isthmus. It differs from the adjoining portions of the neural tube in never undergoing any special development. It eventually forms the velum medullare anterius and through its lateral and ventral walls pass fibre tracts connecting other parts of the neural tube.

The mesencephalon and diencephalon do not differ materially from the preceding (three weeks) stage, though in the hypothalamic region one can recognize two shallow pockets in the midline in the floor, the more oral one being the anlage of the infundibulum and the more caudal one being the mammillary recess. The optic evagination has undergone considerable modification, the inversion

Table showing Subdivisions of Neural Tube and their Derivatives.

	Main divisions.	Subdivisions.	Derivatives	Lumen.
Brain	Prosencephalon (Anterior vesicle)	Telencephalon	Cerebral hemisphere Rhinencephalon Corpora striata	Oral end of third ventricle Lateral ventricle
		Diencephalon	Optic thalamus Optic tract Hypothalamus	Third ventricle
	Mesencephalon (Middle vesicle)	Mesencephalon	Colliculi Tegmentum Crura cerebri	Aqueduct of Sylvius
	Rhombencephalon (Posterior vesicle)	Metencephalon	Cerebellum Pons	Fourth ventricle
		Myelencephalon	Medulla oblongata	
Spinal cord	.....	.....	Spinal cord	Canalis centralis

of its lateral wall changing it from a simple vesicle to an eye cup which remains connected with the brain wall by a narrow hollow stalk. The former constitutes the eyeball and the latter the optic

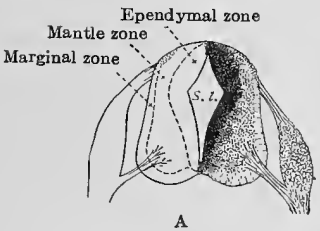
nerve. The subdivisions of the telencephalon are more clearly marked in Fig. 28 than in Fig. 26. It is easy to recognize the protruding pallium separated from the optic evagination by the corpus striatum and from the thalamus by the margo thalamicus. The wall in front of the corpus striatum and adjacent to the median line (lamina terminalis) constitutes the anlage of the rhinencephalon. The subdivisions of the neural tube that can be recognized toward the end of the fourth week, in embryos about 7 mm. long, may be summarized as in the accompanying table (p. 39).

(b) The Central Nervous System at the End of the First Month.

By the end of the first month there is completed what we may call the primary stage in the growth of the nervous system. The primary neurons forming the peripheral nerves are by that time well laid down; all their chief peripheral branches and plexuses are indicated, and centrally the nerve roots can be traced into the substance of the walls of the neural tube, where the nuclei from which the motor roots arise can be definitely outlined, and the sensory roots can be recognized as forming definite longitudinal fibre bundles, extending upward and downward in the outermost layer. The higher neuron systems, however, are still in a rudimentary state, and in sections through the brain and cord at this time we see only the primary apparatus differentiated. Such co-ordinating centres as the pons, olive and cerebellum are still undeveloped, and the forebrain, further than presenting the beginning threefold division into ependymal, mantle, and marginal zones, shows little evidence of differentiation and still remains a relatively simple thin-walled tube. This period in development thus corresponds to a rudimentary nervous system in which there is found only the apparatus necessary for the simple cerebrospinal reflexes, the system of primary neurons.

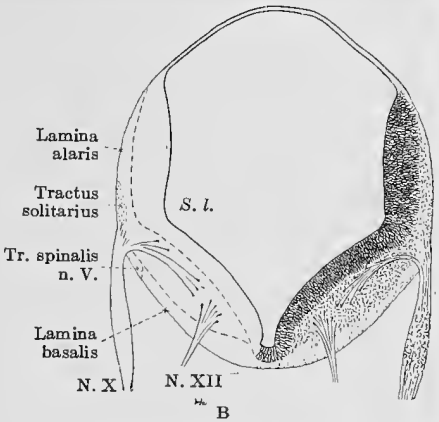
The outer form of the brain and spinal cord and their relation to the body outline are shown in Fig. 86. A series of transverse sections through the same specimen is shown in Fig. 31. It is at once seen that the greatest bulk of the central nervous system is formed by the rhombencephalon and the spinal cord. Of these two the rhombencephalon is relatively the larger; it is approximately two-thirds as large as the whole spinal cord and is as large as the midbrain and forebrain taken together.

The spinal cord is largest in the cervical region and from there gradually tapers down to the coccyx, except in the lumbosacral region, where it is somewhat larger again. The tendency toward cervical and lumbar enlargements is plainly indicated. The cord in cross section (Fig. 31, A) presents a rounded quadrilateral outline. It consists principally of two thick lateral walls. These



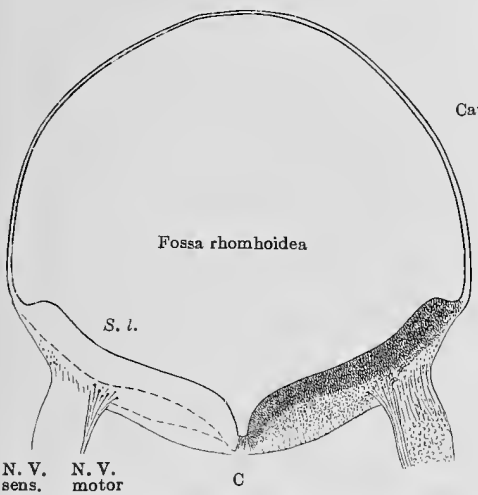
A

Cross-section through the spinal cord at the height of the fourth cervical segment.



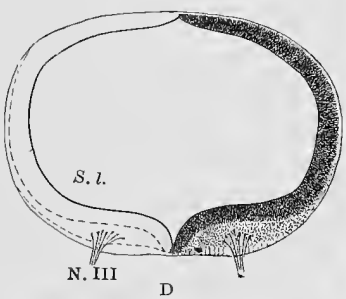
B

Caudal portion of the rhombencephalon with the vagus and hypoglossal nerves.



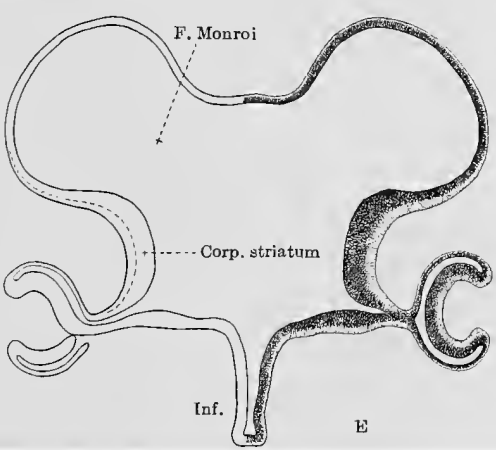
C

Cranial portion of the rhombencephalon with the sensory and motor roots of the trigeminal nerve.



D

Mesencephalon with the oculomotor nerve.



E

Prosencephalon showing plan of the hemispheres, the optic vesicles, the third ventricle, and the infundihulum.

FIG. 31.—Series of transverse sections through the central nervous system of human embryo one month old, made from tracings taken from the model shown in Fig. 86. These are all on the same scale of enlargement and thus graphically represent the relative size and thickness of the neural tube in the different regions. *S. l.*, sulcus limitans. Enlarged 25 : 1.

are united ventrally and dorsally in the median line by what we have previously recognized as the floor plate and roof plate, which are here reduced to narrow seams. The thick lateral walls are subdivided by a longitudinal furrow, the sulcus limitans, into ventral and dorsal portions, known respectively as the basal and alar plates. The ventral or basal plate is the thicker of the two. Its thickness is largely due to the proliferating cells of the mantle layer, the anlage of the future anterior horn. Among these are grouped clusters of neuroblasts whose growing processes extend out through the marginal zone and are assembled to form the anterior nerve roots. The dorsal nerve roots enter the cord opposite the sulcus limitans and form in the marginal zone a longitudinal strand which is the forerunner of the posterior funiculi of the cord. In the marginal zone, in addition to the prominent bundle of axons derived from the posterior roots, there can be seen scattered axons running both longitudinally and transversely which belong to the co-ordinating neurons of the mantle zone. It is these that later form in large part the anterolateral tracts of the cord.

In the transition from the spinal cord to the rhombencephalon the most striking difference consists in the widening out of the thin roof plate and the accompanying flaring apart of the alar and basal plates. As a result of this the lumen of the neural tube widens out from the narrow lanceolate cleft characteristic of the spinal region to the capacious fourth ventricle. Opposite the entrance of the trigeminal nerve the lumen is larger at this time than in any other part of the neural tube.

The lateral walls of the rhombencephalon have a larger area in cross section than the lateral walls in the spinal region (Fig. 31, B, C). Their form and degree of differentiation, however, are essentially the same. There is the same sulcus limitans separating them longitudinally into basal and alar plates; and, as in the spinal cord, there is the marginal zone containing the longitudinal fibre tracts, and the mantle zone consisting of clusters of proliferating neuroblasts which in part form the nuclei of the motor nerve roots. The ependymal zone is made up of closely packed and deeply staining primitive cells. The layer is several cells thick and the uneven line separating it from the mantle zone indicates that it is still active and giving off cells to the latter.

The arrangement of the nuclei of origin of the nerves connected with the rhombencephalon and the entering fibres of their sensory rootlets is on the same general plan as in the cord. The motor nuclei are grouped in a longitudinal column in the mantle zone of the basal plate. The fibres supplying somatic muscles pass directly ventralward through the marginal zone and emerge as the rootlets of the hypoglossal and abducens nerves, as shown in

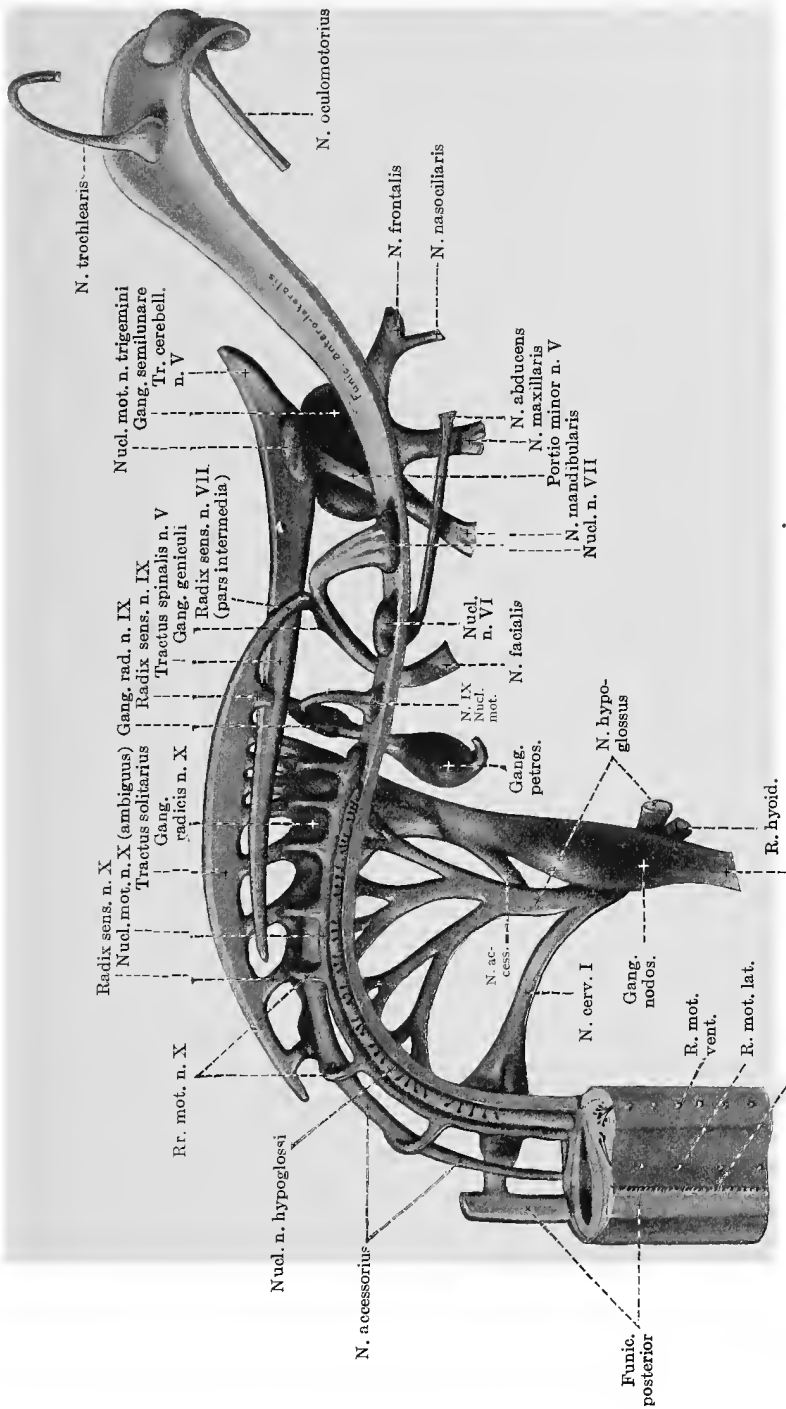


FIG. 32.—Reconstruction showing the cranial nerves in a 10 mm. human embryo (Huber col. No. 3). The brain wall is removed so as to show the primary sensory paths and motor nuclei of the different nerves.

Figs. 31, B, and 32. In the lateral part of the basal plate is the nuclear series supplying motor fibres to visceral musculature. These fibres pass lateralward and unite with the entering sensory fibres of the corresponding nerves. It is these fibres that constitute the motor elements in the trigeminal, facial, glossopharyngeal, vagus and spinal accessory nerves. This series of lateral motor nuclei may be subdivided on the one hand into a part that lies directly lateral to the somatic motor group, constituting eventually the nucleus ambiguus and the nucleus of the facial nerve, and on the other hand into nuclei massed nearer the entrance of the sensory fibres. The latter is well represented in case of the trigeminal nerve and in lesser degree in the dorsal motor nuclei of the ninth and tenth nerves. (Compare Figs. 31, B and C, and 32.)

The sensory fibres enter the marginal zone near the junction of the basal and alar plates, and immediately form longitudinal tracts analogous to the posterior funiculi of the spinal cord. The entering fibres of the seventh, ninth and tenth nerves in this manner unite to form the tractus solitarius, as shown in Figs. 32 and 96. The entering fibres of the trigeminal nerve form a similar but separate bundle. In the latter case we can recognize a cephalic limb extending to the anlage of the cerebellum and midbrain and a caudal limb extending toward the spinal region. A similar but smaller tract is formed by the entering fibres of the acoustic nerve, which at this time consists mostly of vestibular fibres. In addition to the tracts mentioned there are present in the marginal zone a few early representatives of the correlating fibres which later form the formatio reticularis and system of arcuate fibres and their longitudinal extensions. Near the median line the marginal zone is somewhat thicker from the presence of such fibres.

That portion of the alar plate in front of the trigeminal nerve constitutes the anlage of the cerebellum, but as yet it shows no apparent difference from the alar plate of the caudal half of the rhombencephalon.

The so-called rhombic grooves or transverse furrows, shown in Figs. 33, 34, and 95, are sharply marked at this time in the floor of the fourth ventricle. These grooves evidently form an important feature in the early growth of the rhombencephalon. They have been reported in a variety of different mammals (pig, sheep, dog, cat, rabbit, and rat) beside man and seem to be fairly constant in form and number. In man they are best seen during the third and fourth weeks. At first they are described as involving the whole thickness of the wall so that they can be seen both on the inner and outer surfaces of the brain wall (Gage, 1905). At the fourth week the outer surface of the wall is smooth and the grooves involve only the ependymal layer. After the fourth week the grooves rapidly disappear, leaving no marking that can be seen in the adult.

There are six rhombic grooves. The most cephalic one is in the region of the pontine bend, and they extend from there caudally as shown in Fig. 34. They bear a constant relation to the cranial nerves, which is indicated in Figs. 33 and 95. If the grooves are labelled *a, b, c, d, e,* and *f,* then it can be seen that we have the following relations: the trigeminal nerve arises conjointly from *a* and *b;* the facial nerve (motor root) runs transversely beneath the floor of groove *c,* which usually is the deepest and most

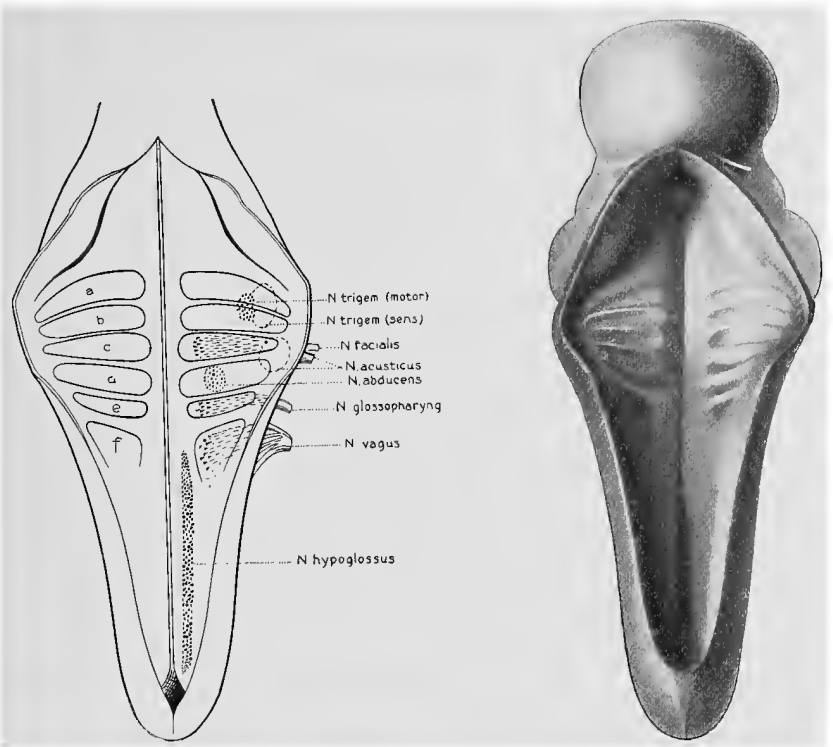


Fig. 33 Fig. 34

Fig. 33.—Diagram showing relation of the cranial nerves to the floor of the fourth ventricle and the rhombic grooves, being the same specimen as shown in Fig. 34.

Fig. 34.—Dorsal view of model showing rhombencephalon of human embryo one month old, being the same model shown in Fig. 86. The thin tela chorioidea is removed, exposing the floor of the fourth ventricle and rhombic grooves. The anlage of the cerebellum is formed by the alar plates cephalad to the pontine flexure. Compare with Fig. 33.

sharply cut of all six grooves; the acoustic nerve has its attachment to the alar plate adjoining grooves *c* and *d;* the abducens nerve arises from *d,* a shallow and somewhat quadrilateral groove; the glossopharyngeal nerve (motor portion) runs under the floor of the narrow groove *e,* and the motor roots of the vagus arise from *f,* which groove merges caudally into the general floor of the ventricle.

This nerve distribution is constant in the different mammals, and it is very likely that in this we have an explanation of the

significance of these grooves. The predominant view regarding them heretofore has been that they are neuromeric and in a series with the spinal segments and the coarser transverse divisions of the mid- and forebrain. Instead of this, if emphasis is laid on the fact that they stand in constant relation to the lateral group of cranial nerves (fifth, seventh, ninth and tenth), then they may be fitted in with and form part of the branchiomeric system. This view has in its favor the fact that they are not only united by nerve trunks, but also numerically correspond to and are embryologically contemporary with the branchial and facial arches in the manner shown in the following table:

Maxillary process.....	N. trigeminus	.....	Groove *a*
Mandibular arch.....		.....	Groove *b*
Hyoid arch.....	N. facialis.....		Groove *c*
—	N. abducens.....		Groove *d*
Third branchial arch.....	N. glossopharyngeus.....		Groove *e*
Fourth branchial arch.....	N. vagus.....		Groove *f*

The one discordant feature is groove *d,* which has no corresponding branchial arch. As yet we have no satisfactory explanation for either the aberrant course of the abducens nerve or its connection with this particular groove.

In the region of the midbrain the basal plate is much like that of the rhombencephalon and is in about the same stage of differentiation. In its mantle zone are the clusters of neuroblasts constituting the nuclei of the third and fourth cranial nerves. The fibres from the former pass through the marginal zone directly ventralward, as shown in Figs. 31, D, 32, and 86, and emerge from the hollow of the mesencephalic bend. The fibres of the fourth nerve on the other hand pass dorsalward just beneath the ependymal layer and decussate in the roof at the junction of the mid- and hindbrains and emerge directly after their decussation. No satisfactory explanation has as yet been given for this dorsal decussation of the fourth nerve.

The alar plates of the midbrain are thinned out and extend around dorsally to meet in the median line, the roof plate thus being reduced to a narrow seam. The only evidence suggesting the later development is found in the ependymal layer which forms an extensive germinal bed from whose cells are to be derived the neuroblasts composing the future corpora quadrigemina. The ependymal and mantle zones still exist as one layer. It is the outer portion that gradually becomes differentiated as the mantle zone and that gives origin to the quadrigeminal neuroblasts.

The outlines between the mesencephalon, thalamencephalon, and prosencephalon can be distinctly made out both externally and internally. The prosencephalon is characterized by a prominent lateral evagination whose lumen is to form the lateral ventricle

and is connected with the main lumen of the neural tube by the large foramen of Monro. It is the wall of this pouch that is to form the future cerebral hemisphere, as will be described later. Two other evaginations are developed from the floor of the prosencephalon to form the special sense organs of smell and sight. The former at the end of the first month is just making its appearance in the form of a slight depression in the lumen of the anterior brain wall just lateral to the lamina terminalis and does not yet form a distinct pouch. The visual apparatus is much further advanced. As seen in Fig. 31, E, we have a well-formed optic cup connected by a hollow optic stalk with the floor of the prosencephalon at its junction with the thalamencephalon.

The thalamencephalon as yet shows little sign of differentiation, though it is possible to divide it into a ventral portion that is to form the hypothalamus and infundibulum, and a dorsal portion that is to form the thalamus. The latter is continuous with and resembles the alar plate of the midbrain.

(c) The Spinal Cord from the End of the First Month to Maturity.

A general sketch of the formation of the neural tube and the differentiation of its walls and its change in form up to the completion of the first month has been given. The further changes by which it becomes converted into the adult spinal cord now remain to be considered.

In considering the different elements taking part in its further development it is important to follow the subdivision of the wall of the cord into its three constituent layers or zones (ependymal, mantle, and marginal), tracing the fate of each up to the adult condition. At the same time one should keep in mind the four-sided form of the cord, consisting of two lateral walls united ventrally by a floor plate and dorsally by a roof plate. The roof and floor plates retain their primitive characteristics throughout and are only modified secondarily, due to the changes in the adjoining portions of the lateral walls. The lateral walls on the other hand undergo enormous growth, and it is the character of their thickening that determines the shape of the cord.

The lateral walls are subdivided into a ventral or basal plate and a dorsal or alar plate, the junction between the two corresponding to the sulcus limitans. These are also known as the anterior "Markcylinder" and posterior "Markprisma" of His. From the first of these are developed the anterior gray columns or horns, the motor nerve roots, and the surrounding funiculi of longitudinal fibres (anterolateral ground bundles). From the dorsal or alar plates are developed the posterior gray columns, the substantia gelatinosa and the dorsal funiculi into which the posterior nerve

roots enter. The basal plate is primarily a motor apparatus and the alar plate is primarily a sensory one.

The basal and alar plates are united by an isthmus-like intermediate portion known as the "Schaltstück" of His. This area, owing to the shrinking of the tissues, particularly the radial framework fibres, in prepared specimens is usually sharply demarcated on the surface of the cord by two longitudinal furrows, the marginal groove directly in front of the entering posterior roots and the cylinder groove at a point about midway between there and the emerging anterior roots. From the gray substance of this area are developed many of the internal arcuate fibres, and the adjoining marginal zone becomes converted into the formatio reticularis and supplies a pathway for the spinocerebellar and cerebrospinal tracts.

In Figs. 36, 37, 38, and 39 are shown the typical stages in the conversion of the neural tube with its three primitive zones into

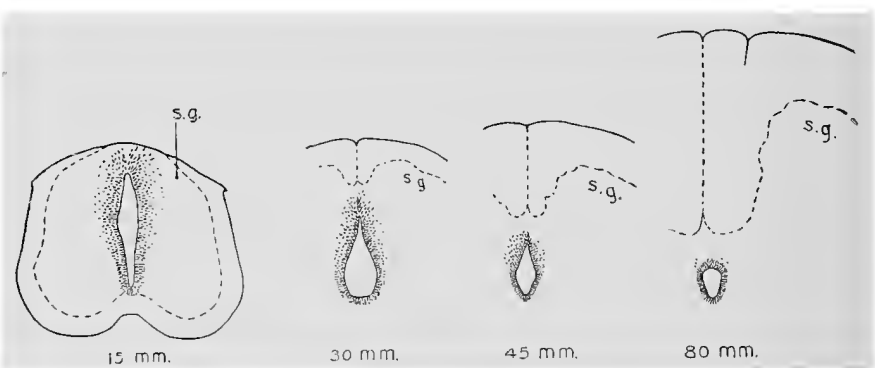


FIG. 35.—Diagram showing the fate of the ependymal layer and the formation of the posterior median septum and the central canal of the spinal cord. The approximate length (crown-rump) of the embryo is indicated in mm. below each stage. *s. g.*, dorsal gray column and substantia gelatinosa.

the more complicated solid cord as found in the adult. Starting with the ependymal zone and tracing it through these successive stages we meet with the appearances that are schematically shown in Fig. 35. To facilitate comparison these are all drawn on the same scale of enlargement.

It can be seen that at the beginning of the second month (15 mm.) the lumen of the cord is still relatively large, and that from that time on up to embryos of 80 mm. it decreases in actual size and still more so in size relative to the size of the cord. The shape of the lumen passes through characteristic changes. As seen in transverse section it is at first (15 mm.) an elongated oval slit, and is wider in the dorsal half. At 30 mm. the condition is reversed and the lumen is wider in the ventral portion, while the dorsal portion is reduced to a narrow slit. Eventually the dorsal portion becomes obliterated and there only remains the rounded ventral

portion, and it is this that forms the permanent central canal. The longitudinal furrows that have been described as indenting the sides of the lumen are probably to be classed as shrinkage phenomena, since they are not present in razor sections of unembedded pig embryos. The most constant of these furrows is the sulcus limitans at the junction of the basal and alar plates.

The ependymal cells that form the ventral portion of the lumen differ already in the 15 mm. stage in character and arrangement from those forming the dorsal portion. They are more compactly arranged and form a narrow band that is more sharply separated from the adjacent mantle zone than is the case in the dorsal

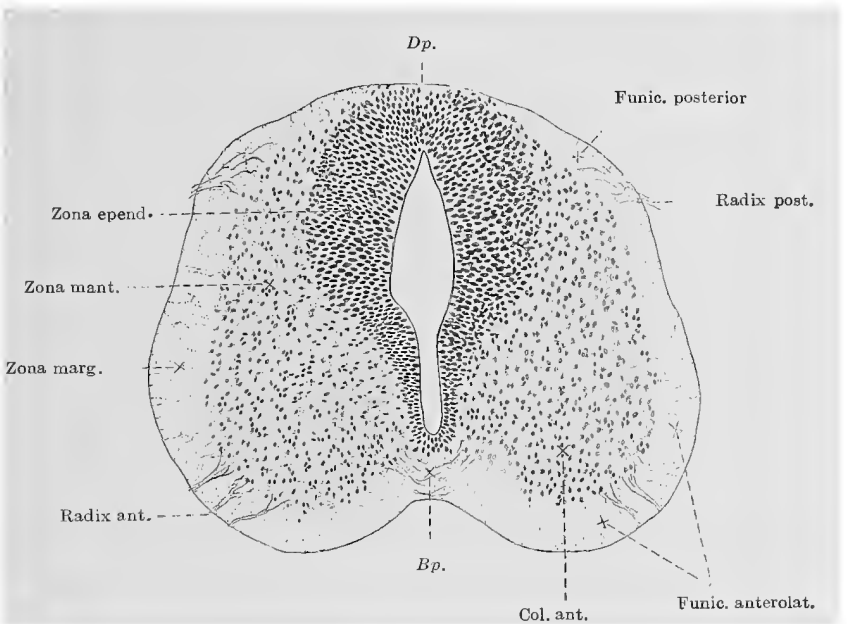


Fig. 36.—Cervical spinal cord of a human embryo 15.5 mm. long. Enlarged 60 : 1. *Dp.*, roof plate; *Bp.*, floor plate, in which the anterior commissure is developing. (After Bryce.)

portion of the cord. If we may regard the ependymal zone as a germinal bed delivering proliferating cells to the mantle zone then it is apparent that this phenomenon is practically completed in the ventral portion and the remaining cells are entering the resting stage, while the process is still in active operation in the dorsal portion. The ventral portion of the ependymal zone, like the ventral portion of the cord in general, may be regarded as further advanced in its development than the corresponding dorsal portions.

In embryos from 15 mm. on, coincident with the formation of the dorsal columns of gray matter, there is a gradual subsidence of the proliferation of ependymal cells around the dorsal portion, and the whole ependymal border comes to a resting stage

and forms a narrow, sharply demarcated border for the central canal. In doing this the size of the canal is decreased through the approximation and fusion of the walls of its dorsal portion. In Fig. 37 this process of fusion is in active operation. As the walls come together the cells lose their radial direction and form a unilateral compact strand which is soon replaced by a sparsely nucleated seam of supporting tissue like that forming the framework of the mantle zone. It is the extension of this seam of closure that eventually forms the posterior median septum. The ventral end of the septum is a fixed point and its further growth

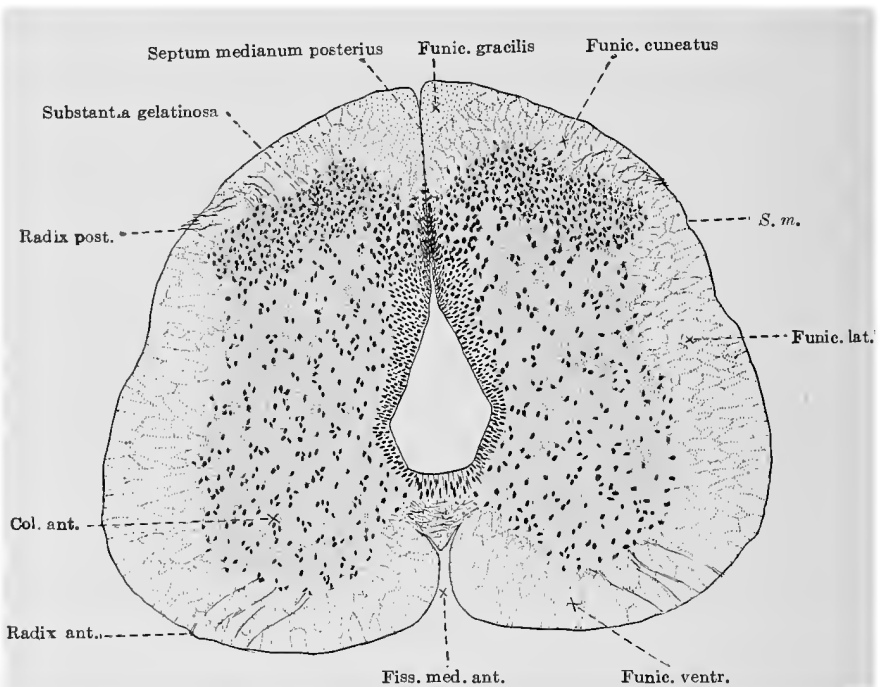


FIG. 37.—Cervical spinal cord of a human embryo 30 mm. long (Huber collection, No. 15). Enlarged 60 : 1. *S. m.*, junction of lateral and posterior funiculi, which point in shrunken specimens is marked by a deep groove.

and elongation, coincident with the development of the dorsal funiculi, must be considered as taking place principally at the dorsal end.

The development of the mantle zone is closely associated in the earlier stages with that of the ependymal zone and the line of demarcation between them is ill-defined. As has been described in the section on histogenesis of nervous tissues the mantle and ependymal zones were originally one common layer, and the mantle zone may be regarded as a proliferation and differentiation of the outer ependymal cells. Later, as the anterior and posterior columns of gray substance begin to take form (15 mm.), the ependyma

gradually enters upon its resting stage and from then on becomes sharply marked off from and takes no further part in the development of the mantle zone.

On comparing Fig. 36 to 39 it is seen that in 15 mm. embryos we can already speak of an anterior gray column (horn) which is composed of a supporting framework and clusters of developing neuroblasts. The processes from the neuroblasts are assembled into rootlets which emerge on the ventrolateral border of the cord as the anterior nerve roots. The anterior columns in the later stages enlarge and their contour becomes irregular and eventually

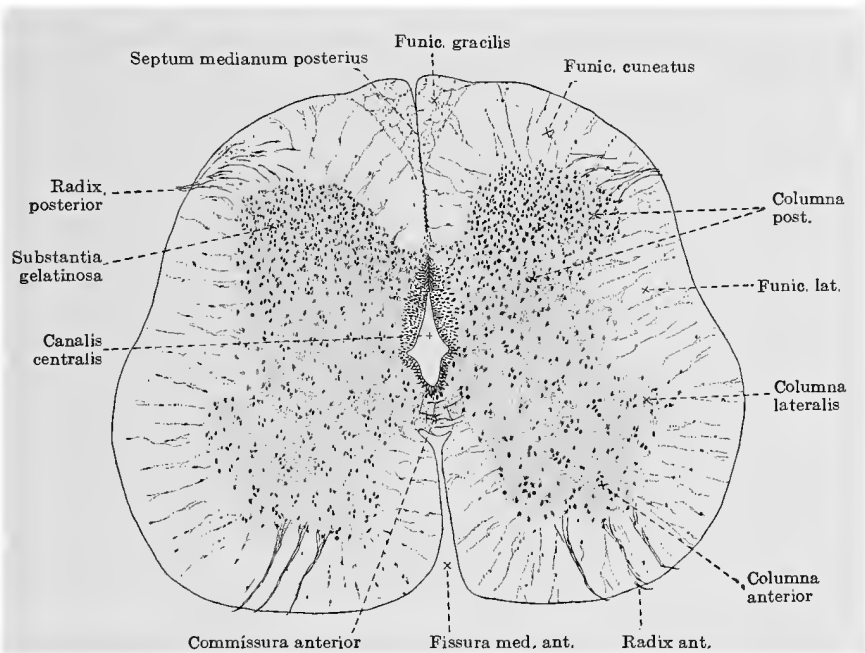


FIG. 38.—Cervical spinal cord of a human fetus 45 mm. long (Huber collection, No. 18). Enlarged 45 : 1. This figure should be compared with Figs. 36, 37, and 39, all of which represent the same region in its different stages of development.

we can recognize a lateral division, the so-called lateral horn. In the 80 mm. embryo (Fig. 39) there is presented practically the adult form. The enlargement from 30 mm. on consists partly in the elaboration of the supporting framework and partly in the increase in size of the contained neuroblasts. The growth of the latter involves also their processes, so each ventral column would become larger through the growth of its own processes as well as the invading processes from other portions of the mantle zone. The elaboration of the supporting framework and development of the processes of the neuroblasts results in a greater separation of the neuroblasts from each other and gives the mantle zone the appearance of being more sparsely nucleated. There are also cer-

tain supplementary factors in the growth of this tissue due to the process of vascularization and later due to the acquisition of myelin sheaths.

The formation of the dorsal gray columns (posterior horns) occurs somewhat later than the ventral ones. In the 15 mm. embryo (Fig. 36) it is possible to outline that portion of the mantle zone that is to form them. They possess, however, very little at that time either in structure or form that is characteristic; the cells of the ependymal zone of that region are still actively crowding outward to become incorporated in the mantle zone. In em-

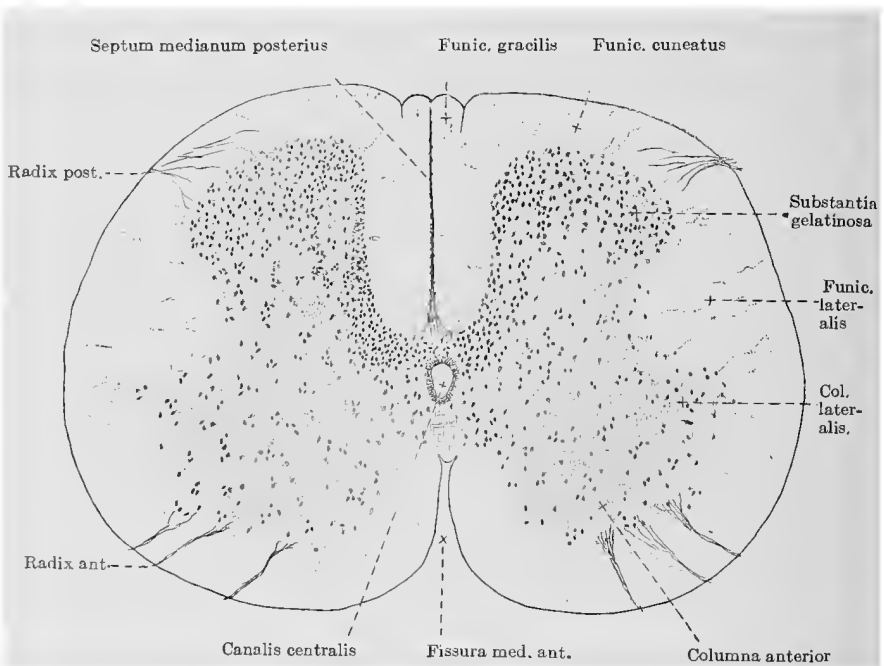


FIG. 39.—Cervical spinal cord of a human fetus 80 mm. long. Enlarged 30 : 1.

bryos of 30 mm. the outline of the dorsal columns commences to take form and masses of neuroblasts group themselves so as to form a cap at the dorsal border, which eventually becomes the ganglionic mass known as the substantia gelatinosa. The further elongation of the mantle zone into typical posterior columns can be seen by comparing Figs. 37, 38, and 39.

As has already been shown the roof plate as such disappears with the formation of the posterior median septum. The floor plate, however, persists and is formed in part by the ependymal cells which extend from the lumen radially outward to the surface of the cord, forming the bottom of the anterior longitudinal fissure. In addition to the ependymal cells the floor plate is made up of the processes from the heteromeric neuroblasts of the mantle

zone, whose decussation eventually constitutes the anterior commissure. Neuroblasts of this character are found in considerable numbers in the inner portion of the mantle zone and are analogous to the internal arcuate fibres found in the hindbrain. The processes forming the anterior commissure cross the median line in the mantle zone. A marginal layer can scarcely be said to exist in the region of the floor plate.

The development of the marginal layer (Randschleier of His) and its conversion into the white substance of the cord are dependent upon the foreign cells whose axons penetrate this zone and thread their way through its meshes forming the longitudinal fibre tracts of the cord. These axons may be classed into five main groups: (*a*) dorsal root fibres arising from the spinal ganglia; (*b*) short intersegmental fibres (ground bundles) arising from neuroblasts of the mantle zone and serving to connect adjacent levels of the cord; (*c*) long suprasegmental fibres connecting the cord nuclei with higher centres; (*d*) long descending fibres connecting nuclei of the hindbrain with lower levels in the cord; and (*e*) long fibres forming the descending palliospinal tracts. Of these fibre groups (*a*) and (*b*) make their appearance first (end of first month). Very soon afterward groups (*c*) and (*d*) appear (beginning of third month). The last fibres to appear are those belonging to group (*e*) (end of fifth month). The axons belonging to group (*a*) form a tract of fibres (funiculi posteriores) that always remains separated from the remaining fibres. Groups (*b*–*e*) partly merge into one another forming the anterolateral funiculi and thus cannot be so sharply outlined. In shrunken specimens the radial fibres of the marginal zone contract and cause the longitudinal fibres to present the appearance of being arranged in distinct bundles. The posterior funiculi in such specimens stand out with exaggerated distinctness.

The anterolateral funiculi do not meet in the middle line owing to the interposition of the floor plate. The latter plays only a passive part in the further growth and thus subsequent to the growth of the adjacent mantle and marginal zones there is formed the deep anterior median fissure, in which are found the nutrient blood-vessels of the cord. The formation of this fissure is readily seen by comparing Figs. 36 to 39.

The growth of the posterior funiculi is dependent on the addition of new fibres derived from the spinal ganglia and also on the extension upward of overlapping fibres from lower segments of the cord. At the end of the first month they form an oval bundle in the marginal zone, and when a piece of cord is examined with a low-power lens these fibres can be seen forming a white longitudinal band on the dorsolateral surface of the cord. In the median line the marginal zone is very thin or absent, so that the

nuclear substance of the ependymal and mantle layers can be seen projecting between the posterior funiculi of the two sides. As these bundles enlarge they become thicker and spread toward the median line, where they eventually meet. As they meet in the median line they bend forward, as is shown in Fig. 35, and fill in the space left by the receding ependyma. It may be supposed that their presence plays a part in the stimulation of the production of the posterior median septum, which forms between the right and left halves. As these fibres crowd ventralward the posterior gray columns extend dorsolateralward and the resulting form of the combined posterior funiculi is wedge-shaped as found in the adult. In the cervical region in embryos between 20 and 60 mm. (Figs. 37 and 38), there is a V-shaped portion of these funiculi in the dorsal part at the median line that differs in appearance from the remainder. This is regarded (His) as the primitive column of Goll. The difference in appearance is doubtless due to the fact that it consists entirely of longitudinal fibres destined for the gracile nucleus at the cephalic end of the cord, and is not constantly giving off collaterals to the gray substance as the other fibres of the funiculus seem to do. In the process of shrinkage such collaterals draw in or flatten the remaining funiculus, while it leaves the dorsomedian wedge (column of Goll) unaffected. The latter consequently stands out prominently in all shrunken specimens. In older cords, as the supporting framework becomes more complete, the contrast between these two portions becomes less noticeable.

The myelinization of the fibres of the cord does not begin until about the fifth month of fetal life and is not completed until between the 15th and 20th year (Flechsig, '90, Popoff, '88, Bechterew, '87, and Trepinski, '98). It becomes first apparent in the anterior and posterior roots and the ventral commissure. Very soon afterward the ventrolateral ground bundles begin to show scattered myelinated fibres and likewise a portion of the posterior funiculi.

Three typical stages in the process of myelinization of the cord are shown in Fig. 40. On comparing these it will be seen that the formation of myelin occurs along certain tracts or systems of fibres, and owing to this difference in the time at which they acquire their myelin we are able to map out the different levels of the cord into definite functional areas. One of the latest systems to become myelinated is the pyramidal tract, which can still be seen at the seventh month (Fig. 40) as an open area. It becomes myelinated between the ninth month and second year.

Though the anterior and posterior roots show the beginning of myelinization about the same time, the process is simpler in the anterior roots, and their myelinization is uniformly completed at a

time when not more than one-half of the fibres of the posterior roots show any myelin. The fibres of the posterior roots become myelinated in a series of rather definite stages. Each root can thus

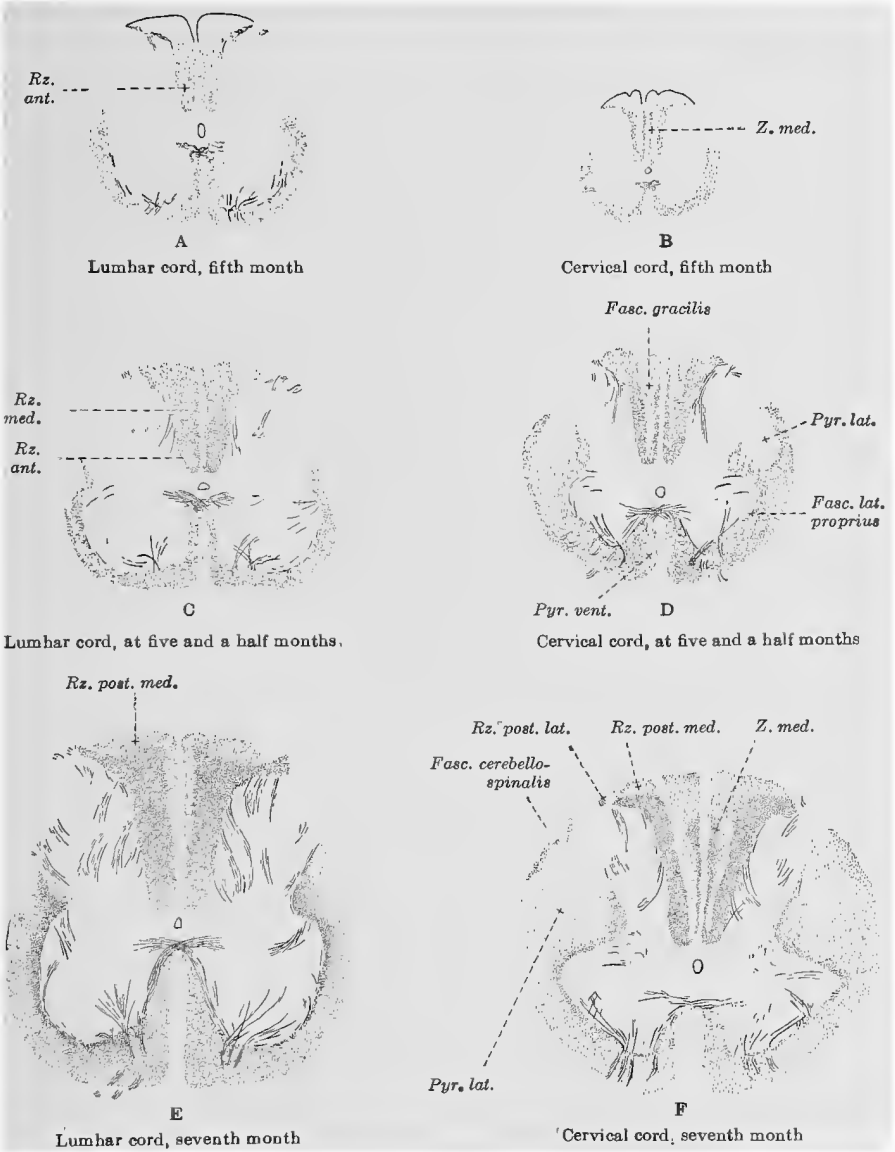


FIG 40.—Diagram showing the myelinization of the spinal cord at different periods in fetal life. *Rz. ant.* anterior root zone; *Rz med.* median root zone; *Rz. post. med.*, median posterior root zone; *Rz. post lat.*, lateral posterior root zone (Lissauer); *Z. med.*, median zone; *Pyr. lat.*, fasciculus cerebrospinalis lateralis; *Pyr. ventr.*, fasciculus cerebrospinalis ventralis. (After Trepinski.)

be subdivided into a number of different fibre groups. Likewise on the basis of this difference in their myelinization the fibres of the posterior funiculi have been subdivided into five different em-

bryonic fibre systems, which present a characteristic grouping in the different levels of the cord, as shown in Fig. 40. These systems are as follows:

1. *Anterior root-zone,* consisting of fibres from posterior roots which after a longer or shorter course in the posterior funiculi disappear in the anterior portion of the posterior horns (*Rz. ant.,* Fig. 40). It extends throughout the whole length of the cord and is the first system in the posterior funiculi to begin myelinization.

2. *Middle root-zone* consists of a group of fibres derived from the posterior roots, which lie between the anterior and posterior root-zones. This zone may be divided into two divisions, first and second, the former becoming myelinated in embryos 19 to 20 cm. long and the other somewhat later. The fibres of the first system after a short course enter the column of Clark, and in regions where this is absent they are lost in the gray substance connecting the anterior and posterior horns.

3. *Posterior root-zone* is divided into a median portion and a lateral portion. The fibres of the median portion pass mostly forward and after entering the posterior horn they extend to the region of large ganglion cells in the anterior horn. The fibres of the lateral portion are apparently derived from the posterior roots and end in the substantia gelatinosa, constituting Lissauer's column.

4. *Median zone* lies against median septum and is most distinct in the cervical and upper two-thirds of the thoracic region. The course of its fibres is not known, but it is apparently distinct from the fasciculus gracilis.

5. *Fasciculus gracilis* (column of Goll), commencing at the tenth thoracic segment, extends upward in a compact bundle to reach the nucleus gracilis. The source of its fibres is not known.

It will be seen that three of these systems are derived from fibres in the posterior roots, and in two of them the source of the fibres is not definitely known. In the order of their myelinization the different systems may be grouped as follows:

First stage.....	Anterior root-zone
Second stage.....	Middle root-zone (first division)
	Median zone
Third stage.....	Fasciculus gracilis
	Middle root-zone (second division)
	Posterior root-zone (median division)
Fourth stage.....	Posterior root-zone (lateral division)

The caudal end of the spinal cord exhibits certain departures from the uniform development characterizing the rest of it, to which special attention may be directed. If one examines a sagittal series through an embryo 11 cm. long, as shown in Fig. 41, it can be seen that the extreme tip of the cord lying in the tail anlage has been closed off to form a simple epithelial sac. The lumen of

the cord above this point becomes obliterated and there results a slender solid strand of nervous tissue which we know as the filum terminale. The epithelial sac becomes the *vestiges medullaires coccygiens* of Tourneux and Herrmann, whose development is described by Tourneux (Précis d'embryologie humain, second edition, 1909, pp. 348, 349) as follows: At the beginning of the third month the neural tube still extends to the extreme end of the vertebral column into the tail bud, and its slightly enlarged tip is closely united to the deep layers of the skin. Toward the end of the third month the spinal column, developing faster than the soft parts, draws along the part of the neural tube that is adherent to it and whose extreme tip remains attached to the skin. As a

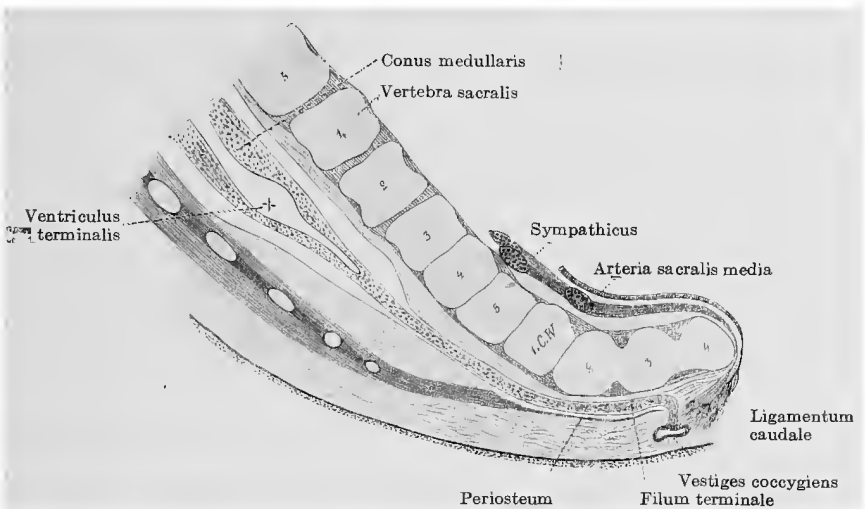


FIG. 41.—Schematic median section through the caudal end of a human fetus 11 cm. long (crown-rump), showing the formation of the vestiges médullaires coccygiens and its relation to the filum terminale. (After Unger and Brugsch.)

result of this unequal growth the terminal or coccygeal portion of the neural tube becomes bent in the form of a loop, the more deeply situated limb of which is attached to the posterior surface of the coccyx (segment coccygien direct), and the other more superficial limb extends obliquely from a caudal and ventral position to one more dorsal and cranial (segment coccygien réfléchi). During the course of the fourth month the more deeply situated limb, the *segment coccygien direct,* atrophies and disappears, while the more superficial one, the *segment coccygien réfléchi,* continues to develop into the fifth month and gives origin to cell cords or cell masses which contain cavities lined either with prismatic or pavement epithelium; these are the vestiges médullaires coccygiens or paracoccygiens. These structures from the sixth month on suffer a progressive atrophy, but it is possible to recognize traces of them up to the time of birth.

The caudal end of the central canal extends through the conus medullaris to the beginning of the filum terminale. At its lower end it undergoes a conical expansion out of which open irregular side pouches and occasionally an elongated blind sac giving the canal the appearance as though the lower end were bent on itself (see Fig. 42). This caudal enlargement of the canal is known as the ventriculus terminalis.

During the earliest stages, up to the time of the highest development of the anlage of the tail, the spinal cord, chorda and mesoderm develop at the same rate. With the reduction of the tail bud the reduction first occurs in the mesoderm, and thus the spinal

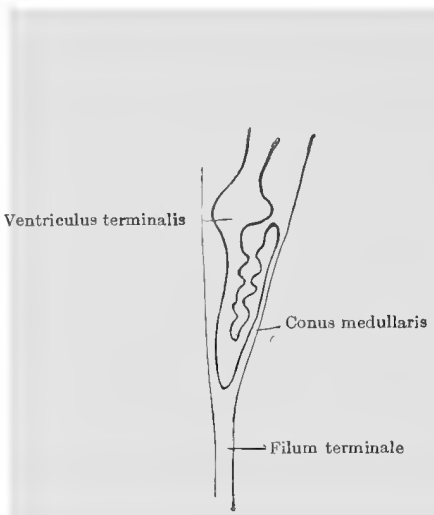


Fig 42

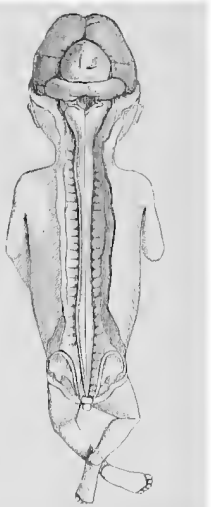


Fig. 43

Fig. 42.—Caudal end of the central canal of the spinal cord in a human fetus 9 cm. long (crown-rump), showing the formation of the terminal ventricle. (After Unger and Brugsch.)

Fig. 43.—Spinal cord exposed from behind in a three months old embryo, at which time the cord still extends to the caudal tip of the vertebral canal. (After Kölliker.)

cord temporarily becomes longer than the vertebral column. With the formation of the coccygeal process there begins a relative increase in the rate of growth of the vertebral column. At the third month, Fig. 43, the cord is about the same length as the vertebral canal, but from the third month on into adult life the vertebral column becomes increasingly longer than the cord. The cord is more precocious than the skeletal system and reaches its full size before the latter has finished its growth.

Owing to this unequal growth during the latter part of fetal life there is a gradual change in the position of the cord in the vertebral canal. Since the cephalic end of the cord is fixed this unequal growth results in its caudal end being drawn upward away from the lower end of the canal. At the time of birth that part of the cord from which the coccygeal nerves arise is found

opposite the third lumbar vertebra; in the adult it is opposite the first lumbar. In this process of shifting, the caudal tip of the cord remains attached to the coccyx, and becomes stretched out into the slender filum terminale. Likewise the nerve roots, their ganglia, with the exception of the ganglion coccygeale, having already become attached in the intervertebral foramina, become stretched out and come to lie in an oblique direction, the most caudal root being longest and most oblique. There is thus formed the cauda equina.

Concerning the development of the blood-vessels of the spinal cord the reader is referred to the corresponding section in the chapter on the development of the blood and vascular system.

The development of the membranes of the cord has been worked up in greater detail in other mammals than in man. According to Sterzi (1900), in the sheep embryo 15 mm. long there is a meningeal mesenchyme, which in embryos 20 mm. long forms a definite membrane. In the 80 mm. embryo this membrane becomes differentiated into an outer layer or dura mater and an inner layer or meninx secundaria, the two being separated by an intradural space. The dural layer is separated externally by the epidural space from an endorhachide, which resembles the dura but is always distinct from it. Finally in the 157 mm. embryo the meninx secundaria is further differentiated into an outer layer or arachnoideal coat and an inner layer or pia mater as seen in the adult.

(d) Development of the Hindbrain from the End of the First Month on.

Up to the end of the first month the rhombencephalon passes through the same general process of development that has been described for the spinal cord. It undergoes the same differentiation into ependymal, mantle and marginal zones. Its walls also are divided into two lateral plates, united ventrally by a floor plate and dorsally by a roof plate. The latter is very broad and is thinned out so as to form an extensive membrane covering in the lumen of the tube. The lateral walls, as in the case of the spinal cord, are subdivided longitudinally by the sulcus limitans into a median basal plate which is chiefly motor, and a dorsolateral alar plate which is chiefly receptive. From the first month on, however, the exuberant growth of intersegmental neurons composing the reticular formation and the development of the suprasegmental ganglion masses and their respective tracts rapidly diminish the resemblance between hindbrain and spinal cord.

At about the fifth week certain alterations occur in the outward appearance of the rhombencephalon, indicating the changes going on within its walls. The most conspicuous is the bending of the axis of the tube resulting in the pontine flexure, as shown in Fig.

30. Whether this is simply due to an overgrowth of the tube in its long axis or whether there is the additional factor of unequal growth of different portions of the wall has not been clearly shown.

Along with the bending there occur noticeable changes in the broad ependymal roof of the fourth ventricle. As shown in Fig. 31, B, and C, the fourth ventricle is completely covered in by the expanded roof plate consisting of a thinned-out layer of ependymal cells, which is attached laterally to the border of the alar plate,

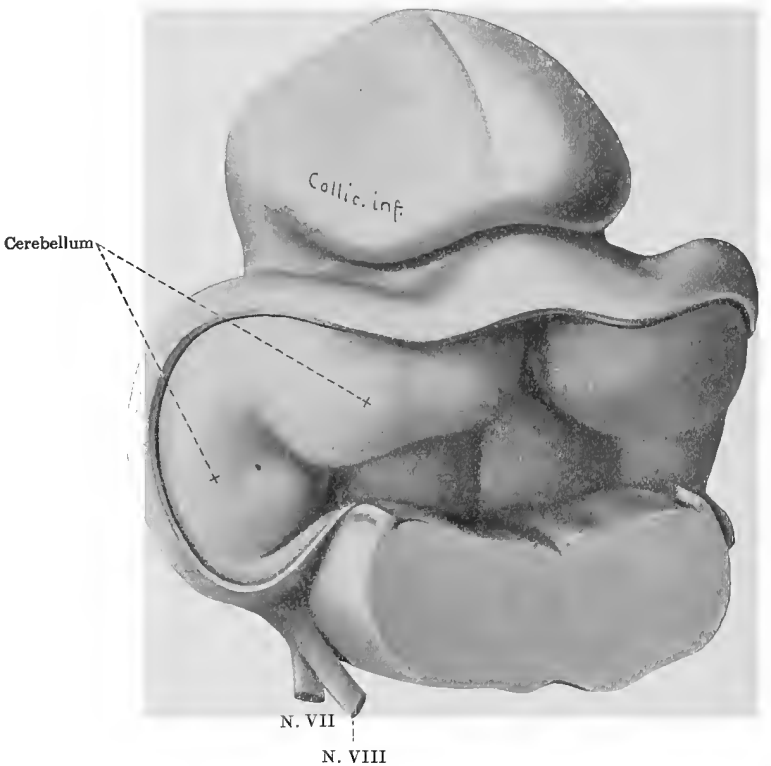


FIG. 44.—Reconstruction showing cephalic portion of the rhombencephalon and adjoining midbrain at end of second month (human embryo 30 mm. long, Mall collection, No. 86). The thickened alar plates form the anlage of the cerebellum and the two halves are still separate. Caudally they are continuous with the nucleus of the acoustic nerve.

the transitional line forming the rhombic lip. Owing to the changes occurring in the alar plate that, particularly in the cephalic half of the rhombencephalon, cause it to become everted and folded back on itself, the rhombic lip becomes partly fused to what was originally ventricular surface of the alar plate. The changes occurring in the rhombic lip may be seen by comparing Figs. 34, 44, and 45, where it is represented as a cut edge, the whole ependymal roof being removed. It is this rhombic lip that forms the tænia of the fourth ventricle and the obex at its caudal apex.

At the same time with the formation of the pontine flexure there is produced a transverse fold (plica chorioidea) in the ependymal roof. This extends outward on each side into the lateral recess which is formed by the overgrowth of that part of the alar plate that is to form the cerebellum and tuberculum acusticum (see Fig. 45). This marks the beginning of the chorioid plexus of the fourth ventricle. The chorioid plexus is formed by ependymal epithelium and its covering of vascular mesoderm. They unite in forming minute villous-like folds which project within the lumen of the ventricle. These folds are first found along the line of the

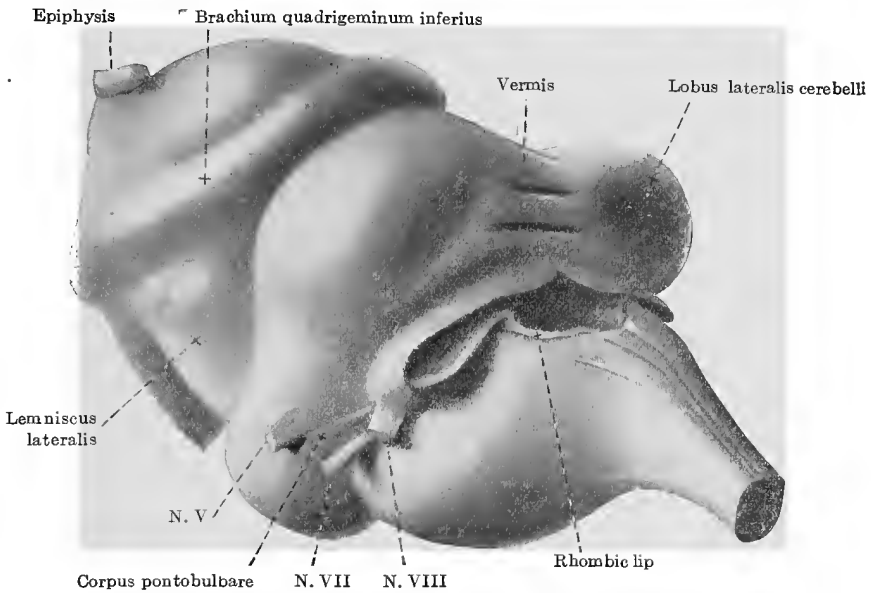


FIG. 45.—Reconstruction showing the outer form of the hindbrain at the end of the third month (human fetus 9.5 cm. long, Mall collection, No. 146.)

transverse chorioid fold, and from there the formation spreads caudally until nearly the whole posterior medullary velum is converted into a chorioid mass, the tela chorioidea inferior. Originally the fourth ventricle is completely roofed in as has been seen, but later there are found apertures which are formed secondarily, one in the caudal portion, the foramen of Magendie, and one in each lateral recess, the foramina of Luschka. The presence of these foramina has been denied by some investigators.

Before referring to further changes in the outward form of the rhombencephalon we will consider the histological changes that produce them.

As has already been seen, by the end of the first month the primary neurons belonging to the cranial nerves are clearly differentiated. In Figs. 86, 32, and 96 their relation to each other and

to the walls of the neural tube are shown. Their relation to the rhombic grooves is shown in Fig. 33. The further growth of the rhombencephalon results from the elaboration of neuroblasts from the ependymal and mantle zones which form the following structures: (*a*) receptive nuclei for the cranial nerves, comparable to the dorsal horns of the spinal cord, the axons of which form the median and lateral lemniscuses; (*b*) intersegmental neurons, constituting the reticular formation for co-ordination of different groups of primary neurons; (*c*) suprasegmental nuclei with afferent tracts which are laid down subsequent to and hence are external to the reticular formation, of which the olive is a conspicuous example; (*d*) efferent tracts from cerebellum and midbrain; and (*e*) the descending pyramidal tract from the cerebral cortex.

The neuroblasts derived from the basal plates are chiefly those that form effector fibres for the cranial nerves. As they will be described at length with the peripheral nervous system, their description here will be omitted. It should be pointed out, however, that their growth is relatively precocious, and that the differentiation of the basal plate begins first and is finished before that of the alar plate. The ependymal layer comes to the resting stage early, about the end of the second month. The subsequent development of the basal plate, aside from the part it takes in the differentiation of the formatio reticularis, is passive, and is dependent on the invasion of neuroblasts from the alar plate and the ingrowth of foreign fibres in its marginal zone.

The differentiation of the formatio reticularis is not confined to the basal plate, though it is first apparent there. As in the spinal cord, it consists of intersegmental neurons derived from the mantle zone, the processes of which to a large extent cross the median line as internal arcuate fibres. The crossing of these fibres marks the beginning of the raphé. After crossing they form a longitudinal bundle in the marginal zone analogous to the ventral ground bundle in the spinal cord, and corresponding in position to the median longitudinal fasciculus of the adult oblongata, though, as will be pointed out, the latter contains other fibres in addition to these. The processes of some of the more lateral neuroblasts, instead of crossing within the mantle zone, penetrate the marginal zone and make their way along its surface, thus forming external arcuate fibres. In addition to the internal and external arcuate fibres (heteromeric), the formatio reticularis is early characterized by radially directed neuroblasts whose processes extend toward the marginal zone to form tautomeric intersegmental fibre tracts. The reticular formation is eventually subdivided into a gray portion (formatio reticularis grisea) containing cell bodies and shorter tracts, located in mantle zone, and a white portion (formatio reticularis alba) consisting of long tracts

and located in the marginal zone. The great development of the reticular formation is an important determinative factor in the morphology of the adult oblongata. Three stages in its development are shown in Figs. 46 and 47. In the same figures is shown the conversion of the original floor plate into the median septum and raphé. It will be noticed that, as in the case of the spinal cord, the marginal zones of the two sides do not fuse, being always separated by the prominent radial processes of the ependymal cells, which extend from the lumen to the surface of the brain.

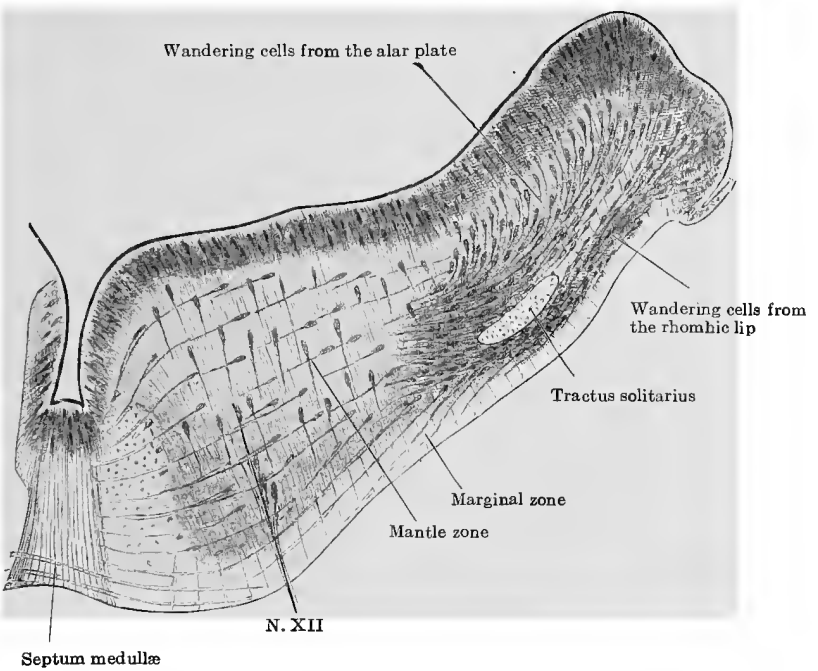


FIG. 46.—Transverse section of medulla oblongata of a human embryo at end of fifth week (10.5 mm. long), showing ventromedial migration of neuroblasts from the alar lamina and rhombic lip. (After His, 1891.)

It is in the development of the alar rather than the basal plates that the rhombencephalon departs so widely from the type found in the spinal cord. While the initial changes have been taking place in the basal plate the cells of the ependymal zone of the alar plate have been actively separating off to join the mantle zone, preparatory to forming receptive nuclei for the peripheral nerves, as well as other nuclear masses, making up intersegmental and suprasegmental tracts and centres. Originally, as has been seen, the afferent peripheral fibres on entering the wall of the neural tube unite to form longitudinal tracts which extend upward or downward in the marginal zone over a varying number of segments. In the rhombencephalon such tracts are represented by

the tractus solitarius, spinal limb of the n. trigeminus, and fibres coming up from the posterior funiculi of the spinal cord. Later there are added the fibres of the restiform body and fibres from the lateral funiculi of the cord. Thus originally we have here as in the spinal cord a central gray portion sharply marked off from a peripheral white portion, the latter consisting of distinct funiculi. This resemblance is, however, very soon diminished

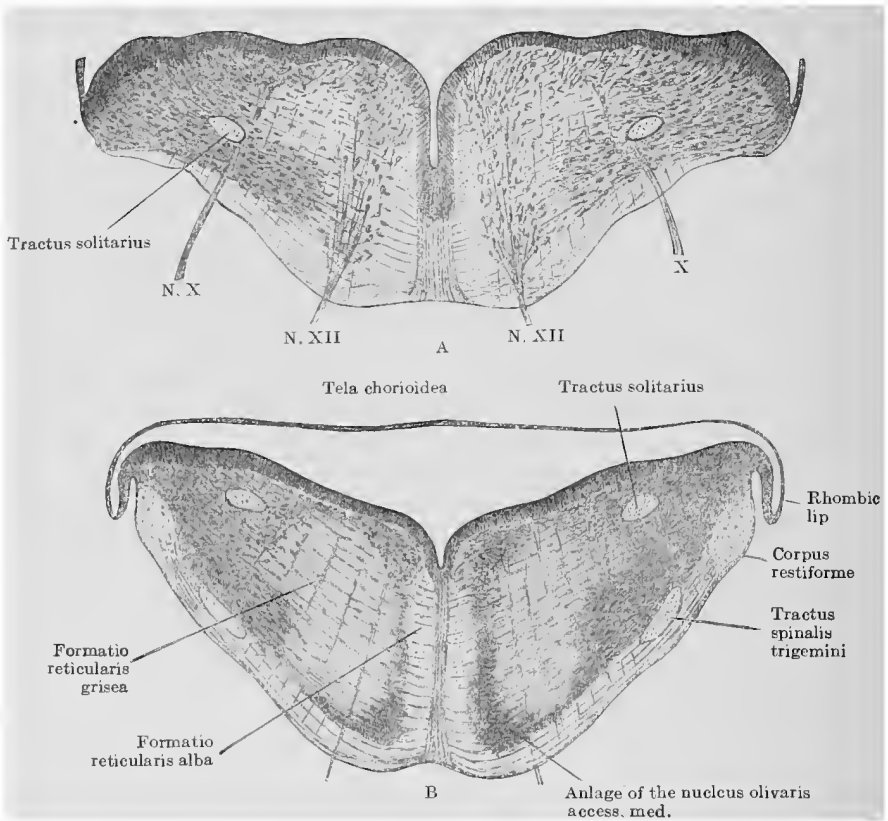


FIG. 47.—Transverse sections of the medulla oblongata, showing the development of the formatio reticularis and olivary nucleus. A, embryo 13.6 mm. long (5 weeks). Enlarged 40 : 1. B, embryo 22 mm. long (8 weeks). Enlarged 10 : 1. (After His, 1891.)

by the profuse growth of the alar mantle zone which invades the marginal zone partially enveloping the tracts and spreading them apart.

The profuse proliferation of the neuroblasts in the alar mantle zone is indicated in Fig. 46, and by comparing this with Fig. 47, A and B, the eventual fate of these cells can be seen. They form clusters along the tractus solitarius, and the descending fibres of the n. vestibularis and n. trigeminus which become the receptive nuclei for these particular fibres (nucleus tracti solitarii, nucleus vestibularis spinalis and substantia gelatinosa). At the caudal

end in a similar way the gracile and cuneate nuclei are formed in which the fibres from the posterior funiculi of the cord terminate. From these receptive nuclei axons are developed which make their way largely as internal arcuate fibres through the formatio reticularis, decussating to the opposite side to form a longitudinal tract near the median line (lemniscus medialis) which forms an afferent path to the midbrain and thalamus.

In addition to these receptive nuclei there are other nuclei formed from the alar neuroblasts that serve as connecting paths to the suprasegmental centres, cerebellum and forebrain. The most conspicuous of these are the pontine nuclear mass and the nucleus of the olive. These are formed by virtue of the extensive power of migration possessed by the cells of the alar plate. The formation of the olivary nucleus is shown in Figs. 46 and 47. The migratory process begins at the beginning of the second month. At this time massed cells can be seen making their way through the mantle zone toward the median line, the cells from the median portion of the alar plate passing median to the tractus solitarius and the cells from the lateral border passing lateral to it and separating it from the marginal zone to which it originally belonged. Toward the end of the second month a distinct group of these migratory neuroblasts have assembled near the median line, constituting the anlage of the median accessory olive (Fig. 47, B). By the third month subsequent groups are added laterally to form the convoluted inferior olivary nucleus. The majority of the olivary neuroblasts are probably the products of proliferation of migratory cells after the completion of their migration. Their axons decussate and join with spinal cord fibres to form the restiform body. The restiform body can be recognized by the eighth week.

At the extreme lateral border of the alar plate at the rhombic lip are found cells which retain their primitive embryonic appearance into adult life. Others invade the marginal zone and emerge on the surface of the wall. Some of them then migrate toward the median line by a superficial path peripheral to the marginal zone. The exact fate of these cells remains to be studied. It is possible that the more caudal ones take part in the formation of the arcuate nuclei, and possibly also the olivary nuclei. The more cephalic ones just back of the acoustic region form a narrow migratory path from the rhombic lip around to the ventral surface of the pontine flexure. This path persists in the adult as a fibroganglionic band known as the corpus pontobulbare, described by Essick (compare Fig. 49). It is possible that it is the proliferation of these cells that produces the nuclei of the pons. It is also possible that the pontine neuroblasts come from the mantle zone of that region and reach the surface by emerging through the mar-

ginal zone, as apparently happens with the cortical cells of the cerebellum. The pons makes its appearance between the second and third month. The axones from its proliferating neuroblasts decussate across the median line in front of the formatio reticularis and the lemniscus medialis, and pass to the cerebellum on the opposite side forming the brachium pontis. As the pons is developing the corticospinal fibres (pyramidal tract) make their way along its ventral surface and become enveloped among its proliferating cells and fibres. Accompanying the corticospinal tract are other fibres from higher centres which terminate among the cells of the pons and thus become connected with the cerebellum.

The alar plates of the cephalic end of the rhombencephalon undergo extensive and specialized development. They form that which eventually becomes the largest part of the hindbrain, *i.e.*,

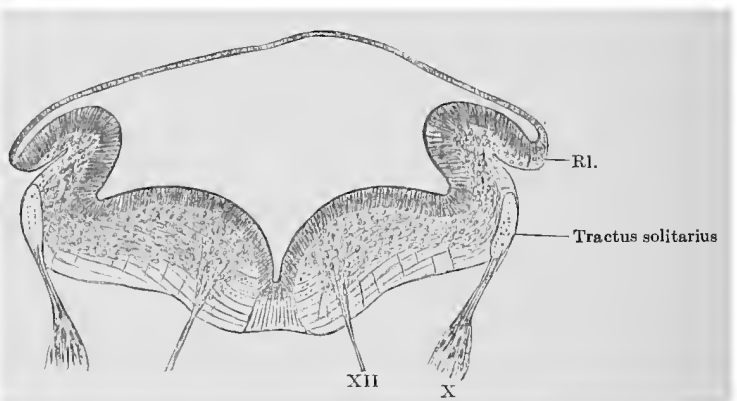


FIG. 48.—Transverse section of medulla oblongata of a human embryo 9.1 mm. long, showing folding of rhombic lip (*Rl.*). This feature is most marked in the region of the pontine flexure.

cerebellum, and in addition the acoustic nucleus. As can be seen by comparing Figs. 34, 44, and 45, the acoustic nucleus is formed from the thickened rhombic lip at the pontine flexure, at the point where the lateral recess develops. The rhombic lip becomes everted and is folded against and is partially fused with the lateral surface of the remaining alar plate, as is schematically shown in Fig. 48. The fibres of the acoustic nerve enter at the lower edge of this mass. As the trunk of the nerve differentiates itself into cochlear and vestibular portions (embryos 20–30 mm. long), the terminal nucleus also becomes differentiated into a median portion (vestibular) and a lateral portion (cochlear). These become more sharply separated from each other by the development of the restiform body whose fibres pass between them. The vestibular nucleus remains closely connected with the cerebellum and most of its axons terminate there. The cochlear nucleus remains quite independent of the cerebellum. Its axons pass across the ventral

border of the reticular formation and decussate to form the trapezium. The superior olive in which many of these fibres terminate can be seen by the eighth week, apparently developing from migrant alar neuroblasts in a similar way to the inferior olive. The axones from the superior olive and trapezium extend forward along the ventrolateral border of the formatio reticularis to the inferior colliculus constituting the lateral lemniscus. This path is partly nuclear and partly fibrous, and is virtually a forward extension of the superior olive. Later the fibre element predominates through the increase in number and length of fibres, resulting in the separation of the superior olive from a smaller nucleus, the nucleus of the lateral lemniscus, which were originally one continuous structure. From its position it can be seen that the trapezium is laid down subsequent to the formatio reticularis. Still later occurs the descent of the corticospinal tract which with the growth of the pons nearly entirely covers in the trapezium on its ventral surface.

Before considering the development of the cerebellum it may be pointed out that the characteristic features of the adult rhombencephalon are only the result of the further growth of the structures that have been mentioned. In the floor of the ventricle we meet with swellings produced by the nuclei of the hypoglossal and abducens nerves, lateral to which is a longitudinal furrow representing the sulcus limitans. Lateral to this furrow are the structures derived from the alar plate, including the vestibular field and the terminal nuclei of the trigeminal and vagoglossopharyngeal nerves (ala cinera). Secondary tracts and nuclei invade the floor of the ventricle producing the characteristic striæ acusticæ, nucleus intercalatus and funiculus teres. The ventricle is closed in caudally by the rounded elevations (clava and cuneus) caused by the large gracile and cuneate nuclei. The olivary nuclei produce lateral swellings on each side (olives), and ventrally emerging through the pontine nuclear mass are the prominent corticospinal tracts (pyramids).

THE CEREBELLUM.

The character of the cerebellum at the end of the first, second and third months is shown in Figs. 34, 44 and 45 respectively. This covers the period from the time when it exists as simple bilateral alar plates to the time when it fuses across the median line as a transverse mass consisting of a median vermis and two lateral lobes. Its later enlargement and the formation of its characteristic lobes and fissures are shown in Fig. 49.

At the end of the first month the alar plates of the rhombencephalon cephalad to the pontine flexure differ very little from the rest. They are a little thicker and present a moderately convex

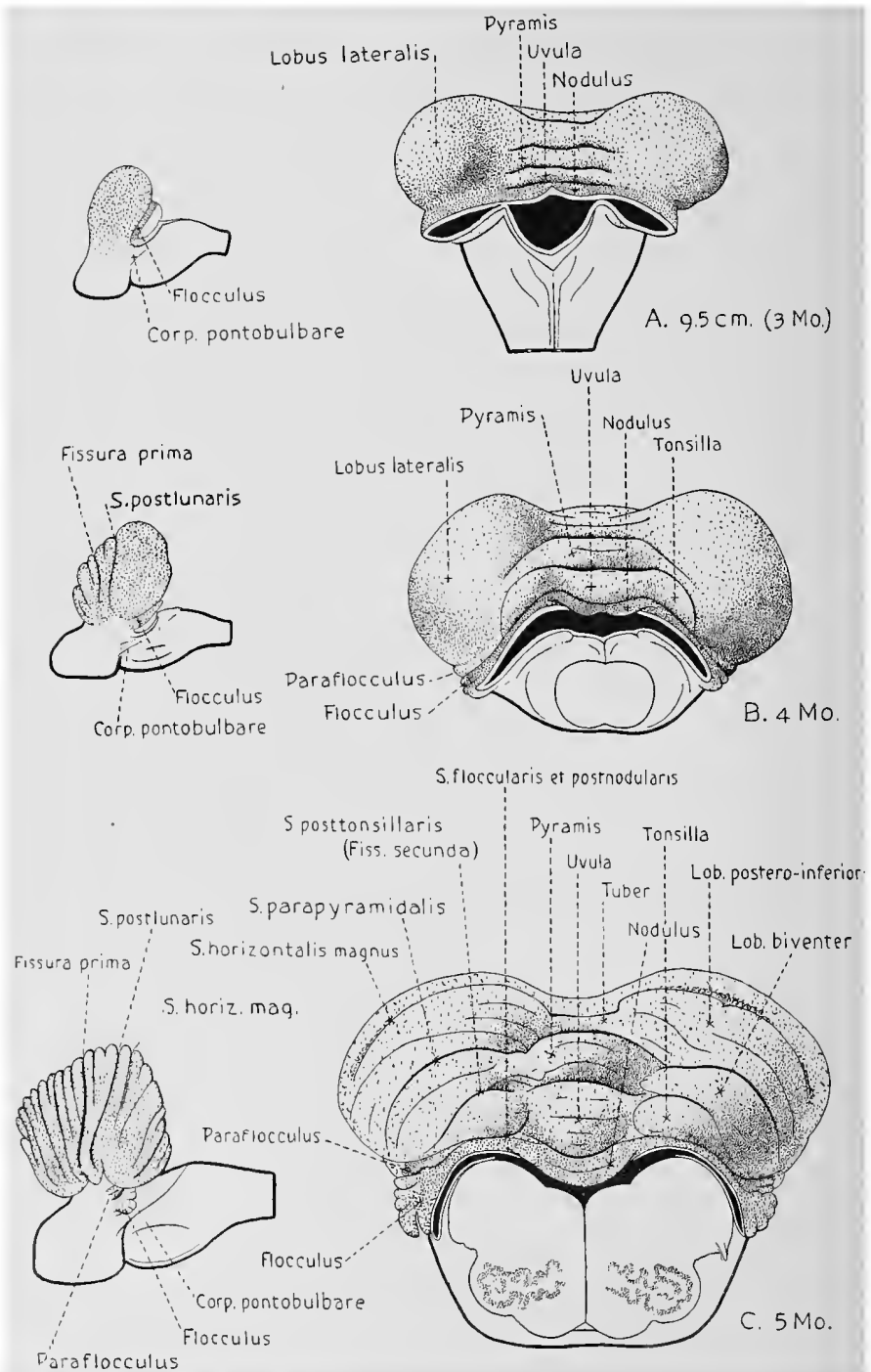


FIG. 49.—Three stages in the development of the fissures and convolutions of the cerebellum, as seen from behind. At the left are shown lateral views of the same specimens on a smaller scale of enlargement A is from the same model shown in Fig. 45; B and C are drawings made from dissected specimens.

surface toward the ventricle. Anteriorly they converge toward the median line, being united by a narrow seam just behind the exit of the trochlear nerve. Attached along their free edge is the tela chorioidea forming the roof of the fourth ventricle.

During the second month the cerebellar plates, owing to the active proliferation of cells in their mantle zone, rapidly thicken and bulge inward toward the ventricle. They also come to lie transversely so that what was originally a longitudinal dimension becomes a transverse one. This change in position is apparently due to the marked increase in the pontine flexure that occurs at this time. The cerebellar plates not only increase in thickness but also in length (*i.e.*, transverse dimension), so that they become cramped in position and show a tendency to be thrown in folds. Further irregularity may be due to unequal growth in different portions. The growth is more marked in the cephalic half than in the caudal or lateral half. Near the median line on each side can be seen a swelling that corresponds to the vermis, which like the cerebellum itself originally consists of bilateral halves separated from each other by the roof plate.

During the third month (Fig. 50) the cerebellar mass comes to bulge outward, instead of inward toward the ventricle as before, which is evidently due to the fact that the proliferating mantle zone cells find less resistance in that direction, the marginal surface being more yielding than the ependymal surface. The cerebellum now consists of two convex masses (lateral lobes) connected laterally by a ridge (brachium pontis) with the developing pons. At the same time the fusion across the dorsal median line has commenced. The fusion begins on the dorsal surface and gradually involves the whole thickness of the wall, the last portion involved being the ependymal membrane and rhombic lip. Before the fusion is completed the outer surface of this region has commenced to show transverse fissures marking off the primitive lobes of the vermis.

We have already seen how the rhombic lip takes part in the development of the acoustic nucleus; likewise in the cerebellum it plays an important part, giving origin to the nodulus and flocculus. At the third month it forms a distinct ledge, still notched in the median line, and along its free edge is attached the tela chorioidea. In conjunction with the acoustic lip it forms the lateral recess.

Between the third and fifth months the outer form of the cerebellum is completed by the formation of its principal lobes and fissures, the steps of which process are shown in Fig. 49. This lamellation is evidently due to the fact that the cortical region undergoes greater cell proliferation than the deeper portion, and since this growth is chiefly in the longitudinal axis it results in

fissures that run transversely to that axis. As the cortical differentiation and development of fissures occur together, we have in the latter an index of the former. It will thus be noticed that the vermis, and the anterior portion adjoining it are the first to show signs of this process. The floccular region begins to show fissures at about the same time. These may be regarded as the more primitive parts of the cerebellum, and are found to be the most constant in different vertebrates. The lateral lobes which form the so-

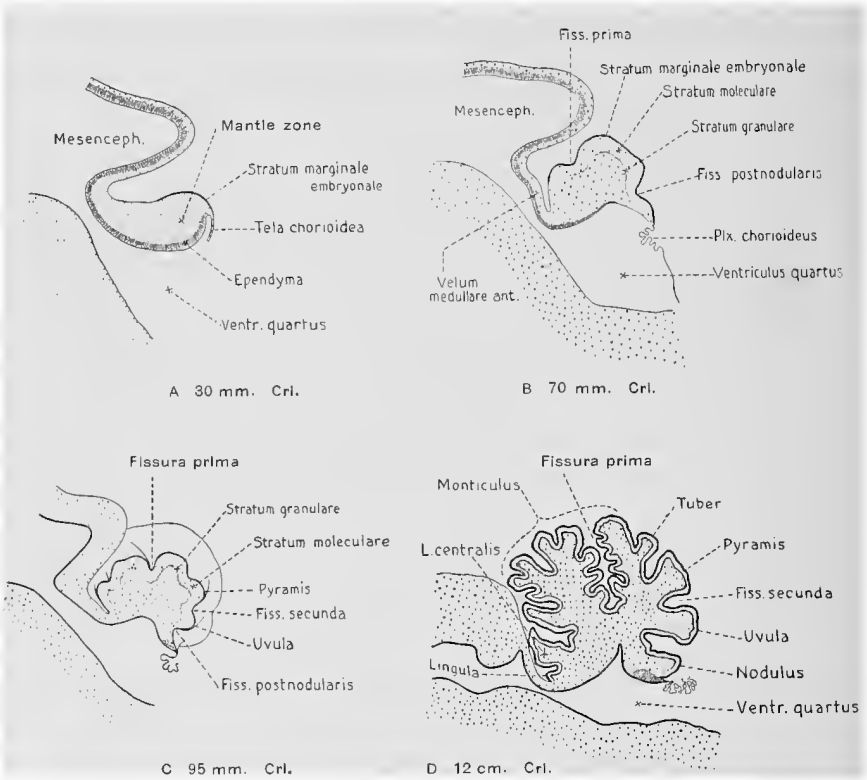


FIG. 50.—Sagittal sections through the cerebellum at or near the median line, showing the development of the fissures of the vermis and the formation of the cerebellar cortex.

called hemispheres of the adult organ are still smooth at the fourth month and it is not until the fifth month that they receive their fissures, which are partly intrinsic and partly extensions of fissures from the vermis. It is evident that phylogenetically the lateral lobes are recent structures. Later they increase enormously in size and eventually cover in the entire posterior portion of the vermis. It is supposed that their extensive growth in man is correlated with the large pons, and that in turn with the large pallium. Bolk, 1906, suggests that if we are to consider the cerebellum as the co-ordinator of muscle contraction then we may assign the muscles of the median line, which are common to all

vertebrates, to the vermis, and the muscles of the extremities to the lateral lobes, the high development of the upper extremities in man explaining the marked development of his lateral lobes.

The lateral lobes are the lateral extensions of the median lobe. The median lobe is bounded anteriorly by the primary fissure and posteriorly by the secondary fissure. Everything in front of the primary fissure comprises the anterior lobe, and everything posterior to the secondary fissure comprises the posterior lobe (tonsil, uvula, nodule, and flocculus). The detailed development of the surface markings of the cerebellum can be seen by comparing Figs. 49 and 50. It should be noted that the great horizontal sulcus that is so prominent in the adult is relatively late in appearing; at the fifth month it only exists as a shallow furrow. The median longitudinal fissure, which is found on the posterior and inferior surface in the adult, is produced by the excessive growth of the lateral lobes whereby they close in over the vermis posteriorly. This rolling in of the lateral lobes toward the median line has already commenced at the fifth month (Fig. 49, C).

On tracing the fate of the rhombic lip in Fig. 49, where it is stippled darker than the rest of the cerebellum, it is seen that from the median portion there is developed the nodulus, which is the last portion of the vermis to show its bilateral character. From the lateral portion is developed the flocculus. The paraflocculus is derived from the lateral portion of the cerebellar plate immediately adjoining the rhombic lip.

The alar plate from which the cerebellum is formed, like the rest of the neural tube, at the outset has the typical ependymal, mantle and marginal zones, the ependymal zone toward the ventricle and the marginal zone toward the outer surface. It is through secondary development and migration that the cerebellar plate becomes covered with the layer of cells which eventually form its cortex, as will presently be seen.

At the end of the second month (30 mm.) the demarcation between ependymal and mantle zones is still poorly defined, and it is apparent that cells from the ependyma are still being contributed to the mantle zone. Later (70 mm.) the ependyma, with the exception of the portion situated at the rhombic lip, gradually enters upon its resting stage and assumes the form seen in adult specimens. The ependymal cells at the rhombic lip differ from the rest of the ependyma in that they continue to show active proliferation late in embryonic life. The same feature is shown throughout the whole rhombic lip but is more marked in the portion belonging to the cerebellum.

The most characteristic feature of the cerebellum is its cortex. We have already seen that originally the outer surface of the cerebellar plate is formed by the marginal zone and is devoid

of nuclei. The neuroblasts which are found there later, constituting the cerebellar cortex, reach the surface by a process of migration. The steps by which the non-nuclear marginal zone becomes converted into a ganglionic layer by the invasion of these neuroblasts are shown in Fig. 50. This figure represents sagittal sections at or near the median line in four successive stages. At 30 mm. it can be seen that a layer of closely packed cells (stratum marginale embryonale) from the rhombic lip is spreading over the surface of the cerebellar plate, covering half of it in, the remaining portion being still non-nuclear. At 70 mm. this invasion of surface cells has extended so as to cover in the whole cerebellar plate, excepting the thinned-out portion that is to become the anterior medullary velum. At the same time a second layer of cells (stratum granulare) may be seen spreading from the rhombic lip forward and lateralward in the same direction as the marginal layer but beneath the surface in the outer part of the mantle zone. The space between it and the marginal layer corresponds to the stratum moleculare. In fetuses 95 mm. long these layers form well-marked strata running parallel with the surface of the cerebellum, dipping down where there are fissures. In fetuses 12 cm. long the surface of the cerebellum is greatly increased in extent, in the first place by actual growth of the whole cerebellum and in the second place by the infolding of the surface due to the rapidly increasing number of fissures. The cortex through further proliferation presents thicker and more sharply defined strata. We now (12 cm.) have an arrangement possessing a close similarity to the adult, viz., a central portion, fibrous and sparsely nucleated, covered in by a convoluted cortex consisting of three distinct strata. Concerning the source of the cells forming the cortex there remains some doubt. It is apparent that the cortex formation begins at the rhombic lip and spreads from there forward and lateralward; that is, it spreads from the free edge of the original alar plate toward the junction of the latter with the basal plate. This applies to all three of the primitive cortical layers. It is also evident that the outermost layer (stratum marginale embryonale) is directly continuous with the ependymal zone of the rhombic lip. On this account it has been suggested by Schaper, 1894, that the rhombic lip constitutes a germinal bed from which cells are given off and that these cells migrate along the surface and so form the outer layer as indicated in Fig. 51. It is conceivable that the deepest layer (stratum granulare) is also derived in the same way, its cells migrating out from the region of the rhombic lip along the outer border of the mantle zone. There is, however, no proof that the outer cells of the mantle zone do not take part in the formation of any one or all three of the cortical layers.

The later histogenesis, as seen in Golgi specimens in other mammals, is shown in Fig. 52. The development is not completed

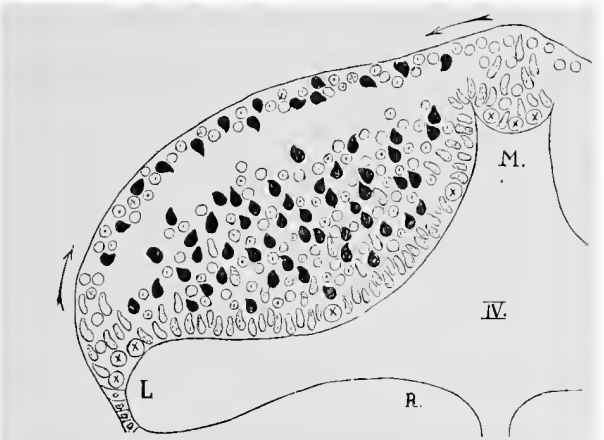


FIG. 51.—Schematic drawing showing the differentiation and migration of cerebellar neuroblasts in the teleost. Arrows indicate the migration of cells from the rhombic lip over the surface of the cerebellar plate. The different cells are indicated in the same way as shown in Fig. 3. (After Schaper.)

until very late, sometime after birth. The development of the granule cells seems to occur through a process of unipolarization, like the T-formation described in the spinal ganglion cells, and

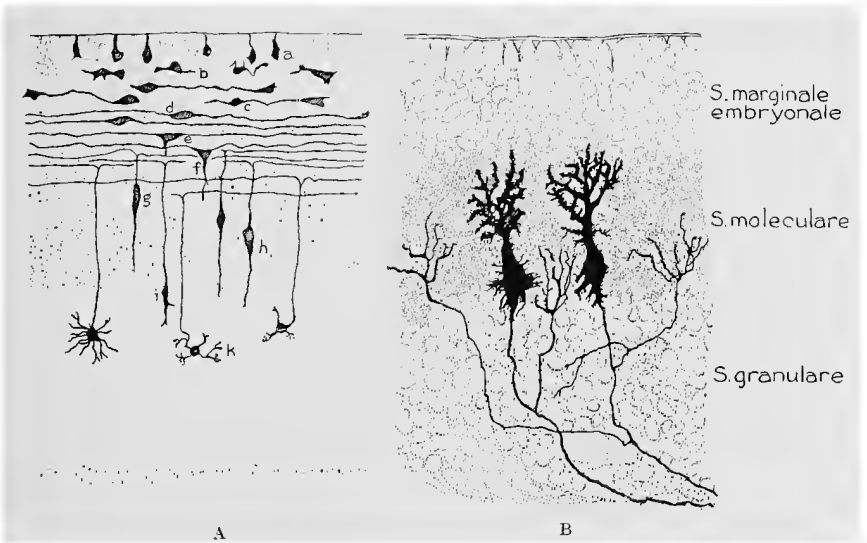


FIG. 52.—Sections showing the histogenesis of the cerebellar cortex. (After Cajal.) A, schematic section showing the migration of granule cells from the surface to the stratum granulare, and different stages in their differentiation, *a* being the youngest and *k* the fully formed cell. B, section through the cerebellar cortex of new-born dog, showing two Purkinje cells with partially formed dendrites, axones, and terminal aborizations.

subsequent migration inward to the granular layer. The successive steps in this process are shown in Fig. 52, A, of which *a* is the earliest undifferentiated stage and "*k*" the fully formed

granule cell. The dendrites of the Purkinje cells do not form until the migration of granule cells is completed. The outer layer (stratum marginale embryonale) disappears in man several years after birth.

Many of the mantle zone cells take no part in the formation of the cortex. Some of them form the neuroglia framework through which the fibres of the central white substance pass. Others become neuroblasts which are grouped to form the internal nuclei of the cerebellum. In embryos toward the end of the third month (50–95 mm.) the nucleus dentatus can be outlined in the interior of the lateral lobe, conforming to the outer form of the lobe. From its anterior border strands of axones emerge passing forward to be assembled in the two brachia conjunctiva, which can be traced forward to their decussation and connection with the red nuclei of the midbrain (see Fig. 53).

Later, as the nucleus dentatus becomes more sharply outlined, it assumes the convoluted form seen in the adult. Median to the dentate nucleus, in the vermis, the mantle zone neuroblasts are grouped to form the paired tegmental nuclei to which acoustic fibres can be traced by the end of the third month. Other nuclei formed supplementary to the dentate nucleus are the emboliform and globular nuclei. Of the centripetal tracts to the cerebellum the restiform body and the centripetal fibres from the acoustic and trigeminal nerves are the first to become well marked (second month). By the end of the third month the middle cerebellar peduncles containing fibres from the pontine nuclei may be distinctly traced to the lateral lobes of the cerebellum. The final development and completion of the arborizations of these fibres is not finished until sometime after birth.

(e) Development of the Midbrain.

As has been previously mentioned the midbrain is a portion of the epichordal brain and is closely affiliated in its manner of development and general form with the rhombencephalon and spinal cord. As in the latter two we can recognize on each side a basal plate and alar plate, the alar plates being large and united above by a narrow seam (roof plate). The wall forming them at first consists of a combined ependymal and mantle layer covered in by a non-nucleated marginal layer. Later the mantle layer becomes clearly differentiated from the ependymal layer, forming thereby three distinct strata (ependymal, mantle, and marginal). The differentiation between ependymal and mantle layers is completed in the basal plates about the end of the first month (Fig. 31, D). In the alar plates it is considerably later, about the third month. In their later development the alar plates form

suprasegmental ganglion masses (corpora quadrigemina) in a manner analogous to the development of the alar plates of the hindbrain that form the cerebellum.

The basal plates conform even more than the alar plates to the form seen in the rest of the epichordal system. The points of difference are mainly dependent on extrinsic factors. As in the hindbrain they give origin to motor nerves which become covered in by a modified formatio reticularis and the marginal zone is traversed by long suprasegmental fibre tracts (peduncles of cerebrum). In Fig. 53 is shown a reconstruction of the midbrain of an embryo about three months old, in which the more prominent structures of the basal plate are indicated. The nuclei of the third

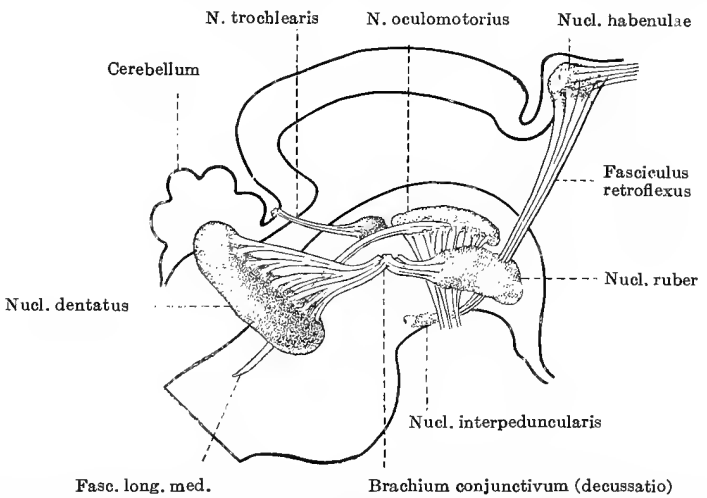


FIG. 53.—Reconstruction of the midbrain of a human embryo 80 mm. long (Mall collection, No. 172) showing the relations of the red nucleus and the decussation of the brachium conjunctivum connecting it with the dentate nucleus of the cerebellum.

and fourth cranial nerves maintain their position near the floor of the lumen like the hypoglossal and abducens nerves in the hindbrain. The trunk of the fourth nerve, however, bends around dorsally to decussate in the roof as we have already seen. It runs directly dorsalward at first, but later owing to the growth of the inferior colliculus it is crowded backward and assumes a distinctly caudalward course before its decussation.

Associated with the third and fourth nerves is the median longitudinal fasciculus, which forms an intersegmental bundle belonging to the formatio reticularis, extending throughout the whole length of the mid- and hindbrains and into the anterolateral fasciculus of the spinal cord. It is apparently for the most part made up of axons which run a short course in the bundle and serve to connect the motor nuclei of the eye muscles (Nn. oculomotorius trochlearis and abducens). It probably contains axons from

other cranial nerve nuclei (Nn. facialis, acusticus, and hypoglossus). It also contains the fibres of the rubrospinal tract and fibres from the superior colliculus. Next to the entering fibres of the sensory nerves this is one of the earliest tracts in the epichordal system to become well outlined.

The origin of the nucleus ruber is not definitely known. It forms in the mantle layer as a portion of the formatio reticularis and by the end of the third month it is sharply outlined, and the decussating brachia conjunctiva connecting it with the dentate nucleus can be clearly recognized, as seen in Fig. 53. From its resemblance to the inferior olive we may assume that it develops in a similar manner. The fibres of the fasciculus retroflexus (Meynerti) traverse it on their way to the interpeduncular nucleus.

The mantle zone structures of the midbrain region become closed in ventrally and laterally by the tracts of the marginal zone. The first of these are the median lemniscus and the lateral lemniscus, which are usually included with the formatio reticularis as comprising the tegmentum. Later there are added ventrally the fibres connecting the cerebral cortex with the pons, medulla oblongata and spinal cord, which can be recognized toward the end of the third month. The subsequent increase in size of these ventral tracts produces the projecting masses known as the peduncles of the cerebrum.

The alar plates by their large size indicate that they are to form a large organ, though in man owing to the recession of the optic lobes the superior colliculus never attains the size found in lower vertebrates. The alar plates are at first separated by a narrow seam or furrow, and in young specimens, if there is any maceration, this seam (roof plate) is easily stretched and the alar plates may then overlap one another. With the subsequent thickening of the alar plates this median furrow disappears. This thickening also causes the lumen to decrease in proportionate size. Instead of a considerable cavity or midbrain ventricle we eventually have the narrow aqueduct of Sylvius connecting the third and fourth ventricles.

The details in the differentiation of the alar plates have not been fully studied in man, but we know that like the cerebellar plates they are characterized by the migration of neuroblasts to their outer surface. These neuroblasts proliferate and develop into more or less stratified ganglionic masses which, together with the deeper lying cells, form the superior and inferior colliculi. The more superficial layers correspond to the cortex of the cerebellum, and the deeper cell masses correspond to the dentate and tegmental nuclei. The fibres from the optic tract and lateral lemniscus can be plainly traced to the colliculi by the end of the third month.

The optic tract fibres disappear beneath the superficial ganglion layer of the superior colliculus, while the lateral lemniscus spreads over the surface of the inferior colliculus. At about the same time the inferior brachium connecting the inferior colliculus with the median geniculate body can be recognized as shown in Fig. 45.

(f) Development of the Diencephalon.

The division of the prosencephalon into the telencephalon and diencephalon has already been referred to. The telencephalon from the outset differs widely from the type seen in the epichordal portion of the nervous system, and at a casual glance would seem to have nothing in common with it. The diencephalon, however, forms an intermediate link, and though it merges directly into the telencephalon, yet it resembles the epichordal system in many ways, particularly in the early stages.

As seen in Fig. 54, we can speak of an alar plate and a floor plate, united dorsally by a roof plate and ventrally by a floor

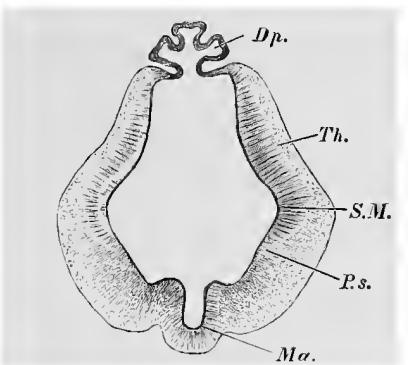


FIG. 54.—Section through the diencephalon of a five weeks human embryo. *Dp.*, roof plate (chorioid plexus); *Th.*, alar plate (thalamus); *S. M.*, sulcus limitans (sulcus hypothalamicus): *P. s.*, basal plate (hypothalamus); *Ma.*, mammillary recess. (After His.)

plate, differing from the spinal cord up to the fifth week only in the absence of a ganglion crest and motor nerves. The alar plate like the alar plate of the epichordal system is predominantly sensory. It rapidly thickens, due to the proliferation of the neuroblasts which are to form the receptive nuclei for the optic and cochlear tracts and for the fibres of the medial lemniscus. These nuclei are massed together to form the thalamus which constitutes the largest part of the diencephalon. The lateral nuclei (geniculate bodies) are spoken of as the metathalamus.

The thalamus is separated from the hypothalamus by the sulcus hypothalamicus which extends forward to the optic recess. This sulcus apparently is analogous to the sulcus limitans. It persists into adult life. The hypothalamus or basal plate portion

lacks the motor elements which form so large a part of the basal plate in the epichordal system. Its principal function seems to be in connection with the special structures which are developed in the floor plate, the hypophysis and mammillary bodies (see Figs. 55 and 56). It is also from this portion that the corpus Luysi is developed, and through the caudal part of its marginal zone the large tracts pass from the internal capsule constituting the pedunculi cerebri.

The anterior boundary of the floor of the diencephalon may be regarded as constituted by the transverse ridge formed in the floor by the optic chiasm (Johnston). This ridge extends later-

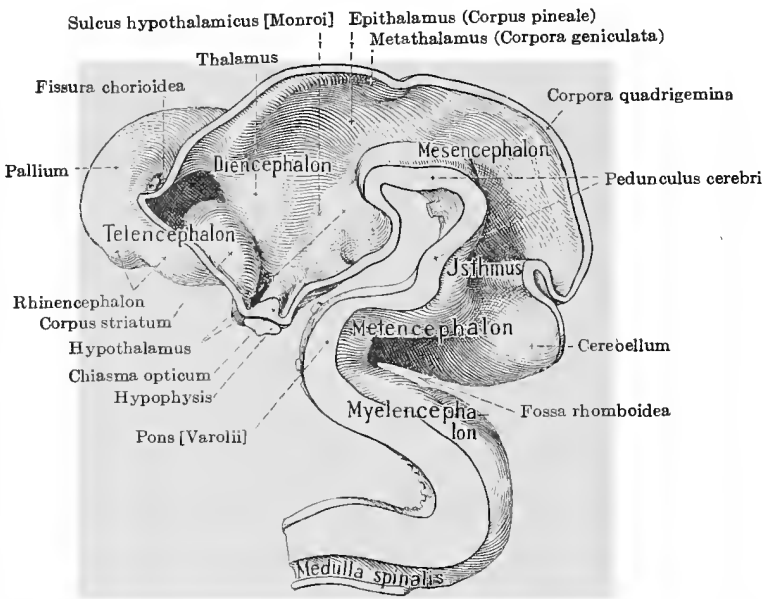


FIG. 55.—Brain of a human embryo 5 weeks old (13.6 mm.), median view of the right half. (After a His model, from Spalteholz.)

ally into the basal plate as the pars optica hypothalamica. Caudal to it (Fig. 56) is a pouch representing the beginning of the infundibulum. During the fourth week an extension of this pouch (infundibular process) comes into contact with a similar pouch formed from the stomodæal epithelium (Rathke's hypophyseal pouch). The latter finally becomes detached from the oral epithelium and becomes incorporated with the infundibular process to form the hypophysis. The nervous and epithelial elements remain distinct throughout and constitute its two lobes. The epithelial pouch is at first flat and lies in front. It later develops two horns which envelop the infundibular pouch laterally. During the latter half of the second month vascular epithelial sprouts are developed from the pouch forming a mass of tortuous tubules, and finally

(third month) obliterate the original cavity, converting it into a solid glandular organ. In the meantime the lumen of the nervous infundibular process has become shut off from the rest of the infundibular cavity, though the process always remains attached to the infundibulum. It becomes converted into a solid mass of tissue resembling neuroglia, and is closely united with the epithelial portion by a connective-tissue capsule and forms the posterior lobe of the organ.

The diencephalic floor caudal to the infundibulum forms the tuber cinereum, and still further caudal the mammillary recess from the walls of which the mammillary bodies are formed.

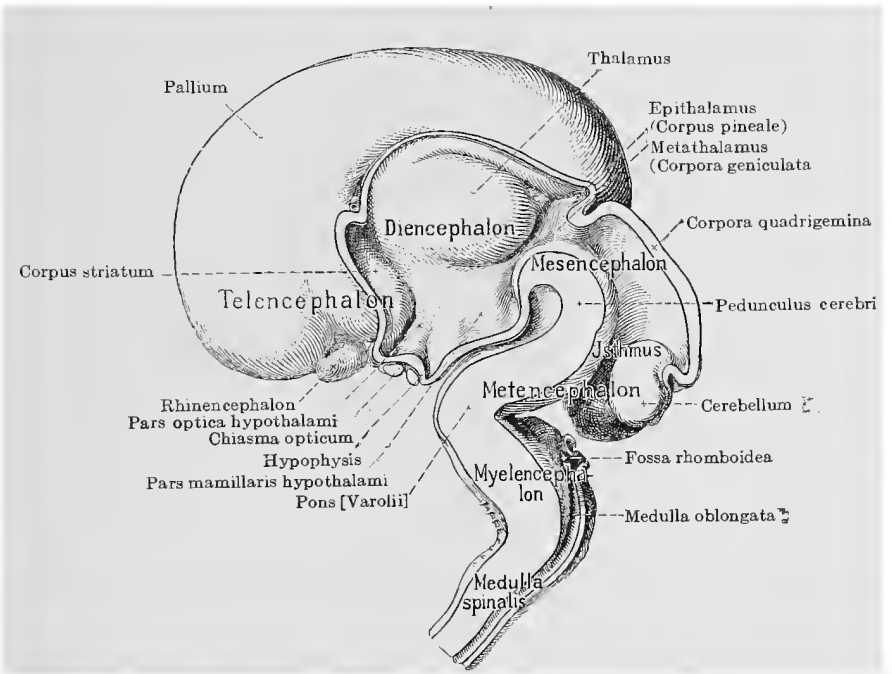


FIG. 56.—Brain of a human fetus in the third month, median view of right half. (After a His model, from Spalteholz.)

The roof plate of the diencephalon is bounded anteriorly and posteriorly by two transverse grooves. The posterior one appears toward the end of the first month and always remains a well-marked groove. The posterior commissure crosses through its substance. The anterior boundary is formed by the velum transversum in a line with the foramen of Monro. The identity of this groove is best recognized in the early stages, 5–10 mm., after which the complications of the forebrain development obscure it. It marks the boundary between a part of the third ventricle that belongs to the telencephalon and a part that belongs to the diencephalon (see Fig. 26).

A dorsal view of the roof plate is shown in Fig. 57 and a median view in Fig. 56. It consists of a thin ependymal plate uniting the two thalamic plates. At the fourth week it is smooth. Proliferation of its cells causes it to expand and form an outward ridge which is soon thrown into longitudinal folds, as shown in Fig. 54. These folds project into the ventricle as the ectodermal lining of the tela chorioidea of the third ventricle. The increase of these folds and the development of a vascular mesodermal coat

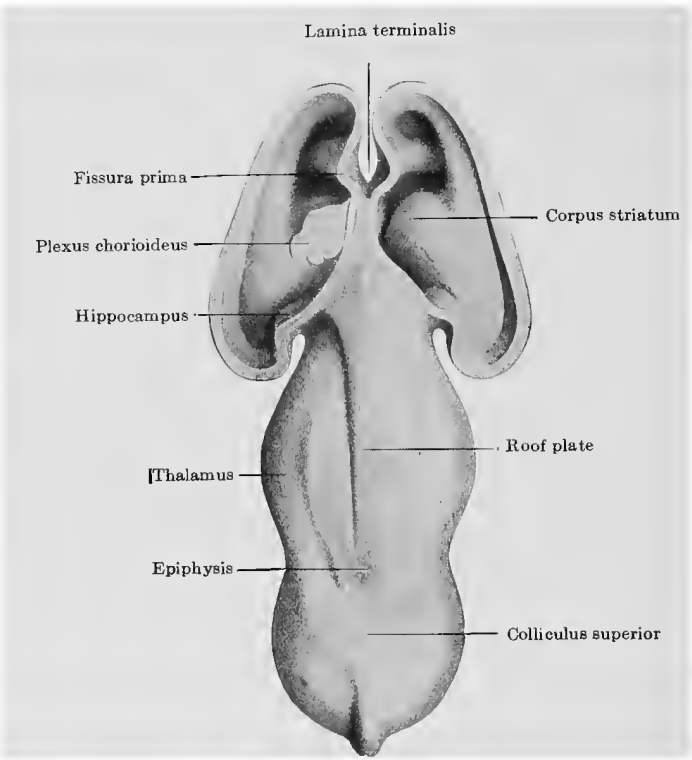


FIG. 57.—Dorsal view of a model of the prosencephalon of a human embryo at the beginning of the sixth week (13.6 mm.). The pallium is partly removed, exposing the interior of the lateral ventricles. This is from the same specimen shown in Fig. 55. (After His.)

complete the formation of a typical chorioid plexus. Orally this chorioid roof is continued into the telencephalon where it forms a pointed pouch overlapping the lamina terminalis and the contained commissures. At the foramen of Monro it is continuous with the similarly formed chorioid body of the lateral ventricle. At the posterior, or epiphyseal end of the roof, there is another small chorioidal pouch formed which overlaps the epiphysis. The anterior chorioidal pouch apparently corresponds to the paraphysis of the lower vertebrates.

Laterally the roof plate is attached along the borders of the thalamic plates. At the line of junction there are formed the

epithalamic structures known as the ganglia habenulæ and the epiphysis. The habenular apparatus bears a relation to the thalamic plate similar to that of the rhombic lip to the alar plate in the hindbrain. The habenular nuclear mass can be recognized by the fifth or sixth week as a longitudinal ridge on the dorsal surface of the diencephalon along the edge of the thalamic plate. In fetuses 80 mm. long, as seen in Fig. 53, the nucleus can be outlined and the stria medullaris and fasciculus retroflexus traced to their terminal connections. The former extends forward along the edge of the thalamic plate and spreads out over the surface of the future anterior nucleus of the thalamus.

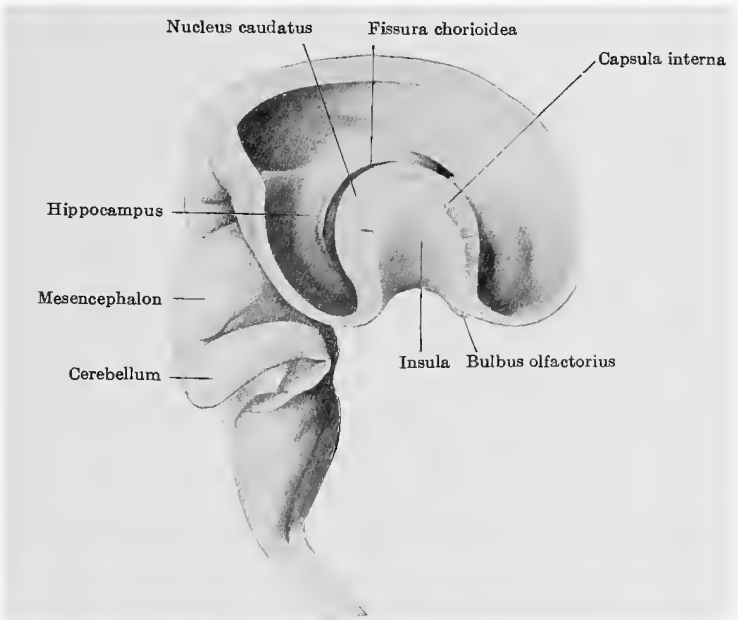


FIG. 58.—Lateral view of brain of a human embryo about three months old (crown-rump length 53 mm.). Part of the hemisphere wall is removed, showing its thickness and exposing the interior of the lateral ventricle. (After His.)

The epiphysis is formed at the caudal end of the diencephalic roof. At the fifth week, Fig. 57, it appears as a rounded elevation of the roof. In the groove behind it the posterior commissure crosses and in the groove in front of it the dorsal or habenular commissure. It thus originally consists of a thin ependymal diverticulum between these two commissures. Subsequently its walls are thickened and incorporate some of the adjacent vascular mesoderm to form the adult organ. In the human embryo the epiphysis never reaches the advanced stage of development seen in reptiles (pineal eye).

The ventricle of the diencephalon, at first a relatively broad space, becomes thinned down to a narrow cleft owing to the thick-

ening and crowding in of the lateral walls. The space is still further reduced by an actual approximation and fusion of a portion of the thalamic plates. In this manner there is produced the commissura mollis, the extent varying in different subjects. It is very large in lower mammals.

We thus see that the diencephalon consists of three main regions, the hypothalamus, the epithalamus, and, largest of all, the thalamus proper (including the metathalamus or geniculate bodies). The hypothalamus and epithalamus are the most primitive in character and their fibres are the first to develop. During the second month the following tracts become established in the hypothalamus: (*a*) fasciculus mammillotegmentalis; (*b*) fasciculus thalamomammillaris; and (*c*) columna fornicis. At the same time in connection with the epithalamus there are developed: (*a*) stria medullaris; (*b*) commissura habenularis; (*c*) fasciculus retroflexus; and (*d*) commissura posterior. Advanced development of the thalamus is characteristic of the higher vertebrates. In the human embryo, though it develops somewhat slower, yet it eventually predominates over all the rest of the diencephalon. By the end of the second month the acoustic fibres have reached the median geniculate bodies, the optic tract fibres the lateral geniculate bodies, and the fibres from the median lemniscus the ventrolateral thalamic nucleus. At the same time these nuclei give off fibres that extend into the corpus striatum forming the thalamic radiation. Some of them can be seen passing through to reach the developing neopallium (compare Figs. 63 and 73).

(g) Development of the Telencephalon.

When we come to the extreme oral end of the neural tube it is no longer possible to clearly recognize an alar plate or basal plate as seen everywhere else in the tube. The sulcus limitans, however, is usually considered as curving downward along the posterior border of the optic evagination to the median line just in front of or along the transverse ridge caused by the optic chiasm. (Compare Figs. 26 and 28.) In this sense practically the whole telencephalon may be regarded as corresponding to an elaboration of the alar plate.

The broad expanse of this portion of the neural plate in the earliest stages (Fig. 23) indicates its importance. As we have already seen, before the closure of the tube is completed (Figs. 26 and 28), the telencephalon has become differentiated on each side into a bulging portion marking the future pallium or hemisphere and a basal portion which is to form laterally the corpus striatum and medially the rhinencephalon. The optic evagination is on the boundary line between the latter and the diencephalon.

The further steps in the differentiation are shown in Figs. 55, 56, 59, and 60. Comparison of these figures shows that though these primary regions of the telencephalon undergo great change in size, form and position, yet they maintain their identity throughout. It is the extensive development of the pallium that is the most striking feature; whereas the rhinencephalon, which is so massive in lower vertebrates, at its most favorable embryonic stage in the human embryo composes not more than one-twentieth part of the bulk of the telencephalon, and in the adult a far smaller proportion. The corpus striatum is closely united with the thalamus, and it is through this that the connection between telencephalon and diencephalon is principally maintained. It shares with the

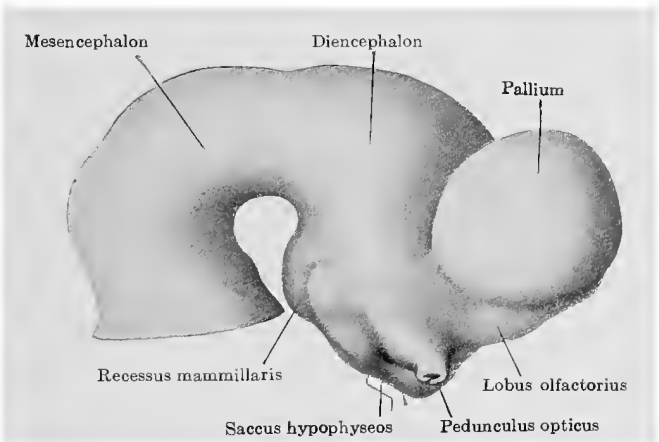


FIG. 59.—Lateral view of the forebrain of a human embryo 10.2 mm. long. Taken from a model. It shows the beginning of the overlapping of the diencephalon by the pallium. Compare with Figs. 29 and 86. After His.)

thalamus in the development of the pallium. Through these two centres pass all the paths of communication to and from the cortex, excepting the insignificant portion belonging to the olfactory system.

CORPUS STRIATUM AND PALLIUM.—The change occurring in the telencephalon toward the end of the first month is a very important one and should be carefully noted in order to understand the development of this region of the brain. As can be seen by comparing Figs. 28 and 55, it represents the transition from the neural tube type to the typical paired hemispheres opening out laterally through the foramen of Monro. The latter is produced not as an actual constriction but secondarily through the fact that its boundaries remain nearly stationary while the pallial walls undergo enormous expansion. The expansion of the pallial walls is shown in Figs. 59 and 60. From around the borders of the corpus striatum they expand orally, dorsally and caudally, gradually covering in the whole diencephalon and more caudal parts of the

brain. In Fig. 60 we can recognize the oral end as the frontal lobe, its inclosed cavity being the anterior horn of the lateral ventricle. The caudal end curves downward to form the temporal lobe, its inclosed cavity being the descending horn of the lateral ventricle. Later, fetuses 10 cm. long, the caudal portion presents two lobes or poles, the temporal lobe having become more ventral and the new occipital lobe forming the extreme caudal end, its cavity corresponding to the posterior horn of the lateral ventricle (see Figs. 76 and 77).

During the expansion of the pallial walls the median lamina uniting them does not share in the growth, and there is thus formed

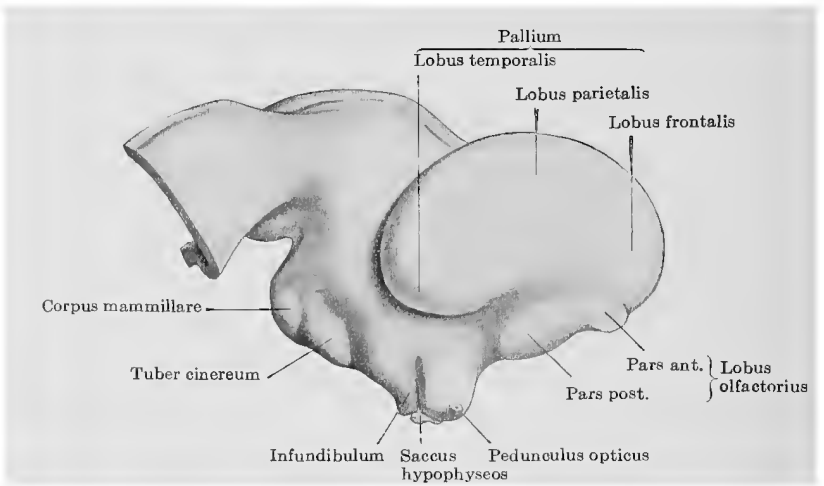


FIG. 60.—Lateral view of the forebrain of a human embryo 13.6 mm. long. Taken from the same specimen shown in Fig. 57. Comparison with Fig. 59 shows the growth of the pallium and the manner in which it overlaps the diencephalon. (After His.)

the great longitudinal fissure between the two hemispheres, which eventually becomes occupied by a mesodermal septum, the falx cerebri. The lamina uniting the two hemispheres is continuous anteriorly with the lamina terminalis and might properly be regarded as belonging to it. Posteriorly it is continuous with the diencephalic roof plate. We have already seen how the latter becomes folded and vascularized to form a chorioidal roof for the third ventricle. A similar change occurs in the pallial wall near its junction with the diencephalon. The wall becomes very thin and folds into the lumen of the lateral ventricle, carrying with it vascular mesoderm (Fig. 62) and thus finally forms a chorioidal body within the ventricle. If the chorioidal body is removed there is left a cleft in the wall, the approximate position of which is shown in Fig. 64, and which corresponds to the fissura chorioidea. That portion of the hemisphere wall ventral to the fissure apparently never undergoes active development. In the portion

dorsal to it is developed the hippocampal system. Anteriorly the chorioidal formation is continuous with the chorioidal roof of the third ventricle. The whole chorioidal mass forms an irregular Y, the stem being the roof of the third ventricle and the two arms being the chorioidal bodies of the lateral ventricles. The arms begin at the foramen of Monro and differ from the stem in being better developed and projecting into the ventricle. The relations of these structures are considerably modified later by the changes occurring in the lamina terminalis due to the formation of the interforebrain commissures which will be spoken of again in connection with the hippocampus. In all other regions of the neural tube we find chorioidal formation limited to the roof plate and this gives a ground for considering the roof plate of the telencephalon as bifurcated and represented by the two chorioidal fissures. There is, however, no other evidence of such a bifurcation of the oral end of the tube.

Attention has already been called to the ridge formed by the corpus striatum in the floor of the telencephalon (Figs. 28, 57, and 55). It can be seen at the outset that the corpus striatum is directly continuous with the thalamic plate of the diencephalon. In its development it resembles the thalamus and becomes closely co-ordinated with it, but the two always remain distinctly separated from each other, at first by a deep groove and later by the tænia semicircularis. It consists at first of a ridge which spreads out anteriorly in three limbs (Fig. 28), marking off the two divisions of the rhinencephalon. Later, with the expansion of the pallium, the ridge becomes more prominent. It is elongated caudally and curves around the developing stalk of the hemisphere to the tip of the inferior horn, forming the tail of the caudate nucleus. As the wall thickens it projects into the ventricle, and the lateral surface of the same portion of the brain wall, Fig. 60, presents a shallow fossa which continues to become deeper as the surrounding pallium develops. The thickening of the wall at first involves chiefly the ependymal zone, which undergoes an exuberant growth, and exactly in the area corresponding to the future caudate nucleus. Gradually from the ependymal zone a mantle zone is elaborated and furnishes the neuroblasts which become assembled into a typical corpus striatum. The fibre strands from and to the thalamus become arranged in a sharply marked lamina which subdivides the corpus striatum into the caudate and lenticular portions, thus forming the limbs of the internal capsule. It should be noted that this subdivision of the corpus striatum and the formation of an internal capsule are due to the manner in which the fibres traverse it. In some mammals the fibres pass diffusely through the striatum and then the capsule-like arrangement of the fibres is absent.

The division between thalamus and corpus striatum is most evident in midembryonic life. At the end of the third month a deep groove separates them. Subsequently as they become larger and as the nerve-fibres connecting them increase, this groove be-

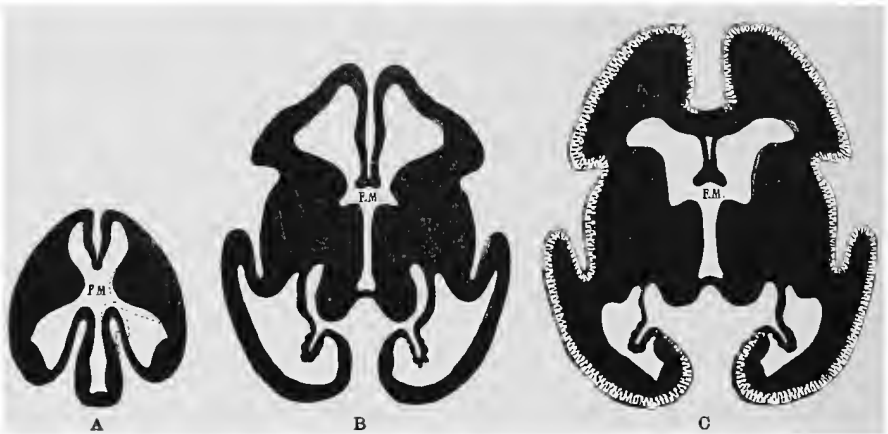


Fig. 61.—Schematic horizontal sections through the forebrain of human embryos, showing three stages in the fusion of the thalamus and corpus striatum. A, embryo of about 6 weeks (15 mm.); B, fetus during the fourth month; C, fetus during fifth month (crown-rump length 150 mm.). *F. M.*, foramen of Monro. (After Goldstein.)

comes flattened out, and they come to form one solid ganglionic mass separated from each other only by the tænia semicircularis. It is thought by some that in this process an apposition and fusion occurs between the anterior end of the thalamus, the medial pallial

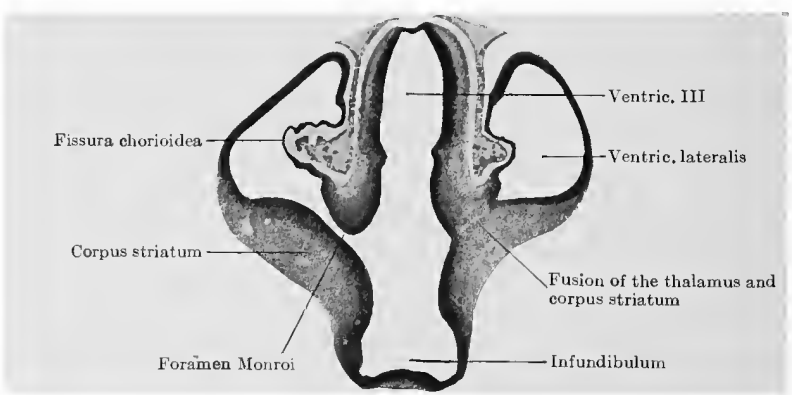


Fig. 62.—Transverse section through forebrain of human embryo of about six weeks (16 mm. long), showing on one side the fusion of thalamus and corpus striatum. Compare with Fig. 61, A. (After His.)

wall and the corpus striatum, as shown in Fig. 61. The same result, however, would occur if it were a simple thickening of the wall produced by the massive connections developed between thalamus and corpus striatum. In Fig. 62, on comparing the two sides it would seem as though such a fusion had occurred; but it

should be remembered that the two sides are not cut at the same level, that one is through the foramen of Monro and the other is just below or caudal to it.

At the end of the fifth month, as seen in Fig. 63, the relation and form of the corpus striatum are practically those of the adult. The form of the internal capsule can be clearly made out. It contains: (*a*) fibres connecting the thalamus with the corpus striatum and pallium; (*b*) optic and acoustic fibres from the metathalamus to the pallium; (*c*) projection fibres from the pallium (pyramidal

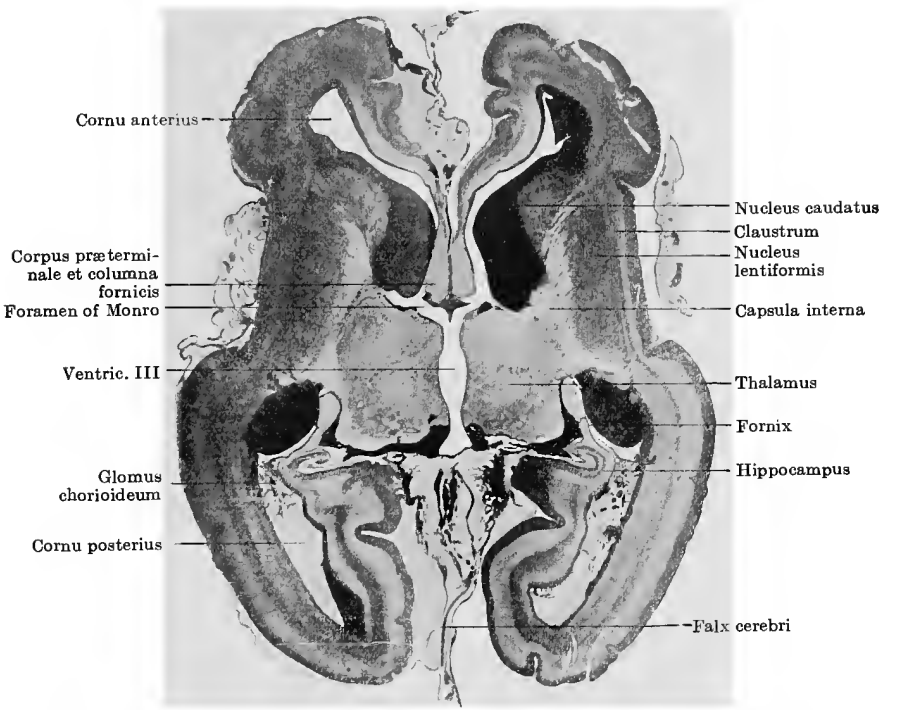


Fig. 63.—Horizontal section through the forebrain of a fetus about five months old (crown-rump length 160 mm.). This represents a stage intermediate between B and C in Fig. 61. (After His.)

tract). The stria semicircularis, though it is on the border line between diencephalon and telencephalon, probably belongs to the latter. It can be recognized early (80 mm.), as it curves around the thalamic border. It is shown in Figs. 66, 67, and 68.

Rhinencephalon.—The olfactory apparatus consists of a basal portion and a cortical or pallial portion. The basal portion includes the olfactory bulb, olfactory stalk, the median and lateral olfactory tracts and the region of the anterior perforated space which merges on the one hand with the tip of the temporal lobe and on the other with the preterminal body which partly forms the septum pellucidum.

All of these parts are derived from the basal portion of the telencephalon median to the corpus striatum (see Fig. 55). The cortical portion of the rhinencephalon belongs to the pallium and is designated as archipallium in contradistinction to the remainder or neopallium. It consists of an extension of the basal preterminal area dorsalward and forms the median margin of the pallium along the dorsal border of the chorioidal fissure. In the adult we know it as the hippocampus, the dentate fascia, and it probably includes a strip of cortex bordering along the hippocampus. It differs from the basal portion in that the cells composing it are arranged in the form of a cortex with characteristic strata.

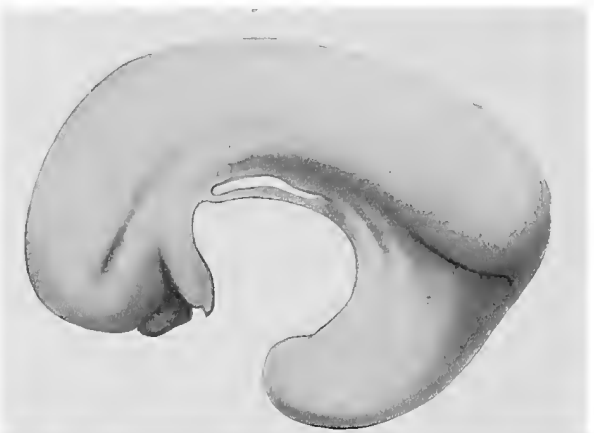


FIG. 64.—Median wall of the telencephalon of same specimen shown in Fig. 58, showing the fissura chorioidea and under it a narrow strip of the lamina infrachorioidea. The fissura prima extends upward from the olfactory lobe marking off the anterior border of the præterminal body. In front of it is the accessory arcuate fissure. The calcarine fissure is sharply marked. The hippocampal fissure curves around parallel with the inner margin of the specimen. (After His.)

In Figs. 66, 67, and 68 the median view of the brain is shown in its later stages of development exposing this general region. That portion of the pallium possessing a uniform cortical layer is shown in lighter color than the remainder and corresponds in general to the neopallium. The darker portions form the archipallium and thus represent the olfactory apparatus. If we are to consider that portion of the cortex adjoining the hippocampus as olfactory and belonging to the archipallium (G. Elliot Smith), then to complete the pallial portion of the olfactory system the dark shading should be spread wider to include this. The basal portions of the olfactory apparatus are shown in the same figures. Lateral views of the same stages are shown in Figs. 76 and 77. The relations of the basal portions can be best seen, however, in a ventral view, as given in Fig. 65, where its different parts are indicated. The boundaries of the olfactory apparatus in this figure are marked by the dorsal border of the lateral olfactory gyrus and the gyrus ambiens.

The olfactory apparatus can be traced back to a still younger stage in Figs. 55 and 60, which present median and lateral views of the brain at the end of the fifth week. At this period, as seen in a lateral view, there is a distinct field marked off ventral to the Sylvian depression which represents the basal portion. It consists of two elevations. The anterior one is formed by a shallow pocket opening out of the ventricular cavity. The further evagination of this results in the formation of the hollow olfactory bulb whose form in later stages we have already seen. It can be readily understood how this extending tubular process becomes narrowed down in its proximal portion to form the olfactory stalk, commonly spoken of as the first pair of cranial nerves. In man the lumen of this process is eventually obliterated.

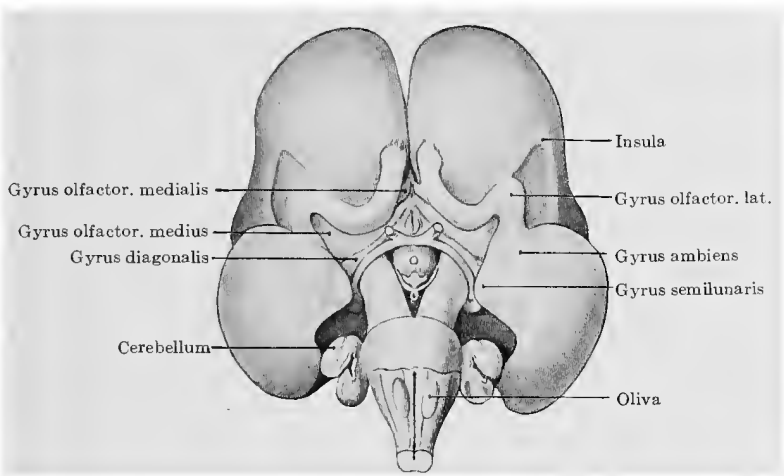


FIG. 65.—Ventral view of brain of a four months old human fetus, showing the olfactory apparatus. (After Kollmann.)

The posterior olfactory elevation becomes a thickened portion of the wall instead of an evagination and represents the anterior perforated space. Mesially (Fig. 55) it extends upward, bordering along the lamina terminalis, and forms the preterminal body of Elliot Smith; and is directly continuous with the olfactory pallium along the fissura chorioidea. In the older stages the olfactory tracts were already laid down. At this stage they are just beginning to appear. According to His, a little before this time, in embryos Nl. 10.9 mm., filaments can be recognized connecting the nasal epithelium with the olfactory pocket (anterior olfactory elevation) of the brain wall, *i.e.*, before we can yet speak of an olfactory bulb or stalk. About the same time the fibres of the median olfactory tract begin to extend dorsalward from the olfactory pocket to the preterminal body. By the time the olfactory bulb has become partially constricted from the general brain wall

fibres can be seen extending backward from it along the dorsolateral border of the posterior olfactory elevation (anterior perforated space) and constituting the lateral olfactory tract, whose fibres are distributed to the archipallium covering the apex of the temporal lobe.

In embryos under four weeks old the rhinencephalon can only be recognized as the space between the lamina terminalis and the internal ridge formed by the corpus striatum (Fig. 28). According to His the three limbs of the striate ridge mark out the two fossæ which we have seen as prominences on the lateral surface corresponding to the olfactory bulb and the anterior perforated space.

Interforebrain Commissures.—In connection with the olfactory apparatus there are the tracts connecting it with the hypothalamus (fornix) and the commissural tracts uniting the opposite sides of the telencephalon (anterior commissure, commissure of fornix and corpus callosum). The development of these structures can best be understood by comparison of Figs. 66, 67, and 68, which represent three stages in their development.

In these figures the lamina terminalis is shown as though cut in the median sagittal plane, while the commissures are left longer so that their cut ends project from the surface. It will thus be seen that they all cross through the substance of the thickened lamina terminalis and are thus confined to the original walls connecting the two hemispheres. The use of the term "lamina terminalis" is made in a broad sense. It is not restricted to the ependymal seam that originally closes off the anterior end of the tube, or its immediate derivatives; but includes also a certain amount of neuroglial tissue from the adjacent wall which becomes incorporated with it. In this sense we may speak of a fusion of the median walls of the precommissural bodies, but the process only occurs in a narrow line immediately in front of the lamina terminalis and the derived tissue becomes a definite part of the latter. Its further enlargement is produced by the stretching of its boundaries by the entering commissural fibres. A narrow lamina terminalis suffices originally, as only a few slender bundles cross at first. As further fibres are added the fibre mass spreads open a space for itself, in which process a portion of the precommissural body is appropriated, and the eventual lamina terminalis presents a large surface in the cut median section, including the whole corpus callosum and the septum pellucidum. The widening of the boundaries of the lamina terminalis occurs rapidly in fetuses between 80 and 150 mm. It is distended dorsalward and anterolateralward through the growth of the corpus callosum, the shape of which in turn is determined by the expanding pallium. As a result of this tension there is a new arrangement of its tissue, and

in the readjustment a ventricle is formed, the so-called fifth ventricle or cavum septi pellucidi. This becomes lined with a smooth neuroglial membrane. The ventricle is only present where there is a large corpus callosum.

It should be mentioned that, according to some authors (Goldstein, 1903), the commissures are developed entirely within the lamina terminalis, in the narrower sense, the adjacent walls not contributing anything to it. On the other hand, according to Zuckerkandl, 1901, there is an approximation and fusion of a considerable area of the median walls with resorption of the previously interposed mesodermal falx. This forms a "massa commissuralis" through which the fibres subsequently cross. In the process of fusion he describes an active proliferation of the cells of the wall, forming "wulstartige Vorsprünge," which meet and fuse in the median line. The description given above corresponds essentially with that given by G. Elliot Smith (1895) and Marchand (1909).

Of the three commissures the anterior commissure and the commissure of the fornix are the more primitive, and they both serve as commissures for the archipallium. The fibres of the fornix make their appearance early along the chorioidal margin of the hippocampus and form a bundle increasing in size as it extends forward. It passes over the foramen of Monro to reach the precommissural body where it gives off and receives fibres. It then extends ventralward to the hypothalamus in the region of the mammillary body (pillar of the fornix). In the region of the precommissural body the two fornix systems exchange fibres forming a commissure between the two hippocampal gyri. Originally this commissure lies directly dorsal to the anterior commissure, as seen in Fig. 66. Subsequently it is drawn backward owing to the change in the position of the hippocampi, which in turn are carried backward by the ventral extension of the temporal lobe.

The development of the corpus callosum is closely connected with that of the fornix commissure, being practically a derivative of it. The latter is a commissure of the archipallium and the former of the neopallium, the one starting where the other stops. Owing to the great development of the neopallium in man the corpus callosum soon predominates.

In fetuses 80 mm. long (Fig. 66) its fibres can be recognized in the medial wall of the hemisphere streaming toward the upper part of the lamina terminalis, where it crosses together with the commissure of the fornix, forming a rounded bundle on the dorsal surface of the latter. The first discoverable fibres contributed to it are found in the median wall in the vicinity of the point of crossing. As further fibres are added they form a layer that can be gradually traced spreading backward and lateralward through

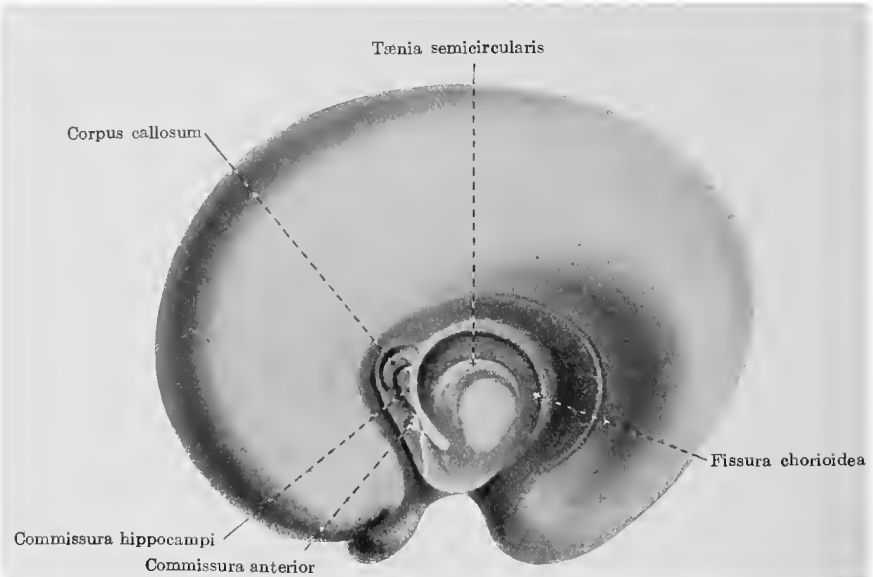


FIG. 66.—Median view of a model of the telencephalon of a human fetus three months old (80 mm. long, Mall collection, No. 234a). It shows the cut ends of the commissural bundles crossing in the lamina terminalis. The thalamus is removed, exposing through the fissura chorioidea, the lateral ventricle and nucleus caudatus. Comparison of this figure with Figs. 67 and 68 shows the development of the corpus callosum and its relation to the commissure of the hippocampus.

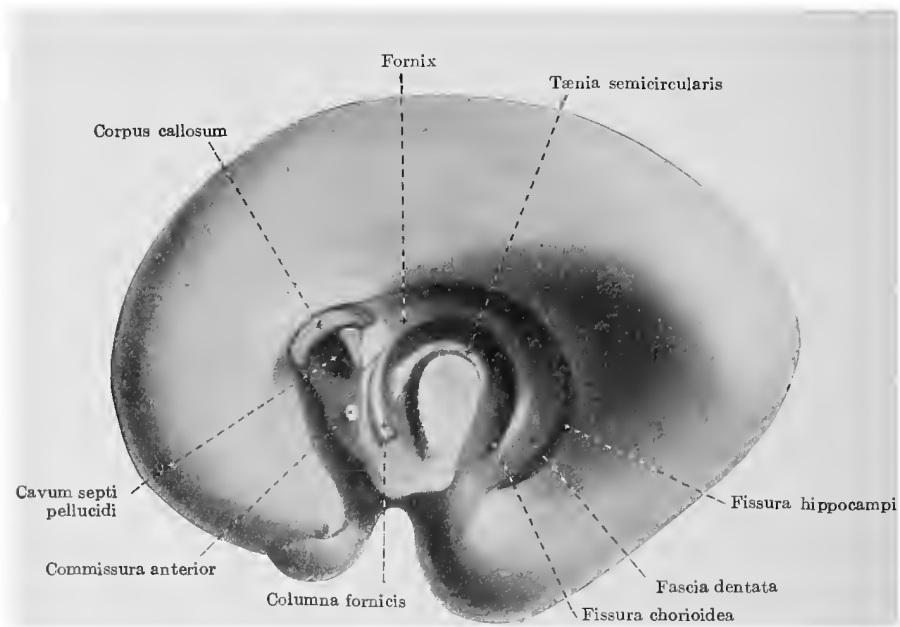


FIG. 67.—Median view of a model of the telencephalon of a human fetus about 4 months old (95 mm. long, Mall collection, No. 146). It shows the same structures seen in Figs. 66 and 68. The lamina terminalis has become thickened at the expense of the corpus præterminale, and a cavity has developed in it forming the cavum septi pellucidi. The fissura hippocampi has deepened, it being the first step in the covering in of the fascia dentata.

the pallium to the regions more distant from the lamina terminalis. It is quite probable that the growth of these fibres starts simultaneously in all parts of the pallium, and it is natural that it is in the region of the lamina terminalis that the accumulation of them is first sufficient to be recognized as a definite layer. The form of the corpus callosum in fetuses 95 mm. long is shown in Fig. 70, where its relation to the brain wall can be seen. It lies nearer the ependyma than the outer surface. The model represents only

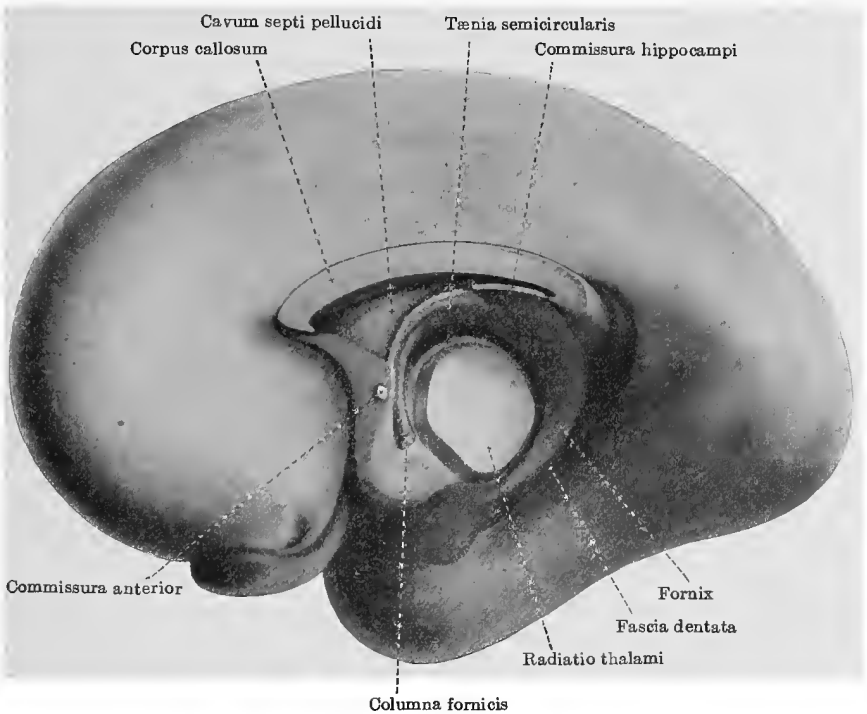


FIG. 68.—Median view of a model of the telencephalon of a human fetus of the fifth month (150 mm. long, Mall collection). Here the commissural systems are practically those of the adult. The fascia dentata extends up over the splenium of the corpus callosum and reappears at the front end (genu) and is continuous with the præterminal body and enlarged lamina terminalis. Compare with Figs. 66 and 67.

that part that could be distinguished as a stratum. It is probable that callosal fibres reach much further than this.

The addition of fibres occurs interstitially, the new fibres growing in everywhere between the old ones. As seen in cross section, it very early takes on a typical form. In fetuses 95 mm. long, Fig. 67, we can recognize the anterior end as the genu and the posterior end as the splenium, the latter always remaining in contact with the fornix commissure. With the further growth of the pallium and the addition of new fibres to the corpus callosum we have in 150 mm. fetuses, Fig. 68, relations which are practically those of the adult. It will be seen that like the pallium it has

grown both posteriorly and anteriorly. As the splenial end spreads caudalward it covers in the diencephalon, carrying the commissure of the fornix with it. The latter gradually becomes flattened out on the under surface of the corpus callosum to form the psalterium.

The striæ of Lancisi represent tissue connecting the dentate fascia with the precommissural body. By comparison of Figs. 66, 67, and 68 it can be seen how the two are closely connected at first (practically continuous). The tissue connecting them may be regarded as regressive fascia dentata. It soon is stretched out in a narrow strand by the enlarging corpus callosum. Some of the fibres in this substance are frequently laid down in advance of the corpus callosum, so that the fibres of the latter pass between them and incorporate them. Thus the anterior end of the adult corpus

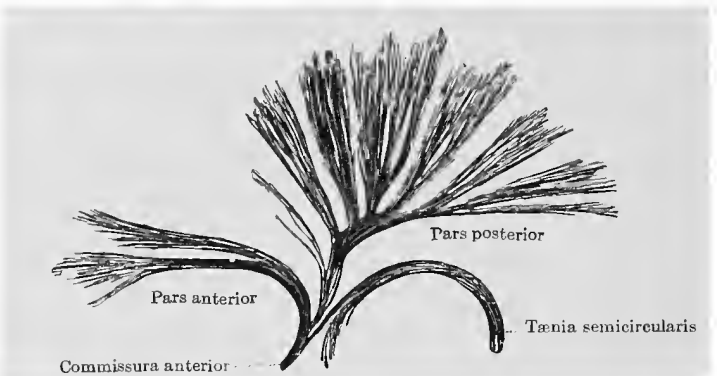


FIG. 69.—Right half of the anterior commissure dissected out from the brain of an 80 mm. pig fetus, viewed from above and from the median side. Its constituent elements are shown and its connection with the tænia semicircularis

callosum is found to be traversed by some of these fibres, on their way through the wall of the septum pellucidum to the precommissural body.

The anterior commissure, as it appears when dissected out in the pig embryo, is shown in Fig. 69. It consists of two divisions, an anterior or olfactory division and a posterior division. The olfactory division arises principally (in pig embryos) in the brain wall in the neighborhood of the olfactory evagination. The posterior division arises between the corpus striatum and the overlying cortex and thus corresponds in position to the fossa of Sylvius. It forms a concave lamina in which the corpus striatum rests. Owing to the fibres streaming from the corpus striatum to the pallium it is difficult to determine whether its fibres are derived mesially from the corpus striatum or laterally from the superimposed cortex. In Fig. 69 it is shown how the fibres composing it form confluent fan-like bundles which point ventralward and become incorporated into two main bundles, anterior and

posterior, which in turn unite and point toward the lamina terminalis to meet the similar formation from the opposite side. In the earlier stages it is possible to recognize the anterior commissure fibres before they have reached the median line. As it approaches the median line it receives a communication from the tænia semicircularis. In Fig. 70 is shown the relation of the anterior commissure in a 95 mm. human fetus, being essentially like

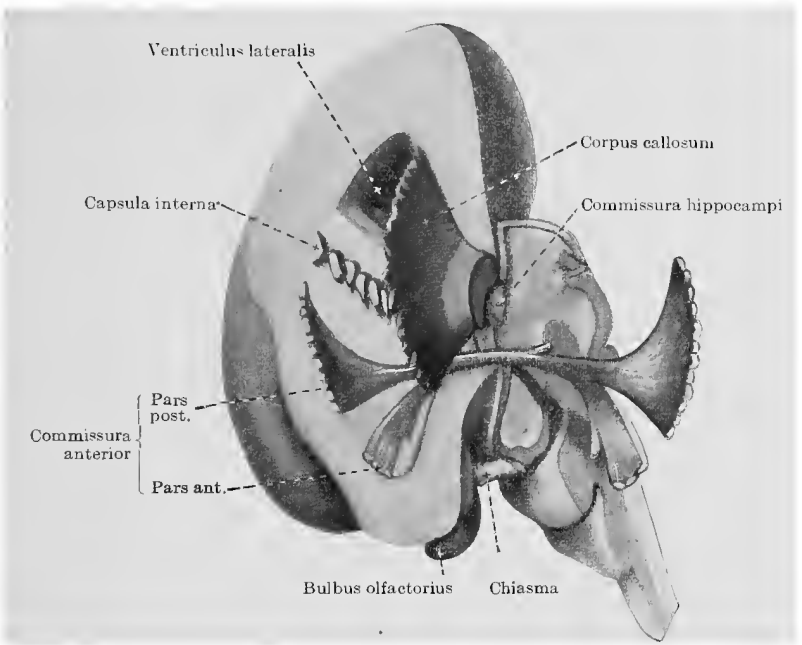


FIG. 70.—Anteromedian view of a model of the fibre tracts of the same brain shown in Fig. 67. One half of the brain stem is preserved intact. In the front part of the telencephalon everything is removed excepting the fibre tracts, exposing the corpus callosum, pillar and commissure of the fornix, two divisions of the anterior commissure and the internal capsule. The last subdivides the corpus striatum into the caudate and lenticular nuclei. On the left side the connection from the tænia semicircularis to the anterior commissure is shown.

that seen in dissections of pig fetuses. Of the olfactory division some strands apparently come from the olfactory stalk, and others from the hemisphere wall in the immediate neighborhood.

DEVELOPMENT OF THE WALL OF THE HEMISPHERE.

Up to the end of the second month the wall of the hemisphere remains thin and relatively undifferentiated. The increase in thickness and development of the wall that begins to be noticeable at that time does not occur uniformly in all regions at the same time, but is always more advanced in the basal portions adjoining the corpus striatum, and from there it gradually extends toward the median line over the whole pallium. In the accompanying table is given the thickness of the wall and its constituent zones in

embryos from six weeks to fetuses four months old, the measurements in each case being taken at approximately the same region,—*i.e.*, the basal portion of the lateral wall.

Table showing Thickness of Hemisphere Wall and its Constituent Layers in Human Embryos from the Sixth Week to Fetuses of the Fourth Month, Compiled from Measurements given by His, 1904.

Approximate age and size of embryo.	6 weeks. Nl. 16 mm.	8 weeks. Nl. 22 mm.	10 weeks. Crl. 46 mm.	12 weeks. Crl. 50 mm.	14 weeks. Crl. 60 mm.	16 weeks. Crl. 120 mm.
Total thickness	.145	.5	.6	.8	1.1	4.
Ependymal zone (Matrix)	.085	.16	.15	.15	.17	.2
Mantle zone						
a. Nuclear portion						1.6
b. Sparsely nucleated portion (Zwischenschicht)	.035	.25	.34	.41	.65	1.4
Marginal zone						
a. Pyramidal layer	.....	.06	.085	.2	.24	.8
b. Non-nuclear marginal layer	.025	.03	.025	.04	.04	

Microscopic examination of the wall at about the sixth week (Fig. 71) shows that it still consists, like the wall of the original neural tube, of an outer sparsely nucleated or marginal zone and an inner richly nucleated or ependymal zone. The cells forming the outer portion of the latter are further differentiated and are more loosely arranged, thus constituting a third or mantle zone. In its finer structure the wall consists of a syncytium of spongioblasts and neuroblasts having the same form and relation that has already been described under the histogenesis of the spinal cord. According to His (1904), it presents one characteristic that is not found elsewhere,—*i.e.*, the stratum cribrosum. This is situated in the marginal zone, and consists of lateral processes from the spongioblastic framework so arranged as to form a thin nucleated barrier between the inner and outer part of this zone.

At about the eighth week in the inner portion of the marginal zone there is formed the cortical layer of pyramidal cells which is the essential feature of the pallium. The formation of this layer begins in the region of the corpus striatum and gradually extends around the circumference of the pallial wall to the mesial surface as far as the olfactory margin, where it is modified to form the olfactory cortex. It is formed by the migration of developing neuroblasts from the ependymal and mantle zones into the marginal zone. According to His (1904), these migrating future pyramidal cells advance toward the outer surface as far as the stratum cribrosum, where they accumulate and form a compact layer. This migration is most active during the third month and continues well into the fourth. In Fig. 72 is shown a portion

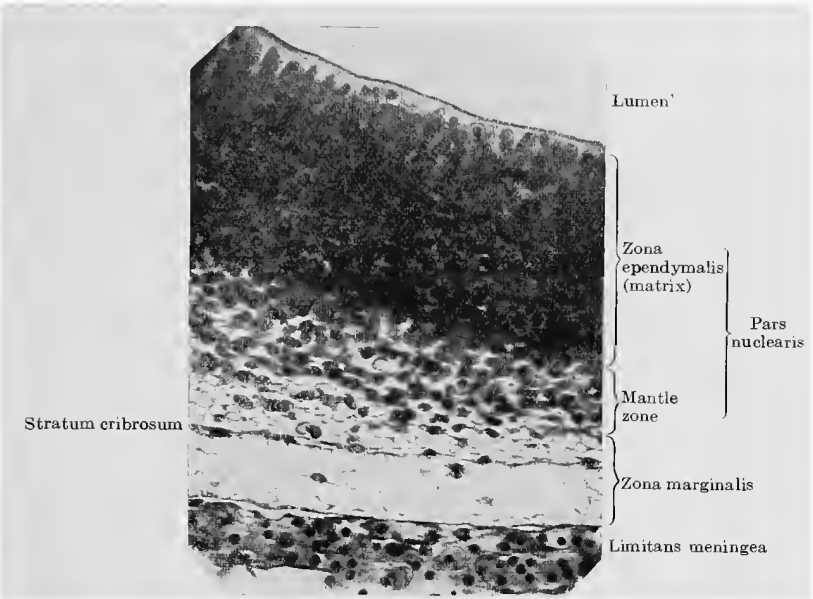


FIG. 71.—Section through hemisphere wall of a human embryo at about the sixth week (16 mm. long) before the development of the cortical layer. (After His.)

FIG. 72.—Hemisphere wall of a human fetus at about the eleventh week (crown-rump length 46 mm.), showing the wandering of the neuroblasts from the interior of the wall toward the outer surface where they form the pyramidal or cortical layer. (After His.)

of the brain wall of an embryo about 3 months old. On the inner surface of the marginal zone is a well-developed cortical layer, toward which numerous other neuroblasts can be seen wandering from the mantle zone. The mantle zone has become much broader, and can be subdivided into an inner nuclear portion, consisting of proliferating neuroblasts and spongioblasts, and an outer wider portion, or intermediate layer (Zwischenschicht), which seems to

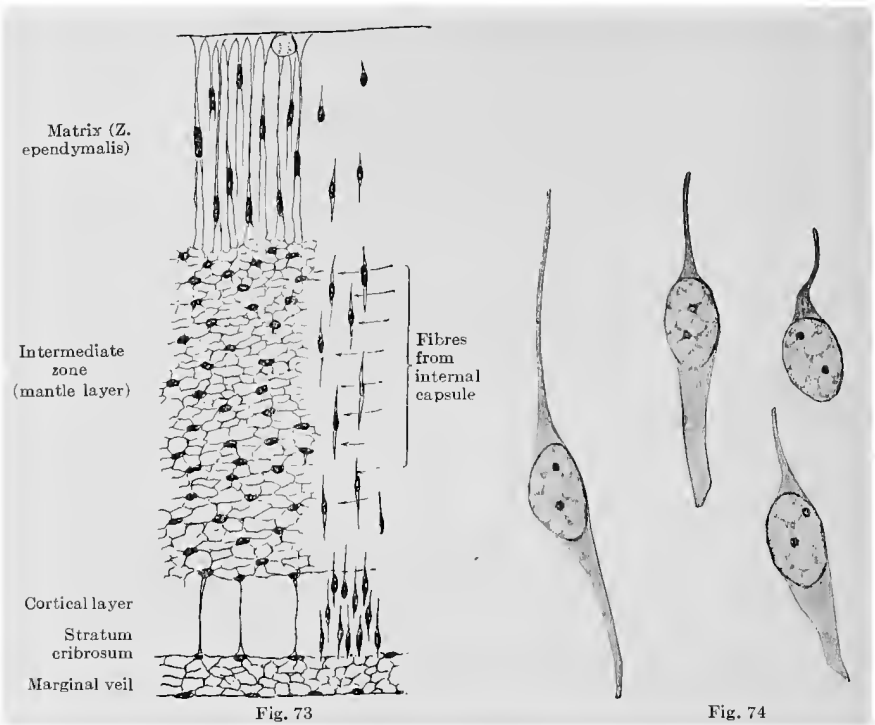


Fig. 73 Fig. 74

FIG. 73.—Schematic drawing showing structure of hemisphere wall at the end of the third month. On the left side is shown only the spongioblastic framework; on the right side are shown the wandering neuroblasts and their accumulation to form the cortical layer. The arrows indicate ectogenous fibres from the internal capsule. Compare with Fig. 72. (After His.)

FIG. 74.—Pyramidal neuroblasts during the period of migration. The lower process is broader and more irregular. It becomes the apical process. The other is more slender; it is pointed toward the ependyma and becomes the axone. (After His.)

be sparsely nucleated, owing to the extensive invasion of fibres from the internal capsule. A schematic section of the wall at this time is shown in Fig. 73. On the left is shown the spongioblastic framework and its formation into different layers, the nuclei representing future neuroglial cells. On the right are indicated the wandering neuroblasts moving radially outward to form the cortical layer. In their journey they have to make their way through the meshes of the framework and through the entering fibres from the thalamus and corpus striatum. During this period of migration the pyramidal cells usually possess a bipolar character, as shown in Fig. 74. The advancing end is broader and more irregu-

lar and becomes the apical process. The slender central end (*i.e.*, toward the lumen) becomes the axone. The development of lateral dendrites and attainment of the characteristic adult form does not occur until about the time of birth.

Up to the fourth month the wall remains relatively thin and the ventricle large. From then on the wall rapidly thickens, owing mainly to the great increase in fibres in the intermediate layer. These fibres at first are all ectogenous fibres, from the thalamus and corpus striatum. Subsequently there are added the axones from

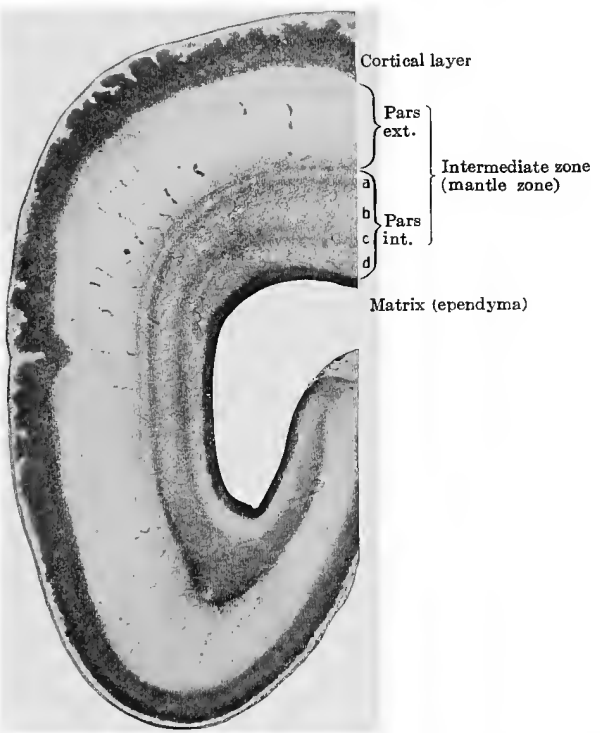


FIG. 75.—Section through hemisphere wall at the end of the fourth month (crown-rump length 120 mm.). The intermediate (Zwischenschicht) zone is rapidly becoming thicker, owing to the increase of incoming and outgoing fibres. It is this layer that eventually forms the central white substance of the brain. Its inner portion is subdivided into the following layers: *a*, outer transitional layer; *b*, outer striated layer; *c*, inner transitional layer; *d*, inner striated layer. At this period the wandering of the cortical neuroblasts is completed. (After His.)

the developing neuroblasts of the cortical layer (autochthonous). It is this fibrous layer that eventually forms the massive white substance of the hemisphere. With the increase in the thickness of the wall the ventricle apparently becomes smaller. The appearance is due in part to the difference in relative growth of the two, and in part to the change in shape of the ventricle, from a wide vesicle to a narrow slit.

As shown in Fig. 75, the inner portion of the mantle zone still possesses many nuclei, belonging to the supporting framework,

which are now arranged in layers. The ependyma does not appear as active as heretofore, although it apparently is still giving off spongioblasts that are to form the neuroglial elements of the white substance. The cortical or pyramidal layer has taken up all its wandering neuroblasts from the deeper layers and is sharply marked off from the subjacent intermediate layer. It is already beginning to subdivide itself into two separate layers, the outer portion being somewhat denser than the inner portion. During the sixth and seventh months, with the further differentiation of the cortical cells, they become grouped into six distinct layers, corresponding to the stratification of the adult cortex. Certain portions of the cortex exhibit modifications of this six-layered arrangement, the strata being increased or decreased in number or varying in thickness. Thus the adult cortex presents various histological areas, each possessing its own characteristic stratification. The visual cortex is a particularly marked example. Its characteristic consists in the subdivision of the internal granular layer into two layers, between which is formed a conspicuous white line, the so-called line of Gennari. Another departure from the general type is found in the hippocampus and fascia dentata, which differ in the well-known way from the cortex seen in other regions.

On the outer surface of the cortical layer there is frequently seen during the fourth month, as shown in Fig. 75, an irregular fungiform clumping of cells, the so-called Retzius papillæ. These, however, are an artefact, being a result of partial maceration of the tissues.

FORMATION OF SULCI AND CONVOLUTIONS.

In the further growth of the brain wall the white matter continues to increase in thickness, while the cortical zone (gray matter) remains spread out in a relatively thin layer, its expansion taking place in a plane parallel with the surface of the brain wall. To accommodate this increase in the extent of its surface the outer surface of the brain wall is thrown into folds. The lines along which the principal folds form correspond (usually) to the boundaries of different histological areas, due perhaps to the difference in their time of development or possibly in consequence of their different reaction to the tension existing between the gray and white substance. Since the different histological areas represent constant functional areas, the fissures are therefore more or less constant.

The first fissures to appear (about the third month) are those associated with the primitive olfactory system, the hippocampal and rhinal. The hippocampal or arcuate fissure forms along the border of the dentate fascia, as shown in Fig. 67. An accessory arcuate fissure on the median wall dorsal to the hippocampal fissure

is described by His as occurring about the same time. By other writers (Hochstetter, Goldstein) this and the so-called fissura prima are regarded as post-mortem phenomena. The fissura prima, or anterior arcuate fissure, is described by His as being the first fissure to appear (the second month). It is found on the median wall near the olfactory bulb, and extends upward in front of the præterminal body of G. Elliot Smith (that is, the trapezoid body of His). Part of it is thought to persist as the fissura parolfactoria posterior. According to His, an extension of the pia mater extends into and corresponds in form to the fissure, and he argues that therefore it must be a real fissure. His opponents deny its presence in well-preserved brains. The rhinal fissure

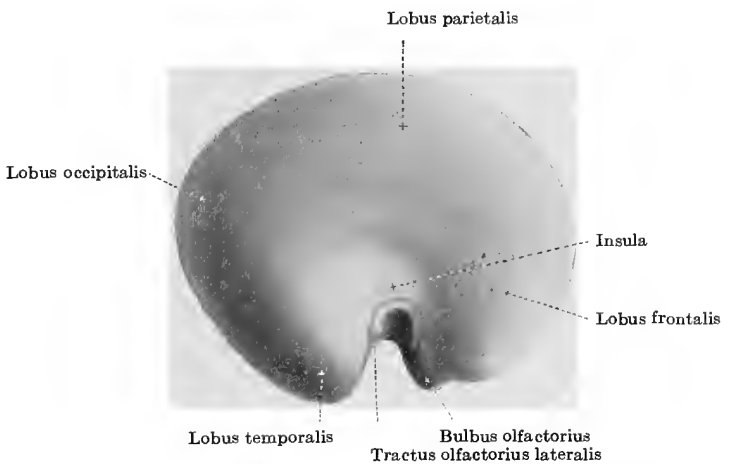


FIG. 76.—Lateral view of reconstruction of cerebral hemisphere of a human fetus about three months old (crown-rump length 80 mm., Mall collection, No. 234a). The rhinal fissure is situated along the upper border of the tractus olfactorius lateralis. The dark-shaded portion at the base represents that portion that is not covered in by a typical cortical layer.

(Fig. 76) separates the lobus piriformis from the neopallium, but in man, owing to the suppression of the olfactory apparatus, it always remains insignificant.

The development of the Sylvian fissure is not completed until after birth, but the first stages in its formation can be seen at the third month. On comparing Figs. 76, 77, and 79 it will be seen that its formation is dependent on the fact that the brain wall in the region of the corpus striatum does not enlarge as rapidly as the parts adjacent to it. This at first expresses itself in the formation of a shallow depression, the fossa Sylvii (see Fig. 76). As the neighboring temporal, frontoparietal, and orbital portions become thicker they form in-rolling walls or lips, the so-called opercula, which finally cover in the retarded portion or insula. The lines along which the lips meet constitute the fissure of Sylvius. The temporal and frontoparietal opercula are formed first. The

frontal and orbital opercula are very late in development. They do not begin to form until the insula is already partly covered in by the temporal and frontoparietal opercula, and they do not

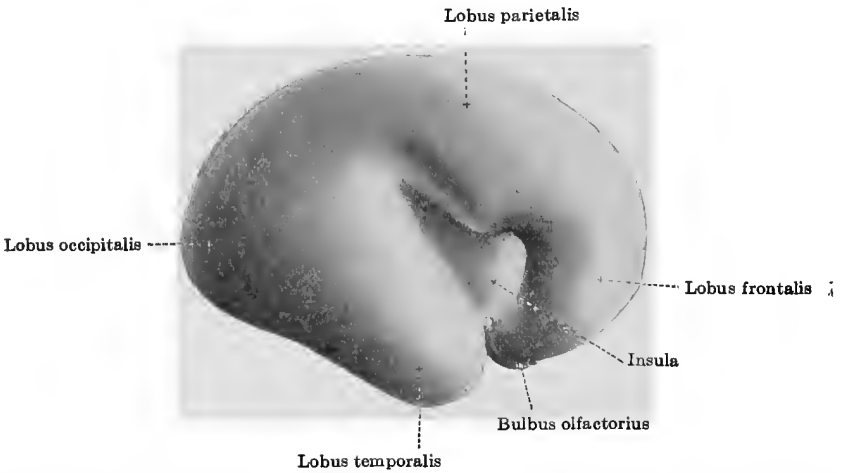


FIG. 77.—Lateral view of reconstruction of cerebral hemisphere of human fetus at the beginning of the fifth month (crown-rump length 150 mm., Mall collection). A portion of the tractus olfactorius lateralis can be seen at the lower border of the insula.

come into apposition with each other and the other two opercula, so as to close in the anterior part of the insula, until after birth. In Fig. 77 the advanced growth of the temporal, occipital, and parietal lobes, corresponding to their primitive functions, is very evident. The frontal lobe whose functional activity is the last to be required is correspondingly backward. In consequence the brain in fetuses between 50 and 150 mm. long, when seen from above or in front, as in Fig. 78, resembles in its outward appearance the smooth forward tapering brain seen in some of the lower mammals,—*e.g.*, rabbit. Variations in the degree of development of the frontal operculum determine the shape of the two anterior limbs of the Sylvian fissure between which it lies. When well developed, it separates the two Sylvian limbs from each other so that they assume a U shape; when less developed, it forms a V shape; or, if so poorly developed that the orbital and frontoparietal opercula meet so as to occlude the frontal operculum from the main limb of the fissure, then we have a Y shape. In some forms of arrested development the anterior portion of the fissure of Sylvius is defective and the insula remains partly exposed.

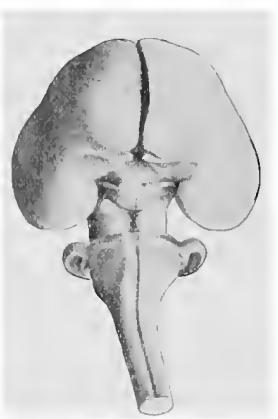


FIG. 78.—Anterior view of brain of a human fetus of about the same age as shown in Fig. 76. (After His.)

The hippocampal, rhinal, and Sylvian fissures develop along boundary lines of brain areas that differ markedly both in structure and in rate of development. The calcarine, parieto-occipital, and central fissures also represent boundary lines of areas that differ histologically, but the differences are not so marked as in the former cases, and the fissures appear somewhat later, during the fifth month. They are soon followed by the collateral, inferior and superior precentral, postcentral, superior temporal, superior and inferior frontal, parolfactory, interparietal, callosomarginal, and orbital fissures, all of which appear during the sixth or seventh month.[2] The character of these fissures at the end of the seventh month is shown in Figs. 79, 80, and 81. These fissures first appear as shallow furrows, and an individual fissure may first appear as

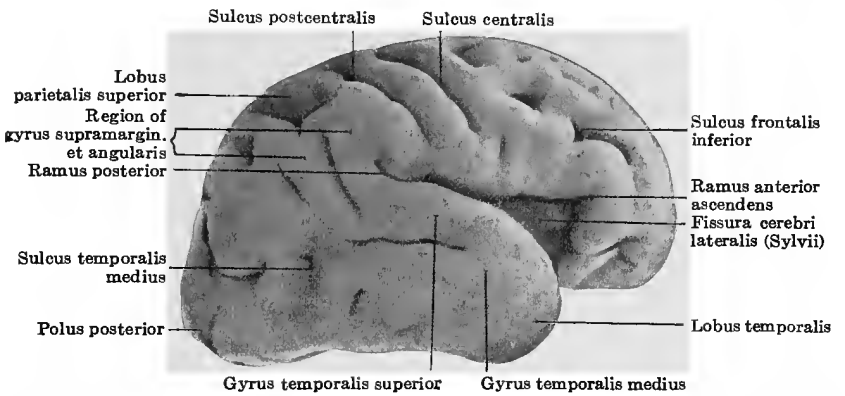


FIG. 79.—Lateral view of the cerebral hemisphere of a human fetus at the end of the seventh month, showing the formation of the early fissures. Compare with Figs. 76 and 77. (After Kollmann.)

several short furrows which as they deepen subsequently unite into a continuous furrow. The calcarine fissure, somewhat like the hippocampal fissure, involves the whole thickness of the brain wall and produces an elevation within the ventricle, the calcar avis. The parieto-occipital fissure apparently also causes at first

[2] A distinction is frequently made between sulci and fissures, based on the conditions found in the adult. The term sulcus is used for the more shallow grooves, and the term fissure for the deeper ones, those which in their development involve the whole thickness of the brain wall and influence the form of the ventricle. Thus we speak of the fissure of Sylvius, the longitudinal, the hippocampal, the collateral, the calcarine, and the parieto-occipital fissures; all other grooves are designated as sulci. From the embryological stand-point it might be better still further to restrict the term fissure and limit it to the fissure of Sylvius and the longitudinal fissure. We would then have the term sulcus as representing all those furrows which are formed as actual grooves in the brain wall, and the term fissure would be limited to the clefts that result secondarily from the unequal growth of major brain regions, and are not true indentations in the original surface of the brain wall.

an infolding of the brain wall. This, however, disappears with the thickening of the wall. It is possible that it is to be classed as an artefact together with the so-called transitory fissures. The transitory fissures consist of sharply marked furrows frequently found indenting all parts of the cortex during the third and fourth months. They are irregular in form and position and are only found at this time. It is to be remembered that at this period the human hemisphere consists of a large thin-walled vesicle whose walls have not yet developed a firm framework, and, even with good material and with great care in its treatment, it is difficult to prevent artificial foldings of the wall when the specimen is immersed in preserving fluids.

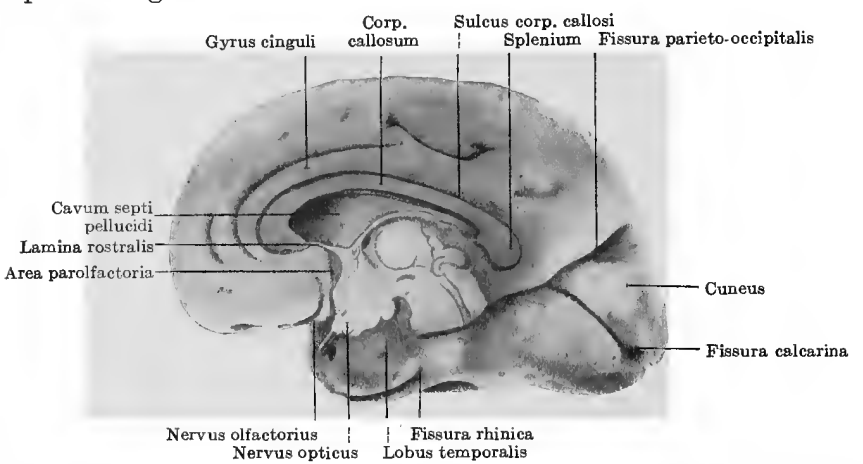


FIG. 80.—Median view of the cerebral hemisphere of a human fetus at the end of the seventh month, being the same specimen shown in Fig. 79. (After Kollmann.)

These primary fissures constitute boundaries of primary functional areas of the pallium. Subsequently association areas are developed around them, forming new cortical territories, and as these expand new furrows develop to accommodate the growing cortex. The secondary gyri thus formed may crowd the older ones into new forms or even partly replace them by burying them under, as we have seen the insula buried by the adjoining opercula.

DEVELOPMENT OF THE MYELIN SHEATHS.

The final phase in the development of the hemisphere wall consists in the process of myelinization of its nerve-fibres. This does not begin until about the time of birth and it continues from then until the end of puberty. For the details of this process the reader is referred to the studies of Flechsig, to whom we are indebted for almost the whole of our present knowledge of this subject. We will here only give a brief outline of the process.

The process begins in the projection fibres of the four primary sensorimotor fields: 1, the olfactory; 2, the visual; 3, the acoustic; and 4, the somatic. These possess both efferent and afferent elements. In the visual and acoustic mechanisms the efferent element is very small. In the somatic area both the efferent and afferent elements are largely represented, each occupying a definite portion of the total area, the afferent forming the postcentral area (somæsthetic) and the efferent the precentral area (motor). The afferent projection fibres are probably myelinated shortly before the efferent ones.

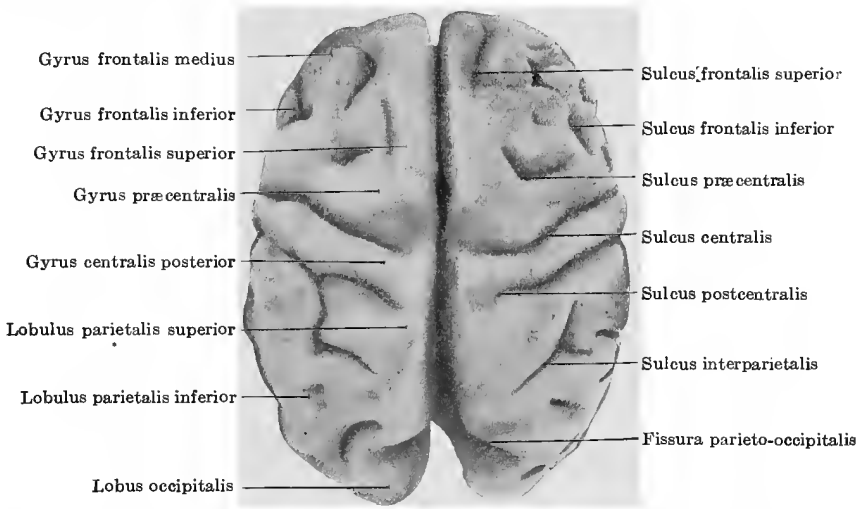


FIG. 81.—Dorsal view of the cerebral hemisphere of a human fetus at the end of the seventh month, being the same specimen shown in Figs. 79 and 80. (After Kollmann.)

The process next spreads to a series of intermediate areas whose projection fibres serve to connect the primary cortical areas with the thalamic and pontine nuclei. The terminal areas to become myelinated are those made up almost entirely of association neurones, whose axones cross in the corpus callosum to the opposite hemisphere or extend to distant or near parts of the same hemisphere.

In concluding this chapter, there is added a table, taken from His (1904), showing the order of development of the different fibre tracts of the central nervous system. The size and approximate age of the embryo or fetus is indicated, and in the columns the first recognizable appearance of a given tract is indicated by a check.

Table showing Order of Occurrence of Fibre Tracts of Brain. (After His.)

Size in mm. In the 1st and 2d month the neck-rump length is given, in the 3d month and later the crown-rump length	1st month.	2d month.											3d month.					4th month.			5th month.
	6.9	10.2	10.9	13.8	15.5	15.7	16	17	17.8	18.5	19	22	29	35	46	50	56	60	83	120	160
Fasc. spinalis N. trigemini	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fasc. solitarius	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fasc. longitud. medialis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fasc. mamillo-tegmentalis	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
N. olf. and striæ olf. med	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Commissura posterior	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fasc. retroflexus	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lemniscus medialis	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Decussating olive fibres	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Thalamic radiation	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stria med. of thalamus	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+	+	+
N. opticus, chiasma	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+	+	+
Fasc. restiformis	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+
Capsula interna	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+	+	+	+	+
Median portion of commiss. ant	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+	+	+	+
Columna fornicis	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+
Corpus fornicis	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+
Corpus callosum	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+	+
Fibræ pontis	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+
Pyramidal tracts	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+	+

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III. PERIPHERAL NERVOUS SYSTEM.

SPINAL NERVES.

The ventral roots of the spinal nerves are derived from the mantle layer of the neural tube, as has been previously referred to. Processes from the neuroblasts situated in the mantle layer are assembled into rootlets which emerge in a continuous longitudinal series along the ventrolateral border of the tube. Outside of the tube these rootlets are grouped into segmental bundles, and after being joined by the fibres of the dorsal roots they constitute complete segmental nerves. The direction taken by the ventral root fibres on emerging from the tube varies according to the size and position of the ganglion crest. In the human embryo it is almost

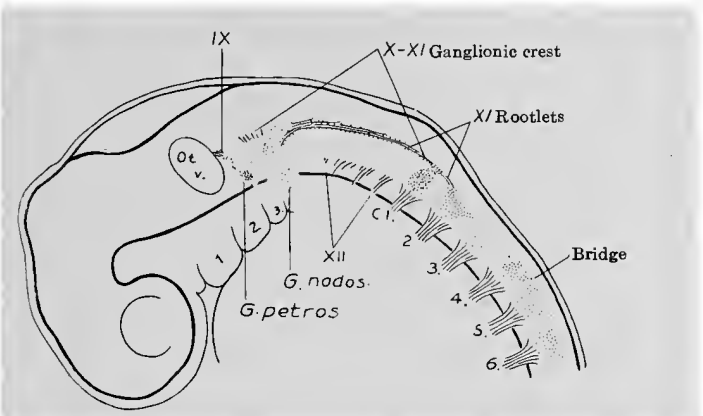

FIG. 82.—Reconstruction of a portion of the peripheral nerves of a human embryo 4 mm. long (Hertwig collection, No. 137). Enlarged 22 : 1. *Ot. v.*, ear vesicle.

directly lateral. In some sections of the 5.5 mm. pig in the author's possession the ventral roots extend dorsalward through the mesenchyma at an angle of 30° to reach the ventral border of the ganglion mass.

The dorsal roots are derived entirely from the ganglion crest. This structure can be seen in the 4 mm. embryo, Fig. 82, as a flattened cellular band which extends caudalward from the auditory vesicle along the lateral border of the neural tube to its extreme tip. As will be referred to later, the ganglion crest of the hindbrain is similar to and by some described as continuous with that of the spinal cord (p. 139). That part of the crest which corresponds to the spinal cord is characterized at this time by segmental incisures along its ventral border. The dorsal border of the crest remains intact until the appearance of the dorsal rootlets, in the meantime constituting a cellular bridge connecting the more ventral ganglionic clumps. In embryos at the end of the fourth

week (Fig. 83) fibrous processes can be seen cropping out from the dorsal border of the crest and attaching themselves to the spinal cord. They appear first in the cervical region and somewhat later can be seen in the more caudal part of the crest. These are the primitive dorsal rootlets. They enter the marginal zone of the tube and eventually form a longitudinal bundle corresponding to the dorsal funiculus of the adult cord. Peripherally they

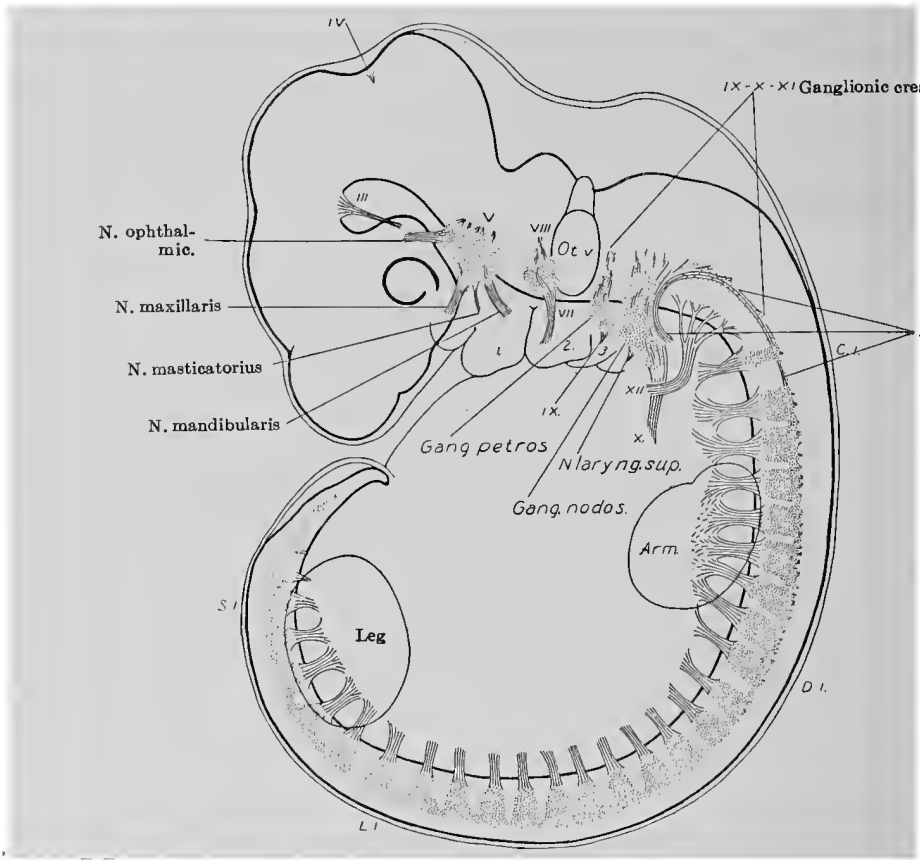

Fig. 83.—Reconstruction of the peripheral nerves of a human embryo 6.9 mm. long (His collection, Br. 3). Enlarged 16.7 : 1.

can be traced back to cell clusters in the crest, the processes from several cells uniting in a common fibrous strand. With the formation of these rootlets there is a gradual disappearance of the dorsal bridge, and there is thereby produced a complete segmentation of the ganglion crest. The ventral end of the ganglia extend forward and end diffusely among the fibres of the ventral roots. The cells are in a state of active differentiation, and the developing fibrous processes can be seen joining the more precocious ventral roots.

In embryos 9 to 10 mm. long (Fig. 84) the differentiation of the ganglion-cells and their fibrous processes has advanced to a point where the chief parts of a typical spinal nerve may be recognized. There is the dorsal root and its sharply outlined ganglion and a well-defined ventral root joins it, the two together forming the nerve-trunk. At the same time that the dorsal and ventral roots unite to form the main trunk, they both give off lateral fibres which form the dorsal branch, the so-called posterior primary division, which breaks up among the cells that are to form the long muscles of the back, supplying these and extending through to reach the integument. The remainder of the nerve-trunk is continued forward as the ventral branch, or anterior primary division. From its median side there is given off the ramus

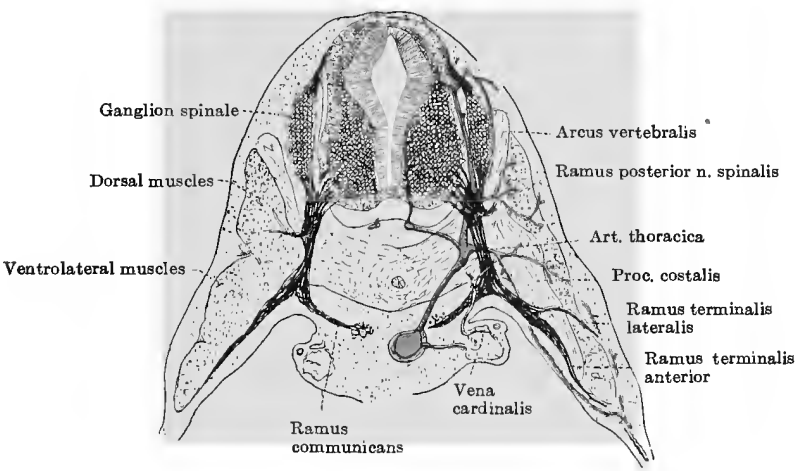

FIG. 84.—Diagrammatic transverse section through a thoracic segment of a 9 mm. human embryo. Enlarged 25 : 1. (After Bardeen and Lewis, 1901.)

communicans, which extends toward the aorta and ends in the sympathetic ganglion cord. The main trunk terminates in two branches, the anterior and lateral terminal branches, from which arise the anterior and lateral cutaneous branches of the adult, and which in the thoracic and abdominal regions give off branches to the musculature of the front and lateral body wall. The relation of these branches to the individual muscles is shown at a later stage in Fig. 85. In the same figure can be seen the loop-formation in the intercostal space that occurs before the bifurcation of the trunk into the lateral and anterior terminal branches is completed.

Throughout the spinal region there is a tendency for the adjacent nerve-trunks to unite at the place where the lateral terminal branches arise, and there is formed thereby a series of intersegmental loops. This loop- or plexus-formation may involve either

the lateral or the anterior terminal branches, or both. Its degree of development depends upon the complexity of the parts supplied.

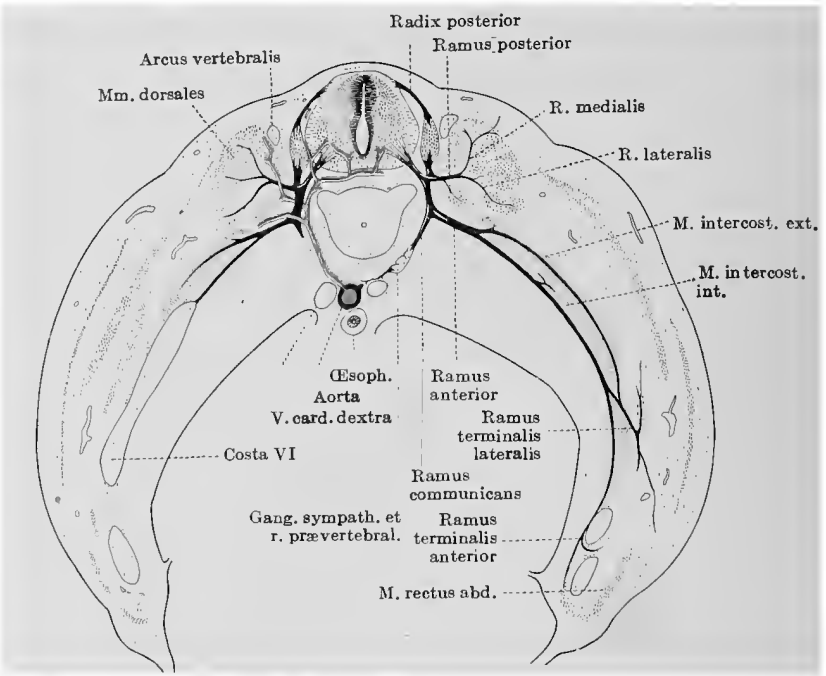

FIG. 85.—Diagrammatic transverse section through a thoracic segment of a 17 mm. human embryo (Huber collection, No. 14), showing a typical thoracic nerve. Enlarged 15 : 1.

In three regions it is particularly marked, and there are thus produced the cervical, brachial, and lumbosacral plexuses.

Cervical Plexus.

In the cervical region the anterior and lateral terminal branches form two separate plexuses; the former produces the deep cervical plexus, and the latter the superficial cervical plexus. The superficial cervical plexus consists of the union of the lateral terminal branches into loops, from which are given off the cutaneous branches to the auricular, cervical, and occipital regions. The deep plexus results in the formation of the *ansa hypoglossi* and the *phrenic nerve*. The former is produced by the fusion of the second and third cervical nerves into the descendens cervicis, which unites in a loop with the hypoglossal, together with which the first cervical has been incorporated above. From this loop are given off the short branches which end among the cells that are to form the hyoid musculature.

The phrenic nerve is formed by anterior terminal branches principally from the fourth and fifth cervical nerves. A contribution on the part of the sixth and third nerves may occur. This

nerve can be seen through the transparent arm in Fig. 86. Owing to the position of the diaphragm at this time the course of the nerve is almost directly ventral. Later, as pointed out by His and Mall (Mall, 1901), the points of origin and insertion of the nerve

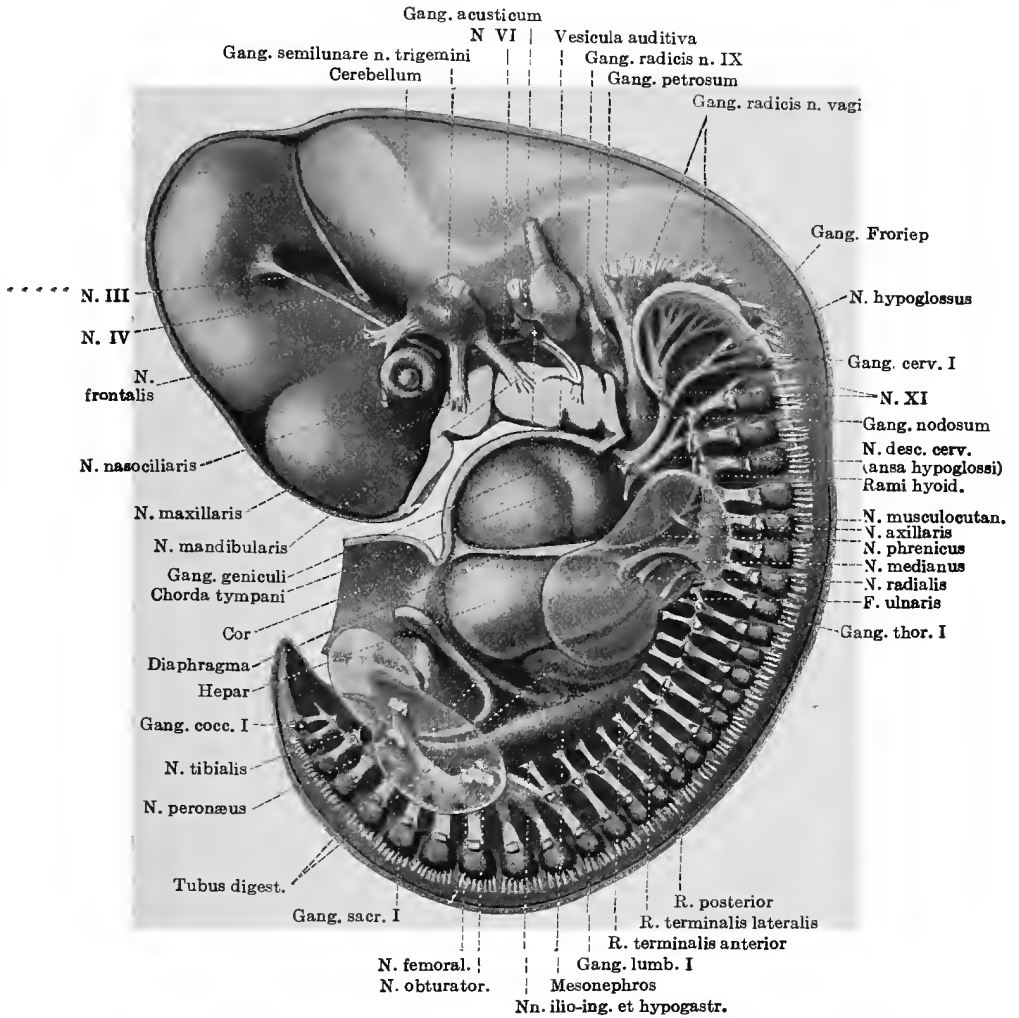

FIG. 86.—Reconstruction of the peripheral nervous system of a human embryo 10 mm. long (Huber collection, No. 3). The arm and leg are represented as transparent masses, into the substance of which the branches of the brachial and lumbosacral plexuses may be followed. Enlarged 12 : 1.

draw gradually apart, due on the one hand to the descent of the diaphragm and the lengthening of the thoracic cavity, and on the other hand to the subsequent elevation of the cervical nerves which accompanies the development of the structures of the neck. It is thus that there results the long caudal course of this nerve that is characteristic of the adult.

Nerves of the Arm and Leg.

In the arm and leg we meet with special conditions which will be better understood if we first refer to two essential factors that were established by the recent experimental work on amphibian larvæ by Harrison (1907). In the first place, he has shown that the nerves which take part in the innervation of a limb are determined by the position and width of the limb bud. A limb bud transplanted to some other part of the body acquires a complete system of nerves, supplied by the region in which the limb is implanted. In the second place, the distribution of the nerves within a limb is determined by its own component structures. The segregation of the developing structures within the limb has a directive action upon the growing nerve-fibres, and determines their grouping into definite characteristic bundles. Even foreign nerves entering a transplanted limb bud are likewise controlled so that they form intrinsic nerves to the limb and assume normal terminal ramifications. These two factors are to be kept in mind in interpreting the normal embryology of these nerves. Our knowledge concerning the details in the development of the nerves of the arm in the human embryo is based principally upon the work of Lewis (W. H., 1902) and of the leg on the work of Bardeen (1907). Large use has been made of their papers in the following description.

When the limb buds first form they consist, to all appearances, of homogeneous mesenchyma and contain no nerves. Very soon, however, opposite the base of each limb bud, presumably stimulated by its presence, the anterior primary divisions of the spinal nerves undergo an exuberant growth and form a solid sheet or plexus of fibres extending toward the base of the limb. In embryos a few days older, coincident with the condensation of the skeletal core, branches from this nerve-plexus can be seen advancing into the limb bud and entering the areas of premuscle tissue that in the mean time have formed a sheath around the skeletal core. The premuscle sheath is not evenly distributed, but from the very start is arranged in the form of muscle groups, and it is between these groups through the intermuscular spaces that the nerves make their way. As the differentiation of the limb continues the nerve trunks extend distalward in the limb and give off muscle branches which enter the muscle groups and supply the individual muscle anlages. The site of nerve entry into a muscle is constant. It is situated near the centre of the anlage on the side toward the main trunk. This point is the seat of the earliest differentiation of the muscle, and according to the Nussbaum law muscle growth extends from here in the direction of the intramuscular nerve branching. Though nerve-fibres and muscle groups seem to make their appear-

ance simultaneously, and even at times the nerves seem to precede the muscles, yet it must be remembered that the experimental evidence clearly shows that the situation and branching of the nerves are entirely dependent on the structural segregation of the developing muscles and skeleton, and this is why the main nerve-trunks are developed in paths situated in the intermuscular areas, and likewise why the larger nerve branches are in the intramuscular septa of individual muscles. As we do not have a metameric distribution of the muscles of a limb, we consequently do not have a true metameric distribution of the nerves.

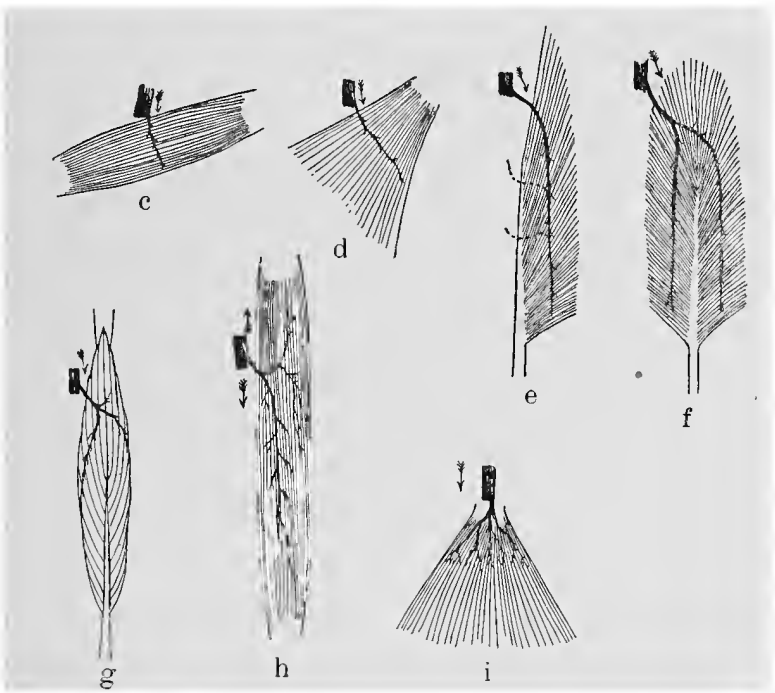

FIG. 87.—Diagram illustrating the influence of the direction of the fibre bundles in different muscle types upon the character of their nerve supply. (After Bardeen, 1907.)

Within the muscle the course of the chief branches is determined by the direction of the fibre bundles, whether they run parallel or are transverse to the main trunk from which the nerve arises. When the fibre bundles of a muscle are transverse to the main nerve-trunk, its nerve and chief branches pass across the fibre bundles midway between the points of attachment, giving off branches on each side which go to form the intramuscular nerve-plexus. When the fibre bundles of a muscle run parallel with the main nerve-trunk, the branches to this muscle, as a rule, enter the proximal third of the muscle belly and extend distally parallel with the muscular fibres, giving off at the same time the branches to the intramuscular plexus. This relation between the

direction of the muscle-fibres and the course of the supplying nerve is shown for different muscle types in Fig. 87. A further influence on the course of nerves is exerted by the migration of the muscles which they supply. The muscle masses, having received their nerves at an early stage, may by subsequent migration draw the nerves a long way out of their original course. This is illustrated by the latissimus dorsi, the trapezius, the diaphragm, and the muscles of the tongue.

The arm bud develops somewhat in advance of the leg bud. In the 4.5 mm. embryo there is a well-defined arm bud, consisting of an apparently homogeneous mesenchyma and having as yet no nerves. A leg bud in a similar stage of development is not met with until we come to embryos about 7 mm. long. The base of the arm bud is usually situated opposite the lower four cervical and first thoracic vertebræ, and the leg bud opposite the five lumbar and first sacral. There is some variation in the position of the limb buds relative to the spinal axis at the time of entrance of the spinal nerves. Consequently there may be a variation of as much as three segments in the origin of the spinal nerves which eventually enter a particular limb, the more cephalic nerves supplying the limb when the limb bud has a more cephalic position and *vice versa*.

In the 9 mm. embryo the central mesenchyma of the leg bud is condensed into sclerogenous tissue corresponding to the hip-bone and proximal part of the femur. This sclerogenous tissue divides the bundles of nerve-fibres streaming into the leg into the main nerve-trunks. The lumbosacral plexus in an embryo of about this age is shown in Fig. 86. The nerves forming it unite into a flattened mass or sheet of fibres which enters into the base of the leg bud, the division into anterior and lateral terminal branches being lost in the formation of the plexus. The further course of the fibres is determined by the framework of the leg. Owing to the cell masses of the bony pelvis and the femur the fibres become grouped into four bundles arranged in two pairs, each consisting of a median and lateral trunk. Of the upper pair the median trunk corresponds to the n. obturator, and the lateral to the n. femoralis. The lower pair represent the n. sciaticus, the median bundle constituting the future n. tibialis, and the lateral the n. peronæus communis. In the 11 mm. embryo, as shown in Fig. 88, the leg is differentiated externally into foot-plate, crus, and thigh, and internally, surrounding the skeletal core, a distinct myogenous zone can be recognized, consisting of muscle groups with intervening intermuscular spaces. The main nerve-trunks have grown well down into the limb between the muscle groups, and the chief muscular and cutaneous branches can be seen. In Fig. 89 is represented a median view of the leg and the adjoining part of the

trunk of an embryo 20 mm. long, showing the relations of the thoracic, lumbar, and sacral nerves to the abdominal musculature and the skeleton of the leg. Both muscular and sensory branches are shown, and it will be seen that the nerve supply of the leg at this time must be considered as essentially complete.

The nerves of the arm in a 9 mm. embryo are shown in Fig. 90. The brachial plexus consists of a continuous sheet of fibres which on reaching the developing humerus is split into a dorsal

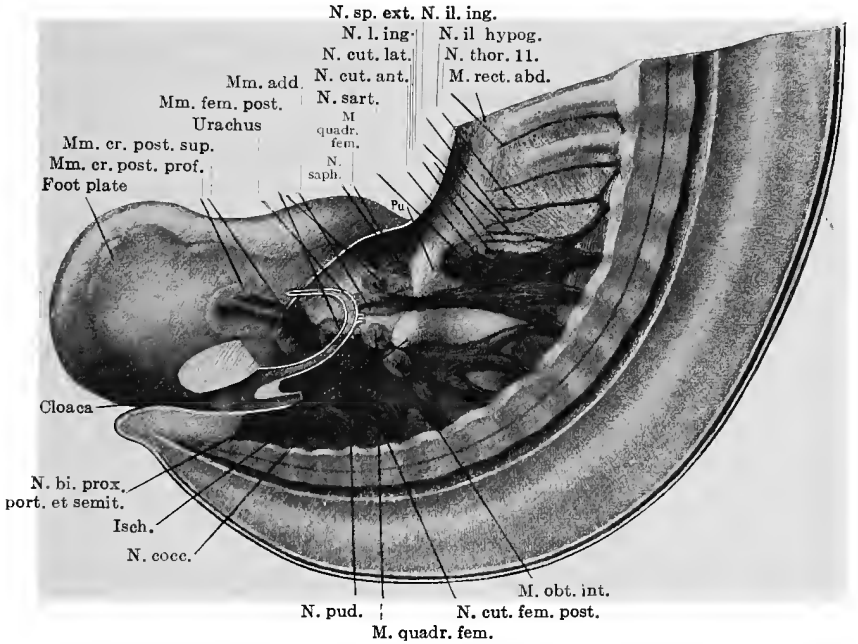

FIG. 88.—Nerves of the leg in an embryo 11 mm. long, age about five weeks. Enlarged 17 : 1. The principal muscle anlages are shown in lighter color. *Isch.*, os ischii; *Mm. add.*, musculi adductores; *Mm. cr. post. sup.*, musculi cruris post. superficiales; *Mm. cr. post. prof.*, musculi cruris post. profundi; *Mm. fem. post.*, musculi femorales posteriores; *M. obt. int.*, musc. obturator int.; *M. quadr. fem.*, musc. quadratus femoris; *M. rect. abd.*, musc. rectus abdominis; *N. bi. prox. port. et semit.*, n. proximalis portionis musc. bicipitis et musc. semitendinosi; *N. cocc.*, n. coccygeus; *N. cut. ant.*, n. cutaneus femoris anterior; *N. cut. fem. post.*, n. cutaneus femoris posterior; *N. cut. lat.*, n. cutaneus femoris lateralis; *N. il. hyp.*, n. iliohypogastricus; *N. il. ing.*, n. ilio-inguinalis; *N. l. ing.*, n. lumbo-inguinalis; *N. pud.*, n. pudendus; *N. saph.*, n. saphenus; *N. sart.*, n. musc. sartorii; *N. sp. ext.*, n. spermaticus ext.; *N. thor.* 11, n. thoracalis 11; *Pu.*, os pubis. (After Bardeen, 1907.)

and ventral division, the former corresponding to the posterior cord and the latter to the outer and inner cords. These cords are immediately broken up into the large branches which pass down in the intermuscular spaces, where the fibres abruptly fray out to enter the premuscle masses. The formation and branches of the brachial plexus, as seen in the 10 mm. embryo, are shown in Fig. 86. The brachial plexus is split by the skeletal anlage into two laminæ from which the various nerves arise. From the anterior or ventral lamina arise the n. musculocutaneus, n. medianus, and n. ulnaris, and from the posterior or dorsal lamina the n. axillaris

and n. radialis. As compared with the lumbosacral plexus in the same embryo it is considerably in advance. It is not until

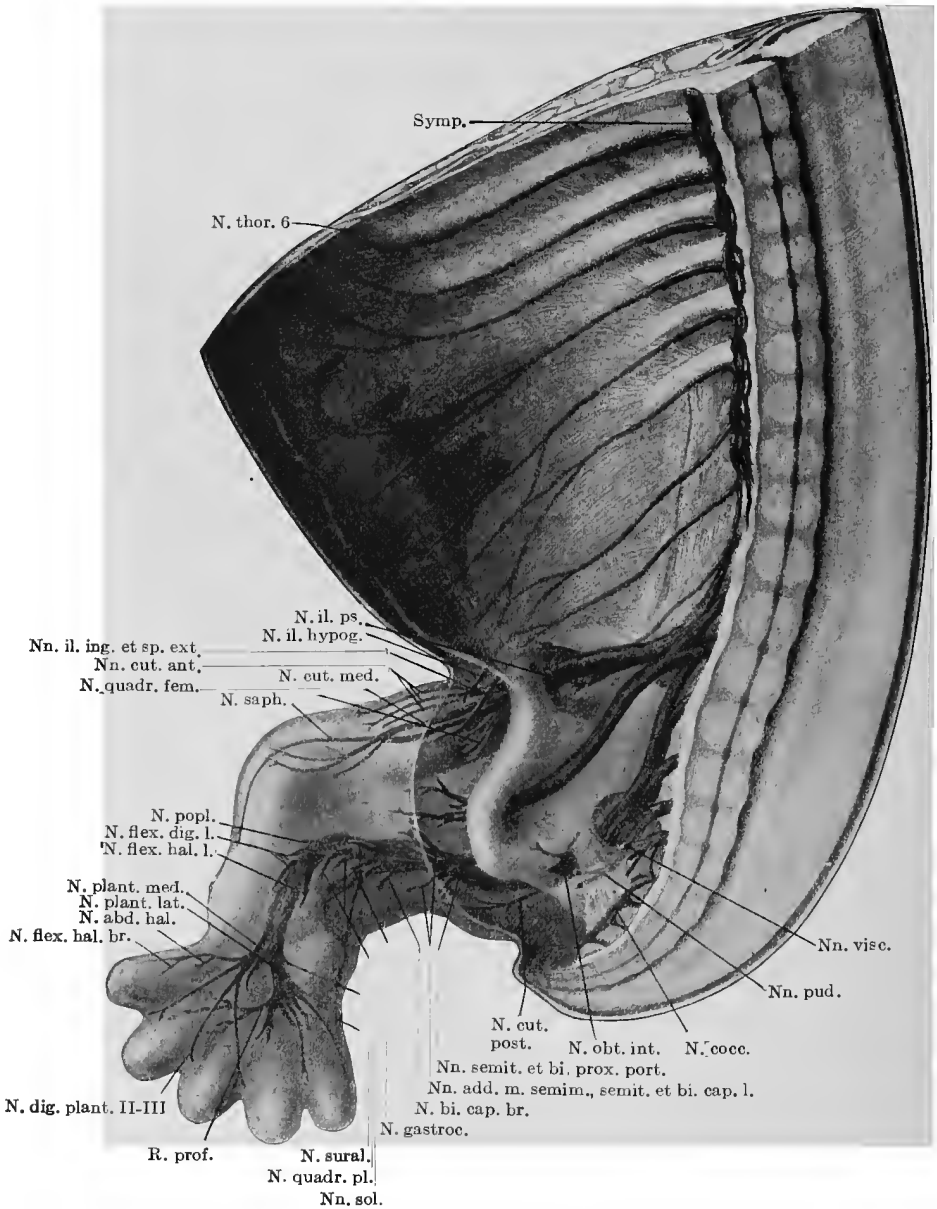

FIG. 89.—Nerves of the leg and adjacent abdominal wall in an embryo 20 mm. long, age about seven weeks. Enlarged 10 : 1. (After Bardeen, 1907.) For the abbreviations see Fig. 88.

later (20 mm.), secondary to the caudal migration of the arm, that we meet with a decided posterior inclination of the brachial plexus; but, aside from this and aside from the proportionate large size

of the nerves as compared with other structures, there is little in their gross morphology to distinguish the nerves of the arm at the

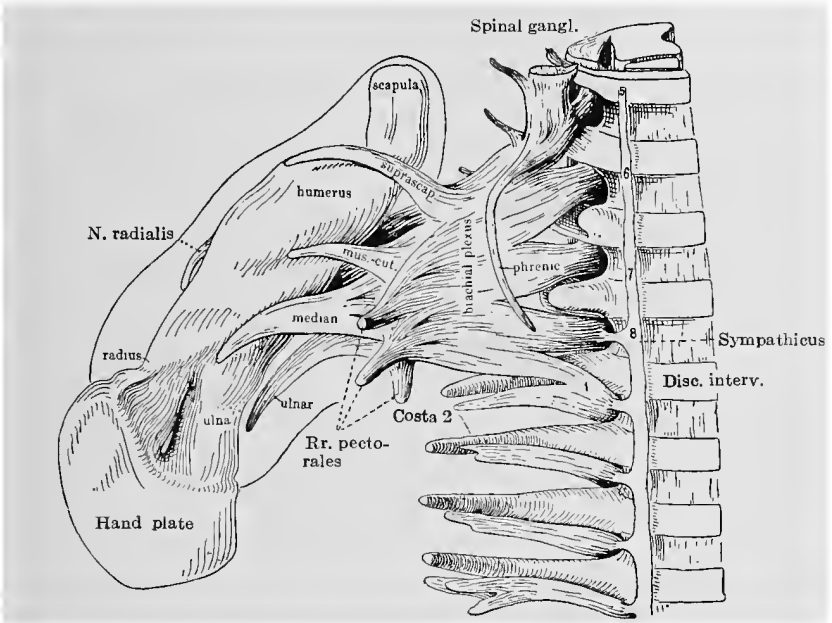

FIG. 90.—Reconstruction of the nerves and skeleton of the arm in a human embryo 9 mm. long. (After W. H. Lewis, 1902.)

end of the first fetal month from those of the adult. In the following table is given the origin of the fibres of the larger nerves of the arm as traced by Lewis (1902) in an embryo of this age:

	Cervical.	Thoracic.
N. suprascapularis	V, (VI)	
N. subscapularis	V, VI, VII	
N. thoracalis longus	VII, VIII	I.
Nn. thoracales anteriores	V, VI, VII, VIII	I.
N. musculocutaneus	V, VI, (VII)	
N. medianus	V, VI, VII, VIII	I.
N. axillaris	V, VI, VII	
N. radialis	V, VI, VII, VIII	I.
N. ulnaris	(VI), VII, VIII	I.

According to Bardeen (1907) the cutaneous nerves first approach the superficial fascia along the line corresponding to the primary margin of the limb bud, and from these areas send branches of distribution over the dorsal and ventral surfaces of the developing limb, as shown in Fig. 91. There exists a considerable variation in the extent of distribution of these branches to the skin. The extensive development of one nerve tends to retard the growth of the neighboring nerves, and diminished development

stimulates them to more active growth. A further source of variation, which is equally true of motor nerves, is that any two nerves that arise in succession—such as the twelfth thoracic and hypogastric, the hypogastric and inguinal, or the lateral cutaneous

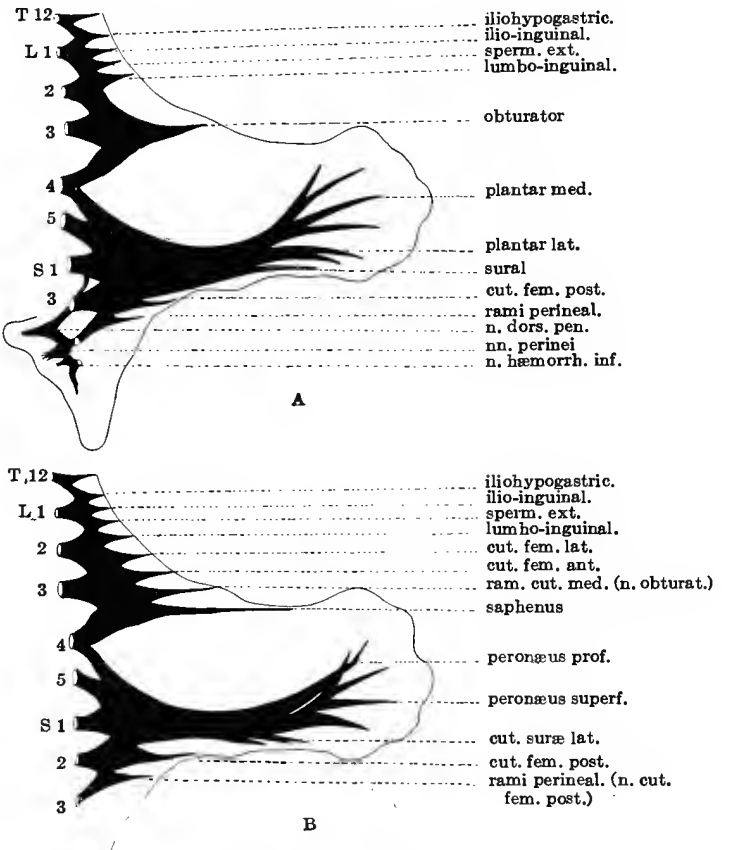

FIG. 91.—Diagram of the cutaneous nerves of the lumbosacral plexus, showing the superficial areas along the margin of the limb bud which are first reached by the tips of the growing nerves. Extending from these foci branches spread eventually over the dorsal and ventral surfaces of the limb. A, ventral group; B, dorsal group. (After Bardeen, 1907.)

and femoral—may be combined into a single trunk for a greater or lesser part of their course. On the other hand, two or more nerve-trunks may carry fibres ordinarily assembled in a single trunk, such as extra iliac and genital branches or an accessory obturator.

CEREBRAL NERVES.

For purposes of description the nerves of the head will be grouped according to their function, following as far as possible the functional systems of Gaskell; *i.e.*, the activities of the organism are separated into somatic and visceral, in each of which there

is the double activity on the part of the nervous system, motor and sensory, making in all four primary functional divisions. Some of the cranial nerves consist of elements belonging exclusively to one functional division,—for example, the n. abducens, which consists entirely of somatic motor fibres,—while others are complex nerves containing elements of more than one system, such as the n. vagus, which contains elements from three functional divisions, somatic sensory, visceral sensory, and visceral motor. The nerves will therefore be grouped according to the predominance of their functional elements as follows:

Somatic sensory.	Somatic motor.	Visceral (motor and sensory).
Olfactory	Oculomotor	Trigeminal
Optic	Trochlear	Facial
Acoustic	Abducens	Glossopharyngeal
	Hypoglossal	Vagus and accessory

In general the basal plate of the neural tube is motor and the lateral or alar plate is sensory; thus, the somatic motor group arises entirely from the basal plate, while the visceral group is connected in larger part (sensory) with the alar plate and in lesser part (motor) with the basal plate. The nerves included under the somatic sensory group are all specialized nerves and have individual processes or lobes of the nervous system devoted to them,—*i.e.*, the olfactory bulb, the eye bulb and stalk, and the tuberculum acusticum.

Nerves of Special Sense Organs. (Special Somatic Sensory.)

These nerves belong to the group of afferent nerves which connect the integument with the central nervous system, and the union of nerve and integument has resulted in the formation of special sense organs,—that is, the olfactory organ, the eye, the ear, and the lateral line system, composed partly of nerve elements and partly of integument. This nerve group is shown in Fig. 92, which represents schematically a typical vertebrate head in which the integumental part of the special sense organs is shown in red. The nose, eye, and ear are the same as seen in man. The lateral line system, however, is absent in man except for a temporary trace which may be seen in 7 mm. embryos in the form of areas of thickened epidermis situated over the second, third, and fourth branchial arches, probably representing the lateral line ganglia incorporated with the seventh, ninth, and tenth cranial nerves of lower vertebrates. By comparing the nerve portions of these organs in Fig. 92 it can be seen that the olfactory nerves, the retinal ganglion-cells, and the acoustic nerve, though differing so widely in their adult morphology, must all be considered as analogous structures.

The *nn. olfactorii* and the *n. opticus* will be described with the special sense organs to which they belong.

The *n. acusticus* develops from a small group of ganglion-cells which can be recognized by the end of the third week, lying closely against the cephalic border of the ear vesicle. Nerve-fibres arise from the proximal pole of the mass connecting it with that part of the neural tube which is to form the tuberculum acusticum, and from the distal pole connecting it with the auditory vesicle. Concerning the origin of these ganglion-cells there still remains some uncertainty. They are evidently not derived from the neural crest; but whether they migrate out from the brain wall or the walls of the developing ear vesicle, or are derived from the ectoderm immediately adjacent to the auditory pit, remains to be determined.

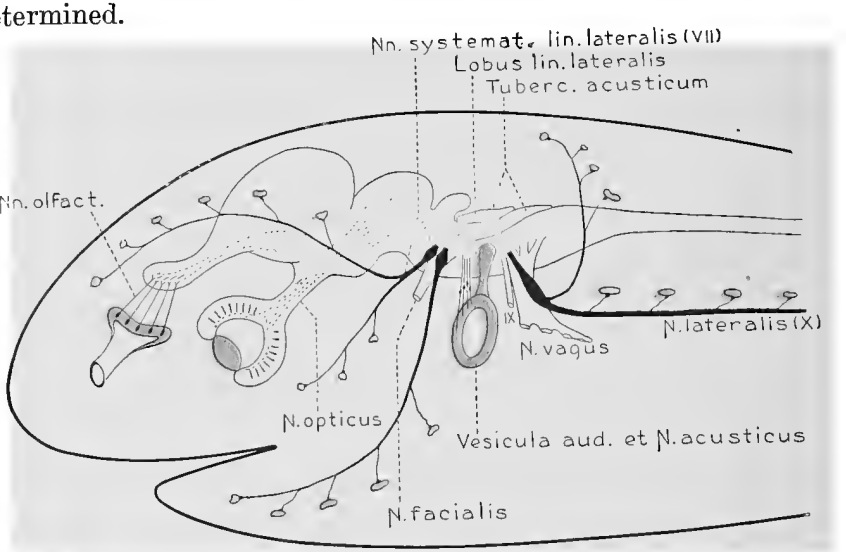

FIG. 92.—Diagrammatic vertebrate head showing the special sense organs that are formed by the union of nerve and integument, the integumental portion being shown in red.

The successive stages in the development of the acoustic ganglion mass and its branches are represented in Fig. 93, which shows its appearance in embryos 4, 7, 9, 20, and 30 mm. long. This should be compared also with Fig. 86. The first step consists in the elongation of the ganglion and partial subdivision into a pars superior and pars inferior, each of which develops its own separate group of peripheral nerve branches. The pars superior forms the ganglion of the nerves to the utricle and the ampullæ of the superior and lateral semicircular canals. The pars inferior forms the ganglion of the nerves to the saccule and the ampulla of the posterior canal. In addition there is derived from the pars inferior a cell mass that becomes differentiated into the ganglion spirale. This makes its appearance in embryos about 9 mm. long, where it can be seen that some of the ganglion-cells on the ventral border of the pars inferior have become massed together

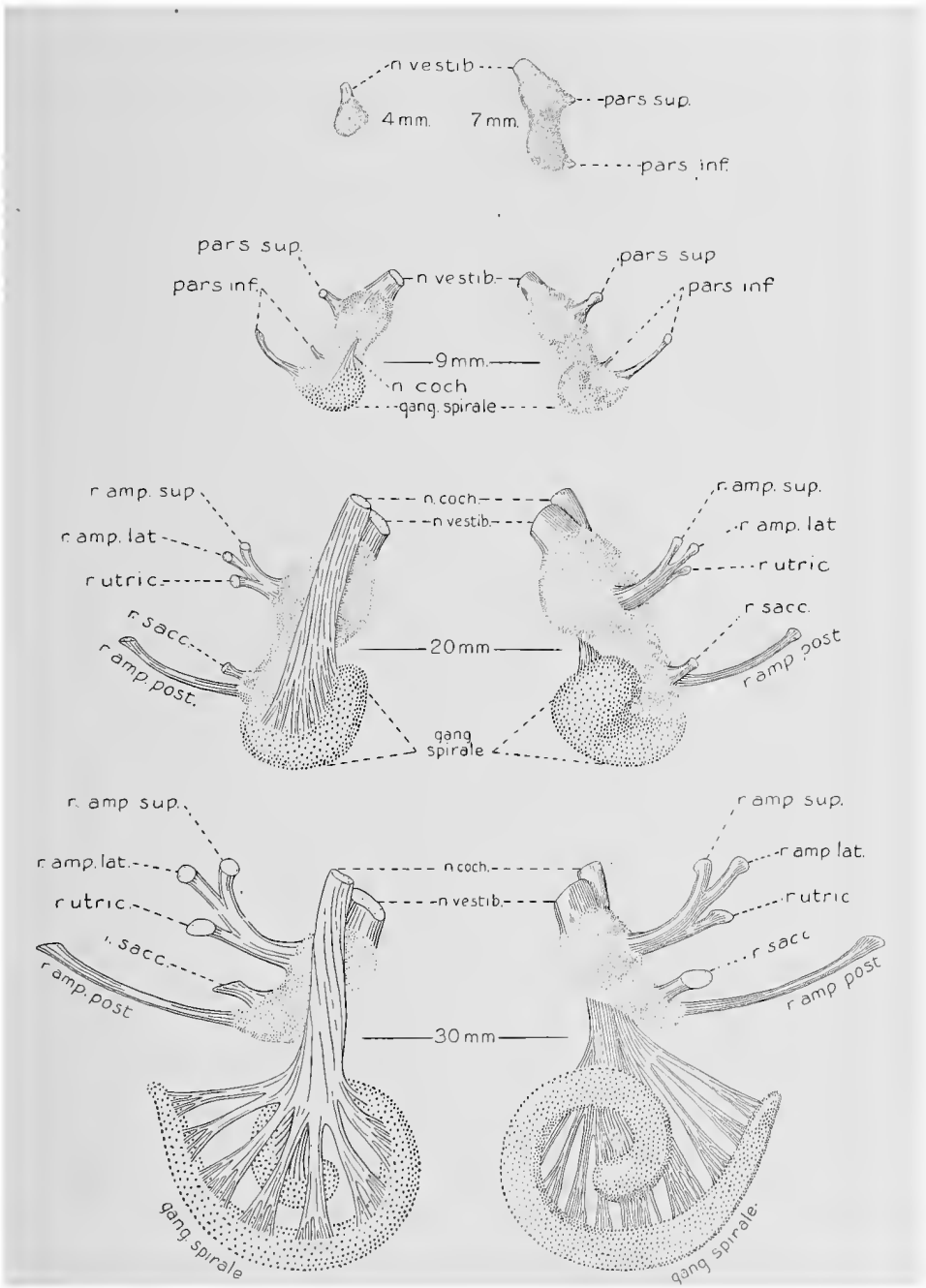

FIG. 93.—Development of the left ganglion acusticum and its nerve branches. The vestibular portion is shown by fine dots and the cochlear (ganglion spirale) by large dots. In the 9, 20 and 30 mm. stages a median view is shown on the left and a lateral view on the right.

to form the anlage of this ganglion; in other words, the ganglion acusticum at this stage consists of an upper division entirely vestibular and a lower division partly vestibular and partly cochlear. The vestibular part of the pars inferior constitutes the so-called *Zwischenganglion* of His, jun.

As the differentiation proceeds and the fibres elongate, the group of cells forming the ganglion spirale becomes separated from the parent ganglion mass, and eventually assumes the spiral form of the adult. The pars superior and pars inferior usually become completely separated, accompanying the subdivision of the vestibular nerve. The embryonic connection between the two may, however, persist. Likewise the path of separation between the pars inferior and the ganglion spirale may be more or less completely bridged over in the adult by a persistent connecting chain of ganglion-cells.

It will be seen that the n. cochlearis is made up entirely of fibres derived from the ganglion spirale, while the n. vestibularis consists of two portions derived respectively from the pars superior and pars inferior of the ganglion vestibulare. Owing to the contiguity of the pars inferior and the n. cochlearis, they become closely united by the developing mesenchymal elements, and this gives rise to the misleading appearance in the adult of the saccule and posterior ampulla being supplied by the cochlear nerve. The vestibular and cochlear divisions of the acoustic complex present the following contrasting characteristics: The ganglia belonging to the vestibular division develop midway along the trunk of the nerve; the ganglion of the cochlear division is situated at the extreme distal end of the nerve and lies closely against the cochlear duct, being later incorporated with it in the cartilaginous capsule, and hence the cochlear terminal branches are short and form a continuous fringe of fibres, while the vestibular terminal branches form discrete nerves of some length; the main trunk of the cochlear division is characterized by the compactness of its fibres and their spiral arrangement, which is already apparent in the 30 mm. embryo, while the fibres of the vestibular division are less compactly bundled and do not have a spiral character. In these particulars the vestibular nerve is the more primitive of the two, and the cochlear nerve must be considered as a portion of the former that has undergone special development.

Somatic Motor Group.

This group consists of the hypoglossal and the three nerves to the extrinsic eye muscles (nn. oculomotorius, trochlearis, and abducens), and in common they all arise from the basal plate and maintain their position near the median line directly beneath the

floor of the ventricle. Their nuclei of origin are considered as a cephalic continuation of the ventral motor column of the spinal cord. The series is shown in red in Fig. 100.

The *n. hypoglossus,* as it appears in the 4 mm. embryo, is shown in Fig. 82. Its rootlets arise from the basal plate of the neural tube in three or four segmental groups in a longitudinal series directly continuous with the ventral roots of the cervical nerves. During the fourth week they grow forward and fuse in a common trunk, which by the end of the first month has made its way around the lateral border of the ganglion nodosum, and there breaks up in its terminal branches in the anlage of the tongue. It is now generally considered that the hypoglossal is a composite nerve made up of the ventral roots of three or four segmental spinal nerves which in the course of phylogenesis have become inclosed by the bony cranium (occipitospinal nerves). This view is supported by the identity in appearance that exists in the earliest stages (Fig. 82) between the hypoglossal rootlets and the ventral roots of the spinal nerves. Furthermore the nucleus of origin of the hypoglossal forms a continuous column with the ventral horn of the spinal cord, as seen in Fig. 100. The fact that there are no dorsal roots and ganglia as in the other spinal nerves is explained on the ground of retrogression of the sensory part of these nerves, involving especially their more cephalic rootlets. Occasionally in the embryo a ganglion, and at times also a dorsal root, is found in connection with the more caudal rootlets of the nerve (Froriep's ganglion), as in Fig. 94. In other cases, where the sensory retrogression is more extreme, there not only is no ganglion of the hypoglossal, but the ganglion of the first cervical is also partially or wholly absent.

In the course of its development the hypoglossal unites with the cervical nerves in the formation of the *ansa hypoglossi.* The steps in the formation of this plexus may be seen in Figs. 82, 83, and 94. The fibres of the hypoglossal and the upper three cervical nerves start out perpendicularly from the neural tube, and due to the curve of the latter they are brought together at a common focus, like spokes in a wheel, and enter together the muscle mass, Froriep's Schulterzungenstrang, that is to form the tongue and hyoid muscles. With the formation of nerve sheaths, adjoining fibres become bound together, so that, as the individual muscles take form and draw apart, the nerves are separated out in the plexus that is characteristic of the nerves supplying these muscles in the adult. As seen in Fig. 86, the essential features of the ansa hypoglossi are completed in the 10 mm. embryo. The first cervical unites with the trunk of the hypoglossal, and lower down leaves it as the descendens hypoglossi, carrying along a varying number of hypoglossal fibres. The descendens hypoglossi unites

with the descendens cervicis, a fused branch from the second and third cervical nerves, and thereby forms a loop, the ansa hypoglossi, from which are given off branches to the hyoid musculature.

The *n. oculomotorius* arises from a group of neuroblasts situated in the ventral part of the mantle layer of the mesencephalon. These neuroblasts converge to form small rootlets, which emerge on the ventral surface of the neural tube in the

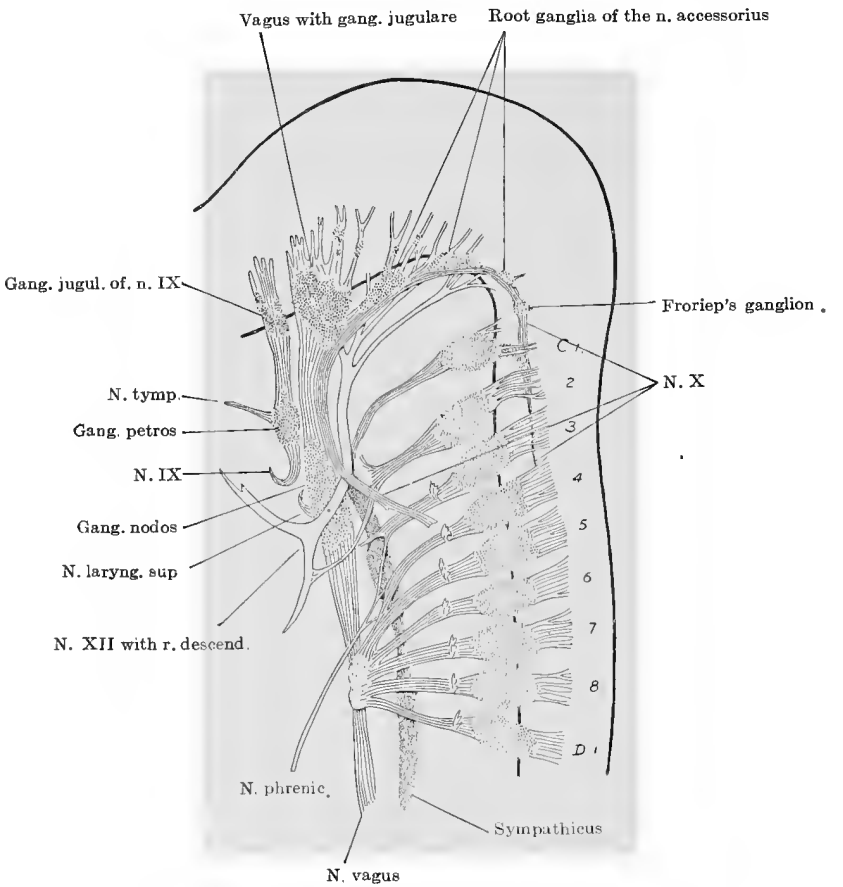

FIG. 94.—Reconstruction of the peripheral nerves on the left side of a human embryo 14 mm. long (Mall collection, No. 144). Enlarged 16.7 : 1.

concavity of the cephalic flexure. Here they unite, as shown in Figs. 10, 83, and 86, in a common trunk, which passes ventralward to the region median to the first and second divisions of the trigeminal nerve, where it breaks up in the cellular mass that is to form the eye muscles. It eventually supplies a root to the ciliary ganglion. There is no sensory ganglion in connection with the oculomotor in the human embryo. In the chick and torpedo, however, large bipolar cells have been described as migrating along

its trunk to take part in the formation of the ciliary ganglion (Froriep, 1902, Carpenter, 1906).

The *n. trochlearis* arises from a cluster of neuroblasts similar and lying just caudal to those of the oculomotor. The rootlets derived from them, instead of emerging directly ventralward, curve dorsalward over the roof of the aqueduct, where they decussate and emerge as a slender trunk which passes ventralward to reach the anlage of the superior oblique muscle. No satisfactory explanation has ever been given for the peculiar dorsal decussation of this nerve.

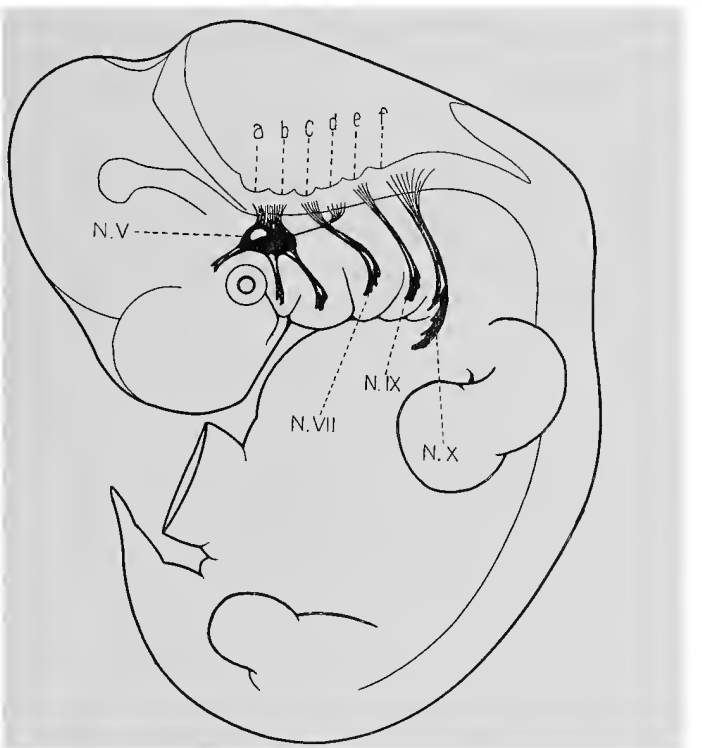

FIG. 95.—Composite sagittal section through a human embryo 10 mm. long, the same shown in Fig. 86, and representing the rhombic grooves and their nerve connection with the branchial arches. The nerve arising from groove d is the n. abducens, which passes median to the ganglion semilunare.

The *n. abducens* arises from a group of neuroblasts in the median part of the mantle zone directly beneath the fourth rhombic groove or neuromere (Figs. 95 and 100). These neuroblasts converge and form rootlets which pass through the marginal zone and emerge on the ventral surface of the neural tube. On emerging, as can be seen in the 10 mm. embryo, they are gathered together in a single trunk, which immediately bends forward at an angle of 90°, and passes forward mesial to the semilunar ganglion to reach the anlage of the external rectus muscle. It has been shown by Bremer (1908) and Elze (1907) that it is not uncommon for this

nerve to have a series of multiple rootlets, with a corresponding caudal prolongation of its nucleus of origin backward into the region of the fifth rhombic groove. On the other hand, it has been further shown by Bremer (1908) that the nucleus of origin of the n. hypoglossus may extend forward and more or less completely bridge in the gap existing between it and the n. abducens. The root fibres arising in such cases from the extreme cephalic end of the hypoglossal nucleus and from the extreme caudal end of the abducens nucleus, instead of joining with their respective nerve-trunks, show a tendency to form "aberrant roots," which pass out in various directions and are lost in the loose mesenchyme. These aberrant roots eventually (during the second month) entirely disappear.

Visceral Group.

The facial, glossopharyngeal, and vagus form a series of similar nerves which consist almost wholly of visceral fibres. Their motor visceral fibres arise from a column of neuroblasts (nucleus ambiguus and nucleus facialis) continuous with the lateral horn cells of the cord. Their sensory visceral fibres arise from the peripheral ganglia and enter the alar plate of the neural tube and form a longitudinal strand which in the adult we know as the *tractus solitarius*. In addition to these visceral fibres there are a few somatic sensory fibres for the supply of the integument of the adjoining region, which arise and have a course similar to the visceral sensory fibres. In aquatic vertebrates there are also the special somatic sensory fibres of the lateral line system, whose fibres join the roots of the facial, glossopharyngeal, and vagus to reach the brain, and the ganglia from which these fibres are derived become incorporated in the geniculate, petrosal, and nodosal ganglia. A trace of these organs is seen in the human embryo in the form of a temporary thickening of the ectoderm directly over the ganglia of these three nerves. The fourth member of this group, the trigeminal nerve, is distinguished by a larger admixture of somatic sensory fibres. The ganglia of all four nerves are derived from the neural crest.

The *n. facialis* is characterized by a large predominance of visceral motor fibres which make up the large motor root of the adult. These motor fibres can be seen in the 10 mm. embryo (Figs. 96 and 100) arising from a group of neuroblasts situated beneath the third rhombic groove or neuromere. The fibre bundles are assembled and pass directly lateral under the floor of this groove and gradually converge to form a solid trunk which emerges from the neural tube just median to the acoustic ganglion. On emerging the motor trunk curves caudalward (Fig. 100) and terminates among the cells of the hyoid arch which are destined to form the muscles of expression.

The sensory fibres of this nerve spring from the geniculate ganglion, which is apparently a derivative of the neural crest. It can be clearly made out toward the end of the third week, lying in front of and separate from the ganglion acusticum. Shortly after a path of loosely grouped fibres can be seen extending from it to the neural tube constituting its proximal root, the n. intermedius. On entering the alar plate it forms, as can be seen in the 10 mm. embryo (Figs. 96 and 100), a fibre path which bends caudalward to join the tractus solitarius. From the peripheral end of the ganglion fibres pass down as the chorda tympani, which finally

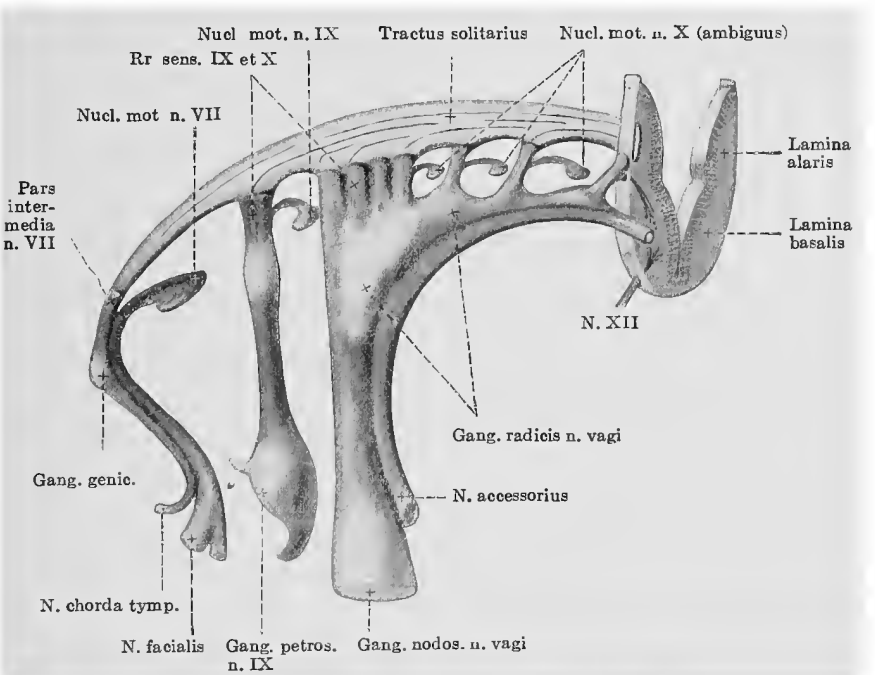

FIG. 96.—Reconstruction of the left facial, glossopharyngeal, and vagus nerves of the same embryo shown in Fig. 86. A transverse section of the neural tube is included in the reconstruction to show its relation to the different nerve-roots. This should be compared with Fig. 100.

leaves the main trunk of the nerve to enter the mandibular arch, eventually joining the third division of the trigeminal nerve. The great superficial petrosal nerve is another peripheral derivative of this ganglion, which makes its appearance shortly after the chorda tympani and extends forward to reach the anlage of the sphenopalatine ganglion. Most authors in comparing the seventh nerve with a typical branchial nerve describe the great superficial petrosal as representing the prætrematic branch and the chorda tympani as the posttrematic branch. In the early embryo the sensory root or pars intermedia, as compared with the motor root, is larger than in the adult. The subsequent marked growth of the

motor root and the relative standstill of the sensory root result in the former becoming the main trunk of the nerve.

Owing to the close relation existing between the facial and acoustic nerves the two are frequently classed as the facial-acoustic complex. However, aside from the fact that the acoustic nerve, in its development in the higher vertebrates, crowds in against the facial nerve and becomes more or less fastened together with it by mesodermal elements, it has no other thing in common, the two being nerves of entirely different embryological and functional significance. The relation between the facial and abducens becomes reversed in the adult from that of the early embryo. The facial at first lies directly under the third rhombic groove, while the abducens is more caudal and is under the fourth rhombic groove. As shown in Fig. 97, the two nerves gradually shift their relative

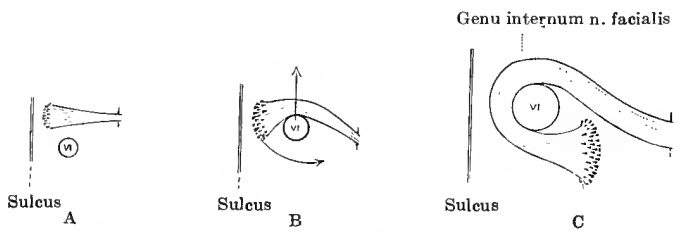

FIG. 97.—Diagram illustrating three stages in the development of the genu facialis, the youngest, A, corresponding to the 10 mm. embryo, and the oldest, C, the new-born child. The relative position of the nucleus of the n. abducens is represented in outline. *Sulcus*, sulcus medianus fossæ rhomboideæ.

positions, the abducens moving forward. This migration results in the bending of the motor root of the facial out of its original course and produces the *genu facialis*.

The *n. glossopharyngeus* possesses a ganglion of the root and ganglion of the trunk, the latter being temporarily connected with the placode over the third arch. As can be seen from the relative size of the ganglia in Fig. 86, the nerve consists almost wholly of sensory fibres, connected peripherally with the structures developing from the second (r. tympanicus) and third (r. lingualis) arches. The tympanic branch is not well defined until we come to embryos between 12 and 14 mm. long. Centrally the rootlets enter the brain wall and, joining with the fibres of the facial, extend caudally (Fig. 96) as the tractus solitarius. The motor rootlets of this nerve arise from a group of neuroblasts in the nucleus ambiguus series, situated beneath the floor of the fifth rhombic groove. The motor bundles extend directly lateral beneath this groove and pass under the spinal tract of the trigeminal and then emerge from the brain wall and join the main trunk of the nerve. This nerve forms a more typical branchial nerve than either the facial or vagus. Its tympanic branch is regarded as the prætrematic branch and the lingual as the posttrematic branch.

The *vagus complex* (n. vagus et n. accessorius) represents several branchial nerves, the motor fibres of which in man have undergone special development for the purpose of supplying the group of muscles derived from its branchial arches. The facial nerve is also a similar nerve; its large motor trunk, as we have seen, is distributed to the muscle-cells of the hyoid arch, and, as these cells group themselves into the muscles of expression and spread forward over the face, the facial branches are drawn along with them. In a similar way the more caudal rootlets of the vagus become predominantly motor, and form a distinct bundle which we know as the spinal accessory nerve, and this bundle is distributed to a group of muscle-cells originally belonging to the more caudal branchial arches, and in man is destined to form muscles for the arm girdle, the mm. sternocleidomastoideus and trapezius. As these muscles spread out into their eventual position the nerve is drawn down across the neck with them. Coincident with the increased importance of this musculature as we ascend the vertebrate scale we meet with increased development of the accessory nerve, and it obtains additional rootlets of origin by spreading down into the region of the spinal cord. As can be seen in Fig. 86, it may reach as far down as the fourth cervical segment. The nucleus of origin of the spinal accessory and other motor rootlets of the vagus constitutes the nucleus ambiguus of the medulla oblongata and a portion of the lateral horn of the spinal cord, the two being continuous (see Fig. 100).

The early stages in the growth of the glossopharyngeal and vagus nerves are shown in Figs. 82, 83, 86, and 94. Their sensory elements are derived from the ganglion crest of the hind-brain in the same manner that spinal ganglia are derived from the ganglion crest of the cord. The crest of the hind-brain and that of the cord are described by some as continuous (Dohrn, 1901), but Froriep (1901) distinguishes between a ganglion crest of the head and one of the trunk, the two overlapping in the occipitospinal region. The cranial ganglion crest migrates ventrally down the side of the neural tube and is soon joined by visceral motor fibres that emerge from the lateral border of the neural tube. In the 4 mm. embryo, Fig. 82, a bundle of such fibres can be seen running along the ventral border of the crest and constituting the primitive n. accessorius. Soon after this the cells of the crest show signs of differentiation and are gradually converted into sensory ganglion-cells with fibrous processes, which attach themselves to the neural tube on the one hand and extend peripherally on the other,—*i.e.*, dorsal rootlets. This fibre development results in the breaking up of the ganglion crest into cell masses, which is not a metameric segmentation such as appears in the spinal region. These masses constitute the ganglia of the roots. The ninth nerve has one, the

ganglion of Ehrenritter; while the tenth, being a composite nerve, has a series of them, the most oral one being the largest. The ganglion of the trunk (ganglion nodosum), as is also true of the ganglion petrosum of the glossopharyngeus, when first identified does not seem to be definitely connected with the root ganglia. Furthermore it differs from the root ganglia in being connected with a rudimentary sense organ (epibranchial placode), as shown in Fig. 98. It, however, is generally considered as a derivative of the ganglion crest.

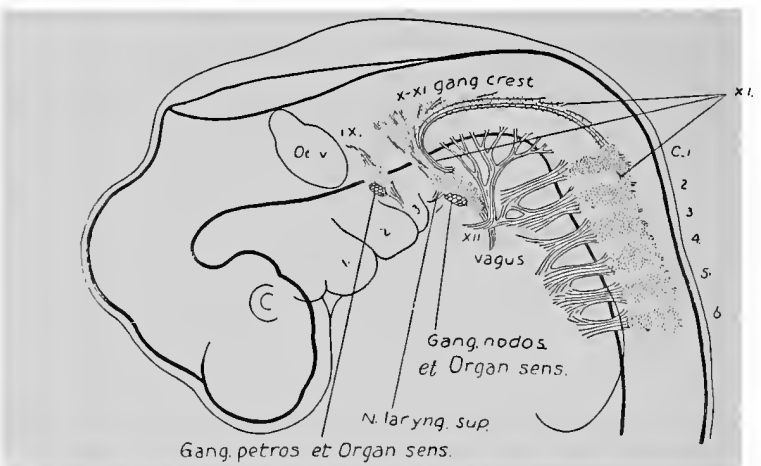

FIG. 98.—Reconstruction of the nerves in the occipital region of a 7 mm. human embryo (Mall collection, No. 2), showing sensory placodes in connection with the petrosal and nodosal ganglia. Enlarged 16.7 : 1. *Ot. v.*, ear vesicle; *gang. crest.*, ganglionic crest.

The formation of the vagus rootlets at a somewhat later stage is shown in Figs. 96 and 100. The motor neuroblasts point dorsolateralward and assemble in a series of rootlets which emerge just ventral to the entrance of the sensory roots. After emergence they turn forward and form a common trunk, which in the spinal region lies between the dorsal roots and the side of the spinal cord. Connected with the motor roots are the sensory roots and ganglia. The development of the ganglia is more pronounced in the cephalic end of the nerve. The more caudal ganglia usually disappear in the adult, except for traces of scattered ganglion-cells found occasionally on the rootlets of the accessory division. Owing to the tendency to regression on the part of the more caudal of the vagus root ganglia, the vagus complex becomes differentiated into a fore part or vagus division which is predominantly sensory, and a hind part or accessory division which is almost wholly motor. In other words, in the course of phylogenesis as the vagus invades the spinal region it is the motor elements that play the prominent part. The more caudal vagus ganglia are not to be mistaken for the Froriep ganglion, which represents a persistent precervical

ganglion. In the one case we have a series diminishing from the head toward the tail, and in the other it is in the opposite direction. The sensory fibres derived from these ganglia enter the wall of the neural tube and immediately unite in a longitudinal tract continuous with similar fibres from the facial and glossopharyngeal, thus completing the formation of the tractus solitarius, whose form and relation to a section through the oblongata region are shown in Fig. 96.

The *n. trigeminus* possesses on its sensory root the largest ganglion of the whole embryo, the ganglion semilunare. Processes which grow out from its constituent cells connect it with the brain on the one hand, and extend as three large trunks on the other into the ophthalmic, maxillary, and mandibular regions. This ganglion has generally been considered as a single undivided mass of cells derived entirely from the ganglion crest (Dixon, 1896). A human embryo of 15 segments has, however, been described by Giglio-Tos (1902), in which the anlage of the semilunar ganglion consists of three separate proganglia, "proganglia neurales," which are connected by a cellular lamina with three other distal or epibranchial proganglia, the whole group being eventually fused into a single ganglion mass. If this is the case, it is probable that the semilunar ganglion arises in part from the ganglion crest and in part from the epibranchial ectoderm. Such a composite character would correspond in some degree with the condition found in lower vertebrates. It has been suggested by Johnston (1908) and others that perhaps the sensory ganglion-cells belonging to the midbrain and the most oral part of the hind-brain become included in the wall of the neural tube, instead of becoming detached with the neural crest. Such cells then never become incorporated in the semilunar ganglion. It is these cells that are supposed to form the mesencephalic root of the trigeminal nerve, their processes extending caudalward beneath the central gray substance to join the main sensory trunk of the nerve at its point of entrance into the wall of the tube.

Processes grow out from the constituent cells of the ganglion and extend peripherally as three large trunks or divisions (see Figs. 83, 99, and 86). The ophthalmic division passes forward and soon subdivides into the frontal and nasociliary nerves; the latter in the 10 mm. embryo is a well-defined branch just dorsal to the eye stalk. The maxillary and mandibular divisions extend downward and break up in their terminal branches among the cells of the maxillary process and mandibular arch respectively. By the beginning of the sixth week the chief branches of these divisions can be recognized. Centrally the ganglion becomes connected with the brain by a large single root, consisting of both somatic and visceral sensory fibres. This enters the wall at the pontine flexure

opposite the first and second rhombic grooves. Within the wall in the marginal zone the fibres form a flattened longitudinal tract, part of which extends caudally as the spinal tract, and part extends forward and upward to enter the cerebellar ridge, as shown in Fig. 100.

In its motor elements the trigeminal nerve departs somewhat from the type represented in the other three nerves of this visceral group. In the others the nucleus of origin is in the basal plate,

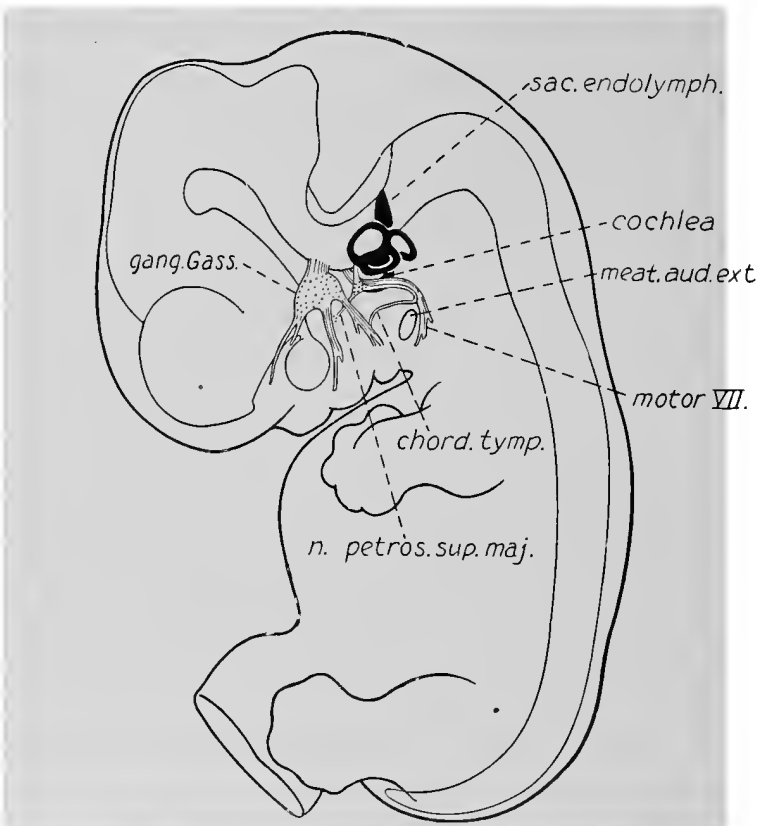

FIG. 99.—Reconstruction of the facial and trigeminal nerves of a human embryo 14 mm. long (Mall collection, No. 144), showing motor and division of the facial sensory. Enlarged 8 : 1.

and the nerve rootlets exhibit a characteristic curved course to reach the point of emergence; while in the trigeminal the nucleus is more lateral and lies directly against the entering sensory fibres, so that the fibres of the motor root pass directly ventralward to fuse with the mandibular division. Its nucleus corresponds to the dorsal motor nuclei found in the adult ninth and tenth nerves, though it is much larger. On analysis it is found that a typical visceral cranial nerve has three central terminations,—sensory root (tractus solitarius), ventral motor root (nucleus ambiguus),

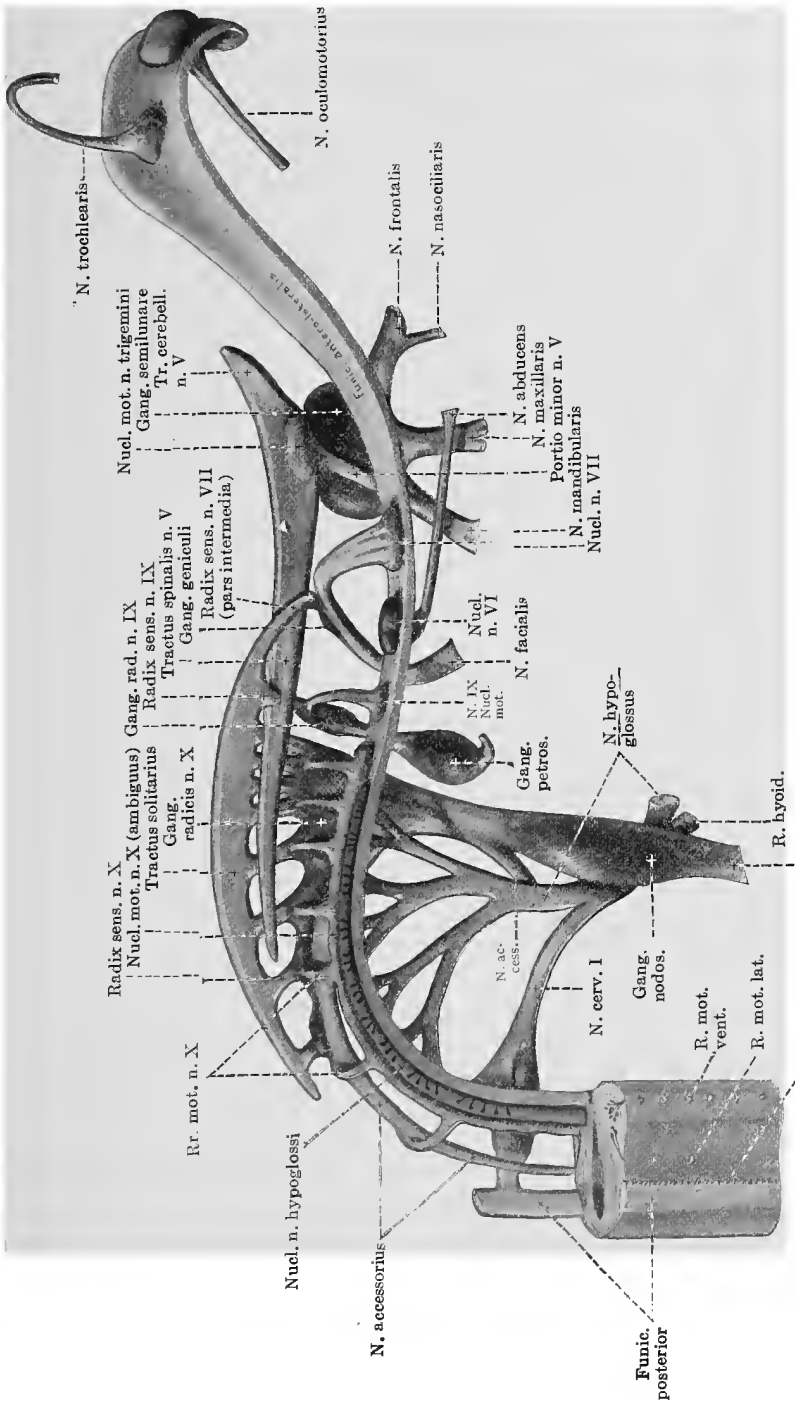

FIG. 100.—Reconstruction of the cranial nerves of the same embryo shown in Fig. 86. The brain is cut away so as to show the primary sensory paths and motor nuclei of the different nerves. The somatic motor nuclei are colored red.

dorsal motor root (nucleus nervi dorsalis). The ventral motor root always has a characteristic curved course between its nucleus and point of emergence, while the nucleus of the dorsal motor root is clustered near the sensory division of the nerve, and from it the root extends to the surface of the brain in a straight line. These three elements are represented in the different nerves in different proportions. The ninth nerve approaches the mean and all elements are fairly represented. In the vagus the curved ventral motor roots are increased in the caudal portions and form the spinal accessory. In the facial the sensory root (n. intermedius) is diminutive, while the curved ventral root becomes the main trunk of the nerve. In the trigeminal it is the straight dorsal motor root that forms the principal motor supply, while the curved ventral motor root must be considered as absent. It should be mentioned, that though the motor root eventually fuses with the mandibular division, in the embryo the motor fibres corresponding to the n. masticatorius have been observed passing on the median side of the ganglion and extending from its distal border, not with the mandibular division, but as a separate trunk (Streeter, 1904).

The cranial sympathetic ganglia derived from the trigeminal nerve will be described under the sympathetic system.

IV. SYMPATHETIC NERVOUS SYSTEM.

The sympathetic system arises in common with the spinal ganglia from that portion of the ectoderm which forms the lateral border of the neural plate, and in common with the spinal ganglia it takes part in the formation of the neural crest. As the neural crest becomes detached and its segmenting parts invade the space between the myotomes and neural tube, certain ganglion-cells separate themselves from its ventral border and independently migrate ventralward into the neighborhood of the aorta. It is these cells that form the connected chain of errant ganglia which we know as the sympathetic system. It is a true derivative of the rest of the nervous system. Originally the two were continuous ectoderm, and the establishment of the former as a distinct and separate system is solely due to its detachment and forward migration.

To witness the successive steps in the development of the sympathetic system it is necessary to commence with embryos that are still in the neural crest stage, 2–3 mm. long. At 7 mm. the cell migration is in active progress, and cellular rami communicantes are already present in some regions; in the 9 mm. embryo the ganglionic cord and splanchnic nerve-plexus are definitely outlined; and finally, in the 16 mm. embryo the differentiation has advanced far enough so that it is possible to recognize the more outlying visceral ganglia and the ganglia of the head and their connecting

branches. Thus, before the completion of the sixth week of embryonic life the essential features of the entire sympathetic apparatus can be clearly made out.

A representation of the derivation of the sympathetic cells is shown in Fig. 101, in which A, B, C, and D represent the successive stages and show schematically the increase in number and forward migration of cells and the subsequent formation of connecting

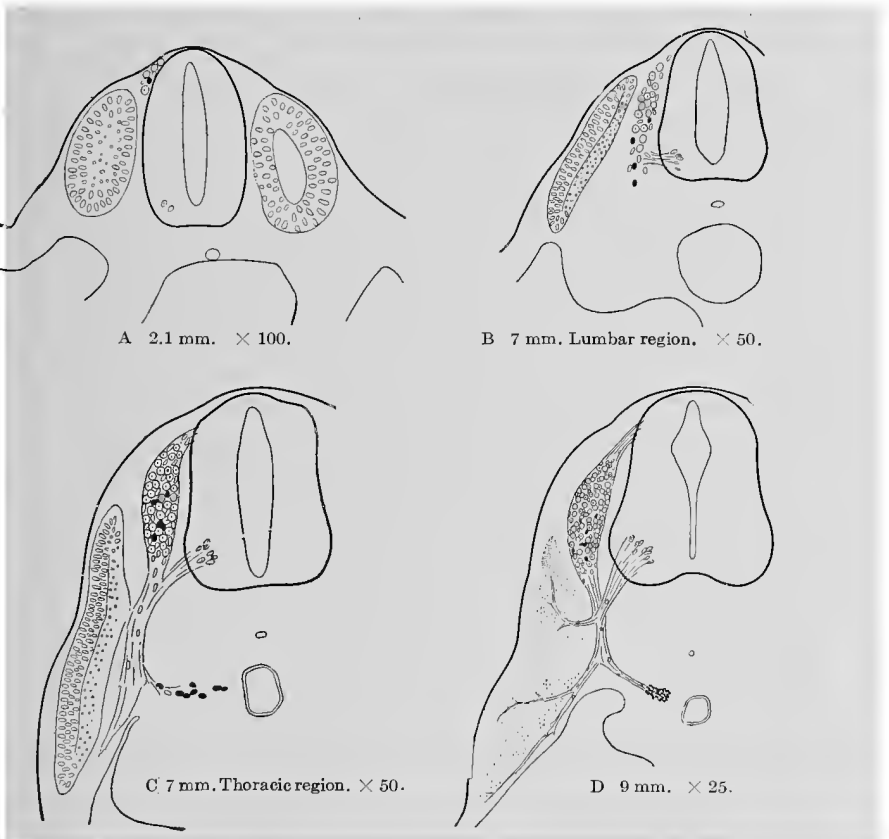

Fig. 101.—Diagram representing the origin and migration of the sympathetic ganglion-cells and their relation to the other components of the neural crest. Sympathetic cells, black; spinal ganglion-cells, dotted circles; sheath cells, white rings. A and D are based on embryos Nos. 12 and 143 of the Mall collection, and B and C on the Buxton embryo, Gage collection.

fibre trunks. The sympathetic cells are shown in black in contrast to the other derivatives of the neural crest,—*i.e.*, the sheath cells and the spinal ganglion-cells. The sheath cells are shown as plain white rings, while the spinal ganglion-cells are dotted.

The three varieties of cells mentioned can be traced back to the neural crest, as indicated in stage A. They are, however, not to be distinguished from each other histologically at this time; it is only for schematic purposes that they are represented in

that way in the drawing. In the next drawing, B, can be seen the increase in size and ventral advance of the entire ganglion mass. The ventral advance is in part secondary to the increase in the number of cells and the consequent forward crowding in the direction of least resistance, and in part it is due to the intrinsic migratory energy of the individual cells. What appears as an ill-defined ragged ventral border, on closer examination can be seen to be made up of branching ganglion-cells reaching forward into the mesoderm in the form of a loose syncytium. In the drawing, for the sake of simplicity the processes are not shown. As seen in B, cells from the loose ventral border of the ganglion mass detach themselves and extend ventralward in advance of the ventral root fibres. The latter can be seen emerging from the neural tube and following along in the wake of the migrating ganglion-cells. Simultaneously with the forward growth of the ventral root fibres and the formation of a definite nerve-trunk, as shown in C, the sympathetic cells continue their migration medianward toward the aorta and thereby form a cellular connected strand which is the primitive ramus communicans. The difference between drawings B and C is that existing between the upper and lower parts of the spinal cord of the same embryo. B corresponds to the upper thoracic region in the 4.5 mm. embryo.

The completion of the segmental type is shown in D, where the sympathetic cells have completed their wandering, and by rapid increase in numbers form a compactly clumped ganglion mass which by fusing from segment to segment extends as a continuous longitudinal cord along the lateral border of the aorta. The cellular ramus communicans is in the meantime replaced by centrifugal fibres from the nerve-trunk which have followed along the migration path, the same fibres that form the white ramus in the adult. Somewhat later centripetal fibres sprout out from the sympathetic ganglia and either work their way backward along the path of the centrifugal fibres, or else form an independent bundle, the future gray ramus. The ramus communicans thus represents a portion of the path along which the sympathetic cells originally migrated. At first consisting of a chain of ganglion-cells spun out by the wandering cells, it is later replaced by an ingrowth of fibres representing spinal axones on the one hand and sympathetic axones on the other; the cells forming the temporary connecting bridge, having in the meantime completed their journey, form a compact ganglion mass near the aorta.

If we judge from the adult conditions we must conclude that there are some sympathetic cells which never wander out from the spinal ganglion mass. Some of these stationary cells are shown in the drawings C and D. Likewise some of the sheath cells do not leave, but remain in the ganglion mass, where they either

form sheaths to the nerve-fibres or else form cell nests encapsulating the ganglion-cells proper. The wandering sheath cells, as seen in B and D, advance simultaneously with the sympathetic cells at the tip of and along with the nerve-fibres, and by the time a well-defined nerve-trunk makes its appearance sheath cells are found scattered along its whole course, as well as along the ramus communicans.

The development of the individual sympathetic ganglion-cell may be divided into three stages. The first, or indifferent stage, covers the period during which it is one of the cells forming the neural crest and spinal ganglion mass; the second, or intermediate stage, corresponds to the period of migration; the third, or terminal stage, is from the time it reaches its permanent position to the attainment of its adult form.

During the first stage the three cell groups derived from the neural crest—*i.e.,* the sympathetic ganglion-cells, the spinal ganglion-cells, and the sheath cells—cannot be distinguished from one another, and may be considered as indifferent ectoderm cells. Together they constitute a moderately compact mass lying between the neural tube and the dorsal border of the myotome. Their body-outlines are ill-defined and show more or less fusion. As compared with the adjacent mesodermal cells they possess more body protoplasm and are not branched. The nuclei are oval or rounded and are marked by deeply staining nucleoli.

During the second or wandering stage the sympathetic cells, as is common with all wandering cells, are characterized by the development of slender protoplasmic processes. The sheath cells also develop similar processes about the same time, and the two cannot be easily distinguished from each other. The nuclei of the latter, however, are somewhat more elongated and take the stain less intensely. The spinal ganglion-cells may be readily identified by the well-defined protoplasmic body which the more advanced ones have in the meantime developed. It is proposed by Kohn (1905) that the sheath cells of this period and the sympathetic cells, because of their similarity and their prevailing presence along the developing nerve, be grouped together under the term *neurocytes.* A syncytial strand of this type of sympathetic cells forms the initial ramus communicans, which can be seen making its way through the mesoderm toward the aorta, entirely devoid of fibres. See accompanying Fig. 102, which shows a similar picture in the rabbit.

With the beginning of the third stage the sympathetic cells undergo their terminal differentiation. They rapidly proliferate and clump themselves into ganglia; while the individual cells develop condensed and sharply outlined protoplasmic bodies and their processes become fibrillar and extend out to take part in the

formation of the various communicating trunks. In passing through these three stages the sympathetic cells do not all develop with equal rapidity, and there is consequently an overlapping of the successive periods; for example, the cells belonging to the ganglionated cord are well along toward the completion of the third stage at a time when the visceral ganglia are still in the second stage, and likewise some parts of the ganglionated cord develop

FIG. 102.—From a cross section through a rabbit embryo, showing chain of sympathetic cells forming the primitive ramus communicans (*rc*), which leads from the fibrous spinal nerve (*n*) medianward toward the aortic region. Enlarged 300 : 1. *nz*. neurocytes ; *bk*, blood-cells. (After Kohn, 1907.)

more rapidly than others, the thoracic region is always in advance of the lower lumbar and sacral and the cranial ganglia.

The earlier writers (Remak, 1847) were of the opinion that the sympathetic system was of mesodermal origin, until Balfour (1877) showed that in selachians the sympathetic ganglia develop as buds or outgrowths from the trunks of the spinal nerves, and hence are ectodermal. Some observers (Paterson, 1890) still adhered long after to the mesodermal origin, yet Balfour's observations were thoroughly confirmed and the ectodermal origin of the sympathetic was generally regarded as thereby established. Later investigators (Schenk and Birdsall, 1878, Onodi, 1886), who worked

on higher forms, including human, modified Balfour's view by describing the sympathetic ganglia as detached parts of the spinal ganglia which are separated off and linked together into a longitudinal chain. It was not until His, jun. (1891), introduced the principle of the wandering of individual sympathetic cells that we approached our present conception. It was surmised by His (1890) and immediately supported by His, jun. (1891), that the development of the sympathetic system is dependent on the active ventral migration of germinating sympathetic cells, which cells, however, do not migrate until a preliminary nerve-fibre framework is laid out in the form of rami communicantes and connecting longitudinal commissures. Along these fibre paths the sympathetic cells wander forward to form ganglia.

The only essential difference between the description of His, jun., and that as given above in the present article, consists in the time of cell migration. The writer is in accord with the recent work of Kohn (1907) in believing that the migration occurs earlier than described by His, and that the cells wander through mesoderm rather than along compact nerve-fibre paths. The same picture is presented in human material that Kohn describes in the rabbit: migrating cells can be recognized in advance of the loose strands of the tip of the growing nerve, and extending through the mesoderm as a bridge of cells toward the aorta; by the time a well-defined nerve-trunk is established the sympathetic cells have already completed that part of their migration, and the cells then found on the nerve-trunk are sheath cells only. A divergent view has been recently published by Cajal (1908), according to which the sympathetic cells in the chick are true motor cells and are derived from the spinal cord. During their germinative stage they migrate out from the cord at the same place at which later the ventral roots emerge.

The cranial sympathetic system departs from the uniform segmental type found in the trunk. It, however, adheres in three ways to the general type: first, the ganglion-cells are apparently derived from a cerebrospinal ganglion mass; secondly, they migrate ventralward and eventually assume a position outside of the bony canal, and thirdly, the ganglia give off fibres which form a communicating trunk along the internal carotid artery, this trunk serving to unite the cranial sympathetic ganglia with each other, analogous to the longitudinal system of communications of the ganglionated cord, with which it is continuous.

The early history of the cranial sympathetic ganglia is less definitely known than that of the trunk system, due to the relatively smaller size, lesser number, and lack of symmetry of the former ganglia, as well as the complexity of the surrounding structures. From the evidence at hand it seems probable that all the

cranial sympathetic ganglia—gg. ciliare, sphenopalatinum, oticum, and submaxillare—are originally derived from the semilunar ganglion mass.

The ciliary ganglion presents certain modifications. In the chick it consists (Carpenter, 1906) of two portions, a smaller dorsal sympathetic portion derived from the semilunar ganglion, and a larger ventral portion containing large bipolar cells (supposedly sensory), derived from the neural tube by migration along the oculomotor nerve. In the same way in the torpedo it is known that cells wander out from the medullary tube and migrate ventralward in company with the growing oculomotor fibres, and eventually fuse with the cells derived from the trigeminal ganglion, together forming a composite ganglion (Froriep, 1902). If there are any oculomotor ganglion-cells in the human embryo, such as are found in the chick and torpedo, they do not apparently pass through a migrating stage, and never leave the neural tube. Consequently the ciliary ganglion here consists exclusively of migrant cells from the semilunar ganglion. We may assume that they behave like the sympathetic cells of the trunk and pass through their wandering stage very early. Their detachment from the parent ganglion mass and forward migration must occur just in advance of the developing nerve-trunks, and it is not until they reach their permanent position that they undergo active proliferation and form a compact cell group.

Both the sphenopalatine and submaxillary ganglia are probably derived entirely from the semilunar ganglion, but it must be borne in mind that they are connected with the geniculate ganglion of the facial, and there is the possibility that the former contains contributing cells which have migrated along the path of the great superficial petrosal nerve and the latter cells which have migrated along the path of the chorda tympani. In the same way the otic ganglion, though developed intimately with the semilunar ganglion, may in part consist of cells derived from the glossopharyngeal nerve through its tympanic branch. However, both their comparative and embryological histories indicate that the facial, glossopharyngeal, and vagus nerves constitute a definite group, one of the characteristics of which is that they retain within their root or trunk ganglia or within the brain tube itself whatever sympathetic ganglion-cells they possess, and consequently there are in connection with them no rami communicantes and no derivative ganglia.

The origin of the four cranial ganglia may be represented as in the adjoining scheme, Fig. 104. The arrows indicate the paths of primary migration, and the dotted lines paths of subsequent intercommunication, by which all the cranial ganglia establish connection with the carotid plexus and so become directly continuous

with the gangliated cord of the trunk. This figure should be compared with Fig. 103, which represents a profile reconstruction of an embryo 16 mm. long. For the purpose of contrast the sympa-

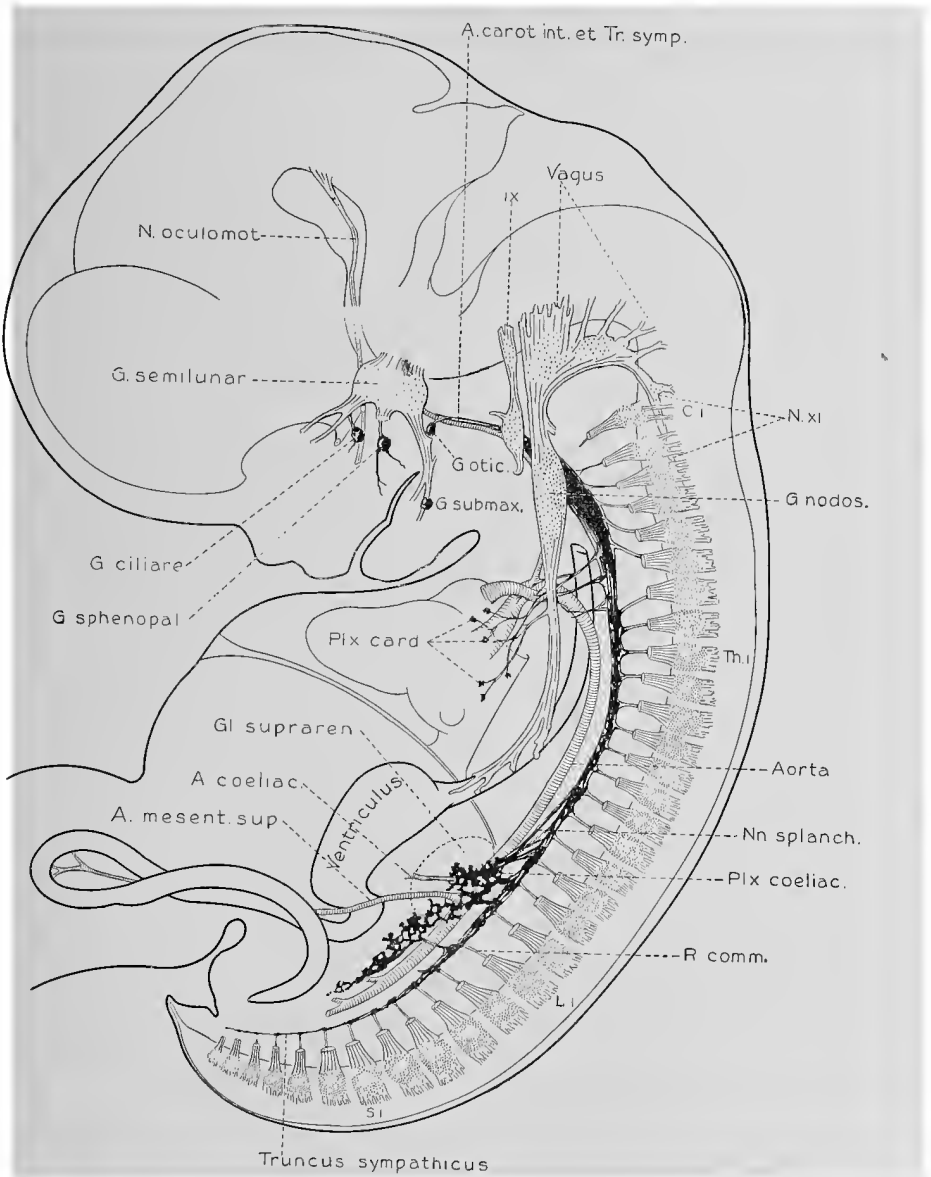

FIG. 103.—Profile reconstruction of the sympathetic nervous system in a 16 mm., nearly six weeks, embryo (Huber collection, VI), enlarged 10 : 1. In order to expose the cœliac plexus and suprarenal gland the stomach is represented as raised forward and to the right.

thetic system is shown in black. The cranial sympathetic ganglia at this time are connected with the semilunar ganglion by longer or shorter branches which are analogous to rami communicantes.

The ganglion ciliare lies closely against the oculomotor nerve, from which it receives some fibres. A true ramus communicans, identical with the radix longa of the adult, connects it with the ophthalmic division of the trigeminal nerve. The sphenopalatine ganglion is connected with the parent ganglion by two or more rami communicantes, the nn. sphenopalatini. These are in part sensory fibres, which pass directly through the ganglion without interruption, connecting the periphery with the semilunar ganglion. It is fibres of this sort that form the major part of the peripheral branches of the ganglion. In case of the otic ganglion there is a less distinct ramus communicans, owing to the fact that the ganglion lies closely against the nerve-trunk and thus there results in the adult a short plexus uniting the two. The submaxillary ganglion presents an even more close union between the ganglion and the nerve-trunk, and the latter in 16 mm. embryos can be seen making its way directly through the substance of the ganglion mass. So here, as in the case of the otic ganglion, there results a plexus of communication between ganglion and nerve-trunk. In speaking of this as the ganglion submaxillare it is done in the sense of including both the submaxillary and sublingual ganglia. As has been shown by both Langley and Huber (Huber, 1896), that which is ordinarily referred to as the submaxillary ganglion is in reality sublingual, while the submaxillary ganglion proper consists of multiple ganglia situated in the substance of the gland along the course of its ducts.

It was shown in Figs. 101 and 104 how the sympathetic cells in the spinal region migrate forward and form ganglia, and it has been also mentioned that these ganglia fuse from segment to segment and thereby form a continuous longitudinal cord of ganglion-cells, the so-called ganglionated cord. This structure is at first purely cellular. Later, fibres make their appearance among the cells; in the 16 mm. embryo, Fig. 103, they are already abundant, particularly in the cervical and thoracic regions. The fibre growth continues in such a manner as to break the continuity of the cellular cord, and produces a longitudinal series of ganglionic masses connected by intervening fibrous bridges, the ganglionic chain as seen in the adult. For the greater part these ganglia are segmental, but in the cervical and upper thoracic region the cells remain massed in larger clumps, and there result ganglia corresponding to from two to five segments.

The prevertebral and visceral sympathetic ganglia are considered by most writers as derivatives of the neural crest in common with the rest of the sympathetic system. They differ only in that their migration extends further than that of the latter: instead of stopping at the side of the aorta, they migrate ventralward through the loose mesoderm into the region of the preverte-

bral plexuses, and some of them still further forward to become incorporated in the walls of the viscera to form the submucous plexus. These paths of migration are diagrammatically shown in Fig. 104. These ganglia reach their eventual position relatively early, so the distance covered in their migration is therefore not so great. Cajal (1908) describes in the chick of 52 hours visceral

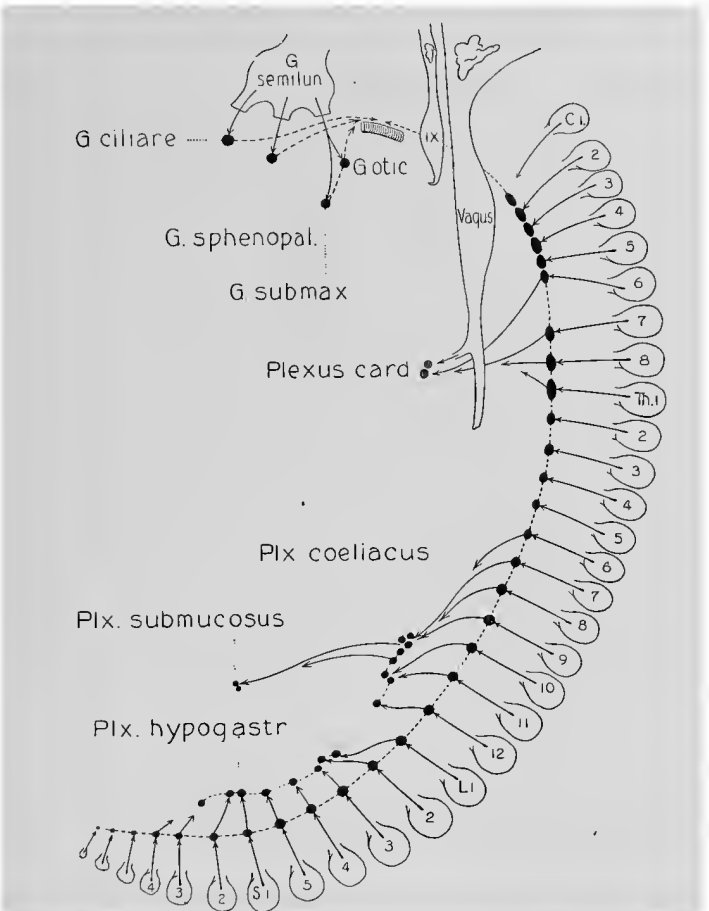

FIG. 104.—Diagram showing the migration paths of the sympathetic cells. Dotted lines indicate secondary subsequent communications which link the ganglia together and form a longitudinal chain continuous throughout head and trunk. Secondary and tertiary migrations result in the formation of prevertebral and visceral plexuses.

sympathetic cells which have completed their migration. In human embryos 16 mm. long the cardiac ganglia are to be recognized. The main features of the cardiac plexus are completed by the time the embryo reaches 19 mm. neck-rump length, as shown in Fig. 105. The cœliac and hypogastric plexuses together with the splanchnic nerves present the picture seen in Fig. 103, and differ from the adult only in the incomplete differentiation of the cells. Continuous with the cœliac plexus is a group of sympathetic

cells which extend through its median surface directly into the substance of the suprarenal gland, and constitute its nerve supply. A portion of these cells, instead of becoming typical ganglion-cells, undergo special development, the details of which are not yet satisfactorily understood. On account of the affinity of these

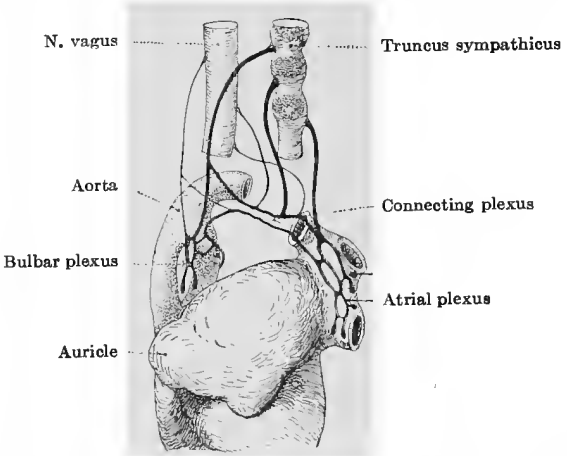

FIG. 105.—Cardiac plexus in human embryos between 10 and 19 mm. long. (After Kollmann, 1907, and His, jun., 1891.)

special cells for the chrome salts, they are designated as chromaffin cells. They are found also in other portions of the sympathetic system, such as in the ganglia of the ganglionated cord and of the abdominal plexuses; to some extent they also form independent bodies, the chromaffin bodies of Zuckerkandl, to which group the carotid glands belong. These structures will be described in detail in the following chapter.

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XV.

THE DEVELOPMENT OF THE CHROMAFFIN ORGANS AND OF THE SUPRARENAL GLANDS.

By E. ZUCKERKANDL, Vienna.

Chromaffin tissue is to be assigned to the group of organs producing internal secretion. It secretes a substance which produces contraction of the non-striped musculature and whose principal function seems to be to maintain the blood-pressure and the vascular tonus at corresponding levels. That the increased blood-pressure produced by suprarenal extract is due to the chromaffin medullary substance of the glands has been definitely proved by A. Biedl and J. Wiesel, who worked with the purely chromaffin aortic bodies of man. The chrome reaction must depend on a coloring of the secretion, for it fails, as Schur and Wiesel have shown, when the adrenalin is exhausted.

The anlagen of the chromaffin tissue, including that of the medullary substance of the suprarenal glands, are primarily associated with the cells from which the sympathetic bodies are formed. This has led many authors to assume a genetic connection between the two kinds of tissue and to derive the chromaffin tissues from sympathetic cells, although only those cells which really form portions of the sympathetic system should be termed sympathetic cells.

The anlagen of the sympathetic and chromaffin tissue consist of an apparently uniform matrix composed of deeply staining cells, which measure 4–6μ and which form what may be termed *sympatho-chromaffin tissue*. The uniformity of the elements is especially striking when one compares a mass of purely sympathetic cells (sympathoblasts) with the cell masses which have wandered into the suprarenal glands but have not yet become differentiated, as they will later entirely or for the most part, into the cells of the medullary portion of the glands (chromaffinoblasts). It becomes clear in such cases, and especially in those in which the chromaffin bodies prevail, that one can only properly speak of sympathetic ganglia when the anlagen of the two kinds of tissue have become differentiated from one another.

As to the genetic character of the chromaffin bodies there has been no unanimity. While F. Leydig, F. M. Balfour, E. Giacomini, and E. Grynfeltt declared in favor of an epithelial nature

and a secretory function for the chromaffin cells, others inclined toward the belief that they were either nervous elements or closely related to these. According to S. Meyer the chromaffin cell-nests of the Batrachia constitute a tissue *sui generis,* which appertains to the nerve tissues and whose function is to provide for the new formation of nerve-fibres. H. Rabl regarded the medullary cells of the suprarenal glands as undeveloped sympathetic ganglion-cells, C. K. Hoffmann described them as sympathetic nerve-cells of peculiar form, and V. Diamare looked upon the chromaffin cells as epithelial cells of nervous origin. A. Kohn at first accepted the view that the chromaffin cells, on account of their origin and final relations, belonged to the sympathetic system. He emphasized the high degree of relationship existing between the chromaffin and the sympathetic cells, but later protested, "on general and special grounds and on principle, against the inclusion of the chromaffin cells among the secretory epithelial cells;" further, he pointed out their difference from the nerve-cells, and, finally, regarded them as elements of a peculiar type of tissue. It is true that all the peculiarities of the chromaffin tissue do not without modification harmonize with the definition which the text-books give for epithelial tissue, but, on the other hand, many of our definitions are made before there has been a collation of all the facts necessary for the framing of a definition correct in all details. None of the characters which distinguish chromaffin tissue, such as the abundance of nerves in it, the occurrence of scattered chromaffin cells, and its relations to the sympathetic system, actually exclude it from classification as an epithelial tissue, and yet, as regards especially the last-named character, the relation is merely a topical one and no indication of a common genetic derivation from the ectoderm. One might, of course, advance in favor of this idea the suggestion that the chromaffin cells are derived from other than sympathetic formative cells, but, on the other hand, it may be pointed out that the identity of the elements contained in sympatho-chromaffin tissue need be no reason for deriving the chromaffin cells from the sympathetic ones. On the principle *a potiori fit denominatio* the authors, in accordance with their erroneous conception, must derive the sympathetic ganglia of the plexus cœliacus from the neighboring chromaffin bodies. One can only agree with the remark of A. H. Soulié that the chromaffin cells are structures in juxtaposition with the sympathicus and need not be regarded as nerve-cells nor as derivatives of these. Their function, which should also be taken into consideration in determining the character of a tissue, speaks distinctly as to their glandular nature.

The differentiation of the sympathoblasts and chromaffinoblasts (parasympathetic formative cells) becomes evident rather

late. After their separation is complete the anlagen of the two kinds of tissue are sharply separated: the chromaffin formative cells are, for instance, larger and do not stain as intensely as the small sympathoblasts, which still adhere to the sympathochromaffin type. Furthermore the differentiation appears to bring about a definite separation of the chromaffin and sympathetic elements, for no commingling of the two kinds of cells is to be observed. The occurrence of individual sympathetic cells in the free chromaffin bodies and of individual chromaffin cells in sympathetic ganglia must be regarded as exceptions to the rule. Whether the parasympathetic cells show the chrome reaction at this stage of development is yet to be determined.

In later stages the development of the chromaffin tissue precedes that of the sympathetic. In this connection it may be noted that in the ganglia of the abdominal plexuses extensive parasympathetic bodies are differentiated at a time when the sympathetic formative cells have not yet altered from the original sympathochromaffin type (fetus of 6 cm.). The statement of Soulié that the parasympathetic cells first develop at a time when neuroblasts are present in the sympathetic ganglia is incorrect as a general statement; it can, at all events, be accepted only as referring to the medulla of the suprarenal glands, which, as is known, is late in differentiating.

The chromaffin bodies of the gangliated cord are in general rounded masses, which usually lie in depressions in the dorsal portions of the ganglia (Fig. 106, *ch*). According to A. Kohn they appear later than those of the abdominal plexuses and their appearance does not seem to occur at a definite time, for they are lacking, for example, in an embryo of 28 mm. (in the gangliated cord) completely. They vary in size; exceptionally large bodies occur alongside of small ones. In the new-born child they reach a length of 1.0–1.5 mm. and not infrequently lie entirely or half way outside the capsule of the sympathetic ganglion (Fig. 107). They also vary in number; sometimes individual ganglia have several chromaffin bodies; for example, a ganglionic mass extending from the first to the fourth rib had ten, in another case a ganglion of the abdominal portion of the cord had four, and in still another case six chromaffin bodies occurred in connection with four ganglia of the abdominal portion of the cord.

The chromaffin bodies of the ganglia of the cord are equivalent to the suprarenal bodies of the Selachians, and it is certainly noteworthy that, as a comparative study shows, so far as these bodies are concerned there is a complete continuity from the cartilaginous fishes up to man. F. Leydig first suggested the occurrence of organs in the mammalia that might be regarded as homologous with the suprarenal bodies of the Selachians. He started, it is

true, with an assumption that has since been given up,—namely, that the suprarenal bodies merely represented the medullary substance of the mammalian suprarenal gland broken up into many portions; but his remark, "or perhaps also here (*i.e.*, in the mammals) adequate investigation may reveal in the individual ganglia of the gangliated cord portions that repeat *in petto* the suprarenal bodies," shows that Leydig did not oppose the possibility that in

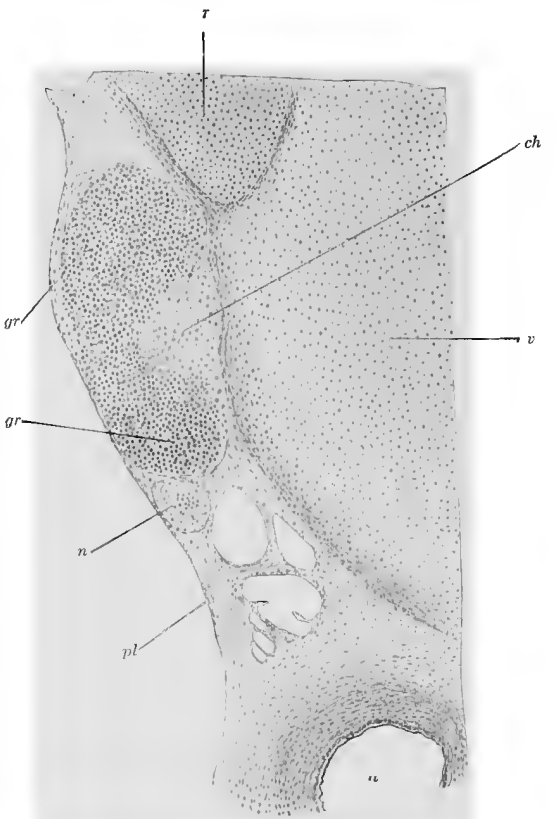

FIG. 106.—Horizontal section through a vertebra (*v*) and a ganglion of the gangliated cord (*gr*) in a fetus of 6 cm. ×70. *a*, aorta; *ch*, chromaffin body of the ganglion; *n*, splanchnic nerve; *pl*, pleura; *r*, rib; *v*, vertebra.

mammals, in addition to the medulla of the suprarenal glands, other chromaffin tissue might also be present in the gangliated cord.

The chromaffin bodies of the ganglia of the sympathetic cord should alone be termed suprarenal organs. Statements to the effect that the suprarenal bodies correspond to the medulla of the suprarenal glands of the higher vertebrates should no longer be made, least of all in text-books. The inaccuracy of such a statement becomes apparent when one considers that in the mammalia,

in addition to its occurrence in the medulla of the suprarenal glands, chromaffin tissue is also associated with the ganglia of the sympathetic gangliated cord.

Chromaffin Bodies in the Ganglia of the Abdominal Sympathetic Plexuses.—These bodies may occur wherever there are sympathetic ganglia. That they occur, as R. Wiedersheim states, "in all organs which are termed glands with internal secretion" is incorrect. In certain plexuses (plexus intercaroticus, cœliacus, suprarenalis, renalis, aorticus, and hypogastricus) they are of constant occurrence; in others (plexus cardiacus, according to Wiesel, and plexus mesentericus inferior) they are inconstant.

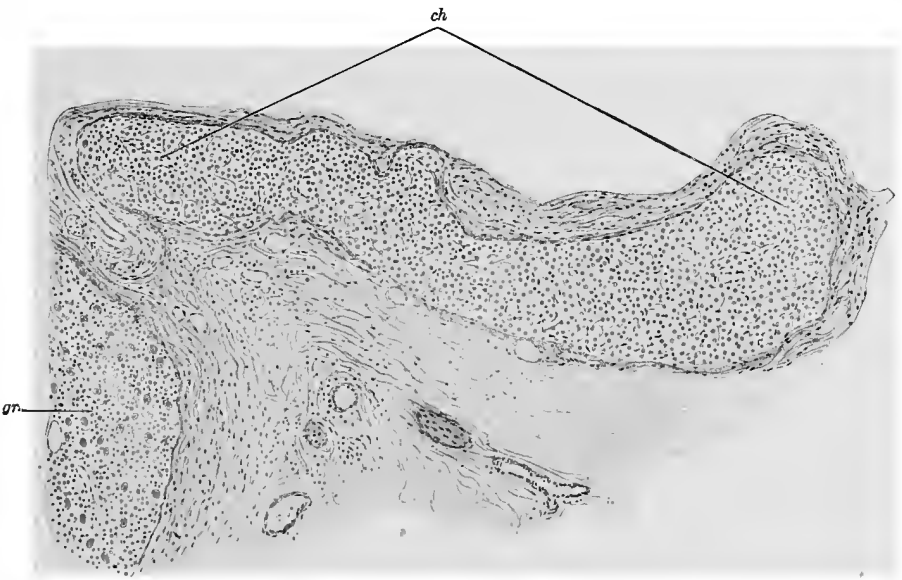

FIG. 107.—Horizontal section through an intercostal space in a new-born child. ×85. Chromaffin body (*ch*) situated outside the capsule of a ganglion (*gr*) of the sympathetic cord.

Of organs in connection with which they occur there may be mentioned the kidneys (surface and sinus renalis), the ureter, the pelvis of the kidneys, the surface of the suprarenal glands, the accessory suprarenal glands, the prostate, the paroophoron (Aschoff, A. Rieländer), the epididymis (Aschoff), the ovary (Bucura), and the retroperitoneal Pacinian corpuscles. Cell masses in the caudal sympathetic ganglia of a Dasypus fetus of 8 cm. seem to indicate that chromaffin bodies may also develop in the caudal portion of the sympathetic cord.[1] They are lacking, so far as is known, in the ganglia associated with the branches of the trigeminus. The coccygeal gland has been erroneously assigned to the chromaffin system.

[1] The cell masses were not situated in the ganglia of the caudal portion of the sympathetic cord, but in ganglia of the caudal arterial plexus.

The *glandula intercarotica* is associated with the plexus intercaroticus. That it belongs to the chromaffin system was recognized by H. Stilling. Before his time this organ had variously been identified as a sympathetic ganglion (Andersch), a nerve gland (H. von Luschka), a vascular structure (J. Arnold), a derivative of the branchial arches (K. Stieda, C. Rabl, Maurer), and, finally, as a derivative of the adventitia of the internal carotid artery (Kastschenko, Marchand, R. Paltauf). According to Paltauf, with whose statements those of Kastschenko and Marchand essentially agree, the carotid gland develops "in man and other animals, and therefore probably in the mammalia in general, without any epithelial anlage from a circumscribed growth of the wall of the internal carotid."

Any attempt to derive this gland from a branchial pouch or from a thickening of the wall of a vessel must fail, since chromaffin cells can only be produced from sympatho-chromaffin tissue. What significance the indistinct thickening of the wall of the internal carotid possesses is yet to be determined; that it represents a structure independent of the anlage of the carotid gland is shown, as A. Kohn points out, by the fact that the thickening can also be observed in those cases in which the gland is situated nearer to the external than the internal carotid (as in the dog). It may further be remarked that nowhere else have similar thickenings of the adventitia of arteries been observed in the neighborhood of chromaffin bodies.

A. Kohn derives the chromaffin elements of the glandula intercarotica from the nerve anlage which passes from the upper cervical sympathetic ganglion between the two carotids. In a 44 mm. pig embryo he finds in this plexus ganglion-cells, some of which have a large and feebly staining nucleus, and believes that these latter cells represent the specific elements of the carotid gland.

Up to the present only scattered observations have been made on the development of the glandula intercarotica in man. R. Paltauf investigated an embryo of 15 mm. and a fetus of 45 mm.; in the former the gland had not yet appeared; it was present in the latter, but the thickening of the internal carotid artery mentioned above was also present. (According to Kohn the cells of the anlage of the gland in a 19 mm. (NL) embryo resemble neither the small, deeply staining ganglion-cells of the intercarotid plexus nor the chromaffin cells.)

In Fig. 108 the anlage of a carotid gland of a 19¾ mm. embryo is shown. The plexus intercaroticus contains richly vascular masses of small cells, which follow the course of the nerves descending from the superior cervical ganglion and are connected with the cells of the ganglion. The process that extends from the ganglion

to the plexus intercaroticus on the medial side of the internal carotid consists apparently of sympatho-chromaffin tissue, and also furnishes the material for the specific cells of the carotid gland. In a 28 mm. embryo the differentiation of the parasympathetic cells is already accomplished.

Chromaffin Bodies in the Abdominal Plexuses.—In the abdominal sympathetic plexuses the sympatho-chromaffin tissue separates

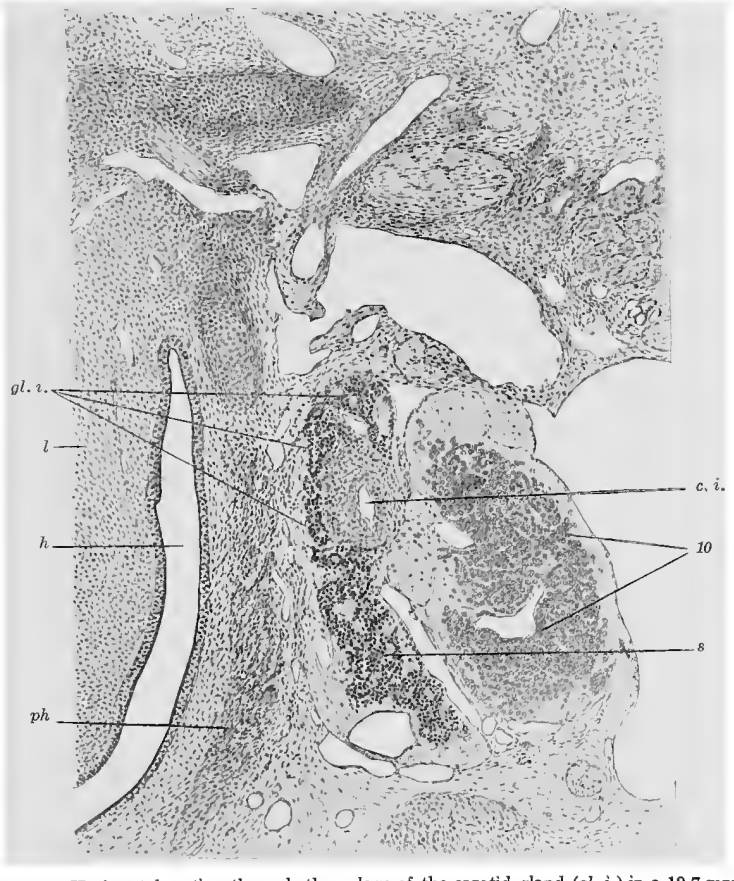

FIG. 108.—Horizontal section through the anlage of the carotid gland (*gl. i.*) in a 19.7 mm. embryo. ×100. *c. i.*, internal carotid artery; *h*, pharyngeal cavity; *ph*, wall of pharynx; *l*, larynx; *s*, superior cervical ganglion; 10, ganglion nodosum of the vagus; the white spaces represent cervical veins.

into an extensive ventral parasympathetic and a much weaker dorsal sympathetic layer; the latter at places also bounds the former laterally. The two kinds of tissue, accordingly, very early arrange themselves in the abdominal plexuses in the manner characteristic of the adult condition (Fig. 109). The youngest embryo with differentiated chromaffin bodies has a length of 18–19 mm. Before this stage sympatho-chromaffin tissue occurs everywhere in the places later occupied by the abdominal sympathetic plexuses,

and is especially abundant in the region between the two suprarenal glands (plexus cœliacus and suprarenalis) and in front of the aorta (Fig. 110). Here it pushes its way between the aorta and the left renal vein and extends downward to below the origin of the inferior mesenteric artery. These masses are mainly destined for the formation of the two extensive aortic bodies (compare Fig. 110 with Fig. 109). In an 18 mm. embryo there are already present on either side two chromaffin bodies, an upper, smaller one above the renal vein and a lower, larger one (aortic body) caudad to this vein. These two bodies extend from the 21st vertebra to in front of the 24th, or on the left side to the disk between the 23d and 24th vertebræ. The vascular connective-

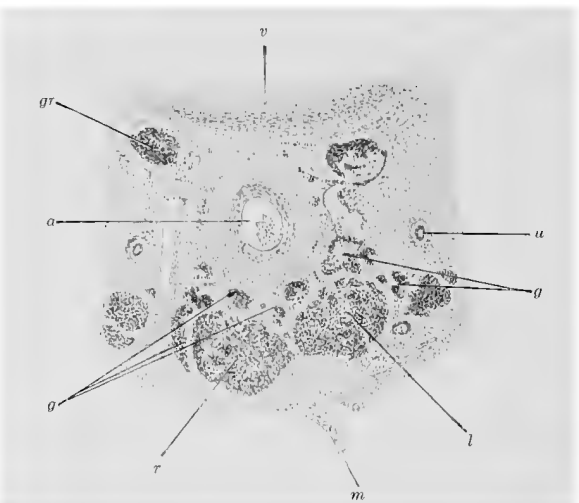

FIG. 109.—Horizontal section through the sympatho-chromaffin anlage of the aortic bodies (*r* and *l*) and through the aortic plexus (*g*) in an embryo of 19 mm. *a*, aorta; *gr*, gangliated cord; *m*, mesentery; *u*, ureter; *v*, vertebra.

tissue trabeculæ in the interior of the body, whose meshes the cell-cords occupy, are already plainly distinguishable in a 19.5 mm. embryo, and in a well-preserved 19 mm. embryo the differentiation of the sympathetic and chromaffin tissues has just begun (Fig. 109). This is at first shown by the cells in the chromaffin bodies (*r* and *l*) becoming in places less closely packed together than they are in the sympathetic ganglia (*g*). It seems that the development of a vascular connective tissue, which divides the cell-masses into cords, permits of a looser texture in the bodies.

In the section figured the chromaffin bodies are separated from the ganglia of the plexus by a cleft (see Fig. 109). This is apparently an artefact due to the knife.

In the course of the further development new chromaffin bodies are added to those already present, so that in all from seven to twenty-six or even more—in one case nearly seventy—of these

bodies may be counted. An increase in the number may also occur by several small bodies developing in place of a single large one.

The largest of all are the aortic bodies (Fig. 111, *r* and *l*); their cranial ends lie at the origin of the superior mesenteric artery or at those of the renal arteries, and their lower ends are situated at the level of the division of the aorta (on the right side) or immediately above this (on the left side). The two bodies lie at the sides of the inferior mesenteric artery and their lateral borders may be in contact with the kidneys and the ureters. In fetuses

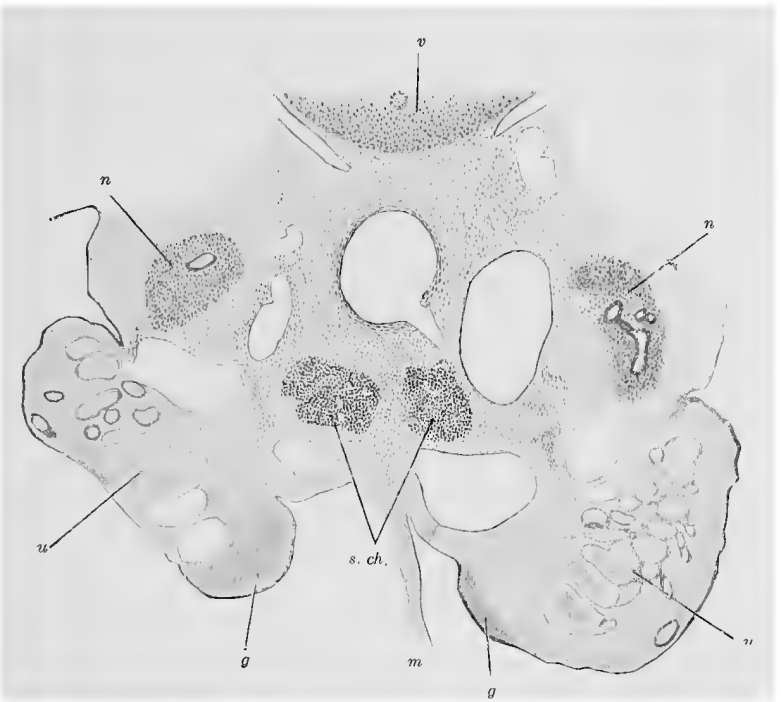

FIG. 110.—Horizontal section through sympatho-chromaffin anlage of the aortic bodies and the aortic plexus (*s. ch.*) in an embryo of 14.5 mm. ×50. *a*, aorta; *g*, reproductive gland; *m*, mesentery; *n*, kidney; *u*, mesonephros; *v*, vertebra.

of 4–5 cm. their length is over 1 mm.; in new-born children the average length of the right one is 11.6 mm. and that of the left one 8.8 mm. The upper ends of the bodies are frequently (14.8 per cent. in new-born children) united by a connecting bridge (isthmus, Fig. 111, *i*), which lies over the aorta below the superior mesenteric artery. When the isthmus is wanting the upper end of the right body sometimes becomes much broadened and a division of the parenchyma into two portions is indicated by a connective-tissue septum (Fig. 111, *D*). In connection with the hypogastric plexus four chromaffin bodies (two on each side) are usually developed; their number may be increased up to seven.

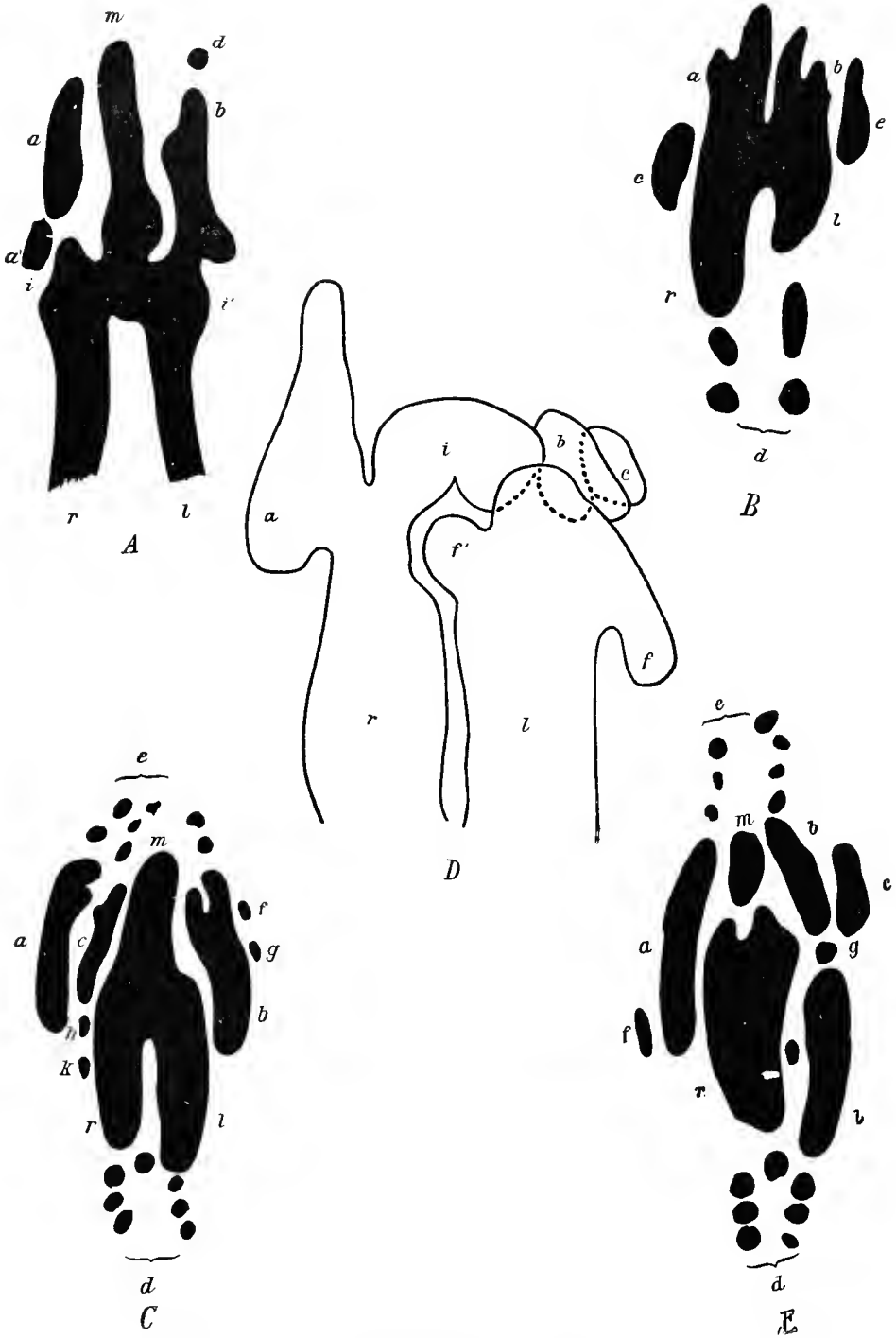

FIG. 111.—Chromaffin bodies of the abdominal plexuses. An explanation of the lettering will be found in the table on p. 167.

Number of bodies.	Isthmus (*i*).	Aortic bodies: *r* (right side, *l* (left side).	Cranial bodies.			Small bodies.
			Right side (*a*).	Left side (*b*).	Median (*m*).	
Fig. 111, *A*, with 12 chromaffin bodies.	Present.....	Branching off from the isthmus. Only the upper halves of the aortic bodies are shown.	Independent and divided into 2 parts (*a* and *a'*). Body *a* lies on suprarenal gland, *a'* lateral to vena cava inf.	Branching off from the isthmus.	Branching off from the isthmus and extending up to origin of sup. mes. art. in front of the aorta.	One (*d*) cranial from process *b* and behind the renal vein; 2 dorsal from process *b*. One in the unpaired and 2 or 3 in the lateral parts of the pl. hypogastricus.
Fig. 111, *B*, with 9 chromaffin bodies.	Present.....	Branching off from isthmus. Cranial part of right body lies lateral to aorta on kidney and suprarenal gland and is especially deep.	Branching off from the isthmus and lying in front of the aorta and on the medial side of the suprarenal gland.	Branching off from the isthmus and lying in front of the aorta.	Wanting.	2 in each lateral half of the pl. hypogast. (*d*); 1 (*c*) in front of pelvis of right kidney, on the anterior lip of hilus; another (*e*) partly on left renal hilus, partly on the suprarenal gland.
Fig. 111, *C*, with 22 chromaffin bodies.	Present.....	Branching off from the isthmus.	Independent, resting on the kidney and suprarenal gland (*a*).	(*b*) corresponding in position to body *a*.	Strong, situated in front of the aorta and extending upward to the origins of the renal arteries.	7 in pl. hypogast. (*d*); 5 on median side of rt. suprarenal, 2 (*e*) on that of left; 2 (*f,g*) lateral to *r*, 1 tangential to kidney and other to ureter; 1 in front of aorta between *a* and *m*.
Fig. 111, *D*, with 13 chromaffin bodies.	Included in the right body and incompletely div. into 2 parts by connect.-tissue sept. in median line.	Independent and at one place quite deep. *f, f'*, processes of left body, former resting on kidney and suprarenal gl. Only upper halves of aortic bodies are shown.	Branching off from the right aortic body and situated on the medial side of the suprarenal gland.	Wanting; perhaps represented by body *b*.	Wanting	2 in the pl. hypogast., 4 in the pl. renalis; 2 between the aorta and the left kidney. 1 on the medial side of the right suprarenal gland; 2 (*b* and *c*) dorsolateral to l and resting on the suprarenal gland.
Fig. 111, *E*, with 26 chromaffin bodies.	Included in the right aortic body.	The left is much smaller than the right.	Independent; rests on the kidney, the suprarenal gland, and the ureter.	Represented by 2 bodies (*b*, *c*). *b* lies in front of the renal art., *c* in front of the vena cava inf. and on the medial surface of the suprarenal gland.	Independent, situated in front of the aorta.	7 (*d*) in pl. hypogast. 7 (*e*), 3 in right and 4 in left, on med. side of suprarenal gl. 1 on dorsal side of each of the bodies *a, b*, and *c*. 1(*f*) lateral to *a*. 1 (*g*) bet. *b* and *e*, sit. in front of renal art. and resting on kidney. 1 bet. *r* and *l* in pl. mes. inf.

Above the aortic bodies other cranial chromaffin bodies occur, either independent or branching off from the isthmus and lying on

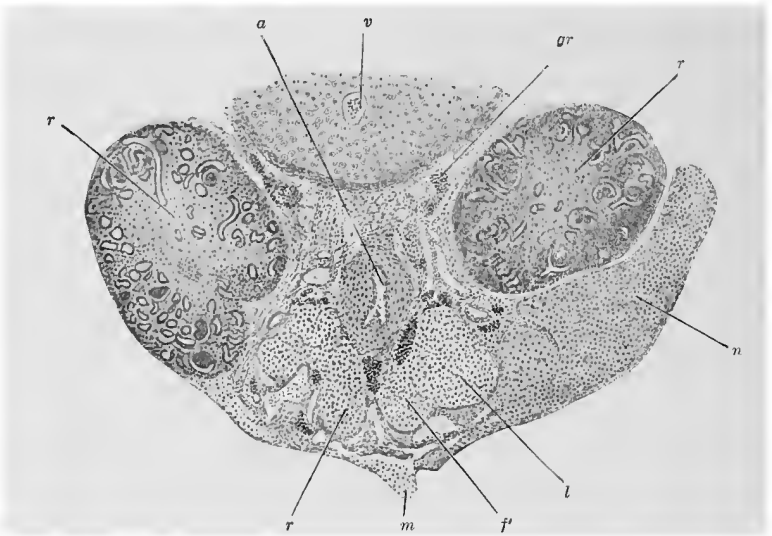

FIG. 112.—Horizontal section through the aortic bodies of Fig. 111, D, passing through the process *f'*. From a 23 mm. embryo. ×40. *r* and *l*, right and left aortic bodies; *a*, aorta; *gr*, gangliated cord; *m*, mesentery; *n*, suprarenal gland; *r*, kidney; *v*, vertebra. The darkly stippled areas in the neighborhood of the aortic bodies represent anlagen of the sympathetic ganglia.

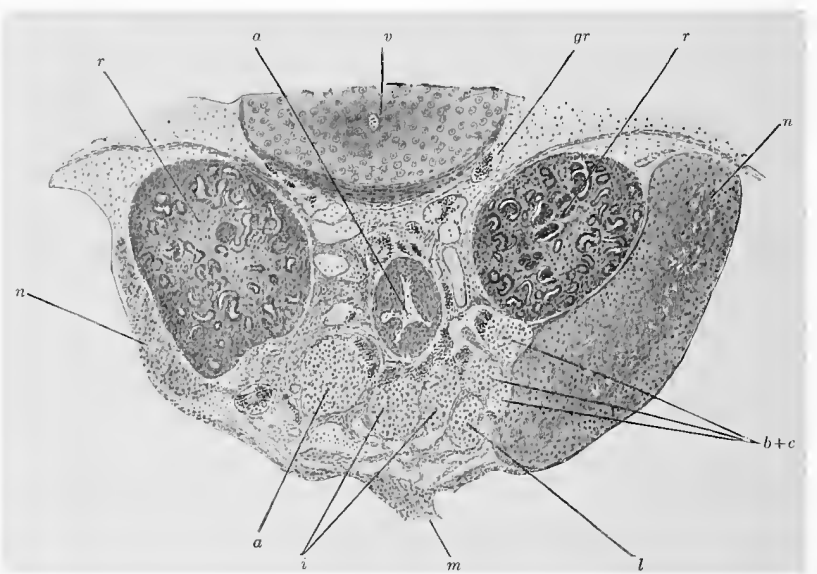

FIG. 113.—Horizontal section through the chromaffin bodies *a*, *i*, *b*, *c*, and *l* of Fig. 111, *D*. From a 23 mm. embryo. × 40. *a*, aorta; *gr*, gangliated cord; *n*, suprarenal gland; *r*, kidney; *v*, vertebra. The darkly stippled areas in the neighborhood of the chromaffin bodies represent anlagen of plexus ganglia.

the plexus cœliacus and plexus suprarenalis. Most frequently there is a large body on each side on the medial border of the suprarenal gland (Fig. 111, *A* and *B*). These bodies may be prolonged down-

ward for some distance, lateral to the isthmus; they are not infrequently of considerable thickness (Fig. 112) and may be divided into two portions along their anteroposterior diameters. It may also happen that two lateral bodies are formed on each side, in which case one lies in front of the aorta and the other on the suprarenal gland (Fig. 111, *B*). Occasionally, in addition to the lateral bodies a median one also branches off from the isthmus and extends in front of the aorta up to the origin of the superior mesenteric artery.

The fact that the chromaffin bodies of the plexuses send off processes or branch, brings it about that the same body may be cut

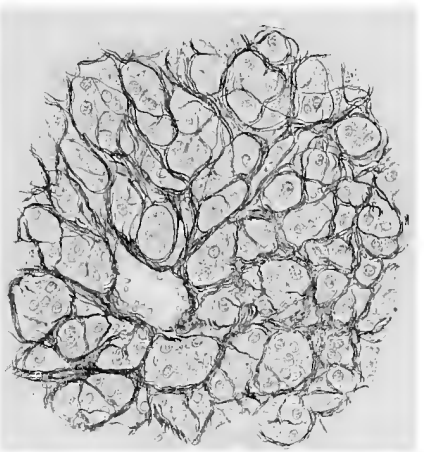

FIG. 114.—Horizontal section through the chromaffin aortic body of a new-born child (Bielschowsky's stain). ×200.

several times, so that in the study of sections more bodies may seem to be present than is actually the case (compare Figs. 111, *D*, and 113).

The size of the chromaffin bodies in relation to the neighboring organs may be seen from Figs. 112 and 113. Compare, for instance, the aortic bodies or the isthmus with the aorta.

In the new-born child the chromaffin bodies of the plexuses have a smooth, light-brown surface; the capsule sends numerous processes into the interior, which primarily bound the cell cords (Fig. 114). The vascular system is richly developed in them.

The chromaffin bodies of the plexuses are in no way homologous with the suprarenal bodies, even although they are identical in structure. There is, of course, correspondence between the two kinds of bodies in so far that all chromaffin bodies are derived from sympatho-chromaffin tissue, but the topographical factor must not be neglected to the extent of identifying, without further evidence than this, bodies that occur in association with the gangliated cord with others that occur in the ganglia of the plexuses.

In the post-fetal periods of life the chromaffin bodies present signs of degeneration without actually disappearing. In adults the aortic bodies can no longer be perceived by the naked eye, although microscopic investigation will reveal the presence of chromaffin tissue in the regions formerly occupied by them. Thus it was not possible to dissect out the aortic bodies in the body of an individual of 39 years of age, but microscopic investigation showed the presence of chromaffin bodies, 1.5 cm. in length but

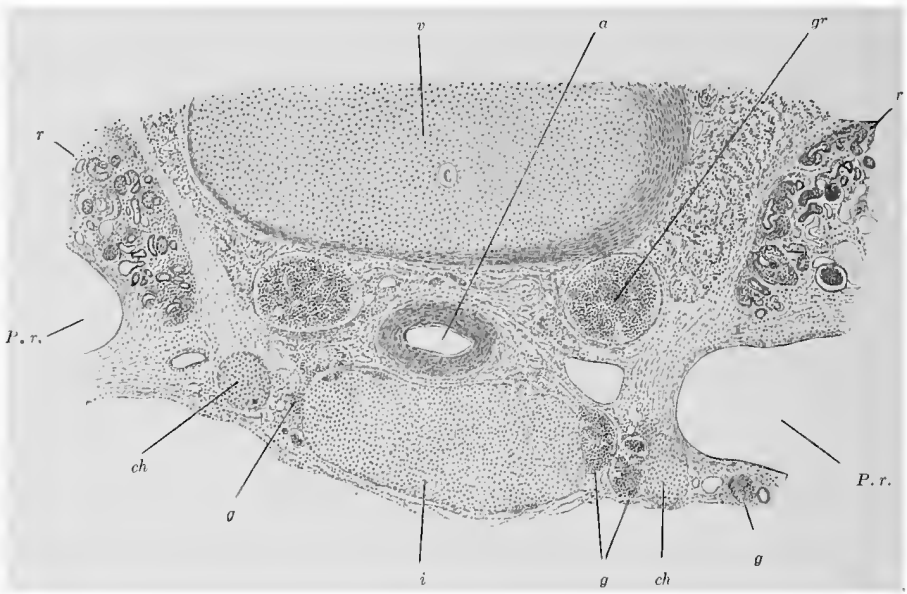

FIG. 115.—Horizontal section through the isthmus (*i*) of the aortic bodies of an embryo of 60 mm. *a*, aorta; *ch*, chromaffin body on the pelvis of the kidney (on the left side) and in front of a branch of the renal artery (on the right side); *g*, anlagen of plexus ganglia; *gr*, gangliated cord; *r*, kidney; *P. r*, pelvis of kidney; *v*, vertebra.

poor in parenchyma, in the sympathetic trunks running on either side of the inferior mesenteric artery in front of the aorta. Similar observations were made upon a child of nine years and a youth of nineteen; but in these two cases, as well as in that of a youth of fifteen with well-preserved aortic bodies and a child of two years whose aortic bodies were poor in parenchyma and showed signs of hyaline degeneration, the bodies under consideration could be detected macroscopically.

The Suprarenal Gland.

The suprarenal glands are composed of two substances, the cortex and the medulla, differing in their structure and development. The former is derived from the cœlom epithelium, the latter from the sympatho-chromaffin tissue. The cortical cells appear before those of the medulla and the cortex is already a relatively

large body before it receives the anlage of the medulla. The embryonic suprarenal glands of man and also of the other mammals resemble for some time the interrenal bodies of the Selachians, which, as is known, are composed throughout life of cortical substance only.

A. H. Soulié finds the first traces of the suprarenal glands in an embryo of 6 mm., and in correspondence with this Poll correctly assigns their appearance to the beginning of the fourth week of development. The anlage of the organ, according to Soulié, takes the form of buds composed of cells which project from both sides of the root of the mesentery into the mesoderm situated ventral to the aorta. In a 6.5 mm. embryo of my collection the region of the future suprarenal gland is indicated by mitoses in the cœlomic epithelium, and beneath the epithelium formative cells are closely aggregated, although they do not yet show the characteristics of the cortical cells. In an 8 mm. embryo the glands are already definite organs, completely separated from the cœlom epithelium. With this the observations recorded in the Normentafel of Keibel and Elze agree. In a 9 mm. embryo the suprarenal glands are already vascularized, but the central vein becomes visible only later (according to the material at my disposal only in an embryo of 23 mm.).

In young embryos the suprarenal cortex is composed of elements that are larger than the sympatho-chromaffin cells and stain readily when treated with the ordinary staining reagents. The connective-tissue capsule of the organ has a somewhat looser texture on the medial than is the case on the lateral surface, a condition that has some importance in connection with the immigration of the sympatho-chromaffin tissue.

The suprarenal glands that have separated from the cœlom epithelium in embryos of from 8 mm. to 12 mm. lie on either side in a *projection of the posterior wall of the cœlom* (*the suprarenal ridge*) which is situated medial to the mesonephros, that is to say, between this and the mesentery, and is continued cranially, without any distinct delimitation, into the dorsal portion of the pleuroperitoneal membrane (the dorsal pillar of the diaphragm), a portion of the gland projecting into this pillar. The suprarenal ridge and the pleuroperitoneal membrane are separated from the mesonephros by a groove.[2]

In an embryo of 11 mm. in the region of the stomach and the caudal extremity of the lungs the suprarenal ridges have united by means of a fold (the caudal limiting fold of Hochstetter) with the dorsal surface of the liver on the right side and on the left

[2] Similar relations occur in animals, the differences being only those of detail. Thus, for example, in an 11 mm. cat embryo the suprarenal ridge does not project as much as in man and is not separated from the mesonephros by a groove.

with the junction of the stomach and œsophagus. The caudal limiting fold, which separates the caudal portion of the pulmonary niche from the lateral portion of the abdominal cavity, has the same relations in man as in other mammals. A comparison of a horizontal section through this fold in a human embryo of 11 mm. with a similar section of a 10 mm. cat embryo shows almost exact correspondence. In Hochstetter's figure of a horizontal section through the fold in a 10.2 mm. cat embryo the suprarenal gland, it

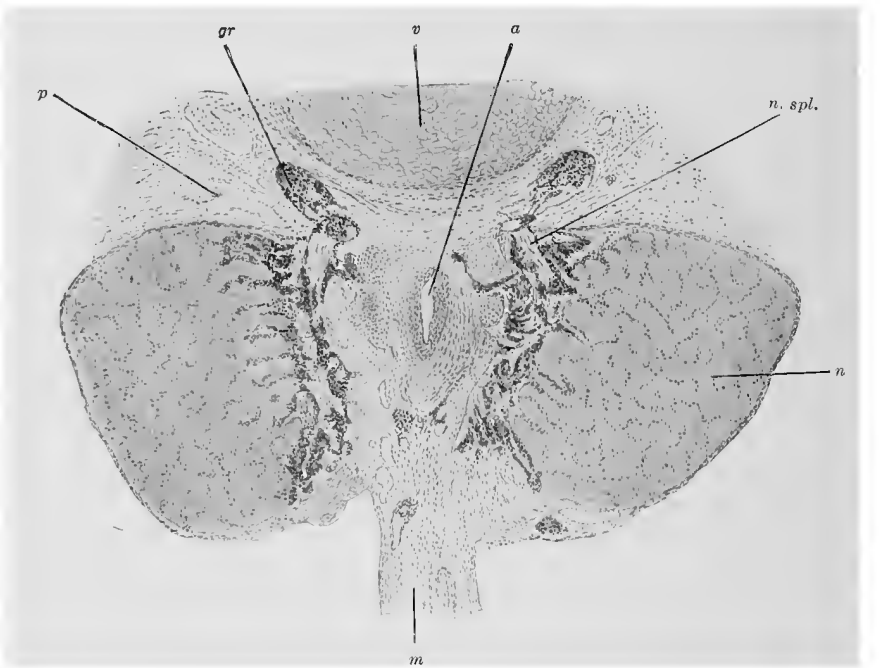

FIG. 116.—Horizontal section through the suprarenal gland (*n*) of a 17 mm. embryo. ×60. *a*, aorta; *gr*, gangliated cord; *m*, mesentery; *n. spl.*, splanchnic nerve; *p*, pleuroperitoneal cushion; *v*, vertebra. The darkly stippled masses, traversed by nerves, lying on the medial side of the suprarenal glands and sending processes into their substance, are sympatho-chromaffin tissue.

is true, is not shown, but, as I have convinced myself, the dorsal half of the fold is given off from the suprarenal gland also in the cat.

The posterior surface of the gland rests upon a coarsely meshed, almost œdematous, pleuroperitoneal cushion (the tissu muqueux lâche peripleural of Brachet), which, as in animals, projects extensively behind the thoracic portions of the cardinal veins (Fig. 116). In embryos of 14 mm. and 15 mm. this cushion has an extensive development, while in an embryo of 28 mm. it has already undergone a great amount of retrogression. The mesonephros and the suprarenal ridges are also attached to the cushion.

The medulla of the glands is formed by the migration of masses of sympatho-chromaffin cells from the medial side toward

the centre of the organ, so that they surround the central vein as the anlage of the medullary nucleus. In no preparations could the immigration of parasympathetic cells be observed, to say nothing of fully differentiated medullary cells. The elements of the migrating cell masses, which are entirely or for the most part composed of chromaffin formative cells, are sharply distinguished from the neighboring cortical cells by their smallness and their intense stain (Fig. 118, *s. ch.*). It is conceivable that their "im-

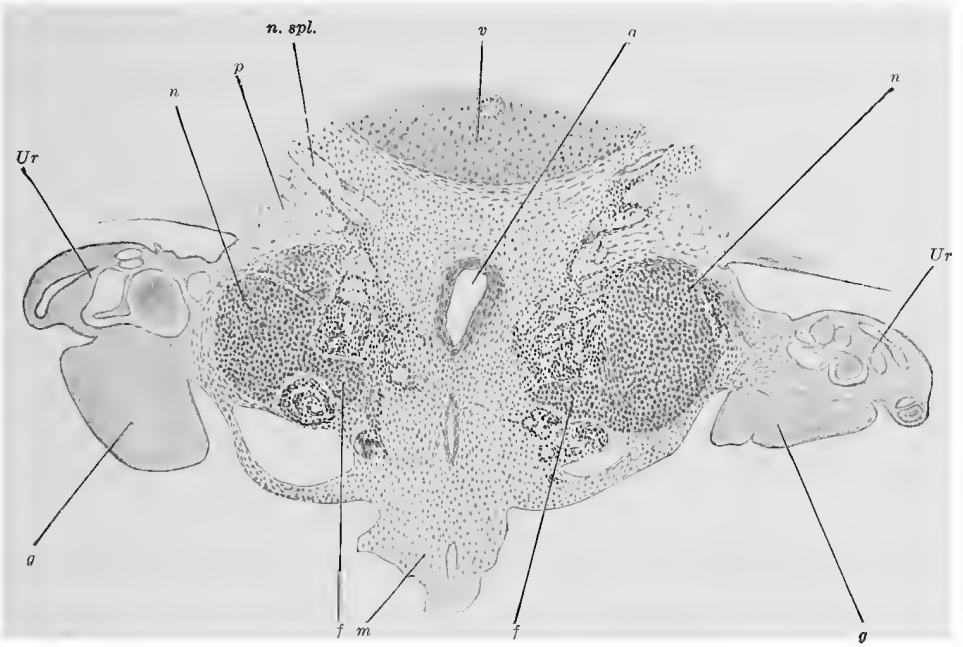

FIG. 117.—Horizontal section through the region of the suprarenal glands in an embryo of 15 mm. ×50. *a*, aorta; *f*, process of the suprarenal gland (*n*) that projects into the sympatho-chromaffin tissue (represented by the darkly stippled masses medial to the gland); *g*, reproductive gland; *m*, mesentery; *n. spl.*, splanchnic nerve; *p*, pleuroperitoneal cushion; *Ur*, mesonephros; *v*, vertebra.

migration," the cause of which has not yet been explained, may be inhibited and that the primitive form of the glands may exceptionally persist even in man.

The immigration of the sympatho-chromaffin tissue begins, as A. H. Soulié also finds, in embryos of about 19 mm. Processes of the adjacent sympatho-chromaffin tissue may, it is true, be observed penetrating and splitting up the medial portions of the glands even in embryos of 8 mm. (Fig. 116), and in some cases cortical processes (Fig. 117, *f*) or accessory suprarenal glands occur at an early stage in this region, but the immigration at these stages does not extend far beyond the region mentioned.[3]

[3] Cortical processes not infrequently persist and project by their free terminal portions into the neighboring nerve-plexus.

The association of the various cell masses to form the sympatho-chromaffin medullary nucleus of the glands does not take place until quite late. In embryos of from 6 cm. to 11 cm. (vertex-breech measurement) some masses have already reached the central vein, others, indicating that the immigration into the cortex is still continuing, have reached as far as the zona glomerulosa, and even in a fetus of 19 cm. the sympatho-chromaffin formative mass intended for the gland has not yet reached the centre of the organ. At first the central vein is surrounded by a continuous

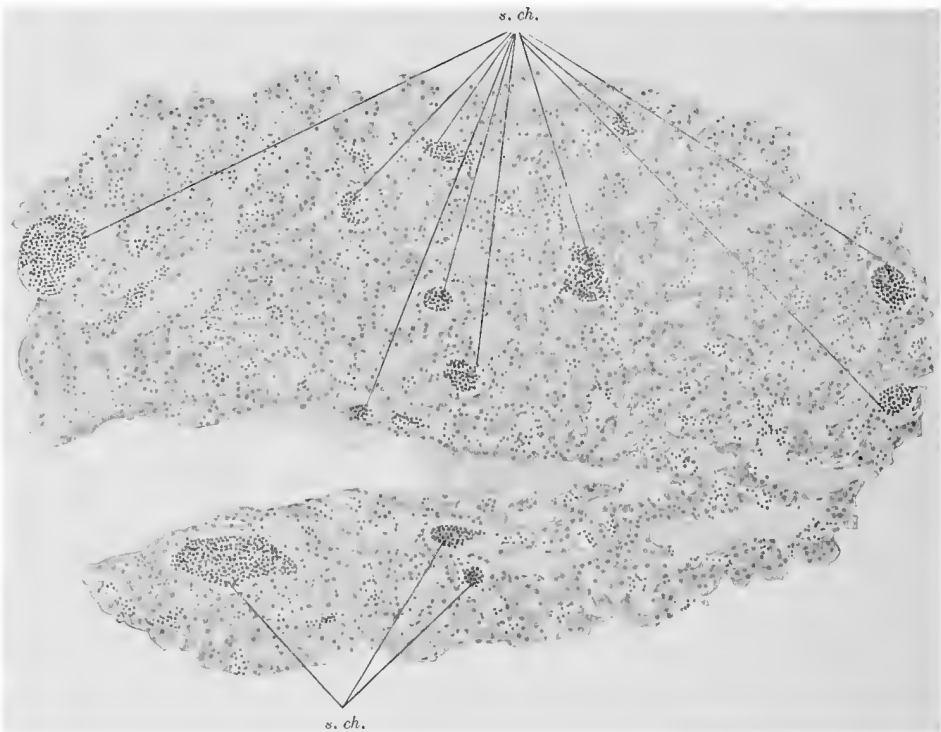

FIG. 118.—Section through the suprarenal gland of an embryo of 95 mm. (vertex-breech measurement), showing immigrated masses of sympatho-chromaffin cells (*s. ch.*). Some of these have already penetrated to the central vein.

layer of sympatho-chromaffin tissue only at a circumscribed region. On the other hand, in an embryo whose suprarenal gland had reached a greatest length of 9 mm. the immigration of the medulla was completed and the extensive medullary nucleus surrounding the central vein already gave the chrome reaction. In view of these observations, the remark of R. Meyer that already in an embryo of 26 mm. the sympathetic cells had reached the centre of the organ seems scarcely reliable.

The immigration of sympatho-chromaffin tissue into the gland seems to be continued even in post-fetal life, for J. Wiesel has found cell masses in the cortex even in new-born children.

In contrast with the fact that in an embryo of 19 cm. sympathochromaffin tissue still occupies the place of the medullary substance, it seems worthy of remark that occasionally in young fetuses (5–6 cm.), in addition to the wandering cell masses toward the centre of the gland, a circumscribed area of the medial surface together with the adjacent cortical layers is infiltrated with parasympathetic tissue. The circumstance that parasympathetic tissue is already developed in the region mentioned, while the adjoining cell masses destined to form the medulla have not yet passed beyond the stage of formative cells, indicates that it is a question of local parasympathetic infiltration.

Occasionally the path of the completed immigration is indicated by a process of the medulla, either simple or divided into several portions, which, directed toward the surface, either ends

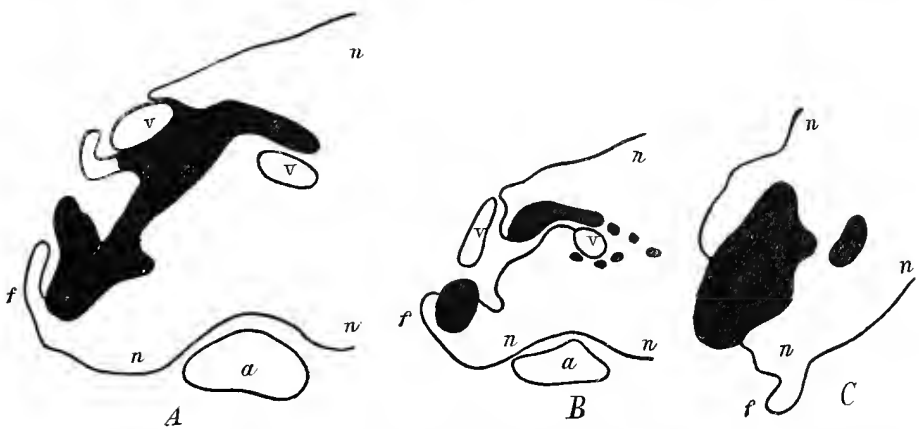

Fig. 119.—Sections through the medial portion of the suprarenal gland of a new-born child. *a*, accessory suprarenal; *f*, process of the suprarenal gland (*n*); *v*, veins. The chromaffin tissue and the medulla of the suprarenal gland in black.

there or passes over into a neighboring chromaffin body (Fig. 119). A similar condition has been observed in various mammals, as, for instance, in the mouse by M. Inaba.

The differentiation of the cortex into three layers takes place rather late. The zona glomerulosa is lacking even in the older fetuses, and according to O. Scheel it is formed between the second and third year and only reaches the characteristic adult structure in the later years of childhood. The zona reticularis may be recognized in an embryo of 14.5 mm., and it would seem, as Gottschau and Mitsukuri have suggested, that its form is determined by that of the venous network, which, as is known, has an extensive development. The superficial layers of the cortex, even in older fetuses, are occupied by cells which, as A. Kohn has also pointed out, are smaller than the other cortical cells. They stain blue on treatment with hæmatoxylin and eosin, whereas the cells of the

zona fasciculata and those of the zona reticularis take the eosin. A. Roud, who stained the suprarenal of the mouse with eosin and toluidin, observed a similar reaction; he recognized a cyanophil zona glomerulosa as a younger form of the remaining eosinophil cortical cells.

The Development of the Accessory Suprarenal Glands.

The majority of authors agree that the accessory suprarenal glands represent separated portions of the parent organ, and J. Wiesel succeeded in showing that the immigration of the sympatho-chromaffin tissue plays an important part in the separation. This immigration, that is to say, produces a cleavage of the medial surface of the suprarenal gland, as a result of which there is a separation of smaller or greater portions of the gland. This mode of development concerns, however, only those accessory suprarenal glands that occur in the region where the cleavage of the cortex by the sympatho-chromaffin tissue occurs.

The accessory glands either remain in the vicinity of the principal gland or they may eventually be situated far away from it if they become associated with organs that alter their position (accessory suprarenal glands on the spermatic vessels, in the ligamentum latum, and on the epididymis).

The accessory glands consist for the most part only of cortical substance, yet the fact that they occasionally also contain medullary substance shows that their separation is frequently due to the sympatho-chromaffin tissue. In fifty children that were examined with a view to determine the occurrence of accessory suprarenal glands, only one was found containing medullary substance. It was imbedded in the cœliac plexus, and one half of it consisted of a chromaffin body and the other half of cortex. A process of the suprarenal gland, similar to that represented in Fig. 119, *B, f,* had probably separated from the principal organ in this case. In other cases the chromaffin tissue migrates toward the centre of a cortical process, and thus there is formed later an accessory gland which is a diminutive copy of the principal organ. The accessory glands with medullary substance are accordingly divisible into two groups, those with peripheral and those with central medullary substance. Medulla and cortex may interpenetrate to such an extent that a process of the cortex or an accessory gland may consist of a thin cortical layer enclosing in addition to chromaffin tissue some scattered cortical trabeculæ.

Accessory glands may also be formed in another way, namely, by portions being separated from the surface of the cortex in the region of the capsule, the general conditions remaining normal. To such separations are to be referred the nodular projections and spherical accessory glands that so frequently, even in large

numbers, are to be found scattered over the surface of the suprarenal glands. They frequently imbed themselves in cavities in the organ and should not be confused with adenomata. Some of the nodes may come to lie in clefts in the neighboring sympathetic plexuses, and these show their origin from the superficial layer of the cortex by the fact that they are composed of zona glomerulosa alone. O. Aichel recognizes still another mode of formation for the accessory glands, in deriving those associated with the reproductive organs from cross canals of the mesonephros that are in process of retrogression. This idea, however, is quite as erroneous as another of the same author, by which the accessory glands are identified with the suprarenal bodies.

A. H. Soulié also assigns the free chromaffin bodies to the category of accessory suprarenal glands. He seems to cling to the old idea that these bodies belong to the medullary substance of the suprarenal glands. The atrophy which they undergo later on is explained by their having no connection with the suprarenal gland with which they should be associated functionally. The incorrectness of this last supposition is shown by the fact that the chromaffin bodies do not atrophy in all mammals (for example, in Cavia cobaya), and in the Selachians an intimate relationship between the interrenal and suprarenal bodies does not really exist. Furthermore it may be pointed out that the anlage of the medullary substance is also originally free and lies outside the suprarenal glands. The primitive condition of the chromaffin bodies is represented by independent organs, entirely unconnected with the suprarenal glands, and for this very reason there are no grounds for terming the free chromaffin bodies accessory suprarenal glands.

Finally, it may be remarked, that the formation of accessory suprarenal glands from special buds of the cœlom epithelium is also conceivable, but up to the present there is no evidence that such a method occurs.

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XVI.

THE DEVELOPMENT OF THE SENSE-ORGANS.

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General Considerations.

Not only are stimuli perceived that come to the body from the exterior, but also the internal conditions, such as the position of the joints and the tension of the muscles. For the reception of both kinds of stimuli special apparatus, the sense-organs, may be developed. On account of the surpassing importance and the variety of the external stimuli, the sense-organs for their reception are much more perfectly and variously developed than are those for the perception of internal processes; indeed it is even doubtful whether the tendon and muscle spindles should be regarded as sense-organs, and the lamellate bodies have recently on good grounds been denied that character (Ramström, 1908, and von Schumacher, 1907). Furthermore it is to be noted that the entire external skin possesses in addition to other functions that of a sense-organ; its development, as well as that of the hairs and hair-disks which belong to it, has been considered in a special chapter.

In the higher sense-organs (the eye and ear) and the olfactory organ the portions which receive the stimuli are derived from the ectoblast. The gustatory organs, as will be shown later, are possibly, indeed probably, derived from the entoblast. As regards the organs of internal sensation, free nerve terminations must be regarded as the stimulus receptors, just as they are in the external skin; that which at first sight appears to be the sense-organ should really be regarded as accessory apparatus and is developed from the mesoblast.

The Touch-cells, the Lamellate Corpuscles (Vater-Pacinian Corpuscles), the End-bulbs (W. Krause's Corpuscles), the Touch-corpuscles (Meissner's Corpuscles), the Sexual Corpuscles.

It has just been pointed out above that free nerve terminations must be regarded as the stimulus receptors in all the organs mentioned here. As to the development of the accessory apparatus, if the skin and its organs, which have been specially considered, be left out of the question, very little is known. The development of the lamellate corpuscles in man has not, to my knowledge, been investigated in recent times.

Henle and Kölliker made some observations upon them in 1844. These authors recognized them in the sixth month of preg-

nancy as cell masses without any special arrangement of the cells; in the new-born child they appeared to be quite similar to those of the adult, except that they were smaller and had little or no fluid between the lamellæ. W. Krause (1860) found them relatively far developed at a much earlier period. "A corpuscle from the volar surface of the index-finger of a fetus at the end of the fifth month of pregnancy, which he measured, had a length of 0.29 mm. and a breadth of 0.11 mm.; the outermost capsule was quite distinct and the innermost was also recognizable; the rest were merely indicated and possessed an enormous number of oval nuclei arranged lengthwise. Transverse fibres could not be detected. The nuclei just mentioned occurred also in the central cavity, which was 0.225 mm. in length and 0.018 mm. in breadth, and in its axis was a very distinct, glistening terminal filament which had a diameter of 0.0038 mm. and ended close to the peripheral part of the inner cavity with a slight enlargement."

Davydow (1903) has recently investigated the development of the lamellate corpuscles of the cat, but I know of his results only through Weinberg's abstract of them in Schwalbe's Jahresbericht, Neue Folge, Bd. x (1904). According to this the Vater-Pacinian corpuscles in their earliest stages consist of a small number of connective-tissue cells. By rapid increase these cells soon form round or oval cell groups; the roundish elements become altered centrally into elongated ones, and finally all are employed in the formation of the lamellæ of the developing Pacinian corpuscle. In the new-born cat a rapid increase in the number of Pacinian corpuscles takes place by budding. In the division the Timofejew apparatus is usually formed from a common fibril-bundle, an arrangement which indicates the possibility of a functional coöperation of several Pacinian corpuscles.

There are also some observations on the development of the touch-corpuscles by W. Krause (1860). He found them in a seven months' fetus in the tips of the papillæ of the vola manus. According to Krause the new-born child possesses in its little fingers and toes just as many touch-corpuscles as does the adult individual, and it must therefore possess a more delicate sense of distance. New touch-corpuscles and especially terminal corpuscles do not form after birth. With these results those of Ranvier (1880–1881) do not quite agree. Ranvier starts with observations made by Langerhans (1873) on young children. According to him the development takes place essentially after birth. In the new-born child one sees in vertical sections through the finger pulp at the summit of most of the papillæ, immediately below the first row of epithelial cells, some transverse striæ and, somewhat deeper, an island of roundish mesoblast cells. The transverse striæ represent a nerve telodendron: the nerve ascends directly to the summit of the papilla and there divides into a small number of branches, which terminate in enlargements. These branches lie horizontally, as if they had been forced up through the cell island against the bases of the epithelial cells. In children 50 days old the nerve

telodendron has developed greatly, its branches are more numerous and thicker and the mesoblast cells have penetrated between them (Fig. 120). In the sixth month the upper lobe of the composite corpuscle has reached its definitive form. It is well delimited, and in its interior one sees a certain number of telodendra separated by cells that are weakly flattened transversely. The second lobe is in process of formation. At the base of the first lobe one sees, that is to say, a new nerve telodendron and beneath this is a group of roundish cells that seem about to penetrate it. The contradictions contained in the observations of Krause and Ranvier are perhaps only apparent ones. Ranvier has not examined the youngest stages and Krause has not considered the development of the finer parts of the small organ. Krause (1869) has also investigated the development of the spherical end-bulbs in the conjunctiva bulbi of man; in a six months' fetus they had the appearance of masses of nuclei or cells, nevertheless they already possessed a distinct investing membrane.

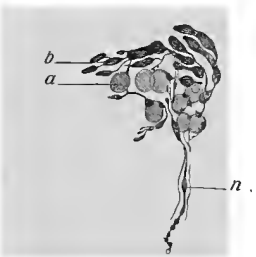

FIG. 120.—Touch-corpuscle of a child of 50 days, treated with gold chloride. *n*, nerve; *b*, nerve telodendron, between the branches of which the cells of the subjacent node are penetrating. (After Ranvier, from his Histologie, translated by Nicati and Wyss, Leipzig, 1877.)

The Epibranchial Sense-Organs.

Epithelial thickenings that may be found dorsal to the branchial clefts of embryos of from 4 to 12 mm. may be regarded as rudimentary sense-organs. These thickenings, which are termed sense-placodes, occur in connection with the vagus, glossopharyngeal, and facial nerves, and less distinctly with the trigeminus, cells being given off from the ganglia of these nerves: they may then be transformed into small epithelial pouches. See regarding them Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen (1908), Plates 10–45, Ingalls (1907), and the chapter in this work on the development of the peripheral nervous system. The placodes have probably a great importance from the standpoint of comparative anatomy and embryology. It is supposed that the auditory and olfactory organs have been formed from such placodes, and the lens of the eye has also been derived from a placode; this may have been originally the actual sense-organ. On this point see Brachet (1907a and 1907b).

The Gustatory Organ.

The tongue is frequently spoken of simply as the organ of taste, and one may say of a person that he has a good tongue just as one might say he has a good eye; but on the one hand the tongue

is not merely a gustatory organ, and on the other hand, the organs that are receptive for taste, the taste-buds, are not limited in their distribution to the territory of the tongue. Accordingly the development of the tongue will be treated along with that of the digestive tract, and we have to discuss here in the first place the development of the taste-buds. Brief consideration must also be given to those papillæ of the tongue which are to be regarded as accessory organs of the gustatory sense. The territory within which taste-buds are found in man is quite extensive. Their principal situation in the adult individual is on the papillæ vallatæ; but they have also been described as occurring on the papillæ foliatæ and the papillæ fungiformes, on the under surface of the tongue on the plica fimbriata (Ponzo, 1905[1], 1905[2], and 1907), on both surfaces of the epiglottis and also in the mucous membrane of the larynx itself, and in the region of the arytenoid cartilages (Davis, 1877). They are also said to occur in the anterior surface of the soft palate, especially in the neighborhood of the uvula (A. Hoffmann, 1875, W. Krause, 1876). Von Ebner (1899) has not been able to find them in this situation, and J. Schaffer (1898) believes that the thickened ends of papillæ have been confused with taste-buds; Ponzo (1907), however, has recently stated that he has found them in the human fetus on the palatine tonsil, on the palatine arches, and on both surfaces of the soft palate. Such contradictions are probably to be explained by the fact that, as will be seen, the taste-buds are at first more widely distributed than they are later on, and undergo a partial retrogression which apparently is not of quite the same extent in all individuals. Very generally the gustatory organs have been regarded as being of ectodermal origin (see Schwalbe, Lehrbuch der Anatomie der Sinnesorgane, p. 36); this view is not, however, free from objection. It is not possible, it is true, to delimit exactly in the mouth cavity the ectoblastic and entoblastic territories; but the majority of the taste-buds lie undoubtedly within the entoblastic territory, and even although epithelial encroachments are possible, yet it seems difficult to suppose that the ectoblast has penetrated into the region of the larynx. The first thorough investigations of the development of the taste-buds in man were undertaken by Tuckermann (1889, 1890[1], 1890[2]), who also reviewed the older literature, for Hoffmann (1875) and Lustig (1884) had already published statements concerning the fetal conditions. Tuckermann failed to find taste-buds in a fetus of ten weeks, but did find them in one of fourteen weeks; he concluded, therefore, that they were formed during the twelfth week of intra-uterine life. The first statements, accompanied by figures, concerning the actual histological differentiation of the buds were made by Gråberg (1898), and his account will be followed here.

In a fetus of about three months (11 cm. vertex-sole length) this author could not recognize any anlagen of the papillæ vallatæ, but he found two ridges of the mucous membrane at the back part of the tongue which were placed obliquely and met in the median line to form an angle open anteriorly. These ridges are the foundations for the papillæ vallatæ. The epithelium covering the ridges is growing even at this stage into the stratum proprium in the form of simple invaginations and is dividing the ridges into papillæ. The first anlagen of the taste-buds are accordingly to be found in this fetus, but they are not as yet clearly defined (Fig. 121). The basal cells of the epithelium have lost their usual low cylindrical form and have increased in size noticeably. It is noteworthy that already in this earliest stage of development a nerve is in connection with that portion of the epithelium from which a taste-bud is differentiating, and Gråberg believes that it may have

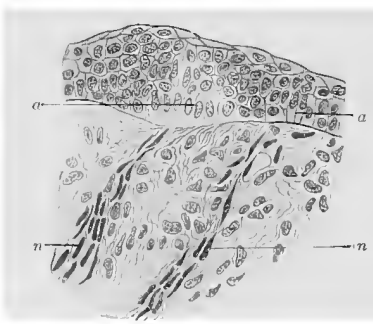

Fig. 121.—Frontal section through a papilla vallata of an 11 cm. human fetus. (After Gråberg. Schwalbe's Morphol. Arbeiten, vol. 8, 1898, Pl. 11, Fig. 1.) *a*, places at which the formation of taste-buds is beginning; *n*, nerves.

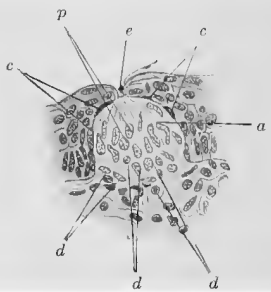

Fig. 122.—Frontal section through a papilla vallata of a 21.3 cm. human fetus. (After Gråberg, Schwalbe's Morphol. Arbeiten, vol. 8, 1898, Pl. 11, Fig. 4.) *a*, indifferent cells; *c*, extrabulbar cells; *d*, basal cells; *e*, gustatory pore; *p*, pillar cells.

a direct influence on the differentiation. Fig. 122 shows a further developed, well-defined taste-bud with a gustatory pore, from a fetus of 21.3 cm. vertex-rump measurement; a differentiation of the cells of the taste-bud into extrabulbar, basal, and pillar cells has also taken place to some extent, and, in addition, there are also present cells of an indifferent nature. So soon as they have become well differentiated the cells of the taste-bud reach the surface of the epithelium; then the gustatory pore is formed by the epithelium at the sides of the taste-bud increasing in thickness while the cells of the bud itself have almost completed their growth in length. The appearance of the taste-buds and their degree of development are in general subject to great variation. In the new-born child the different kinds of cells which constitute a bud are readily recognizable in transverse sections, neuro-epithelial cells, pillar cells, basal cells, and the extrabulbar cells; Gråberg failed to find only the rod-shaped cells of Hermann, but, on the other hand, he believed that he could distinguish the striated

margin of the inner gustatory pore, or ciliary corona of Schwalbe, as well as the hairs projecting into the pore. Many taste-buds undergo degeneration during the latter portions of intra-uterine life and after birth, and the degeneration process affects the first-formed buds situated on the upper free surfaces of the papillæ vallatæ, furthermore those on the papillæ fungiformes and those on the anterior surface of the epiglottis, on the tonsils, the soft palate, and on the plica fimbriata. Thus, Kiesow (1902) in almost mature fetuses in the majority of cases found taste-buds on the lingual surface of the epiglottis; after birth they vanish. According to Stahr (1901) the abundance of buds on the different kinds of papillæ is associated with the degree of elaboration of the form of the papillæ, their size and number. The vallate papillæ are late to become fully formed, and when they do the papillæ fungiformes assume a less definite form; they become relatively smaller and

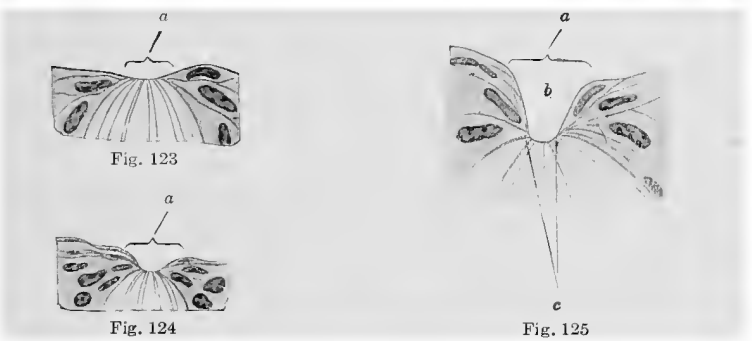

Fig. 123 Fig. 124 Fig. 125

FIGS. 123–125.—The summits of three taste-buds from a human fetus of 21.3 cm. *a*, in Fig. 123, indication of the gustatory pore, in Fig. 124, its anlage, and in Fig. 125, outer gustatory pore; *b*, gustatory canal; *c*, inner gustatory pore. (After Gråberg, Schwalbe's Morphol. Arbeiten, vol. 8, 1898, Pl. 11, Figs. 8–10.)

less numerous, and their epithelium partly loses its buds and becomes cornified. In the new-born child taste-buds occur on all the fungiform papillæ. The significance of the different kinds of papillæ for the function of taste alters during the life of the individual. The fungiform papillæ have their greatest abundance of taste-buds, and with that their chief period for functioning as taste-organs, in the new-born child; for the vallatæ and the foliatæ these conditions occur in the adult. As regards the degeneration of the taste-buds on the upper surfaces of the papillæ vallatæ, Gråberg finds that in fetuses of 24.5 and 39.5 cm. their outlines become indistinct and the nuclei of their cells shrivel. Occasionally leucocytes seem to invade them. The degenerated buds are carried to the surface and thrown off by the growth of the epithelium.

The papillæ vallatæ, foliatæ, and fungiformes may properly be regarded as organs accessory to the taste-buds. The first appearance of the fungiform papillæ is shown in the Normentafel of Keibel

and Elze in Plates 62, 64, and 66, in embryos less than 20 mm. in length. Gråberg has described and illustrated by some diagrams (Fig. 126, a–d) the development of the papillæ vallatæ. The ridges that precede the anlagen of these papillæ have already been described, and also the process by which they are broken up into the individual papillæ. The annular walls are formed from definite epithelial growths, derived from the epithelial ridges that bound the primitive papillæ, and, lateral to these, extending down into the stratum proprium. The stratum proprium on its part then projects up into the epithelial thickening, raising the epithelium over it and thus producing on the free surface of the mucous membrane surrounding the papillæ a slight elevation, which is the

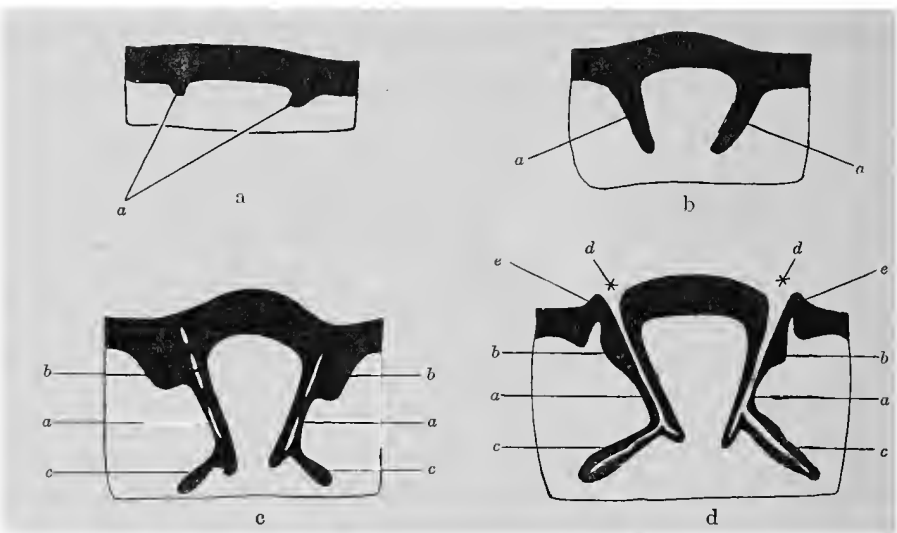

Fig. 126, a–d.—Diagrams illustrating the development of the vallate papillæ and their adnexæ. (After Gråberg, Schwalbe's Morphol. Arbeiten, vol. 8, 1898, p. 121–122.) *a*, "primary," *b*, "secondary" epithelial downgrowths: *c*, anlagen of glands of von Ebner; *d*, fossæ; *e*, annular wall.

anlage of the annular wall. The fossæ are formed by the fusion of small clefts that develop in the epithelial downgrowths that separate the papillæ. The glands of Ebner appear as solid outgrowths which extend laterally from the lower edges of the epithelial downgrowths. Later they acquire a lumen by the degeneration of their central cells, but even in the new-born child they are not everywhere fully developed. Until after birth the growth of the fungiform papillæ is mainly in length (Stahr, 1901), the fungus shape being acquired with the development of secondary crops of papillæ, by which a second stage in the growth of the papillæ is characterized; now for the first time can the papillæ be said to have a foot and a head. The secondary papillæ have already appeared in children of a few months, and in these all fungiform papillæ still bear taste-buds, whereas in the tongue of the adult

fungiform papillæ without buds occur. In the adult the epithelium often cornifies to form long tips, yet papillæ also occur whose epithelium is in part cornified and in part bears buds. Transitions between vallate and fungiform and between fungiform and filiform papillæ do not occur.

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The Olfactory Organ.

As is well known, the gnathostomatous vertebrata may be divided into monorhinous and amphirhinous forms. By their monorhinous condition the Cyclostomes stand in contrast to the rest of the vertebrates. Kupffer (1884) has sought to bridge the gap between the two conditions, and his views have for that reason secured much acceptance. He regards the ciliated groove at the anterior neuropore of Amphioxus as an olfactory organ. The Cyclostomes, in addition to the unpaired anlage of the olfactory organ, the "unpaired olfactory placode," situated close to the neuropore, had also paired organs situated more laterally, the lateral "olfactory placodes," which secondarily fused with the unpaired one; the rest of the vertebrates in addition to the lateral olfactory placodes had also the anlage of the unpaired placode, but this latter degenerated.

This view has been opposed by Peter (1901); he contends that an unpaired olfactory plate occurs in the rest of the vertebrates in the region of the neuropore, and I can from my own observations confirm his statements. The first anlage of the olfactory organ in man is formed by a paired convex area, covered by thickened epithelium (sensory epithelium), situated near the point where the anterior neuropore has closed. Van Wyhe (1882) has maintained that the olfactory nerve is only apparently the first cranial nerve; in reality it is the second, the optic being the actual first and the succession being reversed by the cranial flexure. This would also be the case with the corresponding sense organs. Nussbaum (1900) has also reached the same conclusion, and says, "Consequently the spot where the optic anlage leaves the brain has been secondarily transferred from the dorsal to the ventral surface and at the same time pushed caudally, on account of the forebrain flexure. By this the optic nerve, as Van Wyhe has already pointed out, has become the second cranial nerve, although it was originally on the dorsal surface in front of the olfactory nerve, which is counted as the first cranial nerve in adult vertebrates."

Hatschek (1909) has also quite recently made the same statement. The question depends upon what is to be regarded as the anterior end of the medullary plate. If the infundibulum repre-

sents its original anterior end and the regions of the chiasma and the recessus opticus have been formed by suture, and if the optic vesicles, as must also be assumed, are dorsal structures corresponding to the part of the edge of the medullary tube which has in this region united by suture, then Van Wyhe is correct. I regard this primary question, however, as not yet settled, and accordingly cannot regard it as settled that the olfactory nerve really lies caudal to the optic (compare also Keibel; 1889).

The sensory epithelium of the olfactory placodes is at first, especially ventrally, imperfectly marked off from the epithelium that covers the rest of the head. This condition was found by Keibel and Elze (Fig. 127) in an embryo of 4 mm. in its greatest length (Normentafel, Plate 10); the olfactory areas were already distinguishable in an embryo of 3 mm. described by Bromann (1896) (Normentafel, Plate 11), while Hammar (Normentafel, Plate 9) could not find them in an embryo with a greatest length of 4.7 mm.

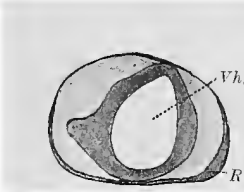

FIG. 127.—(From Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen, Fig. 9 e.) ×30. *R*, olfactory area; *Vh*, forebrain.

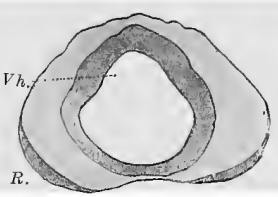

FIG. 128.—(From Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen Fig. 12 k.) ×30. *R*, olfactory area; *Vh*, forebrain.

The delimitation of the olfactory epithelium is more perfect in the embryo of Plate 14 of the Normentafel (4.9 mm. nape-breech length, 4.7 mm. vertex-breech length) (Fig. 128).[1]

In an embryo with a greatest length of 5.3 mm. (4.6 nape length) the olfactory areas are still convex, but are beginning to be more sharply delimited dorsally. They then become flattened (Fig. 129) (Normentafel 21, greatest length 6.75 mm.) and later begin to be depressed in their dorso-lateral part (Fig. 130) (Normentafel, Plate 24, in an embryo of 6.5 mm. greatest length = nape-breech length, vertex-nape length 4.7 mm., vertex-brow length 3.0 mm., age fairly certainly 21 days; also Normentafel, Plate 25, greatest length = nape length 6.25 mm.). In an embryo of 8 mm. (Normentafel, Plate 30 and Fig. 21 b) the olfactory area, according to Hammar, is feebly depressed, and in its caudal portion, which has deepened into a pocket, the nasal groove has formed. This embryo corresponds with that which His (1880–1885) figured in Fig. 29, p. 46, of the third part of his Anatomie menschlicher Em-

[1] Della Vedova (1907) has already described olfactory fossæ in an embryo of 4.7 mm.

bryonen, and which has also been figured by Kallius (1905) and has formed the basis of his description; I repeat His's figure here as Fig. 132 for comparison, although I have some doubts whether it correctly represents the normal conditions. The nasal fossa is surrounded by a marginal swelling which is interrupted below

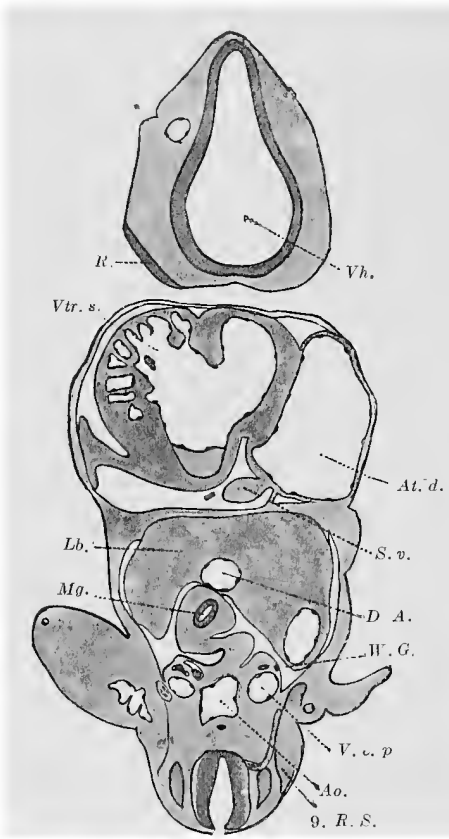

FIG. 129.—(From Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen, Fig. 16 i.) ×25. *Ao*, aorta; *At. d.*, right atrium; *D. A.*, ductus venosus Arantii; *Lb.*, liver; *Mg*, stomach; *R.*, olfactory area; 9. *R. S.*, ninth body somite; *S. v.*, sinus venosus; *V. c. p.*, posterior cardinal vein; *Vh*, forebrain; *W. G.*, Wolffian duct.

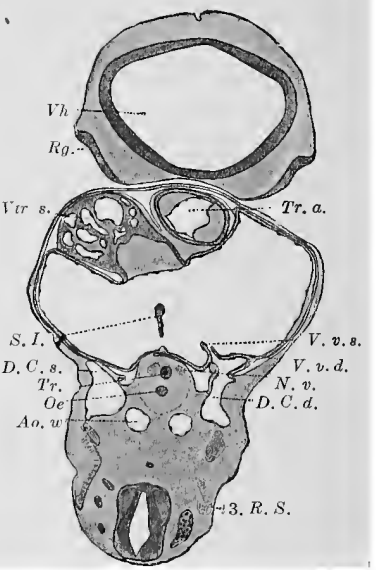

FIG. 130.—(From Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen, Fig. 18 f.) ×20. *Ao. W.*, aortic root; *D. C. d.* (*s.*), right (left) Cuvierian duct; *N. v.*, vagus nerve; *Oe.*, œsophagus; *Rg.*, olfactory fossa; 3. *R. S.*, third body somite; *S. I.*, septum primum; *Tr.*, trachea; *Vh.*, forebrain; *Vtr. s.*, left ventricle; *Vv. v. d.* (*s.*), valvula venosa dextra (sinistra).

toward the maxillary process. The lateral limit of the swelling covers only a part of the medial wall of the nasal fossa. A process on the medial limb His identified as the processus globularis (p. g.?), and further down, where the medial edge comes into relation with the maxillary process, there is a larger projection, and internal to this a small round, rather deep and sharply margined depression (J. O.?), which His regarded as the earliest anlage of Jacobson's organ. I have never seen the earliest anlage of Jacob-

son's organ of this form in man, it appears in my opinion as a groove, and the projection also which His identifies as the processus globularis I would not so identify, but would suggest that the swelling near the maxillary process and external to the depression designated by His as Jacobson's organ is much more probably the structure that should be identified with the processus globularis. I follow, accordingly, my own observations here and must leave it for later investigations to decide which are correct.

Some further observations are necessary for a comprehensive account of the development of the nasal fossæ, and the formation of the face must be recalled. In a stage such as that shown in Fig. 133 the oral fossa is bounded above by the frontal process, to the right and left by the maxillary processes, and below by the

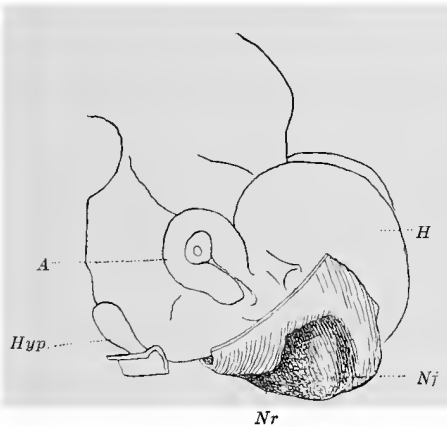

FIG. 131.—(After Hammar, from [Keibel and Elze, Normentafel, Fig. 21 b.) ×25. *A*, eye; *H*, cerebral hemisphere; *Nf*, olfactory area; *Nr*, nasal groove.

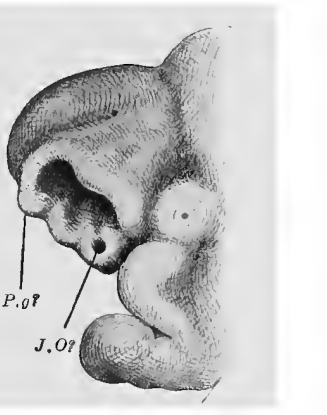

FIG. 132.—(After His, from Anat. Menschlicher Embryonen, III, p. 46.) ×20. View of the anterior portion of the head of a human embryo from the left side. *P. g ?*, marked by His (without ?) as the processus globularis; *J. O ?*, marked by His (without *?*) as Jacobson's organ.

mandibular processes. Since a projecting angle is formed where the right and left mandibular processes meet, the entrance into the oral fossa has a pentagonal form. The two upper lateral angles, where the maxillary processes are better developed, extend as the lachrymal grooves as far as the eyes; they therefore bound the frontal process laterally. In the territory of the frontal process there is now formed, as we have seen, on either side a nasal area (His).[2]

The nasal area is at first convex, in correspondence with the form of the surface of the frontal process, and even when the epithelium has become sharply delimited on all sides it is not recognizable on superficial examination. Only when it becomes flattened, and especially when it begins to be depressed, is it dis-

[2] Area nasalis, olfactory area (His).

tinct. These first processes may be determined essentially by growth of the epithelium covering the nasal area (Peter, 1900 and 1902), but in man observations for determining this point have not been made. Later the margins of the area become raised by the growth of the surrounding mesoderm and thus deepen the nasal fossa, or rather the nasal grooves, for the wall surrounding the olfactory area is interrupted orally. In this stage, shown in its earliest stages in Fig. 134, the anlagen of the olfactory organ are separated by almost the entire breadth of the frontal process. It is customary to term the portion of the frontal process lying between the areas the middle frontal process and the lateral portions the lateral frontal processes; these latter coincide almost exactly with the lateral nasal processes, which project lateral to the olfactory grooves. Quite different is the relation of the medial

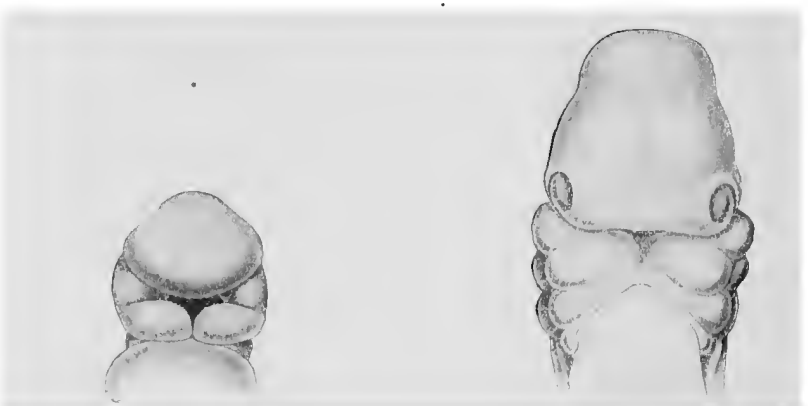

FIG. 133.—Head end of an embryo seen from n front. (After Rabl, Entwicklungsgeschichte des Gesichtes, 1902, and corresponding practically with Embryo *M* of His.) ×20.

FIG. 134.—Head of an embryo of 8.3 mm. N L. en face. (After Rabl (1902), Entwicklungsgeschichte des Gesichtes.) This corresponds almost with Fig. XIV of the Normentafel of Keibel and Elze. ×10.

nasal processes to the middle frontal process; they originally occupy only a very small lateral portion of it. The further transformation of the nasal grooves into the primitive nasal cavities is brought about by the maxillary processes coming into contact and fusing with the lower ends of the medial nasal processes. These lower ends project markedly forward and are known as the processus globulares (His). The fusion takes place from within outwards and occurs as the processes meet, so that the primitive nasal cavities in man, as in the rest of the mammalia,[3] are never connected by a groove with the primitive mouth cavity; there is no reservation of a choana, so that the primitive nasal cavities, which open anteriorly by the external nares, are blind

[3] Echidna alone forms an exception. (Seydel, Denkschr. med. nat. Ges., Jena, Vol. 6, 1899.)

sacks and are at first shut off from the mouth cavity (Hochstetter, 1891 and 1892, Keibel, 1893, Della Vedova, 1907). By the coming in contact of the maxillary processes with the processus globulares, the nasal grooves become gradually closed and the external nares more and more narrow; finally, the lateral nasal process comes into contact with the medial one and assists in bounding the primitive nasal cavity laterally and below, as I can state in confirmation of Peter's (1902) results. At the close of this developmental process (Fig. 135) the upper border of the mouth is formed by the maxillary processes and the medial nasal process and the lower border of the nares by the medial and lateral nasal processes. (Compare also Vol. I, p. 83, Fig. 64.) The primitive nasal cavities are shut off from the palate, but their epithelium is in connection with that of the mouth cavity by a plate of epithelium (Fig. 136). While this epithelial plate becomes transformed at its posterior end into a membrane, the bucconasal mem-

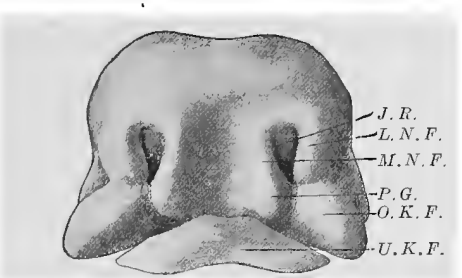

FIG. 135.—Model of the anterior part of the head of a human embryo of 10.5 mm. (After Peter, from Hertwig's Handbuch, vol. II_2, p. 53, Fig. 60.) Ventral view. ×12.5. *J. R.*, Jacobson's groove; *L. N. F.*, lateral, *M. N. F.*, medial nasal process; *P. G.*, processus globularis; *O. K. F.*, maxillary, *U. K. F.*, mandibular process.

brane (Hochstetter), and finally tears, the primitive choanæ being thus produced, the mesoderm of the maxillary processes and of the lateral nasal processes is growing toward that of the medial nasal processes; it eventually destroys the epithelial plate and forms the primitive palate. This can be regarded as consisting of a facial portion, from which the upper lip is formed, and an oral portion, the premaxillary palate. The mesoderm of both portions is furnished by the maxillary and medial nasal processes, the lateral nasal processes participating only at the lower border of the nares.

While the developmental processes just described have been taking place, the middle frontal process has been gradually becoming smaller and the two nasal openings have been brought closer together. On the middle frontal process there may be distinguished laterally the medial nasal processes, each ending in a processus globularis, between these the trough-like depressed infranasal area (His), and above this the area triangularis (His), above which, again, is the part of the head which projects owing

to the anlagen of the cerebral hemispheres (Fig. 135). The infranasal area is separated from the area triangularis by an angle that is at first indistinct but later becomes more sharply defined and from which the border and tip of the nose are formed; the area triangularis becomes the dorsum of the nose and the infranasal

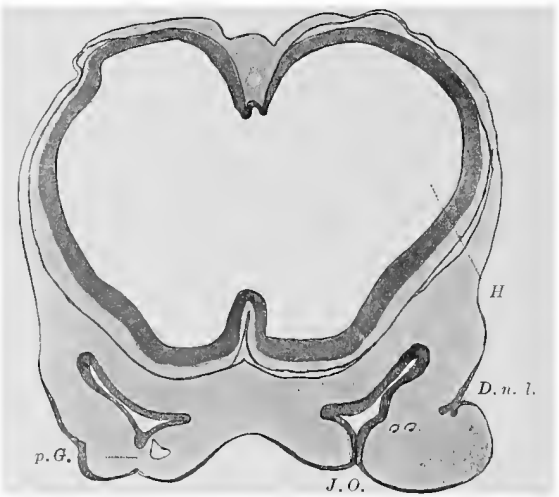

Fig. 136.—(After Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen, Fig. 32 a.) ×20. *D. n. l.*, nasolachrymal duct; *H.*, cerebral hemisphere; *J. O.*, organ of Jacobson; *p. G.*, primary palate.

area is transformed into the septum. His believed that the nasal septum had a paired origin, because in the stages in which the nasal openings are close together the medial nasal processes are almost in contact in the median line and the whole of the portion of the middle frontal process lying between them has become a

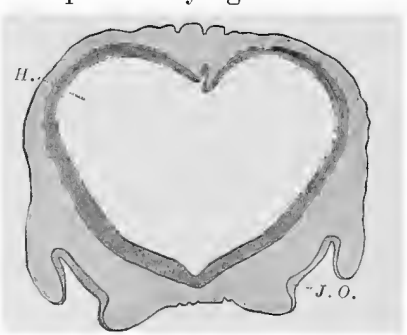

Fig. 137.—(After Keibel and Elze, Normentafel zur Entwicklungsgeschichte des Menschen, Fig. 24 i.) ×20. *H.*, cerebral hemisphere; *J. O.*, Jacobson's organ.

rather deep groove. This groove may, as a rule in many animals but exceptionally in man, persist, forming a median lip cleft. Normally this embryonic cleft closes by the growth of the mesoderm forcing the epithelium out of the cleft, not by the medial nasal processes coming into contact and uniting, so to speak, by a suture. In my opinion, therefore, it is not proper to speak of an actual

paired anlage of the nasal septum, although the material for it is thrust in toward the median line from the right and the left.

We have now in the first place to consider the anlage of the *organ of Jacobson* and that of the *conchæ*, and then the *transformation of the primitive into the definitive nasal cavities.*

The *organ of Jacobson* [4] in man appears as a groove-like depression on the medial wall of the olfactory fossa. I have seen

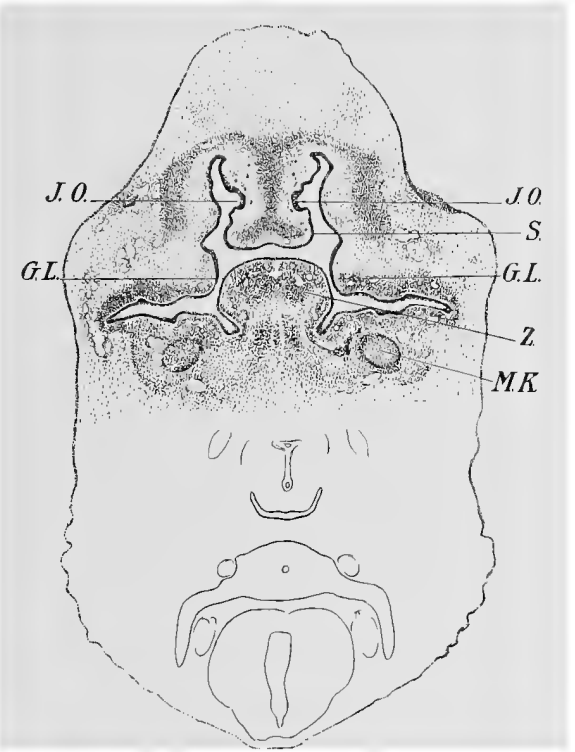

FIG. 138.—Section through the head of a human embryo of 18.5 mm. greatest length. (Collection of Robert Meyer, No. 32; Normentafel of Keibel and Elze, Plate 64, Fig. XXI.) × 15. *G.L.*, palatal process; *J.O.*, Jacobson's organ; point of union with the nasal cavity; *S.*, nasal septum, in which there is a common blastema for the cartilage of the septum and Jacobson's cartilage; *Z.*, tongue, in which the musculature is beginning to differentiate. The tongue (*Z*) lies between the palatal processes. An early stage of the dental ridges may be recognized.

its earliest anlage in an embryo of 8.5 mm. greatest length (Normentafel, 32). Fig. 137 shows it in section in an embryo of 9.2 mm. greatest length, 8.8 mm. NL. (Normentafel, Plate 38). It is seen further developed (Fig. 136) in an embryo of 14 mm. (Normentafel, Plate 51). The groove has deepened and it then closes from behind forwards. The mouth of the cylinder produced in this way narrows, and on its medial wall there forms olfactory epithelium, in connection with which, however, no cilia have yet been observed; glands also develop. In the human fetus the organ

[4] The organ of Jacobson was discovered by Fr. Ruysch in 1703.

lies in the anterior portion of the nasal septum; in a fetus of about ten weeks Kallius (1905) found it on both sides with a length of 0.42 mm.; its entrance was narrow and led into a greatly (about tenfold) enlarged sack. About this time one can readily observe, as Kölliker first pointed out, that branches of the olfactory nerve pass from Jacobson's organ to the brain.[5] In the twentieth week of fetal life the organ, according to Kallius, has reached the height of its development. Later it varies greatly and may completely degenerate, even in the embryo, but, on the other hand, it is not infrequently found and has often been described in the adult. (Compare on this point Merkel, 1892.)

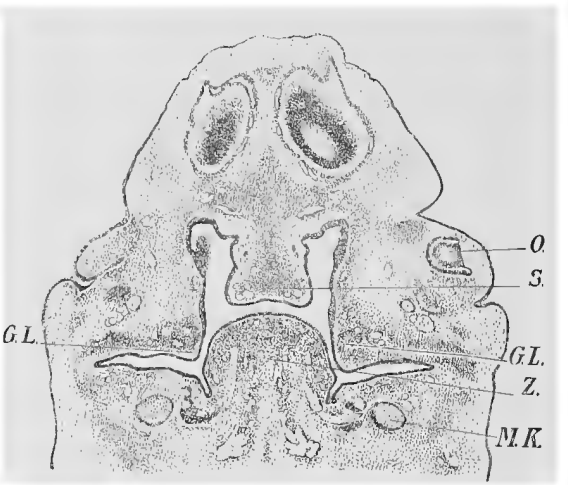

FIG. 139.—Section through the head of the embryo of Fig. 13½. The section lies 150 μ further caudad. The cerebral hemiepheree and one eye have been cut, but Jacobeon'e organ ie no longer visible. The lingual and hypoglossal nervee are entering the tongue. The lettering ae in Fig. 138. ×15.

A case in which it was present in the adult in a quite exceptional degree of development has recently been recorded by Mangakis (1902). Although Peter (1901[2], p. 71) again repeats the view already frequently stated, that the organ is often destroyed in extra-uterine life as the result of frequently occurring catarrh of the nasal mucous membrane, yet I agree with Merkel (1892) that there are no sufficient grounds for this opinion, since the organ often disappears in the fetus. A supportive apparatus for Jacobson's organ is also formed, Jacobson's cartilages. According to Mihalcowics (1898), these cartilages separate from the cartilage of the nasal septum, but, like Kallius (1905), I find that they arise independently. At first only one cartilage anlage is to be seen on either side, "but in the fourth to the fifth month one sees several, usually three, a larger one that is frequently somewhat curved, and two smaller" (Kallius). Originally also the cartilages are

[5] Della Vedova incorrectly doubts this.

situated close to the organ of Jacobson, but later they separate from it. Their relationship to Jacobson's organ has been called in question and they have been described as the vomero-nasal cartilages (see Spurgat, 1893 and 1896); in my opinion this is incorrect, for comparative embryology shows that these human cartilages are to be homologized with the typical Jacobson's cartilages of the mammals. How the comparison is to be followed out in detail, when in later stages three cartilages are present, will be considered further on. Della Vedova (1907) believes that the lateral wall of the cartilaginous nasal skeleton also takes part in

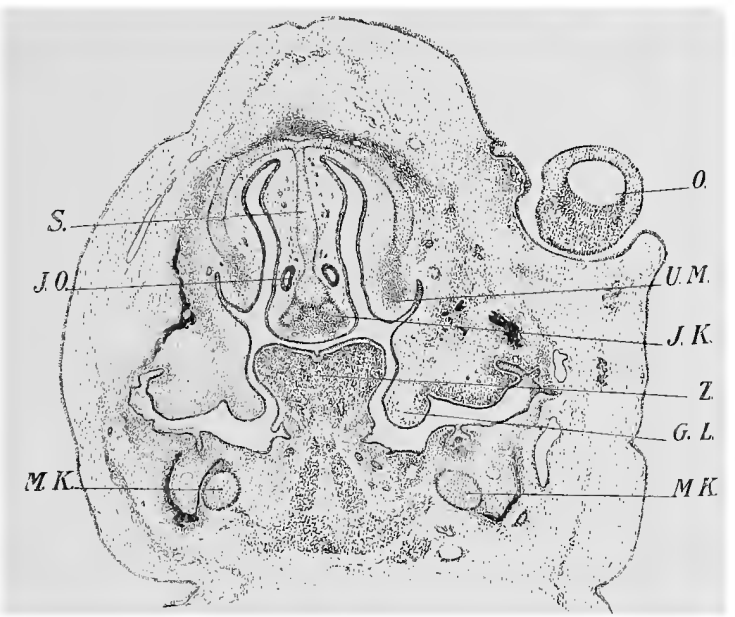

Fig. 140.—Section through the head of a human embryo of 2 mm. greatest length. (Collection of Robert Meyer, No. 321; Normentafel of Keibel and Elze, Plate 84.) ×15. *G.L.*, palatine processes; *J.K.*, Jacobson's cartilage; *J.O.*, Jacobson's organ; *M.K.*, Meckel's cartilage; *O.*, eye; *S.*, cartilaginous nasal septum; *U.M.*, inferior concha (maxilloturbinal). The bony anlagen (maxillary and mandibular) are black.

the formation of these cartilages, and, with Mihalcowics (1898), regards them as the remains of a plate that in other animals closes the nasal cavities below. That Gegenbaur (1886) should deny the occurrence of an organ of Jacobson in man, when the relation of the olfactory nerve to the organ during development had previously been clearly shown by Kölliker (1883), is surprising.

Gegenbaur identifies the structure that is here described as the organ of Jacobson with the septal gland first described by Steno. From what has been said, there cannot be any doubt but that in the human Jacobson's organ we have a portion of the olfactory organ which possesses special functions in many animals, but has become rudimentary in man.

Some stages in the development of Jacobson's organ are shown in Figs. 139 to 144, and the development of Jacobson's cartilages may be followed in Figs. 138, 139, 140, 143, and 144. It will be seen that they arise from a blastema common to them

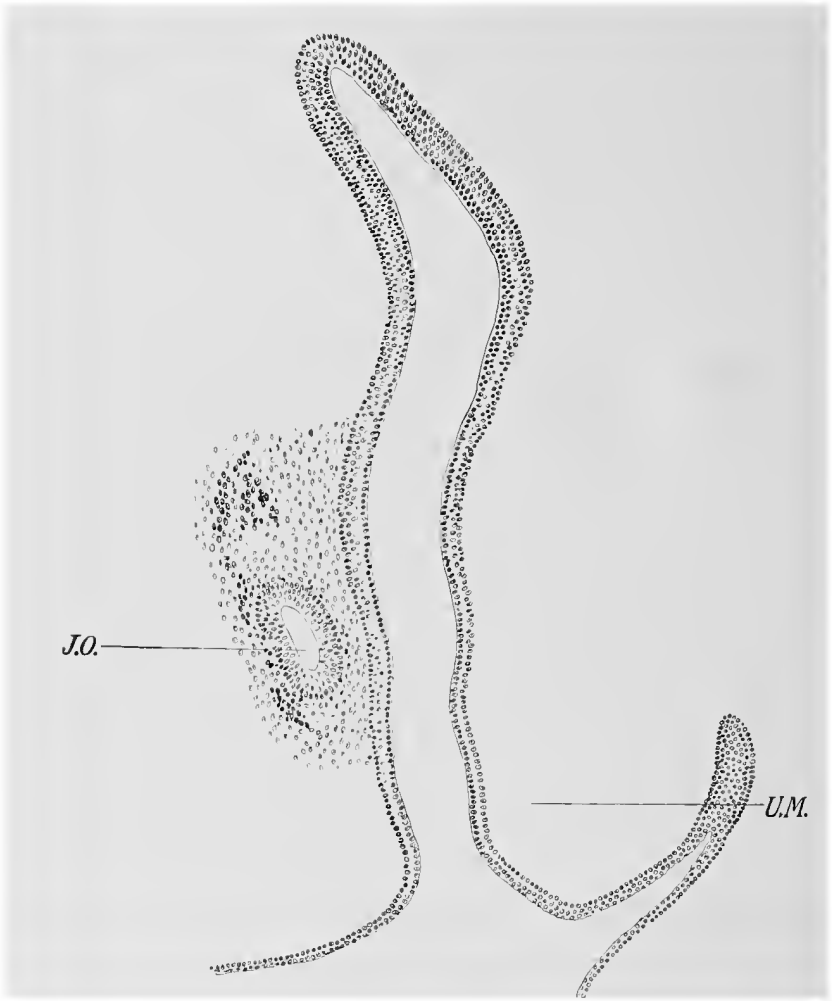

FIG. 141.—A portion of the right side of Fig. 140 more enlarged. × 95. *J.O.*, Jacobson's organ; *U.M.*, inferior concha (maxilloturbinal). Over a considerable portion of the epithelium of the nasal cavity there is a sort of covering layer.

and the cartilage of the nasal septum (Figs. 138 and 139); from their first appearance, however, they are sharply marked off from the cartilage of the septum (Fig. 140). Fig. 141 shows the right side of the nasal cavity under higher magnification. The formation of nerves in connection with the organ of Jacobson is taking place, and in the epithelium of the nasal cavity a peculiar double-layered condition is noticeable. The most superficial cells are

arranged like a covering layer, except in those regions which are already recognizable as sensory epithelium. The same condition obtains also in older stages, as may be seen from Fig. 143 (fetus of 4.2 cm. sitting height), and it certainly deserves a thorough investigation. Fig. 142 shows a stage intermediate between Figs. 140 and 143. The palatal processes have come into contact, but the epithelium has not yet been forced out by connective tissue along the line of suture. The right and left nasal cavities are still in continuity below the septum. Fig. 144 shows some sections taken from a frontal series through a fetus of 47 mm., the sections following one another in apicocaudal direction. In Fig. 144, *A*, two very short lateral processes (*p*) branch out from the septal cartilage and very soon separate from it (Fig. 144, *B*, *p*), but

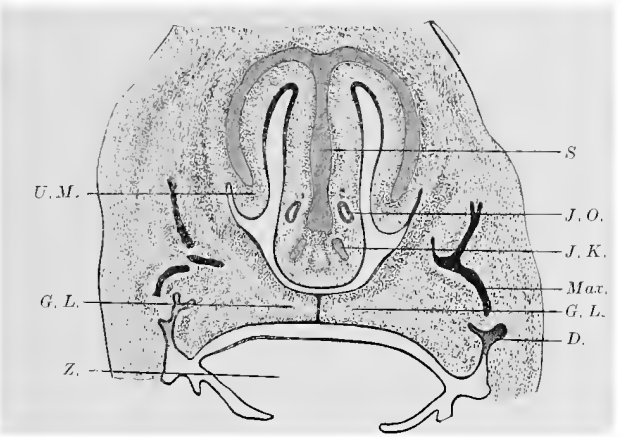

Fig. 142.—Frontal section through the head of a human embryo about 8 weeks old, taken 1.9 mm. from the most anterior point of the head. (After Kallius, in Bardeleben's Handbuch, vol. 5, Section 1, Part 2, p. 202, Fig. 70; somewhat modified.) *D.*, dental anlage; *G. L.*, palatal processes; *J. K.*, Jacobson's cartilage; *J. O.*, Jacobson's organ; *Max.*, anlage of the maxilla; *U. M.*, inferior concha (maxilloturbinal); *Z.*, tongue. ×15.

the septal cartilage, which is very thin in places, is never connected with any of the other cartilages. Basal from these processus laterales ventrales (Zuckerkandl, 1909) there then appears on either side a cartilage plate (Fig. 144, *C*, *pl*), which soon divides into a medial and a lateral portion (Fig. 144, *D*, *l* and *m*). While first the cartilage indicated by *l* and then that indicated by *p* disappear, a small piece separates from *m* (Fig. 144, *E* and *F*). According to Zuckerkandl (1909), this much is at least certain, that the medial portion of the plate *pl* becomes Jacobson's cartilage and that the portion *p* is to be homologized with the processus nasalis lateralis of other forms. He does not suggest an homology for the cartilage *l*.

The development of the *conchæ* takes place entirely in the region of the sensory epithelium,—that is to say, in the region of the primitive nasal cavities. The conchal apparatus of the human

nose, like the human olfactory organ in general, is reduced, so that it is impossible to obtain a satisfactory understanding of it without the aid of comparative anatomy and embryology.

The way toward a satisfactory understanding of it has been shown especially by the work of Killian (1895, 1896, 1902) and Peter (1902 [2]); but the observations of Zuckerkandl (1887, 1892 [1] and 1892 [3]) and Schönemann (1901) should also be mentioned. According to Peter, the conchæ arise as well on the lateral as on the medial wall of the primary nasal cavities,[6] the maxilloturbinal and nasoturbinal arising from the lateral and the ethmoturbinals from the median wall. Fig. 145 shows a section through the pos-

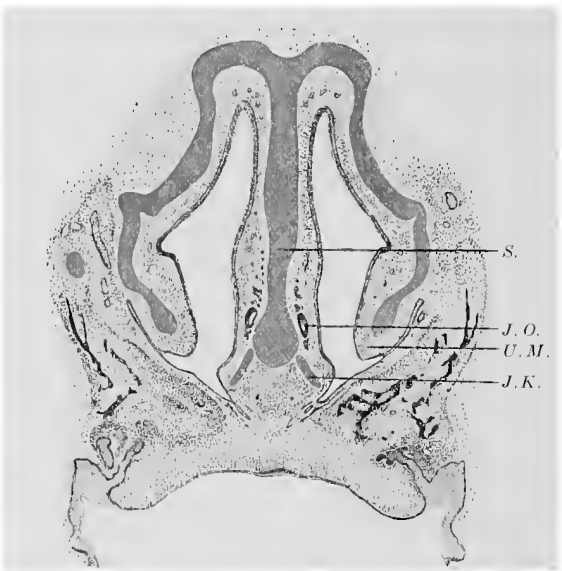

FIG. 143.—Frontal section through the nasal cavities and the palate of a fetus of 4.2 cm. (sitting height). (Keibel's collection.) × 15. *J.K.*, Jacobson's cartilage; *J.O.*, Jacobson's organ; *U.M.*, inferior concha (maxilloturbinal); *S.*, cartilaginous nasal septum.

terior portion of the olfactory fossa of a rabbit embryo of 3.5 mm. head length; the dorsal region of the medial wall is slightly bent away from the lateral one, and the slight swelling above the bend represents the first ethmoturbinal. How it is transferred from the medial to the lateral wall is made clear by Fig. 146; it is brought about by the ingrowth of the epithelium at *x*. In a similar manner two other ethmoturbinals are formed independently from the septal wall in the rabbit, in the region of the posterior blind sack of the nose (Fig. 147). The one which is first formed is in embryonic life completely divided into two secondary ridges by a groove. From the lateral wall the conchal structures which Peter terms the conchæ obtectæ are formed below the rostrally projecting

[6] Della Vedova (1907) has recently opposed this view.

border of the first ethmoturbinal. In front of these, in the region of a cleft which is bounded anteriorly by the sharply marked posterior border of the nasoturbinal (the processus uncinatus), the maxillary sinus is sinking in in a downward direction.

Peter has made it probable that the ethmoturbinals are formed from the medial wall in man also, but he has not been able to

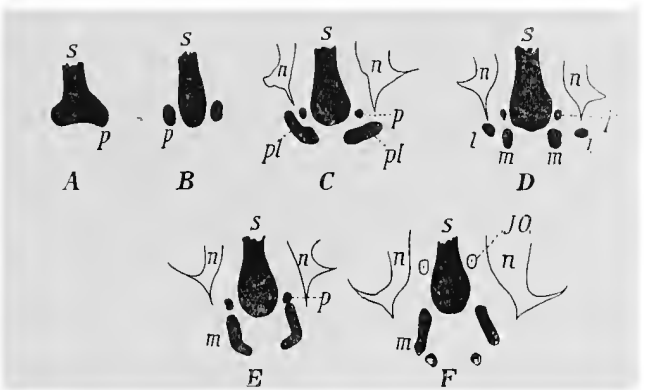

Fig. 144.—Frontal sections through the nasal septum of an embryo of 47 mm. The sections have been taken from a series passing in the apicocaudal direction. (After Zuckerkandl, 1909.) *s*, septum; *p*, ventral lateral process; *pl*, cartilage plate below *p*; *m* and *l*, portions formed from cartilage *pl*; according to Zuckerkandl, *m* becomes Jacobson's cartilage.

demonstrate it. As a difference in the human development as compared with that of the rabbit, it may be noted that the nasoturbinal is very rudimentary and develops very late; it becomes

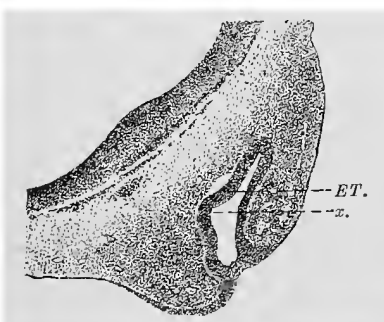

Fig. 145.—Section through the posterior blind sac of the olfactory organ of a rabbit embryo of 3.5 mm. head length. ×50. (After Peter, from Hertwig's Handbuch, vol. II₂, p. 61, Fig. 69 a.) *ET.*, ethmoturbunal; *x.*, bend in the medial wall.

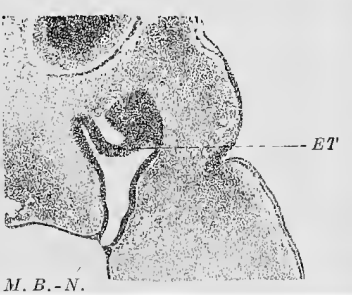

Fig. 146.—Section through the oral end of the olfactory organ of a rahhit embryo of 8.5 mm. vertex-hreech length. ×50. (After Peter, from Hertwig's Handbuch, vol. II₂, p. 61, Fig. 69 b.) *ET.*, ethmoturhinale I; *M. B.-N.*, bucconasal memhrane.

the agger nasi (Peter, 1901 [2], p. 64). In early stages the maxilloturbinal alone is present; it occupies the posterior two-thirds of the lateral wall throughout its entire height. Gradually it becomes more sharply marked off, especially ventrally; the groove thus formed becomes the inferior nasal meatus. It is interesting to note that in man a dorsal lamella is added to this concha in

the fourth month (Mihalcowics, 1896 [2], p. 71),[7] so that at this stage it recalls the doubly coiled maxilloturbinal of many mammals. Only late does the agger nasi appear as a slight elevation above the inferior concha and in front of the first ethmoturbinal. In an

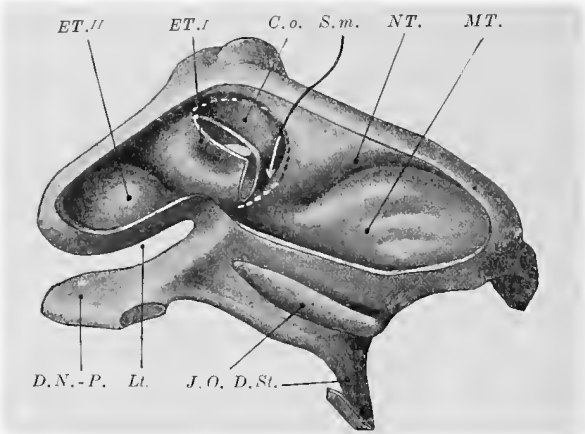

FIG. 147.—Nasal cavities of a rabbit embryo of 13 mm. head length, seen from the medial side after removal of the upper part of the septum. ×15. (After Peter, from Hertwig's Handbuch, vol. II_2, p. 60, Fig. 68 h.) A portion of ethmoturbinale I has been removed and its contour is indicated by a broken line. *C. o.*, concha obtecta; *D. N.-P.*, nasopharyngeal duct; *D. St.*, Steno's duct; *ET.I*, first, *ET.II*, second ethmoturbinal; *J. O.*, Jacobson's organ; *Lt.*, lamina terminalis; *MT.*, maxilloturbinal; *NT.*, nasoturbinal; *S. m.*, maxillary sinus.

embryo of 30 mm. vertex-breech length Peter finds a second ethmoturbinal behind the first, and behind this still other four in maximo may appear (Killian). That a new ethmoturbinal is interposed

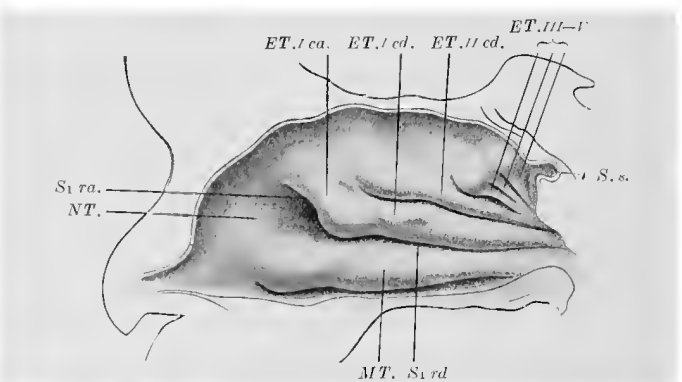

FIG. 148.—Lateral wall of the right nasal cavity of a fetus from about the ninth or tenth month. ×1.5. (After Killian, Arch. für Laryngologie, vol. 3.) *ET.I–ET.V*, ethmoturbinale I–V; *ET.II cd.*, ethmoturbinale II crus descendens; *ET.I ca.*, ethmoturbinale I crus ascendens; *ET.I cd.*, ethmoturbinale I crus descendens; *MT.*, maxilloturbinale; *NT.*, nasoturbinale; S_1 *ra.*, first principal groove, ramus ascendens; S_1 *rd.*, first principal groove, ramus descendens; *S. s.*, sinus sphenoidalis.

and grows out between two of those already present, as Zuckerkandl supposes, I cannot admit; nor can I agree with Della Vedova's (1907) criticisms of Killian, whose preparations I have seen.

[7] Compare also Killian (1896), Pl. II, Fig. 39, and the text-figures.

In the description of the succeeding developmental processes I follow Killian, differing from him only in that, with Peter, I do not term nasoturbinal (agger nasi) ethmoidale I, but contrast the nasoturbinal, maxilloturbinal, and conchæ obtectæ as lateral

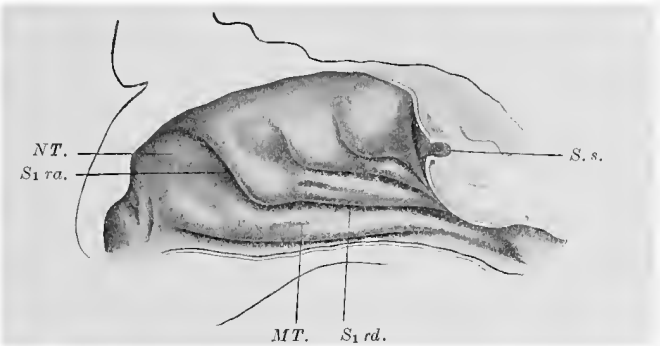

FIG. 149.—Lateral wall of the right nasal cavity of a fetus from the ninth or tenth month. ×1.5. (After Killian, Arch. für Laryngologie, vol. 3.). *MT.*, maxilloturbinale; *NT.*, nasoturbinale; *S1 ra.*, first principal groove, ramus ascendens; *S1 rd.*, first principal groove, ramus descendens; *S. s.*, sinus sphenoidalis.

conchæ with the ethmoturbinals which are medial conchæ. Killian's ethmoturbinale II is accordingly termed ethmoturbinale I in the figures taken from his works, and similarly with the others. Killian has acquiesced in this alteration of his nomenclature.

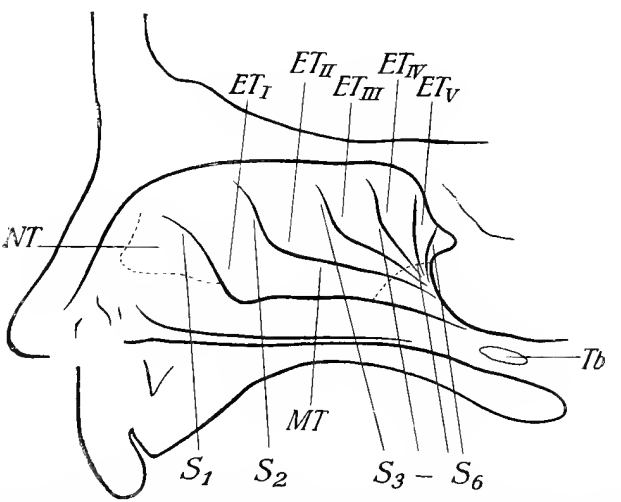

FIG. 150.—(After Killian, Arch. für Laryngologie, vol. 13.) *ETI–ETV*, ethmoturbinale I–V; *NT*, nasoturbinale; *MT*, maxilloturbinale; *S1–S6*, first to sixth principal groove; *Tb*, opening of Eustachian tube.

Figs. 148 and 149 show the lateral nasal walls of two fetuses of the ninth to the tenth months; Fig. 150 is a combined diagrammatic figure representing the maximal number of ethmoidalia, an arrangement that only very rarely occurs. In addition to the maxilloturbinal and the nasoturbinal (agger nasi) five ethmoturbinals may be recognized, the free edge of each of the anterior

ones forming a crus ascendens and a crus descendens, while where the two crura meet there is a more or less pronounced lobulus with a nodulus, which is to be compared with the tip of the ethmoturbinals of the mammals. In addition to these principal conchæ Killian finds other accessory conchæ in the principal grooves, and accessory grooves may also develop on the conchæ. Fig. 151 shows the middle meatus of a human embryo of the sixth month; the anterior part of the middle concha has been removed. One sees between the bulla ethmoidalis, which is formed by two conchæ obtectæ, and the processus uncinatus the infundibulum; in it lie three infundibular accessory conchæ; the groove between the upper

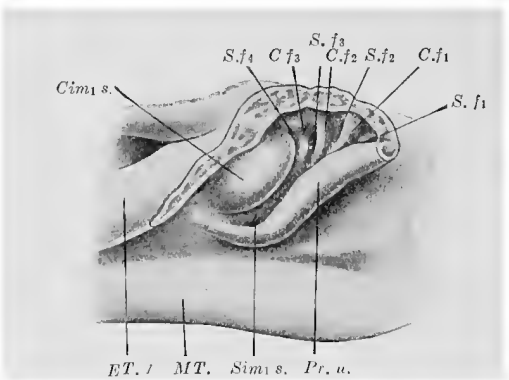

FIG. 151.—Middle nasal meatus of a human fetus of the sixth month. The anterior part of the middle concha, *ET.I*, has been removed. There are to he seen ahove the hulla ethmoidalis (*Cim*1 *s.*) and the processus uncinatus (*Pr. u.*) three frontal conchæ (*C. f*1–3) on the lateral wall of the frontal recess and bounded by four frontal grooves (*S. f*1–4). (After Killian, Arch. für Laryngologie, vol 13.) *MT.*, inferior concha (maxilloturhinale); *Sim*1 *S.*, groove hetween the upper and middle infundihular accessory conchæ.

and the middle one is marked Sim_1s. Above the bulla ethmoidalis and the infundibulum lies the upper part of the recessus ascendens, the frontal recess, with three frontal conchæ bounded by four grooves. The development of the nasal cavities is complicated by the formation of the sinuses and the ethmoidal cells; also fusions of grooves and parts of grooves occur (Killian), a phenomenon that may, at least in part, be regarded as a compensation for growth processes (Schönemann, Peter). Killian's account is followed here. The three posterior crura ascendentia fuse throughout their whole extent, but only the anterior borders of the anterior three fuse, in such a manner that each unites with the upper surface of the next succeeding concha; thus recesses are formed under the anterior parts of the conchæ, the recessus ascendentes, the first of which is the recessus frontalis, already mentioned. The rami descendentes IV–VI become completely obliterated, but the anterior three only partially, so that the free margins persist and form the definitive conchæ, which, accordingly, represent only the crura descendentia of the original principal conchæ. From recessus ascendens III a posterior ethmoidal cell may be formed;

frequently a cell then unites with it, which has its origin from the portion of the groove corresponding to the ramus descendens. The superior recess of the second groove also becomes a posterior ethmoidal cell, the groove itself becomes two cells, an upper and a lower, which are separated by an accessory concha (Killian, 1895 [2]). From the recessus superior of the first groove, whose upper part Killian has named the recessus frontalis, the upper and anterior ethmoidal cells (frontal cells) arise.

In addition the recessus frontalis gives origin to the sinus frontalis; indeed it may be completely transformed into that cavity

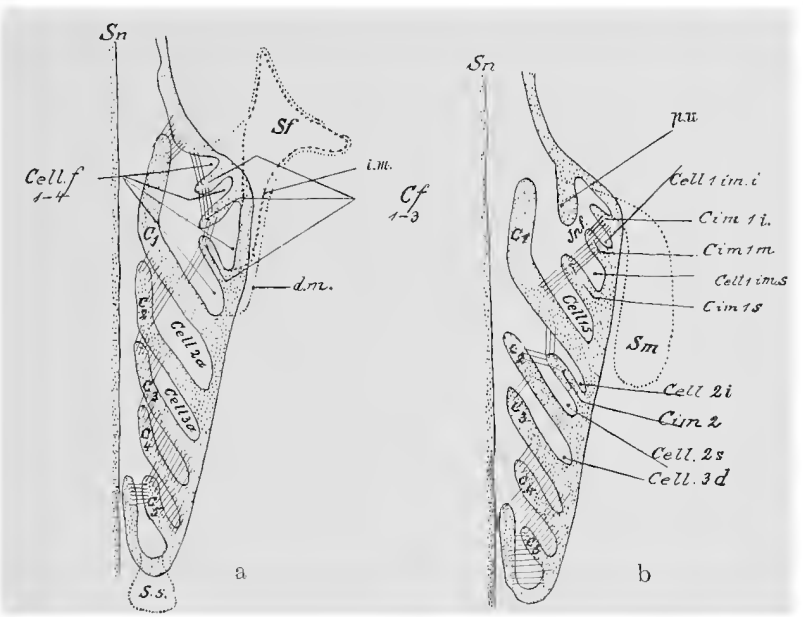

FIG. 152 a and b.—Diagrammatic horizontal section through the right half of a human nose of primitive structure, a on an upper and b on a lower level. (After Killian, from Peter, Entwicklungsgesch. des Geruchsorgans, in Hertwig's Handbuch, vol. II_2, p. 68, Figs. 73 a and b.) C_1–C_5, principal conchæ (ethmoturbinalia); below and between these the principal grooves with ascending (in a) and descending (in b) rami and with accessory (*Cim.*) and frontal conchæ (*Cf.*); *Inf.*, infundibulum; *p. u.*, processus uncinatus; *S. f.*, frontal sinus, formed directly (*d. m.*) or indirectly (*i. m.*); *S. m.*, maxillary sinus; *S. s.*, sphenoidal sinus; *S. n.*, nasal septum. The regions of fusion recognized by Killian are indicated by parallel lines.

or else the sinus is formed by one of the frontal cells protruding between the frontal conchæ mentioned above. These conchæ themselves usually vanish completely by fusing with one another and with neighboring structures; the third one may fuse with the upper end of the bulla ethmoidalis. The frontal sinus grows very slowly; it is still wanting at the time of birth (Della Vedova, 1907) and at puberty has only the size of a pea.

The maxillary sinus develops at about the middle of the third month of intra-uterine life from the recessus inferior of the first groove.[8] At first it is only a small depression, which soon becomes

[8] According to Vedova (1907), it forms in the first half of the third month.

a sack. In correspondence with its point of origin the fully formed sinus opens usually into the most posterior and lower portion of the infundibulum. Only after the eruption of the milk-teeth does it enlarge and begin to assume its characteristic pyramidal form; up to the fifth or sixth year of life it is round. In 10 per cent. of cases there now arises above the centre of the middle concha an accessory opening. The sphenoidal sinus is the most posterior part of the nasal cavity itself, separated by fusion processes; as it increases in size it gradually penetrates the body of the sphenoidal bone. Two diagrammatic horizontal sections (Fig. 152, a and b) through the right half of the nose show clearly the relation of the embryonic arrangement to that of the adult.

The inferior concha is the maxilloturbinal of comparative anatomy and the agger nasi the nasoturbinal. The middle concha is derived from the descending and a small part of the ascending portion of ethmoturbinale I.

The superior concha, when it is present, corresponds to the descending portions of ethmoturbinalia III and IV.

The superior meatus corresponds to the descending ramus of the second groove, the supreme meatus to the descending ramus of the third groove.

The accessory spaces may be classified as in the following table, in which the spaces between two principal conchæ are regarded as of the first order, those between principal and accessory conchæ as of the second order, and those between two accessory conchæ as of the third order.

Level.	First principal groove.			Second principal groove.		Third principal groove.	
Upper	I order: Frontal groove with frontal sinus (if developed directly)	II order: First and fourth frontal cell (cell *f*1 and cell *f*4)	III order: Second and third frontal cell (cell *f*2 and cell *f*3)	I order: Ascending cell (cell 2*a*)	II order:	I order: Ascending cell (cell 3*a*)	Usually unite to form one.
		with frontal sinus (if developed indirectly)					
Lower	.....	Upper cell (cell 1*s*)—middle ethmoidal cell (Bulla-cell). Recessus inf. (lower part of infundibulum) with maxillary sinus.	Upper and lower intermediate cell (cell 1 *im. s.* and *i*)	.....	Upper and lower cell (cell 2*s* and 2*i*)	Descending cell (cell 3*d*)	

The septal folds, plicæ septi, which may be seen on the nasal septum in fetal life, have nothing to do with the formation of the conchæ; they lie in the region of the vomer and were seen and figured by Ruysch (1703). Killian (1895) has studied them carefully and Figs. 153, a and b, are taken from his paper. Even in a three months' fetus the epithelium in this region is thicker than

elsewhere on the septum and the septal folds are formed by the ingrowth of furrows covered with epithelium.[9]

They can first be recognized with the naked eye in the fourth month; from that time on the proportion of septa on which they may be seen increases until the end of the eighth month and then diminishes again until birth. After birth the folds usually disappear; if they persist they not infrequently form, by hypertrophy, tumor-like structures in the adult.

The *development of the olfactory nerves* has not been carefully investigated in man, but there is no reason for supposing that it takes place differently from what occurs in other vertebrates. In

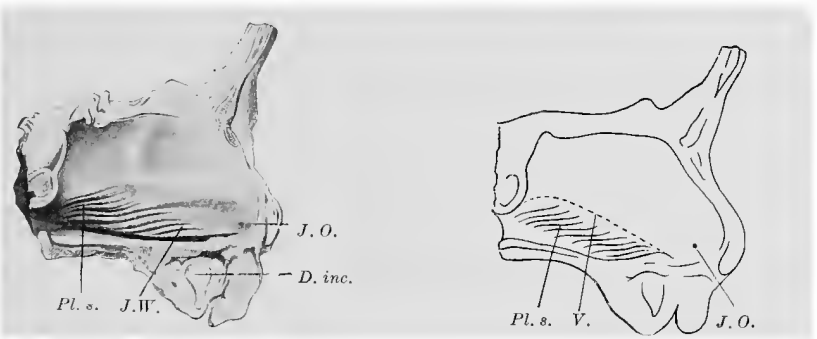

Fig. 153a Fig. 153b

FIG. 153a.—Nasal septum of a human fetus of 31 weeks, showing the plicæ septi in unusual perfection. Natural size. (After Killian, Arch. für Laryngologie, vol. 2.) *Pl. s.*, plicæ septi; *J. O.*, Jacobson's organ; *J. W.*, Jacobson's swelling with septal folds; *D. inc.*, upper middle incisor tooth.

FIG. 153b.—The same septum as is shown in Fig. 153a. The boundary of the vomer is shown (*V.*), otherwise the lettering is as in Fig. 153a.

these the olfactory fibres are formed as outgrowths from the basal portions of the olfactory cells, extending to the brain. Some cells also wander out from the epithelium and are later to be found scattered along the entire length of the olfactory nerves, appearing like ganglion-cells; their processes extend on the one hand to the olfactory epithelium and on the other to the brain. It has already been stated that olfactory nerve-fibres also develop from Jacobson's organ. Why nerve-fibres develop from only a very small portion of the primitive sensory epithelium of the olfactory fossa becomes clear when it is remembered how small the olfactory region of the fully developed nose is in comparison to the relative area of the primitive nasal fossa. For data on this point reference may be made to the observations of Brunn (1892), to Kallius in von Bardeleben's Handbuch, and to the account, given later on, of the relation of the primitive to the definitive nose.

The glands of the human nose, the small Bowman's glands, develop in the third and fourth months as solid processes. "In

[9] For further information concerning these structures and also for a possible function for them, see Killian (1895[1]).

the new-born child they are weakly developed on the floor of the nasal cavity, but more abundantly on the medial surface of the inferior concha'' (Kallius, 1905). They reach their complete development only after birth.[10]

Della Vedova (1907) states that a mucous degeneration of the epithelium of the nasal cavities occurs in early stages, but I cannot confirm this statement. He found the first cilia in a fetus of 5.7 cm. in the region of the lower concha and the middle meatus. In a fetus of 10.5 cm. (first half of the fifth month) they occur everywhere.

Up to the present the development of the primitive nasal cavities has alone been considered, and it must now be pointed out that, although the largest and most important part of the definitive nasal cavities arise from these, yet a portion of the primary mouth cavity becomes incorporated into the nasal cavities

FIG. 154.—Palats of a 3.8 cm. human fetus. (After Dursy, from Peter, Entwicklung dss Gsruchsorgans, in Hertwig's Handbuch, vol. II_2, p. 56, Fig. 63.) *Ae.*, external apsrturs; *Ch.*, primitive choanæ; *G.*, palatal process; *z.*, anlags of the uvula.

by the formation of the definitive palate and together with the primary nasal cavities forms the definitive ones.

It will be remembered that the primary nasal cavities open secondarily into the primary mouth cavity, the primary choanæ being thus formed. With the more rapid growth of the facial region of the head these primary choanæ increase in length and become slit-like. In this stage the nasal cavities are separated from the mouth cavity by the primary palatal processes (Dursy, 1869), which I do not always find well developed. These processes are formed by the margins of the primary choanæ growing somewhat toward one another; they lie in the region of the lower border of the medial frontal process and in that of the medial border of the maxillary process. The tongue, as soon as it has developed, lies close against the primitive choanæ. Now (in the seventh to the eighth week)[11] the secondary palatal processes appear in the primitive mouth cavity on the inner side of the maxillary processes;

[10] More detailed statements regarding these glands have been made by Della Vedova (1907). This author found their first anlagen as solid processes on the inferior concha and in the middle meatus of a 9.2 cm. fetus; in a fetus of 10.5 cm. he saw lumina appearing in them, and in one of 15 cm. their tubuli were richly branched.

[11] Della Vedova (1907, 1908) gives for this, as well as for the general formation of the palate, earlier dates than do other authors.

they begin at the anterior end of the primitive choanæ and extend to the region of the pharynx; about their middle a projecting knob may be seen (Fig. 154, *z*), the anlage of the uvula.

The primary palatal processes appear at first as inconspicuous folds of the mucous membrane on the inner surface of the roots of the secondary palatal processes; these are at first almost sagittal in position, their free edges looking downward and embracing the anlage of the tongue. This relation is shown in Figs. 138, 139, and 140.

In later stages the free edges of the secondary palatal processes are directed toward one another and the tongue is no longer between them. How this alteration in the relative positions of the palate and tongue has been brought about has been variously explained. His (1885, 1901) supposed that the tongue actively withdrew itself,[12] and if this did not happen properly a cleft palate results. In support of his view he refers to cases in which the tongue is withdrawn on one side and not on the other. Fick (1902) at first agreed with His; later he speaks in opposition to the idea of an upward bending of the palatal plates. According to his view, there must occur an extensive alteration in shape of the palatal and alveolar processes, which requires time for its accomplishment. He calls attention to a ridge in the pig, which, by further growth, produces a palatal plate having from the first its proper position above the tongue. According to this view the essential thing would be a change of form by growth and not active movement of the tongue. This is apparently the view held by Anna Pölzl (1904), although her account of the process is not altogether clear to me. The closure of the secondary palate is made possible "by the tongue growing forward out of the space between the palatal plates without coming into it behind."

The palatal plates themselves grow above the tongue in a horizontal direction, changing their form. Schorr (1908), who at my suggestion has recently investigated the question, comes to the conclusion that the change of position of the palatal processes is the result of a series of complicated phenomena depending on the principle of unequal growth; the tongue and the palatal plates play quite independent parts in the process, but their parts must also be closely coördinated in order that a normal result may be brought about. The tongue changes its position and the secondary palatal processes become bent up by unequal, regular growth. A ridge, such as Fick described for the pig, Schorr could not find. "The depression and elongation of the tongue and the tendency

[12] His says, "This withdrawal (of the tongue) may be induced by active muscle centractions,—*i.e.*, by depression of the lower jaw and by movements of the tongue."

of the palatal plates to gradually bend upwards produce a slow gliding movement between the lateral surfaces of the tongue and the medial surfaces of the palatal plates, a constant adaptation of one to the other and, in addition, a gradual change of position of one part after the other from before backwards."

When the palatal plates have become bent up, they bound the secondary palatine cleft (Dursy), which becomes obliterated by the fusion of the plates. Contact between them takes place first behind their anterior ends and from there the fusion proceeds in both directions: it is completed in the eleventh or twelfth week. The epithelium originally present along the line of contact is forced out by the mesoderm, but portions of it may persist as epithelial pearls (Lebouc̨q, 1881) and may also give rise to cysts (Dursy, 1869).

Posteriorly the fusion extends as far as the uvula, which is formed from a paired anlage,—that is to say, it extends beyond the territory of the nasal cavities, and anteriorly also the plates do not fuse completely; in this region there later projects between them the anterior part of the septum, and only the nasopalatine ducts (ductus incisivi, Stenonis) persist, at first as solid cords of epithelium. After the palatal processes have fused in the median line, the two sides of the nasal cavity are still for a time continuous beneath the anlage of the septum (Fig. 142); later, by the fusion of the lower border of the septum with the palate, they become completely separated from each other and open by the secondary choanæ into the pharynx posteriorly.

By the processes that have just been described a portion of the primary mouth cavity becomes added to the nasal cavity. In embryos one may indicate, with Schwalbe (1882, 1887, p. 51 et seq.), the boundary between the territories belonging to the primary and secondary nasal cavities by a line extending from the nasal opening of the incisive canal to the anterior inferior angle of the body of the sphenoid bone; later this line will not represent the boundary, since the posterior portions of the second and third conchæ project beyond the line into the region of the short nasopharyngeal passage. The nasopalatine ducts, whose formation has already been described, later acquire for a time a lumen; then it disappears except at its upper and lower ends, which may to a greater or less extent persist. In the nasal cavities these remains of the nasopalatine ducts lie close to either side of the septum; on the palate they are on either side of the papilla palatina, which is formed in the region of the part of the nasal septum which takes part in the formation of the palate.

To recapitulate once more, the entire nasal floor is formed in the region just behind the external nares by a part of the lateral nasal process, by the premaxillary palate, by a small part of the

lower border of the nasal septum, and by the anterior part of the palatal processes of the maxillæ.

The external nares, as Kölliker (1879, p. 767) found and as Retzius (1904 [1] and 1904 [2]), Peter (1901 [2], p. 72), and Della Vedova (1907) have recently thoroughly demonstrated, are for a time (from the second to the sixth month, Kallius) closed by epithelial growths, formed (according to Peter), in man at least, at first only from the median walls. These epithelial masses are especially prominent at the anterior end of the nasal vestibule and for a time project from the external nares. Posteriorly they extend to the nasoturbinal. "In the fifth to the sixth month," according to Della Vedova (1907) even in the fourth month, "the solution of the closure begins, apparently by the degeneration of the middle masses of epithelium. But for a long time one still finds remains of the epithelium in the open nares" (Kallius, 1905, p. 220).

The development of the *nasal skeleton* has been considered in connection with the skull; only a few remarks, taken essentially from Kallius (1905, p. 212 et seq.), are necessary here. I may first point out that in the conchæ of the nose the skeleton, as was formerly supposed, is not the primary structure. The swellings of the mucous membrane are the primary structures and the cartilage does not grow into these, but arises in them.

Quite briefly also the question as to the *mechanism of the growth of the conchæ* may be considered. Schönemann (1901) confirms the view of Born and Legal (Peter, 1901 [2], p. 55) that the conchæ are cut out of the lateral walls of the nasal cavities by grooves and that they are accordingly persistent portions of the nasal walls and not evaginations into the lumen of the nasal cavities; the epithelium must, therefore, grow towards those regions of the connective-tissue matrix where it finds the least resistance. Peter believes that Schönemann in this view has attributed to the connective tissue "an altogether too important part in the outgrowth of the epithelial grooves." It seems to me, on the contrary, that he underestimates the rôle of the connective tissue, whose growth also has its part to play in the formation and form of the conchæ and elevations, and Kallius (1905, p. 203) does likewise.

The formation of the cartilage tissue begins in the seventh to the eighth week in the region of the body of the sphenoid bone. It advances thence apically in the septum; it is always further developed in this than in the lateral walls, where it forms in the various conchæ; in the wall of the inferior meatus and in the floor of the nasal cavity no cartilage forms. "When the cartilage has formed in the regions mentioned, the cartilaginous skeleton (of the nose) consists of a sagittal unpaired plate in the nasal septum and of lateral paired plates, continuous with the former and forming the lateral walls and roof of the nasal cavity. Yet the

union of the lateral and median plates is complete only in the anterior parts, in what will later be the roof of the external nose; posteriorly there is at first a wide opening, elongated in the sagittal direction, through which the fibres of the olfactory nerve pass. Then individual rods of cartilage develop, which divide the large opening into several smaller ones. By the increase of the partitions of the opening the cartilaginous cribriform plate is eventually formed."

In a fetus of nine weeks the cartilaginous septum is continuous anteriorly with the lateral plates. These are curved in their lower portion and project into the maxilloturbinals; they are not yet in connection with the orbital plates; on their medial surfaces, those turned towards the septum, the anlage of the middle concha may be recognized as a quite small projection. Figs. 155 and 156

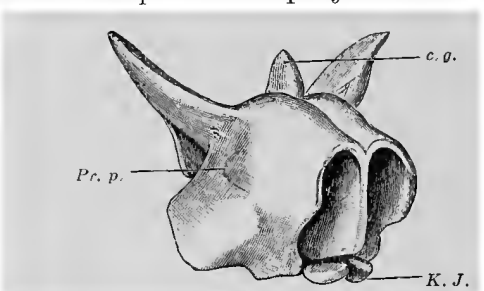

FIG. 155.—Reconstruction of the cartilaginous skeleton of a human fetus of about 12 weeks, seen from in front and partly from the side. (After Kallius, from Bardeleben's Handbuch, vol. 5, Part 1, p. 213, Fig. 77.) ×30. *c. g*, crista galli; *K. J.*, Jacobson's cartilage; *Pr. p.*, processus cartilagineus paranasalis.

are of a reconstruction from a fetus of twelve weeks; the small, somewhat indistinct ridge in front of the anlage of the cartilage of the middle concha (*m.M.*) forms the cartilaginous basis of the nasoturbinal. The orbital plates have now united with the nasal capsule; the cartilaginous anlage of the cribriform plate has not yet formed, but in its place there is a single large foramen. The Jacobson cartilages, whose development has already been described (p. 196, 197), are formed. Mention may also be made of the processus cartilagineus paranasalis (Mihalcowics), which later becomes incorporated in the upper jaw.

The cartilaginous nasal skeleton in part becomes transformed into bone (ethmoid and inferior concha); another portion becomes overlaid by connective-tissue osseous anlagen, and where this happens the cartilage is for the most part absorbed. The cartilaginous portion of the septum and the cartilages of the external nose of the adult are persistent portions of it. These parts do not, however, remain unchanged, but are divided by ingrowing connective tissue (Mihalcowics, 1898, 1899, 1900, Kallius, 1905). Thus the cartilaginous septum usually becomes separated from the anterior portions of the lateral cartilages and remains per-

manently connected with them only posteriorly; thus also are formed the alar cartilages, whose peculiar configuration begins to appear in the sixth month of uterine life.

The main points of the development of the external nose have already been described on p. 192. It was also pointed out there how greatly the parts originally lying between the nasal cavities were compressed from both sides; this process also makes relative progress later. The entire space between the two processus globulares is represented in the fully formed individual only by the philtrum of the upper lip, the space between the entrances into the nasal cavities of the embryo only by the border of the nasal septum between the adult external nares; in this region there occurs occasionally an absolute reduction of the distance. His [13] found it in a five weeks' embryo to be 1.7 mm., in a seven weeks' one 1.2

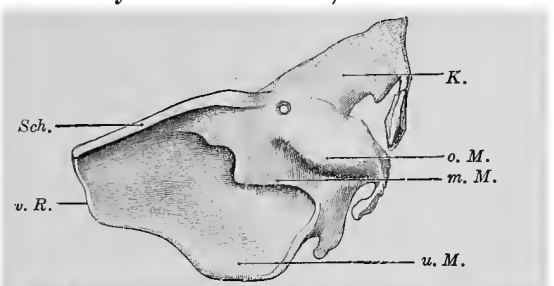

FIG. 156.—Reconstruction of the cartilaginous skeleton of the right lateral wall of the nose of a human embryo of about 12 weeks. The cut surface formed by cutting through the roof of the nose is unshaded. (After Kallius, from Bardeleben's Handbuch, vol. 5, Part 1, p. 213, Fig. 78.) ×30. *o. M.*, *m. M.*, *u. M.*, cartilages of the superior, middle, and inferior conchæ; *K.*, wing of sphenoid bone; *v. R.*, anterior border.

mm., and in a somewhat older one 0.8 mm. The further formation of the external nose is dominated in later stages of development principally by the outgrowth of the middle portion of the nasal angle together with the tip of the nose, whereby the dorsum is formed. The nares, which originally looked directly forward, become directed downward; their upper borders in the embryo lie at first very high, later, as may be perceived by a comparison with the position of the eyes, decidedly lower. The development of the individual form of the external nose begins only long after birth and lasts until puberty; it will not be followed further, but in a general way it may be remarked that the nose in women frequently retains more or less of its infantile habitus.

The development of the nasal cavities after birth has been thoroughly studied by Merkel (1885–1890) and Disse (1889). I give what are essentially the results of these investigators in the summary by Kallius (1905). "If one compares the nasal cavities of the child with those of the adult, one finds that the ethmoidal

[13] Cited from Kallius, 1905, p. 218.

and maxillary portions are of equal height in the adult, while in the child the ethmoidal part is twice as high; the maxillary portion must therefore gain considerably in height during growth. In the seventh year of life the definitive proportions are first acquired, and growth proceeds very slowly."

In the new-born child the inferior concha reaches the floor of the nasal cavities, and the inferior meatus is therefore very narrow and the nasal exit also. The middle meatus is mainly used as the air-passage. Only after the milk dentition has fully erupted is there a better development of the nasal spaces. Thus the inferior meatus becomes pervious at about this time, although it remains quite narrow until about the seventh year. With the eruption of the molar teeth the maxilla, and with it the nasal cavities, elongates from before backward.

With the formation of the body of the maxilla, which occurs at this time, its wall and the middle concha, which is fastened to this, undergo a downward movement. In this, however, the entrance into the maxillary sinus, which is of the proper size when the teeth break through, does not participate, and it therefore comes to lie at the upper part of the cavity which is enlarging downwardly.

When the change of dentition begins there is a cessation of the growth of the maxilla until puberty, when the change of the dentition is complete.

This corresponds in general with the growth of the skull, in which Merkel (1882 and 1885–1890) recognizes two periods; one lasts until the seventh year, then follows a pause, and the second period begins with puberty.

The growth relations of the upper jaw may also be determined from the position of the pharyngeal opening of the tuba auditiva; in the fetus it lies below the level of the palate, in the new-born child at its level, and in the second year of life at the level of the posterior end of the inferior concha (maxilloturbinal). Furthermore, the upper jaw is also pushed somewhat anteriorly during its growth, whereby the orthognathous face of the new-born child assumes a more or less pronounced prognathous form.

Some of the *malformations* in the nasal region may be explained as inhibitions of the development. The median lip cleft has already been referred to (p. 194) as an inhibition phenomenon occurring in the region of the upper lip and nasal septum. When disturbances of the formation of the primitive palate occur, the condition known as harelip is produced. To explain its formation it is not necessary to assume that the contact of the maxillary process with the processus globularis of the medial nasal process is entirely suppressed; it may follow this, for if the growth of the mesoderm fails (see p. 193) the fused epithelia may again become

separated by further growth. Naturally all variations may occur; the lateral nasal process may come into contact with the medial one but the contact of the maxillary processes may fail, or, on the other hand, the fusion may fail in general (compare Fig. 157).

If the secondary palatal processes fail to come into contact, so that the formation of the secondary palate is incomplete, a cleft palate, palatum fissum, results. In such cases one side of the nasal cavity may be closed below by the fusion of the downgrowing septum with one of the palatal plates. A fusion of the nasal septum with the united palatal plates may also fail to occur. This inhibition is practically important if at the same time harelip occurs on both sides; then the portion of the upper lip that lies between the two clefts and the nasal septum protrude greatly, on

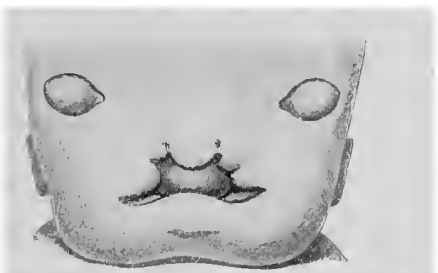

FIG. 157.—Defective formation of the lips and palate in a fetus of about three months. ×5. (After His, Anatomie menschlicher Embryonen, Part III, p. 43, Fig. 28.)

account of the septum not being anchored posteriorly. Naturally both harelip and cleft palate may occur simultaneously.

That the septal folds may not only persist but even become hypertrophied has already been stated.

Other malformations, such as the closure of the external nares and of the choanæ, receive no explanation from the developmental history and are probably to be referred to intra-uterine pathological conditions.

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DEVELOPMENT OF THE EYE.

The eyes of vertebrates differ from those of all other animals, with the exception of the ascidians, in that their apparatus for receiving the light stimuli has its origin from the anlage of the central nervous system, while in other animals, as would seem to be the natural way, it arises from the epidermis. Consequently the eyes of the vertebrates are all constructed upon the same plan, a plan which occurs only here and there among invertebrates (in the edge of the mantle of the lamellibranchs Pecten and Spondylus and on the back of the pulmonate mollusk Onchidium). Among the invertebrates the eyes vary greatly in structure, decided differences occurring in members of the same class, indeed even in closely related species. Attempts to derive the eyes of vertebrates from those of invertebrates have not been lacking, but in my opinion these have so far been unsuccessful.[14] To these vain attempts I would also add that of Boveri (1904) who would derive the vertebrate eye from the optic cells of Hesse in Amphioxus.

Much more readily can a relationship of the vertebrate eye to those of the ascidians be imagined; indeed, Froriep (1906) has recently shown that it is probable that the ascidian eye is not to be regarded as an unpaired structure, but is the right member of a pair, its fellow of the left side having degenerated. Also both the vertebrate and ascidian eyes are cerebral eyes. However, even on this point, one must accept the cautious statement of Froriep, who maintains that there can be no question of the phylogenetic derivation of the vertebrate eye from that of the ascidian larva by direct descent, although both organs have come from an identical type, which the optic pits of the vertebrate embryo resemble more closely than does the eye of the ascidian larva.

The attempt of Brachet (1907,[1] 1907 [2]) to derive the eye, and especially the lens, from an epibranchial sense organ, a placode, has already (p. 182) been mentioned.

Preparatory to a detailed consideration of the development of the human eye I shall give a synopsis of the process.

The first anlage of the eye of vertebrates and of man appears in the most anterior portion of the still open anlage of the brain as the optic pits, foveolæ opticæ. Fig. 158 shows these pits as they are seen in section from a human embryo of 2.6 mm., with 13 or 14 pairs of primitive somites (compare Plate 6 of the Normentafel of Keibel and Elze), and in Fig. 159 there is shown under a higher magnification a neighboring section of one of the pits. The pits are here fairly well developed, and there can be no doubt

[14] Compare, on this point, F. Keibel (1906 [2]) and the recent works of Brachet (1907 [1], 1907 [2]) and Lubosch (1909).

that they are also recognizable in man in the yet widely open medullary tube, at a stage corresponding with that shown in the model prepared from one of Keibel's pig embryos (Fig. 160). If the medullary tube be supposed to close, the pits would be converted into the optic vesicles. These are broad evaginations of the most anterior part of the brain anlage, the ventricular cavity of the brain being prolonged into them to form their cavities, so that one may very well speak of the optic ventricles. Later the anlagen of the optic vesicles become more sharply separated from the anlage of the forebrain and acquire stalks, the optic stalks (pediculi optici), as may be seen from Fig. 161. A transverse

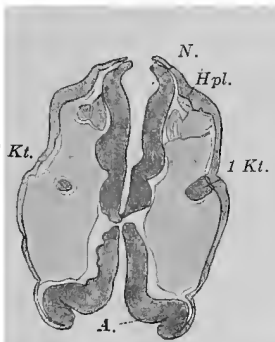


Fig. 158

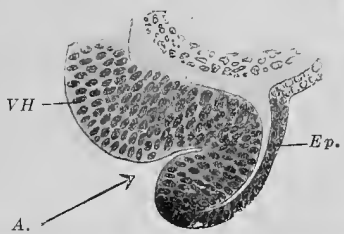


Fig. 159

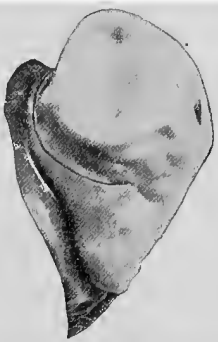


Fig. 160

Fig. 158.—(From the Normentafel of Keibel and Elze, Fig. 6b.) *A.*, anlage of the eye; *Hpl.*, auditory plate; 1 *Kt.*, first branchial pouch; *N.*, neuromere. ×15.

Fig. 159.—Section through an optic pit of Fig. 158 more highly magnified. (After Low, 1908, p. 247, Fig. 13.) *A.*, anlage of the eye; *Ep.*, anlage of the epidermis; *VH.*, forebrain.

Fig. 160.—Rostrolateral view of the head of a pig embryo (*Sus scrofa*) of 4.7 mm., with 10 primitive somites and 16 days old. Drawn from a model by F. Keibel (1897). (After Froriep (1905), in Hertwig's Handbuch, vol. II_2, p. 156, Fig. 159.) ×ca. 25

section through an optic vesicle before the stalk is distinctly developed is shown on the left side of Fig. 162. The section is taken from an embryo of 4 mm. (compare Plate 10 of the Normentafel of Keibel and Elze).

Sections through distinctly stalked vesicles are shown in Figs. 163 and 164; they are taken from the embryos of 4.9 and 4 mm. of Plates 14 and 13 of the Normentafel, the larger one (Plate 14) having 35 and the smaller (Plate 13) 34 pairs of primitive somites; the optic vesicles of the larger embryo are, however, less developed than those of the smaller one; Fig. 164 especially shows the transition of the optic vesicle to the optic cup, which must now be considered.

The optic cup, cupula optica or vesicula optica inversa, is formed from the optic vesicle by its distal wall becoming thickened and its distal and ventral portions invaginating toward the proximal layer. The invagination extends for some distance along the stalk of the optic vesicle, which has now become the stalk of the

optic cup, pediculus cupulæ opticæ. Such an optic cup is shown connected with the brain in Fig. 165, drawn from a model by His.

During the transformation of the optic vesicle into the optic

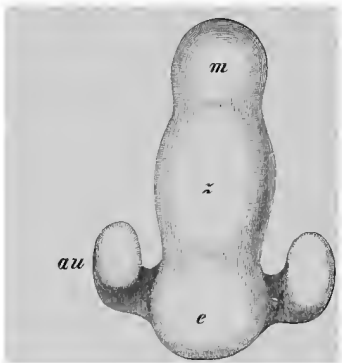


Fig. 161.—(After His, 1889, from Froriep in Hertwig's Handbuch, vol. II₂, p. 183, Fig. 187.) ×ca. 50. *au*, optic vesicle; *e*, telencephalon; *m*, mesencephalon; *z*, diencephalon.

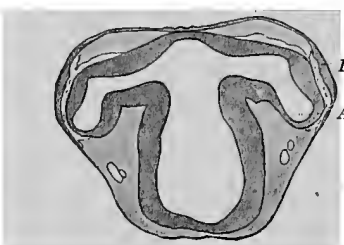


Fig. 163.—Section through the anterior part of the head of a human embryo of 4.9 mm. (From the Normentafel of Keibel and Elze, Fig. 12h.) ×30. *A.*, anlage of the optic cup; *L.*, anlage of the lens.

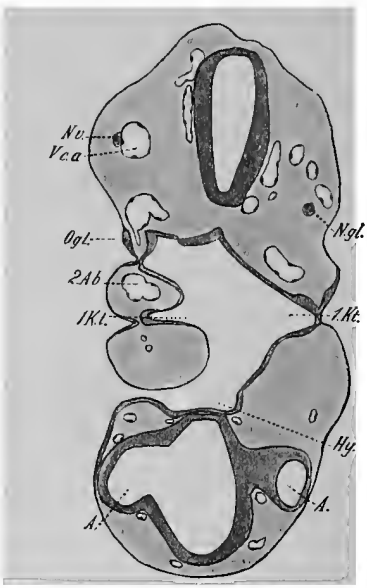


Fig. 162.—(From the Normentafel of Keibel and Elze, Fig. 9d.) ×30. The right optic vesicle (the left in the figure) is in wide connection with the ventricle of the forebrain, the stalk of the left vesicle (the right in the figure) is cut tangentially. *A.*, optic vesicle; *2A.b.*, second branchial arch artery; *Hy.*, hypophysis; *1Kt.*, first branchial pouch; *N.gl.*, glossopharyngeal nerve; *N.v.*, vagus nerve; *O.gl.*, branchial sense-organ on the glossopharyngeal nerve.

cup some other processes of importance for the development of the eye have begun. The epithelium over the proximal part of the optic vesicle at first thickens (already indicated in the stage shown

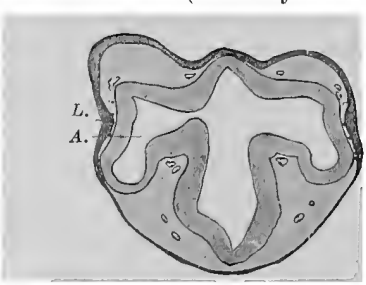


Fig. 164.—Section through the anterior part of the head of a human embryo of 4 mm. (From the Normentafel of Keibel and Elze, Fig. 11f.) ×30. *A.*, anlage of the optic cup; *L.*, anlage of the lens.

in Fig. 162), then becomes differentiated from the surrounding tissues as the lens plate, and finally becomes depressed to form the lens pit. These stages are shown in Figs. 166 a and b and 167

a, b, and c. The lens pit then closes to form the lens vesicle, as is shown in Fig. 168 a and b. Fig. 169 is from an embryo of about the same stage as that of Fig. 168 and is shown under greater magnification; it is from an embryo of Hochstetter's collection (compare the Normentafel of Keibel and Elze, Plate 28 and the figure xiii; also Elze, 1907). In the outer layer of the anlage of the retina traces of pigment are to be seen, and the lens vesicle has just closed, the point of closure being still recognizable. The inner, distal wall of the optic cup is greatly thickened. In the interior of the lens vesicle, in addition to scattered degenerating cells,

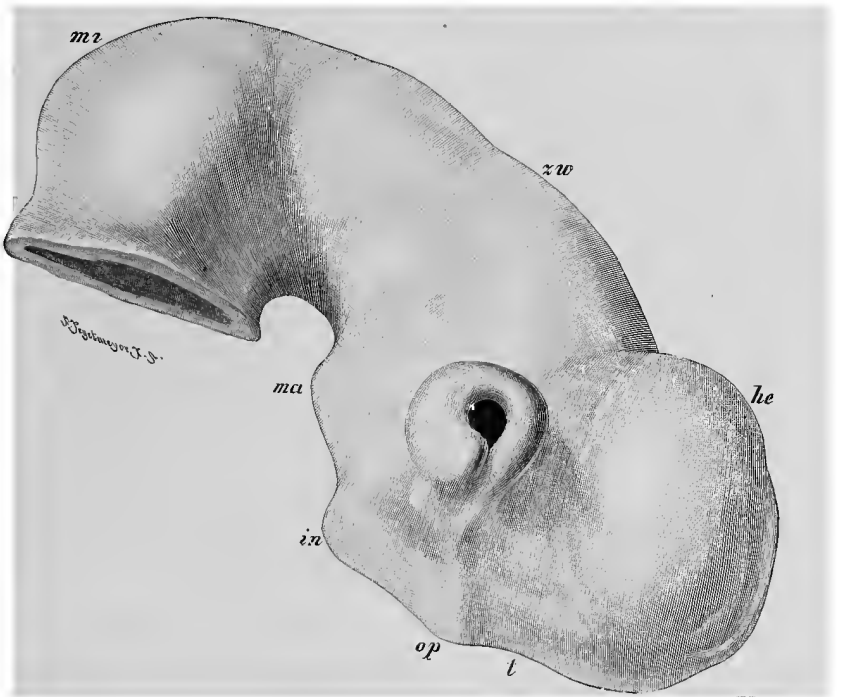


FIG. 165.—Mesencephalon and telencephalon of a human embryo from the end of the fourth week, seen from the right side and from below. Prepared from His's wax model by Fr. Ziegler. (From Froriep (1905), in Hertwig's Handbuch, vol. II_2, p. 184, Fig. 188.) ×ca. 37. *he*, cerebral vesicle; *in*, infundibulum; *ma*, mammillary process; *mi*, mesencephalon; *op*, torus opticus; *t*, lamina terminalis; *zw*, diencephalon.

there is a mass of cells resting on the proximal wall. From the lens vesicle, in a manner to be fully described later, the lens and the lens capsule are formed. The distal layer of the optic cup may from its mode of origin be termed the lamina inversa cupula or from its later fate the retinal layer, and at first the lens lies close upon it, so that it almost or completely fills the cavity of the cup, the antrum cupulæ, but later the retinal layer of the optic cup and the proximal layer of the lens gradually separate from each other. In this way is formed the cavity for the vitreous humor, cavum hyaloideum oculi, in which the vitreous humor, corpus vitreum, is formed in a manner that will be described later.

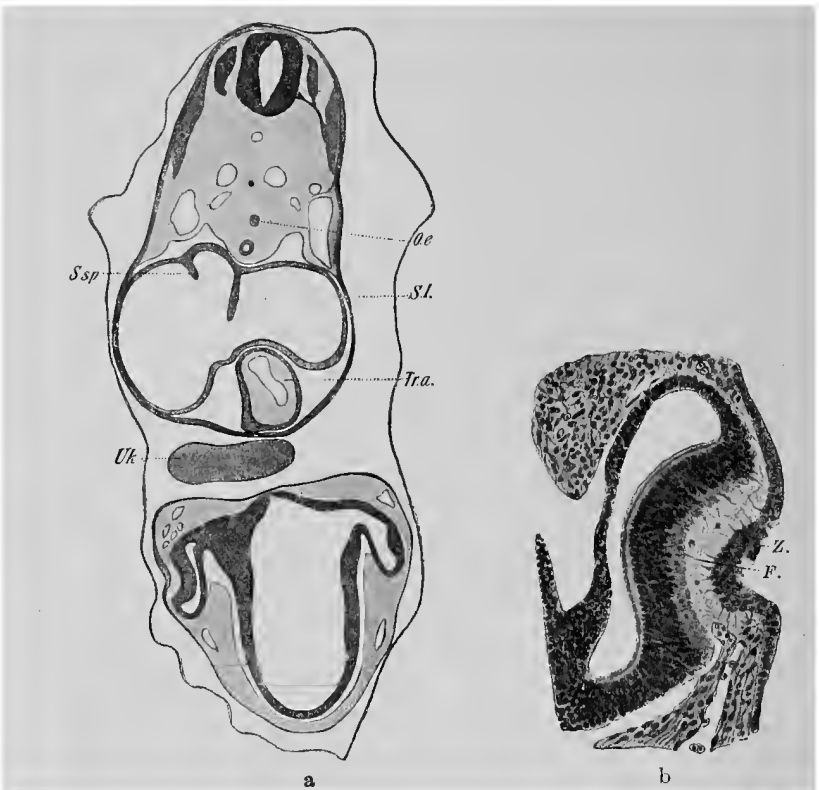


FIG. 166 a and b.—a: Section through the anterior part of the head and through the heart region of a human embryo of 5 mm. ×25. b: Section through the anlage of an eye of the same embryo. ×100. (After drawings by Hammar, from the Normentafel of Keibel and Elze.) *F.*, thread-like tissue between the lens and the anlage of the retina; *Oe.*, œsophagus; *SI*, septum I (Born); *S.sp.*, septum spurium (His); *Tr.a.*, truncus arteriosus; *Uk.*, lower jaw; *Z.*, cell mass in the lens pit.

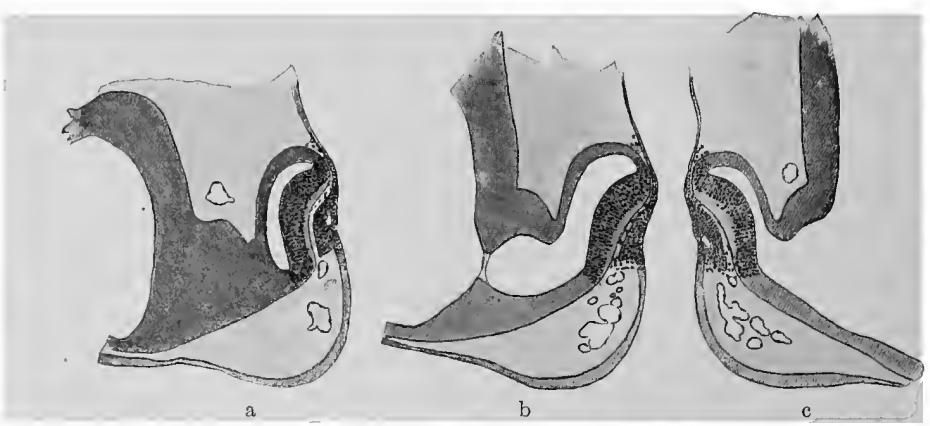


FIG. 167 a, b, and c.—a and b: Sections through the right optic cup and the pit-like anlage of the lens with its epithelial growth; mesenchyme cells occur between the distal layer of the optic cup and the anlage of the lens. c: A corresponding section through the anlage of the left eye. ×50. (From the Normentafel of Keibel and Elze.)

Figs. 170, 171, and 172 will serve to complete the description so far as it has been given. I am indebted to Professor Hochstetter for them; they have been drawn from models prepared by F. Dedekind of Innsbruck under Hochstetter's direction. Figs. 170 and 171 are from models that have been divided into an anterior and a posterior part in the line of the chorioidal fissure; one looks from behind on the apical half of the right eye. The model represented in Fig. 170 is from the embryo *Braus* (greatest length = nape length, 6.3 mm.), which Hochstetter has figured in

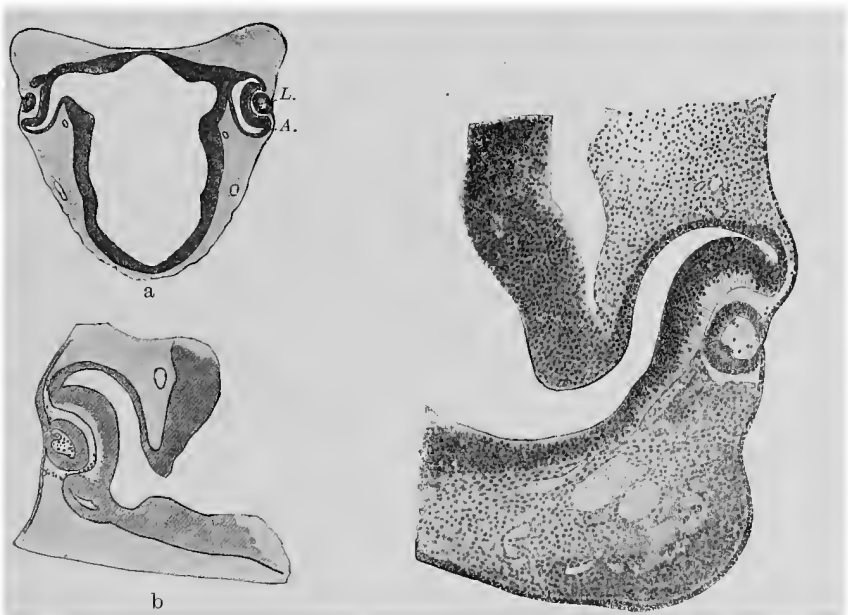


FIG. 168 a and b.—a: Section through the anterior part of the head of a human embryo of 6.25 mm., passing through the optic cup and the lens vesicle which is being constricted off from the epidermis. In the interior of the lens vesicle there is a mass of degenerated cells, shown more distinctly in Fig. b. a×20; b×50. (From the Normentafel of Keibel and Elze, Fig. 18 b and d.)

FIG. 169.—Section through the optic anlage of an embryo of 7 mm. From a drawing kindly furnished me by Professor Hochstetter of Vienna. ×100. For explanation see text.

his "Bildern der äusseren Körperform einiger menschlicher Embryonen" (Munich, 1908), and also in the sixth chapter of the Handbuch as Fig. 47 (p. 77). The stalk of the optic cup is short and broad. The lens pit is still open and for the most part lies close upon the distal layer of the cup; a blood-vessel, the hyaloid artery, is beginning to penetrate between the distal layer of the optic cup, which is the anlage of the retina, and the lens. The embryo from which the model represented in Fig. 171 was prepared was Embryo Chr. 1 of Hochstetter's collection. It has been figured by Hochstetter (l. c.) and by Keibel and Elze in the Normentafel, Fig. XIII (compare Plate 28 of the Normentafel); Fig.

169 shows a section through the optic anlage of the same embryo, which has been thoroughly studied by Elze (1907). The stalk of the optic cup has become somewhat longer and narrower, and the

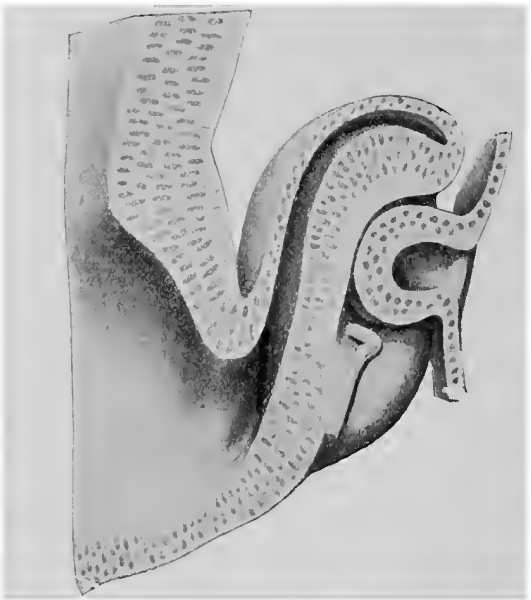


FIG. 170.—Apical half of one of the optic anlagen of an embryo of 6.3 mm. greatest length (nape-length), seen from behind. After one of Hochstetter's models prepared by F. Dedekind of Innsbruck. ×100. For explanation see text.

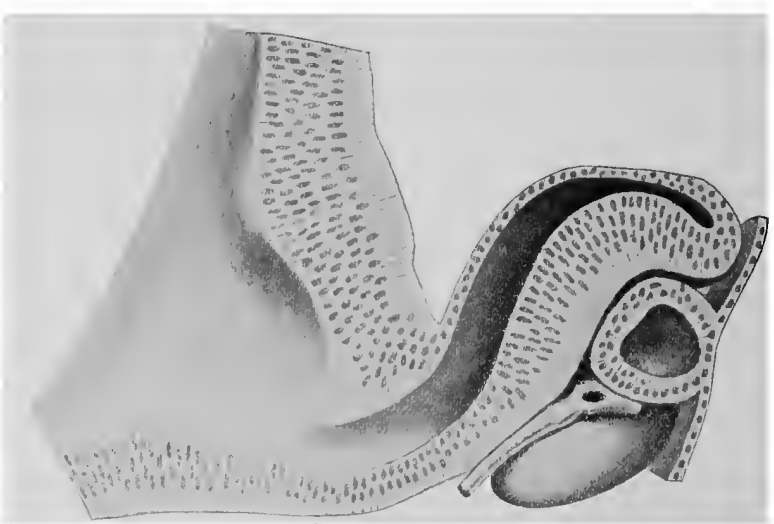


FIG. 171.—Apical half of one of the optic anlagen of an embryo of 7 mm., seen from behind. After one of Hochstetter's models prepared by F. Dedekind of Innsbruck. ×100. For explanation see text.

distal layer of the cup is decidedly more thickened. The lens has just closed and is still connected with the epidermis. The space for the vitreous body, between the distal layer of the optic cup

(anlage of the retina) and the lens, has become somewhat broader and the hyaloid artery shows the formation of an island. Fig. 172 shows the optic cup of an embryo of 12.5 mm. seen from the side and from below; one looks directly into the chorioid fissure and through the proximal region of this into the cavity for the vitreous body. The chorioid fissure is almost closed; it is narrowest at its middle. Distally one sees the lens surrounded by the border of the optic cup. The degree of development of the organs of the embryo (Ma [1] of Hochstetter's collection) from which this model was prepared is shown in the Normentafel of Keibel and Elze in Plate 56.

We may now, in the first place, take up the development of the lens. After it has separated from the epidermis its anlage lies at first close to the layer that gave origin to it, but later the two

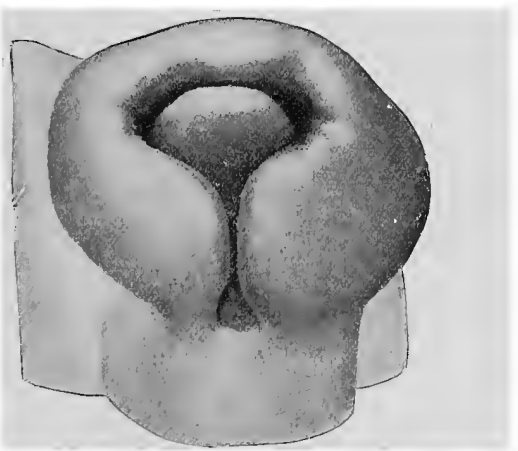


Fig. 172.—Optic anlage of an embryo of 12.5 mm. seen from the side and from below. From one of Hochstetter's models prepared by F. Dedekind of Innsbruck. ×100. For explanation see text.

structures become separated by mesoderm, mesenchymatous cells growing in between them (Fig. 173). In these cells is formed the anterior chamber of the eye; the larger distal portion of the cells becomes the substantia propria of the cornea, together with Descemet's membrane and the endothelium of the chamber, the much smaller proximal portion gives rise to the portion of the capsula vasculosa lentis which has long been known as the pupillary membrane and which degenerates before birth. The mesodermal tissue that surrounds the optic cup is continuous with the anlage of the cornea, and from it there are formed the chorioid, corpus ciliare, iris, and sclera. While these structures, whose development will be followed in detail later on, are forming, important changes take place in the region of the optic cup and of its stalk. In its thin proximal layer, the lamina externa cupulæ, pigment is deposited and it becomes the pigment layer of the retina.

The distal layer, the lamina inversa cupulæ, or, as it has already been named, the retinal layer, undergoes further differentiation. As far forward as the ora serrata it becomes the actual retina; distal to that it thins to become the pars cæca or the regio cilio-iridica, which, as its name indicates, is again separable into a pars ciliata and a pars iridica.

It may be mentioned here that the musculus sphincter and the musculus dilatator pupillæ are formed from the pigment layer of the cupula optica in the iris region. The chorioid fissure, fissura cupulæ, which is formed by the optic vesicle invaginating not directly distally, but ventrally and distally, becomes closed, and

FIG. 173.—Section through the optic anlage of a human embryo of 11 mm. (Embryo P_1 of Hochstetter's collection; the embryo is figured in Hochstetter's series of figures, in the Normentafel of Keibe and Elze, where a statement of the degree of development of its organs is given, and on p. 74, Fig. 52, of this Handbook.) The pigment, which is abundantly deposited in the outer layer of the optic cup and which extends almost into the optic stalk, does not show under the magnification (× 100) employed. The thickened proximal wall of the lens vesicle fills about the half of the lumen of this structure, and in the lumen are degenerating cells. × 100.

thus the bulbus oculi is formed. It is connected with the brain by the optic nerve, into which the stalk of the optic cup becomes transformed.

Later the lids are formed as protective and accessory apparatus; they are folds of skin which grow over the anlagen of the eye from above and below, and, for a time, they fuse together completely, so that the bulbus oculi is completely closed off from the outer world. By the formation of the lids the conjunctival sac is formed, and from this the lachrymal glands are developed, while the lachrymal sac and the lachrymo-nasal duct are connected with it by the lachrymal canals. Mention may also be made of the

development of the third eyelid, the plica semilunaris, the caruncula lacrimalis, and the eye muscles.

Now that a general idea of the development of the eye and its accessory apparatus has been obtained, we may return to the first developmental processes and consider for a little the optic pits. Their early appearance in the still open medullary tube has already been mentioned; thus during their earliest formation the light-perceiving organs lie at the surface, and in this stage the part of the retina which corresponds to the rods and cones, the receptors for the light stimulus, is turned towards the light. It has been stated in the introduction to this section that it is in this stage that Froriep (1906) finds the primitive form common to the eyes of vertebrates and ascidians. It is noteworthy that in this stage the optic pits lie immediately in contact with the ectoderm, no mesodermal cells intervening, but the mesoderm seems to have penetrated further in a slightly older stage, a section of which has been figured by Bryce (1908). Low (1908, p. 248) concludes that the cells of the wall of the pit must be arranged in several rows, since the nuclei are arranged on several levels, but from the situation of the mitoses I hold them to be arranged in a single layer, the nuclei alone being in several.

It may be noted here that the anlagen of the optic pits in the Amphibia are present *in posse* before they are visible. This is shown by the experiments of W. H. Lewis (1906) and Spemann (1906); portions of the medullary plate corresponding in position with the optic pits if removed and implanted elsewhere give rise to optic vesicles.

On the closure of the medullary tube the optic pits become transformed into the optic vesicles.

As to the correctness of the description of the development of the optic vesicle given here there can be no doubt; yet I may point out that another view would still seem to persist. In the first place, Druault, following Dareste, gives it in Poirier's Traité d'anatomie humaine (vol. 5, p. 1007) and Van Duyse (1904) also adheres to it. According to this view the anlage of the optic vesicle lies originally in the ectoderm covering the anlage of the head and only wanders into the anlage of the brain during the closure of the medullary tube. This hypothesis clearly owes its origin to the apparent absurdity involved in the origin of an organ for the reception of light stimuli in the interior of the body. That the hypothesis is false is shown by direct observations in man and in many animals and, in addition, by the experiments that have just been cited.

The optic vesicles are at first in wide communication with the ventricles of the fore-brain, but gradually they become stalked, the stalk, however, when it is developed, not being attached to the middle of the vesicle, but somewhat ventrally, as is shown in Fig. 161. As is shown in the embryo from which Fig. 162 is taken, the proximal wall of the optic cup becomes somewhat thickened at an early stage, but it must be composed of a single layer of cells in this stage and also later, as is shown by the mitoses; the nuclei,

however, are in several layers. Mesoderm has already become interposed in quantity between the distal wall of the cup and the ectoderm, but it disappears again later either completely or with the exception of very slight traces. This is shown on Plates 7, 8, 9, 10, 11, 13, 14, 17, 18, 19, and 20 of the Normentafel of Keibel and Elze (1908). The conditions in the human embryo are apparently the same as those that I observed (1895, 1897) in a very complete series of pig embryos.

By the distal wall of the vesicle becoming thickened and invaginating toward the proximal and upper wall, the vesicle is transformed into the *optic cup*. The idea that formerly obtained, that the invagination and the transformation of the vesicle into the cup was due to the anlage of the lens, must be given up, for the thorough study of the normal process of development speaks against such a view, as do also occasional malformations (Rabl, 1898) and, especially, the results of experimental investigations (W. H. Lewis, 1904, Spemann, 1901); these last show that anlagen of optic vesicles, implanted in abnormal situations, will become transformed into optic cups without any formation of a lens. Such experiments have shown that in certain amphibia not only is the stimulus supplied by the distal wall of the optic vesicle to the ectoderm lying over it necessary for the formation of a lens, but also that the stimulus arouses the ectoderm to lens formation not only in the region where this takes place in normal development, but also elsewhere. In this connection importance is to be attached to the fact that in mammalia, and also in man, the contact of the distal wall of the optic vesicle with the ectoderm lying above it is reëstablished at the time of formation of the lens. Froriep (1905 [1]) has endeavored to determine the exact method by which the transformation of the vesicle into the cup is brought about. He comes to the conclusion that it is produced not so much by an invagination of the floor of the cup as by an outgrowth of its margin. According to this view, the pupillary opening (os pupillare cupulæ) and chorioid fissure of the cup are gaps persisting between the outgrowing walls. But when Froriep states that the motive for this formation of the cup and the chorioid fissure is "that the apparatus for the reception of light may keep open the shortest path to the central organ," he is merely offering a restatement of the facts rather than an explanation of them. The chorioid fissure, by which vessels for the vitreous body pass into the cavity of the cup, closes later on, and there then remains only the pupillary opening of the cup and the opening where the arteria centralis retinæ penetrates the optic nerve, at the point where the fissure originally faded out upon the optic stalk.

According to Szily (1907), who bases his conclusion on models prepared from human embryos as well as on others from higher

vertebrates, the closure of the chorioid fissure takes place first at about the middle of its length and thence proceeds in both the proximal and the distal direction. Zumstein and Osaki (1901 [1] and 1902 [2]), who also worked by the wax-plate method, found that it closes from the distal toward the proximal end ("from before backwards"), and Keil (1906) found the same thing in the case of the pig. Minot (1894) found just the reverse; according to his observations, the closure takes place first at the proximal end. Further observations seem necessary to settle this point; perhaps it is a case of variable conditions.

The fetal chorioid fissure explains a number of forms of coloboma as inhibition phenomena, since, if it does not close, the development of the chorioid, the corpus ciliare, and the iris is also inhibited in the region of the persistent fissure. But all colobomata are not inhibition formations. In order to bring them all into this one category arbitrary rotations of the optic cup have been assumed; yet even these movements of the optic vesicle and cup do not suffice to explain all the cases. (See also H. Virchow, 1901, and Hippel, 1903.)

The optic anlagen during their development undergo some more or less important changes of position, among which may be recognized certain ones that are associated with changes in the anlagen of the brain; these changes are more especially correlated with the vertex bend of the brain and need not be further considered here. In addition there are also changes which may be regarded as peculiar to the optic anlagen, although they also may be induced by the connection of the anlagen with the brain. At first the eyes are directed laterally, but with the development of the face they move medially—and this is especially marked in man —so that the optic axes make with one another a gradually diminishing angle. According to Kollmann (1898), the angle in the sixth week of development is 90°. Dedekind (1909) finds that the optic nerve of an embryo of 19 mm. vertex-breech length and 12 mm. head length forms an angle with the median plane of about 65°, while in the fully developed condition this angle is decidedly less, only about 38° or 40°. In addition to this change of position several authors have described a rotation of the anlage of the bulb around its long axis. Vossius (1883) has placed the amount of this rotation at about 90°, basing his estimate on the facts, first, that the point of entrance of the blood-vessels into the optic nerve is at first below and in the median line, whereas in the adult individual it is situated more laterally; secondly, that the m. rectus superior comes to lie beneath the m. levator palpebræ superioris, although it is originally lateral to it; and, thirdly, that the bundles of nerve-fibres in the optic nerve pursue a spiral course.

Deyl (1896) has shown that the conclusions of Vossius are not tenable. The investigations of Strahl (1898) and Henckel (1898) have shown that Deyl's criticisms of the results of Vossius

were entirely justified, but they also showed that in younger stages than had been studied by Vossius and Deyl—that is to say, before the third month—a rotation through about 45° occurred. Originally the fissure in the distal portion of the optic nerve lies in the lower inner quadrant, but later the point of entrance of the a. centralis retinæ is situated exactly or almost exactly in the under surface. After the third month no further alteration in the position of the point of entrance of this artery can be observed. A movement of the m. levator palpebræ superioris over the medial border of the m. rectus superior does, it is true, take place to a certain extent, but it has nothing to do with a rotation of the bulb. Even the rotation in the earliest stages has quite recently been disproved by Dedekind (1908).

The development of the *lens* has been followed by C. Rabl (1898, 1899, 1900) throughout the entire vertebrate series. Of mammals he studied especially the rabbit, although the pig was

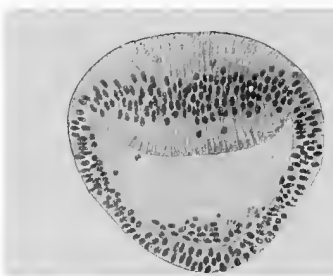


FIG. 174.—Lens of a human embryo of from 30 to 31 days. ×130. (After C. Rabl, from Froriep in Hertwig's Handbuch, p. 225, Fig. 213.)

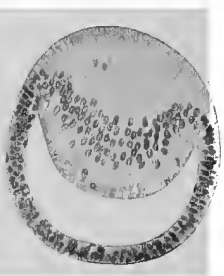


FIG. 175.—Section through the lens of a human embryo of 12.5 mm. greatest length. (Hochstetter's embryo Ma_1, Normentafel of Keibel and Elze, Plate 56.) From a drawing kindly furnished by Professor Hochstetter. ×130.

also used for later stages; human embryos were also investigated, and additional details as to these are furnished by the Normentafel of Keibel and Elze (1908). The earlier stages of development of the human lens are very similar to those in the rabbit. In an embryo of 4 mm. (Normentafel, Plate 10), the anlage of the lens is already recognizable as a thickened epithelial plate (Fig. 162); in an embryo of 4.9 mm. greatest length (Normentafel, Plate 14) there is a distinct lens plate (Fig. 163), and this is seen to be slightly concave in Fig. 164 (from the embryo of Normentafel 13). Figs. 166 a and b (from Normentafel 20) show a rather deep lens pit, the concavity being greater ventrally than dorsally. At the bottom of the pit are some cells, which have probably separated from the remaining cells of the lens plate in a manner similar to what was observed by Rabl in the rabbit. Fig. 167 a–c show the commencement of the closure of the lens vesicle, which, in the region where it has closed (Fig. 167c), has a triangular form. Figs. 168 a and b show a lens vesicle that has just closed. The

closure does not take place at the centre, but more dorsally, and at the point of closure a knob of cells projects into the lumen of the vesicle, which also contains a number of degenerating cells.

Fig. 169 also shows degenerating cells in the lumen of the vesicle, which has now separated from the ectoderm; the proximal wall of the vesicle has become thickened and its cells are preparing to elongate into the lens fibres. A somewhat more developed stage is shown in Fig. 173, and even in this degenerating cells occur in the lumen. The lens shown under higher magnification in Fig. 174, taken from Rabl, is not quite so far advanced; in this there is

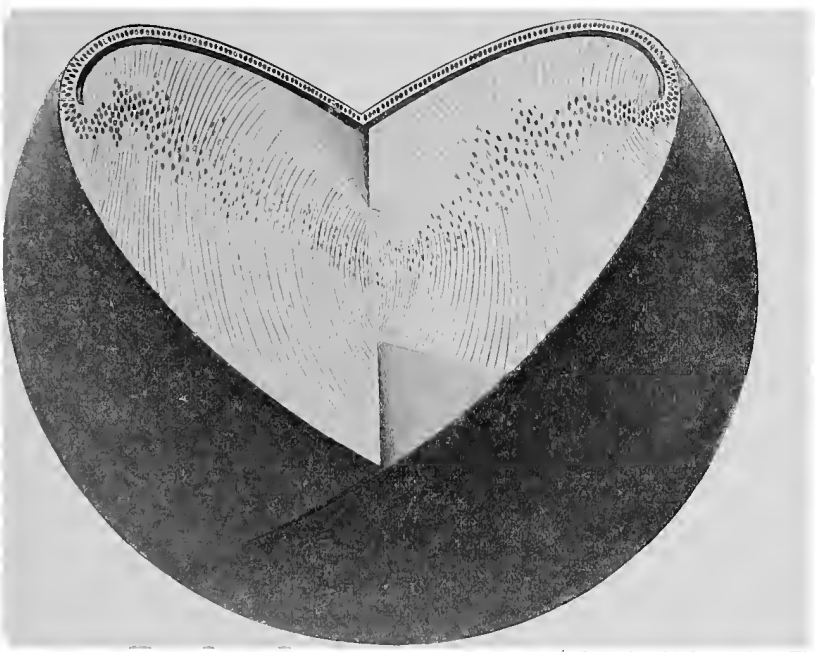


Fig. 176.—A lens at the time of the formation of the lens sutures (end of the third month). The right upper quadrant has been removed. One sees the lens epithelium, its continuity with the lens fibres at the equator.

seen in the lumen, in addition to some scattered cells, a mass of them lying on the distal wall. Rabl suggests that these cells may be an inheritance from remote ancestors and may have served in anamniote ancestors to separate the lumen of the lens provisionally from the outer world, just as occurs to-day in the Selachians. In a later stage of development the cells disappear; they are no longer to be seen in the stage shown in Fig. 175, which is taken from a human embryo of 12.5 mm. greatest length. The section is from the embryo from which the model shown in Fig. 172 was prepared (Hochstetter's embryo Ma_2, Normentafel of Keibel and Elze, Plate 56). In many mammals such cell proliferations are much more abundant than in man and may fill the entire cavity of the lens pit.

The observations of C. Rabl (1898, 1899, 1900) and Herr (1893) have shown that in human embryos, as in those of other animals, the lens fibres after they have reached a certain length (in man about 0.18 mm.) no longer increase by division, but only grow in length. The cell multiplication which leads to the formation of additional lens fibres, and with it the occurrence of karyokinetic figures, now becomes limited to the anlage of the lens epithelium, and is found most active where this epithelium becomes continuous with the lens fibre mass. In this region there occurs as development proceeds a regular meridional arrangement of the epithelial cells, by which rows of fibres are produced, which may be termed the radial lamellæ of the lens (Rabl, 1898, 1899, 1900). Even in embryos of 15 and 17 mm. greatest length Tandler finds the lens vesicle a solid structure (Normentafel of Keibel and Elze, Plates 60 and 65). The nuclei of the lens fibres have already at an earlier period arranged themselves in a curve convex toward

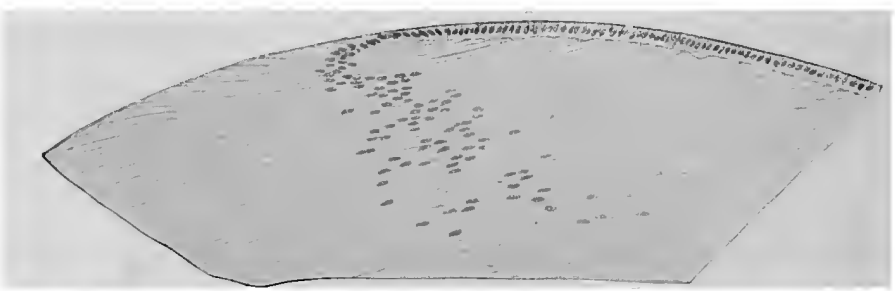


Fig. 177.—Transition of the lens epithelium into the lens fibres, in a fetus at the beginning of the fourth month. From a drawing kindly furnished by Professor Hochstetter. ×200.

the exterior (Figs. 174 and 175), and later these nuclei degenerate, beginning at the centre. Soon after the separation of the lens from the ectoderm a lens capsule can be recognized; in all probability this is formed in mammals and in man, as it has been shown to be formed in reptiles and birds, from cells of the lens anlage and not from mesoderm, which, however, comes into intimate relation with it as the tunica vasculosa lentis. At the end of the third month the formation of the lens sutures begins; they owe their existence to the peripheral fibres becoming longer than the central ones. The proximal suture, which is placed horizontally, is the first to appear, and then the distal one. This is represented in Fig. 176. Fig. 177 shows the transition of the lens epithelium into the lens fibres in a fetus at the beginning of the fourth month, after a preparation by Hochstetter; it will serve as a complement to Fig. 176, which is schematic. The lens sutures become transformed in man into the lens stars, and first of all into triradiate stars, such as are seen in the human lens from the fifth month of development. Rabl (1900) has followed accurately in pig embryos the conversion of the linear sutures into the triradiate stars.

The lens is almost spherical in the third month, its proximo-distal axis indeed slightly exceeding the equatorial diameter (Froriep, 1905 [2]). In an embryo of 19 mm. vertex-breech length Dedekind (1909) found the proportion of the sagittal to the equatorial diameter to be 1 : 1.14. Other data concerning the growth and modification in form of the lens will be given when the growth of the eye as a whole is under consideration.[15]

We may now consider the development of the *vitreous body,* one of the most difficult problems of embryology. The account of it given here is based on the results obtained by the numerous workers who have attacked the problem within recent years and on my own observation, but at the same time I would point out that I do not consider the question as definitely settled. For this reason I shall add an account of some discordant views.

Both ectoderm and mesoderm appear to take part in the formation of the vitreous body, the retinal layer of the optic cup and the vasifactive mesoderm which enters the cavity of the optic cup with the vessels through the chorioidal fissure and around the edge of the lens; perhaps other mesodermal tissue also enters. The portion of the tissue that is derived from the retinal layer of the optic cup may be termed the primitive vitreous body. It appears upon the inner surface of the lens as soon as the cavity for the vitreous body begins to form between the lens and the retinal layer. At first non-cellular vitreous tissue arises from the whole extent of the retinal layer, but after the formation of the pars cæca, and with the progressive differentiation of the retina proper, the formation of this tissue ceases in the region of the latter; only in the region of the pars cæca does it continue to form for some time, and from this region the fibres of the zona ciliaris arise. In what relation the mesodermic vitreous tissue, which begins to develop a little later than the ectodermic, stands to its predecessor and, accordingly, how the definitive vitreous body is formed, remains doubtful to me. Froriep (1905[2], p. 244) says on this point, "Both tissues appear to become most intimately united, in such a way that a new tissue element, the definitive vitreous body, is formed, the character of which is determined not by the exceedingly delicate and perishable ectodermal portion, but by the strongly-developed mesodermal constituent."

This would be a condition of great fundamental importance, a fact that was correctly perceived by Szily (1904, 1908), who regards the formation of the vitreous body merely as a special case of development of an embryonic supporting tissue. According to him, throughout the entire body of the embryo a non-cellular, fibrous supporting tissue is formed by the basal cells of all epithelial layers—no

[15] It may at least be mentioned here that in Amphibia the lens can be regenerated from the epithelium of the iris. An historical review of the observations on this point is given by Fischel (1909) in his work on the regeneration of the lens.

matter from which of the germinal layers they may have been formed—giving off fibrous processes which have arisen from intercellular bridges or protoplasmic processes. Later mesenchyme cells become associated with this non-cellular supportive tissue and an intimate protoplasmic connection develops between them and the fibres. In this way is formed the embryonic connective tissue with its two components, the mesenchyme cells and the fibrillar matrix. From now on the newly added cells take upon themselves the nutrition and growth of the fibres arising from the original sources. The primitive vitreous body, according to von Szily, is therefore formed not from the retina alone but from at least both the retina and the lens. In exactly the same manner is formed, for example, the tissue of the cornea. In this case also primitive fibrous connections are formed between the distal wall of the lens and the ectoderm lying over it; just as similar connections are made between the proximal wall of the lens and the retinal layer of the optic cup, and the stroma tissue of the cornea is formed by an association of mesenchyme cells with this primary fibrous substance. In his account of the development of the vitreous body and cornea Bryce (1908) has followed Szily, as has also V. Knape (1909), at least so far as the chick embryo is concerned. It seems to me, however, that such an idea is confronted with great difficulties, as, for instance, the relation between the cornea and the sclera.

Dryault (1904) gives a very different account of the genesis of the vitreous body. Starting from the observations of Retzius (1894), he assumes the vitreous body to be primitively mesodermal,[16] but this becomes replaced by a secondary ectodermal structure derived from the retinal layer of the optic cup. In this way Cloquet's canal is formed, it being in reality not a canal at all, but the primary mesodermal vitreous body with its vessels, forced to the axis of the eye. "In fact, this cord represents the primitive vitreous body forced to the centre of the eye by the development of the definitive vitreous body." The wall of Cloquet's canal is the thickened layer of the secondary vitreous body that bounds the primary body. This is the condition of affairs at the sixth month of fetal life; after birth one finds no trace of the canal in man, the primary mesodermal vitreous body having been completely replaced by the secondary one.

Lenhossék (1903) regards the entire vitreous body as a derivative of the lens; but, on the other hand, the zonula fibres, according to him, are formed quite independently of the vitreous body and may grow out from the pars ciliaris of the retina. The hyaloid membrane has nothing to do with the vitreous body genetically; it is formed from the retina.

The older teaching, to which some recent authors, such as Carini (1899), Nussbaum (1900), and Spampani (1901), have returned, is to the effect that the vitreous body is a mesodermal structure which grows into the cavity of the optic cups through the chorioid fissure. That a mesodermal anlage of the vitreous body is not invaginated into the optic cup by the lens was long ago shown by Kessler (1877) and myself (1886, 1895), and this has been confirmed by all recent careful investigations.

For further information on the question of the vitreous body mention may be made of the works of the following authors, in addition to those already cited: Tornatola (1897, 1898), C. Rabl (1898, 1899, 1900, 1903), Fischel (1900), Addario (1902, 1904–5), van Pée (1903), Kölliker (1903, 1904), Cirincione (1903[1,2,3], 1904). Haemers (1903), Fuchs (1905), and Wolfrum (1907).

The vessels of the eye have an intimate connection with the

[16] Dryault, however, did not study the early stages in which this condition is supposed to occur, and consequently begs the actual question.

formation of the vitreous body, since man, like the mammals in general, possesses in embryonic and fetal life an arteria lentis, ramifying in the capsula vasculosa lentis and vasa hyaloidea propria.[17] Fig. 178 represents the vitreous body, lens, and retina of a human fetus of the sixth month, according to O. Schultze. The a. lentis, before it reaches the lens, divides into the branches passing to the tunica vasculosa lentis; the distal portion of the capsula vasculosa lentis (the so-called membrana pupillaris) has been removed together with the iris. The retina is reflected and is

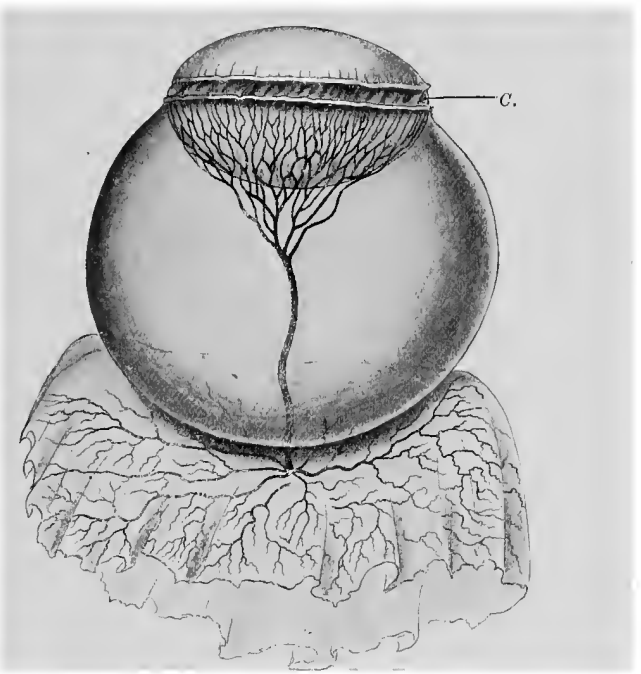


FIG. 178.—Vitreous body, lens, and the reflected retina of a human fetus of the sixth month. No vessels of the vitreous body are to be seen except the arteria lentis. *C.*, corpus ciliare. (After O. Schultze 1892), Plate II, Fig. 9.) For further description see text.

already vascularized up to the ora serrata, whereas in the third month of fetal life no retinal vessels are to be observed; the existence of a membrana vasculosa retinæ, which will be considered later, is denied by Versari (1903, 1909) for man. The vasa hyaloidea propria have already disappeared; their degeneration be-

[17] I follow the nomenclature of Froriep (1905[2], p. 245), compare also H. Virchow (1901), and use the term A. hyaloidea in a broad sense. It includes the following:

A. hyaloidea
- Axial
  1. Vessels of the ridge or shelf-like structures in the suture of the optic cup.
  2. Arteria lentis.
- Peripheral
  3. Vasa hyaloidea propria.
  4. Retinal vessels.

gins in the third month and proceeds from the periphery toward the centre. Fig. 179 shows the distal part of the tunica vasculosa lentis of a human fetus of the eighth month, in which marginal loops have already developed from the original uniform network. The blood supply of the tunica vasculosa lentis is threefold: it receives arterial blood from the proximal direction through the arteria lentis, from the equator through vessels from the arteriæ hyaloideæ propriæ, and when these degenerate through the arteria lentis, and from in front through the long ciliary arteries (by means of the circulus iridis major). The venous return is entirely by way of the chorioid and falls directly into the venæ vorticosæ.

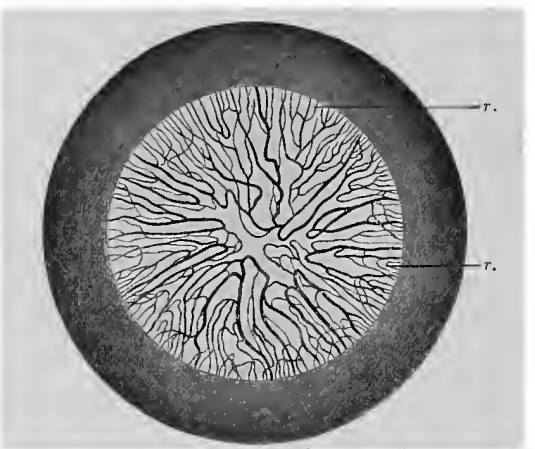


FIG. 179.—Pupillary memorane of a human fetus of the eighth month. *r*, marginal loops. (After O. Schultze (1892), Plate I, Fig. 2.)

Accordingly the growth zone of the lens, its equator, is supplied in a special manner; in this region there is an exceedingly delicate network of exceptionally fine capillaries, which receives its blood from all three arterial supplies.

The earliest stages in the development of the eye-vessels are not yet sufficiently known, notwithstanding the work of Versari (1900 [1], 1900 [2], 1903, 1909) and Dedekind (1909). For the rabbit there exists a very thorough study by Fuchs (1905). According to him, the arteria hyaloidea arises as a blind bud from a circular vessel situated at the margin of the optic cup. This primary hyaloid artery enters the ventral portion of the cavity of the optic cup from the caudal side and forces a connection with the vessels of the choriocapillaris in the medial end of the chorioid fissure; the secondary hyaloid artery so formed unites later with the arteria ophthalmica interna. The arteria hyaloidea of the rabbit is, consequently, a complex vessel. The earliest development of the retinal vessels in man has been described by Versari (1903, 1904), but the description that follows here is based on the accounts given for mammals. Kessler (1877) has shown for the rat, and O. Schultze (1892) for the pig, the ox, and other mammals, that the retinal vessels arise independently of the arteria hyaloidea and ramify independently in the retina from the point of entrance of the optic nerve.

The observations of Voll (1892) agree with those of Schultze; he shows that mesoderm cells penetrate into the optic bulb with the arteria hyaloidea and

form a swelling in the depressed centre of the papilla of the optic nerve, from which they spread out over the vitreous surface of the retina. Thus the membrana vasculosa retinæ is formed and this is soon vascularized from the papilla. In addition to the works mentioned, that of H. Virchow (1901) may also be consulted.

The development of the human retinal vessels differs, according to Versari (1903, 1904), from what has been described in mammals in several particulars. The cellular cushion of mesoderm that occupies the place of the later excavation on the papilla of the optic nerve does not extend out over the edges of the papilla

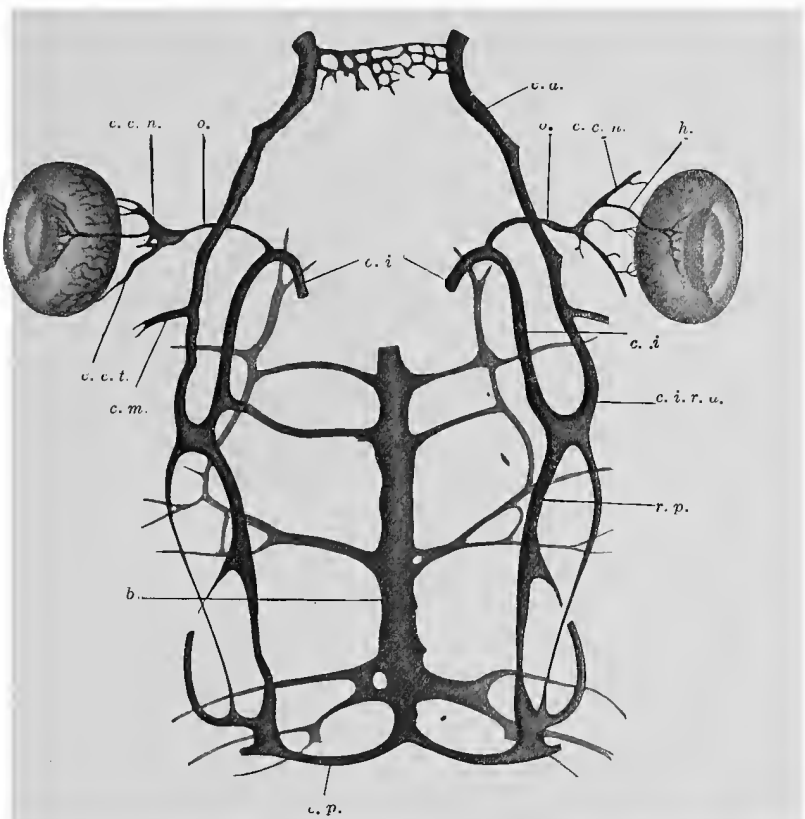


Fig. 180.—The arteriee of the base of the skull and of the eye in a human embryo of 22 mm. From an injected preparation. *b.*, art. basilaris; *c. a.*, art. cerebral. ant.; *c. c. n.* and *c. c. t.*, art. ciliarie comm. naeal. and temp.; *c. i.*, art. carotis intern.; *c. i. r. a.*, art. carotie intern. ram. ant.; *c. m.*, art. cerebral. media; *c. p.*, art. cerebral. profunda; *h.*, art. hyaloidea; *o.*, art. ophthalmica; *r. p.*, ramue communicane poeterior. (After Versari, 1900.)

upon the surface of the retina, but spreads out beneath the layer of nerve-fibres, so that from the beginning the vessels lie in the substance of the retina and there is no distinct membrana vasculosa retinæ. The beginnings of the retinal vessels are not extensions of cilio-retinal arteries and retino-ciliary veins, but buds from the arteria hyaloidea and the two primitive veins of the optic nerve. In fetuses of 36 cm. the vessels have reached the inner reticular

layer, and in those of 42 cm. the inner granular and even the outer reticular layer.

Some figures taken from Versari (1900 [1], 1903) will give a better idea of the relations that have been described and will serve as a complement to the text. Fig. 180 shows the injected vessels at the base of the skull in an embryo of 22 mm. vertex-breech length. From the a. carotis interna (*c.i.*) there arises on either side the a. ophthalmica, and each of these divides into a nasal and a temporal a. ciliaris communis (*c. c. n.* and *c. c. t.*); the nasal a. ciliaris communis gives off the a. hyaloidea (*h.*). In many cases the a. hyaloidea arises at the point of division of the a. ophthalmica. From the arteriæ ciliares communes very fine branches are given off which supply the vascular network of the chorioid, but this is not well shown in the figure. At this time the

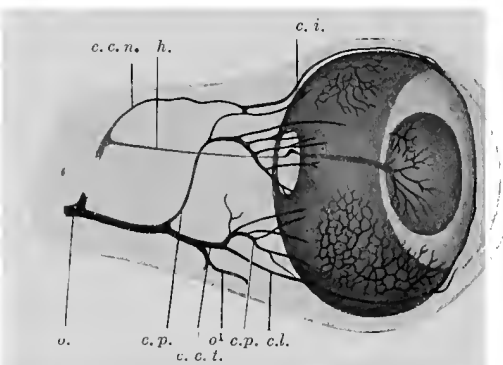


FIG. 181.—The vessels of the right eye of a 5 cm. human etus. From an injected preparation. *c. l.*, art. ciliar. post. long.; *c. p.*, art. ciliar. post. breves; *o.*, continuation of the art. ophthalmica. The remaining letters have the same significance as in Fig. 180. (After Versari, 1900[1].)

majority of the vessels for the chorioid arise from arteriæ ciliares communes during their course within the wall of the bulb, from the portion which later becomes the arteriæ ciliares posteriores longæ. Occasional branches are also given off before the arteriæ ciliares communes enter the territory of the bulb; thus even before a. hyaloidea there is given off from the a. ciliaris communis nasalis a small branch, which is to be regarded as an a. ciliaris posterior brevis. While fine branches pass to the chorioid from the arteriæ ciliares posteriores longæ in many mammals, even in the adults, they are no longer to be found in human fetuses of 5 cm. The vessels of the right eye of such a fetus are shown in Fig. 181. From the a. ophthalmica (*o.*) arise the two arteriæ ciliares communes, a nasal (*c. c. n.*) and a temporal (*c. c. t.*), and from the nasal the arteria hyaloidea (*h.*) arises; the arteriæ ciliares longæ give off the arteriæ ciliares posteriores breves (*c.p.*) and are then to be termed throughout their further course the arteriæ ciliares posteriores longæ (*c.l.*); *o.* is the peripheral continuation of the

a. ophthalmica. Fig. 182 shows a sagittal section through the point of entrance of the optic nerve into the bulb in a 7 cm. fetus. The arteria hyaloidea (*h.*) is cut longitudinally; where, as the art.

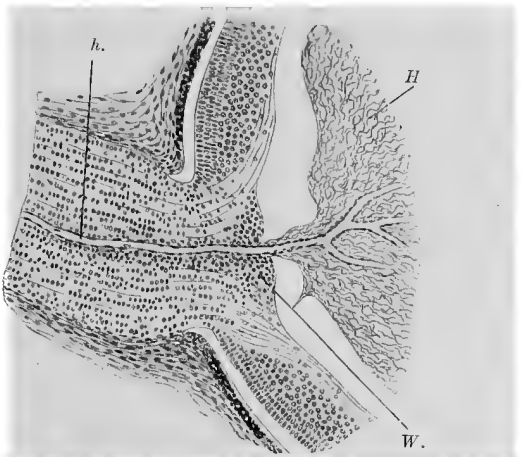


FIG. 182.—Sagittal section through the point of entrance of the optic nerve in a human fetus of 7 cm. *H.*, vitreous body; *h.*, art. hyaloidea; *W.*, cellular swelling in which the retinal vessels are beginning to form. (After Versari, 1903.)

lentis, it enters the substance of the vitreous body it is surrounded by a swelling composed of cells, and in this later the retinal vessels will begin to develop. Even in a fetus of 10 cm. these vessels, as

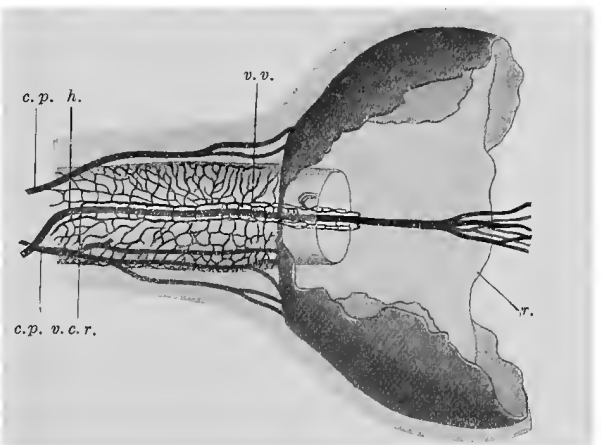


FIG. 183.—Injected preparation of the eye vessels of a 10 cm. fetus. *c. p.*, principal stem of the art. ciliares post.; *h.*, art. hyaloidea; *r.*, retina; *v. c. r.*, vena centralis retinæ; *v. v.*, veins surrounding the art. hyaloidea from which the vena centralis retinæ arises.

such, have not yet begun to form, as may be seen from Fig. 183; yet Versari was able to find, in the substance of the swelling which surrounds the a. hyaloidea in the region of the papilla of the optic nerve, some cell-cords, two of which were in connection with the wall of the a. hyaloidea. Attention should also be directed to the

small venous vessels in the optic nerve and especially in the neighborhood of the a. hyaloidea (*v. v.*). From these the vena centralis retinæ (*v. c. r.*) develops. In the substance of the vitreous body the companion veins of the a. hyaloidea, which here becomes the a. lentis, are completely wanting. Actual retinal vessels, permeable to blood, were first found by Versari in fetuses of 12 cm.; they are shown in Fig. 184 (*a. r.* and *v. r.*). The a. hyaloidea seems to be dilated in a spindle-like manner at the point of origin of the retinal arteries (*a. r.*), and from this point onward it may be termed the a. lentis. The development of the v. centralis retinæ has made considerable progress; Fig. 185 shows the appearance it presents in sections. The figure is reconstructed from some sagittal sections through the eye of a fetus of 13 cm.;

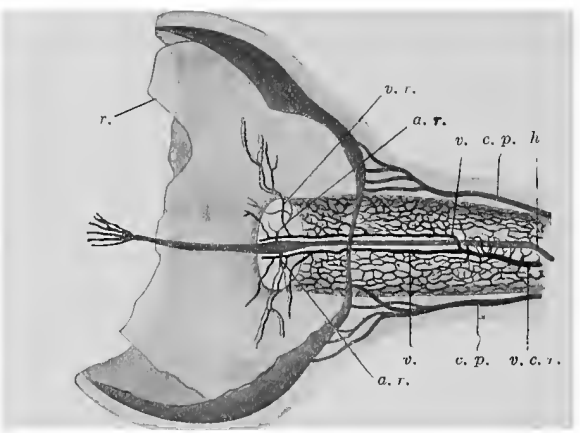


Fig. 184.—Injected preparation of the eye vessels of a 12 cm. fetus. *a. r.* and *v. r.*, arteriæ and venæ retinæ; the remaining letters as in Fig. 183. (After Versari, 1903.)

the veins (*v. r.*) are represented as black and the arteries (*h., a. l., a. r.*) as gray. Fig. 186 a–c represent sections through the injected retina of fetuses of 19 cm., 36 cm., and 42 cm. One may perceive from these how the retinal vessels penetrate more and more deeply.

Greater or smaller remnants of the embryonic vessels occasionally persist in man; they are inhibition structures and may have a practical importance. Compare on this point Hippel (1900) and Brückner (1907).

We come now to a consideration of the differentiations which the optic cup and its individual parts undergo during the further course of development. The outer (proximal) layer of the optic cup becomes transformed into the *pigment epithelium of the retina.* The pigment makes its appearance in embryos of from 7 to 9 mm. greatest length (compare Normentafel, Plates 29–43), and first of all in the region of the pupillary border, whence it extends

backward towards the optic stalk.[18] The *retinal layer* becomes differentiated into the pars optica and the pars cæca, this latter again giving rise to the pars ciliaris and the pars iridica.

The pars optica is separated from the pars cæca by an ora

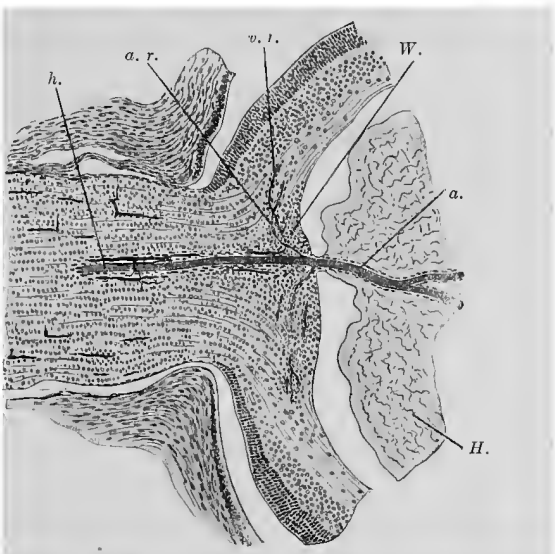


Fig. 185.—Section through the point of entrance of the a. hyaloidea into the optic bulb of a fetus of 13 cm., reconstructed from several sagittal sections. *a. l.*, art. lentis; *a. r.*, retinal artery; *H.*, vitreous body; *h.*, art. hyaloidea; *W.*, swelling around the point of entrance of the a. hyaloidea, in which the retinal vessels have been formed. (After Versari, 1903.)

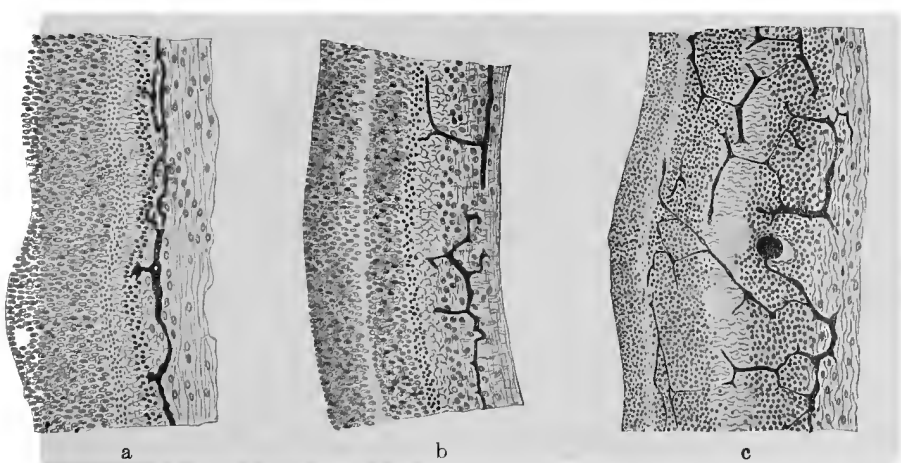


Fig. 186 a–c.—Sections through injected retinæ; to the right the layer of nerve-fibres, to the left the outer layer which gives rise to the rods and cones. One sees the gradual penetration of the vessels. Fig. 186a: Sagittal section of the retina in the neighborhood of the optic papilla, from a fetus of 19 cm. Fig. 186b: A similar section from the posterior hemisphere of the bulb of a fetus of 36 cm. Fig. 186c: A section similar to the preceding for a fetus of 42 cm. (After Versari, 1903.)

[18] According to Ucke (1891), the pigment extends into the optic stalk in embryos of the chick and sheep, and O. Lange (1908, p. 12) has reported the same thing for man.

serrata even in the fetus, and O. Schön (1905 [1, 2]) in denying the existence of an ora in the new-born child is undoubtedly incorrect, as the observations of O. Schultze (1902) and others have shown.[19] The separation is associated with the formation of the ciliary body and its ciliary processes. In the fourth month of development the margin of the retina lies at the ciliary margin of the iris, but

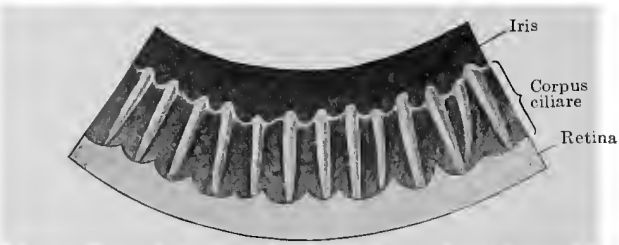


FIG. 187.—Iris and corpus ciliare of a fetus in the second half of the fourth month. (After O. Schultze (1902), Plate I, Fig. 5.)

the more the ciliary body with its processes enlarges, the more the margin of the retina retreats proximally, and, since the retinal layer does not keep pace with the ciliary body in the increase of its surface, there results a corresponding thinning of the layer. The degree of development of the ora serrata also varies greatly in the fetus. Fig. 187 shows the iris, the corpus ciliare, and the

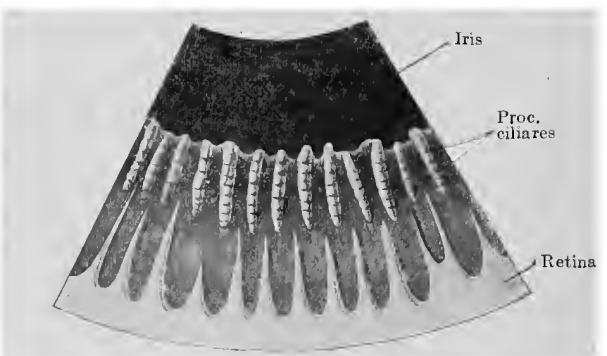


FIG. 188.—Iris and corpus ciliare from a prematurely born fetus of the eighth month. (After O. Schultze (1902), Plate I, Fig. 6.)

distal edge of the retina, its ora serrata, of a fetus in the second half of the fourth month. An unusually strong development of the teeth of the ora serrata is shown in Fig. 188, from an eight months' fetus prematurely born; almost all the teeth extend through the entire breadth of the orbiculus ciliaris. Streaks of pigment, in which the pigment layer of the retina is thickened to form ridge-like structures and which very usually extend from

[19] Quite recently O. Lange (1908, p. 20) seems to have returned to Schön's view, but certainly without sufficient reason.

the tips of the teeth of the ora serrata into the orbiculus ciliaris, are relics of the greater thickness which the retina originally possessed throughout the entire region of the orbiculus; the streaks vary greatly in their development in different individuals.

The *pars optica* of the retina differentiates in a proximo-distal direction, the maculo-papillary region being the first to develop completely. Sections through the retina of an eight weeks' embryo still present, according to Chiewitz (1887), a purely epithelial character, except for the layer of nerve-fibres. Two principal layers of nuclei are separated by a clearer intermediate zone, in which more scattered nuclei (spongioblast nuclei) occur. At two and one-half months before birth all the layers of the retina are complete. An intermediate granular layer first appears in a five months' fetus at the spot where the macula lutea will later form, and in the same region the first cones appear at a slightly earlier date (17 weeks[20]). The fovea centralis begins to form after the sixth month and is present in fetuses of seven and a half or eight months. During its formation the outer fibre layer develops in the outer granular layer and the transitory radial fibre layer, which later disappears but is still present in the nine months' fetus, appears in the inner granular layer between the spongioblasts and its other elements, the layer being traversed obliquely by the elongated and diverging radial fibres. The layer of multipolar ganglion-cells at its first formation consists of about seven tiers of cells, but as the entire layer becomes increased in surface extent its elements separate to form a single layer, the original condition persisting only in the macula lutea.

The fovea centralis has, contrary to earlier opinions, nothing to do with the chorioidal fissure. Its formation begins in the seventh month and proceeds from the inner toward the outer layers (Chiewitz, 1887). Its appearance is preceded by a thickening of the corresponding region, so that the concavity is a secondary formation. Chiewitz suggests that individual variations in the behavior of the cerebral layer at the bottom of the fovea may be due to persistence of an earlier or later stage of embryonic development.

The histological differentiation of the retina has been more thoroughly followed by Ramon y Cajal (1896) in the cat, dog, rabbit, calf, and mouse. Fig. 189 represents a section through the retina of a new-born cat, in which the differentiation is taking place. The multipolar cells are the first to develop; these next form their axis-cylinder processes and then the dendrites, these latter at first extending out on all sides, though later only the ascending (distal) ones persist, the others atrophying. At an early date those bipolar cells that are destined to become rod cells can be distinguished from those that will form cone

[20] According to Falchi (1888[12]), the rods have begun to form in a fetus of 21.3 cm.

cells. Both first produce the proximal process (unipolar stage) which comes into connection with the membrana limitans externa, but the cone cells have a greater amount of protoplasm and consequently stain more darkly with Golgi's silver method. The distal processes arise later; they develop to various degrees and may occasionally extend almost to the zone of multipolar cells. The nuclei of the cone cells finally approach the membrana limitans externa and then their proximal (descending) processes all extend to the same level. Rod and cone cells are peculiar structures that can be classified neither as nerve- nor neuroglia-cells. Finally the rods and cones develop. The horizontal cells at first give off processes in all directions, but later their cell bodies become smaller and the dendrites spread out in a single plane, that of the outer reticular layer, their axis-cylinder processes at the same time increasing in length. The Müllerian cells correspond to the glia-cells of the rest of the central nervous system; they differentiate at an early stage and traverse the retina from the lamina limitans interna to the lamina limitans externa. Their nuclei are at first scattered through the entire thickness of the retina, with the exception of the layer of multipolar ganglion-cells, but later they assemble in the inner granular layer. At times two nuclei may be found in many of the cells, a condition which Ramon regards as an indication of cell multiplication.

Pigment is formed in the *pars cæca* of the retina, the pigment extending over the margin of the optic cup into it and reaching finally the region of the corpus ciliare. Up to the end of the seventh month Szily (1902 [1, 2]) finds between the two layers, where they pass into one another, a cavity, which he regards as a circular sinus. With the disappearance of this sinus the anterior epithelial layer sinks into the concavity of the margin of the optic cup. In a fetus of 10 cm. the outer layer of the cup is pigmented only up to the region of the peripheral border of the circular sinus. From here outward the pigment diminishes in amount and is continued over the edge of the cup into the inner lamella only as a few granules. At the middle of the fifth month it has reached to about the middle of the iris; during the latter portion of intra-uterine life it reaches the region of the ciliary processes, but does not actually extend into these even in the new-born child.

The most noteworthy point in the development of the eye, and one that is full of significance for histogenesis in general, is the fact that the musculus sphincter and the musculus dilator pupillæ take their origin from the iris portion of the outer (proximal) layer of the optic cup. These muscles are therefore formed from ectodermal epithelial cells. This mode of development of the dilatator was first recognized by Grynfeltt (1898[1,2]) in the rabbit, in which it begins to occur at 14 days after birth; later Nussbaum (1900) noted its occurrence in birds and mammals (mouse). Similar results have also been obtained in man. According to Heerfordt (1901 [1]), the formation of the muscle-cells begins in the 24–30 week of fetal life. The nuclei withdraw from the outer ends of the cells, and the non-nucleated, strongly pigmented portions of the cells fuse to form a diffusely pigmented lamella, whose protoplasm retains its continuity with the nucleated

portions of the cells. Then the non-nucleated portions arrange themselves radially, and fibres, also directed radially, appear in them and later arrange themselves in bundles. The pigment col-

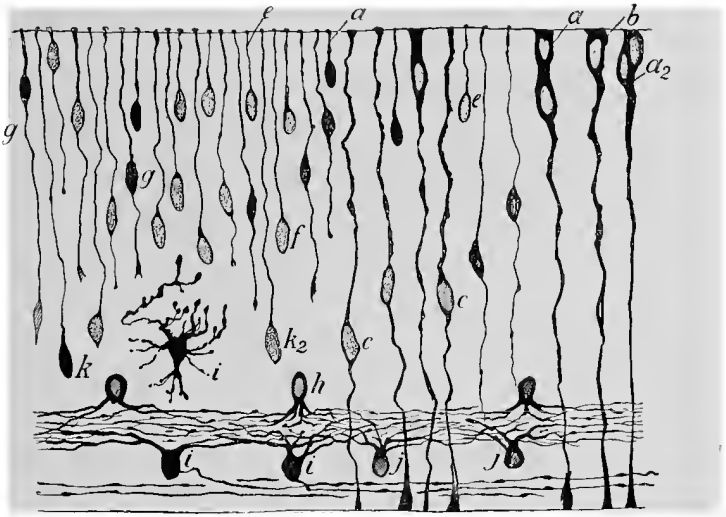
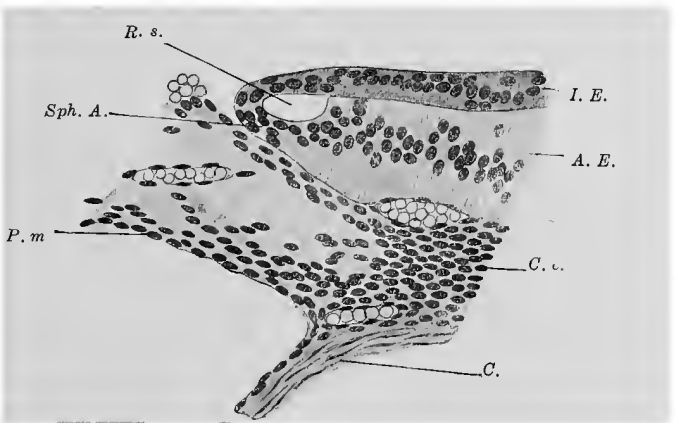


FIG. 189.—Section through the retina of a new-born cat. *a* and a_2, epithelial cells with two nuclei; epithelial cell with peripheral nucleus; *c*, epithelial cell of the ordinary type, the nucleus lying at about the middle of the retina; *d*, embryonic cone cell in the unipolar stage; *e*, rod cell in the corresponding stage; *f*, rod cell with a deeply seated cell body; *g*, cone cell in the transition stage; *h*, amacrine cell; *i*, ganglion cells; *j*, displaced amacrine cells; *k*, embryonic cone cell whose cell body lies near the outer reticular layer; k_2, a similar rod cell. (After Ramon y Cajal (1896), Plate XII, Fig. 1.)



IG. 190.—Margin of the optic cup of a fetus of 10 cm. *I. E.*, inner epithelial layer; *A. E.*, outer epithelial layer of the optic cup; *R. s.*, circular sinus; *Sph. A.*, anlage of the sphincter; *P. m.*, pupillary membrane; *C. c.*, corpus ciliare; *C.*, cornea. (After Szily, 1902[1].)

lects in the nucleated portions of the cells, and each of the fibres then stands in connection with a pigmented, nucleated portion of a cell, which lies on the proximal side of the fibre and with it forms a typical, epithelial, smooth muscle-cell. The development of the musculus sphincter pupillæ has been followed in man by Szily (1902 [1, 2]) and Herzog (1902). Szily finds its earliest anlage in a

fetus of 10 cm. in a very slight aggregation of irregularly placed epithelial nuclei at the margin of the optic cup (Fig. 190). The corresponding cells grow towards the ciliary body as a lamella-like process, and an elongation of them becomes noticeable very early. The pigment, which even at first was but sparingly developed,

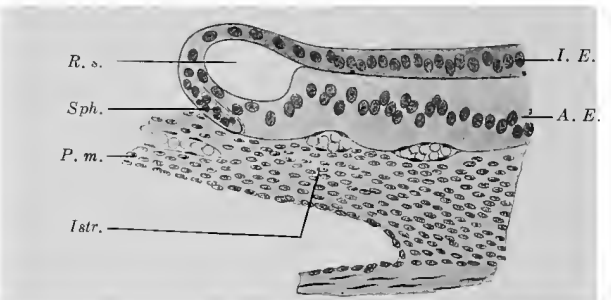


FIG. 191.—Radial section through the anlage of the iris of a 10.2 cm. fetus. *I. E.*, inner, *A. E.*, outer epithelial layer of the optic cup; *R. s.*, circular sinus; *Sph.*, sphincter; *Istr.*, stroma of the iris; *P. m.*, pupillary membrane. (After Szily, 1902.)

later vanishes almost completely. In fetuses of eight and nine months the relations with the dilatator have developed, and even in the new-born child the muscular sphincter is still in intimate connection with the epithelium at the pupillary margin. Figs. 191, 192, and 193 show some stages in the development, after Szily.

The *optic nerve* develops from the stalk of the optic cup, this, however, giving rise only to the neuroglial scaffolding, the nerve

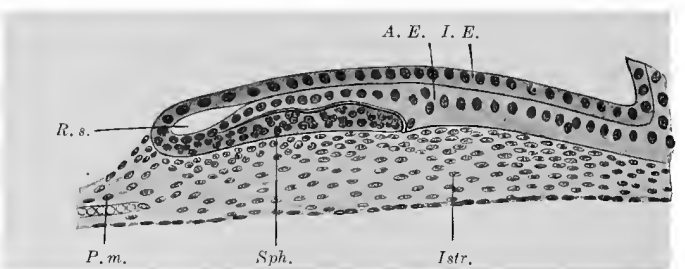


FIG. 192.—Radial section through the anlage of the iris of a fetus of 24 cm. *I. E.*, inner epithelial layer; *A. E.*, outer epithelial layer; *R. s.*, circular sinus; *Sph.* Sphincter; *Istr.*, stroma of the iris; *P. m.*, pupillary membrane. (After Szily, 1902[1].)

fibres arising for the most part from the multipolar cells of the ganglion retinæ and therefore growing centripetally; in addition there is a much smaller number of centrifugal fibres, which have their terminations in the retina. I first (1889) called attention to the fact that in reptilian embryos the first optic-nerve fibres grew from the retina centrally; then His (1890) arrived at the same result for man and Froriep (1891) confirmed it for Selachians. As the result of numerous observations, this condition seems to me to be general. The existence of nerve-fibres in the distal portion of the optic nerve is noted as occurring in an embryo

of 15.5 mm. vertex-breech length in the Normentafel of Keibel and Elze (Plate 61); in an embryo of 17 mm. greatest length they have reached the recessus opticus, although in another of 20 mm. greatest length they are still remote from that point (Plate 65). For a detailed account the Normentafel may be consulted, and it

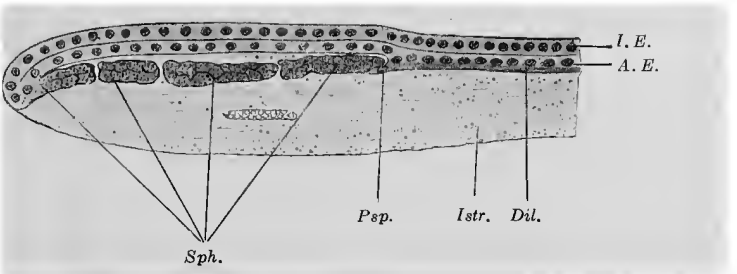


FIG. 193.—Radial section through the sphincter region of the anlage of the iris of a new-born fetus. *I. E.*, inner epithelial layer; *A. E.*, outer epithelial layer; *Sph.*, sphincter; *Dil.*, dilator; *Psp.*, pigment spur; *Istr.*, stroma of the iris.

is also shown there how the lumen of the optic stalk gradually becomes obliterated. Figs. 194 and 195 show sections through the optic nerve of a mouse embryo of 12 days, the section represented in Fig. 194 being proximal to that shown in Fig. 195. A connec-

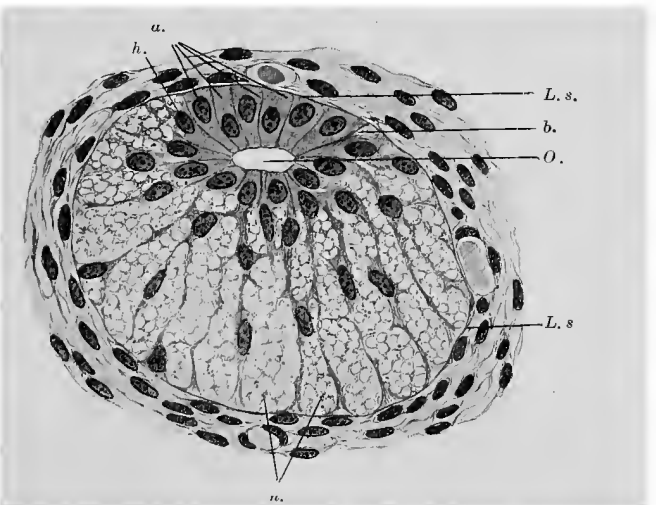


FIG. 194.—Section through the optic nerve of a mouse embryo of 12 days. (After Krückmann, 1906.)

tive-tissue scaffolding is later added to the neuroglial one (Jacobi, 1905, Krückmann, 1906).

The chorioid, together with the corpus ciliare, the musculus ciliaris, the iris, and the sclera, develop from the dense mesodermal tissue that surrounds the optic cup. Somewhat less simple is the development of the cornea. Its mesodermal foundation must first penetrate between the distal surface of the lens and the ectoderm, and in this tissue the anterior chamber of the eye, which separates

the corneal anlage from the distal layer of the capsula vasculosa lentis, is formed. Mention has already been made (p. 233) of the special view as to the development of the cornea and connective tissue in general advocated by Szily (1904, 1908). The vessels of the chorioid and of the choriocapillaris develop without any com-

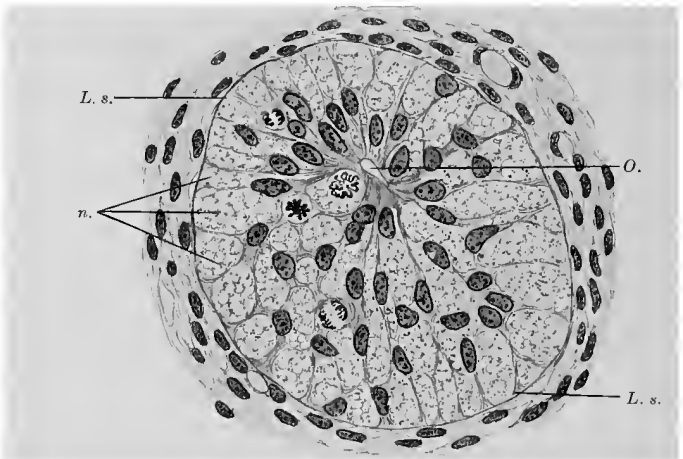


FIG. 195.—Section through the optic nerve of a mouse embryo of 12 days; the section is distal to that shown in Fig. 194. The lettering in both figures has the following meaning: *a.*, epithelial cells, the so-called primitive glia; *b.*, the beginning of the vacuolization and extension phenomena in the protoplasm of the glia cells as a result of the penetration of neurofibrillæ; *h.*, cells of the primary glia in which the neurofibrils (*n.*) first appear near the limitans superficialis (*L. s.*); *L. s.*, limitans superficialis of the optic nerve; *n.*, neurofibrillæ; *O.*, lumen of the optic stalk. (After Krückmann, Plate IX, Fig. 8.)

plications from the abundant vascular supply which, even at an early stage, surrounds the optic cup.

The musculus ciliaris undoubtedly develops from the mesenchyme tissue which is arranged in a lamellate manner around the

FIG. 196.—Section through the anterior part of the bulbus oculi of an embryo of 23 mm. vertex-breech length (embryo T_1, from the collection of the first anatomical Institute in Vienna; Normentafel of Keibel and Elze, Plate 79). *v. K.*, anterior chamber. ×80. (From a drawing kindly furnished by Professor Tandler).

optic cup (Herzog, 1902). In the region of the sclera this mesenchyme secretes collagen substance and separates into the fibrillar sclera tissue and the stroma of the chorioid which is destitute of collagen, with the exception of what is contained in the walls of the blood-vessels. The conversion of the lamellated mesenchyme tissue into smooth muscle tissue is associated with the preservation

of the form of the cell body as well as of the nucleus and with the persistence of the protoplasmatic characters of the cell body, whereby the nucleus and cell body undergo a variable increase in size. At the same time the cells assume a closer arrangement and become more densely aggregated in the line of the pull of the later muscle. The first formation of the ciliary muscle is found in fetuses of 12 cm. and its development is completed in the seventh or eighth month.

In the sixth month the lamellate mesenchyme tissue of the uvea becomes looser by the development in it of numerous blood-vessels; as a result the layered mesenchyme tissue within the layer occupied by the large vessels assumes what Herzog (1902) has termed a "reticular formation," its cells becoming stellate pigment-cells. External and internal to the vessels, those of the choriocapillaris excepted, the tissue retains its lamellate arrangement and differentiates into cells which Herzog regards as endothelial, into flat cells which form sheets, and into a peculiar kind of cells of doubtful character but which Herzog regards as rudimentary muscle-cells.

The description which follows, of the development of the anterior chamber and of the structures in the angle of the chamber, is based essentially on the observations of Seefelder and Wolfrum (1906), but the work of Gabriélidès (1895 [1, 2]), Jeannulatos (1896[1, 2]), and Fritz (1906) may also be mentioned. In the Normentafel of Keibel and Elze, on Plate 79, the existence of an anterior and posterior chamber is shown in an embryo of 23 mm. vertex-breech length (Tandler), and Plate 84 shows them in an embryo of 26 mm. greatest length. Fig. 196 represents a section through the anterior part of the bulbus oculi of the embryo figured in Plate 79 of the Normentafel. I am indebted to the kindness of Professor Tandler for the drawing. The anterior chamber (*v. K.*) is plainly recognizable in the figure; when, therefore, Seefelder and Wolfrum recognize Descemet's endothelium in a fetus of 53 mm. and Descemet's membrane in one of 70 mm., but fail to perceive any indication of the chamber, it must be supposed that the latter must again become for a time indistinct and that these authors have not really observed its first formation. At the end of the fourth month Descemet's membrane is formed throughout its entire width and the sinus of Schlemm is indicated. At the end of the fifth month the ciliary processes [21] are recognizable and also the sclerocorneal network that fills the outer portion of the chamber

[21] Szily (1902 [1], p. 168) notes that the formation of the ciliary processes is not limited exclusively to the region of the ciliary body in the embryo, but also takes place in the region of the primitive anlage of the iris, relying for proof of this in a section through the iris of a 19 cm. fetus, which he reproduces in his fig. 3.

where it abuts in the sclera, but the ligamentum pectinatum iridis, situated more internally, is not yet visible. According to Seefelder and Wolfrum, the first indication of the anterior chamber is to be seen at this time as a circular cleft in the region of the pupillary border of the iris. At the beginning of the sixth month the ligamentum pectinatum is also formed. In the middle of the same month the portion of the anterior chamber in front of the distal pole of the lens can be detected, but it is as yet narrow. At the beginning of the seventh month the scleral swelling becomes evident and the sinus of Schlemm becomes wider. In the eighth month the chamber becomes noticeably deeper and at places the formation of the ligamentum pectinatum pushes its way, wedge-like, between the longitudinal and circular bundles of the ciliary muscle. In the ninth month the membrana pupillaris, together with the capsula vasculosa lentis, has disappeared and the ligamentum pectinatum has become smaller. In the new-born child remains of the ligamentum pectinatum are still present and the angle of the chamber is, as a rule, acute. As regards the *cornea* I would note that in embryonic and fetal life it is not vascularized, as was formerly sometimes supposed (Hirsch, 1906).

The eyelids make their appearance in embryos of about 20 mm. greatest length (compare Normentafel, Plates 67, 68, 70, and 71). In the description of their development I follow Ask (1907, 1908) for the most part, but would make mention also of the observations of Contino (1908).

The lid margins are already completely fused in a fetus of 33 mm., the epithelial fusion extending from the sides towards the middle of the palpebral fissure. In later stages it involves not only the actual margins of the lids but also the neighboring portions of the epidermis and extends both nasally and temporally far beyond the corresponding palpebral angles (Schweigger-Seidel, 1866). The separation of the lids is accompanied by a process of cornification (compare also Seiler [1890] for the dog and Nussbaum [1900] for the mouse), which first affects the intermediate cells most distant from the basement membrane. It extends not only from the outside (front), but also from the cornified wall cells of the hair canals of the eyelashes, from those of the hairs developing within the zone of fusion and from the corresponding cavities at the mouths of the sebaceous glands of the lids; finally it also begins independently at the innermost part of the zone of fusion, where the formation of a deep groove lined with epithelium of the epidermis type precedes the complete separation of the lids.

The development of the cilia resembles that of the other body hairs; the ciliary sudoriparous glands (Moll's glands) arise as outpouchings of the basal cells on the anterior sides of the anlage of the cilia, immediately in front of the anlagen of the ciliary

sebaceous glands. The tarsal glands arise from the epithelium of the innermost (most posterior) portions of the fused margins of the lids, as epithelial buds (Königstein, 1884). The glands of the upper lid exceed those of the lower in length only after the middle of embryonic life. The first anlage of the tarsus appears some what early as an aggregation of mesoderm cells in the posterior portions of the lids, but it obtains its definitive character only after the further development of the tarsal glands.

The caruncula lacrimalis takes its origin from the lower lid, whose most nasally situated tarsal glands and ciliary anlagen are separated from those of the rest of the lid by the opening of the lower lachrymal canal, which at first is situated relatively some distance laterally. This portion of the lid becomes pushed nasally and deeply to form the carunculi, and the connecting folds of the lower fornix are the result of the covering in of the caruncle. Only exceptionally do anlagen of ciliary sudoriparous glands develop in the caruncula. The nictitating membrane appears soon

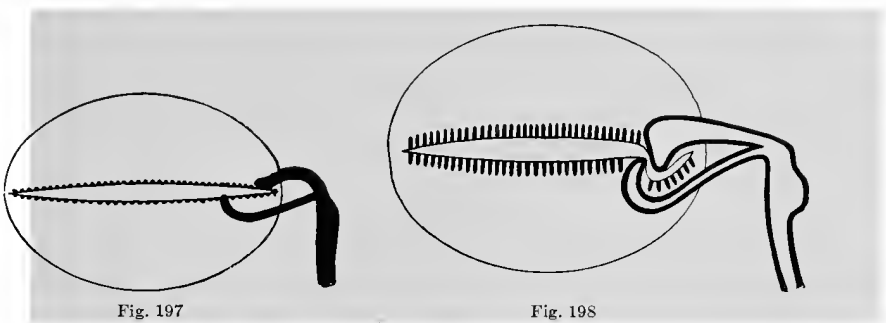


Fig. 197 Fig. 198

FIGS. 197 and 198.—Explanation in the text. In both these figures the lids which are actually fused are shown separated. (After Ask, 1907.)

after the lids and is quite independent of the caruncula, which forms only much later. It is relatively larger during certain stages of fetal life than it is later, and it seems regularly to develop a rudimentary gland. Fig. 197 shows the relation of the openings of the lachrymal canals on the upper and lower lid of a fetus of 40 mm.; the position of the future tarsal glands, which are lacking at this stage, is represented diagrammatically. Fig. 198 shows the openings of the lachrymal canals and the grouping of the tarsal glands in a fetus of 19 cm.; the anlage of the caruncle is separating from the lower lid. Fig. 199 shows a model of the eyelids of the right eye in a fetus of 25 cm., seen from the inside; the anlage of the caruncula is distinctly separated from the lower lid.

Keibel and Elze found the earliest anlagen of the *lachrymal glands* in embryos of from 22 to 26 mm. (Normentafel, Plates 80, 82, 83, 84), as knob-like ingrowths from the conjunctival epithelium. Their further development has recently been thoroughly studied

by Speciale-Cirincione (1908[1,2])[22]. He finds the gland at a somewhat later stage than Keibel and Elze, in a fetus of 32 mm., about the 70th day of development. Five or six ectodermal ingrowths of

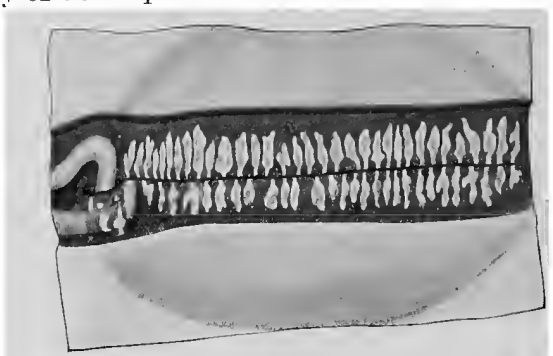


Fig. 199.—Explanation in the text. (After Ask, 1906.)

the conjunctival epithelium form very quickly one after the other in less than a day. Their position is shown in Fig. 200. They are situated in the upper part of the outer conjunctival fornix at the point where the conjunctiva of the lid passes over into the fornix. The anlagen are at first knob-like, but become quickly (in the course of a few hours) transformed into club-shaped struc-

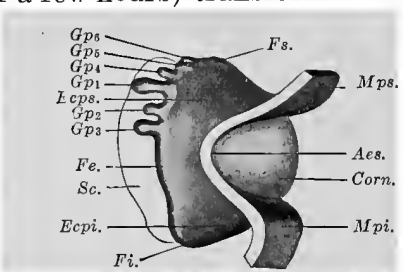


Fig. 200.—Reconstruction of the conjunctival sac and the lachrymal gland of a fetus of 32 mm. (sitting height probably) seen from the outer surface. *Aes.*, external angle; *Corn.*, cornea; *Ecpi.*, ectoderm of the conjunctiva of the lower lid; *Ecps.*, ectoderm of the conjunctiva of the upper lid; *Fs.*, external fornix; *Fi.*, internal fornix; Gp_{1-6}, epidermis (ectoderm) buds arising from the upper external angle of the fornix and representing an early stage in the development of the lachrymal gland; Gp_1 is club-shaped, Gp_{2-4} are small knobs, Gp_{5-6}, are slight outgrowths; *Mpi.*, margin of lower lid; *Mps.*, margin of upper lid; *Sc.*, sclera. ×25 (After Speciale-Cirincione, 1908[2].)

tures; these grow exclusively in length and in a few days are converted into epithelial cords destitute of a lumen. The first branchings of the five or six first formed primordial cords are observed in fetuses of 30 mm.; in those of from 40 mm. to 60 mm. additional anlagen appear, which begin to branch in fetuses of 54 mm. In fetuses of 38 mm. the division of the lachrymal gland into an orbital and a palpebral portion by a laterally directed expansion of the tendon of the levator and by Tenon's capsule has begun, and

[22] While these pages were being printed there appeared the careful paper of Ask (1910), in which, in addition to the development of the lachrymal gland proper, that of the conjunctival accessory glands (glands of Krause and Wolfring) is also described. The comparative anatomical relations are also considered.

it becomes completed in fetuses of 60 mm. The orbital part is formed exclusively by the portions of the first five or six primordial cords which lie on the far side of the interglandular septum; the palpebral portion, by branches given off before the cords perforate the interglandular septum and by the buds and branches of the later-formed primordial cords. Fig. 201 shows these relations. In the cords, which are at first solid and are formed of large, polyhedric cells with round nuclei and homogeneous protoplasm, a lumen is formed in fetuses of 50 mm. by the breaking down of the central elements, and after the appearance of the lumen one can plainly distinguish, according to Speciale-Cirincione, two layers, the layer of the secreting cells and that of the basal cells.

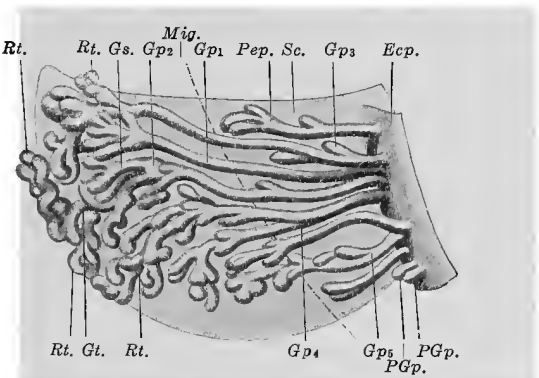


FIG. 201.—Reconstruction of the lachrymal gland of a fetus of 50 mm. (probably sitting height). Six anlagen (primordial cords) traverse the interglandular memhrane (*Mig.*) and, together with their hranches, form the orbital portion of the lachrymal gland. Other anlagen do not reach the interglandular memhrane (*Mig.*); they form the palpebral portion of the gland, together with branches given off from the cords intended for the orbital portion, hefore they perforate the interglandular membrane. Gp_1, a primordial cord with hranches only at its orbital end; Gp_{2-3}, cylindrical primordial cords richly branched at their orbital ends and giving off huds from their portions which traverse the lid; Gp_4, primordial cord which divides into two secondary cords in the palpebral portion of the gland, the hranches of these lying in the orhital portion; *Gs.*, secondary cords; *Gt.*, tertiary cords; *Ecp.*, epithelium of the palpebral conjunctiva; *Mig.*, interglandular membrane ("lateral expansions of the levator"); *Pep.*, branched primordial cords helonging to the palpebral portion of the gland; *PGp.*, primordial huds helonging to the palpebral portion of the gland; *Rt.*, terminal hranches; *Sc.*, sclera. ×25. (After Speciale-Cirincione, 1908[2].)

The accessory conjunctival lachrymal glands are formed, according to Falchi (1905), in a fetus of 31 cm. In the new-born child the lachrymal gland has not yet reached the height of its development, having only one-quarter to one-third the size of the adult gland (Kirschstein, 1894) and differing also in the appearance of its cells (Axenfeld, 1899 [23]); that it actually is without function at this time has been correctly denied (De Wecker, 1899, Baratz, 1902). Goez (1908) has quite recently reinvestigated the lachrymal gland at different ages and in general confirms the results of Kirschstein (1894). From the first year onward there is a gradual change in the histological structure of the gland. "The

[23] Compare also Schirmer in Gräfe-Sämisch. Handbuch der gesamten Augenheilkunde, 2d edition.

height of the glandular epithelium becomes gradually less and the lumen becomes correspondingly wider, and at a more advanced age the gland assumes quite an altered appearance, owing to a strong increase of the interstitial connective tissue. With advancing age a distinct involution of the gland occurs."

The mode of formation of the lachrymal passages, the ductus nasolacrimalis, the saccus lacrimalis, and the lachrymal canals are also quite clearly understood in man (Fleischer, 1906, and Matys, 1906). As Born (1879, 1883) and his pupil Legal (1881, 1883) showed for the Sauropsida and Mammals, so too in man the ductus nasolacrimalis arises as a solid epithelial bud, which grows down freely through the mesoderm to the nasal cavity from the conjunctival portion of the lacrimo-nasal groove. Consequently the lachrymal canals do not represent the original connection of the anlage with the conjunctival epithelium, but this original connection is lost; the canals bud out from the still solid ductus lacrimalis and secondarily acquire their connection with the margins of the lids.

Accounts of the conditions in mammals, in which the processes are essentially the same as in man, have been furnished by Fleischer (1906) for the pig and rabbit and by Matys (1905) for the marmot (Spermophilus citillus) and the pig. In the apes, according to my own observations (1906[1]), the processes take place as in man. Thus, in a Macacus cynomolgus of 13.5 mm. greatest length (Plate 14) the solid ductus nasolacrimalis, whose distal end is still far from the nasal cavity, has lost its connection with the ectoderm at its orbital end and divides there to form the anlagen of the two lachrymal canals (compare also Plates 17, 18, 20, 21, 22). In an embryo of Nasalis larvatus of 25.2 mm. greatest length (Plate 23) the ductus nasolacrimales do not quite reach the epithelium of the nasal cavities, the lachrymal canals have reached the epithelium but have not yet fused with it. Slightly less developed is a Semnopithecus maurus of 26 mm. greatest length (Plate 24).

Early anlagen of the ductus nasolacrimales in embryos between 9 mm. and 11 mm. greatest length are shown in the Normentafel of Keibel and Elze in Plates 47, 48, and 49. In the embryo shown in Plate 84 (26 mm. greatest length) neither have the ductus nasolacrimales quite reached the epithelium of the nasal cavities nor the lachrymal canals that of the margins of the lids. According to Cosmettatos (1898), the lachrymal passages acquire a lumen in the third month of fetal life. It appears first in the upper portion and then proceeds from above downward, and is completed shortly before birth. According to Monesi (1904), the opening at the lower end of the duct is formed by the medial wall becoming broken through, and the groove which frequently occurs below the opening is thus explained as the lateral wall of the portion so opened.

No satisfactory account as yet exists as to the development in man of the muscles that move the bulbus oculi.

This is true with regard to the mammals, in general, notwithstanding the work of Corning (1899) on the rabbit and of Reuter (1897) on the pig. The question of the development of the eye-muscles is associated with the difficult problem of the metamerism of the head. In general, following van Wijhe (1882[1]), the oculomotor musculature—*i.e.*, the musculus rectus superior, inferior, and internus and the musculus obliquus inferior—is supposed to be derived from the first head metamere, the musculus obliquus superior, supplied by the trochlearis, from the second, and the musculus rectus externus, supplied by the abducens, from the third. In reptilia and birds the oculomotor musculature arises from the wall of the head cavity, which, however, does not always reach a complete development. In Lacerta the head cavities are formed in embryos with one or two primitive somites from the entoderm at the anterior end of the chorda. This anlage forms a cell mass extending laterally on either side and possessing only a cleft-like cavity or indeed none whatever; for a considerable time it remains connected with the tissue from which it is formed by a cord of cells (the intermediate cell cord). Similar conditions have also been observed in mammals (the rabbit) by Corning (1899) and in birds (the duck) by Rex (1897). Later a lumen, which soon becomes much enlarged, appears in each of the lateral masses, and while the intermediate cord degenerates, the epithelial walls of the head cavity give rise to the oculomotor musculature. At its dorsal and ventral portions a slight out-pouching appears, from which a proliferation of epithelial cells takes place, and there is thus formed a dorsal and a ventral muscle anlage. These separate completely from the epithelium of the walls of the head cavities and grow toward their final points of origin and insertion, that is to say, toward the anterior end of the chorda and toward the bulbus. The walls of the head cavity take no essential part in the formation of the mesenchyme, but those portions that are not used in the formation of the muscles persist in the midst of the ingrowing mesenchyme and are to be recognized at a relatively late period as cords or bars of epithelial cells. The branches of the oculomotor nerve lie at first on the surfaces of the muscle anlagen that are turned toward the bulbus. The musculus rectus externus arises in Lacerta from a mass of cells, whose epithelial arrangement indicates their derivation from a head cavity. The anlage lies at first on the lateral and posterior wall of the oculomotor cavity, and the musculus obliquus superior arises from the dorsal portion of the anlage which grows out above the bulbus. It separates from the parent tissue and secondarily grows to its later points of origin and insertion.

Reuter's investigations began, unfortunately, with a somewhat advanced stage, with a pig embryo of 22 days. Such an embryo already shows the anlage of the eye musculature with the corresponding nerves, while nothing is yet to be seen of the mandibular musculature. The anlage has the form of a somewhat thick, stalked demilune, the abducens nerve passing to the stalk from behind; the oculomotor passes to the anlage from above, and the trochlearis somewhat later becomes connected with the uppermost point of the demilune. The two limbs of the demilune surround the optic stalk. In the further course of development the anlage of the musculature wanders forward toward the optic nerve and loses its posterior limb (stalk), which is pushed forward by the anlage of the neighboring vena jugularis. The two remaining limbs unite to form a ring, which gradually assumes a cup-like form and surrounds the anlage of the eye. Sheet-like anlagen, corresponding to the later muscles, now grow toward the bulbus, the recti and obliqui forming first. The separation of the individual muscles proceeds from the bulbus toward the apex of the orbit, the connective tissue which occurs between the various forward extensions penetrating the muscle mass and bringing about its division. Before this is completed, however, the musculus retractor bulbi separates from the anlage of the musculi recti and, as the last of the eye muscles, the levator palpebræ superioris arises from the medial border of the rectus superior. Corning (1899, p. 65) has criticised Reuter's results, on the ground that he derives

all the muscles from a common anlage. I cannot here discuss the very complicated problems connected with these muscles which yet await solution, but would mention for reference, in addition to the works already cited, those of van Wijhe (1882[2]), Miss Platt (1891, 1897), C. K. Hoffmann (1896, 1897), Neal (1897, 1898), Sewertzoff (1895, 1898), Oppel (1890), and Corning (1900). Attention may also be called to the work of Nussbaum (1896, 1899, 1900), who, on the basis of the law of nerve and muscle growth discovered by himself, concludes that the musculus obliquus superior of the mammals is not quite equivalent to that of the lower vertebrates, but contains an additional element. If the portion of a nerve between its central origin and the point of entrance into the muscle be termed its extramuscular portion, and its ramifications within the muscle its intramuscular portion, then the intramuscular portion will show the direction of growth of the striated muscle-fibres. We can in this manner recognize the portion of the muscle that has been formed after the union of the nerve with the muscle. The points of entrance of the nerves into the four recti muscles lie in the mammals and in man near the optic foramen on the inner surfaces of the muscles; in the case of the obliquus superior the nerve enters the outer surface near the optic foramen, and the nerve reaches the obliquus inferior only about the middle of the muscle belly. It may therefore be supposed that the recti and the superior oblique muscle gradually approach the corneal margin during embryonic growth. Nussbaum has been able to show this in various mammals. The obliquus superior, like the musculi recti, grows from the back part of the orbit toward the bulb, and its terminal tendon gradually passes from the anterior into the posterior portion of the bulbus oculi.

Zimmermann (1898) has described in man structures which are perhaps to be regarded as the remains of a head cavity. In an embryo of 3.5 mm. nape length there were several (on the right three, on the left seven) clearly defined, small, completely closed vesicles, whose walls were formed of epithelium-like cells, situated near the epithelium of the mouth cavity, lateral to the internal carotid artery and Rathke's pouch, and somewhat behind the eye vesicle, in a region where the mesoderm was slightly richer in cells than elsewhere. Henckel's observations (1898) show that the musculus levator palpebræ superioris is still lacking in embryos of 20 mm.; it separates from the musculus rectus superior, probably from its medial border; in fetuses of 60 mm. it lies medial to that muscle and in those of 75 mm. it overlaps its medial edge. At the end of the fourth month it has acquired its definitive position above the superior rectus.

In conclusion some statements may be made concerning the growth of the eye and the eye of the new-born child, this latter having a quite different structure from that of the adult (Merkel and Orr, 1892). The portion from the entrance of the optic nerve to the fovea centralis is completely formed at this time, but the more anterior portions of the bulbus lag decidedly behind in their growth. The cornea, it is true, is relatively large (compare also Greef, 1892), but, on the other hand, the ciliary body is small and must grow much more rapidly than the cornea in order to attain its definitive size. The lens enlarges only in its equatorial diameter, its axis actually becoming smaller. The region of most dis-

tinct vision remains stationary, but the medial portion of the bulb enlarges in general more than the lateral, and the cornea and lens are accordingly pushed laterally until their central points, which were at first situated medially, come to lie in the optic axis that passes through the fovea centralis. The physiological excavation of the papilla is present in the new-born child (compare also Hippel, 1898). Fig. 202 gives a representation of the points mentioned; it shows a diagrammatic section of the eye of a new-born child enlarged five diameters. The contours of the adult eye,

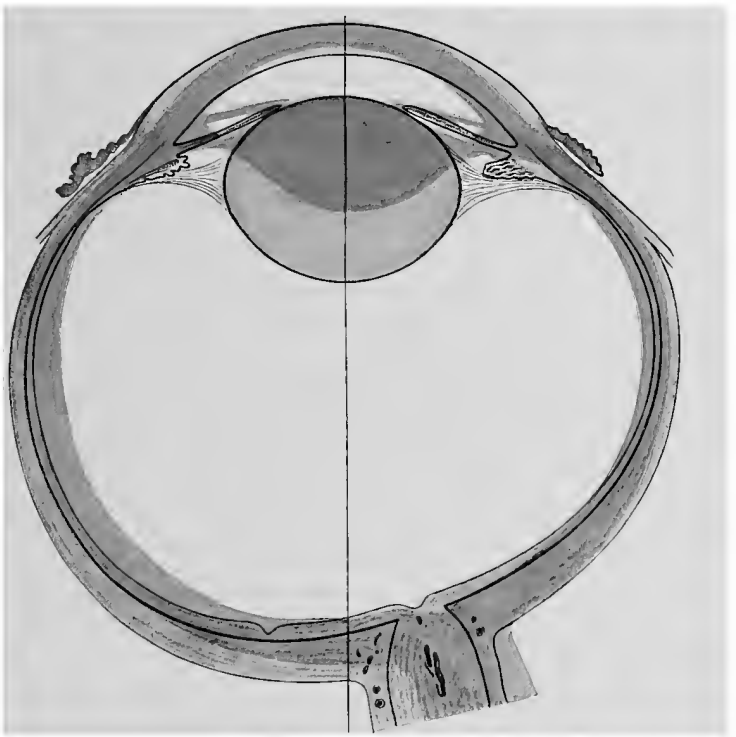


FIG. 202.—Schematic section of the eye of a new-born child, enlarged five times. The contours of an adult eye, when lens is accommodated for near vision, have been reduced to the size of that of the new-born hild and are represented in red. (After Merkel and Orr. 1892.)

whose lens is accommodated for near vision, have been reduced to the size of the eye of the new-born and are represented in red. To the right a ciliary process is shown, to the left a depression between two ciliary processes. According to Hippel, the wall-like thickened margin of the fovea centralis is not yet formed in the new-born child and the shining reflection at the periphery of the fovea is not seen with the ophthalmoscope, but in children of four weeks a thickening can be perceived. The fibres of the optic nerve are never myelinated at birth, but become so at about the tenth week after birth.[24] Weiss (1894, 1895, 1897) found that the eye

[24] Held (1896) showed that in animals born with the eyes closed the stimulus of light hastened the development of the myelination.

after birth increased in weight 3.25 fold, while the entire weight of the body increased 21 times. The increase in the volume of the eye is about 3.29 times. The correspondence of the increase of the eye with that of the brain, which is about 3.76 times, is striking, and the growth of the eye and that of the brain are completed earlier than that of the rest of the body. Of the diameters of the eye the vertical (with reference to the position of the eye in the body) is that which increases most rapidly, while the sagittal one, which is the greatest at birth, shows the least increase; as a result, the shape of the eye becomes almost spherical in children of nine years, and later the vertical diameter exceeds the sagittal. As may be seen from the relations of the eye muscles, the sclera grows almost equally in both its distal and proximal portions. For further data concerning the growth of the eye, in addition to the authors already mentioned, the following may be consulted: Dieckmann (1896), Duclos (1895), Halben (1900), O. Lange (1901), Baratz (1902), and Hippel (1898[2]).

LITERATURE.

(On the development of the eye.)

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THE DEVELOPMENT OF THE EAR.

The ear of mammals and of man consists of the actual sense-organ, the inner ear (labyrinth and cochlea), and the sound-conducting apparatus, the middle and outer ear. In addition to its function in hearing, which belongs only to the cochlea, the inner ear also serves for the perception of the condition of equilibrium. The epithelial lining of the inner ear comes from the ectoderm, that of the middle ear from the entoderm, and that of the outer ear again from the ectoderm.

The inner ear of the mammals and of man in its early stages of development resembles exactly the corresponding organs of invertebrates, yet it is not correct to derive it directly from these. The sound-conducting apparatus has been developed within the vertebrate stem, after an aquatic mode of life had been exchanged for one that was amphibious or terrestrial.

The Inner Ear.—The anlage of the auditory organ has been frequently regarded as serially homologous with the anlage of the olfactory organ, the lens, and the epibranchial sense-organs or placodes (compare p. 129 and 182); but this question will not be considered here. The anlage of the auditory organ, like that of the olfactory organ and lens, first appears as a plate of thickened ectoderm, which may be termed the auditory plate, and it occurs in this condition in an embryo of about nine pairs of mesodermic somites (Normentafel of Keibel and Elze, Plate 4). In an embryo

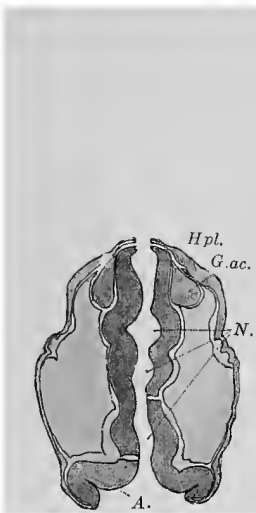

FIG. 203.—*A.*, optic anlage; *G. ac.*, ganglion acusticum; *Hpl.*, auditory plate; *N.*, neuromeres. ×25. (After Keibel and Elze, Normentafel, Fig. 6a.)

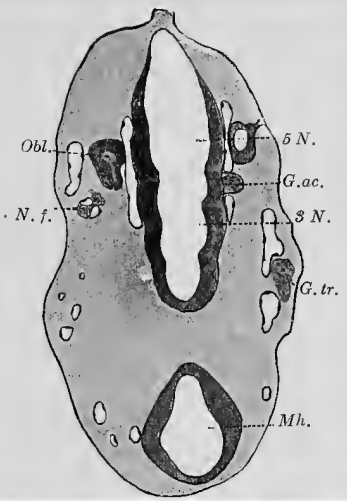

FIG. 204.—*G. ac.*, ganglion acusticum; *G. tr.*, ganglion trigemini; *Mh.*, mid-brain; *3N.* and *5N.*, third and fifth neuromeres; *N. f.*, nervus facialis; *Obl.*, auditory vesicle. ×30. (From Keibel and Elze, Normentafel, Fig. 9c.)

of thirteen or fourteen pairs of somites (Normentafel, Plate 6) these thickened areas of ectoderm become slightly depressed, as is shown in Fig. 203, and the auditory plate begins its transformation into the auditory pit. As may be seen from Fig. V^{r} of the Normentafel, these depressed areas lie dorsal to the second branchial grooves. The auditory pits now deepen rather rapidly, so that in an embryo of 2.5 mm. which had twenty-three pairs of somites (Normentafel, Plate 7) they are almost closed. When the closure is complete the auditory vesicles still remain for a time in connection with the ectoderm by a short, solid cord of cells, and even when this has disappeared one may still recognize its point of attachment in the ectoderm and in the auditory vesicle, which has now become almost spherical (Normentafel, Plates 8–11 and 13–20). When thus formed the auditory vesicle is in relation medially to the medullary canal in the region of the fifth neuromere and laterally to the ectoderm (Fig. 204), from which it becomes separated by mesoderm almost immediately after its closure.

Very early, in some cases even while it is still in connection with the ectoderm (Normentafel, 13), the *recessus labyrinthi,* which later becomes the *ductus* and *sacccus endolymphaticus,* is formed. Fig. 205 a–d shows four successive sections through the right auditory sac, and the anlage of the recessus labyrinthi can already be recognized in Fig. 205a. It arises in man, as in other mammals and in birds, in immediate relation with the point of closure of the auditory vesicle, and is therefore comparable to the ductus endolymphaticus of the Selachians.

Even although this homology is no longer clearly shown in the development of the reptilia, yet I can see no reason for doubting the equivalence of this structure throughout the entire vertebrate series. For a discussion of this question compare Keibel (1899), Krause (1901[1]), Peter (1901), and Alexander (1901).

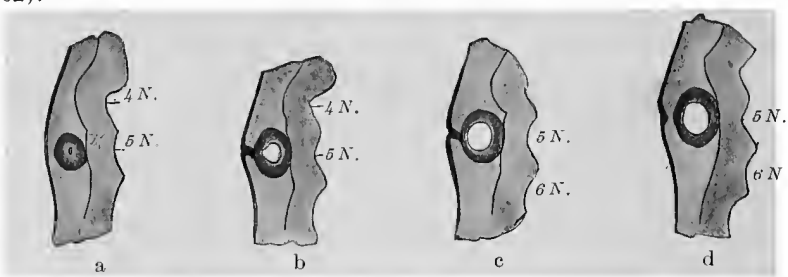

FIG. 205 a–d.—*4 N., 5 N., 6 N.,* fourth, fifth, and sixth neuromeres. × 30. (From Keibel and Elze, Normentafel, Figs. 11 b–e.)

Later the point of origin of the recessus labyrinthi or ductus endolymphaticus becomes transferred from the dorsal to the medial wall of the auditory vesicle by a portion of the lateral wall of the vesicle growing upward between the ductus and the body wall. At a rather early period a portion of the extremity of the ductus becomes enlarged to form the saccus endolymphaticus, yet this structure does not represent the actual extremity of the recessus, for, as Tandler [25] has described and as I also have found, this is drawn out into a thread-like structure that later disappears. The further development of the auditory vesicle in man has been described by W. His, junior (1899), and by Streeter (1906–1907); for its development in mammals the works of Krause (1890), Alexander (1900), and Denis (1902) may be consulted.

Fig. 206 shows the left auditory vesicle of an embryo of 6.9 mm. (age, according to His, about four weeks) seen from the outer surface. From the dorsal, broader portion of the vesicle the semicircular canals are differentiating and from the narrower ventral portion the anlage of the cochlea. The semicircular canals arise as pouches, the anterior and posterior canals from a pouch which forms from the dorsal border of the vesicle, and the external

[25] In the Normentafel of Keibel and Elze, Plates 55 and 65.

canal, somewhat later, from another pouch that is directed laterally. The dorsal pouch becomes divided by a slight notch into an anterior and a posterior portion, and then the borders of the three pouches now formed become thickened, while the two epithelial layers at the centre of each come together and fuse, the epithelial plates thus formed later degenerating and their places being taken by mesoderm. The broadened margins of the pouches, whose lumina are of course in communication with the cavity of the auditory vesicle, are the anlagen of the semicircular canals; of these the anterior is the first to be completed, then the posterior, and the external is the last. From the ventral end of the vesicle the cochlear anlage grows out.

Fig. 207 a and b show the vesicle of an embryo of 11 mm.

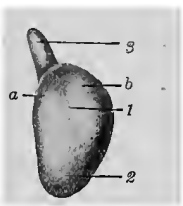

Fig. 206.—Left auditory vesicle of a human embryo of 6.9 mm. nape length (age about 4 weeks). Seen from the outer surface. ×25. *1*, vestibular portion; at *a* and *b* the vertical semicircular canals are indicated as low folds; *2*, cochlear portion; *3*, recessus labyrinthi (aquæductus vestibuli, ductus endolymphaticus). (After His, Jun., Arch. für Anat. und Physiol., Anat. Abth. Suppl., 1889, Plate 1, Fig. 4.)

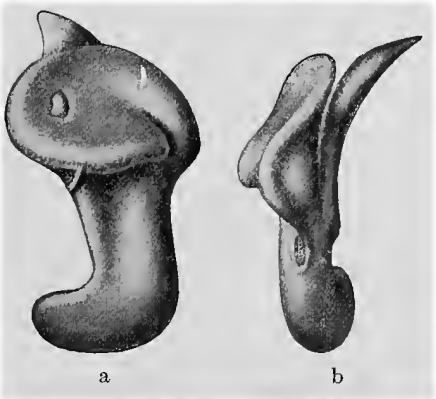

Fig. 207 a and b.—Left anlage of the labyrinth of an 11 mm. human embryo seen from the lateral surface (a) and from behind (b). ×25. (After Streeter, American Journ. of Anat., vol. 6, 1906.)

seen from the lateral surface (Fig. 207a) and from behind (Fig. 207b). In the anterior part of the upper pouch a perforation has already formed in the epithelial plate, and at the notch of the upper pouch the crus commune of the anterior and posterior canals is forming. In Fig. 208 the canals are formed, the anlage of the cochlea has commenced to coil and is quite distinctly separated from the saccular portion of the labyrinth above. The separation of the sacculus and utriculus is also recognizable, although it is not yet very pronounced; it is formed as a fold which grows in from the lateral surface towards the point of origin of the ductus endolymphaticus. Fig. 209 shows a model of the membranous labyrinth of a 30 mm. fetus seen from the median surface. Except for the separation of the sacculus and utriculus, which is still far from complete, the definitive conditions are almost reached. The fold that separates the utriculus and sacculus grows deeply into the origin of the ductus endolymphaticus and divides it in such a manner that the ductus remains in communication with both

structures. Some diagrams will render this process more readily understood. The first of these (Fig. 210a) represents a frontal section through the head of an embryo, the anlage of the labyrinth being cut on either side of the brain in such a way that the ductus endolymphaticus, the anterior part of the upper pouch, the lateral pouch, and the anlage of the cochlea have come into the plane of the section; that the cochlea should do so is actually not possible, since at a very early stage it no longer lies in a single plane.

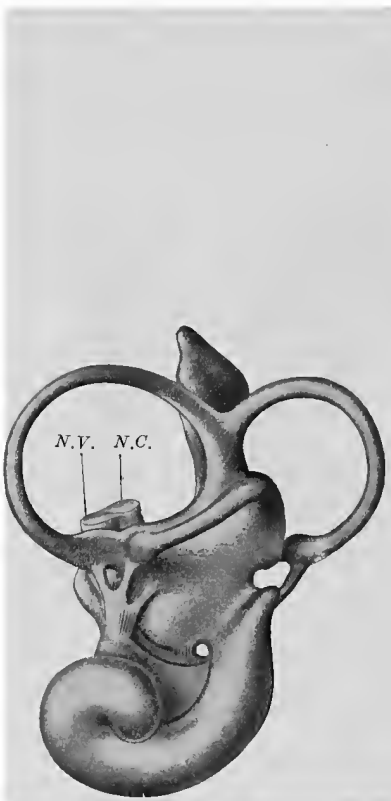

Fig. 208.—Anlage of the left labyrinth of a 20 mm. human embryo seen from the lateral surface. ×25. *N.V.*, nervus vestibularis; *N.C.*, nervus cochlearis. (From Streeter, The American Journ. of Anat., vol. 6, 1906.)

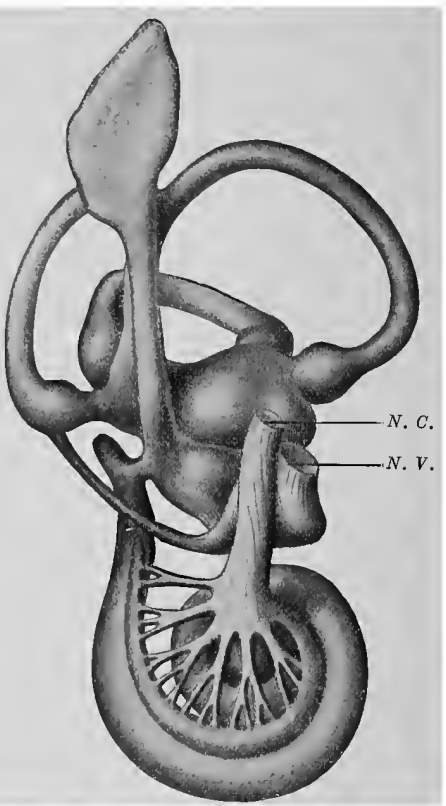

Fig. 209.—Anlage of the left labyrinth of a 30 mm. human embryo seen from the medial surface. ×25. *N. C.*, nervus cochlearis; *N.V.*, nervus vestibularis. (From Streeter, The American Journal of Anat., vol. 6, 1906.)

In Fig. 210b the marginal portions of the anterior and lateral pouches are broader, and the central portions have come closer together; the cochlea has begun to separate and the fold that will separate the sacculus and utriculus has commenced to form. In Fig. 210c the marginal portions of the anterior and external pouches persist as semicircular canals, the epithelial plates which originally united them with the utriculus being indicated by broken lines, the canalis reuniens is fully formed and the separation of sacculus and utriculus is complete, so that the ductus endo-

lymphaticus communicates with each of these cavities only by a narrow canal.

The histological differentiation of the epithelium in the anlagen of the special sensory areas of the ear follows immediately upon the ingrowth of nerves into them, so that it would seem to be provoked by this ingrowth (R. Krause, 1901, in Hertwig's Handbuch, vol. 2, part 2, p. 108). The epithelium of the auditory vesicle is at first one-layered, and even later the arrangement of its nuclei in several strata is not necessarily evidence that it has become

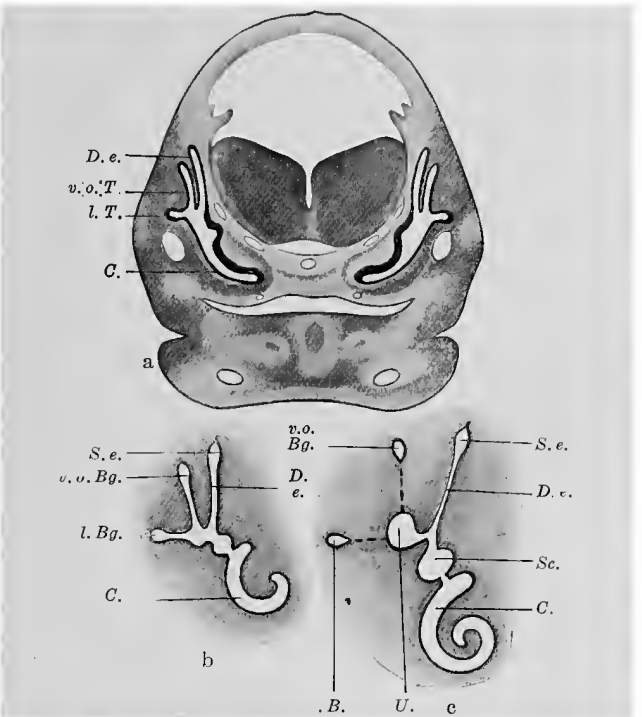

FIG. 210 a–c.—Diagrams of the development of the labyrinth: a represents a frontal section through the head of an embryo, cutting both labyrinths; b and c represent the further transformations of one labyrinth. For further description see text. *l. Bg.*, *v. o. Bg.*, anlagen of the lateral and anterior semicircular canals; *C*, anlage of the cochlea; *D. e.*, ductus endolymphaticus (recessus labyrinthi, recessus vestibuli); *Sc.*, sacculus; *S. e.*, saccus endolymphaticus; *l. T.*, *v. o. T.*, lateral and anterior upper pouches (predecessors of the semicircular canals).

many-layered. The differentiation of the epithelium is most pronounced in the cochlea, proceeding in this organ from the basal coil to the apex. The originally cylindrical cavity of the cochlea becomes triangular, and on its basal wall two epithelial swellings appear, a larger one towards the axis of the organ and a smaller one situated more laterally. The cells of the larger swelling secrete the membrana tectoria,[26] Siebenmann observing that in

[26] According to Rickenbacher (1901), the marginal zone is secondarily secreted from the smaller epithelial swelling in the guinea-pig. Discordant results have also been obtained in the guinea-pig by Czinner and Hammerschlag (1898).

an embryo of 4.5 cm. its formation begins in the uppermost coil. Then the greater part of its cells undergo a diminution in height, so that they separate from the membrana tectoria and the sulcus spiralis internus is formed; from this swelling, however, as Van der Stricht (1908) has shown in a bat (Vesperugo noctula), the inner auditory and inner supporting cells are formed (Fig. 211).

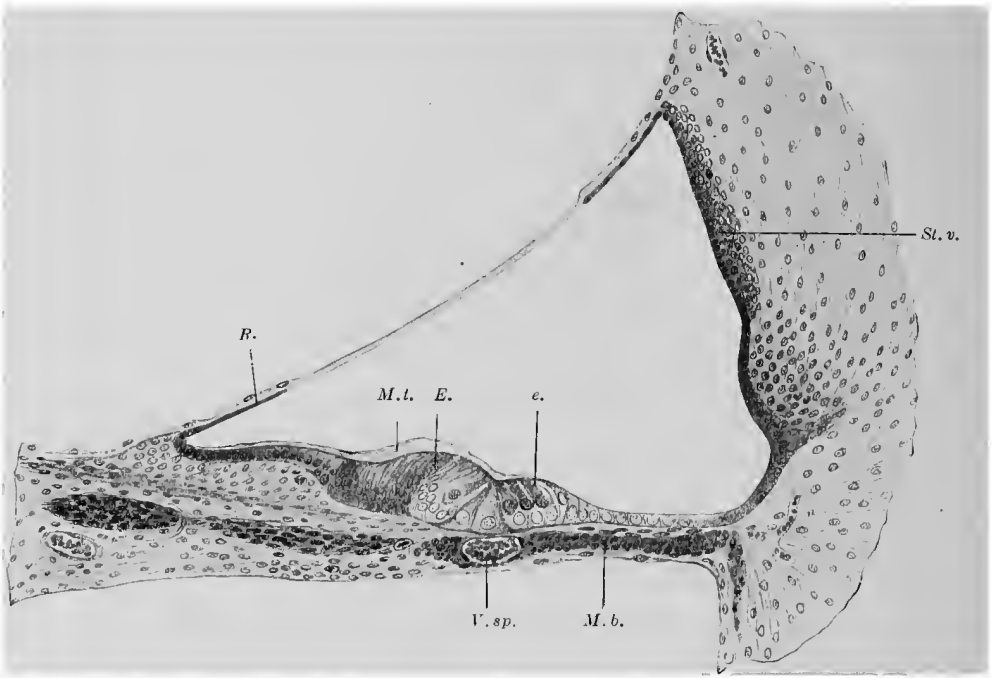

FIG. 211.—Radial section through the cochlear canal of a new-born child, from a preparation kindly supplied by Professor R. Krause, of Berlin. ×150. Reissner's membrane was defective and is represented only diagrammatically where it was lacking. *E.*, larger, *e.*, smaller epithelial swelling; *M. b.*, membrana basilaris; *M. t.*, membrana tectoria; *R.*, Reissner's membrane; *St. v.*, stria vascularis; *V. sp.*, vas spirale.

While referring the reader to the original paper for the literature of the question and for details, it may nevertheless be noted that in Vesperugo noctula the membrana reticularis of the cristæ and maculæ acusticæ is not actually a cuticular formation, but rather a system of protective ridges. As to the participation of the larger and smaller epithelial swellings in the formation of the elements of the organ of Corti, there are formed

I. From the larger swelling:
   1. A row of inner auditory cells.
   2. A row of inner supporting cells.

II. From the smaller swelling:
   1. A row of inner rod cells.
   2. A row of outer rod cells.
   3. Three rows of outer auditory cells.
   4. Three rows of Deiters's cells.
   5. Hensen's cells.

Later there occurs a pushing of the cells from the periphery toward the axis. The inner rod cells form from the beginning a cell row uninterrupted by any

other cell, while the outer ones, on the contrary, are commingled with the outer sensory cells; this condition explains the numerical difference between the outer and inner rod cells in the adult.

The development of the stria vascularis is as yet uncertain; Retzius supposed that its epithelium became vascularized, while others contend that the elements lying between the blood-vessels are connective-tissue cells and others believe them to be of mixed origin.[27]

The epithelial sense-organ becomes enclosed within a membranous and a bony capsule. The mesenchymatous tissue in its neighborhood condenses and becomes converted first of all into cartilage, which, however, does not extend quite to the epithelium, being separated from it by a layer of connective tissue, which, while thin on the outer surfaces of the semicircular canals and cochlea, is elsewhere well developed. Around the semicircular canals, the utriculus, and sacculus this tissue soon separates into three layers,—a perichondrial layer, a dense membranous layer resting directly upon the epithelium, and an intermediate loose mesenchyme, which is usually described as mucous tissue. In the cochlea special conditions obtain. Its modiolus and lamina are not preformed in cartilage, the dense connective tissue which appears in the regions of these structures at a relatively late period ossifying directly; the tissue, however, which encloses the cochlear canal behaves like that which surrounds the semicircular canals. The transverse section of the cochlear canal from being circular becomes triangular, the anlage of the lamina spiralis being attached to its inner angle. Upon its outer side there lies only a relatively thin sheet of dense connective tissue, while on the other two sides, on the upper one, which becomes the epithelium of Reissner's membrane, and on the lower, from which the organ of Corti is formed, and also on the modiolus and the anlage of the lamina spiralis, the mesenchyme becomes divided into three layers as described above. The spaces occupied by the loose mesenchyme are converted by the disappearance of that tissue—Böttcher (1869) speaks of a fatty degeneration—into the perilymphatic spaces, in the case of the cochlea into the scala vestibuli and the scala tympani. This transformation begins in the vestibular region, where the space first formed is termed the cisterna vestibuli. Some strands of the tissue persist in connection with the semicircular canals, and probably serve to maintain them in their proper position. In the cochlea the formation of the scalæ proceeds from the base towards the tip.

It may be noted that, according to Gaupp (1907, p. 881), the ear capsule of the mammals and of man cannot be regarded as exactly homologous with that of the amphibia and fishes. Gaupp says: "Several peculiarities in the configuration of the labyrinth region in the amniotes, especially in mammals, become intelli-

[27] Compare Merkel (1893), who cites the older literature, Leimgruber (1903), and Shambaugh (1906).

gible in the supposition that the ductus cochlearis during its development penetrates into the lateral part of the base of the chordal portion of the skull and transforms this original solid portion of the skeleton into a part of the 'ear capsule.'" The ear capsule of the mammals is accordingly equivalent to the ear capsule of the amphibia plus an additional part derived from what was originally a portion of the base of the skull.

For accounts of the ossification of the ear capsule one may consult Vrolik (1873) and Siebenmann (1897); for the postembryonic growth of the labyrinth Alexander (1902) and Sato (1903).

The development of the n. acusticus and its ganglia is closely related to that of the labyrinth, and in the description of it given here I shall follow the account given by Streeter (1906–1907), which differs from that of His, junior (1889), in showing a closer relation of the ramus sacculi and of the ramus ampullæ posterioris to the utricular and ampullary branches and a greater independence of the n. cochlearis. The acustico-facialis ganglion is originally a single cell mass lying in front of the anlage of the auditory vesicle, but later it forces its way between that structure and the lateral wall of the anlage of the brain. At a rather early period the geniculate ganglion of the facialis separates from the outer side of the cell mass, nerve-fibres from which have already penetrated the central nervous system. After the separation of this ganglion one can distinguish in the acoustic ganglion a pars superior and a pars inferior, and from each of these (in an embryo of 7 mm.) a nerve passes towards the auditory vesicle (Fig. 212). In an embryo of 9 mm. the ganglion cochleæ becomes distinct at the lower border of the ganglion complex and one sees fibres growing from it towards the brain (Fig. 213 a and b), and a second twig, the ramus sacculi, has arisen from the pars inferior. Figs. 214 a and b and Figs. 215 a and b, after Streeter (1906–1907), show the further separation of the ganglion cochleæ in embryos of 20 and 30 mm. greatest length.

The development of the middle ear in man has been made clear by the thorough investigations of Hammar (1902).[28] Three periods may be recognized in the development: 1, the period of the primary tympanic cavity (formation period, Hammar), beginning in the first month (embryo of 3 mm.) and lasting into the seventh week (embryo of 18.5 mm.); 2, the period of the tubotympanic canal (Hammar's separation period), ending in the beginning of the third month (embryo of 24 mm.); and 3, the transformation period, in which the tubotympanic canal is transformed into the definitive tympanic cavity and the tuba auditiva; this last period is not completed at birth, but is continued into postfetal life. A dorsal prolongation of the first pharyngeal groove forms at an

[28] Of older works on mammals that of Piersol (1888), who studied the rabbit, may be mentioned.

early period, and takes the form of a flat pouch whose tip and outer wall are at first in contact with the ectoderm of the first branchial groove, although in the fifth week they become separated

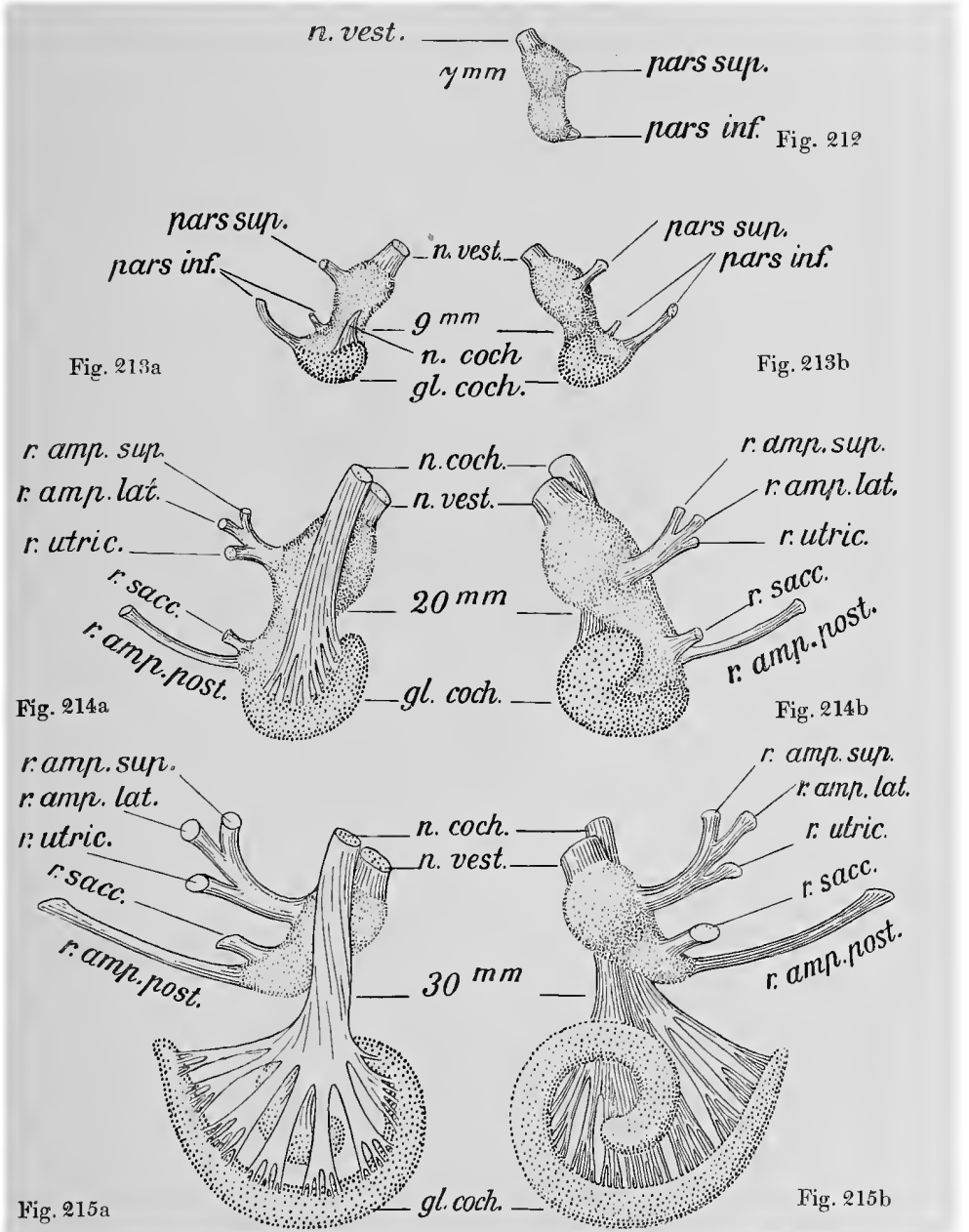

FIG. 212–215b.—The differentiation of the left ganglion acusticum into the ganglion vestibulare and the g. cochleare and the development of its branches; the g. vestibulare is finely stippled and the g. cochleare coarsely. Figs. 213a, 214a, and 215a are views from the medial surface and Figs. 212, 213b, 214b, and 215b from the lateral. (After Streeter, 1906–1907.)

from it by mesenchyme growing in between in the dorsoventral direction (Fig. 216, *Dors. I*).

The tip of the dorsal prolongation is the anlage of the anterior recess of the tympanic membrane; from it the tubotympanic groove (*tt. R.*) extends orally to the pharynx, and aborally is the groove for the tensor tympani (*T. R.*), this latter groove extending medially to the root of the second visceral arch into the posterior tympanic groove and through this into a dorsal prolongation of the second pharyngeal groove (*Dors. II*). Between the tubotympanic and the tensor grooves the roof of the pharynx

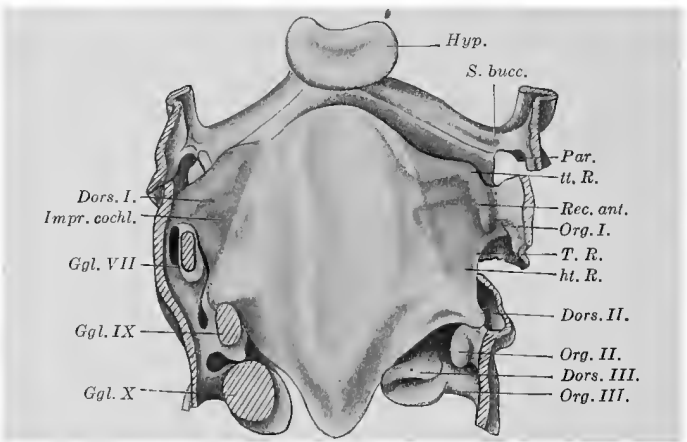

FIG. 216.—Pharynx of an 8 mm. (nape-length) human embryo seen from the dorsal surface, the chorda, aorta, and branchial arch arteries having been removed. The anlage of the tympanic cavity and tuba is represented by a yellowish color. ×28. The following explanations of the lettering serve also for Figs. 217, 218, and 219 a and h. *Amb.*, incus; *Cochl.*, cochlea; *D. nl.*, ductus nasolacrimalis; *Dors. I, II, III*, dorsal prolongations of the 1st, 2d, and 3d pharyngeal grooves; *F. conch.*, fossa conchæ; *Ggl. VII, IX, X*, ganglion of the facialis, glossopharyngeus, and vagus; *Ggpl.*, plate of the external auditory meatus; *Ham.*, malleus; *Hgr.*, manuhrium mallei; *ht. R.*, posterior tympanic groove; *Hyp.*, hypophysis; *Hyp. St.*, stalk of hypophysis; *Impr. cochl.*, impressio cochlearis; *Meck.*, Meckel's cartilage; *N.*, nasal cavity; *Org. I, II, III*, 1st, 2d, and 3d hranchial cleft organs; *Par.*, parotid gland; *Pfh.*, tympanic eminence; *pr. bv.*, processus hrevis mallei; *pr. Gg.* primary auditory meatus; *pr. P.*, primary tympanic cavity; *pr. Zl.*, primary dental ridge; *R.*, Reichert's cartilage; *Rec. ant.*, recessus membranæ tympani anterior; *Rec. post.*, recessus membranæ tympani posterior; *T. R.*, groove for the tensor tympani; *tt. R.*, tubotympanic groove; *tub. R.*, tubal groove; *vt. R.*, anterior tympanic groove. (After Hammar, Arch. für mikr. Anat., vol. 59, 1902.)

is depressed by the auditory vesicle (impressio cochlearis, *Impr. cochl.*).

The dorsal prolongation of the first pharyngeal groove (together with its various parts, such as the tubotympanic groove, the tensor tympani groove, and the anterior tympanic pouch), the posterior tympanic groove, and the portion of the impressio cochlearis which at first lies medial to these structures, form the *primary tympanic cavity;* its area is represented in Fig. 216 by a yellowish color. The ventral part of the first pharyngeal groove, into which the tympanic cavity is at first prolonged, soon atrophies completely. When the first pharyngeal and branchial grooves become separated, the primary tympanic cavity is forced by the thickening basis cranii from its upright wing-like position into a horizontal

one (Fig. 217). The tubotympanic and posterior tympanic grooves increase in height and thereby the tubotympanic groove becomes divided by a knee-shaped bend into a very short *tubal* and a much longer *anterior tympanic groove,* while the posterior recess of the tympanic membrane (*Rec. post.*) becomes formed at the oral end of the posterior tympanic groove. Between the anterior and posterior recesses of the membrana tympani lies the blastema of the tendon of the tensor tympani, producing a notch, the incisura tensoris tympani (*T. E.*). Behind the incisura the lateral wall of the tympanic cavity is pushed inwards by the anlage

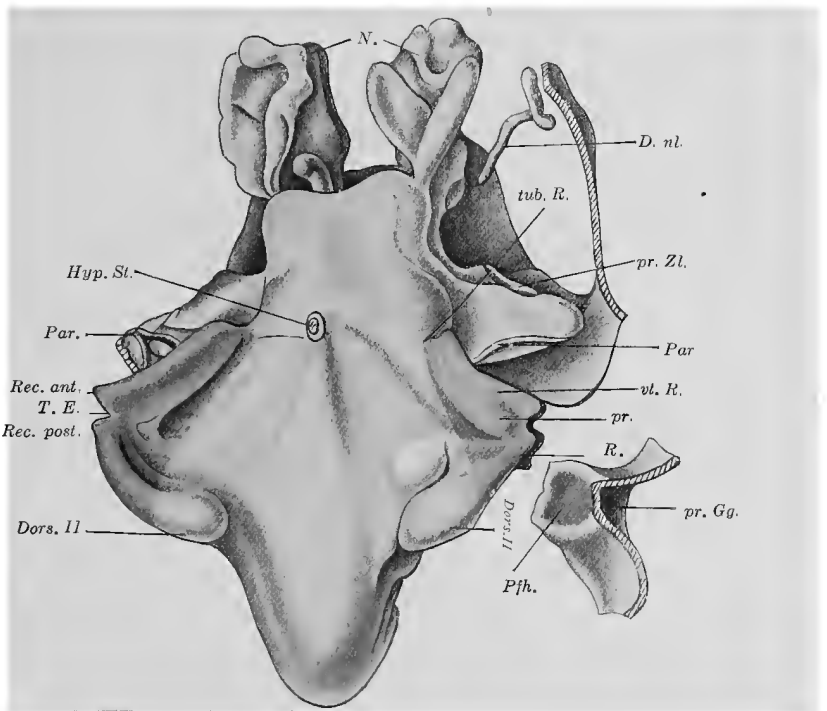

FIG. 217.—Pharynx and the neighboring parts of a human embryo of 18.5 mm. (nape-length) seen from the dorsal surface. ×21. The lettering as in Fig. 216. (After Hammar, Arch. für mikr. Anat., vol. 59, 1902.)

of the manubrium mallei, forming the impressio manubrii. "This impression lies aboral to the point of contact of the first branchial groove and the first pharyngeal pouch; the manubrium mallei consequently projects," according to Hammar, "into the tissue of what will later be the second arch." It must, however, grow into this secondarily, since, as will be seen later, it belongs genetically to the first branchial arch.

The *tubotympanic canal* is formed from the primary tympanic cavity by a constriction which takes place in an aboral-oral direction, and it is on this account that Hammar speaks of a period of separation. The beginning and end of this period are shown in

Fig. 218 and Fig. 219 a and b. The constriction begins at the boundary between the aboral end of the posterior tympanic groove and the dorsal prolongation of the second pharyngeal groove, and is produced by a proliferation of the tissue of the second branchial arch. By it the elongated, slit-like pharyngeal opening of the primary tympanic cavity is gradually shortened, and, finally, the tubotympanic canal forms a triangular, prismatic tube, slightly enlarged towards its posterior blind end and directed laterodorsally and aborally from its entrance into the pharynx. Its anterior *tubal* portion, which the tubal groove has helped to form, is at first quite short. During the transformation period, which now

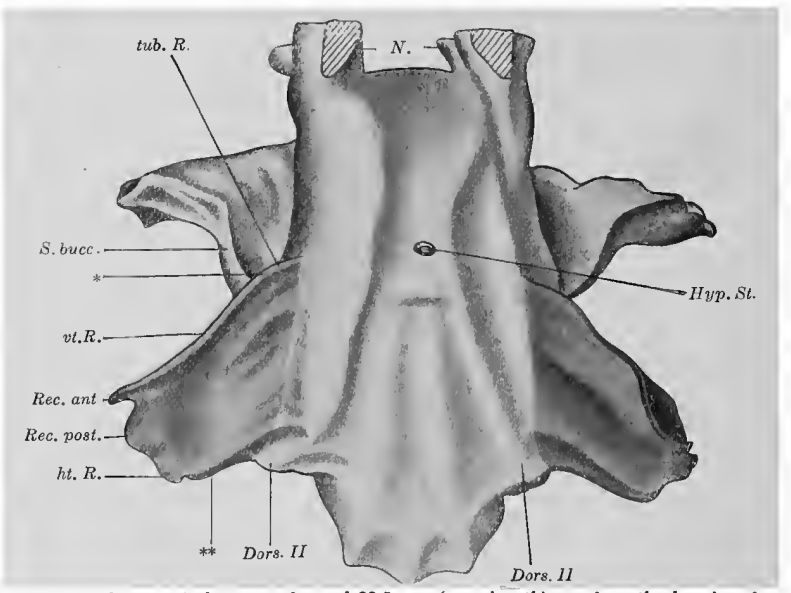

Fig. 218.—Pharynx of a human embryo of 20.5 mm. (nape-length) seen from the dorsal surface. ×21. * (as in Figs. 219 a and b) at the knee-shaped bend where the tubal part of the tubo-tympanic canal meets the much longer tympanic portion, which is directed laterally and aborally; **, boundary between the primary tympanic cavity and the rest of the second pharyngeal pouch (*Dors. II*). For explanation of the lettering see Fig. 216. (After Hammar, Arch. für mikr. Anat., vol. 59, 1902.)

succeeds, the tubotympanic canal assumes a flattened, slightly spiral form; it stands at first with its walls almost horizontal; but becomes directed along the outer surface of cartilaginous ear capsule, which is increasing in length, so that from the third to the fifth month it has an almost vertical position. In the sixth month the os petrosum rotates around its long axis towards the outer side, the cupola of the cochlea becoming depressed, and a temporary depression of the tympanic cavity is thereby produced, so that its walls again assume an almost horizontal position. In the seventh month the cavity gradually returns to the half-upright position, which it still retains at birth.

The tuba grows rapidly in length, and on the formation of its cartilage (in the fourth month, according to Siebenmann, 1897)

its lumen becomes slit-like. In the third month (fetus of 50 mm.) the lumen of the tympanic cavity disappears for the most part by

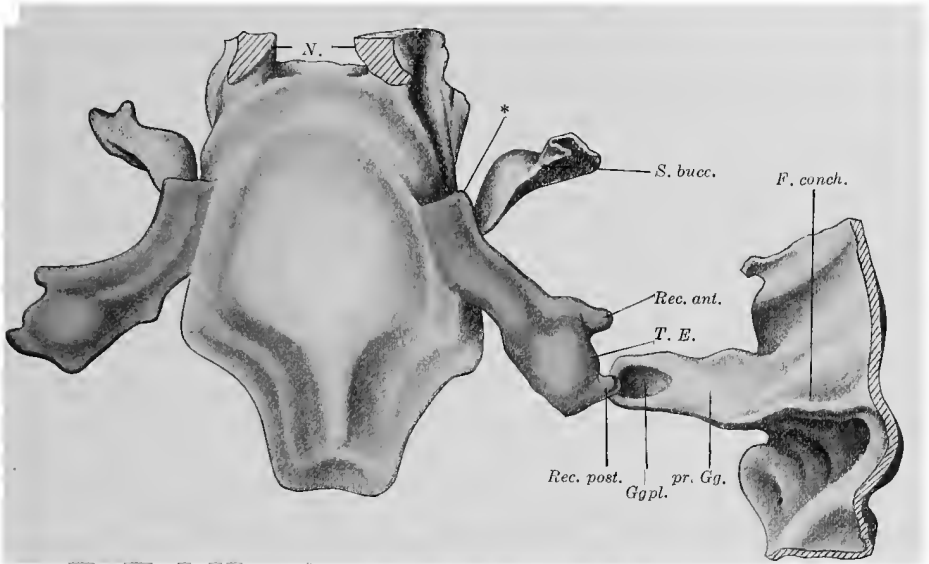

FIG. 219a.—Pharynx and right external auditory meatus of a human embryo of 24 mm. (nape-length) seen from the dorsal surface. ×21. For explanation of the lettering see Fig. 216. (After Hammar, Arch. für mikr. Anat., vol. 59, 1902.)

its epithelial surfaces coming into contact, but it is again completely restored at the beginning of the fourth month (fetus of 90 mm.) and persists from that time onward, although it becomes

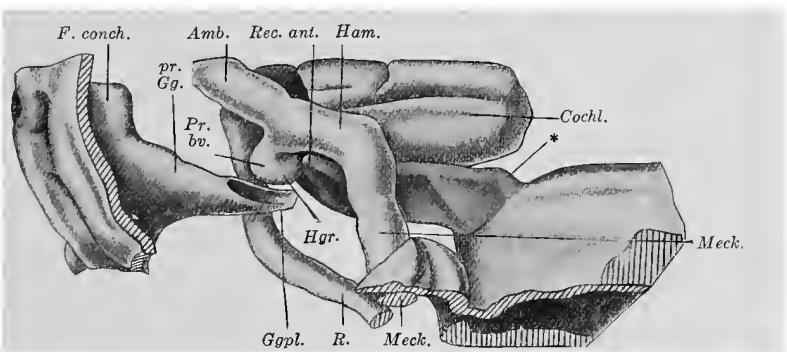

FIG. 219b.—The same with the cartilaginous labyrinth, the malleus and incus, and Meckel's and Reichert's cartilages seen from the oral surface. ×21. For explanation of the lettering see Fig. 216. (After Hammar, Arch. für mikr. Anat., vol. 59, 1902.)

very narrow in the sixth month, owing to the depression of the cavity which then takes place. Concerning the further development of the tympanic cavity the following may be said.[29] To-

[29] I shall use the terms lateral, medial, anterior, posterior, upper, and lower in the sense in which they are ordinarily used in connection with the fully developed tympanic cavity.

wards the end of fetal life the posterior (more rarely the anterior) recess of the tympanic membrane gives off a process, which extends upwards from the processus brevis of the malleus on the lateral wall of the tympanic cavity; this forms Prussak's space. The enlargement and further development of the tympanic cavity is associated with the presence of a submucous, peritympanic areolar tissue, which makes its appearance in the third or fourth month and is fully formed in the sixth or seventh. It forms two masses, the tympanic and the epitympanic areolar tissues. The tympanic tissue appears first on the inner wall of the cavity and later on the lower and posterior walls, but is lacking over the summit of the promontory. The epitympanic tissue lies above the cavity; in the seventh month it surrounds only the aditus and does not correspond in its dimensions with the later extent of the tympanic cavity, but a growth of it takes place commensurate with this extension. Furthermore the extension of the tympanic cavity in the later fetal months does not take place gradually and continuously, but to a certain extent discontinuously, a phenomenon that finds its explanation in the fact that a breaking down of the areolar tissue to form cavities filled with fluid takes place at intervals and with the absorption of the fluid the tympanic cavity seems suddenly to extend into the region thus prepared for it.

Imbedded in this areolar tissue are originally the auditory ossicles, the chorda tympani, muscle tendons, and ligamentous connective tissue, and, as the tympanic cavity enlarges, all these structures become inclosed in folds of its mucous membrane. Hammar (1902) has followed the development of each of these folds, but I can only refer to his investigations here. In addition to the typical and constant folds, whose origin has just been explained, others also occur which are simple reduplications of the mucous membrane and as such are very variable and frequently quite transitory. According to the statement in the majority of text-books (Kölliker, 1879, Minot, 1894, O. Schultze, 1894, Kollmann, 1898, Tourneux, 1st ed. 1898, Bryce, 1908), the areolar tissue disappears only after birth, the tympanic cavity at that time almost or completely lacking a lumen. Frequently, too, the disappearance of the tissue has been brought into direct causal relationship with the occurrence of respiration and this idea has gained some forensic importance. Wendt (1893) says: "1. When in a mature or nearly mature fetus or in a new-born child the thickening of the mucous membrane of the tympanic cavity is found to be still completely existent, an energetic respiration, intra-uterine or post partum, has not yet occurred." "2. When the mucous membrane of the tympanic cavity is found degenerated or without macroscopic enlargement in a fetus or a new-born child, a strong respiration, intra-uterine or post partum, has taken

place.'' Consequently he holds that the investigation of the tympanic cavity (the ear test) is capable ''of replacing the lung test within certain limits.'' Among more recent authors Aschoff (1897, p. 295) and Siebenmann (1897) have pronounced against this view and the conditions have been more fully elucidated by Hammar (1902).

Pneumatic cells are to be found at the close of fetal life in process of formation, especially from the upper squamosal portion of the cavity and, to a lesser extent, from the petrous portion and from the posterior and lower parts of the actual tympanic cavity.

The development of the auditory ossicles seemed to have been finally settled, after long discussion,[30] by the observations of Baumgarten (1892), Dreyfuss (1893), Zondek (1895), Hegetschweiler (1898), and especially of Broman (1898, 1899), when Fuchs (1905) again unsettled the whole matter.

I shall give here, in the first place, Broman's account. According to him, the dense mesodermal blastema masses of the first and second visceral arches are each divided in their proximal parts into a lateral and a medial portion by the trigeminus and facialis respectively. From the first arch are formed the malleus, incus, and Meckel's cartilage, the incus from the proximal part of the lateral blastema, and the malleus and Meckel's cartilage from the distal part of the medial blastema; the distal part of the lateral blastema is largely used in the formation of the outer ear.

From the second arch are formed the stapes and Reichert's cartilage, both coming from the medial blastema and being originally connected by a bridge, which Broman terms the interhyal. From the proximal part of the lateral blastema of the second arch is formed the laterohyal (Broman)—the intercalare of Dreyfuss—which later fuses with the capsule of the labyrinth; the distal part of this blastema takes part in the formation of the outer ear. Broman believes that he has proved that skeletal parts of different origin have also their own prechondral nuclei; in the region where two such nuclei come into relation with one another there will be at least transitorily a disk of blastema (''intermediate disk''). These conditions are found in the anlagen of the auditory ossicles. Considering first of all the incus, its anlage unites with the labyrinth capsule while still in the blastemic stage and again becomes distinctly separated from it only as it passes into the prechondral stage. The previously established connection with the anlage of the stapes becomes the crus longum and from the intermediate disk the articulation develops; the posterior part of the blastema forms the crus breve. In general the incus acquires its definitive form while still in the prechondral stage, only the processus

[30] For the important morphological questions connected with this problem and for the historical development of the discussion see E. Gaupp (1899).

lenticularis forms later, after the beginning of ossification. This begins at a single spot in the upper part of the crus longum and extends finally into the processus lenticularis, which, since it possesses no ossification centre of its own, cannot be regarded as an epiphysis.

The malleus shares a prechondral nucleus with Meckel's cartilage; it is separated from the incus by an intermediate disk, in whose place a joint will form at a somewhat late date,[31] Schmidt (1903) finding the first indication of a joint cavity in a fetus of 9.6 cm. vertex-breech length. In the cartilage stage it is still united with Meckel's cartilage and only becomes separated from it at the commencement of ossification. This takes place from a single centre, situated in the neck. The so-called processus anterior (Folii) is not formed by it; it is a membrane bone that unites with the rest of the malleus at a late period (in the sixth fetal month, according to Dreyfuss, 1893, p. 652).

The blastema of the stapes is perforated by the stapedial artery, and in the earlier stages of its development it is known, on account of its form, as the annulus stapedialis. Both it and Reichert's cartilage have their own prechondral cartilage; the interhyal, situated between the stapes and Reichert's cartilage, never reaches the prechondral stage, but the laterohyal has its own prechondral nucleus. Up to the second half of the third month of embryonic life the stapes remains ring-shaped, but at that time it begins to assume its definitive form, and at the end of the third month the stapedial artery also, as a rule, disappears. The capsule of the labyrinth takes no part in the formation of the foot-plate of the stapes. The precartilage in the vestibular fenestra of the human embryo does not, it is true, become directly transformed into connective tissue, as it does in the rabbit and guinea-pig, but becomes transitorily true embryonic cartilage (Dreyfuss, 1893), and finally becomes converted into a thin layer of connective tissue, which does not differ from the perichondrium of the fossa of the fenestra. The precartilage of the cochlear fenestra is transformed directly into connective tissue in man also. The centre of ossification for the stapes is situated usually in its base.

The connection of Reichert's cartilage with the capsule of the labyrinth is formed by the laterohyal. The malleus and incus consequently belong to the first visceral arch and the stapes to the second; the labyrinth capsule does not take part in the formation of the stapes, as it does in that of the functionally corresponding skeletal structure of the amphibia.

Quite different are the results obtained by Fuchs (1905) from

[31] Concerning the mode of articulation and the manner in which the articulations develop, very discrepant statements exist. Compare Schmidt (1903).

a study of the rabbit. He denies any primary ontogenetic relation between the anlage of the stapes and that of the hyoid cartilage; the entire stapes is formed from the capsule of the labyrinth. The connection of the malleus-incus anlage with the cartilage of the first arch is also secondary.—Since fundamental differences in the developmental processes in man and the rabbit are excluded, there is here an irreconcilable contradiction. It may be remarked that, according to my experience, there is great difficulty in tracing back a skeletal structure to the early prechondral stages,[32] and it carries with it the dangers of subjective interpretations. In my opinion, however, one may for the present accept the old view of Reichert that the malleus and incus are formed from the first visceral arch and the stapes from the second, for the topographical evidence upon which Fuchs bases his conclusions does not seem to be free from objection; Siebenmann (1894), who regards the discussion over the origin of the ossicles from the first or second visceral arch as quite superfluous, and contends that each of these structures, as well as Meckel's and Reichert's cartilages, is a quite independent element, disregards too much the importance of comparative anatomy for his position to be seriously discussed.

It may finally be remarked that at birth the auditory ossicles have already reached their definitive size (Urbantschitsch, 1876). Nevertheless they later increase in weight, with the exception of the stapes, which has already attained its definite weight in the eight months fetus (Eitelberg, 1884, Bistrzycki and von Kostanecki, 1891).

Concerning the muscles of the middle ear only a few remarks are necessary. The tensor tympani has made its appearance at the end of the second month (Broman, 1899), and is connected at its distal end with the tensor veli palatini, a connection which is dissolved at the end of the third month, although it may persist throughout life (Schwalbe, 1887, p. 506).[33] The stapedius arises at the middle of the third month. According to C. Rabl (1887), it seems to form a genetic group with the m. stylohyoideus and the posterior belly of the digastric.[34] The muscle is surrounded by a membrane of connective tissue, which later ossifies (Broman, 1899, Dreyfuss, 1893) to form the eminentia pyramidalis.

The cartilage of the tuba auditiva is formed in the fourth

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[32] This naturally holds true also in the estimate of Broman's statements concerning these stages.

[33] According to Killian (1890), the tensor tympani is derived from the m. pterygoideus and with this ultimately from the m. adductor mandibulæ of the Selachians. A thorough description of its development in the pig has been given by Eschweiler (1904).

[34] Killian (1890) derives the stapedius from the m. depressor maxillæ inferioris of the Selachians.

month (Krause, 1901[2]); Zuckerkandl (1906) found no trace of it in a human fetus of 5.1 cm. It has no relations to the visceral skeleton.

A classic account of the development of the human auricle or pinna was given by His (1885), and to it additions have been made by Gradenigo (1888) and especially by G. Schwalbe (1889[1,2,3], 1895, 1897). Mention should also be made of the recent investigations by Henneberg (1908), for, although they did not include human embryos in their scope, yet they yielded such uniform results in forms as widely separated as the rat and rabbit on the one hand and the pig on the other, that a far-reaching importance

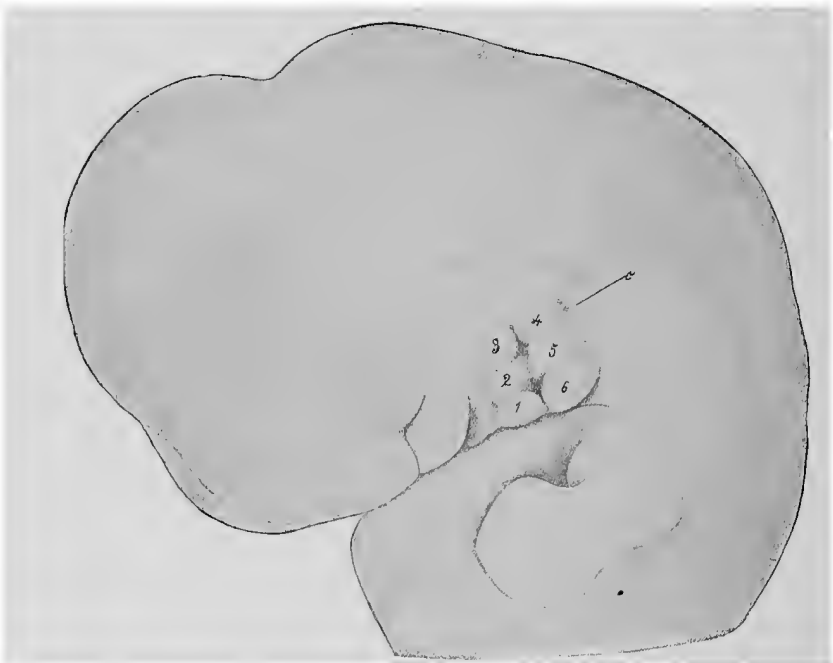

FIG. 220.—Cranial end of a human embryo at the beginning of the second month, with the auricular hillocks. ×12. c, Schwalbe's free auricular fold. (After Schwalbe, from Bardeleben's Handbuch, vol. 5, 2, p. 127, Fig. 12.)

may be credited to them. In this connection, finally, the observations of Baum and Dobers (1905) on the pig and sheep may be mentioned.

The region surrounding the first branchial groove develops in such a way that three elevations or hillocks (auditory hillocks, auricular hillocks, colliculi branchiales) are formed on the mandibular arch and three more on the hyoid arch. They are numbered in Fig. 220 from the ventral toward the dorsal extremity of the mandibular arch and in the contrary direction on the hyoid.

Behind the three hyoid hillocks the *free auricular fold* is formed, according to Schwalbe quite independently, as a fold of the

integument similar to what occurs in the formation of the eyelids; it is identical with the structure which His termed the cauda helicis and Gradenigo the helix hyoidalis. Later a slight swelling appears over the dorsal end of the first branchial groove; it unites caudally with the free auricular fold; apically it fuses with the third hillock and then extends ventrally to in front of the beginning of the second. The investigation of the further history of these structures is unusually difficult, and I give herewith, after

Embryological term.	His (man).	Gradenigo (man and mammals).	Schwalbe (man).	Baum and Dohers (pig and sheep).	Henneberg (rat, rabbit, and pig).
1. *Mandibular hillocks:* Hillock No. 1..	Tragus...	Depressed beneath the surface	Tragus.....	Tragus.....	Tragus
Hillock No. 2..	Helix	(Proc. infer. hel. mand.) crus helicis	Crus helicis....	Crus helicis, anthelix	Crus helicis, part of helix
Hillock No. 3..	Helix	(Proc. sup. hel. mand.) degensrates	Part of helix ascendens (antsrior)	Helix ascendens..	Helix
2. *Hyoidal hillocks:* Hillock No. 4..	Anthelix..	(Proc. sup. hel. hyoid.) crus inf. anthelicis in part	Crus inf. anthelicis	Cranial plica long	Part of scapha, crus anthel. sup.
Hillock No. 5..	Antitragus	(Proc. inf. hsl. hyoid.) degenerates	Crista anthelicis inf. ?	Anthelix, middle plica longitudinalis, tip of auricle	Part of scapha, crus anthel. inf.
Hillock No. 6..	Lobulus auriculæ	Depressed beneath the surface	Antitragus.....	Caudal plica long., which later disappsars; antitragus?	Part of scapha, antitragus, plica antitragica = crista anthel. inf.
3. Helix hyoidalis (Gradenigo), free auricular fold (Schwalbe), cauda helicis (His)	Helix	Helix and antitragus	Helix posterior (posterior helix fold), lohulus auriculæ	The remaining parts of the auricle; antitragus	
4. Helix mandihularis (Gradenigo)	.....	Helix and tragus..	Anterior helix fold (part of the helix ascendens)		

Schwalbe and Henneberg, a synoptical table of the results obtained by different investigators.

I have not been able to get a clear picture from the investigation of the human embryos at my disposal, but it seems certain that the tragus is developed from the first auricular hillock and the antitragus from the sixth, and that the auricular lobe is a later formation that has nothing to do with the hillocks. According to Schwalbe, the point of union of the secondary swelling with the free auricular fold marks the point of the satyr tubercle; Darwin's

tubercle is formed almost at the middle point of the border of the free auricular fold. A folding over of the posterior border of the auricle, which is so pronounced in mammals and leads to temporary epithelial adhesions, is to be observed in the human ear at the beginning of the third month; the unfolding takes place in the course of the third month, and the partially covered anthelix again becomes visible. Three angles then become evident on the posterior border, which is not yet curved in upon itself: an upper one, the apical angle which corresponds to the satyr tubercle, a posterior one, corresponding to Darwin's tubercle, and a lower posterior one (Fig. 221 a and b).

In the fourth month there is formed on the lateral surface of the free auricular fold between the helix ascendens and the posterior edge of the auricles a system of folds, first described by Schwalbe (1897) and consisting of five swellings separated by shallow grooves (Fig. 222). The swellings correspond to the longitudinal ridges of many mammalia, but they have already dis-

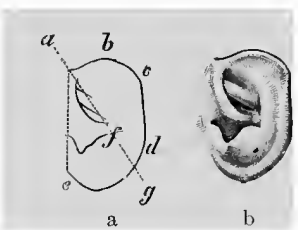

FIG. 221 a and b.—Left auricle of a sixtb montb's buman fetus. *ac*, base of the auricle; *c*, tip of tbe auricle; *b*, apical tubercle; *d*, lower posterior angle, incisura auris posterior; *a f g e*, hillock region; *a b c d g f*, free auricular fold. (After Scbwalbe, from Bardeleben's Handbucb, vol. V₂, p. 130, Fig. 13 a and b.)

FIG. 222.—Left auricle of a buman fetus of tbe fourth montb. ×2. The five transitory transverse folds are developed; tbey correspond to tbe longitudinal ridges of tbe ears of long-eared animals. (After Schwalbe, from Bardeleben's Handbucb, vol. V₂, p. 130, Fig. 14.)

appeared in the human ear in the fifth month. In the fifth and sixth months the auricle has the shapes that Schwalbe has characterized as the Macacus and Cercopithecus forms. As to the growth relations of the auricle one may consult Schwalbe in Bardeleben's Handbuch (1897).

The auricular cartilage in man, according to Münch (1897), is an independent formation and remains independent; it shows no relations to the hyoid cartilage during its development. The auricular muscles are derived from the platysma (Ruge, 1887).[35]

Turning now to the development of the external meatus, we must return to a stage in which the first branchial groove is at the height of its development, the auricular hillocks having just appeared. In such a stage one may, with Kastschenko (1887[1,2]), recognize in man also an upper, middle, and lower auricular

[35] Dobers (1903–1904) holds that in the pig and sheep the muscles of the posterior portion of the auricle are not derived from the platysma.

groove; the upper one in man is, however, merely indicated and corresponds to the point at which the facialis organ (the first visceral cleft organ of Hammar) has formed, and only at this point does the entoderm of the first pharyngeal pouch come into contact with the ectoderm of the branchial groove. This contact is soon lost and the upper auricular groove disappears without leaving a trace. The middle and lower auricular grooves become cut off ventrally by the union of the first and sixth auricular hillocks, between which the incisura intertragica persists, and form the fossa angularis (His). The transformation of this fossa angularis into the cavity of the auricle is associated with the transformation of the auricular hillocks and the formation of the auricle, concerning which, as has been already pointed out, the results are not quite concordant. From the ventral part of the fossa, dorsal to the incisura intertragica, the primary meatus, according to Hammar, grows inwards in the latter half of the second month as a slight, funnel-shaped canal. In opposition to Moldenhauer (1877) and Urbantschitsch (1877), Hammar expressly states that it is not formed and elongated by a thickening of the tissue surrounding it. In the fourth and fifth month the lumen of the primary meatus is temporarily occluded in its inner portion by the thickening of its epitrichial layer. This closure, however, disappears with the occurrence of the cornification of the epidermis, and the meatus again becomes provided throughout its entire length with a lumen, which persists until birth, and only towards the end of fetal life is more or less narrowed by the vernix caseosa. In the beginning of the third month the meatal plate (lamina epithelialis meatus), which is essentially a prolongation of the lower wall of the primary meatus, grows inwards and soon reaches the outer end of the tympanic canal (Fig. 219 a and b), and then pushes its way inwards and downwards along the lower wall of the tympanic cavity. The portion of the plate that is in relation with the lower outer portion of the wall of the tympanic cavity becomes rounded and is to be distinguished as the tympanic portion from the part that is more lateral in position. In the seventh month a splitting of the plate occurs and the lumen so formed becomes continuous laterally with that of the primary external meatus, the *definitive* or *secondary meatus* being thus formed. The lumen of the tympanic portion of the meatal plate forms the recessus meatus. In general the region of the primary meatus corresponds to the cartilaginous portion of the adult passage, but in the roof it extends also into the region of the osseous meatus. The structural differences of the integument in different portions of the definitive meatus stand in relation to its manner of development. The development of hairs and glands is limited to the region of the primary meatus, while the part de-

rived from meatal plate (with the exception of the tympanic membrane) has the lower surface of the epidermis ribbed and possesses no hairs or glands. At birth the recessus meatus has almost acquired its definitive size, the postfetal growth effecting for the most part the remaining parts of the meatus.

Concerning the development of the tympanic membrane Hammar (1902) states that from the beginning the inner end of the primary meatus is pushed downwards and outwards by a rounded elevation, the tuberculum membranæ tympani. As the primary meatus grows inwards this tubercle is also carried inwards, and when the primary meatus and the tympanic cavity have come to lie opposite each other it becomes the primary tympanic membrane, into which the manubrium and processus brevis of the malleus have now grown. Later, by a thinning and modification of its connective tissue, it becomes the definitive tympanic membrane. In a fetus of 4.3 cm. vertex-breech length Dreyfuss (1893) was already able to distinguish three layers in it, one corresponding to the subcutaneous tissue, a second, the membrana propria, which stands in intimate relations to the annulus tympanicus, and a third, the submucous tissue of the tympanic cavity. That these three layers are present from the beginning and that the middle one is to be regarded merely as an unossified portion of the annulus tympanicus cannot, assuredly, be accepted. The membrane obtains a free outer surface only after the splitting of the meatal plate has taken place.[36] The *pars flaccida* is formed in the last month of fetal life. In the fifth month a short ridge is formed at the anterior part of the boundary between the tympanic and non-tympanic portions of the meatal plate, above and in front of the processus brevis of the malleus. On the splitting of the meatal plate in the seventh month, this ridge becomes converted into a groove open to the meatus, the *terminal groove,* and against the floor of this groove Prussak's space, formed from the tympanic cavity, applies itself in the tenth month and so forms the pars flaccida. Concerning the growth relations of the meatus one may consult Schwalbe (1897, p. 171) and Symington (1885, 1889).

Much has been written concerning differences in the form of the external ear, on account of attention having been directed to them from the psychiatric and criminalistic stand-points. Their importance in these respects has certainly been greatly overestimated. Occasionally fetal ear forms are to be observed in adults, and these may be regarded as inhibitions of development (compare, in addition to Schwalbe, 1895, 1897, Schäffer, 1892).

[36] Dreyfuss (1893) gives an account of the manner in which the special relations of the manubrium mallei and tympanic membrane are brought about. The work of Draispul (1890) is rather inconclusive.

A cleft which traverses the lower portion of the pinna between the tragus and antitragus has had a certain importance assigned to it in connection with the question of the inheritance of traumatisms. It was supposed that in such ears the ear lobe was divided because the mother's ear lobe had been divided by an ear-ring. Careful studies showed (His, 1889, Israel, 1890, Rohrer, 1894, von Swiecicki, 1890) that the cleft did not really lie in the region of the ear lobe, but between the anlagen of the tragus and antitragus and that at all events the phenomenon was to be regarded as an inhibition of development, the first and sixth auricular hillocks remaining more or less widely separated.

Fistulæ auris congenitæ seem to me to be referable to inhibitions of development in the region of the dorsal part of the first branchial groove (upper auricular groove, facialis organ). Gradenigo (1893) explains them as an insufficient closure of the furrow between the crus prætragicum—corresponding to the spina helicis (scutulum)—and tragus, and His (1889) refers them to an insufficient fusion of the furrow between the crus helicis and supratragicum (prætragicum of Gradenigo). Schwalbe (1889[2], 1889[3]) believes many of the anterior auricular appendages to be abnormally developed spinæ helicinæ (scutula) separated from the main cartilage, and the same view has been expressed by Gradenigo (1893).

For accounts of malformations of the human auricle one may consult, in addition, Moldenhauer (1892), Piel (1904), and Alexander (1904).

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XVII.

THE DEVELOPMENT OF THE INTESTINAL TRACT AND RESPIRATORY ORGANS.

By OTTO GROSSER, Prague; FREDERIC T. LEWIS, Harvard University; and J. PLAYFAIR McMURRICH, University of Toronto.

INTRODUCTION.

By FREDERIC T. LEWIS.

Formation of the Intestines from the Umbilical Vesicle.—In the youngest human embryos which have yet been obtained, the entoderm forms the lining of a more or less spherical sac, which the early anatomists named the umbilical vesicle (*vesicula umbilicalis*). The vesicle enlarges with the growth of the embryo, and during the second month it is a conspicuous object. At birth it is still present.

It was observed at birth by Hoboken, in 1675, as a granule of oval shape, white, about the size of a hemp-seed, with indurated contents. It was probably the umbilical vesicle which Diemerbroeck found in an embryo of the sixth week, and described in 1672 as a sac, the size of a small hazel-nut, filled with clear fluid. But the first satisfactory description of this structure in a human embryo is credited to Albinus, who published an excellent drawing of it in 1754, and referred to it as the *vesicula ad umbilicum parvuli embryonis.* The vesicle was lodged between the amnion and chorion near the distal end of the umbilical cord, and a slender thread-like prolongation extended from it, through the cord, to the body of the embryo. Beyond this point Albinus did not follow it for fear of damaging his specimen.

At the beginning of the nineteenth century the umbilical vesicle was recognized as a constant structure in young human embryos and its significance was being discussed (Lobstein, 1802). Wrisberg had shown that blood-vessels passed from it into the mesentery of the embryo. Oken believed that the embryo was nourished through the umbilical vesicle, and in 1806 he published a notable treatise, in which he declared that the following propositions would be proved with absolute certainty:

(1) The intestines of embryos originally do not lie in the abdominal cavity, but arise from a vesicle, situated outside of the amnion, called the *vesicula umbilicalis* in man, and the *tunica erythroides* in other animals.

(2) The intestines do not lie in the vesicle as in a sac, but they are a prolongation of it, as the duodenum is a prolongation of the stomach. The prolongation splits into an anterior and a posterior intestine, both of which pass through the umbilical cord into the abdominal cavity, one part going to the anus, the other to the stomach.

(3) The stalk of the vesicle, between the splitting of the intestine and the vesicle, becomes obliterated after some weeks, closing and becoming cut off like an umbilical artery; it appears at first as the cæcum, and later also as the vermiform process, so that at this place there is no continuity in the intestines but an angular *splicing* with a valve.

(4) The intestines now begin to draw back toward the umbilicus and finally enter the abdominal cavity, so that all embryos necessarily have the so-called umbilical hernia.

These propositions were defended by Kieser in 1810, who published an interesting figure of the intestines of a three months' human embryo, a reduced copy of which is shown in Fig. 223. He found that the coils of the intestine were lodged in the umbilical cord and not in the abdominal cavity. He was uncertain whether the intestinal tube continued across the insertion of the stalk of the umbilical vesicle, but, influenced by Oken, he wrote, "It appears as if the ends

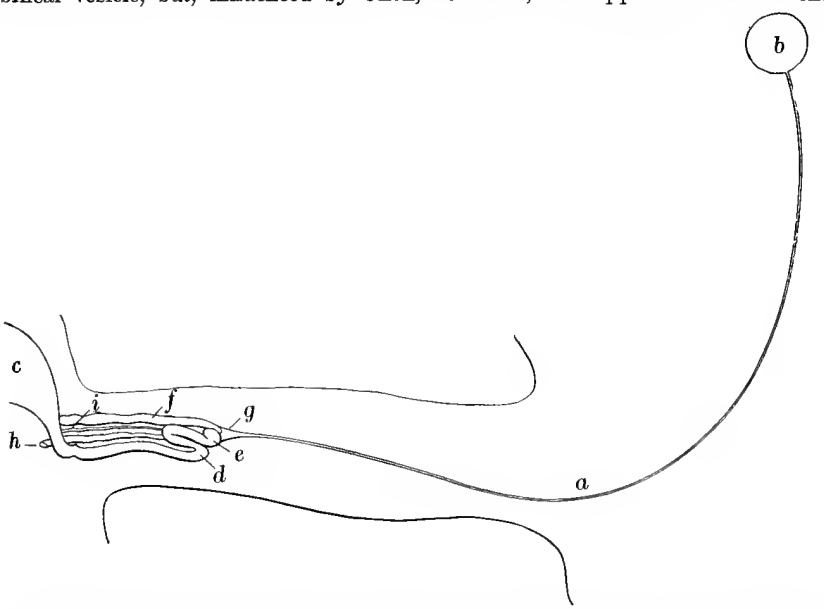

FIG. 223.—Kieser's figure, reduced and re-lettered, showing the umbilical cord of a human embryo of three months, the intestines within it, the cord of the umbilical vesicle (*a*), and the vesicle itself (*b*); *c*, lower part of stomach; *d*, coil of the gastric portion of the intestine which has a blunt end at *e*; *f*, anal part of the intestine, also with a blunt end; *g*, "cord of the umbilical vesicle as it surrounds the two ends of the intestine like a funnel;" *h*, vena omphalo-mesenterica; *i*, arteria omphalo-mesenterica.

of the two parts of the intestine were here still divided." The gastric portion is represented as ending in a knob-like expansion, which is in contact with the blunt end of the anal half of the intestine and with the cord of the umbilical vesicle, at a place where later the cæcum and vermiform process will appear. The cord of the vesicle is a prolongation of the mesentery, in which both the blood-vessels and the tube connecting the vesicle with the intestine have become obliterated.

In Oken's chapter entitled "Proof that all mammals possess an intestinal vesicle and that the intestines arise from it," he says, "I could easily extend this proof over the classes of egg-laying animals." The human umbilical vesicle had already been compared with the yolk-sac of birds, and in 1768 Caspar Friedrich Wolff had published his fundamental studies upon the development of the intestine in the chick. He found that the primitive intestinal cavity is in the dorsal part of the yolk. From this cavity he saw a slender prolongation, which admitted a fine needle, grow forward to make the stomach and œsophagus. This prolongation is

called the *fore-gut.* Somewhat later in the development of the chick, Wolff saw a similar prolongation grow backward to make the rectum, and this is the *hind-gut.* Between the two is the *mid-gut,* open below toward the yolk, and becoming relatively small as the fore-gut and hind-gut lengthen, partly at its expense. Thus Wolff saw in the chick what Oken later conjectured for man, and what has since been actually observed, namely that the intestine arises by the outgrowth of fore-gut and hind-gut respectively, from the dorsal part of the cavity of the yolk-sac.

Separation of the Intestines from the Yolk-sac.—The term yolk-sac, *sacculus vitellinus,* since it is applicable both to lower animals and to man, has largely replaced the term umbilical vesicle. The name mid-gut, although in common use, may well be abandoned. The fore-gut can then be sharply defined as that portion of the intestine anterior to the attachment of the yolk-sac, and the hind-gut as the part which is posterior. The attachment of the yolk-sac, broad at first, becomes reduced to a slender stalk, the base of which may remain as a diverticulum of the intestine.

Oken wrongly supposed that a portion of the yolk-stalk persists as the vermiform process. This error was corrected by Meckel (1812) in a most thorough manner. An out-pocketing of the human small intestine, usually about an inch in length but sometimes several times as long, had frequently been observed. It was generally found opposite the mesenteric attachment, about three feet from the beginning of the large intestine. Sometimes it was turned toward the mesentery. Its walls included all of the layers which enter into the formation of the intestinal tube, with which its lumen was in free communication. Meckel regarded the opinion of Fabricius, that such diverticula arise from the pressure of substances within the intestinal canal, as improbable. He saw the diverticulum several times in children at birth, once in an embryo of six months and twice at three months. Since it is a congenital structure, essentially constant in position, Meckel sought to explain it through the normal development of the intestinal tract, and concluded as follows: "Even into the third month of embryonic life a small elevation remains in the lower part of the small intestine as a trace of the former connection (with the yolk-sac), and if this is retained beyond this time it appears as a blind appendage." Meckel found one abnormal case in which it remained as an open duct extending from the intestine to the umbilicus, accompanied by its vessels which were still pervious. He saw cases also in which the obliterated vessels formed cords extending from the diverticulum of the intestine across the abdominal cavity to the umbilicus. Such cords have frequently been observed, and, as Meckel recorded, they may lead to adhesions and intestinal obstruction. The diverticulum was found not only in man but in other mammals. Cuvier had seen it in birds, and Meckel concluded that it was a constant structure in ducks and geese, in which, moreover, its genesis from the yolk-sac could be clearly demonstrated. Thus the true embryonic interpretation of the *diverticulum ilei* was clearly established by Meckel. He found also that "the vermiform process appears first as a little knob which gradually enlarges considerably." "I saw it arise thus in the human embryo, as Wolff had seen the cæca in the chick, where previously no trace of them could be identified." This conclusion is in accord with later observations.

The Allantois.—Several human embryos have been obtained which are so young that neither the fore-gut nor the hind-gut has begun to grow out from the cavity of the yolk-sac. In most of these, however, the tubular entodermal outgrowth known as the

allantois is present. The allantois grows out from the posterior portion of the yolk-sac near its dorsal surface. When the hind-gut pushes out, the allantois is carried with it, so that then it empties into the terminal part of the hind-gut, which is called the cloaca.

In the horse, cow, and pig the distal portion of the allantois dilates enormously, forming a somewhat cylindrical vesicle, so attached to its stalk that the entire allantois is T-shaped. At certain stages the terminal vesicle is many times the size of the embryo. Thus, with an embryo goat of eighteen days Haller found an allantoic sac two feet long, whereas the embryo itself measured less than two inches (twenty lines). The allantoic sac is found between the amnion and the chorion, to which it may be adherent.

The part of the allantois near the intestine, which develops through subdivision of the cloaca, is commonly called the *allantoic stalk*. Its formation will be fully considered in the chapter on the urogenital tract.[1] A part of the allantoic stalk expands to form the bladder. Between the apex of the bladder and the allantoic sac, the allantois remains slender and is known as the *urachus*. The urachus extends from the bladder into the umbilical cord.

The allantois has been known for centuries. According to Fabricius ah Aquapendente (1600), "The membrane is called ἀλλαντοειδὴς because it is similar to ἀλλᾶς, that is, sausage. But it must not be understood that it resembles anything filled with chopped meat, with which sausage skins are usually filled (for it contains only urine), but because its form seems similar to a sort of intestine from which sausages are generally made; hence it is called *allantoic,* that is, intestinal, by Galen and early writers. According to Suidas, ἀλλᾶς seems generally to he used in the sense of ἔντερον, although this too cannot be denied, that in such membranes, along with urine, particles like chopped meat or sausage are sometimes found."

The solid particles referred to may be the *hippomanes* found in the allantois of the horse, and said to be known to Aristotle (Bonnet, 1907, p. 194).

Many attempts were made to find an allantois in human embryos, but at the beginning of the nineteenth century no agreement had been reached. Hale in 1701 had announced "The Human Allantois discover'd," but. according to Oken and Velpeau, it was probably an amnion which he described. Lobstein declared that the human yolk-sac was the allantois. "Who will not be entirely in doubt," Oken wrote in 1806, "when one finds that writers have described as allantois the most heterogeneous things which were ever seen?" It soon became established, however, that in human embryos a slender urachus extends from the bladder into the umbilical cord, accompanied by the umbilical arteries. Velpeau, in 1834, thought that after the urachus had passed the whole length of the cord it became lost in a porous tissue hetween the amnion and the chorion, and that this tissue represented the allantoic sac. Von Baer, in 1837, declared that what was found between the amnion and the chorion had been somewhat rashly interpreted as the allantois. "The true allantois it certainly is not."

Allantoic vesicles continued to be reported for many years, until finally the fundamental relations of the human allantois were established by His. He wrote as follows (1885, p. 222): "I designate as *body-stalk* [pedunculus abdominalis] that thick cord which in very young embryos forms a connection between the

[1] See also page 322.

embryo and the chorion. . . . The main portion of the body-stalk is loose connective tissue with a few smooth muscle-cells; its dorsal surface has an ectodermal covering, and the ventral half surrounds the allantoic duct and the two umbilical arteries running with it. . . . A vesicular or even only a free allantois has never been found in human embryos, and the slender duct in the body-stalk, the *allantoic duct* as I have formerly named it, is indeed only a very rudimentary representative of the structure which is so large in many mammals."

Although the human allantois may be described as rudimentary because of its small size, it is nevertheless differentiated very early. Keibel and Elze (1908, p. 152) have recorded that it appears in man and the apes before any segments have formed.

It arises somewhat later in Tarsius, but still before there are any segments. It first appears in pigs of four or five pairs of segments, in rabbits of about eleven pairs, and in chicks of more than twenty pairs.

In the first human embryo which is now to be described, the body-stalk will be seen connecting the yolk-sac with the chorion. Into this stalk in the second specimen the allantois has grown out, thus forming the first subdivision of the entodermal tract.

THE EARLY DEVELOPMENT OF THE ENTODERMAL TRACT AND THE FORMATION OF ITS SUBDIVISIONS.

By FREDERIC T. LEWIS.

Peters's Embryo. Yolk-sac.—It has been inferred from comparative studies that the human entodermal tract arises as a solid mass of cells, and diagrams of this hypothetical stage have been published by Keibel, Schlater, and others. In the youngest embryos which have been observed, however, the entodermal cells surround a cavity. This is the condition in an embryo obtained by Peters (1899) at the autopsy of a suicide who had taken caustic potash one month after her last catamenia. Bryce and Teacher (1908) estimate the age of this embryo as 13½ to 14½ days. It is generally conceded to be the youngest properly preserved human embryo yet described. The embryo extended through nineteen 10 μ sections, and was cut "obliquely to the longitudinal axis." A drawing of only one section was published, and this is reproduced in Fig. 224. The cavity of the yolk-sac contains round masses of coagulum. It is bounded by a layer of entodermal cells which are not everywhere distinct. The entoderm in this section appears to be completely surrounded by mesoderm, which forms the outer layer of the wall of the yolk-sac. A strand of mesoderm

extends from the yolk-sac to the chorion, bounding a space designated *Sp* in the figure.[2]

Dorsal to the yolk-sac is the amniotic cavity, bounded above by a thin layer of amniotic ectoderm and below by the very thick embryonic shield, also ectoderm. According to von Spee, who studied Peters's specimen (Peters, 1899), "It is impossible to speak of an isolated body-stalk which connects the embryo with the chorion, because almost the whole embryonic formation seems imbedded in a thickening of the chorionic mesoderm. Whether the first small beginning of an entodermal diverticulum (allantoic duct) has already started to grow out from the caudal end, and

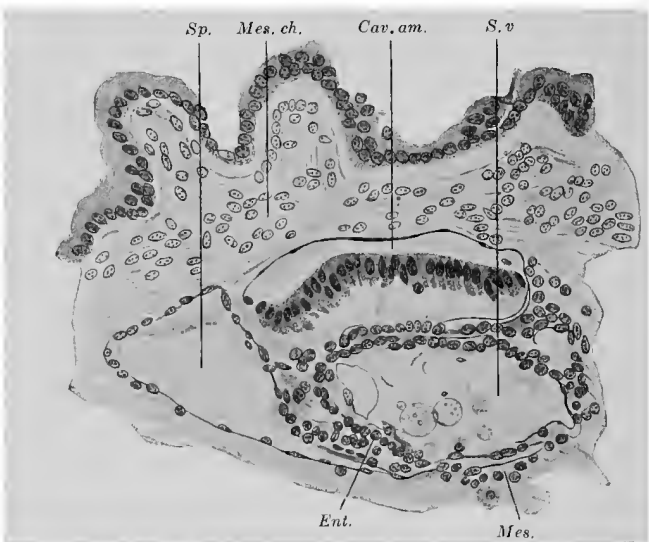

FIG. 224.—Obliquely longitudinal section of Peters's embryo. (After Peters.) *Cav. am.* (cavum amnii), amniotic cavity; *S. v.* (sacculus vitellinus), yolk-sac; *Ent.*, entoderm, and *Mes.*, mesoderm of the yolk-sac; *Mes. ch.*, mesoderm of the chorion; *Sp.*, "cleft in the exocœlom"(?).

appears in the form of a ring of epithelioid cells arranged about a lumen (in section 11, etc.), remains to me entirely uncertain."

Keibel has modelled Peters's embryo from outline drawings made upon wax plates by Selenka. He failed to find an allantois, but records that the outer surface of the yolk-sac is uneven as if blood and vessels had begun to develop in its mesoderm (Keibel and Elze, 1908). It will be noted that von Spee does not state definitely that Peters's specimen has no allantois. In describing another very young embryo he had recorded that "as compared with the embryonic shield, the allantois is remarkably long, and ought therefore to appear very early" (1896, p. 9).

[2] Grosser, who has examined the specimen, thinks that this space may be the beginning of the cavity of the chorion, and that elsewhere the chorion is filled with loose tissue. Zentralblatt für Physiol., Bd. 22, Nr. 1.

Two other embryos, both removed from the uterus by curetting within a month after the last catamenia, may have no allantois. In one of these "an allantoic duct of the yolk-sac does not stand out clearly" (Beneke, 1904), and in the other "the body-stalk consists *only* of mesodermal cells" (Jung, 1908). Neither of these accounts, however, is convincing in regard to the absence of the allantois, for in the first case the statement is indefinite, and in the second the allantois is not specifically mentioned.

Herzog's Embryo. Yolk-sac and Allantois.—Herzog (1909) has recently described an embryo obtained at the autopsy of a woman who had been struck over the heart by the shaft of a swiftly

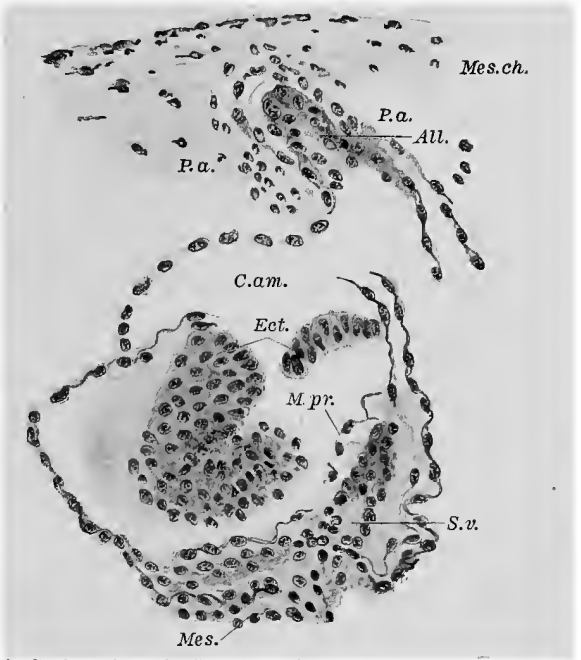

FIG. 225.—Longitudinal section of Herzog's embryo. ×215 diam. (After Herzog.) *Mes. ch.*, mesoderm of the chorion; *P. a.* (pedunculus abdominalis), body-stalk; *All.*, allantois; *C. am.*, amniotic cavity; *Ect.*, ectoderm of the embryonic shield; *M. pr.*, membrana prima, to which some cells are adherent; *S. v.*, yolk-sac; *Mes.*, mesoderm.

moving carriage and almost instantly killed. The specimen is unquestionably normal, and is well preserved histologically, but it has suffered considerable mechanical injury, partly after being mounted. After Herzog had published and described accurate figures of twenty-two successive sections (7 μ thick), including all of the embryo except a portion of the yolk-sac, he deposited the specimen in the Harvard Collection. For the privilege of studying further and modelling this embryo, the writer is under great obligation to Dr. Herzog.

The plane of section is nearly longitudinal. In the section shown in Fig. 225 the allantois is found extending through the

body-stalk toward the chorion. The entoderm of the yolk-sac is seen below, extending toward the allantois, but the connection between the two has been destroyed. It presumably occurred in this section. The ectoderm bounding the amniotic cavity consists of a thin layer above, for the most part broken away in this section, and the thick ectoderm of the embryonic shield below, which is broken into two pieces. The shield is bent upon itself, and the depression shown in the figure is transverse to the axis of the embryo. Between the ectoderm of the shield and the entoderm of the yolk-sac there is a structureless membrane such as Hensen (1875) observed in the rabbit and called the *membrana prima*. It is the detached basement membrane of the ectoderm of the embryonic shield, and was noted by von Spee in Peters's specimen. A layer of mesoderm passes over the ventral surface of the yolk-sac, and

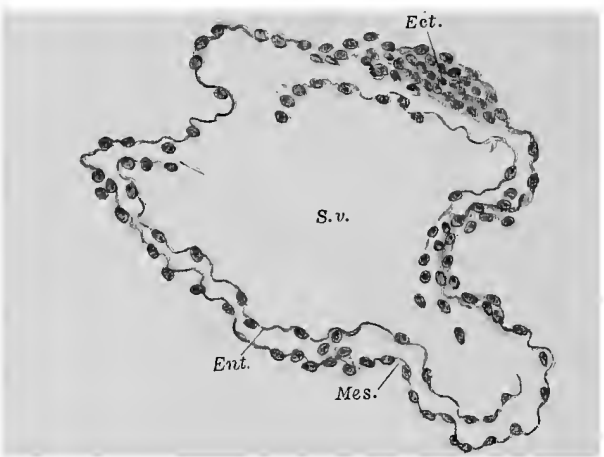

FIG. 226.—Longitudinal section of Herzog's embryo, separated by twelve 7 μ sections from Fig. 3. ×215 diam. (After Herzog.) *Ect.*, a mass of ectoderm bounding the amniotic cavity on the left side of the embryo. *Ent.*, entoderm, and *Mes.*, mesoderm of the yolk-sac *S. v.*

anteriorly (to the left of the figure) it is in relation with the ectoderm of the shield. It does not extend between the ectoderm of the shield and the yolk-sac, and in this respect Herzog's embryo differs from Peters's specimen as described by von Spee. In Fig. 225 the yolk-sac is cut tangentially, but it is evident that toward the allantois its cells are cuboidal. The allantois consists of similar cells and contains a lumen. Over the greater part of the yolk-sac, however, the entoderm forms a very thin layer resembling endothelium, precisely as recorded by Beneke. In the most ventral portion there are occasional cuboidal cells with large round nuclei and protoplasm which projects above the general level into the cavity of the yolk-sac. The mesoderm of the yolk-sac is also very thin, and shows neither vessels nor distinct blood islands (see Fig. 226).

A reconstruction of Herzog's embryo, cut through at right angles with the plane of section, is shown in Fig. 227. The model will be more readily understood in comparison with a similar view of a somewhat older embryo, Fig. 228. In both cases the amniotic cavity sends a prolongation, torn in Herzog's specimen, toward

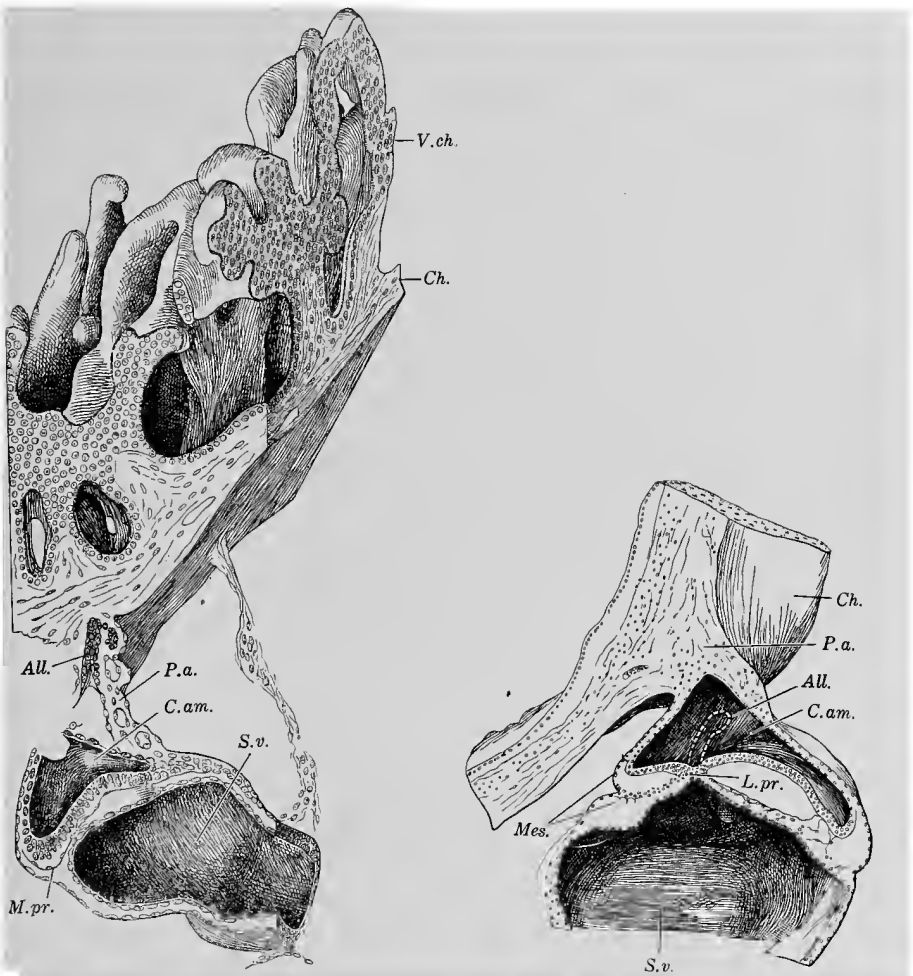

FIG. 227.—Wax reconstruction of Herzog's embryo. The plane of section is transverse to the axis of the embryo. ×100 diam. *All.*, allantois; *C.am.*, amniotic cavity; *Ch.*, chorion; *M.pr.*, membrana prima; *P.a.*, body-stalk; *S. v.*, yolk-sac; *V.ch.* (villi choriales), chorionic villi.

FIG. 228.—Wax reconstruction of Minot's embryo, showing the part corresponding with that drawn in Fig. 227. ×50 diam. *L.pr.* (linea primitiva), primitive streak; *Mes.*, mesoderm. Other abbreviations as in Fig. 227.

the chorion; and in both the amniotic cavity is asymmetrical, extending farther toward the left of the embryo (which is on the right of the figure). In Herzog's specimen the prolongation of the amniotic cavity toward the left is at first tubular; it is then reduced to a solid clump of cells, lodged between the entoderm

and mesoderm of the yolk-sac, and closely applied to the latter (see Fig. 226).

The body-stalk contains the allantois, which is apparently disintegrated near its tip. The terminal sections, however, are well preserved, and the extremity of the allantois is probably recurved. The body-stalk contains also rings of cells, some of them very near the surface. It is not certain that these represent blood-vessels—which would be the first to appear in the embryo—as Herzog interpreted them, and yet it is clear from later stages that the blood-vessels in the body-stalk arise very early. Jung has carefully described similar rings in the body-stalk of his specimen. There are occasional clefts in the mesoderm of the chorion in Herzog's embryo, but they are of doubtful significance. As seen in the reconstruction, a strand of mesoderm extends between the yolk-sac and chorion much as in Peters's specimen.

Von Spee's Embryo "v. H."—In 1896 von Spee published a notable contribution to human embryology, to which reference has already been made. In it he describes an embryo, designated "v. H.," which has heretofore been placed next to Peters's specimen, but which seems older than Herzog's for the following reasons. The axis of the embryo is said to be represented by a *primitive groove* (not well defined, however) which is absent in Herzog's embryo; the mesoderm extends between the ectoderm and the yolk-sac, reaching the median line; the entoderm of the yolk-sac is not flat, but is cuboidal throughout; the mesoderm of the ventral portion of the yolk-sac is thrown into elevations by the blood islands within it. The age of "v. H.," obtained through abortion following influenza five weeks after the end of the last catamenia, has been estimated as 17 to 18 days.

Minot's Embryo. The Primitive Knot.—Hensen (1875), in describing the primitive streak of the rabbit, stated that anteriorly it developed a disk-shaped termination, which he designated as a "knot." He found that the layer of entoderm could be stripped from the embryo except at the knot, where it tore. There the ectoderm and entoderm are intimately blended. This *primitive knot* (often called Hensen's knot) is shown in the reconstruction of a human embryo in Fig. 229. It is possible that it is represented in one section of Herzog's embryo (Fig. 11 of his publication), but von Spee did not find it in "v. H." Toward the allantois from the primitive knot, as seen in Fig. 229, the primitive groove is found, along which the mesoderm fuses with the ectoderm, as shown in the cross section, Fig. 228. Anterior to the primitive knot the thick ectoderm forms the medullary plate, but the medullary groove has not yet appeared. Beneath the medullary plate the mesoderm extends from side to side across the

median line. These conditions are noted as determining the stage of development of this specimen.[3]

The entodermal tract in this embryo still consists of only two parts, the yolk-sac and allantois. As compared with Herzog's

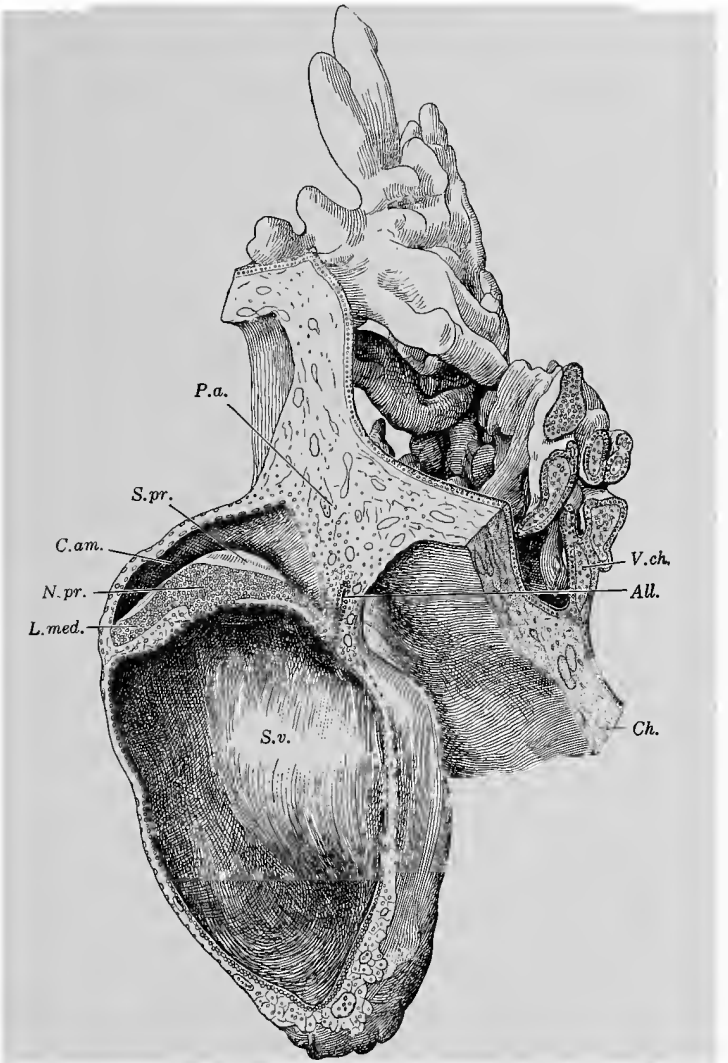

FIG. 229.—Wax reconstruction of Minot's embryo, showing a median sagittal section. ×50 diam *All.*, allantois; *C.am.*, amniotic cavity; *Ch.*, chorion; *L.med.* (lamina medullaris), medullary plate; *N.pr.* (nodulus primitivus), primitive knot; *P.a.*, body-stalk; *S.pr.* (sulcus primitivus), primitive groove; *S.v.* yolk-sac; *V.ch.*, chorionic villi.

specimen, the allantois has increased in length from about 0.12

[3] The specimen, in the form of an intact chorionic vesicle already hardened and in alcohol, was placed at the writer's disposal by Professor Minot, and it may be referred to as Minot's embryo. A full account of it is in preparation, justified by its superb preservation.

to 0.20 mm. It is slightly expanded distally but is not recurved. There is a minute lumen, and the structure connects with the yolk-sac by a small funnel-shaped enlargement. The yolk-sac has grown more rapidly than the allantois, its transverse diameter having increased approximately from 0.25 to 0.75 mm. In the ventral portion of the yolk-sac the entoderm now consists of cuboidal cells, and the mesoderm has been curiously transformed, as shown in Fig. 230. The cells are large and extensively vacuolated, so that the protoplasm in places is reduced to strands. The nuclei are large, round, and pale, each containing a very delicate chromatic reticulum and often a single conspicuous knot of chro-

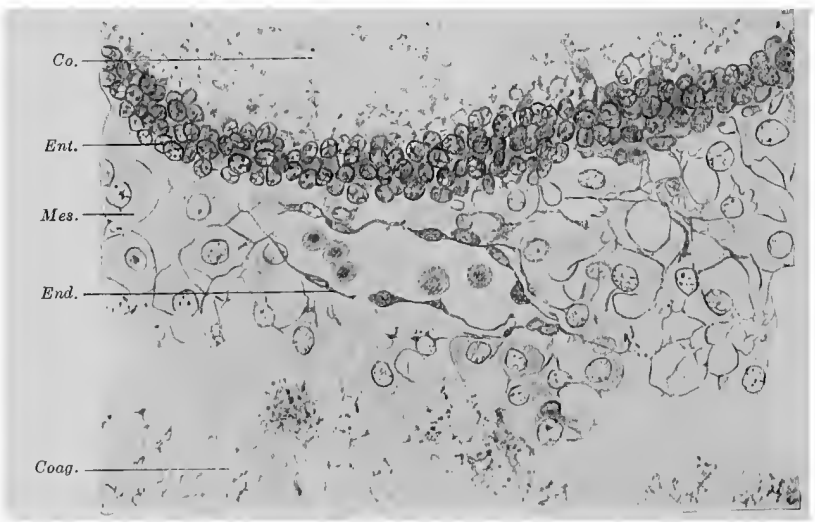

FIG. 230.—A portion of the ventral wall of the yolk-sac of Minot's embryo (Harvard Collection, Series 825, Section 18). ×280 diam. *Co.*, coagulum in the yolk-sac; *Coag.*, coagulum in the chorionic cavity; *End.*, endothelium lining a blood-vessel containing five blood-corpuscles, one of which shows a vesicular nucleus; *Ent.*, entoderm, and *Mes.*, mesoderm of the yolk-sac.

matin. Among these mesodermal cells blood-vessels have appeared, lined by true endothelium. They contain blood-corpuscles, characterized by finely reticular protoplasm, ill-defined cell-membranes, and nuclei which may be round, with distinct chromatin granules, or irregularly shrunken and deeply stained. Sometimes a corpuscle is closely applied to the endothelium as if arising from it.

In a very few places the entoderm of the ventral surface of the yolk-sac sends a prolongation into the mesoderm. In one case the outgrowth is solid, in another it contains a cavity in its outer part, and in a third a detached entodermal cyst is found near the surface of the mesoderm. These appear to be chance irregularities in the expansion of the yolk-sac.

There is granular coagulum within the yolk-sac, and also in the chorionic cavity, but there are no globular formations as in

Peters's specimen. Eternod examined the yolk-sac of a young human embryo (the age is not stated) removed by operation and still living. He states (1906, p. 256), "The very transparent liquid, which fully distended the yolk-sac, had a beautiful golden-yellow color comparable with that of the yolk in the eggs of salmon or trout. Under the influence of light, in a few moments, the color clouded and faded, becoming opalescent." In sections of very young human embryos he found entodermal cells projecting into the yolk-sac or detached and floating within it. In the Minot specimen it is very difficult to find a floating cell, but in embryos less well preserved they occur frequently. To what extent the contents of the human yolk-sac has a nutritive function is wholly undetermined.

In the Minot embryo the lining of the yolk-sac is a simple layer throughout (it is obliquely cut in Fig. 230). In the dorsal half of the sac the entodermal cells are quite flat. The mesoderm also becomes a thin layer, and the blood-vessels are very small. Apparently those in the yolk-sac do not pass into the body-stalk, which, however, contains numerous vessels. There are also many spaces in the chorion, especially near its lower surface, which are probably true vessels. Frequently these contain strands of darkly staining cells, suggesting collapsed endothelium. Similarly in the slightly older Frassi embryo there are "vessels on the yolk-sac, in the body-stalk, and the adjacent chorion; no vessels in the embryo proper." From the study of the specimens thus far considered it appears that the yolk-sac is not the only source of blood-vessels, but that they arise also in the body-stalk and chorion. Recently Dandy has reached this conclusion from the study of an older embryo.

Von Spee's "Gle." Neurenteric Canal. Chordal Plate. Beginning of the Fore-gut.—At a slightly later stage than that just described, a canal develops through the primitive knot, by which the cavity of the amnion communicates with that of the yolk-sac. This *neurenteric canal* has not formed in Minot's embryo, and in the Frassi embryo an aperture could not be demonstrated. Beneke recorded a neurenteric canal in his younger specimen, but his account is not convincing.

Von Spee, however, found a very large canal in an embryo designated "Gle" (1889). The specimen was obtained by spontaneous abortion five weeks after the end of the last catamenia, and Bryce and Teacher estimate its age as 19–20 days. A diagrammatic median section of the embryo is shown in Fig. 231, *A*. Before the embryo was sectioned it was made transparent with turpentine. In the position of the primitive knot (that is, between the anterior end of the primitive groove and the posterior end of the medullary groove) a ring-shaped elevation was seen, 0.13 mm.

in diameter, pierced by a central aperture 0.02 mm. wide. In the series this opening was found in four sections, one of which is shown in Fig. 231, *B*. It will be seen that at the neurenteric canal the ectoderm is continuous with the entoderm. The mesoderm does not form any part of its wall.

Eternod (1899) has recorded two other cases of open neurenteric canals, one in an embryo very much like "Gle," measuring 1.3 mm., the other in an older specimen, measuring 2.11 mm.

The entoderm lining the yolk-sac in "Gle" resembles that in the Minot embryo, except that just beneath the medullary groove

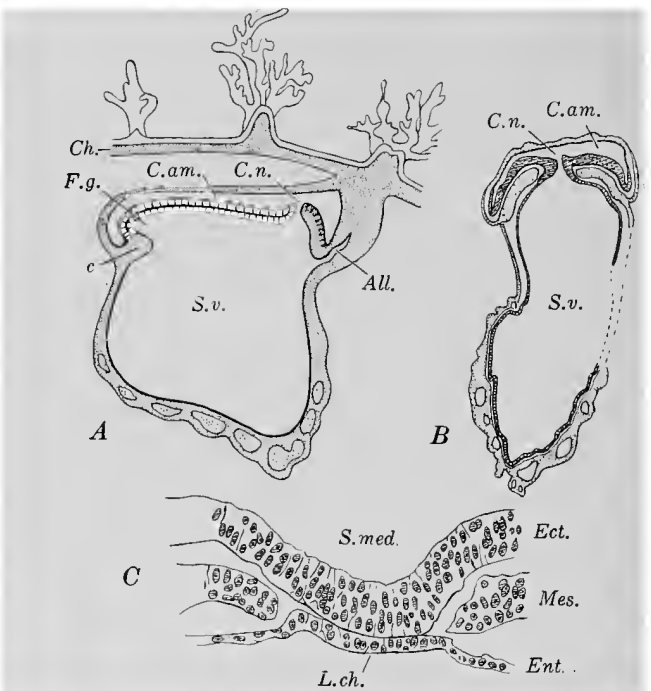

FIG. 231.—Sections of von Spee's embryo "Gle." *A*, median sagittal section from a model; *B*, transverse section through the neurenteric canal, *C.n.*; *C*, portion of a transverse section showing the chordal plate, *L.ch.* (After von Spee.) *F.g.*, "fore-gut;" *S.med.* (sulcus medullaris), medullary groove. Other abbreviations as in preceding figures.

it exhibits a plate of low columnar cells (Fig. 231, *C*). This *chordal plate* gives rise to the notochord and perhaps to a portion of the intestinal epithelium. It begins at the anterior margin of the primitive knot, with which it is continuous. It extends forward as far as the yolk-sac is in contact with the medullary plate. In the anterior part of the embryo there is a slight forward prolongation of the yolk-sac, which is the beginning of the fore-gut (Fig. 231, *A*). The heart is developing in the fold of mesoderm just beneath it. At the opposite end of the embryo the allantois takes a somewhat zigzag course in the body-stalk. Certain portions of

the mesoderm of the body-stalk, as stated by von Spee, are very rich in spaces, some of which have a smooth lining of flat cells

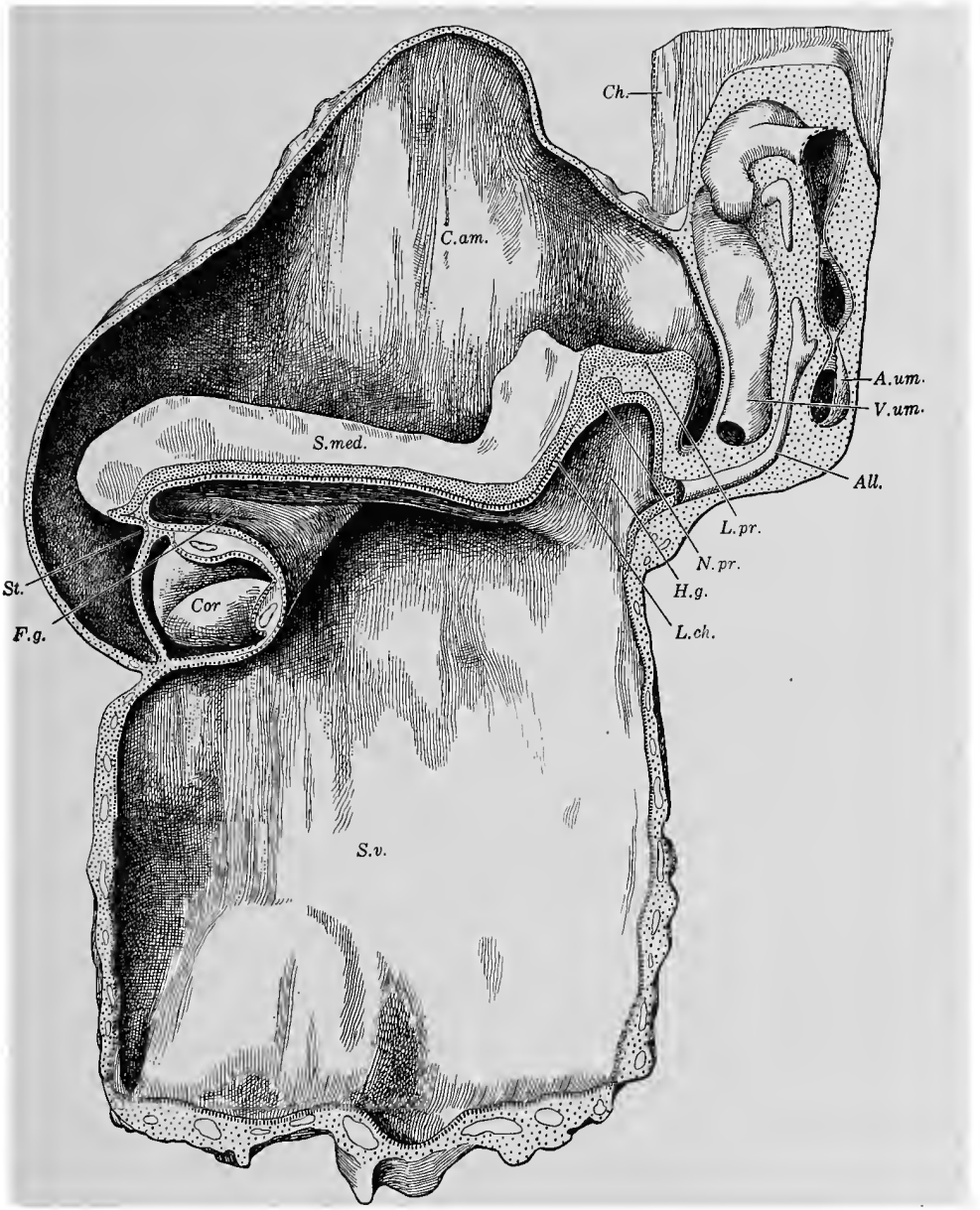

FIG. 232.—Wax reconstruction of Mall's Series 391, showing a median sagittal section of the embryo. ×50 diam. *All.*, allantois; *A. um.*, arteria umbilicalis; *C. am.*, amniotic cavity; *Ch.*, chorion; *Cor*, heart; *F.g.*, "fore-gut;" *H.g.*, "hind-gut;" *L.ch.*, chordal plate; *L.pr.*, primitive streak; *N.pr.*, primitive knot; *S. med.* (sulcus medullaris), medullary groove; *St.*, stomodæum; *S. v.*, yolk-sac; *V. um.*, vena umbilicalis.

like those of embryonic endothelium. The hind-gut has not yet appeared.

Mall's Series 391. Formation of the Hind-gut.—In the Mall collection there is an embryo with seven pairs of somites, measuring about 2 mm. in length, which has recently been described by Dandy. It was obtained through abortion, mechanically induced, and its age is estimated at about 24 days. Fig. 232 is from a model of the embryo, and shows a median longitudinal section.[4] The back bends sharply downward toward the cavity of the yolk-sac. Such flexures occur frequently, but not invariably, in embryos of about this age, and are probably due to imperfect preservation. "The fore-gut is present in thirty-two sections representing a length of 320 microns." It ends blindly in front, and, according to Dandy, it is separated by mesoderm from the ectodermal depression (or stomodæum) which gives rise to the mouth. The presence of intervening mesoderm is, however, difficult to make out, since the tissues are somewhat fragmented in this region. The fore-

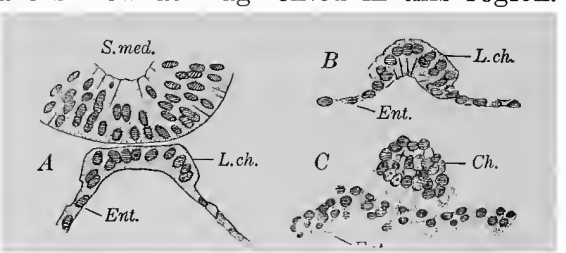

FIG. 233.—Sections showing the separation of the notochord from the digestive tract. *A*, from Mall's Series 391, ×360 diam.; *B*, section in the region of the first pair of somites, and *C*, in the caudal region, of Low's embryo. (*B* and *C* after Low.) *Ch.* (chorda), notochord; *Ent.*, entoderm of the digestive tract; *L. ch.*, chordal plate; *S. med.*, medullary groove.

gut shows a lateral expansion, which is the first pharyngeal pouch. Beneath the fore-gut the heart is well developed.

"The hind-gut is a blind pouch 120 microns in length by sections, but on account of the dorsal kink of the embryo the actual length is somewhat greater." It does not come in contact with the ectoderm so as to form a cloacal membrane (where the anus will later appear), but the bend in the embryo may possibly have caused the separation of the layers. In the decidedly younger Frassi specimen the beginning of the cloacal membrane is said to be present. In Mall's embryo the allantois arises from the ventral surface of the hind-gut and passes into the body-stalk, accompanied by very large umbilical vessels. The allantois has a knob-like branch. The distal end of the allantois is apparently detached. In both portions a narrow lumen is found.

The chordal plate (Fig. 233, *A*), extending along the mid-dorsal line of the yolk-sac, is more sharply defined than in "Gle."

[4] Through the kindness of Professor Mall, the writer has been permitted to study this embryo and prepare a figure to correspond with that of the Minot specimen. This work has been greatly facilitated by Mr. Dandy's publication.

In an embryo of 13–14 somites, described by Low (1908), the chordal plate is still a portion of the wall of the yolk-sac anteriorly (Fig. 233, *B*), but it has completely separated from it posteriorly (Fig. 233, *C*. See also Kollmann, 1890). In older embryos it is detached throughout, and the further history of the notochord, or chorda dorsalis, will be found in the chapter on the development of the skeletal system.

The Cloacal Membrane, Caudal Intestine, and the Later History of the Primitive Knot.—In the Mall specimen the chordal

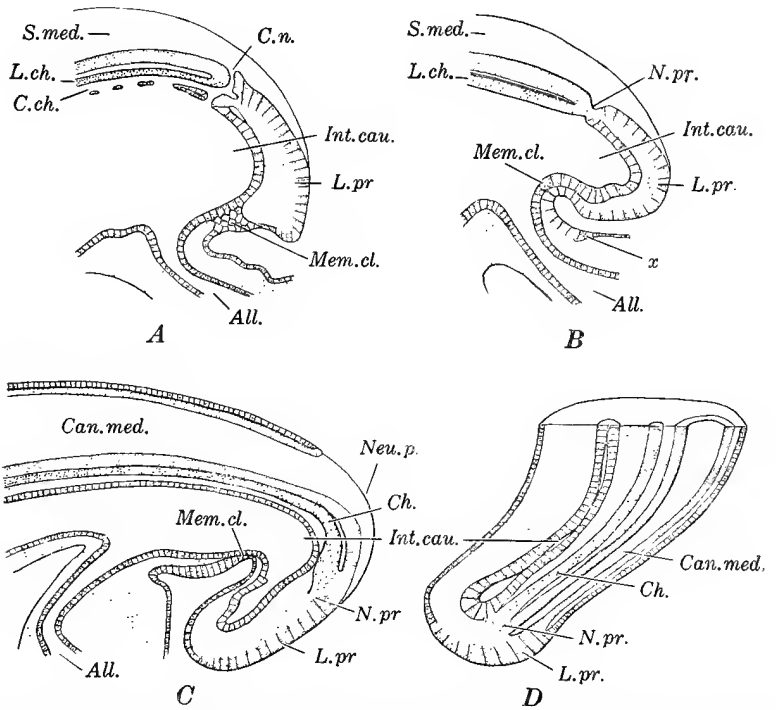

Fig. 234.—Median sagittal sections through the region of the primitive knot. All ×75 diam. *A*, Eternod's embryo with 8 pairs of somites (after Eternod); *B*, sketch of the "Kroemer-Pfannenstiel" embryo, based upon sections published by Keibel and Elze; *C*, Bremer's 4 mm. embryo; *D*, distal portion of the tail of a 7.5 mm. specimen. *All.*, allantois; *Can. med.* (canalis medullaris), medullary tube; *C. ch.*, chordal canal; *C. n.*, neurenteric canal; *Ch.*, chorda; *Int. cau.*, intestinum caudale; *L. ch.*, chordal plate; *L. pr.*, primitive streak; *Mem. cl.*, membrana cloacalis; *Neu. p.*, posterior neuropore, the last part of the medullary groove to close; *N. pr.*, primitive knot; *S. med.*, medullary groove; *x*, extension of the primitive streak (?) beyond the cloacal membrane.

plate ends posteriorly in a rounded knot of tissue in connection with the ectoderm. This is clearly the primitive knot, posterior to which is the primitive streak. There is no neurenteric canal. This region in a similar embryo (2.1 mm. long, with eight pairs of somites) has been figured by Eternod (1906 [2]), as seen in Fig. 234, *A*. The neurenteric canal is still present and leads anteriorly into a chordal canal, the floor of which is formed by detached cells, and the roof of which is the chordal plate. Such a chordal canal

in human embryos has apparently not been found by other observers. Posterior to the neurenteric canal the primitive streak extends to the cloacal membrane, which is "composed of a mass of epithelial cells." In an embryo of 5 to 6 pairs of somites, of which Keibel and Elze have published a series of sections, it is possible that the relations are as shown in Fig. 234, *B*. The dorsal and ventral openings of the neurenteric canal can be found, but the middle part is not pervious. The primitive streak extends to the cloacal membrane, which is described as "the thickened ectoderm applied to the thickened entoderm." Thus the primitive streak passes around from the dorsal to the ventral side of the embryo.

Keibel and Elze believe that the primitive streak extends beyond the cloacal membrane along the body-stalk, for in several sections the ectoderm covering the body-stalk shows a local thickening which is nearly in contact with the allantoic duct.[5] The occasional occurrence of a bladder opening freely along the ventral body wall (*exstrophia vesicæ*) may be connected with this relation. It seems probable, however, that the thickened epithelium along the body-stalk is due to a prolongation of the cloacal membrane in the urogenital area, and that it is not a part of the true primitive streak. The primitive streak is formed by a fusion of ectoderm and mesoderm, but the cloacal membrane is a fusion of ectoderm and entoderm. According to Keibel, however (1896), the cloacal membrane should be regarded as a modified part of the primitive streak, and exstrophia vesicæ represents a persistent portion of the blastopore.

In an older embryo, measuring 4 mm. (Fig. 234, *C*), the position of the primitive knot can still be located. There the notochord ends and the primitive streak begins. It will be observed that the hind-gut has extended beyond the cloacal membrane into the tail. This prolongation is named the caudal (or postanal) intestine.

The tip of the tail of a 7.5 mm. embryo is shown in Fig. 234, *D*. It is still possible to recognize the primitive knot, which at this stage is commonly called the "tail-bud." The notochord terminates in this bud; the caudal intestine fuses with it ventrally, the extremity of the medullary tube dorsally, and the mesoderm laterally. In the 2.11 mm. specimen described by Eternod (Fig. 234, *A*) there is a short prolongation of the chordal canal beyond the neurenteric canal, but there is apparently no other evidence that the notochord ever extends beyond the primitive knot. In a 2.1 mm. specimen described by Mall the obliterated neurenteric

[5] It may be noted that His described the medullary groove as extending along the body-stalk. Anatomie menschlicher Embryonen, iii, p. 224.

canal, represented by a solid cord of cells, is said to communicate with the medullary tube (1897, p. 419). "The location is opposite the twelfth muscle plate, or in the neighborhood of what will later be the position of the first rib." But the location is also at the posterior end of the notochord which will later be near the tip of the tail. It seems probable that if a neurenteric canal should persist it would be found opening externally beyond the limit of the spinal cord and its *filum terminale,* in the coccygeal region.[6]

Marwedel (1901) has described a case which may be interpreted as a neurenteric canal leading into the detached end of the caudal intestine. A child thirteen days old was found to have a sac, 6 cm. long, lined with mucous membrane similar to that of the large intestine and surrounded by muscle coats, opening to the surface between what were "evidently the *cornua sacralia* of the lowest sacral vertebra." The sac had no connection with the rectum or anus.

It should be noted that congenital cysts and sinuses in the coccygeal region are frequent (Mallory, 1892), but they are ectodermal structures, and the persistence of a neurenteric canal has not yet been satisfactorily demonstrated.

The Pharyngeal Membrane and the Præ-oral Intestine.—In describing Mall's specimen with seven pairs of somites, it was

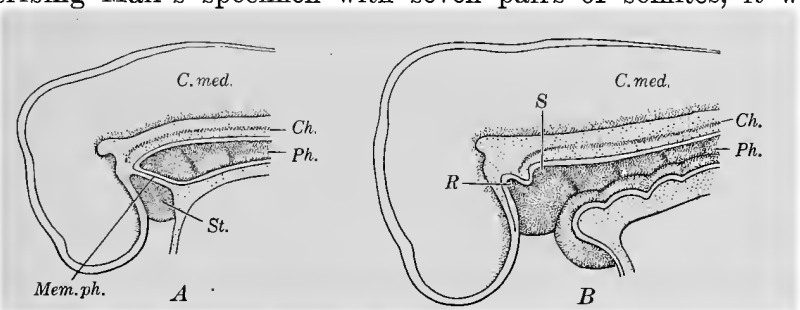

FIG. 235.—The pbaryngeal membrane as figured by His. ×37 diam. *A*, embryo "Lg," 2.15 mm.; *B*, embryo "BB," 3.2 mm. *Ch.*, chorda; *C. med.*, medullary tube; *Mem. ph.*, membrana pbaryngea; *Ph.*, pharynx ("fore-gut"); *R.*, Rathke's pocket (anterior lobe of tbe bypopbysis); *S.*, Seessel's pocket; *St.*, stomodæum.

stated that the anterior end of the fore-gut comes in contact with an ectodermal pouch called the stomodæum or buccal sinus. There the ectoderm unites with the entoderm to form the pharyngeal (or buccopharyngeal) membrane. This membrane is clearly shown in an embryo 2.15 mm. long, as figured by His (Fig. 235, *A*). The digestive tract at this stage has no anterior opening. Just in front of the pharyngeal membrane the ectoderm forms a pocket extending toward the base of the brain. Although this pocket is now generally called the hypophysis, or more precisely the anterior lobe of the hypophysis, it is often referred to embryologically as Rathke's pocket.

In 1838 Rathke described it as follows: "For a long time I have observed in several animals . . . a small irregularly rounded depression which belongs

[6] Professor Mall now regards this embryo of 2.1 mm. as pathological.

to the mucous membrane of the mouth, of which it is clearly a thin-walled outpocketing. . . . Finally I saw that this depression represents the first step in the formation of the pituitary gland" (p. 482). The animals studied included sheep and pig embryos.

On the entodermal side of the pharyngeal membrane a much smaller pocket bulges toward the brain.

This was discovered by Seessel in the chick (1877). He wrote: "Shortly after the hypophyseal pocket has become distinctly formed, on about the fourth day, near and under it a second pocket-like outgrowth of the intestinal layer is seen. . . . Its length compared with that of the hypophysis is as 1:5."

Although His considered that both pockets were represented in the 2.15 mm. embryo, they are better defined in a specimen measuring 3.2 mm. (Fig. 235, *B*). The pharyngeal membrane has largely disappeared. "As the remains of it, there is only the prominence inserted between Rathke's pocket and Seessel's accessory pocket."

In sheep embryos von Kupffer (1894) found a solid entodermal outgrowth extending forward from Seessel's pocket, closely connected with the notochord. Later this mass of cells becomes detached and appears as an appendage of the notochord. It was interpreted as a rudimentary præ-oral intestine. Bonnet (1901) identified a similar structure, but with a lumen, in a dog embryo with sixteen pairs of segments, and Zimmermann (1899) found three sharply defined little cavities near Rathke's pocket in a human embryo of 3.5 mm. These cavities may have been derived from a præ-oral intestine; they are at present the only evidence of such a structure in human embryos.

Thompson's Embryo. Early Stages of the Thyreoid Gland, Lungs, and Liver.—An embryo 2.5 mm. long, with 23 pairs of somites, has been modelled by Thompson (1907). The entodermal tract is shown in Fig. 236, in which the embryo is arbitrarily placed in an upright position, with its ventral surface toward the left of the figure. The yolk-sac has been cut away. It was connected with the intestine by a somewhat constricted neck, called the *vitelline duct,* a part of which is shown in the figure. In ventral view the connection between the duct and the intestine would appear as an elongated opening near the middle of the straight intestinal tube.

The pharynx is separated from the mouth by the pharyngeal membrane, which is already perforated. There is no trace of Rathke's pocket. Four pharyngeal pouches are present, but they are not indicated in the figure. In the median line, connected with the floor of the pharynx, there is a small, hollow, rounded diverticulum, which is the beginning of the thyreoid gland. In earlier stages it has a less constricted neck, as found by Low (1908) in a specimen with 13 or 14 pairs of somites. Posterior to the pharyngeal pouches the entodermal tube suddenly narrows. It becomes compressed laterally so that it has a cleft-like lumen. In this

portion of the entodermal tract, a short distance beyond the fourth pharyngeal pouches, the lungs are indicated by a pair of lateral outgrowths (Thompson), and perhaps by the ventral swelling which is shown in Thompson's figure but not labelled.[7] Beginning with the region where the lung outgrowths are found, and extending backward as far as the liver-bud, the epithelium is markedly thickened.

The liver-bud is a median ventral knob-like outgrowth of the

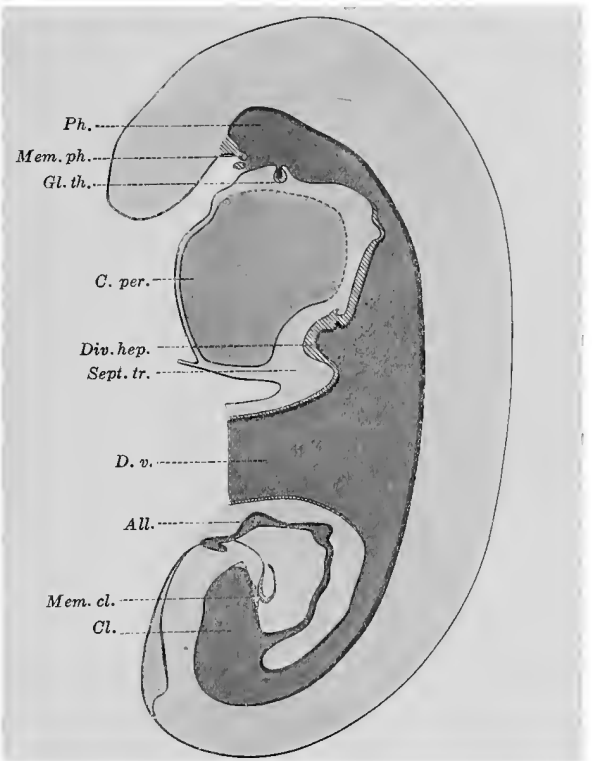

FIG. 236.—Graphic reconstruction of an embryo with 23 paired somites, showing a median sagittal section of the digestive tract. ×40 diam. (After Thompson.) *All.*, allantois; *Cl.*, cloaca; *C. per.*, cavum pericardii; *Div. hep.* (diverticulum hepaticum), liver bud; *D. v.*, ductus vitellinus; *Gl. th.*, glandula thyreoidea; *Mem. cl.*, membrana cloacalis; *Mem. ph.*, pharyngeal membrane; *Ph.*, pharynx; *Sept. tr.*, septum transversum.

digestive tube, extending into the *septum transversum*, which is the layer of mesoderm between the pericardial cavity and the vitelline duct. The hepatic bud contains a cavity which communicates freely with the alimentary canal. There is no trace of the pancreas.

[7] According to Grosser, the pulmonary area in this embryo has been erroneously regarded as the gastric portion of the intestine by Thompson and also by Keibel and Elze (Normentafel, Embryo Nr. 7). In Thompson's embryo the stomach has not yet developed. Compare with Grosser's description of the development of the lungs at the end of this chapter.

Beyond the vitelline duct is the hind-gut, with a rounded lumen. It expands at the cloaca, where it joins the allantois, and extends a short distance into the tail. The allantois is a small tubular structure with two marked dilatations and, at its distal end, "a small swelling bent upon itself."

Separation of the Œsophagus from the Trachea.—In an embryo which has the general shape of Thompson's specimen, but which is somewhat more advanced (Bremer, 1906), the lungs and trachea form a pear-shaped mass attached to the ventral border of the œsophagus. The lower portion of the mass, which bulges toward either side, represents the division of the trachea into the bronchi. Its cavity is still in free communication with that of the œsophagus. The trachea will become separated from the œsopha-

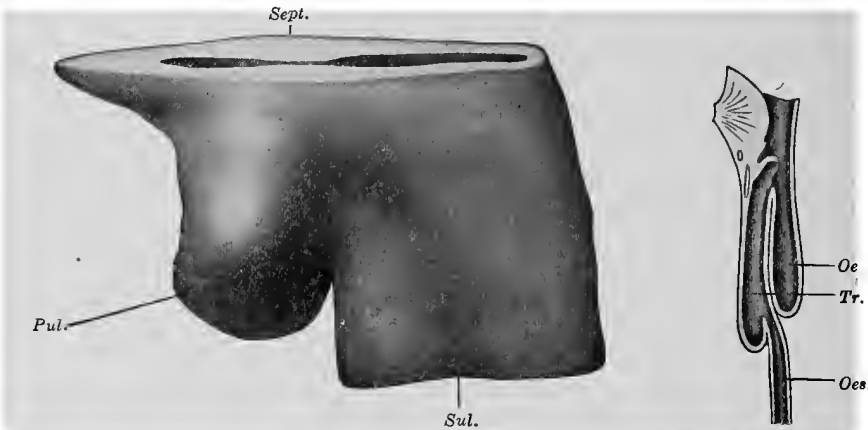

FIG. 237.—Wax model from Bremer's 4 mm. embryo, showing the "lung-bud," *Pul.*, and the adjacent part of the œsophagus. ×175 diam. *Sept.*, tracheo-œsophageal septum; *Sul.*, lateral œsophageal groove.

FIG. 238.—Abnormal communication between the œsophagus, *Oes.*, and the trachea, *Tr.* The upper portion of the œsophagus, *Oe.*, ends blindly below. (After Keith.)

gus by the down-growth of the lung-bud and the upward extension of the notch between the lung-bud and the œsophagus. The notch extends upward following a fusion of the lateral walls of the fore-gut, which begins from below (His, 1885, p. 17–18). The approximation of the lateral walls to form the tracheo-œsophageal septum is seen at the top of Fig. 237.

In the most common anomaly of the œsophagus, which must arise at the stage under consideration, the œsophagus is transversely divided into two parts. The upper portion ends blindly below, and the lower portion arises from the trachea near its bifurcation (Fig. 238), or even from a bronchus, into which its lumen opens.

This malformation is detected soon after birth, since milk cannot enter the stomach. Happich (1905) has tabulated the records of 59 cases. Sometimes the

two portions of the œsophagus are connected by a strand containing smooth muscle-fibres, but "it is entirely unknown whether there is any remnant of epithelium in the interval." No epithelial connection has been recorded. Although this complex anomaly is common, a simple communication between œsophagus and trachea, when these are otherwise normal, is extremely rare. Forssner (1907) and Giffhorn (1908) have discussed the origin of the divided œsophagus and explained it with diagrams.

To produce the common form of the anomaly the lower portion of the tracheo-œsophageal septum must fail to develop, thus leaving the œsophagus in communication with the lower part of the trachea. In the model shown in Fig. 237 there is externally, on either side of the œsophagus, an oblique depression in the epithelium with a corresponding internal elevation. It is so situated that if the walls of the œsophagus should coalesce along this groove a ventral portion would be cut off, communicating freely with the trachea near its bifurcation. The groove does not reach the dorsal border of the œsophagus, but extends downward toward the liver. However, the part of the œsophagus dorsal to this groove has a narrower lumen than the ventral part; to produce the anomaly, this portion must become occluded. Apparently the lateral œsophageal groove, which seems correlated with the shape of the adjacent body-cavity, has not been previously described.

It has been thought that the closure of the œsophagus in the anomaly is due to the pressure of neighboring arteries, particularly the right dorsal aorta, and several cases have been found associated with the low origin of the right subclavian artery. Keith (1906) reported four cases, in three of which this abnormal artery was present and crossed to the right side between the two parts of the œsophagus. In the 4 mm. embryo, however, which is close to the stage in which the anomaly must arise, the arteries are not near this portion of the œsophagus. In the embryo of 4.9 mm. shown in Fig. 239 the separation of the œsophagus and trachea has proceeded so far that the anomaly could hardly develop.

The further history of the anterior portion of the digestive tract, including the mouth, pharynx, trachea, and lungs, will be presented by McMurrich and Grosser in separate sections of this chapter.

Ingalls's Embryo. The Formation of the Stomach and Pancreas.—Ingalls (1907) described an embryo measuring 4.9 mm., the digestive tract of which is shown in Fig. 239. Rathke's pocket is present; nothing is said of Seessel's pocket. The pharyngeal membrane has entirely disappeared. The thyreoid gland is still connected with the pharynx, as in Thompson's specimen. The trachea is quite separate from the œsophagus.

"The œsophagus is a tube, circular in cross section, which has thinner walls and is much narrower than the ventrally placed trachea. In the region of the fourth cervical segment it becomes gradually larger, its walls thicken, and at the same time it becomes flattened laterally. Thus it forms the stomach, and the digestive tube then assumes an oblique position, with its ventral border turned somewhat to the right and its dorsal border correspondingly to the left. . . . At its caudal end, where it passes over into the duodenum, the stomach again becomes very narrow." (P. 549–550.)

At this stage, as shown in the figure, the stomach is a well-defined spindle-shaped enlargement of the fore-gut.

The liver has become very large. From the knob-like diverticulum, such as was seen in Thompson's specimen, a great mass of anastomosing cords of cells has grown out, invading the septum transversum. In a cross section of the embryo this mass is

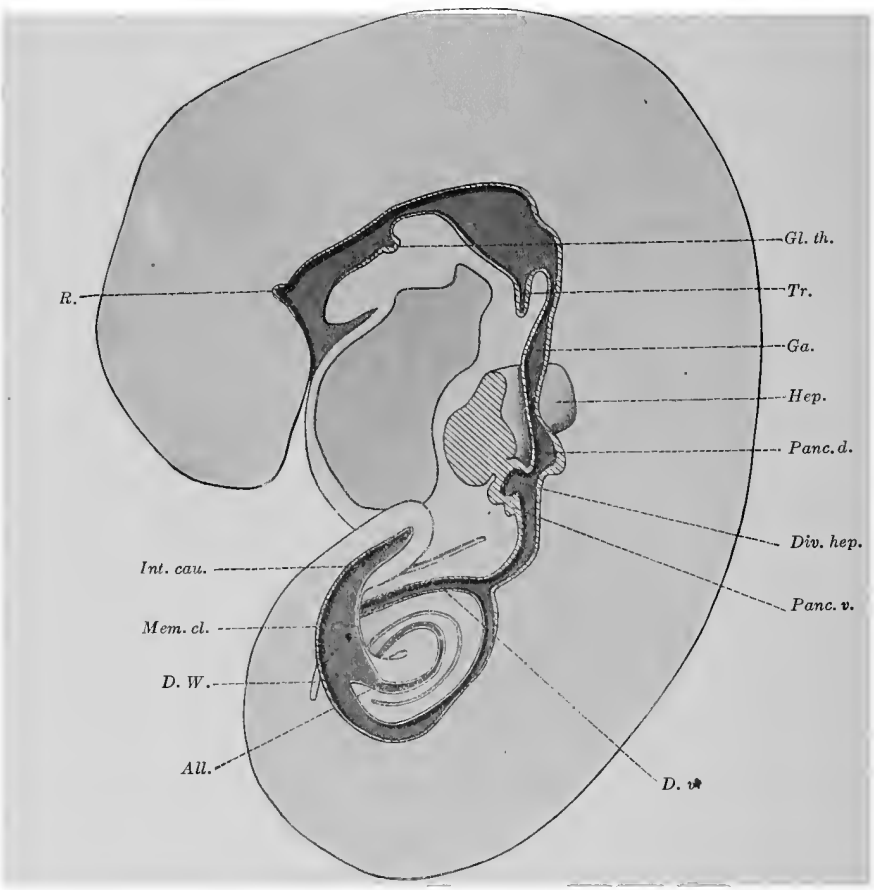

FIG. 239.—The digestive tract of an embryo of 4.9 mm., shown in median sagittal section. ×24 diam. (After Ingalls.) *All.*, allantois; *Div. hep.*, diverticulum hepaticum; *D. v.*, ductus vitellinus; *D. W.* (ductus Wolffi), Wolffian duct; *Ga.* (gaster, ventriculus), stomach; *Gl. th.*, glandula thyreoidea; *Hep.*, medial surface of the right lobe of the liver (hepar); *Int. cau.*, intestinum caudale; *Mem. cl.*, membrana cloacalis; *Panc. d.*, pancreas dorsale; *Panc. v.*, pancreas ventrale; *R.*, Rathke's pocket; *Tr.*, trachea.

U-shaped, and the stomach and duodenum are lodged in the hollow of the U. In sagittal section, as in the figure, the part of the mass which crosses the median line has been cut through. It is shown in section. The inner surface of the right lobe of the liver has also been drawn.

The pancreas of the adult arises in the embryo as two separate organs, namely the *dorsal pancreas* and the *ventral pancreas*. In Ingalls's specimen, between the stomach and the common bile-duct,

the dorsal surface of the duodenum presents a thick-walled outpocketing, which is the beginning of the dorsal pancreas. The ventral pancreas grows downward from the lower side of the hepatic diverticulum, at its junction with the intestine. It is adherent to the wall of the intestine. It contains a minute lumen, not shown in the figure, which appears to communicate with the hepatic diverticulum. (A more detailed account of the development of the liver and pancreas will be found in subsequent sections of this chapter.)

The connection between the yolk-sac and the intestine in Ingalls's specimen is a slender vitelline duct, lined with a single layer of large cuboidal or cylindrical cells. The intestine bends ventrally toward its junction with the duct, and beyond this point is becomes much smaller. It then enlarges toward the cloaca and continues with a relatively large lumen into the tail. Toward the tip of the tail its wall becomes irregular in thickness.

The cloacal membrane does not consist of thickened ectoderm applied to thickened entoderm, as in a younger specimen already described. On the contrary, the ectodermal layer is here so thin that in places it can scarcely be recognized. The entodermal layer is also thinner than in the lateral walls of the cloaca. Keibel (1896) found the ectoderm of the cloacal membrane thinner than the entoderm in a 3 mm. specimen. At 4.2 mm. the layers were indistinguishable, and in discussing later stages he wrote, "The question, how much ectoderm and how much entoderm take part in the formation of the cloacal plate, must remain undecided."

In Ingalls's specimen the allantois shows two small expansions near its distal end. Proximally the allantois joins the cloaca, which is being gradually subdivided, in the cranio-caudal direction, by the growth of the cloacal septum. The Wolffian ducts empty into the ventral part of the cloaca, one on either side, and, although they are not of entodermal origin, they have been included in the accompanying figures.

Embryo of 7.5 mm. Detachment of the Yolk-sac. Origin of the Cæcum and Vermiform Process.—The entodermal tract in an embryo measuring 7.5 mm. is shown in Fig. 240. Rathke's pocket still has a broad connection with the oral cavity, but the thyreoid gland has become detached. The œsophagus is much longer than in Ingalls's specimen. It becomes gradually smaller toward the stomach and then enlarges, but there is no definite boundary between stomach and œsophagus. The epithelial portion of the stomach is flattened laterally, and is so placed that its left side faces somewhat ventrally and its right side dorsally. The stomach passes gradually into the duodenum, the diameter of which is considerably greater than that of the distal part of the small intestine.

The liver consists of a large mass of anastomosing cords of cells, connected with the hepatic diverticulum by a short thick stem which represents the hepatic duct. Distal to the hepatic duct the diverticulum gives rise to the gall-bladder and cystic duct. Proximal to the hepatic duct it forms the common bile-duct (*ductus choledochus*), and it connects with the ventral pancreas just before

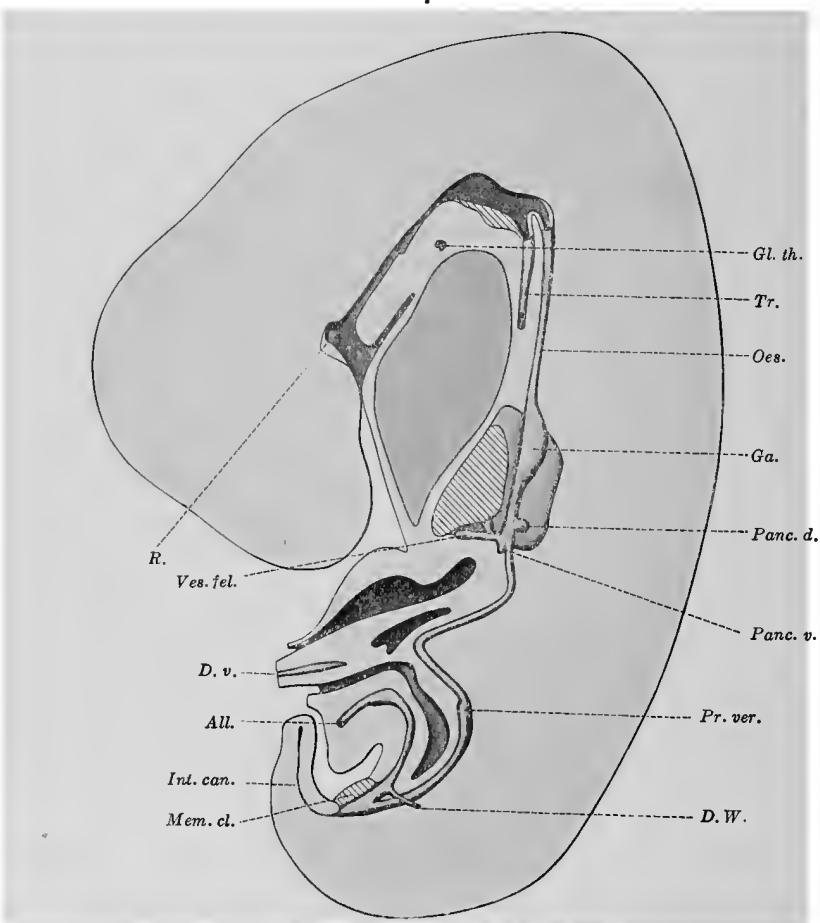

FIG. 240.—The digestive tract of an embryo of 7.5 mm. (Harvard Collection, Series 256). ×16 diam. In addition to the structures lettered as in Fig. 239, the following are shown. *Oes.*, œsophagus; *Pr. ver.*, a dilatation of the lower limb of the intestinal loop, which gives rise to the processus vermiformis and the cæcum, and which marks the boundary between the small intestine above and the large intestine below; *Ves. fel.* (vesica fellea), gall-bladder.

joining the duodenum. The dorsal pancreas is more sharply defined than in Ingalls's specimen.

The slight bend of the intestinal tube toward the vitelline duct, which is seen at 4.9 mm., has increased and now forms the important *primary intestinal loop*. The vitelline duct has become detached from the bend of this loop, and is separated from it by a considerable interval. It lies in a prolongation of the mesentery

which, together with its contents, is called the *yolk-stalk*. The fused vitelline veins lie in a portion of the stalk which has become separated from the rest, forming the upper subdivision shown in the figure.

The detachment of the vitelline duct usually occurs at about this stage. A similar condition has been figured by Elze (1907) in an embryo of "about 7 mm." and by Mall (1891) in a 7 mm. specimen. But sometimes the vitelline duct, reduced to a strand of epithelial cells, retains its connection with the intestine much longer. Keibel and Elze (1908) recorded its presence in an embryo of 12.4 mm. and Thyng has found it in a specimen measuring 13.6 mm. In about 2 per cent. of adults, according to several tabulations, a persistent pouch of the intestine, 3 to 9 cm. long, marks the place where the vitelline duct formerly opened into it. This *diverticulum ilei* of Meckel has already been described, and the pathological importance of persistent remnants of the yolk-stalk has been noted (p. 293). The further history of the detached vitelline duct, which extends through the umbilical cord, and of the yolk-sac, which is lodged between the amnion and chorion at the distal end of the cord, may be found in vol. i, p. 173–174. The account of the yolk-sac as a portion of the digestive tract may be concluded with the following note concerning its entodermal layer. In Bremer's 4 mm. specimen and in a 4 mm. embryo figured by Keibel and Elze, the entoderm presents numerous solid outgrowths and hollow outpocketings (Fig. 241, A). Toward the cavity of the yolk-sac the entoderm has a wavy outline. The gland-like structures were described by von Spee as follows (1896 [2]):

"Such glands arise as little outpocketings of the entodermal lining of the distal pole of the yolk-sac, but they rapidly become elongated sacs, which branch dichotomously, and soon develop expanded club-like or vesicular end-pieces. They extend through almost the entire thickness of the wall of the yolk-sac, but their blind ends remain separated from the body-cavity by a single layer of the mesoderm. The glands are lined by a single layer of prismatic entodermal cells, the protoplasm of which contains many fine vacuoles, and, especially in later stages, an increasing quantity of fat drops blackening with osmium."

In an embryo measuring 9.4 mm. (Fig. 241, B) these gland-like structures are found all over the yolk-sac. Most of them are closed cysts with walls of varying thickness. Occasionally distinct branching is seen. Von Spee believed that the yolk-sac in its glandular stage is an active organ comparable physiologically with the liver. Other investigators have questioned the glandular nature of the yolk-sac tubules, and Meyer (1904) states that, in spite of the large amount of material at his disposal, he is unable to reach any satisfactory conclusion as to the meaning of these

tubules. The entodermal cells of the yolk-sac have been found to contain granules which yield a typical mucin reaction (Jordan, 1907), and bundles of filaments which stain with iron hæmatoxylin (Branca, 1908). According to Branca, the superficial cells are provided with terminal bars, and, except within the glands, some of them show distinct cilia or brush borders. Jordan (1910) failed to find terminal bars or cilia. They do not appear in the specimens shown in Fig. 241, but the appearance which Branca described as a brush border is sometimes clearly seen. In later stages the epithelium lining the yolk-sac becomes stratified, and the diverticula and intra-epithelial cysts disappear. Thus, in an embryo of 23 mm. (Fig. 241, C) the epithelium consists of vacuolated degenerating cells. Subsequently these are lost, and the wall of the yolk-sac is then merely "a dense wavy layer of fibrous connective tissue." In this condition it is found at birth.

In the posterior half of the primary intestinal loop in the 7.5 mm. embryo (Fig. 240), there is an abrupt enlargement of the entodermal tube, which marks the boundary between small and large intestine. The expansion does not affect the dorsal border of the intestine, but is wholly a ventral bulging. The cavity of the large intestine extends slightly forward into the ventral swelling, so that in one section at this point there is a double lumen: the enlargement is therefore already a shallow pouch. This structure is generally considered to be the beginning of the *cæcum.* Keibel and Elze (1908) have noted that the cæcum is indicated in embryos measuring from 6.25 to 7.0 mm. But Tarenetzky (1881) described this enlargement as the *processus vermiformis.* "At this stage . . . a cæcum is not present." He found that an actual cæcum first appeared in an embryo of 65 mm. A distinction between the cæcum and the vermiform process in young human embryos is not easily made, and Toldt (1894) is probably correct in referring to the primary enlargement as the common origin of both. This question is further discussed on page 328.

In the 7.5 mm. specimen the large intestine curves forward to join the allantois at the cloaca. There is still no external opening. The caudal intestine, which in Ingalls's specimen had a wide lumen, is reduced to a strand of cells. Toward the tip of the tail a minute lumen is distinctly seen, ending in a terminal expansion (Fig. 234, *D*). In an embryo of 9.4 mm. (Fig. 242) the caudal intestine has disappeared, except for an isolated nodule of epithelium. Keibel and Elze have shown that it usually disappears at about this stage, but they found remnants of it in one specimen measuring 11.5 mm.

Embryo of 9.4 mm. Torsion of the Primary Loop of Intestine.—The intestinal tube in the 9.4 mm. embryo (Fig. 242) differs from that of the preceding stage chiefly through the disappearance

of the yolk-stalk and the torsion of the intestinal loop. (The considerable changes in the course of the bile-ducts will be described in a separate section.) The torsion of the intestine occurs, in a general way, as follows. The large intestine at first forms part of the posterior half of the intestinal loop, and the loop is in the median plane. Then the loop becomes rotated so that its plane is transverse. The anterior half is then on the right, and the posterior half on the left. Further rotation causes the posterior half to become anterior. In side view the large intestine then crosses the small intestine, as seen in Fig. 242. At a considerably later stage the torsion is completed by the migration of the cæcum

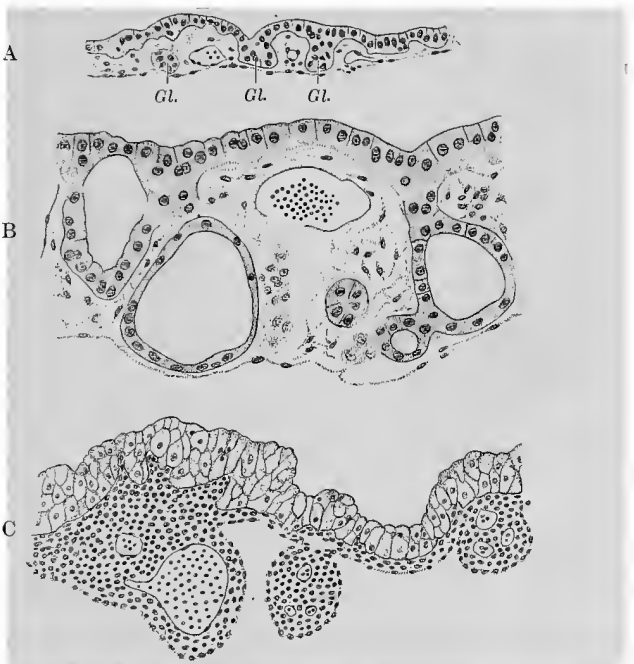

FIG. 241.—Sections of the wall of the yolk-sac. ×115 diam. A, embryo of 4 mm. (Harvard Collection, Series 714); B, embryo of 9.4 mm. (Harvard Collection, Series 529); C, embryo of 23.0 mm. (Harvard Collection, Series 192). Developing "glands," *Gl.*, are shown in A. They have become cystic in B. In C the yolk-sac is degenerating, and the "glands" have disappeared.

to the right side of the body and down toward the pelvis. When this has occurred, the large intestine passes from right to left, ventral to the upper part of the small intestine; it then descends to the rectum on the left of the small intestine.

In an interesting case of "imperfect torsion of the intestinal loop" reported by Reid (1908), the embryonic twisting evidently did not occur. In a man over sixty years of age he found that the cæcum was within the pelvis, a little to the right of the median line. The ascending colon passed gradually to the left, and most of it, together with all of the transverse and descending colon, was on the left side of the body. The small intestine was wholly on the right side, and was not crossed by the large intestine. Similar cases have been described by Faraboeuf

(1885), Descomps (1909), and others. A reversal of the intestinal torsion, which would cause the colon to pass *under* the small intestine, has apparently never been seen.

Embryo of 22.8 mm. The Normal Umbilical Hernia.—

Since 1817, when Meckel published an account of the "formation of the intestinal canal of mammals and particularly of man," it has been well known that, at a certain stage, "the greatest part of the intestinal canal is found within

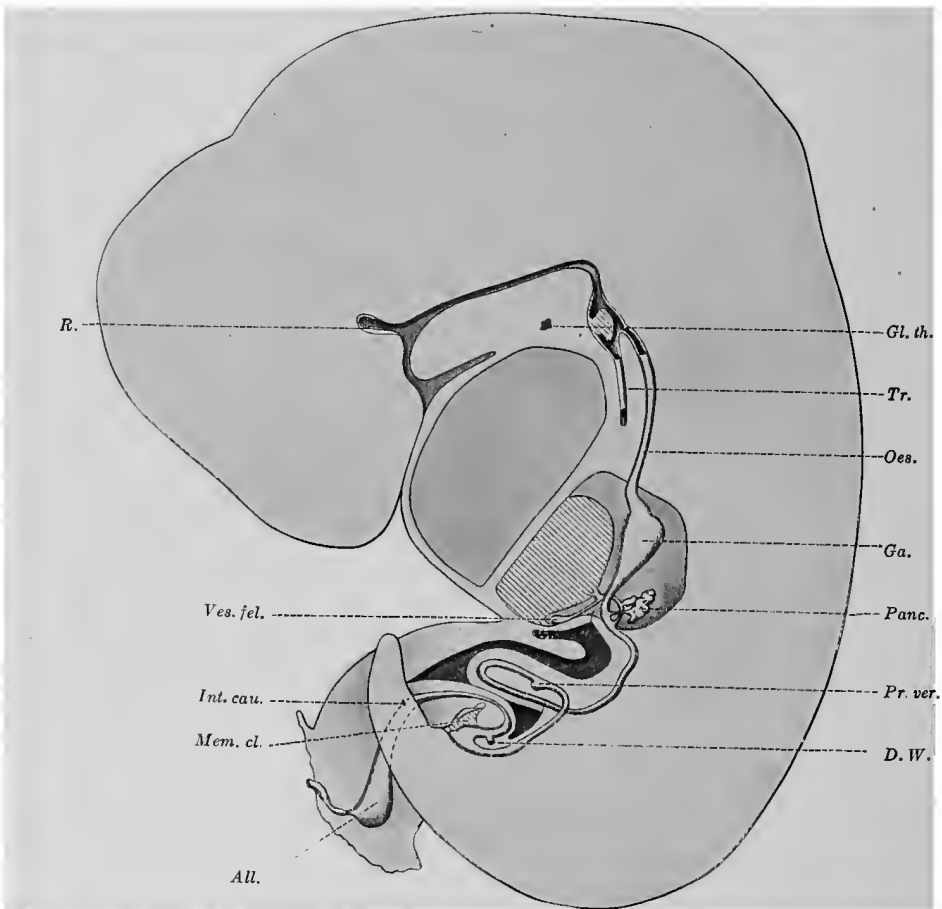

FIG. 242.—The digestive tract of an embryo of 9.4 mm. (Harvard Collection, Series 1005). ×13 diam. The lettering is the same as in Figs. 239 and 240.

the umbilical cord." It had been discovered previously. Meckel observed it in the goat, sheep, cow, pig, rabbit, and man. He says, "Through a very pleasant coincidence Oken and I, at the same time and quite independently of one another, expressed the opinion that in a very early embryonic stage this position of the intestine is normal." According to His (1885), "the underlying cause of the ventral extension of the intestine is doubtless to be sought in its connection with the yolk-sac. . . . As long as the yolk-stalk is present it is attached to the end of the loop extending through the umbilicus." But Mall (1898) states that "before the intestine begins to enter the cord its connection with the duct is

severed." Since the liver grows downward and crowds upon the rapidly elongating intestine, Mall considers that "the intestine must escape if it has a chance, and the cœlomic space within the cord naturally receives it."

The loop of intestine begins to enter the cord in embryos of about 10 mm.; at 22.8 mm. (Fig. 243) the umbilical hernia is well

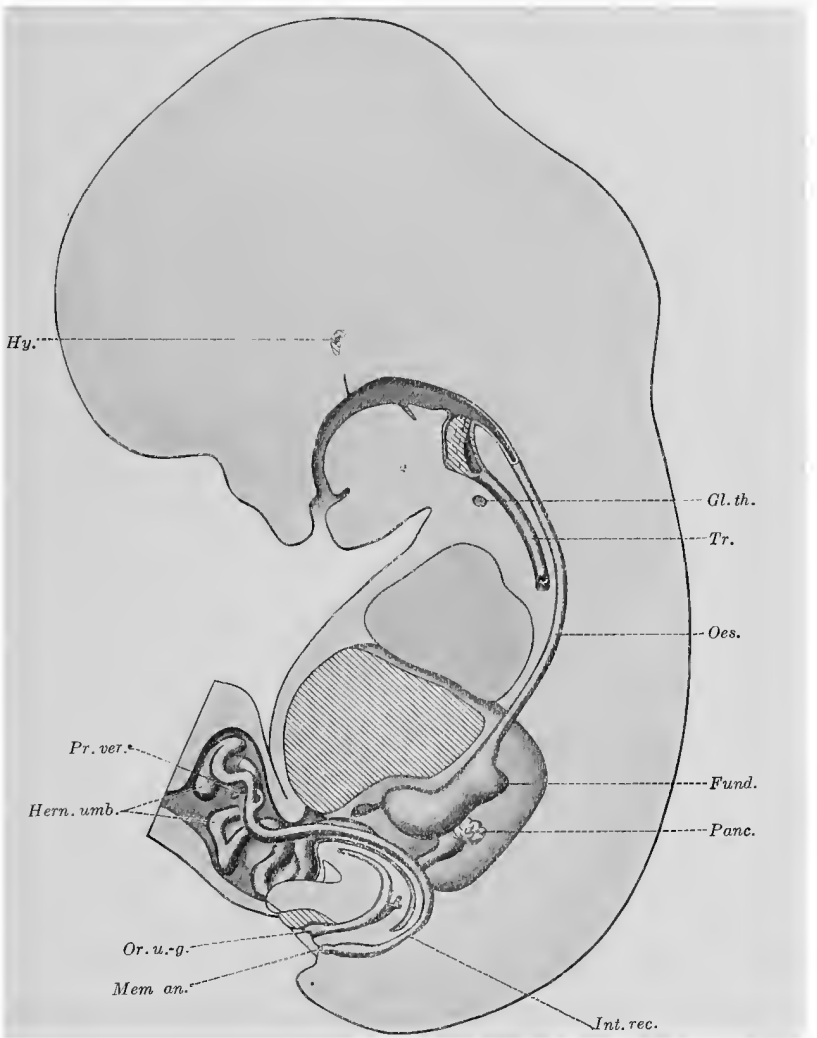

FIG. 243.—The digestive tract of an embryo of 22.8 mm. (Harvard Collection, Series 871). ×6 diam. (Drawn by F. P. Johnson.) In addition to the structures lettered as in previous figures the following are shown. *Fund.*, fundus of the stomach; *Hern. umb.*, coils of intestine within the umbilical cord, forming the umbilical hernia; *Hy.*, anterior lobe of the hypophysis,—the detached end of Rathke's pocket; *Int. rec.*, intestinum rectum; *Mem. an.*, membrana analis; *Or. u.-g.*, orificium urogenitale.

developed.[8] It will be seen that the large intestine presents no

[8] The reconstruction of the 22.8 mm. embryo (Fig. 243), which has not been previously published, is the work of Mr. F. P. Johnson, and the writer is much indebted to him for permission to use it.

well-marked convolutions, but that there are several bends in the course of the small intestine. This is due to the relatively rapid growth of the anterior half of the original loop. According to Mall (1898), there are six primary loops of the small intestine, first indicated in embryos of about 17 mm., and recognizable, in spite of secondary coils, even in the adult. The first loop encircles the head of the pancreas. The third loop is concave below and occurs where the small intestine passes through the narrow umbilical outlet. It is clearly shown in Fig. 243. Loop 2 is between 1 and 3, forming together with 3 an S-shaped curve. The other loops are not so easily defined, but all coils between the cæcum and the place of attachment of the yolk-stalk are included in loop 6.

Mall considers that these coils in the umbilical cord are so fixed that it is not difficult to recognize the various loops after their return to the abdominal cavity. In the adult he finds that loops 2 and 3 make two distinct groups of coils in the left hypochondrium, loop 2 communicating with the duodenum. "After this the intestine passes through the umbilical region to the right side of the body (loop 4). Then the intestine recrosses the median line to make a few convolutions in the left iliac fossa (5), after which it fills the pelvis and lower part of the abdominal cavity between the psoas muscles (6)." He concludes that "the various loops of the adult intestine, as well as their position, are already marked in embryos of five weeks, and the position of the convolutions in the adult is as definite as the convolutions of the brain."

Separation of the Intestine from the Allantois.—In embryos of the stage of Ingalls's specimen (Fig. 239) the cloaca is elongated anteroposteriorly, and the Wolffian ducts empty into its ventral portion. Later this ventral portion is split off from the dorsal part, apparently by the down-growth of the connective tissue between the allantois and rectum. The portion of the allantois [9] below the Wolffian ducts, since both the urinary and genital passages open into it, is then called the *urogenital sinus.*

In the 9.4 mm. embryo (Fig. 242) the urogenital sinus has been formed, but the cloaca still remains as a broad connection between the allantoic and intestinal tracts. By further down-growth of the connective tissue, this connection becomes reduced to a slender passage called the *cloacal duct.* Finally the walls of the duct coalesce and the communication between the intestine and the allantois is obliterated. The connective tissue between the rectum and the urogenital sinus, where it reaches the ectoderm, constitutes the *primitive perineum.*

In Keibel and Elze's tables, a cloacal duct is recorded in embryos from 11 to 12.5 mm. At 15 mm. the "cloaca is still not

[9] It is clearly a matter of definition whether the portion which is added to the allantois by the subdivision of the cloaca should thereafter be called allantois (see Chap. XIX).

fully divided." At 15.5 mm. the "cloaca is just divided, but the epithelia of the urogenital sinus and of the rectum still connect; a mesodermal perineum is not yet formed." Fig. 244, A, from a specimen measuring 18.1 mm., presents this condition. The cloacal membrane is now subdivided into the *urogenital membrane* ventrally and the *anal membrane* dorsally. The mesodermal primitive perineum is about to form, but the urogenital sinus and the rectum are apparently still connected by entoderm. At 22.8 mm. (Fig. 243) the primitive perineum is well developed. It is found at the bottom of a median sagittal ectodermal groove, known as the *ectodermal cloaca.* The anal membrane is also at the bottom of an ectodermal depression which may be regarded as a part of the ectodermal cloaca, but which is termed the *proctodæum* or anal pit. When the edges of the ectodermal cloaca coalesce in the perineal region, so as to form a raphe, the permanent perineum is produced.

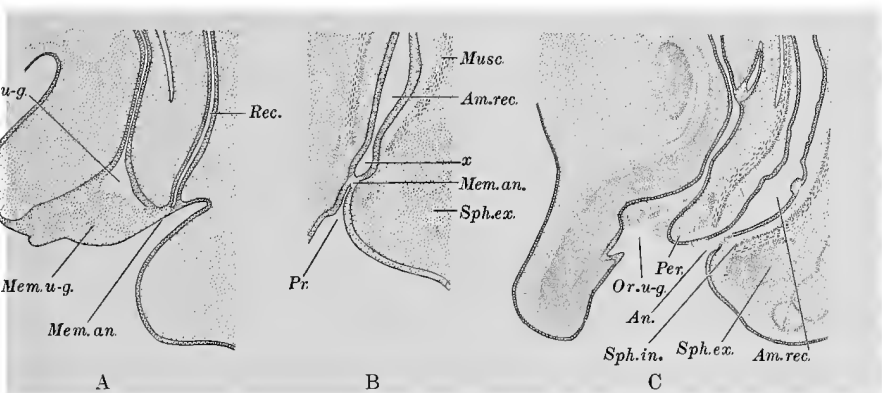

FIG. 244.—Median sagittal sections to show the separation of the rectum from the urogenital sinus. A, embryo of 18.1 mm. (Harvard Collection, Series 1129), ×30 diam.; B, embryo of 22 mm. (Harvard Collection, Series 851), ×25 diam.; C, embryo of 32 mm. (Harvard Collection, Series 292), ×12 diam. *Am. rec.*, ampulla recti; *An.*, anus; *Mem. an.*, membrana analis; *Mem. u.-g.*, membrana urogenitalis; *Musc.*, tunica muscularis (including inner circular and outer longitudinal layers); *Or. u.-g.*, orificium urogenitale; *Per.*, perineum; *Pr.*, proctodæum; *Rec.*, rectum; *Sph. ex.*, M. sphincter ani externus; *Sph. int.*, M. sphincter ani internus; *S. u.-g.*, sinus urogenitalis; *x*, terminal bulbous enlargement of the rectum.

The urogenital tract acquires an external opening before the anal membrane is perforated, and this has occurred in the 22.8 mm. specimen. The further history of the allantois and urogenital tract will be found in Chapter XIX.

The Formation of the Anus.—A sagittal section through the rectum and proctodæum of a 22 mm. embryo is shown in Fig. 244, B. Just before the rectum reaches the anal membrane it forms a bulbous enlargement, seen also in Fig. 243 and in embryos of 17.5 and 18.5 mm. drawn by Keibel. In these specimens the circular and longitudinal muscle layers of the rectum are easily recognized. The terminal swelling of the rectum extends beyond the muscle layers, as recorded by Keibel (1896) in a beautifully

illustrated and fundamental description of the development of the human urogenital tract. In a 29 mm. specimen he described the musculature as follows (cf. Fig. 244, B and C):

"The circular muscle layer ends very abruptly at the level of the little caudal swelling of the intestine, and already it may be referred to as the beginning of the *M. sphincter ani internus.*

"The outer longitudinal layer of the intestinal musculature is arranged differently. It ends at the same level, but no sharp caudal limit can be recognized. The *M. sphincter ani externus* is clearly indicated and is relatively quite large. The cranial border of this muscle is found where the musculature of the intestine ends, therefore at the level of the little caudal entodermal enlargement. The *M. sphincter ani externus* is separated from the epithelium of the intestine by a rather thin layer of connective tissue, which is continuous with the connective tissue surrounding the intestine further cranially, and also with the longitudinal layer of the muscularis, from which strands of cells may be followed into it."

In a 32 mm. specimen (Fig. 244, C) the anal membrane has disappeared. Along the dorsal wall of the anal canal there is a slight indication of the terminal bulbous enlargement, but it seems clear that it is a transient structure. It is probable that the elongated swelling above it gives rise to the rectal ampulla of the adult.

Otis (1905) has studied the external configuration of the embryonic anus, and has found that the development of the external sphincter produces characteristic elevations. In embryos of 21–23 mm. there is a pair of external elevations, one on either side of the anal pit. At 26 mm. these have united dorsal to the anus, thus forming a single crescentic mound. The horns of the crescent grow forward toward the perineum and finally meet, so that the mound encircles the anus.

Malformations of the Anus.—The perforation of the anal membrane normally takes place in embryos of about 30 mm. It is accompanied by the formation of degenerative material staining intensely with eosine, which blocks the outlet and makes the determination of an aperture somewhat difficult. In the Harvard Collection there are embryos measuring 22 mm., 22.8 mm., and 29 mm. in which perforation has occurred, and specimens of 22.8 mm. and 30 mm. in which the anus seems still impervious. Keibel and Elze's series of seven embryos measuring from 22 to 26 mm. includes only one (22.5 mm.) in which the anus is open. A persistence of the anal membrane until birth has been assumed to account for cases of *atresia ani,* in which the rectum ends blindly below, and the anus is represented merely by a slight depression in the skin. In these cases, however, the epithelial connection between

the rectum and anal pit has been lost, so that an invasion of the anal membrane by connective tissue must have taken place. In other cases, known as *atresia recti,* the anal canal is present but it leads into a blind sac of intestine.

In this connection the obliteration of the lumen of the rectum, observed by Keibel in an embryo measuring 11.5 mm., is of interest. He found that "the epithelium of the lower portion of the intestine blocked the lumen at two small places," but since similar conditions were not observed in other specimens he concluded that "this may well be only a chance and meaningless adhesion" (1896, p. 79). Although this observation in human embryos remains unique, Lewis (1903) has recorded a similar condition in pig and rabbit embryos, and it occurs more extensively in birds (Minot, 1900). It has been suggested that its function is to prevent the passage of the excretion of the Wolffian bodies back into the intestine. After the cloacal duct has become obliterated, it is not needed for this purpose, and in these later stages it is not found. It is possible that *atresia recti* may be due to the persistence of such an occlusion, with invasion by connective tissue.

Less common than the simple imperforate anus or imperforate rectum are cases in which the cloacal duct persists, forming

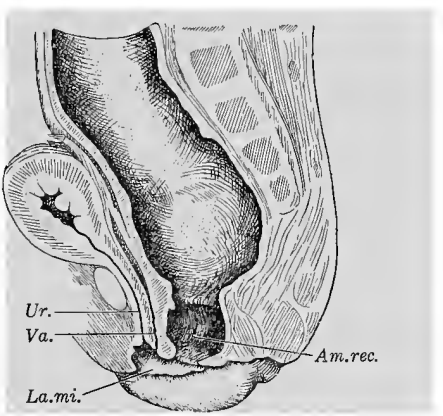

FIG. 245.—Abnormal position of the anus in a child. ½ natural size. (After Mackenzie.) *Am. rec.*, ampulla recti; *La.mi.* labium minus; *Ur.*, urethra; *Va.*, vagina.

a slender passage from the rectum to the raphe of the perineum, scrotum, or under side of the penis, or to the prostatic urethra or bladder. In the female such a fistula may open along the perineal raphe or into the vestibule of the vagina.

An interesting series of diagrams of these cases was published by Stieda (1903). The fistula may exist with a normal anus, but more frequently it is associated with an imperforate condition. Of the many cases reported two examples may be cited.

Reichel (1888) received a patient 25 years of age who complained of involuntary discharge of fæces through the vagina, beginning after her marriage three years before. The anal canal was found to be normal; the perineum was extremely short and the vestibule strikingly deep; the labia were normal. A canal, lined with mucous membrane, was found leading from the rectum to the vestibule directly below the hymen. After discussing the possibility of mechanical injury, etc., Reichel concludes that the abnormal communication between the rectum and the

vestibule was present as a slender fistula from birth, and that it was dilated following coitus. Such a condition would arise in an embryo of about 12 mm. provided that the perineal tissue should encircle the cloacal duct instead of obliterating it.

In 1906 Mackenzie reported the case shown in Fig. 245. The patient died at the age of 1 year and 11 months, having suffered from alternating attacks of diarrhœa and constipation since birth. Robinson described the condition as follows: "The anal passage runs, not in the normal direction, downwards and backwards, but downwards and forwards, and the anal orifice opens into a chamber common to it, the vagina, and the urethra; that is, the anal passage opens, not on the surface behind the genito-urinary chamber, but into a cloaca."

It may be considered that the anal canal in this case, although provided with well-marked anal columns (of Morgagni), corresponds with the slender fistula in Reichel's case, and that the normal anal outlet is not represented. This is Robinson's interpretation. He says, "The entodermal cloacal chamber has never been separated into two parts: it has opened into the anterior part of the external cloacal depression, and the posterior part of that depression, if it existed, has disappeared, no trace of a proctodeal opening being discoverable." It seems possible, however, that the entodermal cloaca has been completely divided but that the primitive perineum has persisted. Thus by an imperfect development of the perineum the normal anal opening is displaced forward. Robinson rejects this interpretation.

Embryo of 42 mm. Return of the Intestines to the Abdominal Cavity.—According to Mall (1895), the return of the intestines from the umbilical cord into the body must take place very rapidly, for in embryos of 40 mm. the intestine is either in the cord or in the abdominal cavity. He found no intermediate stages. Mall was unable to determine the cause of the return, but he showed that the abdominal walls do not bulge forward so as to include the cavity of the cord within the abdomen. The intestines slip back through a rather small aperture, and the cavity in the cord is then obliterated. From a study of pig embryos Mall suggested that the increase of loops within the abdominal cavity, and their rotation, may draw upon the loops in the cord. The enlargement of the umbilical arteries on the under side of the hernia may also exert a favorable pressure. As seen in the reconstruction of a 42 mm. embryo (Fig. 246), the return has taken place, but the abdominal cavity still extends into the cord.[10]

Development of the Cæcum and Vermiform Process.—The first appearance of the intestinal enlargement which is to produce the vermiform process has already been described. In the embryo of 7.5 mm. it is an entodermal swelling on the lower side of the caudal limb of the intestinal loop. After the torsion of the loop it may still project from the lower side of the intestine, as shown in the 9.4 mm. specimen (Fig. 242) and in a 13.8 mm. embryo

[10] In a "Supplementary Note on the Development of the Human Intestine," Mall (1899) described a human embryo of 32 mm. "in which the intestine is in the act of returning from the cœlom of the cord to the peritoneal cavity." The intestine is said to be "sucked back" to fill the space made by the enlargement of the abdominal cavity.

figured by His. But in a specimen measuring 12.5 mm. His has drawn it as projecting from the upper side of the intestine, and

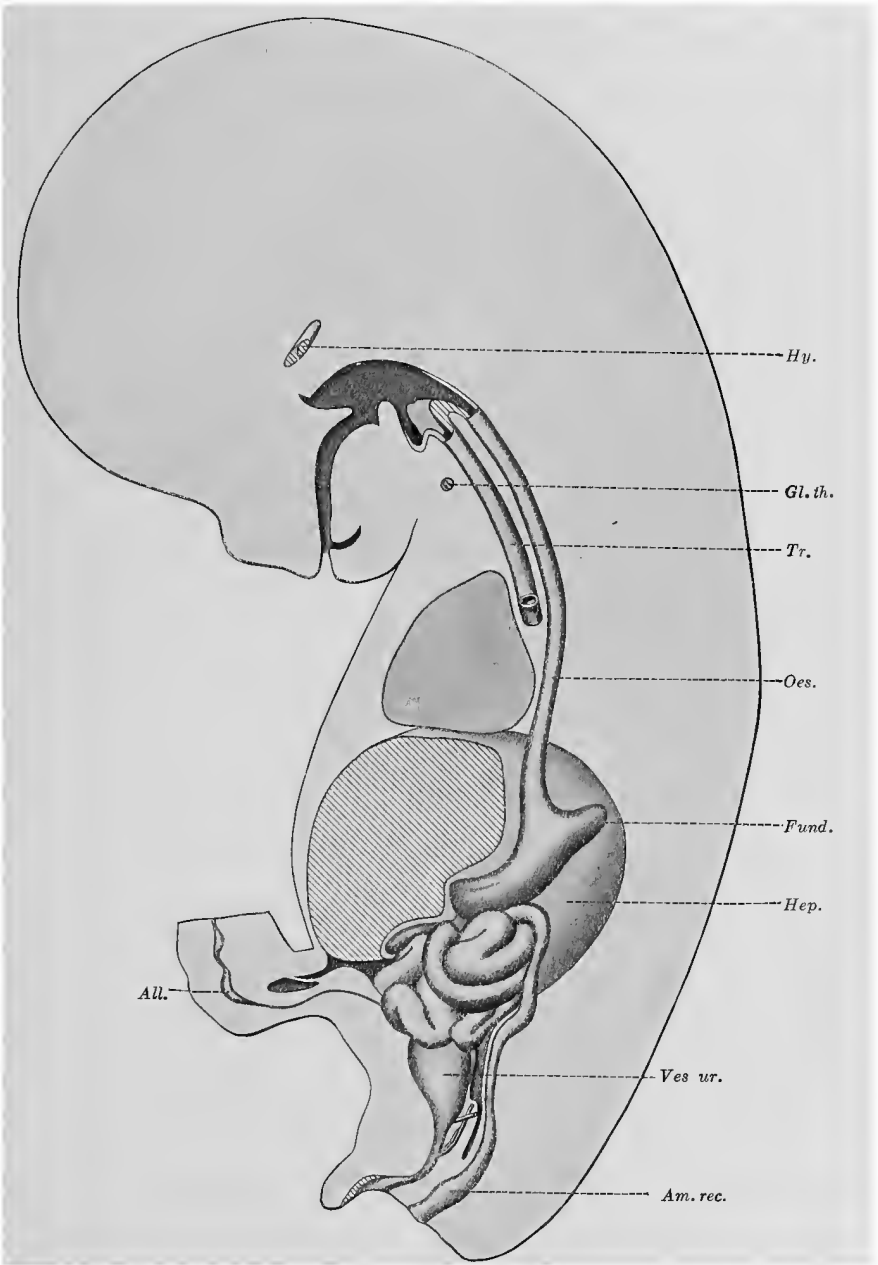

FIG. 246.—The digestive tract of an embryo of 42 mm. (Harvard Collection Series 838). ×4 diam. The lettering is like that in previous figures with the addition of *Ves. ur.* (vesica urinaria), bladder.

it has been similarly figured by Keibel and Elze in an embryo of 14 mm. Mall found it projecting laterally in a 17 mm. specimen.

In all these cases, however, the apex of the projection is directed ventrally (that is, toward the small intestine). With the formation of the umbilical hernia, the vermiform process enters the cavity of the cord (Fig. 243). Later it is withdrawn into the abdomen and comes to lie against the under side of the liver.

Four stages in the development of the vermiform process are shown in Fig. 247, two of which are drawn from models and two from dissections. All are viewed from the median side. Fig. 247, *A*, shows the simple arrangement at 9.4 mm. To produce the condition shown in *B* the tip of the vermiform process must be brought toward the large intestine. Thus a U-shaped bend would result, and this U should then be twisted upon the small intestine

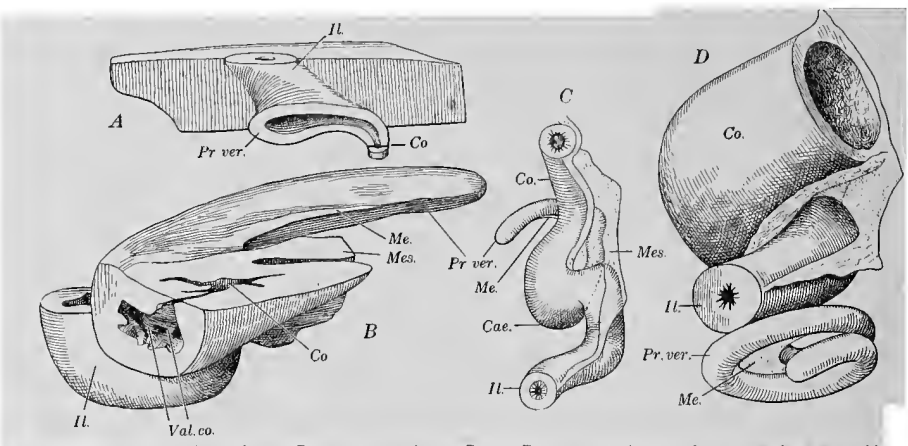

FIG. 247.—Models (*A* and *B*) and dissections (*C* and *D*) to show the development of the vermiform process. *A*, embryo of 9.4 mm. (Harvard Collection, Series 1005), ×50 diam.; *B*, embryo of 42 mm. (Harvard Collection, Series 838), ×20 diam.; *C*, embryo of 95 mm., ×3.5 diam.; *D*, embryo of 218 mm., ×3.5 diam. *Cae.*, cæcum; *Co.*, colon; *Il.*, ileum (small intestine); *Me.*, mesenteriolum; *Mes.*, mesentery; *Pr. ver.*, processus vermiformis; *Val. co.*, valvula coli, represented by two slight vertical swellings between which is the outlet of the ileum.

so that its extremities extend dorsally, with the vermiform process on the right side of the colon. In Fig. 247, *B*, from the 42 mm. embryo, a window has been cut in the round bend made by the vermiform process and the colon, so that the outlet of the ileum is exposed. The ileum empties into the large intestine in the concavity of the bend.

Tarenetzky (1881) has described very similar relations in a 33 mm. embryo as follows:

"The processus vermiformis has assumed an elongated form; it is no longer parallel with the ileum but forms a right angle with it. It has taken a position toward the right and obliquely above and in front of the terminal part of the ileum, so that its tip is already directed somewhat toward the colon. In this manner it forms also a right angle with the colon. The knee-shaped bend at the passage of the vermiform process into the colon is not expanded, so that at this stage no true cæcum is present. The tip of the vermiform process is completely free. Along its base and middle piece there is attached a well-defined peritoneal

fold, which arises from the adjacent ventral right plate of the *mesenterium commune*. This fold is new, and represents the *mesenteriolum* of the vermiform process, the chief vessels to which are contained in it."

The *mesenteriolum* is shown in Fig. 247, *B*, and, as Tarenetzky recorded, a dilatation to indicate the cæcum is not well defined. It has already been noted that Tarenetzky first recognized the cæcum in embryos of 65 mm. Toldt (1894) describes a clearer separation between the cæcum and vermiform process in a "7 weeks" embryo than his figures indicate. In his drawing of a 50 mm. specimen the cæcum can scarcely be distinguished. The demarcation evidently forms very gradually and at a late stage. According to Toldt, the tæniæ of the cæcum are present at birth, and the haustra of the cæcum develop in the first half year, the smallest of them, situated nearest the vermiform process, appearing first; but the cæcum does not acquire the characteristic adult form until the third or fourth year.

It was shown by Toldt that the bending of the vermiform process and cæcum upon the colon gives rise to the valves of the colon. Until this bend occurs there is no indication of the valves. As a result of the bend, the end of the small intestine, where it is caught in the angle, becomes flattened by the adjacent walls of the colon and cæcum respectively. At 42 mm. (Fig. 247, *B*) the aperture is still nearly round, but as the U-shaped bend becomes angular the flattening will result. This explanation accounts for the two lips of the valve, the *labium inferius* being toward the cæcum, and the *labium superius* toward the colon. In the last fetal months and especially after birth, the relatively great expansion of the large intestine, as compared with the ileum, causes the valves to increase in size. In this process the bulging colon and cæcum still further invest the end of the ileum and adhere to it. In case the embryonic bend is not highly developed, imperfect valves may arise by the expansion of the large intestine. Toldt recorded several such cases.

Recently Parsons (1907) has reported the case of an elderly man in whom the cæcum formed a straight continuation of the colon, and there was no valve whatever. He considers that the U-shaped bend had never formed in that individual. Smith (1903) described a case in which a vermiform process was present but there was a "complete absence of a properly constituted cæcum" and no trace of the valvula coli.

The stage of the bend represented in Fig. 247, *B*, is therefore a critical one. In a 95 mm. embryo, Fig. 247, *C*, the vermiform process is still in contact with the liver, and the U-shaped bend is well marked, but the descent of the cæcum toward the pelvis has begun. At 218 mm. (Fig. 247, *D*) the vermiform process has taken its final position. In this case it is coiled so as to make 1½ revolutions.

Form and Position of the Stomach.—At first the stomach lies approximately in the median sagittal plane. It is then a flattened expansion of the digestive tube, with dorsal and ventral borders and right and left surfaces. Gradually it rotates so that its left side becomes ventral and its right side correspondingly dorsal. At the same time the dorsal border is turned to the left and the ventral border to the right. The upper portion of the stomach is displaced to the left side of the body, and the borders thus become curvatures, which are concave toward the right. The original dorsal border forms the greater curvature, and the ventral border becomes the lesser curvature. These changes in position are usually described in connection with the development of the mesenteries. They are best shown in ventral views of the embryo. It may be noted, however, that in the 7.5 mm. embryo the rotation of the stomach has partly occurred, so that the original dorso-ventral axis forms an angle of 20° with the median plane; in the 22.8 mm. specimen the angle has increased to 55°; and in the 45 mm. embryo it is 75° in the pyloric half of the stomach. The cardiac end has not rotated so much, and at 45 mm. its angle is 40°. Thus the pyloric part of the stomach is twisted across the body from left to right.

The *descent of the stomach* has been described by Jackson (1909) as follows: In the 11 mm. embryo the cardia lies opposite the 3d or 4th thoracic segment, and the pylorus opposite the 7th or 8th. In the 17 mm. embryo the two ends of the stomach seem to have reached approximately their permanent positions, the cardia opposite the 10th thoracic vertebra and the pylorus opposite the 1st or 2d lumbar vertebra.

The descent is accompanied by a great elongation of the œsophagus. In a 9.4 mm. specimen the œsophagus measures 1.8 mm. At this proportion it should measure 4.3 mm. in an embryo of 22.8 mm., but its actual length is found to be 8 mm. In Jackson's paper the relations of the stomach to the adjacent viscera in early embryos have been considered.

The most notable external feature in the early development of the stomach is the formation of the fundus, which occurs in the manner described by Keith and Jones (1902). According to these authors, the fundus of the human stomach is developed, not as a general expansion of the gastric part of the fore-gut, but in the form of a localized outgrowth or diverticulum at the cardiac end of the greater curvature (dorsal border). In its manner of origin it has much in common with the cæcum and vermiform process. They find that the outgrowth is best marked in embryos of the third and fourth month. After these months the diverticulum is not so well defined, since it expands and merges with the body of the stomach. The gradual development of the fundus

as a conical diverticulum is shown in the embryos of 9.4, 22.8, and 42 mm. (Figs. 242, 243, and 246).

A very similar diverticulum was observed in pig embryos of 12 mm. by Lewis, who considered that it was characteristic of the pig and gave rise to the well-marked pouch attached to the fundus of the adult. Strecker (1908) has recently called attention to a human stomach described by Luschka " in which the transition from the œsophagus to the stomach took place gradually, and beyond this the fundus possessed a conical appendage directed upward and backward, thereby, to a certain extent, resembling the form of a pig's stomach."

In addition to the dilated corpus and the conical fundus, the embryonic stomach presents a third subdivision,—the tubular *pars pylorica.* As seen in three models of the stomach, from embryos of 16, 19, and 19.3 mm. respectively, this pyloric portion extends toward the right and slightly upward, to the pylorus. In every case the position of the pylorus is indicated by a local dilatation of the epithelial tube, such as is shown in Thyng's model from a 13.6 mm. specimen (Fig. 285, *A,* p. 392). The junction between the corpus and the pars pylorica, measured along the lesser curvature, occurs midway between the pylorus and the cardia. At the place of junction there is an angular bend in the lesser curvature (*incisura angularis*) and an abrupt change in the diameter of the tube.

Another subdivision of the human stomach is that which Luschka (1863) described as the *cardiac antrum.* Sometimes in the adult a bulbous enlargement is found at the junction of the œsophagus and stomach, and this is the region of the special form of glands known as cardiac glands. Strecker has studied this area, and concludes that sometimes a "Vormagen" can be recognized, but in other cases it is totally absent.

In the 22.8 mm. specimen, as seen in Fig. 243, such a subdivision is suggested, but the formation of a distinct cardiac antrum in early human embryos has never been demonstrated.

The further development of the oral cavity and its organs, and of the œsophagus, stomach, and intestine, with their folds and glands, will be considered in the following sections.

The embryology of the branchial region and respiratory system will form the concluding part of the chapter.

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THE MOUTH AND ITS ORGANS.

By J. PLAYFAIR McMURRICH, Toronto.

The Mouth.—The examination of a human embryo a little over 2 mm. in length will reveal upon the ventral surface immediately in front of the yolk-sac a rounded elevation, the heart, and in front of this a somewhat pentagonal depression, the *oral sinus,* the anterior boundary of which is formed by the projecting frontal extremity of the brain, while the remaining sides are formed by the maxillary and mandibular processes of the first branchial arch (Fig. 248). The mandibular processes separate the sinus from the anterior surface of the pericardium, and their union in the middle line is

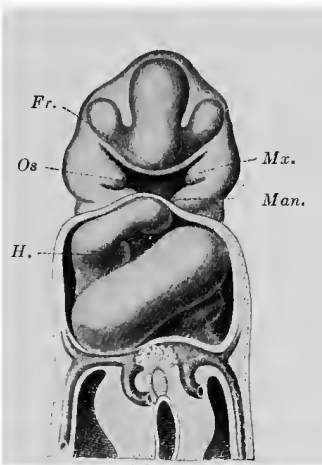

Fig. 248.—Ventral view of the anterior portion of an embryo of 2.15 mm., from a reconstruction. (His.) *Fr.*, frontal process; *H.*, heart; *Mx.*, maxillary process; *Man.*, mandibular process; *Os.*, oral sinus.

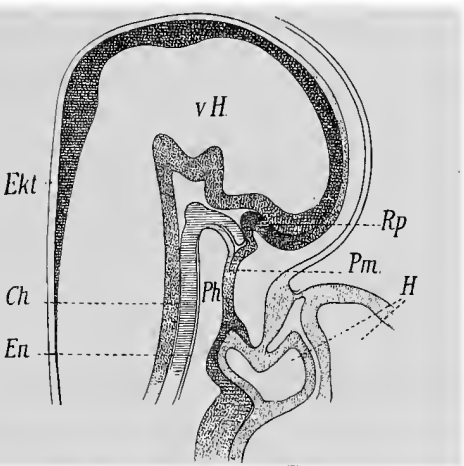

Fig. 249.—Median longitudinal section of a rabbit embryo. (After Keibel.) *Ch*, chorda; *Ekt*, ectoderm; *En*, endoderm; *H*, heart; *Rp*, Rathke's pouch; *Ph*, pharynx; *Pm*, pharyngeal membrane; *v.H*, forebrain.

marked by a groove, which forms the posterior angle of the sinus. The remaining angles are paired, the posterior ones being the angles between the maxillary and mandibular processes of either side, while the anterior ones are formed by the ventral ends of grooves which separate the maxillary process of either side from the frontal process. The floor of the sinus is formed by a thin *pharyngeal membrane* (Fig. 249, *Pm*), which separates it from the pharyngeal cavity and is lined upon its outer surface by ectoderm and upon its inner surface by endoderm, the two layers, indeed, being in contact throughout the entire extent of the membrane, no mesoderm intervening. Immediately anterior to the membrane a pocket-like evagination of the ectoderm toward the base of the brain occurs, forming what is known as *Rathke's pouch*

(Fig. 249, *Rp*), destined to form the anterior lobe of the hypophysis cerebri.

The oral sinus, however, does not correspond to the definitive mouth, which includes also a portion of the embryonic pharynx. Shortly after the stage just described (2.15 mm.), the pharyngeal membrane ruptures and disappears, with the exception of a part of its anterior border, which persists for a time as a transverse ridge upon the roof of the mouth, immediately posterior to Rathke's pouch. Behind this ridge an evagination of the endoderm toward the base of the brain takes place, forming what is known,

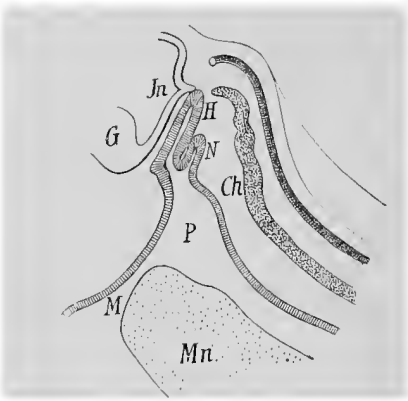

FIG. 250.—Median longitudinal section through the mouth region of an embryo chick of 5 days. (After Seessel.) *Ch*, chorda; *H*, Rathke's pouch; *G*, brain; *M*, mouth; *N*, Seessel's pouch; *P*, pharynx; *In*, infundibulum; *Mn*, mandibular process.

from its discoverer (Seessel, 1877), as *Seessel's pouch* (Fig. 250), a structure whose significance is uncertain.

Seessel's pouch has been described (Nussbaum, 1896) as elongating in embryos of the dog until it came into contact with the hypophyseal downgrowth of the brain, whereupon its lumen disappeared and it eventually fragmented into a number of portions, the uppermost of which remained in connection with the hypophysis and became part of it.

By the disappearance of the pharyngeal membrane the oral sinus becomes continuous with the embryonic pharynx, and the anterior part of the digestive tract is placed in communication with the exterior; the grooves, however, which separate the medial ends of the maxillary processes from the frontal process still maintain the open communication between the mouth cavity and the nasal pits. Later, the region of the frontal lobe which forms the anterior boundary of the oral sinus becomes a flat or slightly concave surface, whose lateral, thickened margins form the medial walls of the nasal fossæ and terminate posteriorly in rounded elevations, the *processus globulares* (Fig. 251). In embryos of 8 mm. the nasal fossæ are still open to the mouth, but later the posterior

border of the lateral wall of each fossa approaches the corresponding processus globularis and eventually unites with it, the fossæ thus becoming converted into pits completely shut off from the mouth (Hochstetter, 1892). Still later the medial ends of the maxillary processes also unite with the processus globulares, these gradually approach each other until they meet in the median line, and the anterior boundary of the mouth is completed, consisting of the processus globulares medially, and laterally of the right and left maxillary processes. At this stage the floor of the nasal pits is separated from the mouth cavity merely by a thin membrane, the *bucconasal membrane,* formed of the nasal epithelium in contact with that of the roof of the mouth cavity, and in embryos of 15. 5 mm. this membrane breaks through and the nasal and oral

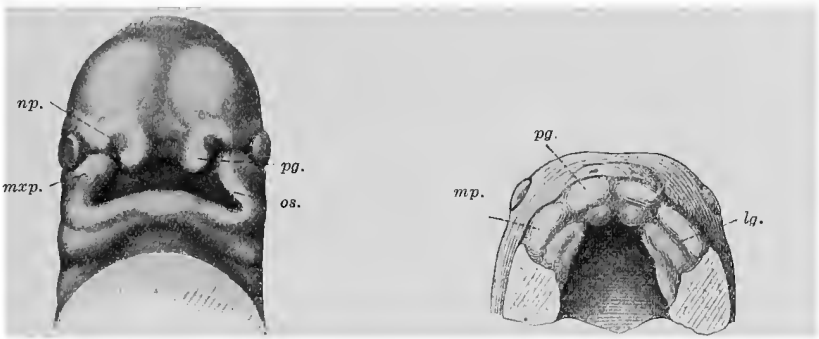

FIG. 251.—Face of human embryo of 8 mm. (After His.) *mxp.*, maxillary process; *np.*, nasal pit; *pg.*, processus globularis; *os.*, oral sinus.

FIG. 252.—Roof of the mouth of human embryo showing the formation of the primary labial grooves. (After His.) *lg.*, primary labial groove; *mp.*, maxillary process; *pg.*, processus globularis.

cavities are again in communication, but the communications, the *primitive choanæ,* are now behind the maxillary processes.

Several abnormalities may arise in connection with the development of the oral sinus, the most frequent of which is *harelip,* consisting in a cleft extending through the upper lip slightly lateral to the middle line on either one or both sides and placing the vestibulum oris in communication with nasal pits. This finds its morphological explanation in a failure of the maxillary processes to unite with the processus globulares, whereby the original connection of the nasal pits with the oral sinus is retained. Other abnormalities of less frequent occurrence are dependent upon the imperfect or excessive development of the connection between the maxillary and mandibular processes from which the cheeks are developed, imperfection in this respect producing an abnormal broadening of the rima oris (macrostomia), and excess to its abnormal diminution (microstomia) or even to its suppression (astomia). Inhibition of the development of the mandibular processes may also occur, the two failing to meet in the median line and thus producing a more or less pronounced defect of the lower portion of the face (aprosopia).

The Formation of the Lips and Cheeks.—Shortly after the fusion of the maxillary processes with the processus globulares is effected, a slight groove makes its appearance on the free border of the frontal process and eventually extends laterally on the

maxillary processes. These are the *primary labial grooves* (Fig. 252), and are due to a downgrowth into the subjacent mesoderm of the epithelium covering the structures concerned. In embryos about 4 cm. in length a disintegration of the central cells of the downgrowths occurs, the result being a deepening of the grooves to form the *secondary labial grooves* (Bild, 1902), which separate the lips from the alveolar portions of the various processes (Fig. 254) and themselves form the vestibulum oris. The portion of the upper labial groove which forms on the processus globulares is at first partly interrupted in the median line by an antero-posterior furrow, which corresponds to the line of union of the two processus globulares. In some mammals, as for instance the rabbit, this furrow persists throughout life as a deep median slit in the upper lip, but in man it becomes almost obliterated and is represented in the adult only by the philtrum. The labial groove, however, does not extend as deeply into the tissue of the frontal lobe in the region of the furrow as it does more laterally, and there is consequently formed in the median line a slight fold lying in the sagittal plane and extending between the lip and the alveolar portion of the jaw, the *frenulum labii superioris.* Its development is associated with the occurrence of the intermaxillary suture, and a similar *frenulum labii inferioris* is formed opposite the intermandibular suture.

At the angle of the mouth the upper and lower primary labial grooves become continuous, and the epithelial downgrowths are here directed laterally and dorsally. By the disintegration of the central cells of the downgrowths in these regions the *buccal cavities* are formed, separating the alveolar portions of the maxillary and mandibular processes from the cheeks. The buccal cavities are thus merely lateral extensions of the labial grooves and the structure of the lips and cheeks is identical, both being formed in these early stages of an external epidermal layer and an internal mucous layer, these two meeting at the angles and margins of the mouth, and between the two a layer of mesenchyme. It is not until after the beginning of the second month of development that muscular tissue begins to make its appearance in the mesenchyme layer, wandering into it from the region of the second branchial arch and bringing with it branches of the facial nerve (see Vol. I, p. 513).

The condition in which the epidermal and mucous layers meet at the margins of the mouth does not, however, persist, but the mucous layer becomes everted to form the red portions of the lips, its meeting with the epidermal layer being some distance away from the actual rima oris. At birth, as was first pointed out by Luschka (1863), the red portion of the lip consists of two parts, an external *pars glabra,* whose surface is quite smooth, and a more

proximal *pars villosa,* covered with numerous minute villosities which contain blood-vessels and may in some cases reach a length of 1 mm. (Fig. 253, A). These villosities, which also occur upon the mucosa of each cheek along a band extending from the angle of the mouth almost to the back of the buccal cavity (Fig. 253, B), make their appearance during the fourth month and are fully developed at the seventh month (Stieda, 1889); they disappear during the first weeks of extra-uterine life, but even in the adult the area occupied by the pars villosa can be distinguished by the

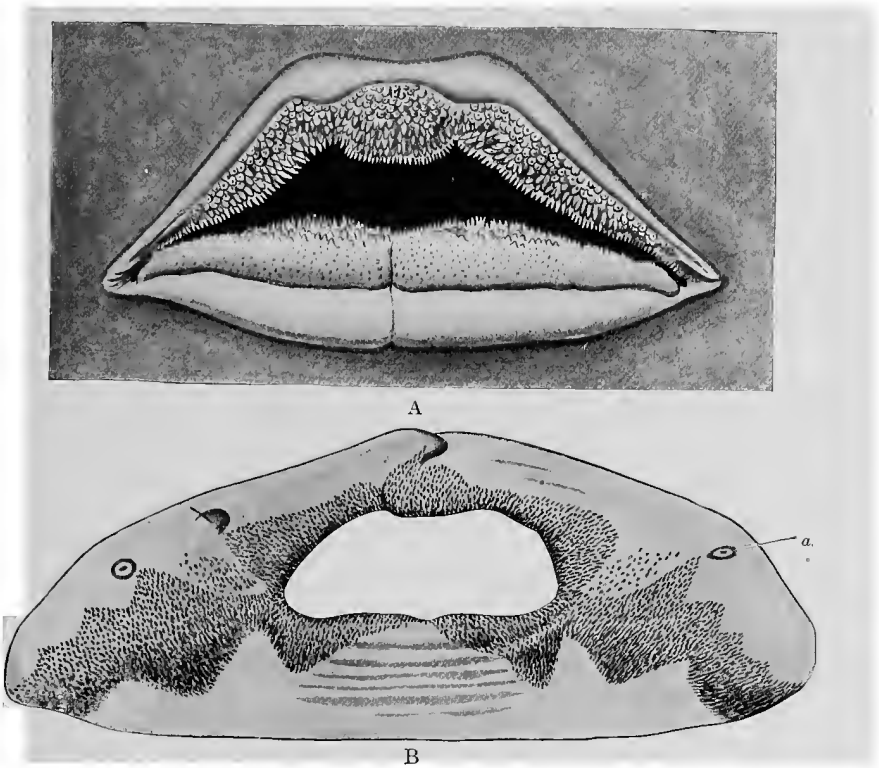

FIG. 253.—A, the lips of a new-born child, showing the villosities and the tubercle; B, the distribution of the villosities upon the vestibulum oris. (After Ramm.) *a*, opening of the parotid duct.

papillæ of its corium being more scattered and more irregular in height than those of the region representing the pars glabra. In addition to this differentiation of the red portions of the lips, there is in the upper lip, from the third month until shortly after birth, a well-marked tubercle, situated in the median line below the philtrum, from which it is separated by a portion of the pars glabra about 1 mm. in breadth (Fig. 253, B). At birth the tubercle is from 5 to 6 mm. broad and has a height of about 4 mm., and it bears along its median line a whitish raphe, continuous below with the frenulum. It is formed entirely from the pars villosa.

As stated, both the tubercle and the villosities of the pars villosa usually disappear during the first few weeks after birth, but indications of the tubercle are frequently to be seen even in the adult, and occasionally the pars villosa remains distinctly recognizable apart from its histological peculiarities, as a roughened projecting area of the red of the lip, separated from the pars glabra by a distinct groove. Such a condition forms what is termed a *double lip*.

The Formation of the Palate.—The mouth cavity formed as described in the preceding pages does not, however, correspond with that of the adult, its roof being formed by the base of the skull, so that it includes portions of what will later be the nasal cavity as well as the mouth cavity proper. The separation of these two cavities is brought about by the formation of the palate, which takes place as follows: At the time of the formation of the labial grooves the maxillary processes have a triangular shape in transverse section, one of the angles being directed medially. As development proceeds, this angle enlarges to form a plate-like fold (Fig. 254, *p*), which projects downward toward the floor of the mouth, between the lateral surface of the tongue and the alveolar

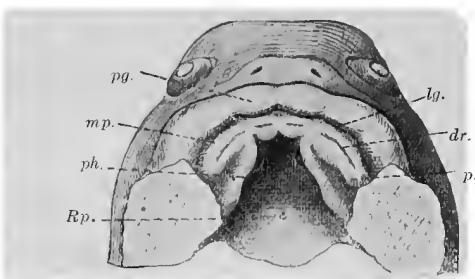

FIG. 254.—Roof of the mouth of a human embryo showing the formation of the palate. (After His.) *dr.*, dental ridge; *lg.*, secondary labial groove; *mp.*, maxillary process; *p.*, palate; *pg.*, processus globularis; *ph.*, pharynx; *Rp.*, Rathke's pouch.

portion of the maxillary process. In these early stages the long axis of the tongue is directed almost vertically and its dorsal surface is still in contact with the base of the skull, but later, with the enlargement of the arch formed by the two mandibular processes, the tongue sinks down between these processes, its tip at the same time becoming bent downwards. By these changes the tongue is withdrawn from between the two palatal plates, and they gradually bend upward so that their free borders are directed medially instead of toward the floor of the mouth. Exactly how this change is effected has been a matter of discussion. His (1901) believed the withdrawal of the tongue from between the two palatal plates to be due to muscular action, and, with Dursy (1869), supposed the palatal processes were simply bent upward to their final horizontal position. Pölzl (1905), however, opposed both these ideas, maintaining that the withdrawal of the tongue was due to changes in the proportions of the parts entering into the formation of the face and that the change of the palatal processes was due to a change

in the direction of their growth and not a mere process of bending upward, basing this latter conclusion on the fact that the palatine nerve, which can be traced into the processes while they still have a vertical position, does not change its course in later stages. Schorr (1908) dissents from this conclusion, and finds that the change is really due to a bending up of the processes, a lively proliferation of the tissue on the oral surface of the processes taking place in the angle between them and the alveolar portion of the jaw (Fig. 255, A and B), so that this angle becomes gradually increased. He finds that the palatine nerve lies lateral to the region in which the proliferation takes place, a fact which explains its retention of its original vertical course; its branches, however, which are directed medially, approach more nearly a horizontal direction as older embryos are examined.

The palatal processes are entirely confined to the maxillary processes, not extending upon the processus globulares (Fig. 254),

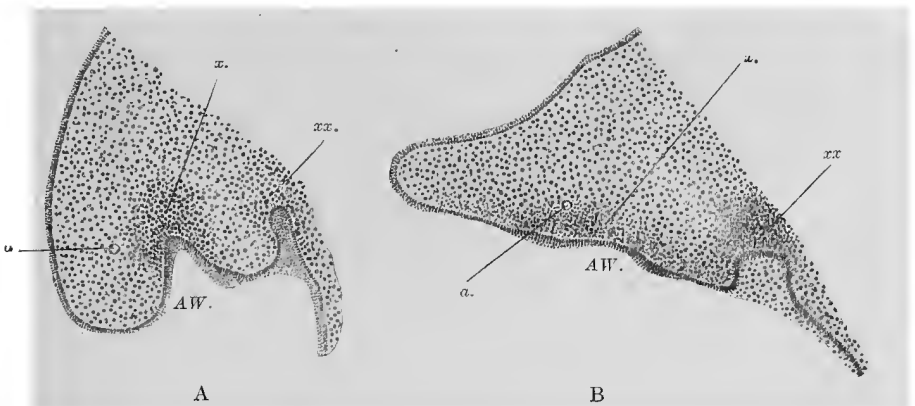

FIG. 255.—Frontal section through the palatine process of a pig embryo of 24 mm. (A) and of 25 mm. (B). (After Schorr.) *a.*, art. palatina; *x.*, proliferating mesenchyme over *AW.*, the angle between the palatine and alveolar processes; *xx.*, proliferating mesenchyme over the dental ridge.

and when they have assumed their horizontal position their free borders are closer together anteriorly than posteriorly, owing to the curvature of the maxillary processes. As the palatal processes increase in breadth in the further course of development, their free borders gradually approach each other and eventually unite, at first anteriorly, the fusion later extending backwards. The mouth cavity proper thus becomes separated from the nasal cavities, these latter now opening posteriorly into the pharynx by the secondary or definitive choanæ, which thus owe their existence to the development of the palate. Furthermore the development of the palate brings about the delimitation of the mouth cavity from the definitive pharynx by the formation of the *arcus pharyngo-palatini,* these being the backward prolongation of the palatal processes upon the lateral walls of the pharynx. They pass down-

ward and backward upon the pharyngeal wall almost in the line of the third branchial arches, the *arcus glossopalatini* and the *sinus tonsillares* being formed respectively by the second branchial arch and the second branchial grooves.

The palatal processes are thus derived entirely from the maxillary processes, and anteriorly, in the median line, there projects backward between them the lower border of the frontal process. With this the palatal processes eventually fuse, but at the meeting point in the median line there remains upon the oral surface a depression known as the *incisive fossa.* Furthermore, the fusion is not perfectly complete; the epithelia on both surfaces become perfectly continuous, but the intervening mesenchyme does not, a strip of epithelium extending through it from the fossa incisiva, upwards, backwards, and somewhat laterally, in the line of fusion

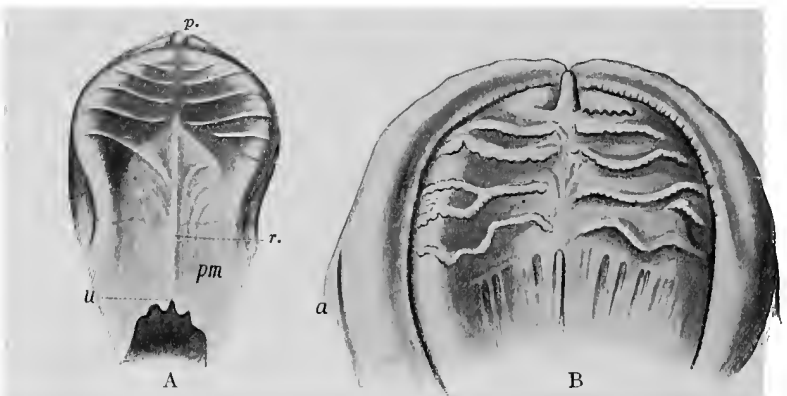

FIG. 256.—Palate of (A) a human embryo of 5.5 cm. and of (B) a new-born child showing the palata ridges. (After Gegenbaur.) *a*, alveolar process; *p.*, incisive papilla; *pm*, velum palati; *r.*, median raphe; *u*, uvula.

of each palatal process with the corresponding processus globularis. The cells of the epithelial strip break down so that a lumen is formed in it, placing the mouth and nasal cavities again in communication anteriorly by what are known as the *incisive canals* (*canals of Stenson*). These usually become obliterated during further development, but occasionally they persist until adult life.

Toward the close of the second month of development ossification begins to extend into the mesenchyme of the palatal processes from the alveolar processes, and the hard palate becomes readily distinguishable from the velum palati; but for a considerable time, up to at least about the middle of the third month, the palate continues to show a distinct median raphe (Fig. 256, A), this indicating the line of fusion of the two palatal processes and terminating anteriorly in the incisive papilla. The uvula also remains distinctly notched for a considerable period (Fig. 256, A), an indication that it is really a bilateral structure and not, as it appears

in the adult, a median unpaired organ. On either side of the median raphe on the hard palate from five to seven almost transverse ridges appear (Fig. 256, A), which represent the palatal ridges occurring in the lower mammals. These ridges later develop minute fringe-like processes on their posterior borders, but at the same time they begin to undergo degeneration, the posterior ones breaking up into rows of papillæ, while the regularity of the anterior ones is disturbed by the formation of cross branches. At birth (Fig. 256, B) the fringe-like processes have almost disappeared, as has also the posterior ridge, and the anterior ones have become very irregular. In this condition they persist throughout childhood, but in adult life they become still more reduced and may eventually disappear altogether.

Inhibition of the development of the palatal processes occasionally occurs, resulting in a failure of their fusion in the middle line, the defect constituting what is known as *cleft palate*. This may vary considerably in its extent, being limited in some cases to the velum palati, in others appearing as a perforation of the palate in the median line, and in others again involving the hard palate as well as the velum palati. In these last cases the cleft cannot continue forward in the median line beyond the anterior extremities of the maxillary processes, since it there meets with the unpaired frontal process, but it may be continued along the line of union of the maxillary and frontal processes on one or both sides, in which case it will usually be associated with harelip.

The Tongue.—The tongue in the amniote vertebrates consists of two portions, quite distinct in their origin and represented in the adult by the body of the tongue anteriorly and the root posteriorly, the two being separated by a V-shaped groove, the *sulcus terminalis*. An examination of the floor of the mouth of an embryo of 5 mm. (Fig. 257) shows a rhomboidal depression in the median line between the ventral ends of the first and second branchial arches, and from this there projects dorsally a rounded tubercle, the *tuberculum impar* of His. Immediately behind this is a deep evagination of the epithelium, which is the median thyreoid evagination, and behind this again is a transverse elevation formed by the ventral ends of the second and third branchial arches, the *copula*. Since the apex of the V-shaped sulcus terminalis corresponds with the foramen cæcum, and since this is the remains of the median thyreoid evagination, it would seem that the anterior portion of the tongue is formed from the region between the first and second branchial arches. It was held by His that it was formed by the enlargement of the tuberculum impar, although as early as 1869 Dursy had described the body of the tongue as having a paired origin, a condition more recently described as occurring in the pig by Born and in man by Kallius and by Hammar (1901). In embryos of 7.5 mm. a swelling appears in the anterior part of the mouth on each side of the median line (Fig. 258, *t*), and the

two increase in size until they occupy the greater part of the interval between the lower ends of the first and second branchial arches, becoming separated from the former by an *alveololingual groove.* The two swellings eventually meet in the median line to form the main mass of the body of the tongue, the amount to which the tuberculum impar participates being probably small, Hammar, indeed, maintaining that it is merely a transitory structure and takes no part at all in the formation of the tongue.

Immediately behind the median thyreoid evagination the lower ends of the second and third branchial arches join to form a median elevation, the *copula* (Fig. 258, *cop*), on the floor of the mouth, and from the anterior portion of this, together with the neighboring portions of the second arch, the root of the tongue develops. His

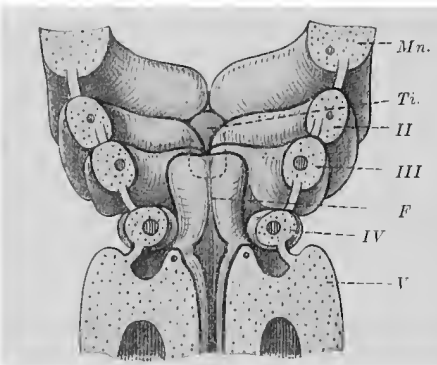

FIG. 257.—Floor of the mouth and pharynx of an embryo of 5 mm. (After His.) *F.*, furcula; *Mn.*, mandibular arch; *Ti.*, tuberculum impar; *II-V*, the branchial arches. The thyreoid evagination is indicated by a dotted line.

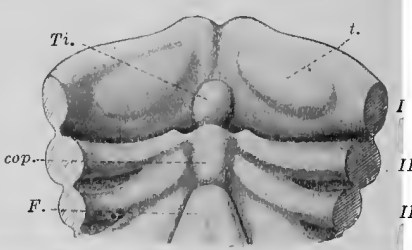

FIG. 258.—Floor of the mouth and pharynx of an embryo of 7.5 mm. (From a reconstruction.) *cop.*, copula; *F.*, furcula; *t.*, anlage of the body of the tongue; *Ti.*, tuberculum impar; *I-III*, branchial arches.

believed that the third arch also took part, but recent observers either limit extensively the participation of this arch or exclude it altogether.

It must be remembered, however, that the tongue is a complex of mucous membrane and muscle tissue, and the statements given above indicate only the regions from which the mucosa is derived in the earlier stages of development. The origin of the musculature has not yet been thoroughly studied in the human embryo, but the fact that it is for the most part innervated by the hypoglossus is indication of its derivation from postbranchial myotomes. When first identifiable the various muscles have already reached the branchial region, so that His assigned the hyoglossus to the third arch, but it is probable that it had already undergone a considerable forward migration before it became recognizable. Indeed, even after it is distinctly differentiated its distribution in the tongue is materially extended, and there is reason for supposing that practically the whole of the tongue musculature under-

goes an extensive migration from the postbranchial region, pushing forward beneath the mucous membrane of the floor of the pharynx and mouth until it occupies the elevations on the floor of the mouth mentioned above. During this migration it invades in succession the territories of the various branchial arches, and consequently the mucosa of the fully developed tongue is supplied by the nerves corresponding to these arches, that is to say, by the trigeminus and facialis anteriorly and by the glossopharyngeus and vagus posteriorly (Fig. 258).

If this view of the development of the tongue musculature be correct, it would seem that a more extensive area of the oropharyngeal mucosa is involved in the formation of the tongue than that associated with the elevations usually regarded as its origins. These undoubtedly represent the first indications of the organ, but with the later elaboration and increase in bulk of its musculature other portions of the mucosa become involved, the complicated innervation being thus produced. It is hardly accurate, therefore, to regard the mucosa of the tongue as being the product of the first and second branchial arches alone, even though its first indications are confined to them. Phylogenetically the copular portion of the tongue seems to be the older, being the only part present in the fishes. In the amphibia also it constitutes the main mass of the tongue, but anterior to it a glandular fold of the mucosa is formed on the floor of the mouth immediately behind the mandibular arch, and in later larval stages this unites with the copular portion representing the body of the amniote tongue. This in its origin is, therefore, essentially a glandular portion of the tongue, with which muscle-fibres, separated from the geniohyoideus, become associated; but in the higher forms its glandular character becomes subordinated and its muscle-fibres increase in number to form the genioglossus. The hyoglossus is probably a derivative of the geniohyoideus, and the intrinsic musculature is apparently derived from these two primary muscles, the transversus linguæ and the vertical fibres from the genioglossus (Fig. 261, GGl) and the longitudinalis from the hyoglossus (Kallius).

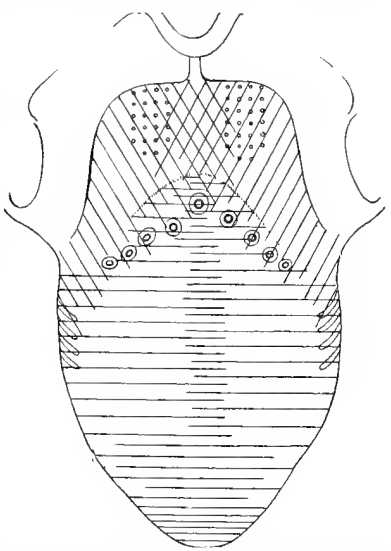

FIG. 259.—Diagram of the distribution of the sensory nerves of the tongue. (After Zander.) The area supplied by the fifth (and seventh) nerve is indicated by the transverse lines, that supplied by the ninth nerve by the oblique lines, and that supplied by the tenth nerve by the small circles.

The fungiform papillæ have become evident in embryos of 50 mm. as elevations of the submucous tissue which project upward into the epithelium, this frequently undergoing proliferation over the elevations so as to produce finger-like papillæ, which are, however, merely temporary structures. The filiform papillæ are at first indistinguishable from the fungiform, only becoming recognizable in embryos of 64 mm. In embryos of 100 mm. taste-buds begin to make their appearance upon the fungiform papillæ, and somewhat later, about the beginning of the fifth month, both varieties begin to project above the general surface of the tongue, owing to the degeneration of the superficial layers of the epithelium in the intervals between the papillæ. The development of the taste-buds on the fungiformes continues during the later fetal months, and at birth, as well as for some time after, the buds are greatly in excess of the number present in the adult, their subse-

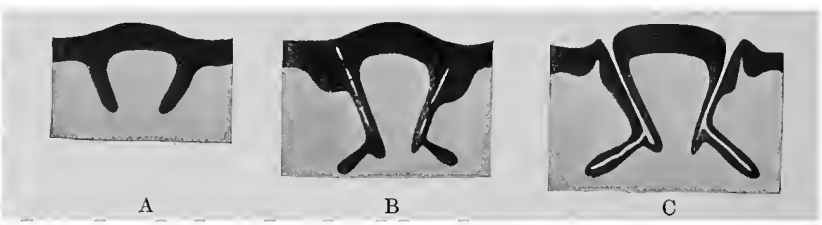

FIG. 260.—Diagrams illustrating the development of the vallate papillæ. (After Gråberg.)

quent reduction in number being associated with the change in the nature of the food of the child occurring at the time of weaning (Stahr).

The vallate papillæ are represented in embryos of 90 mm. by two epithelial ridges, situated toward the posterior portion of the tongue and inclined toward one another in a V-shaped manner, the apex of the V practically corresponding with the mouth of the median thyreoid evagination. From these ridges downgrowths of the epithelium take place into the subjacent submucosa, each downgrowth having the form of a hollow truncated cone whose base is continuous with the mucosa and whose centre is occupied by a portion of the submucosa, which thus becomes surrounded by a solid wall of epithelial cells (Fig. 260, A). During the fourth month lateral outgrowths take place from the deeper edges of the wall, and at about the same time clefts begin to appear in its substance (Fig. 260, B); these increase in size and eventually open to the surface a trench, lined by epithelium, thus surrounding a papilla (Fig. 260, C). The lateral outgrowths from the deeper edges of the downgrowths also become hollow by the degeneration of their central cells and form the glands of Ebner, and during the development taste-buds differentiate from the basal layers of the epithelium. These make their appearance quite early in the

development of the papillæ, being recognizable even in a fetus of three months (Gråberg), and increase in number as development proceeds, being formed not only on the sides of the papillæ but also on their free horizontal surfaces, those in the latter situations, however, for the most part disappearing after birth. The development of the individual papillæ is subject to considerable variation both in number and time, and, as a rule, is not completed until after birth. The foliate papillæ appear much later than the other varieties, being indistinguishable in embryos of four and a half and five months although quite distinct in those of seven months (Tuckerman).

Anomalies of the tongue which may be assigned to interferences with the normal processes of development are not of frequent occurrence. A condition of *diglossia* has, however, been described, in which the anterior portion of the organ is divided throughout the greater or lesser portion of its extent, producing what might be spoken of as a forked tongue. This is especially interesting as indicating the development of the body of the tongue mainly from two primary anlagen, rather than from a single median structure such as the tuberculum impar.

The Salivary Glands.—Of the glands of the mouth the most important are the salivary glands,—that is to say, the parotid, the submaxillary, the sublingual, and the alveololingual. The first three of these are individual glands, formed from a single epithelial outgrowth and having in the adult condition a single duct opening into the mouth cavity, that for the sublingual being known in anatomy as the ductus sublingualis major (duct of Bartholin). The alveololingual glands, on the contrary, consist of a group of glands each of which is provided with its own duct, and they are generally associated with the sublingual gland proper as the glandula sublingualis, a structure which, however, is not comparable morphologically to one of the other salivary glands, but rather to a group of them.

The first of the salivary glands to appear in the embryo is the parotid, which has been detected in an embryo of 8 mm. as a furrow in the floor of the alveolobuccal groove in the neighborhood of the angle of the mouth (Hammar). At first quite small, the furrow gradually elongates, and before the embryo has reached a length of 17 mm. it separates from the epithelium and forms a tubular structure lying beneath the epithelium of the alveolobuccal groove and opening into the mouth cavity at a point which corresponds with the anterior end of the original furrow. Mesenchymatous tissue gradually forces its way between the tube and the alveolobuccal epithelium, and the tube, increasing in length, pushes its way back over the masseter muscle to the neighborhood of the external ear. As it comes into this region the tube or duct, as it may be called, begins to branch at its posterior extremity, the

branches being at first solid outgrowths from the wall of the duct, and, as these increase in number and size and become surrounded by a mesenchymatous capsule, the gland assumes the position and general form of the adult structure. The accessory parotid gland arises as an outgrowth from the duct as it passes over the masseter muscle, and its further development is similar to that of the main gland.

The account given above of the origin of the gland is based on the recent observations of Hammar, and these differ in some respects from those of earlier investigators (His, Chievitz), who first perceived the gland in embryos of seven and a half or eight weeks' development and describe it as formed from a solid outgrowth from the alveolobuccal epithelium. It is worthy of note that the gland is primarily lateral to the internal carotid artery, the posterior facial vein, and the facial nerve, and although these structures may eventually become more or less surrounded by its alveoli, yet their position is always medial to the principal ducts of the gland.

In embryos of the twelfth week Chievitz observed a branch arising from the parotid duct just where it crossed the anterior border of the masseter muscle and passing deeply to come into relation with the internal pterygoid, where it ended blindly in a small enlargement. The same structure was also observed in an embryo of ten weeks, but in this case it had lost its connection with the parotid duct, and the same condition may be observed in embryos of nine weeks or even earlier. What its significance may be is at present uncertain, but the possibility of its being the origin of cystic growths in the cheek is perhaps worthy of mention.

The submaxillary gland appears in embryos of the sixth week (13.2 mm.) as a ridge-like thickening of the epithelium of the alveololingual groove, the anterior end of the thickening lying some distance behind the frenulum linguæ. The ridge later separates from the epithelium from behind forward, and the solid cord so formed grows downward and backward toward the submaxillary region, its enlarged terminal portion branching to form the gland proper, while the remainder of the ridge becomes the duct (Fig. 261, *SMx*) and gradually shifts its anterior connection with the epithelium forward until it reaches the adult position. During this development the duct acquires its lumen, although the buds which form the alveoli of the gland remain solid until a much later period.

The sublingual and alveololingual glands develop in a manner very similar to the submaxillary. They appear as solid downgrowths of the epithelium of the alveololingual groove (Fig. 261, *SL*), the sublingual beginning to form at about the eighth week immediately lateral to the anterior termination of the submaxillary duct, and the alveololinguals somewhat later and posterior to the larger sublinguals. Frequently, however, the sublinguals do not appear (Chievitz), the so-called sublingual gland of the adult then being formed entirely by the alveololinguals, and these also seem to be variable in number, Chievitz finding from 11 to 13 on the two sides in an embryo of the twelfth week, while in one of 40 mm.

I have found 11 on the left side and 9 on the right, the left side also possessing a sublingual gland although it was absent on the right side.

The histogenetic development of the salivary glands is not completed until some time after birth, probably not until after the child is weaned. The canalization of the solid anlagen of the glands proceeds peripherally, and so long as the terminal branches remain solid they have the power of producing additional buds. When, however, the lumen is formed in a bud and it becomes an alveolus, its power of budding is lost, and the further increase in the size of the gland is due to the development of the investing connective tissue and to an increase in the size of the alveoli already present. The specific characters of the cells also become

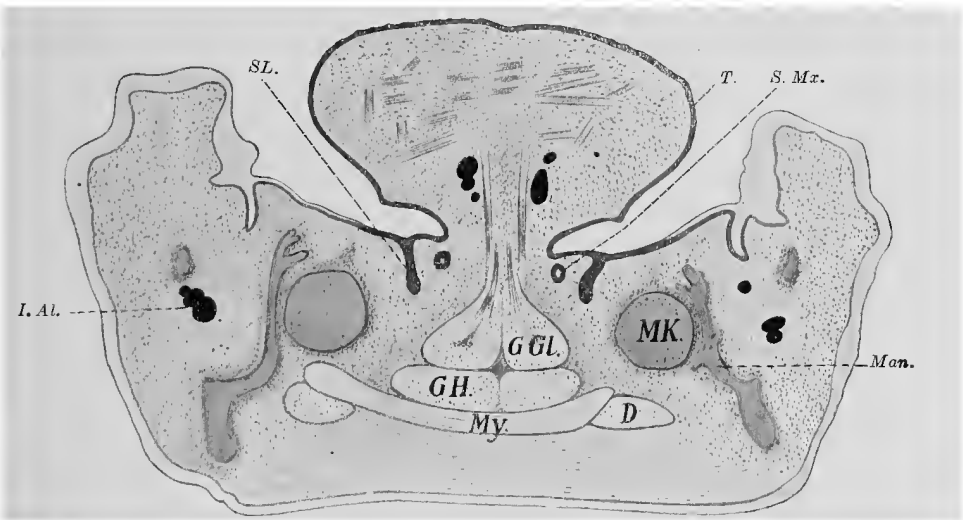

FIG. 261.—Transverse section of the lower jaw and tongue of an embryo of about 20 mm. *D*, digastricus; *G.Gl.*, genioglossus; *GH.*, geniohyoideus; *I. Al.*, inferior alveolar nerve; *Man.*, mandibular ossification; *Mk.*, Meckel's cartilage; *My.*, mylohyoideus; *SL.*, sublingual gland; *S.Mx.*, submaxillary duct; *T.*, tongue.

evident only after the canalization of the alveoli, mucin cells becoming distinguishable in the alveololingual glands of embryos of the 16th week and acinus cells in the parotids of those of five months. The demilune cells of Gianuzzi are developed from the cells lining the alveoli and are only secondarily overgrown by the mucous cells.

Anomalies of the salivary glands are of rather infrequent occurrence; a case of inhibition of the growth of the parotid has, however, been described, the gland being entirely confined to the buccal region, no trace of it occurring behind the masseter muscle.

The Teeth.—At about the time when the primary labial grooves are formed—that is to say, in embryos of about 11 mm.—

a ridge-like thickening of the epithelium appears upon what will be the alveolar portions of the maxillary and mandibular processes and also extends upon the portion of the upper jaw formed from the processus globulares (Fig. 253). These ridges are parallel with and immediately posterior (medial) to the labial grooves, and in later stages they penetrate more deeply into the mesenchyme in a somewhat oblique direction, so that they seem almost to be derivatives of the epithelium of the labial grooves (Fig. 262, A). From the deeper surface of each of these *dental ridges* a series of papillæ project more deeply into the mesenchyme, and in embryos of 40 mm. the deeper surface of each papilla has become concave and the concavity is occupied by a mass of condensed mesenchyme, the *mesenchyme papilla,* the epithelial and mesenchyme papillæ together constituting a *dental papilla* (Fig. 262, B). The number of papillæ so formed is normally ten in each jaw, one

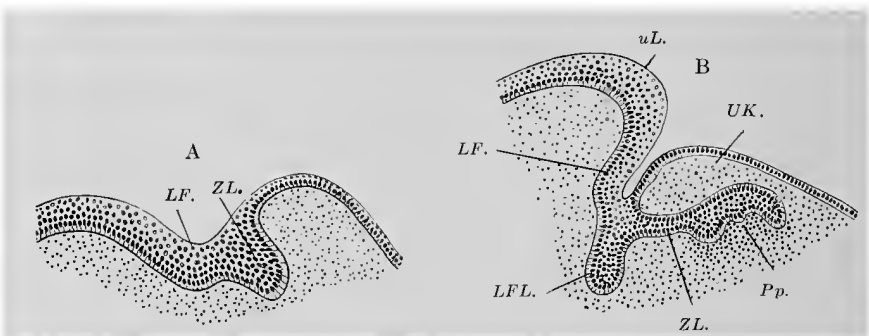

FIG. 262.—Section through the dental ridge of the lower jaw of embryos of (A) 17 mm. and (B) 40 mm. (After Röse.) *LF.* and *LFL.*, labial groove; *Pp.*, dental papilla; *UK.*, lower jaw; *uL.*, lower lip; *ZL.* dental ridge.

corresponding to each tooth of the milk dentition, and as they proceed in their development they gradually separate from the dental ridge, which, on its part, becomes prolonged backward in the mesenchyme beyond the point at which the papilla for the second molar of the milk dentition is formed. Three additional papillæ appear on each side on these prolongations of the ridges, representing the permanent molars, that for the second molar forming, however, only in the sixth week after birth and that for the third molar not until the fifth year. As the papillæ for the milk dentition separate from the dental ridges these begin to degenerate, becoming converted into a network of epithelial trabeculæ (Fig. 263), except along their lingual border, where a continuous cord persists; from this a second series of papillæ arises, from which the permanent teeth, which replace the milk dentition, are formed. As the papillæ for these teeth separate from the cord, it finally undergoes degeneration and, with the other remains of the dental ridges, eventually disappears, except for fragments

of either the cord or the trabeculæ which may persist imbedded in the surrounding mesenchyme and are known as *epithelial pearls.*

In each dental papilla two different structures are concerned, a mesenchyme papilla, from which the tooth pulp and dentine are formed, and an epithelial papilla, which invests the mesenchyme papilla like a cap and gives origin to the enamel, whence it is spoken of, in its later stages, as the *enamel-organ.* Nerves and blood-vessels make their way into the mesenchyme papilla, and certain of its cells arrange themselves in a single continuous layer over its surface and assume a columnar form, constituting the *odontoblasts* (Fig. 264, *Od*) by which the dentine is manufactured. This material appears to be formed by the transformation of a

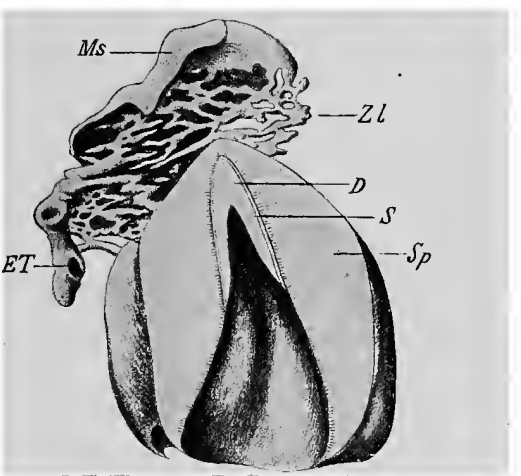

FIG. 263.—Reconstruction of the dental ridge and a papilla of an embryo of 30 cm. (After Röse.) *D*, dentine; *S*, enamel; *Zl*, cord-like remnant of the dental ridge which gives rise to the papillæ of the permanent teeth; *Ms*, oral mucous membrane; *ET*, epithelial trabeculæ representing the original dental ridge; *Sp*, enamel pulp.

portion of the protoplasm of the odontoblasts into a gelatinous substance, which later becomes fibrillar and in which lime salts are eventually deposited. These deposits are at first in the form of spherical concretions, but later the interstices become filled up, numerous minute *dentinal tubules,* branching at their outer ends, traversing the matrix from within outwards and containing slender prolongations of the unaltered protoplasm of the odontoblasts, whose growth during the active period of dentine formation compensates for the loss of substance entailed in the formation of the matrix.

This account of the formation of the dentine follows essentially the results of von Ebner. Recently von Korff has maintained that the dentine has a double origin, the first indication of it being bundles of connective-tissue fibrils, which are formed by the pulp cells of the mesenchyme papilla and extend outward between the odontoblasts. These latter structures produce the interfibrillar substance of the dentine and secrete the lime salts which are deposited in this. While

these results of von Korff bear the stamp of probability, it seems advisable to await their further confirmation before adopting them in their entirety.

The dentine is formed from the outer ends of the odontoblasts and therefore lies immediately internal to the products of the enamel-organ. This differentiates (Fig. 264) into an outer epithelial layer consisting of more or less flattened cells, beneath which is a mass of tissue composed of stellate cells widely separated by the distention of the intercellular spaces, so that the tissue has a spongy appearance. This is the *enamel-pulp,* and internal to it is a single layer of large columnar cells, the *ameloblasts,* which are the active elements in the production of the enamel. The inner cells of the enamel-pulp are usually more closely aggregated than the rest, and form an epithelial-like layer external to the ameloblasts, which is termed the *intermediate layer.* As in the case of the odontoblasts the ameloblasts persist throughout the entire formation of the enamel, each cell producing one of the enamel-prisms. The first indication of the enamel is a delicate cuticular membrane covering the inner extremities of the ameloblasts, and to this succeeds the formation of a series of homogeneous columns, one corresponding to each ameloblast. Later the homogeneous material differentiates into bundles of fibrils, the *enamel processes* (*processes of Tomes*), imbedded in a homogeneous matrix, and, finally, the calcification of the columns ensues, this process being, according to some observers a calcification of the enamel processes, while others hold it to be a deposit of lime salts in the matrix surrounding the fibres. Even before the formation of the enamel is completed the degeneration of the enamel-organ begins, blood capillaries making their way through the outer epithelial layer into the enamel-pulp, which gradually becomes indistinguishable from the surrounding mesenchyme, and finally the layer of ameloblasts

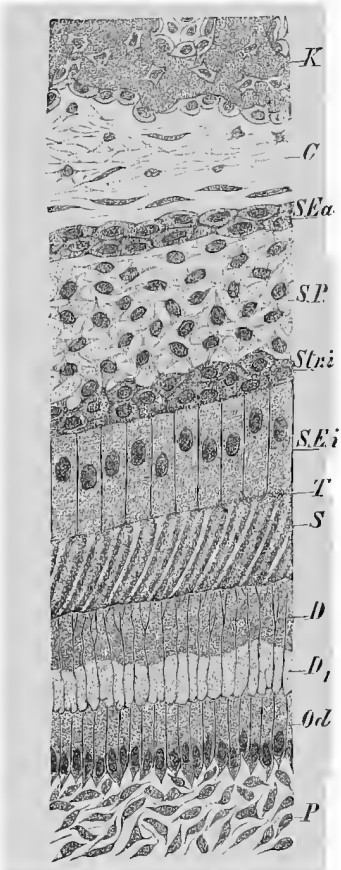

FIG. 264.—Section through a developing molar tooth of Didelphys. (After Röse.) *C*, connective tissue; *D*, calcified, and D_1, uncalcified dentine; *K*, wall of dental alveolus; *Od*, odontoblasts; *P*, pulp cells; *S*, enamel; *SEa*, outer epithelial layer of the enamel-organ; *S.E.i*, ameloblasts; *S.P.*, enamel-pulp; *Str.i*, intermediate layer of enamel-organ; *T*, Tomes's processes of the ameloblasts.

breaks up into fragments, some of which are usually to be found around the roots of the teeth even in the adult.

The cement which covers the dentine of the roots of the teeth is formed from the surrounding mesenchyme by a process identical with that by which membrane bone is formed.

As the teeth increase in size they gradually approach the surface of the alveolar processes and eventually break through the gum, not, however, at a point in the line of the original downgrowth of the dental ridge, but posterior to this, the first teeth to erupt being usually the median incisors, which make their appearance during the last half of the first year after birth. The remain-

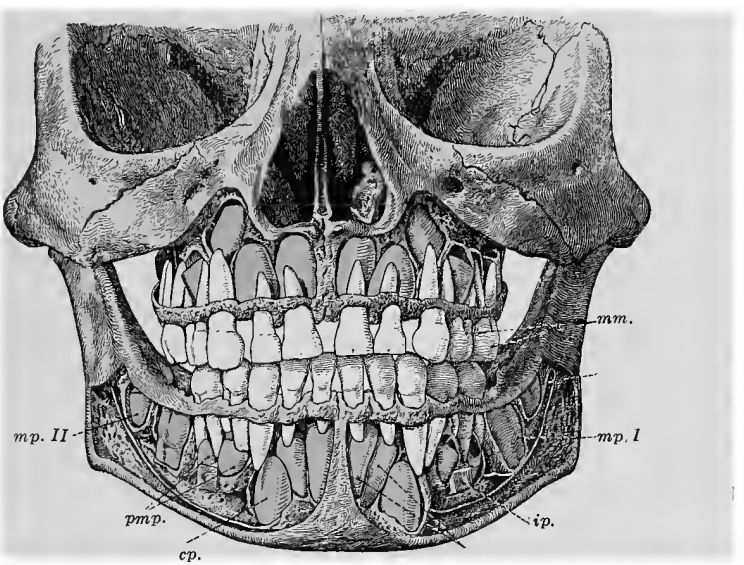

FIG. 265.—Skull of a 5-year-old child showing the milk and permanent dentitions. (After Sobotta.) *cp.*, permanent canine; *ip.*, permanent incisor; *mm.*, milk molars; *mp.I*, first permanent molar; *mp.II*, second permanent molar; *pmp.*, permanent premolar.

ing teeth of the milk dentition appear in succession up to about the middle of the third year. Shortly after their appearance, however, these teeth begin to undergo absorption, this being associated with the continued growth of the permanent teeth (Fig. 265). The milk-teeth lose their shiny appearance, their pulp dies, and an absorption of their roots occurs, beginning at the side in contact with the corresponding permanent tooth and being associated with the appearance of osteoclasts similar to those producing the absorption of ordinary bone. Their alveoli also undergo absorption, and finally their attachments become so feeble that the teeth are readily pulled or broken away.

The exact period of eruption of the various teeth varies con-

siderably according to racial, climatic, and nutritive conditions, but the usual sequence is somewhat as follows:

THE MILK DENTITION.

Median incisors	6th to 8th month
Lateral incisors	8th to 12th month
First molars	12th to 16th month
Canines	17th to 20th month
Second molars	20th to 24th month

THE PERMANENT DENTITION.

First molars	7th year
Median incisors	8th year
Lateral incisors	9th year
First premolars	10th year
Second premolars	11th year
Canines, Second molars	13th to 14th year
Third molars	17th to 40th year

Anomalies are not infrequent in connection with the development of the teeth, leading sometimes to a diminution and sometimes to an excess of the normal number. A case of total congenital absence of the teeth has been observed, and also cases in which there had apparently been a defect of the enamel-organ leading to the development of rudimentary teeth lacking enamel. The fusion of two neighboring tooth germs may also occur, as well as the reverse, that is to say, a splitting of a tooth germ so that an accessory tooth or indeed a number of small teeth may be present in the place of one of the normal teeth. More remarkable are the instances of heterotopy which occur, due apparently to the existence of aberrant processes of the dental ridges extending into regions beyond the alveolar processes. Thus, incisor teeth have been observed to form in the nasal cavity, in the maxillary sinus, and even in the orbit, and molars have developed upon the hard palate. Numerous cases of supernumerary dentitions have also been recorded, one or more teeth being replaced more than once. Many of these cases have been supposed to be really the belated development of the normal permanent tooth, but some do not seem referable to this condition, and must be regarded as due to the persistence in an active condition of portions of the dental ridge or to the awakening to functional activity of some of the epithelial pearls which are remnants of it.

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THE DEVELOPMENT OF THE ŒSOPHAGUS.

BY FREDERIC T. LEWIS.

Early Development.—The œsophagus in the 4.0 mm. Bremer embryo (Fig. 266) is an epithelial tube which is greatly flattened laterally. Its lumen is a well-defined dorso-ventral cleft. In most places the epithelium shows two rows of somewhat elongated nuclei, and the row next the lumen exhibits numerous mitotic figures. In the upper part of the œsophagus, at the place where its lateral walls meet dorsally, the epithelium has only one row of nuclei, but the ventral border is expanded and has three or four rows. This thickened portion, however, belongs with the respiratory tract, which has not yet been separated from the œsophagus. The mesenchyma around the œsophagus is an undifferentiated layer with crowded nuclei and many mitotic figures. Below the

lung-bud, on either side, the mesenchyma is closely connected with the adjacent cœlomic epithelium, from which it is being produced. There is no histological demarcation between the œsophagus and pharynx above or the œsophagus and stomach below.

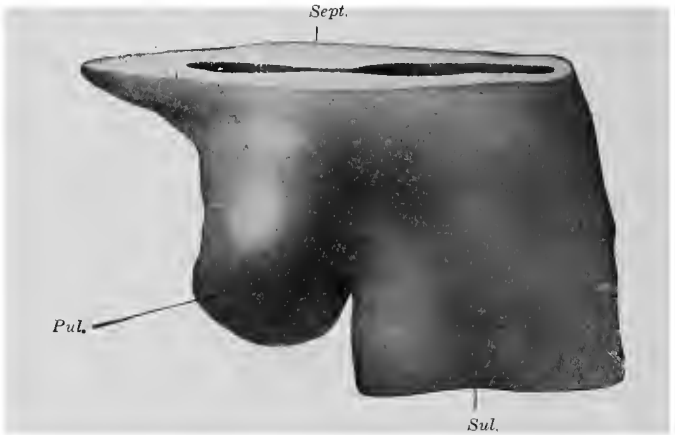

FIG. 266.—Wax model from Bremer's 4 mm. embryo, showing the "lung-bud," *Pul.*, and the adjacent part of the œsophagus. × 175 diam. *Sept.*, tracheo-œsophageal septum; *Sul.*, lateral œsophageal groove.

The Epithelial Tube.—In older embryos, as Forssner recorded (1907), the œsophagus becomes "not only relatively but absolutely smaller in cross section, and the lumen is reduced to a fraction of its former size." In an embryo of 7.5 mm. the most slender portion of the œsophagus has a cross section about one-third as large as in the 4 mm. embryo, and a lumen one-twentieth as large, yet the length of the œsophagus has increased from less than 0.5 mm. to 1.5 mm. The lower portion of the œsophagus remains flattened laterally, but the upper part has become a round tube which is entirely separate from the trachea. It tapers from the larynx downward, and the lumen becomes minute. The epithelium has 3–4 rows of nuclei above, and is quite like the lining of the pharynx. In the narrowest part of the œsophagus there are but two rows. Mitotic figures are seen almost exclusively in the layer of cells bordering upon the lumen.

In four embryos measuring from 8.4 to 16 mm. the epithelial tube of the œsophagus is shaped as follows: At its laryngeal end it is crescentic, with the concavity of the crescent directed toward the trachea. On its way to the stomach it first becomes round and then transversely elliptical. Near the level of the bifurcation of the trachea it is again round and finally it becomes dorso-ventrally elliptical. In this shape it merges with the stomach. In all of these specimens the lumen is pervious throughout, but it contains a reticular coagulum. The epithelium shows from two to four rows of nuclei. Schridde (1907 and 1908) states that in embryos meas-

uring from 4 to 35 mm. the œsophageal epithelium has only two layers, although in thick sections (7–10 μ) the number may appear greater. In a 13 mm. embryo he finds that "in a striking manner, the nuclei of both layers are in the upper ends of the cells, toward the lumen," and this condition was figured by Schaffer in 1904. Jahrmaerker (1906) has described two 8 mm. embryos in which the œsophageal epithelium is composed of two layers of tall cells, with a narrow zone free from nuclei along both the basal and free borders. He finds similar conditions in embryos of 14 and 16 mm. A basal zone free from nuclei is shown in Fig. 267, *A*, but in this section the nuclei are crowded toward the free surface, forming a darkly staining band. Jahrmaerker, in describing embryos of 17 and 18 mm., states that the superficial layer of the epithelium is more deeply stained than the basal layer, but he does not attribute this to a crowding of the nuclei. At 10 mm., as in the smaller embryos, mitotic figures were frequent in the inner layer. In the older specimens no figures were preserved.

Vacuoles in the Epithelium.—In human embryos of about 20 mm., large vacuoles occur in the œsophageal epithelium, so that in cross section the œsophagus may appear to have two or three lumina. This was noted by O. Schultze in 1897. Kreuter (1905) studied the vacuoles, and concluded that they were associated with an epithelial proliferation which led to a temporary occlusion of the œsophagus. He had previously studied the solid œsophagus of various vertebrates, following Balfour and others. Forssner (1907) showed by means of a model that the main lumen of the human œsophagus is not obliterated.

In an embryo of 22.7 mm. Forssner found "an uninterrupted open central lumen with a mass of cavities on either side of it, some of which communicate with the main lumen and others do not; some of them are much smaller and others considerably larger than the lumen itself. These formations may be found scattered along the entire œsophagus (22.7 mm.); sometimes only below (20 mm.), sometimes only above (30.5 mm.). In the 31 mm. embryo the wall of the œsophagus, as compared with the main lumen, is considerably thinner than before. The epithelium is several layered; it shows none of the cavity formations just described and the lumen is everywhere undivided. That this process in the œsophagus has the result of enlarging the lumen appears probable."

Schridde (1908) likewise failed to find an occlusion at any stage.

He denies the presence of vacuoles in the following conclusion: "All these facts go to show that vacuoles never occur in the œsophagus. On the contrary, epithelial bridges are clearly present, having arisen by epithelial proliferation in circumscribed places."

The structures in question are shown in Fig. 267, *B*. Here the central lumen of the œsophagus is bounded by a compact dark zone of nuclei, thus differing from the accessory cavities. *C* and

D in Fig. 267 represent successive sections from a 22.8 mm. embryo. In *C* there are two accessory cavities with compact linings, and the one on the left communicates with the general lumen in *D*. The œsophagus of these embryos has been modelled by F. P. Johnson in a study of the development of the intestinal mucous membrane.[11] His work affords an independent confirmation of Forssner's conclusions, and shows that Schridde was in error in denying the presence of vacuoles.

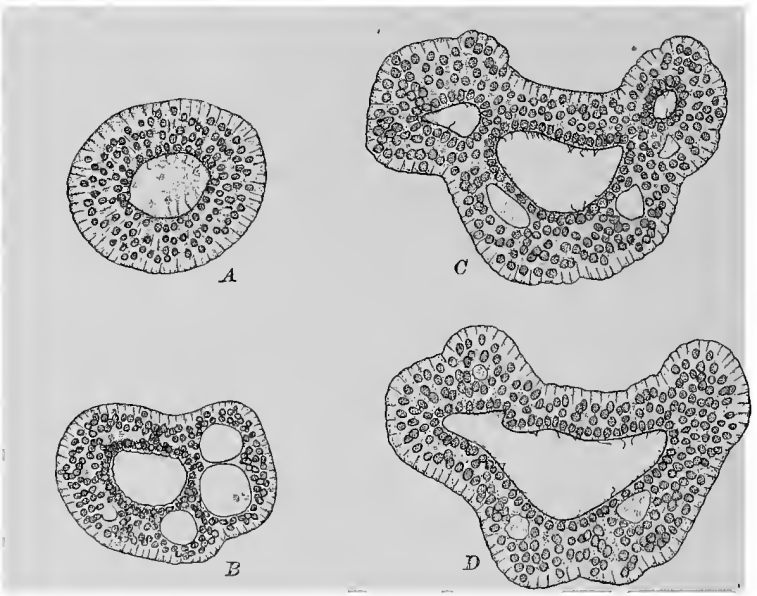

FIG. 267.—Transverse sections of the epithelial tube of the œsophagus. × 160 diam. *A*, embryo of 16 mm. (Harvard Collection, Series 1322). *B*, 19 mm. (Harvard Collection, Series 819). *C* and *D*, successive sections from an embryo of 22.8 mm. (Harvard Collection, Series 871).

Vacuoles have been found in embryos of 14.5 mm. (Keibel and Elze), but they are sometimes absent in those of 18.5 mm. (Forssner). They acquire a maximum development in specimens of about 20 mm. In a 30 mm. embryo there are occasional vacuoles in the upper part of the œsophagus. In a 42 mm. specimen some small intercellular cavities are found, but there are no characteristic vacuoles.

In discussing the origin of the vacuoles, Kreuter has said correctly that "we have no ground for believing that there is a degeneration of cells, but must conclude that it involves throughout only vital processes. . . . A degeneration of cells followed by resorption is nowhere demonstrable." Forssner suggests that

[11] The work of Mr. Johnson, which was undertaken in connection with this chapter, has recently been published in the Amer. Journ. of Anat., vol. 10, p. 521–561, 1910.

there are two sorts of vacuoles, those due to the accumulation of intercellular fluid and those due to an active moving apart of the cells. The cavities in the œsophagus seem to belong to the latter class. It is possible that their formation is associated with the transfer of mitotic activity from the inner to the outer row of cells. A centre of mitosis in the outer layer would account for the local bulging of the epithelium. It is clear that a transfer of mitotic activity from the inner to the outer layer must take place in the embryo, but at what stage this happens is not known. It is generally agreed that the result of the vacuole formation is the enlargement of the lumen.

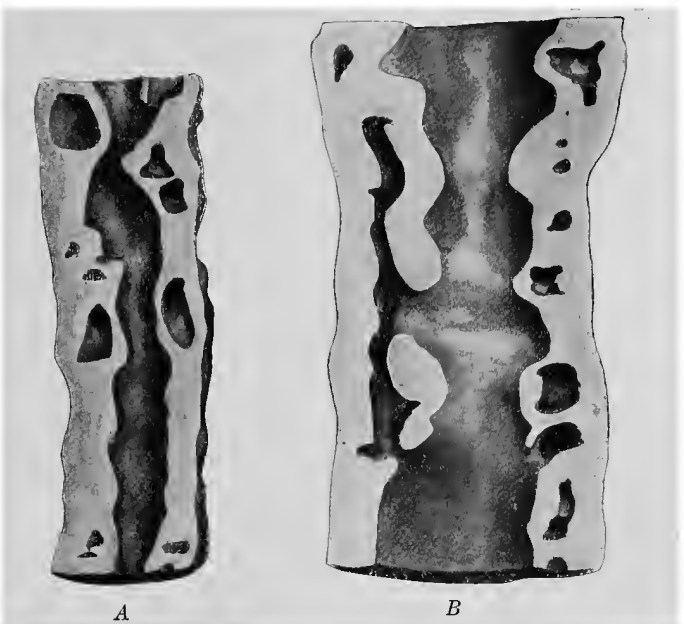

FIG. 268.—Models showing the epithelial tube of the œsophagus cut longitudinally. × 120 diam. (After F. P. Johnson.) *A*, embryo of 19 mm. (Harvard Collection, Series 819). *B*, 22.8 mm. (Harvard Collection, Series 871).

Folds.—In cross sections of the œsophagus in embryos of about 10 mm., the lumen presents a clear-cut, round or elliptical outline. In older embryos, owing to the formation of broad folds, in which the mesenchymal layer takes part, the lumen becomes irregularly crescentic, tri-radiate, or shaped like a "Greek cross" (Fig. 269). The fusion of the vacuoles with the central lumen contributes to the irregularity of the shapes presented. Notwithstanding the secondary folds, however, the early form of the œsophageal tube may be recognized even in 30 mm. specimens. The long axis, which is transverse above, becomes dorso-ventral below. This arrangement suggested to Kreuter that the lower part of the œsophagus shared in the rotation of the stomach, but he concluded that

"mechanical considerations are against this idea." Johnson has described a dorsal and a ventral fold in the middle part of the œsophagus of a 42 mm. embryo, which become left and right respectively as the stomach is neared. The main trunks of the vagus nerves, which are lateral in the upper part of the œsophagus, become dorsal and ventral below, where, however, they are involved in a coarse plexus. This relation lends support to the idea that the epithelial tube may rotate, but to demonstrate this a more

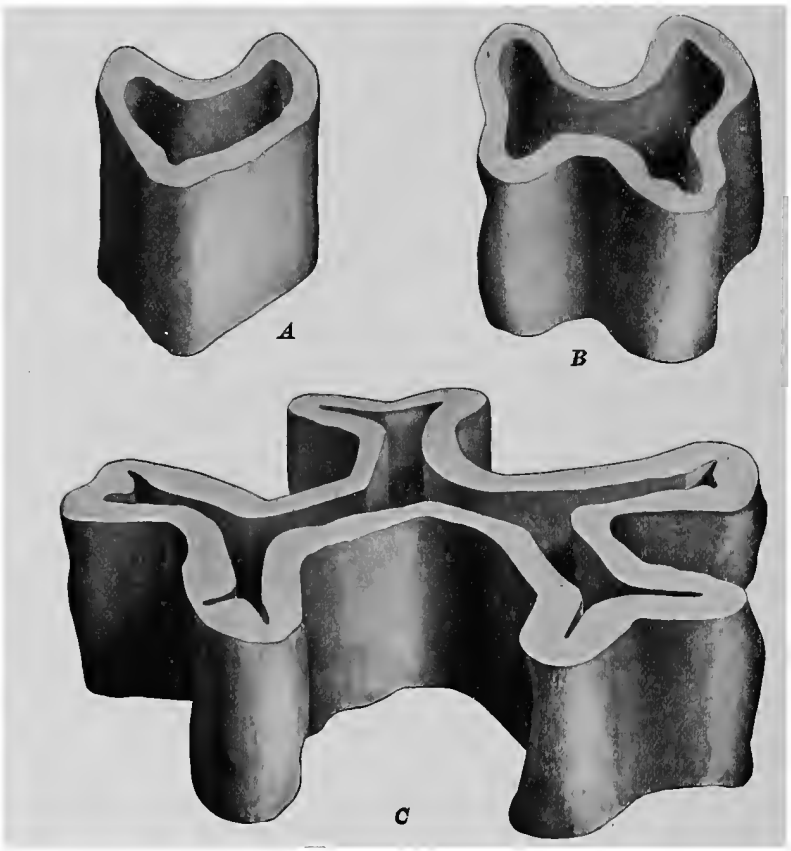

FIG. 269.—Models showing the development of the epithelial folds in the middle portion of the œsophagus. × 90 diam. (After F. P. Johnson.) *A*, embryo of 37 mm. (Harvard Collection Series 820). *B*, 42 mm. (Harvard Collection, Series 838). *C*, 120 mm.

critical study is required. The primary folds in the œsophagus appear to be definitely situated, but those which come later vary in different embryos.

Ciliated Cells.—In 1876 Neumann recorded that in embryos of from 18 to 32 weeks the œsophagus is lined with stratified ciliated epithelium, which, however, is interrupted in many places by non-ciliated areas. He states that by isolating the cells through maceration in Müller's fluid, he obtained all sorts of transition

forms between ciliated columnar epithelium and flat epithelium. In a later publication (1897) he has figured the isolated cells, and has shown that the cilia are associated with distinct basal bodies. The smallest embryo in which the cilia have been found measures 44 mm., and its age is estimated at "about 69–70 days" by Jahrmaerker, and at "10–11 weeks" by Schridde, both of whom described this specimen. Schaffer failed to find cilia in a twelve weeks' embryo. They are apparently absent in a specimen of 42 mm. in the Harvard Collection, but are abundant at 55 mm. Cilia are still present at birth according to several observers, but in the specimens examined by Jahrmaerker and Schridde none were found. Fig. 270 is from the œsophagus of a negro child at birth, in which ciliated cells are abundant.

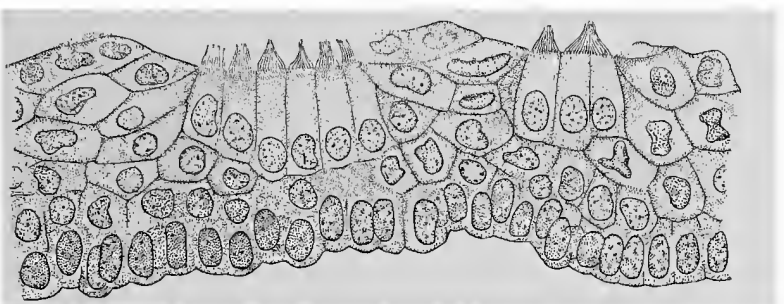

FIG. 270.—Section of the œsophageal epithelium at birth. × 600 diam.

The ciliated cells arise simultaneously in various parts of the œsophagus at a time when the epithelium is two-layered. They appear to belong with the superficial layer, but Schaffer (1904) has found that some of them may be traced through the entire epithelium to the basement membrane. Jahrmaerker nevertheless considers that the ciliated cells belong with the outer layer, in which some cells become ciliated and others do not. He finds that both forms of cells have finely granular, darkly stained protoplasm.

In the 44 mm. embryo, according to Jahrmaerker, the free surface of many non-ciliated columnar cells, generally in small groups or bordering upon the ciliated areas, shows a distinct dark border, which seems to indicate a transition to the ciliated form.

Schridde (1907), by using Unna's Wasserblau-Orcein, found that the ciliated cells have a dark-blue, finely granular protoplasm, and stand out distinctly from the clear columnar cells. He writes: "The discovery of ciliated cells extending to the basement membrane seems to me to be of special significance. In my opinion it is therefore certain that the ciliated cells are not derivatives of the upper layer. . . . We must rather consider that these elements are formed from the basal cells."

However, Schridde has neither figured nor described any darkly stained cell which has not reached the free surface, such as would be expected if certain basal cells were pushing outward.

For a time the number of ciliated cells increases. Thus the ciliated areas in a 99 mm. embryo are more extensive than at 55 mm., as shown in models made by Johnson. The epithelium becomes 3–5 layered, but even in five-layered epithelium, according to Schridde, ciliated cells may sometimes be traced to the basement membrane. Ultimately their basal processes are lost and the ciliated cells appear crowded between adjacent vesicular cells. They are more deeply stained than before, which has been attributed both to compression and to degeneration. It is agreed by Schaffer, Jahrmaerker, and Schridde that the ciliated cells are desquamated, together with the outer non-ciliated cells, and in well-preserved specimens they may be found free in the lumen of the œsophagus. It appears improbable that they lose their cilia and become vesicular cells, as Neumann originally maintained. He seems to have observed various shapes of ciliated cells, rather than transition forms.

Non-ciliated Cells.—Schridde has described the differentiation of the non-ciliated cells as follows: In a 100 mm. specimen (16 weeks) the epithelium appears 4–5 layered, and is composed of clear, polyhedral cells. The lowest layer likewise consists of clear cells, which almost throughout are cuboidal or low columnar in form. In a slightly older specimen, under low magnification, the basal layer appears darkly stained. With an immersion lens, the protoplasm of the dark cells is seen to contain interlacing fibrils. The "fibre-cells" are pushed outward, gradually displacing the clear cells. In embryos between 195 and 240 mm. they are found in all of the layers, but some of the earlier generation of clear cells are retained at birth, and they were seen in a child of three days. Intercellular spaces bridged by fibrils were first found in a child at birth. Keratohyalin granules do not appear in the superficial cells until some time after birth.

Schridde finds the number of layers in the epithelium to be 8–10 in a thirty-six weeks' embryo, 9–10 at birth, and 12–15 three days after birth. In the specimen from which Fig. 270 was drawn, the number of layers is from 3 to 7, and this accords with Rückert's statement (1904) that the flat epithelial covering of the œsophagus at birth is very thin, sometimes consisting of only two layers. The outermost cells, moreover, are not greatly flattened.

In the lower part of the œsophagus at birth, Strecker (1908[1]) found numerous irregular clefts in the epithelium, so disposed that sometimes the intervening cells appeared as pointed epithelial papillæ. In the œsophagus of a child of 13 months he reports true epithelial papillæ with connective-tissue cores. "These are occasionally pointed, but generally they are conical, suggesting in their shape the *papillæ fungiformes* of the tongue." The portion of the œsophagus in which they occur, he regards as belonging with the cardiac antrum or "Vormagen."

Glands.—Small groups of secreting cells, which represent the earliest gland formations in the œsophagus, may be found in embryos of about 78 mm. (3 months). An imperfect series of such a specimen in the Harvard Collection is sufficient to show that these areas are present both at the upper and lower ends of the œsophagus.

Schaffer (1904) described such cells in a 4 months' embryo as follows: "With low magnification a well-defined, small, lighter group of cells was seen

in the epithelium of the lateral pocket of the œsophagus, at the level of the third or fourth tracheal cartilage. With higher magnification I found the typical, several-rowed ciliated epithelium . . . interrupted by a group of clear, remarkably tall columnar cells, arranged in a single layer which bulged slightly above the epithelial surface. The number of these cells, in the cross section, was about ten. Their nuclei, placed well toward the base, formed a row which bulged somewhat toward the underlying tissue. In their finer structure the cells accorded fully with the account which d'Hardivillier (1897) has given of the prismatic gland-cells in a 7 months' embryo. The cells appeared as if empty; only their walls stood out clearly. Their upper ends lacked not only the cilia but the border of basal bodies."

Schridde (1907) found a similar group of five very tall columnar cells in the lateral pocket of an embryo of 105–110 mm. (16–17 weeks). They were at the level of the cricoid cartilage. In regard to their structure he states: "The upper end of these cells was filled with an elongated oval plug, distinctly red-stained, and presenting a well-defined honey-comb structure. That these plugs were of mucus was shown by Unna's stain, which I am convinced offers a good reaction for mucus, and also by staining with mucicarmin."

FIG. 271.—Section through a group of mucous cells near the cardiac end of the œsophagus of an embryo of 240 mm. × 600 diam.

At the lower end of the œsophagus, as seen in older embryos (120 mm. and 240 mm.), such cells are very abundant. Some of them occur in small groups, such as Schaffer and Schridde described (Fig. 271). The secretion, as indicated by the vacuolated protoplasm, nearly fills the cells, so that the nuclei at the basal ends appear compressed. Terminal bars, or intercellular cement lines, are seen at the free surface. These groups of cells are usually, but not invariably, bounded by ciliated epithelium. In the 240 mm. specimen the secreting cells often cover considerable areas which have been evaginated so as to form branching glands (Fig. 272). Usually several short tubules open into a broad cavity, which in turn connects with the central lumen of the œsophagus. The cavities are lined in part with stratified epithelium, and in part with the simple glandular epithelium which may form a portion of the lining of the œsophagus around the outlet of the gland.

A longitudinal section through the junction of the œsophagus and stomach at 120 mm. shows that the irregular clumps of secreting tubules gradually give place to a succession of quite uniform pits. As the distance from the œsophageal epithelium increases, the tubules become less and less branched (Bensley, 1902). The irregular forms, which occur both in the œsophagus and the cardiac end of the stomach, are the *cardiac glands*. The simple tubes, occurring further within the stomach, are *gastric pits*.

At birth the upper group of cardiac glands in the œsophagus may have the simple character which has been described, but as found in the adult they have undergone further development.

They were present in 70 per cent. of the cases examined by Schaffer, being found in the lateral folds of the œsophagus between the cricoid and fifth tracheal cartilages, frequently on both sides. They may appear macroscopically as erosions about 1 mm. in diameter. (The largest area which Schridde observed was 23.5 x 9 mm.) The glands discharge through a dilated duct lined with simple columnar epithelium, which is said to open at the top of a connective-tissue papilla. Tubules of a new sort have grown out from the gland; they consist of cells with round nuclei, and may produce a serous secretion. Certain of the tubules are provided with parietal cells and chief or zymogenic cells, so that the glands resemble those of the stomach. Schridde in 1904 described such areas as "islands of gastric mucosa," and considered that they were remnants of entoderm isolated by the downgrowth of the ectodermal layer (stratified epithelium) from the mouth,—an error which led to prolonged discussion. E. Schwalbe (1905) has found resemblances between the epithelium of the cardiac glands and that of the intestine, even in the production of cells resembling Paneth's cells.

FIG. 272.—Model of a superficial gland from the cardiac end of the œsophagus at 240 mm. ×120 diam. (After F. P. Johnson.) The extent of the glandular epithelium is indicated by the ruled surface; the unruled area is occupied by squamous epithelium.

The lower group of cardiac glands of the œsophagus is usually limited to a zone from 1 to 4 mm. wide, situated at the entrance to the stomach. The glands vary in their development. Those which Strecker figured from a twelve weeks' child are simpler in form than the one shown in Fig. 272, from an embryo of 240 mm. They consist of tall glandular cells forming a simple epithelium. Later, as in the upper group, new tubules develop which may contain chief and parietal cells. The ducts are usually distended and cystic. Between the upper and lower groups cardiac glands are rarely found, but Eberth (1897) has recorded a small area in the beginning of the lower half of the œsophagus in a man 25 years old.

The cardiac glands of the œsophagus have been named by Hewlett (1901) the *superficial glands* (glandulæ œsophageæ superficiales). They do not extend through the muscularis mucosæ. The *deep glands*, which have their secreting portion in the submucosa, arise later.

They are apparently indicated in the 240 mm. embryo by short rounded downgrowths of stratified epithelium. At this stage there is no evidence of secretory activity. At birth, as shown in Johnson's model (Fig. 273), these glands are somewhat tortuous tubes. Some of them show expanded terminal portions and others have begun to branch. Occasionally, as on the right of Fig. 273, a gland is found in which the terminal secretory portion has not yet developed. The lower portion of the ducts is lined generally with low two-layered epithelium, but in some places only a single layer is found. As the duct approaches the surface, its outer cells become somewhat elongated and they are seen to be continuous with the

basal layer of the stratified surface epithelium. The secreting portion consists of typical mucous cells. They are not as slender as those in the cardiac glands, and the part occupied by secretion is more homogeneous. They yield the staining reactions for mucus more readily than the cells of the cardiac glands, the difference being so great that the mucous nature of the latter has been questioned. In the adult the deep glands are said to open *between* connective-tissue papillæ, whereas the cardiac glands open at their summits. This distinction seems arbitrary, especially since the papillæ arise after the glands are present.

FIG. 273.—Model showing three deep œsophageal glands at birth. × 90 diam. (After F. P. Johnson.)

The Outer Layers.—In the œsophagus, as elsewhere in the digestive tube, it is well known that the circular muscle layer is the first of the outer coats to be differentiated.

At 10 mm. it is represented by a concentric layer of myoblasts, separated from the epithelium by a broad band of undifferentiated mesenchyma. The circular muscle is so far outside of the epithelium that it is undisturbed by the epithelial folds and pockets which arise in later stages. In the 10 mm. embryo there are numerous branches of the vagus nerves, some of them associated with groups of cells with crowded nuclei, found just outside of the circular muscle. These represent the myenteric plexus. Occasionally at this stage similar groups of cells appear along the inner border of the muscularis, and these give rise to the *plexus submucosus*.

At 12.5 mm. Keibel and Elze note that the œsophagus shows a circular, but no longitudinal, muscle layer. At 17 mm. they find a strong circular layer, with the longitudinal layer only indicated. Kreuter finds that the circular muscle is already differentiated in the fifth week (9 mm.), but the longitudinal muscle first appears in the eighth week. Happich states that, although the circular muscle in a four months' embryo has attained a considerable strength, the longitudinal muscle is indicated only by very weak fibres. Schridde, on the contrary, finds that both layers are clearly marked at 12.4 mm., and at 21 mm. the longitudinal musculature is everywhere well developed. It is possible that Schridde mistook the conspicuous layer of nerves, found just outside of the circular muscle at 12 mm., for the longitudinal muscle. These nerves, with the undifferentiated ganglion-cells, form a nearly continuous layer.

The longitudinal muscle is perhaps indicated at 30 mm., but at 42 mm. it is thinner and less conspicuous than the layer of nerves which separates it from the circular muscle. At 55 mm. it is present as a definite layer.

The muscularis mucosæ is not found in the 55 mm. embryo. At 78 mm. it is not distinct at the upper end of the œsophagus, but it is very definite below. At 91 mm. it is a well-developed layer of longitudinal fibres equalling the tunica propria in breadth, and thrown into folds corresponding with those of the epithelium.

The development of the striated muscle of the human œsophagus has not been satisfactorily studied. The œsophageal smooth muscle layers at first extend to the larynx, where they contrast sharply with the striated fibres of the inferior pharyngeal constrictor. There is no evidence of a downgrowth of these fibres upon the œsophagus.

In pig embryos, according to McGill (1910), the smooth and striated muscle-fibres of the œsophagus have a common origin in the mesenchymal syncytium. "Until the cross striations appear in the fibrillæ of the striated muscle, both developing tissues look precisely alike." Cross striations were first observed in pigs of 13 mm., but "only a few fibrillæ become striated before the embryo reaches a length of 30 mm."

In cross sections of the upper part of the human œsophagus at 78 mm. the longitudinal fibres are triangular or polygonal, with peripheral nuclei, and they show coarse myofibrils, but the circular fibres do not appear to be striated. Striated circular fibres are distinct at 120 mm. It is probable that these are "a further differentiation of smooth muscle" (McGill).

The musculature of the upper half of the œsophagus in the adult consists chiefly of striated fibres, but Klein (1868) has concluded that smooth muscle in the longitudinal layer begins in the upper quarter. Once in an adult he found that the circular layer, 1 cm. below the upper end of the œsophagus, consisted chiefly of smooth muscle. In another case he found that the ventral part of the longitudinal layer at the upper end of the second quarter consisted chiefly of smooth fibres, but that further down the striated fibres increased so that the relation was reversed. He found no striated fibres in the lower half of the œsophagus. Coakley, however (1892), has described striated fibres intermingled with the non-striated in both coats of the diaphragmatic portion of the œsophagus. The majority were in the inner circular layer. He considers that the pillars of the diaphragm are the source of these fibres.

The layer of mesenchyma between the circular muscle and the epithelium in the 10 mm. embryo is quite free from blood-vessels. Vessels have entered it at 14.5 mm., and at 16 mm. they form a distinct plexus. Beginning at about 30 mm. the inner portion of the mesenchymal layer becomes gradually denser, due to an abundance of nuclei. Thus the tunica propria, consisting of reticular tissue, is slowly differentiated from the fibrous connective tissue of the submucosa. At birth the propria contains abundant blood-vessels, and apparently lymphatic vessels are present also. No lymph nodules were seen in the sections examined. In the œsophagus of a child Klein (1868) found that

the reticulum contained "more or less numerous round cells similar to lymphocytes," but he speaks of nodules only in the adult. The nodules of the œsophagus apparently develop later than those of the stomach and intestine.

As already noted, papillæ of the tunica propria are absent at birth, but in cross sections the basal border of the epithelium presents a slightly wavy outline. Since Strecker finds that in longitudinal sections the basal line is usually straight, he considers that the elevations are ridges and not papillæ. He finds that the œsophagus passes through three stages of development: 1, in which the tunica propria has a smooth contour; 2, in which it has formed ridges; 3, in which there are conical papillæ upon the ridges. At birth the human œsophagus is in the second stage. In a child of 12 months all the later characteristics are present.

Anomalies of the Œsophagus.—In a previous section the anomaly of the œsophagus in which the upper segment ends blindly below and the lower segment arises from the trachea has been discussed (p. 312). It was stated that it must originate in embryos of about 4 mm. This has been confirmed by finding the anomaly well developed in an embryo of 18.1 mm. in the Harvard Collection. In this specimen there is no trace of epithelial connection between the two parts of the œsophagus. Ribbert (1902) has interpreted *traction diverticula* as a modification, or partial development, of this anomaly. In these cases the ventral wall of the œsophagus, near the level of the bifurcation of the trachea, presents a funnel-shaped diverticulum with its apex directed obliquely upward toward the trachea. The epithelial pocket may penetrate the muscle coat, and from its apex a strand of vascular connective tissue generally extends toward the wall of the trachea. The inflammatory conditions which are often found associated with the pocket are regarded by Ribbert as secondary. Although he states that traction diverticula occur chiefly in older people, he believes that in the great majority of cases they have an embryological origin. He considers that there is a defective development of the œsophageal wall at the place where in more radical cases the tracheo-œsophageal fistula occurs.

An examination of the embryos in the Harvard Collection fails to show such a defect. However, Happich (1905) has recorded that in embryos from 8 or 9 mm. to 3 or 4 months, the entire musculature on the ventral side of the œsophagus is thinner than on the dorsal side, as far down as the bifurcation of the trachea. Below the trachea this distinction is wholly lacking. At birth the ventral musculature is slightly weaker than the dorsal, but the difference is almost imperceptible. It is clear, however, that such a thinning cannot account for the anomaly in question, since it extends the whole length of the trachea and disappears at birth. In addition to the general thinning, Happich has found that the circular muscle, in embryos of 3 or 4 months, is completely interrupted in small areas extending through one or two sections. "These places can readily be distinguished from those through which a vessel penetrates the wall." Schridde (1908) found a larger defect, extending through five sections, in that part of the longitudinal muscle layer which is toward the trachea. This, however, was in a 13 mm. embryo, which is a stage when the longitudinal muscle is not ordinarily recognizable.

Riebold (1903 and 1908) believes that the embryological interpretation of traction diverticula is not justified, and he adheres to the older idea that they are pathological. He cites the literature to show that Ribbert's theory has not met with general acceptance, and states that "up to the present time not a single case of traction diverticulum has been found at birth." Lymphadenitis, with

adhesions of the gland to the trachea and a spread of the inflammation along vessels to the œsophagus, is believed to produce a dense scar which draws upon the œsophageal tube, and, as a result of the motions in swallowing, the diverticulum is drawn out. Diverticula may occur wherever a vessel penetrates the muscle, and therefore below the trachea. They may be multiple, and they are not always ventral.

Embryologically it is probable that if the trachea and œsophagus have separated normally at 4–5 mm., the muscle layers which arise at 9–12 mm. will show no local defect at the place of the former separation. Unless the diverticula are primarily epithelial, they are presumably not congenital.

Pulsion diverticula occur on the dorsal wall of the œsophagus, at its junction with the pharynx, where the tube is narrowest and the muscle coat thinnest (Riebold). They apparently have no embryological significance. Diverticula occur also in other parts of the œsophagus. Some of these are evidently of inflammatory origin. D'Hardivillier has asked whether the islands of simple epithelium do not offer places of lesser resistance which would lead to diverticula, and it has been pointed out that pulsion diverticula and these thin areas both occur at the upper end of the œsophagus. Apparently, however, there is no relation between them.

The irregularities in the œsophageal epithelium in embryos of 18–22 mm. have been supposed to give rise to the cases of atresia and stenosis, and possibly to diverticula, but direct evidence is lacking. Atresia of the œsophagus is abnormal in embryos of all stages. Many records of œsophageal anomalies have been gathered by Happich, Kreuter, and Forssner, who have discussed them embryologically.

THE DEVELOPMENT OF THE STOMACH.

By FREDERIC T. LEWIS.

Early Development.—Remak (1855) described the intestinal wall of vertebrates as composed primarily of two layers,—the gland-layer (Darmdrüsenblatt) and the fibre-layer (Darmfaserplatte). The former gives rise to the epithelium and glands, and the latter produces the remaining layers. Schenk (1868), from a study of chick embryos, concluded that Remak had overlooked a third layer, which develops downward from the mesodermic somites and extends between the gland-layer and the fibre-layer. He found that this third layer was clearly connected with the somites, but was separate from the adjacent layers. Therefore he concluded that Remak's fibre-layer produced only the lining of the peritoneal cavity. Schenk's interpretation was rejected by Kölliker (1879, p. 850) and by Maurer (1906). Maurer finds that in all vertebrates the embryonic intestinal wall (including that of the stomach) consists at first of two layers,—the entodermal epithelium and the mesodermal epithelium. The latter, in the Amniota, becomes stratified, and for some time it may exceed the delicate entoderm in thickness. It produces mesenchymal cells, which form a third layer situated between the two primary epithelia.

The mesodermal epithelium covering the digestive tube is called the *splanchnopleure* by Maurer, but, as pointed out by Minot (1901), this usage is incorrect, since the term was introduced by Foster to designate the entire intestinal wall. His (1865) proposed the name endothelium in the following passage (here somewhat abbreviated):

"We are accustomed to designate the layers of cells which cover the serous and vascular cavities as *epithelia*. But all the layers of cells which line the cavities within the middle germ layer have so much in common, and from the time of their first appearance differ so materially from those derived from the two peripheral

germ layers, that it would be well to distinguish them by a special term,—either to contrast them, as false epithelia, with the true, or to name them *endothelia,* thus expressing their relation to the inner surfaces of the body."

The term endothelium, as proposed by His, is itself too extensive, since it includes both the epithelium lining the vessels and that which lines the body cavities. These epithelia, although similar in the adult, are very distinct embryologically. Accordingly Minot (1892) uses the term *mesothelium* for the mesodermal cells bounding the body cavities, and applies endothelium to the vascular system. Thus the nomenclature has become complex. The layer covering the intestine is perhaps best referred to as the cœlomic or peritoneal epithelium.

The two-layered stage of the stomach is seen in the 4 mm. Bremer embryo. Here the fore-gut presents a dorso-ventral cleft-like lumen, both in the œsophageal and gastric regions. The thick cœlomic epithelium is in direct relation with the ventral part of the sides of the fore-gut, as far anteriorly as the lung-bud. Thus laterally the gastric region is in the primary two-layered stage, but dorsally and ventrally, and to some extent on the sides, the entodermal epithelium is bounded by mesenchyma. The mesenchyma appears to be derived chiefly from the cœlomic epithelium, yet it is possible that some has grown down from the somites. In this specimen there is no difference between the œsophageal and gastric epithelium.

In a 10 mm. embryo the gastric epithelium is distinctly thicker than that of the œsophagus, and its nuclei are more elongated. In the sections examined, the nuclei form four or five overlapping rows, but the true number of cell layers is probably less. Jahrmaerker finds that at 8 mm. the gastric epithelium is 2–3 layered, with tall columnar basal cells, whereas both the œsophageal and intestinal epithelia have only two layers. In the 12 mm. embryo he attributes the greater thickness of the gastric epithelium, as compared with that of the œsophagus or intestine, to the tall basal cells which are found in the stomach.

Vessels and Nerves.—The general relations of the stomach in the 10 mm. embryo are shown in Fig. 274. At the œsophageal end, the vagus nerves occupy dorsal and ventral positions. Their bundles of fibres are associated with small clumps of cells with crowded nuclei. The dense layer of mesenchyma, indicating the circular muscle, which is distinct along the œsophagus, gradually disappears at the cardia.

In this region a vessel leaves the stomach and passes through the lesser omentum to enter the ductus venosus (Fig. 274, A). This vein was first described by Broman (1903) as follows:

"In human embryos 5–16 mm. long, there are always one, two, or several branches of the ductus venosus passing through the lesser omentum to the mesodermal wall of the stomach, where they form a thick plexus. The branches of the cœliac artery connecting with this plexus appear to be relatively insignificant, at least in the earlier stages. In older embryos I have sought in vain for the branches of the ductus venosus, and may therefore believe that they have degenerated."

The cœliac artery is seen leaving the aorta in Fig. 274, C. Its branch, the left gastric artery, lies at the root of the great omentum, along which it ascends to the cardiac end of the stomach. The hepatic branch of the cœliac artery is seen beside the portal vein. Subsequently branches of the portal vein and hepatic artery extend to the pylorus and along the greater curvature, thus forming the right gastro-epiploic vessels. In the 10 mm. embryo these appear to be indicated by minute twigs. In a 22.8 mm.

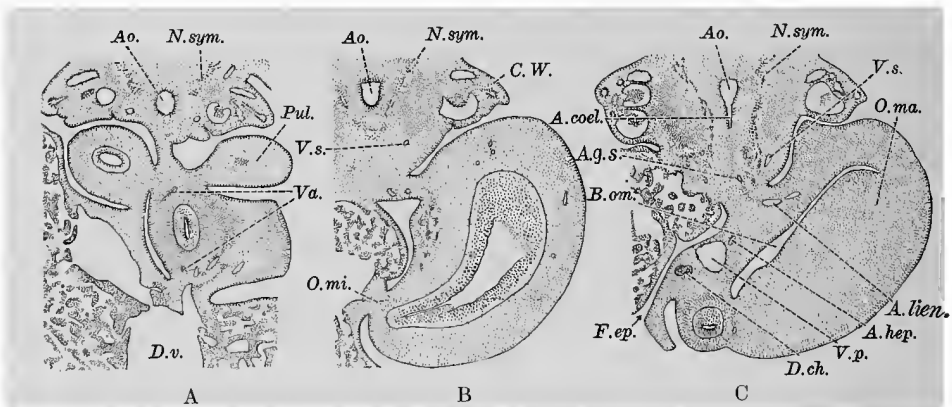

FIG. 274.—Sections of the stomach of a 10 mm. embryo (Harvard Collection, Series 1000). A, through the cardia. B, through the fundus. C, through the pylorus. *A.coel.*, cœliac artery; *A.g.s.*, left gastric artery; *A.hep.*, hepatic artery; *A.lien.*, splenic artery; *Ao.*, aorta; *B.om.*, omental bursa; *C.W.*, Wolffian body; *D.ch.*, common bile-duct; *D.v.*, ductus venosus; *F.ep.*, foramen epiploicum; *N.sym.*, sympathetic nerve; *O.ma.*, greater omentum; *O.mi.*, lesser omentum; *Pul.*, lung; *Va.*, vagus nerve; *V.p.*, portal vein; *V.s.*, left suprarenal vein.

specimen the portal vein communicates with the left suprarenal vein by a vessel which receives branches from the stomach, following the course of the left gastric artery. This communicating vein corresponds with the coronary vein of the adult, by forming an anastomosis between the portal and cardinal systems along the lesser curvature of the stomach.

In the 10 mm. embryo the dorsal and ventral trunks of the vagus nerves unite to form a large ganglionated plexus on the right side of the stomach, nearly in the median plane of the body (Fig. 274, B). A similar arrangement was found in embryos of 9.4 and 14 mm. There are no distinct nerves along the greater curvature, and there is no indication of the muscle layer. In older embryos (14.5 mm.) the sympathetic nerves communicate with this ganglionic mass, but in the 10 mm. embryo the connection could not be demonstrated. The sympathetic nerves are seen extending forward on either side of the aorta, ventral to which they form a cœliac plexus. From the latter, in older embryos, bundles of fibres extend to the stomach along the dorsal mesentery, following the path shown in Fig. 274, B.

Kuntz (1909) has recently published a similar description of the nerves in pig embryos. In 12 mm. specimens he found a vagus plexus around the œsophagus, and "vagus fibres which are still accompanied by numerous cells may now be traced along the lesser curvature of the stomach." There are still no fibrous connections between the cœliac plexus and the plexuses in the digestive tube. In 16 mm. embryos fibrous connections have become established.

There is another path by which sympathetic fibres may enter the stomach. They may extend from the cœliac ganglion to the pylorus, following the gastric branches of the hepatic artery (Fig. 274, C). His, jun. (1897), has figured a section of a 9.1 mm. embryo which shows sympathetic nerves passing to the stomach along this course. In describing a 10.2 mm. embryo he speaks of a branch of the cœliac plexus which is lost in the mesoderm of the pylorus, and, as shown in his reconstruction, it does not anastomose with the vagus. In the specimens in the Harvard Collection the pyloric branches of the sympathetic cannot be identified at such an early stage. It appears rather as if the gastric plexus first extends downward to the pylorus and duodenum, and is then joined by such sympathetic branches as His described. These are distinct in a 30 mm. embryo.

Epithelium and Gastric Glands.—In the 10 mm. embryo the free surface of the epithelium is somewhat wavy, whereas the basal surface is nearly smooth. In 16 and 19 mm. specimens the epithelium exhibits occasional vacuoles and a few scattered pits. The vacuoles are small, and, like the pits, they do not cause the basement membrane to bulge. Sometimes the pits expand laterally within the epithelium so that they are flask-shaped. These structures bear a certain resemblance to the œsophageal vacuoles and the intestinal diverticula to be described later.

Elze (1909) has noted that in the stomach of ape embryos (*Nasalis larvatus*) there are several epithelial buds and diverticula which have the same appearance as the early stages of those found in the intestine.

At 22.8 mm. a few vacuoles are still present. The intra-epithelial pits have become numerous. As seen in Fig. 275, *A*, they are produced by the varying height and characteristic arrangement of cells in an epithelium which has nearly smooth surfaces. In places the epithelium is clearly simple, but elsewhere it may show several rows of nuclei and is perhaps stratified. In a 42 mm. embryo the epithelium is more definitely simple, and the pits form rounded swellings along its mesenchymal surface.

This characteristic stage has been figured by Toldt (1881) in an embryo of the tenth week. It was not seen by Laskowsky (1868), who considered that the gastric glands were produced by the growth of the mesenchymal layer, rather than by epithelial proliferation. His view was accepted by Schenk (1874, p. 117) and others, but Toldt, who considered the pits to be a part of the glands, correctly concluded that "the first formation of the glands is a process which takes place exclusively in the epithelial layer."

At 55 mm. the pits still project but slightly below the general level of the basement membrane. The epithelial cells between adjacent pits, in positions corresponding with *x* in Fig. 275, *A*, have become greatly compressed below, so that the basal portions of a group of these cells resemble a clump of connective-tissue fibres. In all later stages the epithelial cells along the free surface and the adjacent portions of the sides of the pits may exhibit

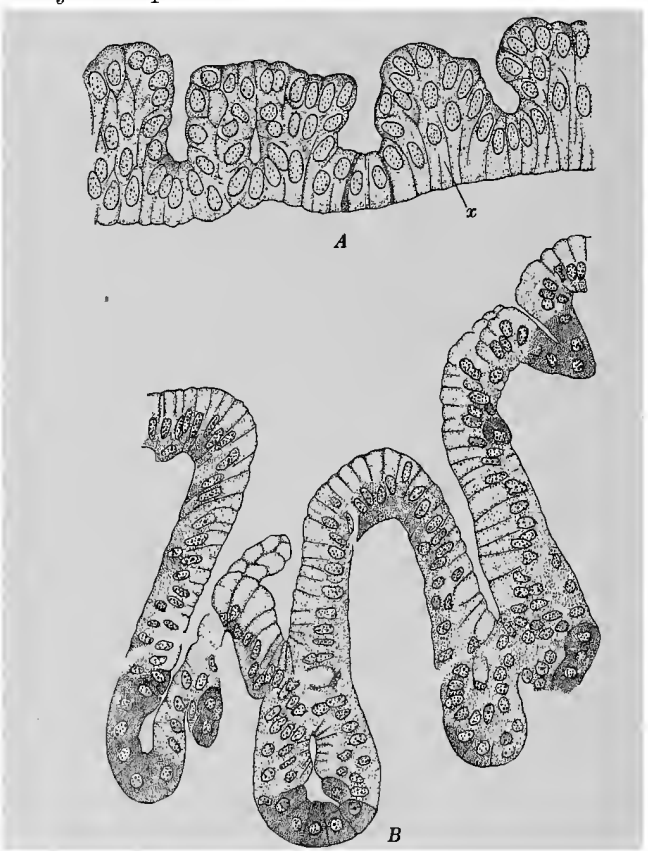

FIG. 275.—Sections of the gastric epithelium. × 330 diam. *A*, from an embryo of 22.8 mm. (Harvard Collection, Series 871). *B*, from an embryo of 120 mm.

slender basal prolongations; they have been described by Baginsky (1882) in a 7 months' embryo, and by Fischl (1891) at birth. In the 55 mm. embryo the outer portions of these cells are clear, suggesting a mucous transformation. This is true of the cells on the sides of the pits, but at the bottom of the pits the protoplasm toward the lumen is coarsely granular.

At 99 mm. there are distinct mesenchymal elevations between the pits. At the bottom of the pits there are small, nearly solid buds of granular cells, which represent the beginning of the glands proper.

The conditions at 120 mm. are shown in Fig. 275, *B*. The glands at the base of the pits already exhibit two sorts of cells, differing from one another in their affinity for eosin. The eosinophilic cells occur chiefly at the blind ends of the glands. Very generally they border upon the lumen. In later stages the eosinophilic cells are peripheral in position and are called parietal cells (delomorphous cells). The non-eosinophilic cells represent the chief or adelomorphous cells of later stages. Between the gland and the pit there may be a constriction, as seen in Fig. 275, *B*. The surface epithelium and that lining the pits is a simple columnar layer, containing mucous cells in various stages of development, but apparently all covered by distinct top plates. Generally the nuclei are elliptical, but occasionally a cell is seen with its nucleus flattened in the basal protoplasm. The basal protoplasm is sometimes eosinophilic, and groups of cells of the parietal type may be found in direct relation with the surface epithelium (as on the right of Fig. 275, *B*). These seem to represent new gland buds. There are also non-eosinophilic basal cells—the *Ersatzzellen* of Ebstein (1870)—which presumably develop into new columnar cells. In young embryos Toldt found these basal cells so abundant that in poorly preserved specimens they may easily give the impression of a stratified epithelium, whereas at birth they are relatively infrequent.

The form of the pits and glands in the 120 mm. embryo is shown in a model made by Johnson, the upper and under surfaces of which are shown in Figs. 276 and 277 respectively. The gastric pits are seen to be clefts rather than tubules, and the intervening tissue may be considered to form imperfectly separated villi. The pits are separated from one another below by irregular ridges of mesenchyma.

Brand (1877) states that in embryos of two and three months the stomach contains numerous villi, and Kölliker (1879) regards the mesenchymal projections between the pits as "villi." Of their later development he says: "In the fourth month the formation of glands has begun in the mucosa, while between the mesodermal villi, which have become longer, low inter-villi and ridges have grown up, marking out spaces like a honeycomb, into which the epithelium sends hollow cylindrical processes." Sewall (1879) found that in the sheep "from the first the mesodermal outgrowths are not papilliform, but take place along continuous lines of greater or less extent, giving rise to ridges which intersect in all directions." Toldt (1881) likewise found, in cat embryos, ridge-like elevations of mesoderm, but he states that it is not to be questioned that in stomachs of human embryos from the third to the fifth month, especially in the pyloric region, villus-like elevations occur, and even true elongated villi. Baginsky (1882) states that "the surface of the gastric fundus in a 4 months' embryo has an exquisite villous appearance." In later stages he finds that the surface becomes gradually smoother as the villus-like elevations disappear. Strecker (1908[1]) describes an exceptional stomach at birth (?) showing typical villi in the cardiac region.

A mesodermal origin for certain epithelial and gland cells has been considered possible by several investigators. Thus, Ebstein thought that the basal cells may proceed directly from the blood-vessels, and Toldt recorded certain appearances suggesting

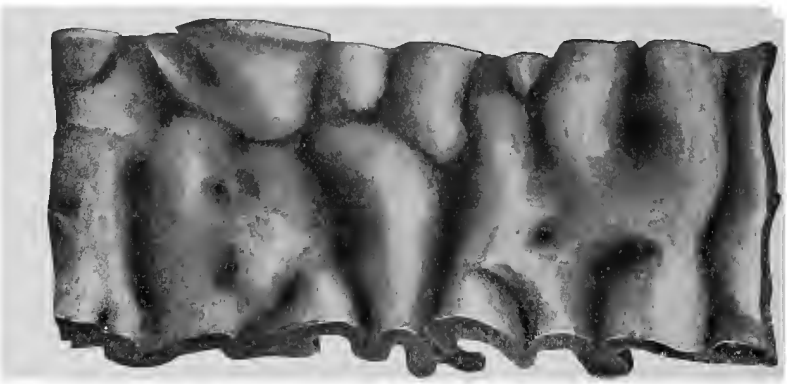

FIG. 276.—Model of the gastric epithelium at 120 mm., showing the free surface. × 120 diam. (After F. P. Johnson.)

that in young stages mesodermal cells wander into the epithelium. Sewall (1879) and more recently Strecker (1908[2]) have described the gastric glands as mesodermal.

Sewall (1879) concluded that in sheep embryos only the early generations of chief and parietal cells are formed from the primitive gland cells, and that the later generations arise in the mesenchyma. The parietal cells appear first in the

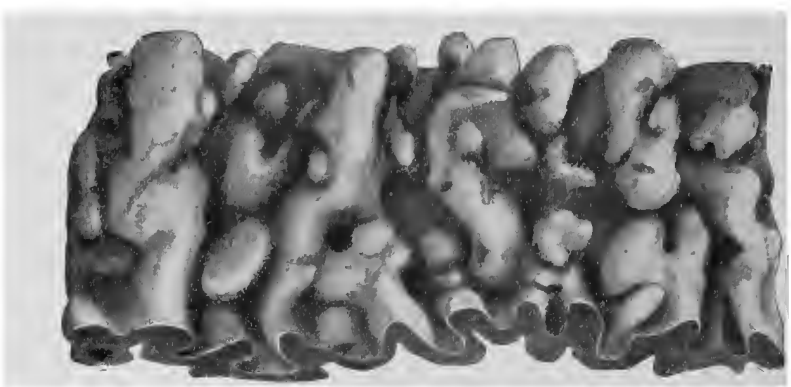

FIG. 277.—Model of the gastric epithelium at 120 mm., showing the basal surface. × 120 diam. (After F. P. Johnson.)

deep parts of the gland (in embryos of about 140 mm.). In later stages he concluded that new parietal cells were produced by the differentiation of the surrounding "mesoblast corpuscles," and that, from the parietal cells so formed, new chief cells developed to replace those broken down in the process of secretion. Physiologically he found that extracts of the stomach of the sheep, "even some time before term, showed a considerable proteolytic power." This function appears to coincide with the specialization of the chief cells. The fluid in the embryonic

stomach was found to be neutral, even after the differentiation of the parietal cells. It yielded an abundant precipitate of mucus.

Toldt (1881) rejected Sewall's conclusion concerning the mesodermal origin of parietal cells, and described the development of the human gastric glands as follows:

"In the fourth and fifth months and also in the beginning of the sixth, parietal cells and their developmental stages are found only at the blind ends of the glands. Beginning with the middle of the sixth month they increase considerably in number and are found everywhere along the sides of the glands, yet they are still in the row of chief cells and therefore border upon the gland lumen. Not earlier than about the middle of the eighth month could I find regularly a considerable number of parietal cells situated on the outer side of the chief cells. At birth and in the first weeks following, this is almost always the case along the sides of the glands, but near and at the base the lumen is still bounded largely by parietal cells which are not fully developed. In children of four or five years all transitions from chief to parietal cells are constantly present in abundance, but later, when the growth of the glands takes place only very slowly, they are seldom found."

According to Toldt the *chief cells* also develop from those which form the walls of the primitive gland. "These cells, differing from the later characteristic chief cells by their cuboidal or polygonal form, their delicate outline, their affinity for eosin, and the strikingly large size of their nuclei, gradually assume the typical form. . . . In man this transformation is completed toward the end of the fifth and in the beginning of the sixth month." Chemical tests showed that pepsin was present in the gastric mucosa in the last half of the sixth month, "long before it passed over into the secretion."

Strecker (1908[2]) examined the stomach at birth, and found conditions which have generally been ascribed to post-mortem disintegration, such as the absence of columnar epithelium on the free surface, the presence of detached gland cells in cavities bounded by the tunica propria, and even a superficial layer of fibrin. All these he regards as normal, and states that "unquestionably the large gland cells appear distributed more or less irregularly in the tissue without any typical arrangement. They seem to be lodged in a well-marked reticular tissue, the meshes of which they fill. . . ." He described the embryonic development of these glands as follows:

The primitive glands are purely epithelial, but in embryos of 100 mm. another sort of gland formation is seen taking place in the tunica propria. "The propria at this stage is not a connective-tissue layer, but an epithelioid organ." It contains many free nuclei (*Bildungskerne*), which produce protoplasmic bodies and form groups of cells, thus giving rise to glands. "Both the chief and parietal cells arise from the same source, namely the *Bildungskerne*." The *Bildungskerne* form autogeneously in the original mesenchymal plate of the intestine, and Strecker names them "mesenchymal-epithelioid corpuscles." Not only are free nuclei found in the propria, but there are also non-nucleated masses of protoplasm. Nuclei wander into these, thus giving rise to giant cells. The multi-nucleate cells are generally found at the base of the glands. Portions of them become split off, so that they produce cell material for the gland tube. Strecker states that a true mitotic division in embryological preparations of the gastric glands has never been found by any investigator, but Salvioli (1891) has recorded abundant mitotic figures in rabbit embryos and has made a special study of their location.

From the fact that Strecker found the non-epithelial origin of glands beginning in 100 mm. specimens, it is probable that the "purely epithelial glands" are the gastric pits, and those arising in the propria are the glands proper. Although, owing to tan-

gential sections, parietal cells often appear isolated in the tunica propria, the conclusion of Sewall and Strecker concerning their mesodermal origin may be confidently rejected. The glands arise as further downgrowths of the pits. In the stomach, as in both small and large intestine, there are at first irregular coarse depressions (pits and intervillous spaces), from the bottom of which glands extend downward. The cells of the pits and villi are characteristically clear, whereas those at the depths of the glands are granular and deeply staining. The transition between the two is not abrupt, as shown in Fig. 275, *B*.

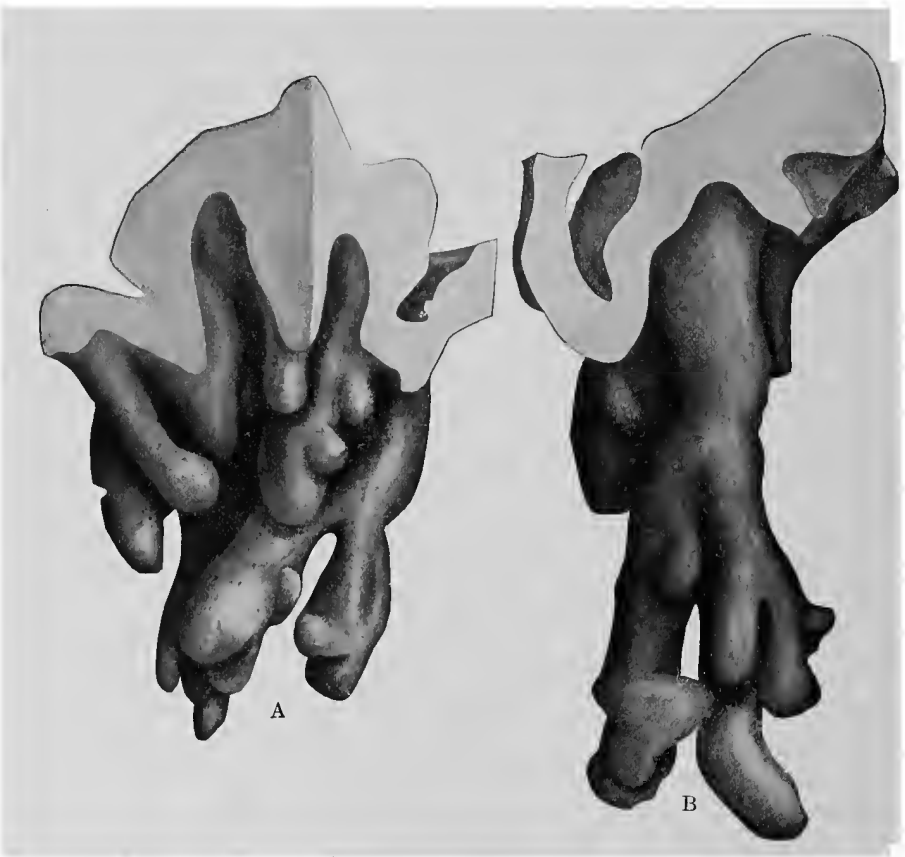

FIG. 278.—Models of the gastric pits and glands, A, at 240 mm.; B, at birth. × 80 diam. (After F. P. Johnson.)

As compared with the pits, the glands steadily increase in length. In a 240 mm. embryo they occupy the basal third of the mucosa; at birth they form nearly half of this layer, and therefore nearly equal the pits. They have branched repeatedly and have increased greatly in number. Their form is shown in Fig. 278, A and B, from models made by Johnson.

Their multiplication has been described by Toldt. He estimated that the total number of gland outlets in the stomach of an eight months' embryo is 128,912; at birth, 268,770; and at ten years, 2,828,560. In the three stomachs referred to, the number of outlets per square millimeter is nearly constant, averaging 56, 51, and 56 respectively. In studying the way in which the glands multiplied, Toldt failed to find primitive stages of gland development among the differentiated glands, but gastric pits were often observed to be partly divided, and he "sees no objection to regarding these divided pits as forerunners of the complete division of the glands."

This method of multiplication would cause a reduction in the number of glands opening into each pit, and some reduction was found to occur. The average number of glands emptying into a pit in the last months of embryonic development is 7; at ten years, 6; at fifteen years, 5; and in the adult, 3. During this period Toldt found, however, that the number of gland tubules in the stomach had increased from 930,000 to 25,179,000, which means that many new tubules have been formed. These arise through lateral sprouts of glands already present. Toldt says that "It may be noted that these hollow sprouts are generally seen to develop at places along the gland wall where one or more parietal cells are situated, and that these pass over into the new gland body."

Epithelium and Glands at Birth.—Fischl describes the gastric epithelium at birth as a "moderately high columnar epithelium with basal nuclei, appearing somewhat lower on the ridges than in the pits; moreover the nuclei in these two places differ, since they appear more elliptical and deeply stained on the ridges, but in the pits they are rounded and decidedly paler." Except that the cells on the ridges seem taller than in the pits, these observations have been verified. The cells exhibit distinct terminal bars. Those lining the pits are producing and discharging mucus, which fills the lumen and spreads over the free surface. The cells bordering upon the free surface contain a more granular protoplasm, and according to Toldt they sometimes give no indication of the formation of mucus.

Disse (1905), by the use of a mucin stain, found that "the true surface epithelium contains only here and there an isolated mucous cell, but chiefly consists of cells containing no trace of mucus." He concludes that, although in some places the mucous layer is well developed in embryos at term, there are other places in the same stomach where mucus is wholly lacking or forms an interrupted layer. Reyher (1904) and Von der Leyen (1905) have found that the mucous layer is continuous. It is possible that the surface cells with granular protoplasm are those which have previously discharged mucus (see Fig. 275, *B*).

Fischl was unable to find mitotic figures among the epithelial cells, but Ascoli (1900) has declared that at birth they may be found in large numbers, in cells containing mucus.

Neumann (1876) repeatedly found well-developed ciliated cells among the epithelial cells of the embryonic stomach. (The age of the embryos is not definitely stated.) Baginsky (1882) described the gastric contents of a 7 months' embryo as alkaline and containing, together with epidermal cells which were probably swallowed with the amniotic fluid, small ciliated cells, generally isolated. In the specimens in the Harvard Collection no ciliated cells were found.

The glands at birth appear distinctly broader, shorter, and more widely separated than in the adult, as noted by Fischl. In seven cases, all from the first half of the first year, he found the parietal cells only partially differentiated, and represented by rounded, rather small cells, often situated near the gland lumen, and never pushing out into the tunica propria. At the end of the second year, he states that they show no essential difference in staining, form, and arrangement from those of the adult, although they are less abundant.

Fischl's difficulty in demonstrating the parietal cells at birth has not been shared by others, Kalopothakès (1894) having reported them as "perfect" in a six months' embryo; but it is doubtless true that neither they nor the chief cells are fully differentiated until after birth.

Cardiac and Pyloric Glands.

The early writers grouped the cardiac and pyloric glands together and named them the mucous glands of the stomach. Thus, Toldt (1881) states that these glands are "quite alike in form and structure," and Strecker has recently noted the "striking similarity" between them. The cardiac glands have apparently been more thoroughly studied than the pyloric, and the literature concerning them has been reviewed by Bensley (1902) and Strecker (1908[1]).

Embryologically the pyloric region very early differs from the remainder of the stomach. In a 42 mm. embryo the pits are deeper and more irregular toward the pylorus, where there is an abrupt transition to the characteristic villi of the duodenum, and this is true of all later stages. At 240 mm. the epithelium of the duodenum is a darkly staining granular layer frequently interrupted by clear globular goblet-cells. The pyloric epithelium is a uniform layer of clear columnar cells filled with secretion, thus resembling the epithelium which lines the gastric pits. In the pyloric region the pits are very deep and they coalesce with one another laterally so that the intervening tissue forms long irregular villi. These have been described by Toldt, Baginsky, and others, but apparently they have not been modelled.

In early stages the entire lining of the pyloric glands is like the surface epithelium. This condition is found in an embryo of 120 mm., and Baginsky has recorded it at 4 months. At 7 months, however, he found, in addition to such glands, others which showed, toward their bases, darker, finely granular cells staining clearly with eosin. In an embryo of 240 mm. there are occasional basal eosinophilic cells which resemble parietal cells. Toldt, however, in twenty stomachs from older embryos and children under five years, failed to find any parietal cells associated with the pyloric glands.

The cardiac glands of the œsophagus have already been described (p. 362). They are groups of short tubules lined with a columnar epithelium resembling that of the pyloric glands.

Passing from the œsophagus into the stomach, the cardiac glands become more elongated and more compactly arranged. Their epithelium gradually blends with that of the gastric pits. In the transition the cells become somewhat shorter and stain less brightly with orange G. At the same time gastric glands appear at the base of the pits, and the number of their parietal cells increases. Toldt considered that there is a sharp distinction between the cardiac and the gastric glands, inasmuch as the cells from which they arise are of very different sorts, but there is undoubtedly a gradual transition between them. In man, however, there is no embryological evidence in favor of Bensley's conclusion that "the cardiac glands are decadent or retrogressive structures derived from the fundus glands by the disappearance of their more highly specialized constituents." On the contrary, the cardiac glands are differentiated very early. They can be recognized in a 91 mm. embryo, in which there are still no chief or parietal cells.[12]

The Outer Layers.—In 10 mm. embryos the gastric wall consists of three layers,—entodermal epithelium, mesenchyma, and peritoneal epithelium. At 16 mm. there is a condensed zone of mesenchyma indicating the circular layer of muscle. It is best defined along the lesser curvature, but it can be identified over the greater portion of the stomach. A uniform layer of mesenchyma extends between the muscle layer and the entoderm. It already contains a plexus of blood-vessels. The nerves and ganglia have spread from the lesser to the greater curvature. They are chiefly outside of the muscularis. At 22.8 mm. there is a slight condensation of the mesenchyma toward the entodermal epithelium, indicating the beginning of the tunica propria. The circular muscle layer is complete, and shows a slight thickening toward the pylorus. A prolonged gradual thickening of this layer, followed by an abrupt thinning at the duodenum, is distinct at 37 mm. and in all later stages. At 37 mm. large lymphatic vessels are seen in the mesentery along the lesser curvature, but apparently they do not penetrate the muscularis. This is true also at 42 mm. At 55 mm. there is a dense tunica propria; no muscularis mucosæ; a submucosa containing blood-vessels and occasional nerves toward the muscularis; a single layer of circular muscle,

[12] The histogenesis of the gastric glands in the pig has recently been studied by Kirk (1910). He finds that the parietal cells arise very early as epithelial cells staining intensely with eosin, situated in the deeper parts of the glands. Kirk confirms Toldt regarding the absence of these parietal cells from the pyloric glands. He finds a very gradual transition between the gastric and cardiac glands, and considers that the latter are retarded or regressive glands, following Bensley. But he states that mucous differentiation occurs slightly earlier in the cardia than in the fundus.

outside of which nerves are numerous; and a relatively wide serosa.

At 91 mm. the muscularis at the cardiac end of the stomach shows a few inner longitudinal bundles. These are seen also at 120 mm. At this stage the outer longitudinal layer of the œsophagus may be followed a short distance over the cardia, external to the circular layer. The greater portion of the stomach has only the circular layer. At 240 mm. an outer longitudinal layer is distinct in the pyloric part of the stomach and it becomes thicker toward the duodenum. Some of its bundles are continuous with the longitudinal layer of the duodenum, but others turn into the thick circular layer near the pylorus, forming the *dilator pylori* (*cf.* Cunningham, 1908). At birth the thin outer longitudinal layer, according to Fischl, is entirely absent in places, especially along the greater curvature.

The *muscularis mucosæ* is indicated at 120 mm. At birth Fischl finds it clearly divisible into an inner circular and an outer longitudinal layer.

Lymphatic vessels appear in the submucosa in embryos of 214 and 240 mm. Lymph-nodules were found at birth in a considerable percentage of the cases examined by Fischl. They were observed in all parts of the stomach; sometimes they were at the base of the glands, and did not extend upward between the tubules.

The longitudinal folds of the stomach, which are often found in preserved specimens, appear to be quite irregular. Toldt has seen them formed by muscular contraction in freshly opened embryonic stomachs of cats, and does not consider them to be "specific formations of the mucosa." Kölliker (1879, p. 854) has recorded the number of such longitudinal folds of the mucosa found in human embryonic stomachs of different ages.

Anomalies of the Stomach.—Congenital pyloric stenosis is essentially an excessive development of the circular musculature of the pylorus. The other layers in this region, especially the longitudinal layer, may be more or less hypertrophied, and the folds of the mucous membrane are sometimes so highly developed that they appear to obstruct the lumen.

There has been considerable discussion concerning the nature of this condition, the literature of which has been analyzed by Ibraham (1905) and Torkel (1905). It appears to be established that the stenosis is not due to spastic contraction of a normal pylorus, since the muscle layer is actually thickened. A thickening through excessive physiological activity before birth has been suggested. More probably the unknown conditions which normally induce the formation of the sphincter muscle have, in these cases, led to an excessive development. Thus, as Cunningham has recorded, the extremity of the pyloric canal protrudes into the commencement of the duodenum, presenting a striking resemblance to the *portio vaginalis* of the *cervix uteri*. In the full-term fetus the protrusion is more marked than in the adult, and in cases of pyloric stenosis it is in all probability still more pronounced. A similar explanation is advocated by Ibraham as according with the relative frequency and remarkable uniformity of the cases observed and the favorable clinical course which they often follow.

Diverticula of the stomach are rare.

Küss (1905) has recorded a case in a man 61 years of age. Along the greater curvature, 6 or 7 cm. from the pylorus, there was a small cavity lined with normal mucous membrane, which penetrated the muscle layers, pushing a few strands before it. Küss states that we are forced to accept a congenital origin for this diverticulum, "perhaps at the expense of an aberrant outgrowth comparable with the evaginations of the duodenum which form biliary and pancreatic ducts." Gardiner (1907) has reported a case of accessory pancreas in relation with gastric diverticula, and he refers to Weichselbaum's similar case in which a gastric diverticulum ended in a nodule of pancreatic tissue. According to Orr (1907), W. F. Hamilton has described a stomach with a diverticulum 2 cm. broad and 3 cm. deep, situated on the posterior wall of the cardiac end, near the œsophagus.

The possible embryonic origin of such diverticula will be discussed under anomalies of the small intestine.

It has long been known that stomachs in the adult are occasionally divided more or less completely into two chambers (hour-glass stomach), and it was generally believed that some of these cases were congenital. It is now admitted, however, that the great majority of them are due to local physiological contraction of the gastric musculature. Delamare and Dieulafé (1906) described a stomach at birth, which was bilocular, owing to a constriction in the middle part of its corpus. They found that the circular muscle was abnormally thick at the place of constriction, and they attributed this to hypertrophy and not to contraction. But Cunningham (1908) concludes that the hour-glass stomach never arises as a congenital deformity.

Quite distinct from the cases of physiological contraction are those in which a large *pars pylorica* is separated by a permanent constriction from the corpus. Gardiner (1907) described such a stomach from a three-months child, in which there was a well-developed accessory pancreas at the place of constriction. A very similar condition is seen in a 19 mm. embryo in the Harvard Collection. Such cases of "hour-glass stomach" must be distinguished from those which are phases of functional activity.

THE DEVELOPMENT OF THE SMALL INTESTINE.

By FREDERIC T. LEWIS.

The early stages in the histogenesis of the small intestine are like those of the stomach, which have already been described. The further differentiation of the epithelial tube proceeds as follows:

Vacuoles in the Duodenal Epithelium.—In embryos of 6.5 and 7 mm. the duodenum usually presents a well-defined round lumen, bounded by a 2–3 layered epithelium. In slightly older embryos

the epithelium proliferates, and vacuoles are formed within it, especially on the dorsal and right sides of the tube. Later the proliferating epithelium bridges and subdivides the original lumen, as seen in the section of a 10 mm. embryo, Fig. 279, *A*. Of the three cavities found in this section, the upper one is a vacuole, and the two lower ones are parts of the original lumen. In this embryo there is still a continuous passage from the stomach to the jejunum. The outer surface of the epithelial tube is generally smooth, but occasionally at this stage—more frequently in somewhat older embryos—the masses of cells surrounding the vacuoles produce local bulgings of the basement membrane. At 22.8 mm. (Fig. 279, *B*) the outpocketings are so numerous that the epithelium appears folded, and mesenchyma has begun to extend

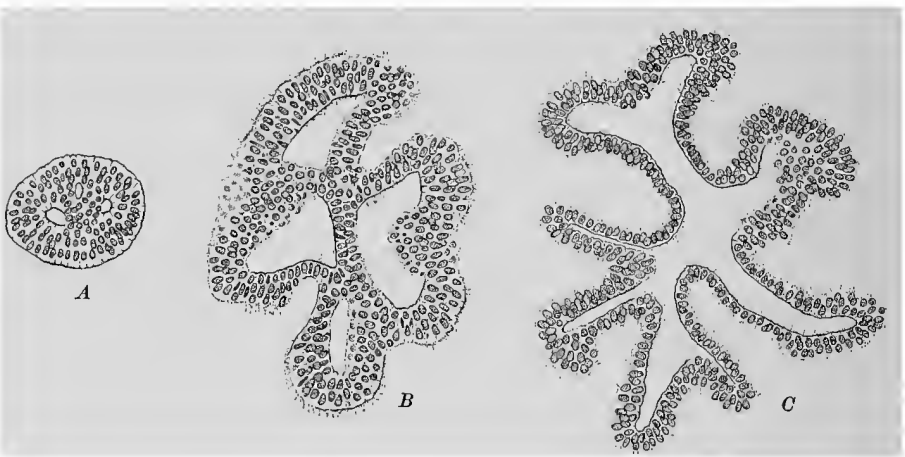

FIG. 279.—Cross sections of the duodenal epithelium. × 130 diam. *A*, at 10 mm. (Harvard Collection, Series 1000). *B*, at 22.8 mm. (Harvard Collection, Series 871). *C*, at 30 mm. (Harvard Collection, Series 913).

inward between the pockets or folds. In sections the vacuoles cannot be distinguished from the main lumen. A model of the duodenum of this embryo, made by F. P. Johnson, shows that the passage from the stomach to the jejunum is completely blocked by epithelial septa (Fig. 280). At 30 mm. (Fig. 279, *C*) the vacuoles begin to become confluent so that a central lumen is re-established. The projections between the vacuoles remain as the foundations of villi.

Tandler (1900) was the first to recognize that the duodenal lumen, in embryos from "30 to 60 days," is normally "more or less completely" obliterated. In an 8.5 mm. specimen he recorded a complete obliteration between the outlets of the duct of the dorsal pancreas and the common bile-duct. At 14.5 mm., when the proliferation is at its maximum, he found that the bile and pancreatic ducts emptied into closed cavities, and that below them the duodenal epithelium formed a solid cord of cells. Forssner (1907) likewise found that, in places, the lumen was completely obliterated in embryos of 11.7, 14, and 22.7 mm.; and at 30.5 mm.

he described transverse septa dividing the lumen into compartments. Other embryos, of 18.5, 21, and 31 mm. respectively, showed no epithelial vacuoles or occlusions. Schridde (1908) failed to find a solid stage.

Tandler considered that the cause of the occlusion was the resistance exerted upon the expanding epithelium by the surrounding mesenchyma. He found that the diameter of the mesodermal tube of the duodenum increased very slowly in embryos from 7 to 15 mm., whereas from 15 to 20 mm. the increase is rapid. Forssner has confirmed this observation, and thinks it "not improbable that purely mechanical factors play a part in producing occlusions." Both Tandler and Forssner have compared the vacuolization in the duodenum with that in the œsophagus.

Vacuoles (Diverticula) in the Jejunum and Ileum.—The lower portion of the small intestine never presents a subdivided lumen such as is found in the duodenum, but its epithelium contains scattered vacuoles, which develop in a very characteristic manner. These vacuoles occur chiefly along the portion of the intestine found within the umbilical cord, and they are situated along the convex surface of the intestinal coils, opposite the mesenteric attachment.

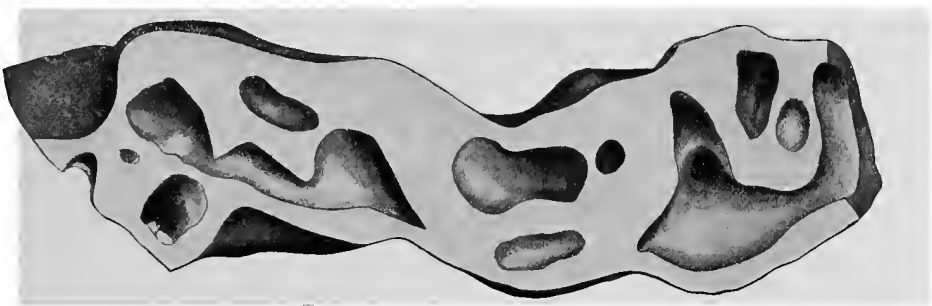

FIG. 280.—Model of the duodenum of a 22.8 mm. embryo (Harvard Collection, Series 871), seen in longitudinal section. × 120 diam. (After F. P. Johnson.)

In an embryo of 14.5 mm. there are three of these structures, all of which are near the bend of the primary loop of intestine. In a 16 mm. specimen seven were counted, and at 22.8 mm. thirty-two were present.

The intestinal vacuoles are first indicated by a concentric arrangement of the basal nuclei, and in this stage they have been described as "buds" or "pearls." In the centre of such a bud a small cavity can often be detected (Fig. 281, *A*). In later stages the cavity communicates with the intestinal lumen, and the bud forms a knob-like basal projection (Fig. 281, *B*). These projections often have a somewhat constricted neck, and the overhanging portion may become asymmetrical, extending aborally along the intestine. Thus Fig. 281, *C*, is an aboral section of the diverticulum shown in *B*. Four of the thirty-two diverticula in the 22.8 mm. embryo project aborally. One diverticulum, longer than any of the others, extends laterally so that its tip penetrates the dense mesenchyma of the muscularis (Fig. 281, *D*). Usually they are in

close relation with the epithelial layer, and they cause no disturbance in the course of the circular muscle fibres. In older embryos (Fig. 281, *E* and *F*) the folded appearance of the epithelium renders the detection of the diverticula more difficult. It is probable that, by the enlargement of their necks, some of them are incorporated in the general epithelial layer. Others, however, retain their identity. One of these was found and modelled by F. P. Johnson in an embryo of 134 mm.,—a stage when the villi are well developed and the intestinal glands are being formed (Fig. 282). Some of the glands open into the base of the diver-

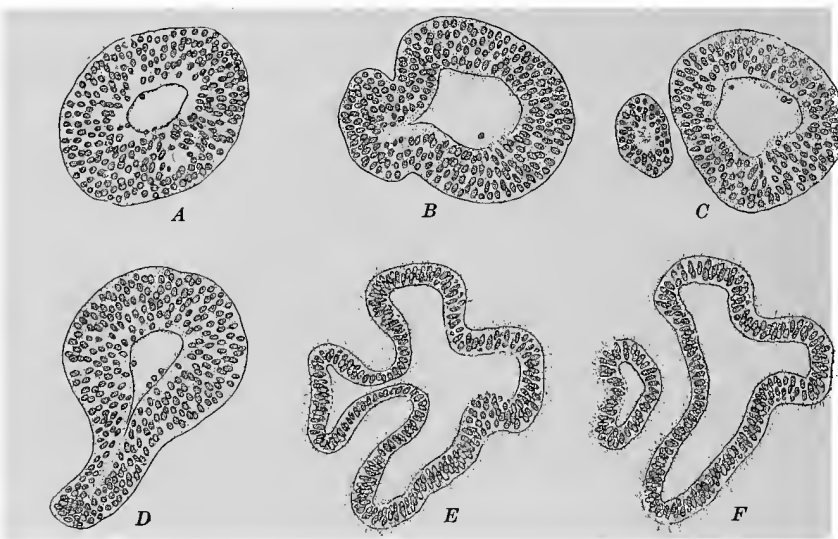

FIG. 281.—Cross sections of the epithelial tube of the intestine, showing the development of diverticula. × 130 diam. *A-D*, from an embryo of 22.8 mm. (Harvard Collection, Series 871). *E* and *F*, from an embryo of 30 mm. (Harvard Collection, Series 913).

ticulum. Around it the mesenchyma is dense and suggests the formation of lymphoid tissue. This is apparently the oldest embryo in which such a structure has been found, and they are not known to occur after birth.

The intestinal diverticula were described independently by Keibel (1905) and Lewis and Thyng (1908). Keibel noted and figured the two stages in their development (buds and diverticula) and recorded their presence in several mammals, including man. Lewis and Thyng described similar structures, but included with them certain more compact buds which occur chiefly on the dorsal wall of the intestine in the lower duodenal region. These were found frequently in the pig. In an 18.1 mm. human embryo there are two buds of this sort situated on the dorsal wall of the intestine as it turns forward to enter the umbilical cord. Lewis and Thyng compared the diverticula with somewhat similar structures found along various epithelial tubes, such as the mammalian bile-ducts and the large intestine in amphibia. They appear to be localized centres of cell proliferation, which either arise in the outer layers of the intestine or are due to the outward displacement of mitotic cells from the innermost layer. Thus mitotic

figures appear to be limited to the inner layer and the diverticula, but their distribution requires further study. Elze (1909) has stated that a sharp distinction should be made between the dorsal diverticula of the upper intestine and the ventral diverticula which arise later lower down. He was the first to record the typical aboral growth of the latter. It is probable that the vacuoles of the œsophagus, stomach, duodenum, and intestine are comparable structures.

The Formation of Villi.—The development of villi begins in the upper part of the small intestine and extends downward. In the duodenum their formation is complicated by the presence of

Fig. 282.—Model of the intestinal epithelium from an embryo of 134 mm., showing villi, glands, and, in the centre, a "flask-shaped gland." × 80 diam. (After F. P. Johnson.)

the epithelial proliferations described in the preceding section. There, as seen in Fig. 279, *B* and *C*, the epithelial tube expands by producing irregular outpocketings. Forssner (1907) agrees with Tandler that the epithelium is invaded by mesenchymal papillæ, but the apparent invasion is probably due to irregularities in the expansion of the epithelium. Such elevations as are seen in Fig. 279, *C*, have been described both as folds and as villi.

According to Meckel (1817), the first elevations are longitudinal folds which become gradually indented along their crests, and are thus broken apart into villi. This interpretation has been defended by Berry (1900), who found folds, but no villi, in a human embryo of 24 mm. At 28 mm. the folds, as seen in his reconstructions, show indications of transverse furrows, as if they were about to break up into blocks or villi, and in later stages he found that villi had replaced the folds. Forssner (1907) agrees with Meckel and Berry. Kölliker (1861), on the contrary, states that the villi arise in the beginning of the third month as wart-like outgrowths of the mesenchymal layer, which push the epithelium before them and become cylindrical. This was confirmed by Barth (1868). Brand (1877) found scattered villi at one and a half months. Voigt (1899), by means of reconstructions of pig embryos, found that depressions and furrows develop on the free surface of the epithelium, marking out areas of greater diameter than the future villi. These apparent epithelial elevations are due to the downgrowth of the surrounding furrows. They are described by Voigt as the bases of the future villi.

Johnson (1910) states that villi begin to develop in 19 mm. embryos. At 22.8 mm. he describes isolated rounded elevations occurring between the pylorus and the duodenal occlusion, and also in the upper part of the jejunum. In a model (Fig. 283, A) he has shown the transition from the villous portion of the jejunum to the smooth part, and has found that the villi in this region arise independently and not as subdivided folds. In the corresponding portion of the intestine of a 24 mm. embryo, the villi

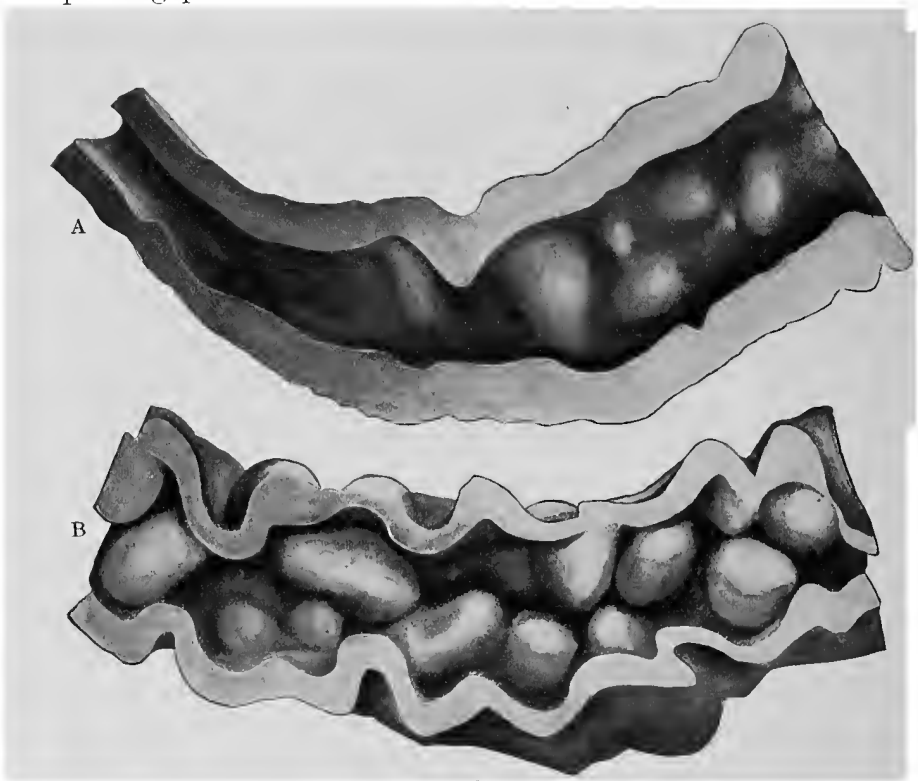

FIG. 283.—Models showing the development of villi in the upper portion of the jejunum. × 110 diam. (After F. P. Johnson.) A, from an embryo of 22.8 mm. (Harvard Collection, Series 871). B, from an embryo of 24 mm. (Harvard Collection, Series 24).

are more numerous (Fig. 283, B). Although they are arranged in five more or less definite longitudinal rows they do not appear as subdivided folds. At 30 mm. villi are found throughout the upper half of the intestine, but there are none in the ileum. The latter, in cross section, generally shows a trifoliate or four-lobed lumen, due to longitudinal folds of variable length. As this portion of the intestine expands, these folds seem to be obliterated, but villi arise at that time and it is possible that the villi in the ileum are remnants of the folds. The definite relation between them described by Meckel and Berry is not shown in Johnson's models. At 42

mm. there are still a few distal coils of the ileum which are without villi. According to Berry they do not extend to the colon at 80 mm., but are found throughout the small intestine at 130 mm.

During these and later stages the villi increase greatly in length, but their diameter remains nearly constant. Many new villi develop among the old ones, and the way in which they are formed is shown in Fig. 279, *C*. At the bottom of an outpocketing a secondary elevation appears, which increases in height with the expansion of the epithelial tube. By relatively rapid growth these elevations attain a length equal to that of the older villi.

Another explanation for the uniform height of the villi is given by Fusari (1904). He finds that the distal ends of the older villi degenerate and are cast off simultaneously, forming, with the mucus, a sort of membrane. This process "is certainly repeated at least twice." These observations, however, have not been confirmed, and the appearances are perhaps due to post-mortem degeneration.

At 55 mm. approximately 12 villi are seen in a cross section of the middle portion of the intestine, and at 99 mm. there are 25. Berry has estimated that in an 80 mm. embryo there are 50,000 villi in the entire intestine, and at 130 mm. the number has increased to 330,000. He finds that fully developed villi and young villi exist in the growing intestine side by side, and this conclusion is well established by the reconstructions of Voigt, Berry, and Johnson.

The epithelium covering the elevations in the 30 mm. embryo is thinner and more definitely simple than that in the depressions. At 55 mm. the epithelial cells of the villi are columnar, with conspicuous cell walls and bulging top plates. The rounded nuclei are somewhat below the middle of the cells, and the protoplasm of the outer part is remarkably clear. In the hollows between the villi the nuclei are more oval and the cells are more crowded. The protoplasm is granular. Altogether the epithelium of the depressions appears much darker than that of the villi. In both regions, however, there are occasional dense triangular or saucer-shaped nuclei, apparently belonging with goblet-cells. Sometimes nuclei are seen displaced outward, but these do not resemble the wandering cells of later stages. Baginsky (1882) contrasted the clear cells of the villi with the dense cells in the hollows between them, as seen in the jejunum at 4 months, and he described the depressions as the first stage in gland formation.

The Formation of the Intestinal Glands.—The intestinal glands (of Lieberkühn) develop gradually among the deeply staining cells in the hollows between the villi, appearing first in the duodenum. As the villi increase in number, the rounded hollows between them give place to narrow clefts, along the base of which knobs and short tubules extend downward. Glands in the form of short tubules are present, near the pylorus, at 78 mm.

At 91 mm. they occur in the middle part of the duodenum, but below this, in the sections examined, they are still absent. They are found in the middle portion of the small intestine at 120 mm., and their size at 134 mm. is shown in the model, Fig. 282.

Brand (1877) found no trace of the glands at 3 months, and states that they first appear in the upper part of the small intestine in embryos of 3 1-2 months (110 mm.?). He considered that they are epithelial pits due to the partial fusion of the bases of adjacent villi. Barth (1868) had previously stated that they are produced by the upward growth of the surrounding mesenchyma, but Kölliker (1861) had described them as tubular downgrowths of the epithelium. Voigt (1899), Hilton (1902), and Johnson (1910) agree with Kölliker.

New glands arise at first as independent buds at the base of the villi, but the older glands branch dichotomously, as observed by Baginsky in a 7 months' embryo. Branched glands are frequent at birth, and doubtless the branches subsequently become independent glands. Thus the number of tubules increases through bifurcation, as in the stomach.

Although the epithelium of the glands is darker and in early stages taller than that of the villi, the transition is gradual. The relation between them is similar to that which obtains, in the stomach, between the gastric pits and glands. But in the stomach the epithelium of the glands becomes more sharply differentiated from that of the pits, whereas in the intestine the difference gradually disappears. At 240 mm. it is less marked than at 134 mm. Goblet-cells are then found near the bottom of the glands, but often the fundus is composed of darker, granular cells. This is the condition at birth, when the glands have become approximately one-fifth as long as the villi. It is possible that the dark granular cells represent the cells of Paneth.

The Duodenal Glands.—According to Brand, the duodenal glands (of Brunner) develop from the intestinal glands, beginning in embryos of 3½ months, but Baginsky failed to find them at 4 months. In a 78 mm. embryo, near the pylorus, some of the intestinal glands appear to be more tortuous than others and occasionally show lateral bulgings near their blind ends. At 120 mm., which is before the appearance of the muscularis mucosæ, certain of them have grown almost to the circular muscle layer, where they terminate in tubules composed of clear cells, entirely unlike the dark cells at the fundus of the adjacent intestinal glands. A longitudinal section through the stomach and duodenum at this stage shows that these duodenal glands are quite close together near the pylorus, but further on in the duodenum they occur at considerable intervals. At 240 mm., as shown in Johnson's model (Fig. 284), the older glands have branched repeatedly. Certain of the bifurcating intestinal glands in this model probably represent the young stages of the duodenal glands.

The secretory cells of the duodenal glands stain a bright yellow with orange G, and exhibit a delicate reticular structure. Thus they resemble the cells of the pyloric glands, which develop at about the same time, and of the cardiac glands, which arise somewhat earlier. The duodenal glands have been regarded as an

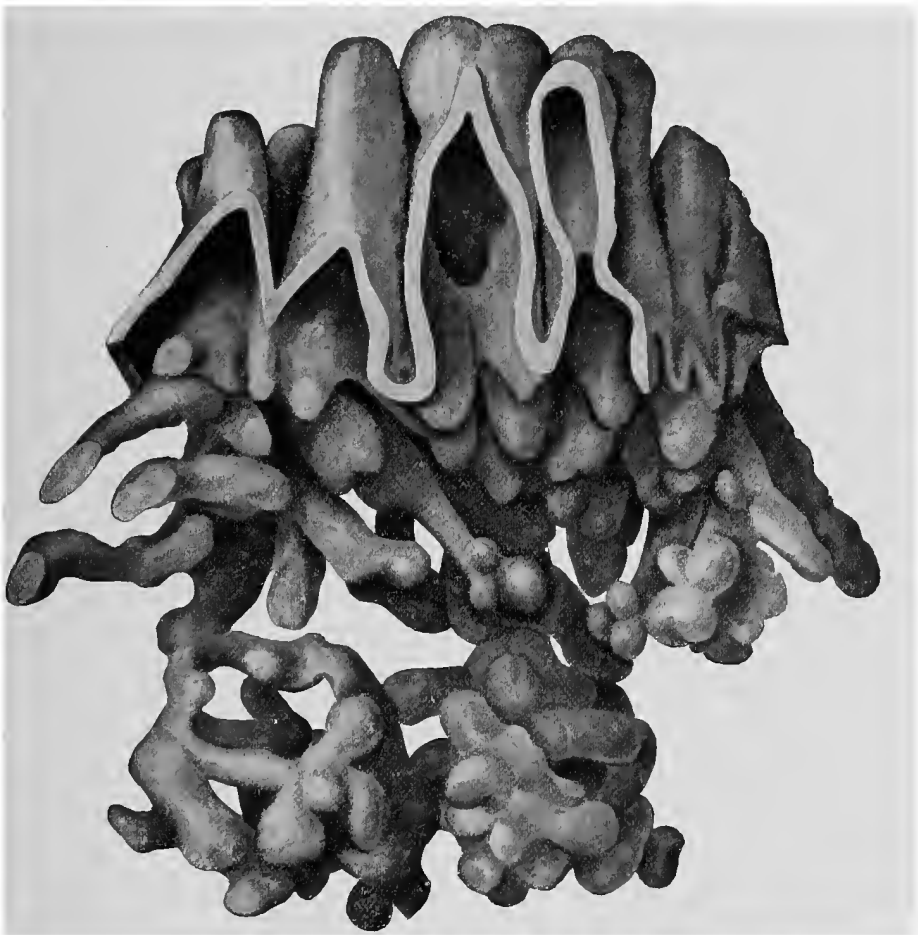

FIG. 284.—Model showing developing duodenal glands in an embryo of 240 mm. × 160 diam. (After F. P. Johnson.)

extension downward of the pyloric glands, but the considerable morphological differences between them in early stages are against this opinion. In the adult, parietal cells have been found in relation with both the pyloric and duodenal glands (Kaufmann, 1906), but, as already noted, they have been found in the cardiac glands of the œsophagus. They have not been seen in the duodenum of the embryo.

Outer Layers.—As elsewhere in the digestive tract, the circular muscle layer is the first product of the surrounding mesen-

chyma. In a 10 mm. embryo, in which this layer is distinct in the œsophagus, but has not yet appeared in the stomach, it may be identified in the duodenal region. Tandler, however, states that it arises at 12.5 mm. In later stages it spreads down the small intestine, and at 22.8 mm. it is present at the junction with the colon. The mesenchyma within the muscle layer contains numerous branches of the superior mesenteric vessels, but no lymphatics. In the duodenal region ganglia are present, and they are found, almost entirely, just outside of the muscle layer. They appear to connect with sympathetic trunks which pass on the right side of the pancreas and also below it. In these specimens it is impossible to determine the lower limit of the vagus plexus, which, according to Kuntz (1909), may invade the small intestine. The nerves to the lower part of the small intestine appear somewhat later. At 42 mm. the ganglia are conspicuous, especially along the line of mesenteric attachment.

The longitudinal muscle layer becomes distinct at about 75 mm. At 134 mm. no *muscularis mucosæ* was seen, but it is present at 187 mm. Apparently this layer appears first in the œsophagus, then in the stomach, and later in the small intestine. Mall (1897 and 1898) inferred that peristalsis occurs in 130 mm. embryos, since in several embryos of this stage he found that the meconium had been propelled downward toward the cæcum.

The *tunica propria* becomes gradually differentiated before the muscularis mucosæ has appeared. It is a dense layer of mesenchyma at 99 mm. The lymphatic vessels, which in earlier stages were present in the mesentery, are now found in the submucosa, but they cannot be seen in the propria. At 240 mm. both solitary and aggregate nodules of lymphoid tissue have appeared in the tunica propria. Their relation to the lymphatic vessels could not be determined in the specimens studied. According to the early observers, the lymphoid tissue arises from the epithelium, and Retterer (1895 and 1897) has more recently defended this interpretation. It was rightly rejected by Stöhr (1889), who concluded that "the lymph-nodules of the intestine arise in the tunica propria, or in the adjacent parts of the submucosa, through mitotic division of the round cells (leucocytes) which are found there." Similarly Czermack (1893) has maintained that the lymphoid tissue develops as a "condensation of the mesenchyma." Czermack is probably correct in concluding that the lymphocytes arise in genetic connection with the reticular tissue. The presence of aggregate nodules (Peyer's patches) in the human intestine at six months and later has been recorded by Kölliker (1861). At seven months Baginsky (1882) recognized very distinctly the central lymphatic vessels within the villi of the duodenum.

The development of the circular folds (*valvulæ conniventes*) requires further study. In the middle portion of the intestine at

78 mm. (3 months?), as seen in longitudinal section, there are frequent slight elevations of the submucosa, in which the muscularis is not involved. These are so small that they displace upward (in longitudinal sections) only five villi. In similar sections at 240 mm. there are about ten villi on either side of a fold.

Meckel (1817) stated that there was no trace of the circular folds until the seventh month, when they appeared as slight elevations readily obliterated on stretching the intestine. At birth he found them still poorly developed. Delamare (1903), on the contrary, states that at birth they are as numreous and relatively as high as in the adult. According to Hilton, these folds are not found in apes, but are peculiar to the human intestine.

Fischl (1903) has studied the elastic tissue of the intestine. He finds that at birth there is no elastic tissue in the walls of the intestine or stomach, except in connection with blood-vessels. It begins to develop in the first weeks after birth.

Anomalies of the Small Intestine.—In addition to the imperfect torsion of the intestinal loop and the presence of Meckel's *diverticulum ilei,* which have been described in a previous section, the congenital anomalies of the small intestine include atresia and stenosis, diverticula, and cysts.

Tandler (1900) concluded that the embryological atresia of the duodenum may sometimes persist and become congenital. He considered this a rare occurrence, since only two cases of intestinal occlusion were found among 111,541 children in Vienna, and nine cases among 150,000 in St. Petersburg. Altogether more than a hundred cases of stenosis or atresia of the small intestine have been described, and rather more than a third of these were found in the duodenum. Thus they are far more abundant in the duodenum than in any other equal length of the intestinal tract. Kuliga (1903), who reviewed the literature, could not decide between inflammatory and developmental causes for these conditions, but Kreuter (1905) and Forssner (1907) both advocate the embryological origin.

The cases vary greatly in degree, and include perforate iris-like folds or valves, complete membranes, and more or less extensive strictures and obliterations of the epithelial tube. Sometimes the muscularis passes smoothly around the blind ends of the divided intestine without extending from one to the other. Cases like that of Preisich (1903), in which, in a boy 6 days old, two valve-like folds were found in relation with the bile and pancreatic ducts, strikingly suggest the conditions in embryos between 15 and 25 mm., and certain of the congenital atresias and stenoses presumably arise at that stage.[13] In other cases, discussed by Forssner, meconium has been found below a complete atresia. This indicates a late origin, possibly through the adhesion of valve-like folds. Moreover, atresia is found in portions of the small intestine where obliteration of the lumen does not normally occur. Such cases may represent the persistence of an abnormal embryological condition. Forssner thinks it probable that exceptionally an epithelial occlusion may be found in all parts of the embryonic intestine.

[13] The 19 mm. embryo in the Harvard Collection, which has an abnormally shaped stomach with an accessory pancreas, shows also a distinct local constriction of the duodenal epithelium. There is an actual stenosis of the descending part of the duodenal loop.

Diverticula of the duodenum, especially near the outlets of the pancreatic ducts, are relatively common. According to Jach (1899), who found but one case in 200 bodies, Schüppel found seven instances in 45 bodies. They are generally round sacs, opening into the duodenum by clear-cut, circular orifices. Since they are not covered by the muscularis, but push their way through it, they have been described as hernias of the mucous membrane, and as *false* diverticula, in distinction from the true Meckel's diverticulum. The latter is covered by the muscular coats. Jach believes that they are generally pulsion diverticula, produced by the distention of the upper part of the duodenum following an obstruction lower down. The obstruction may be a cicatricial contraction, or the pressure from a displaced transverse colon. Their occurrence about the outlets of the bile and pancreatic ducts has been attributed to a deficiency in the muscularis where the ducts penetrate it. But Letulle (1899), who has described two cases, concludes that they are undoubtedly of early embryonic origin. Lewis and Thyng (1908) have stated that the diverticula observed in the embryo may possibly give rise to those in the adult. In Fig. 285 their drawing of a model of a duodenal divertic-

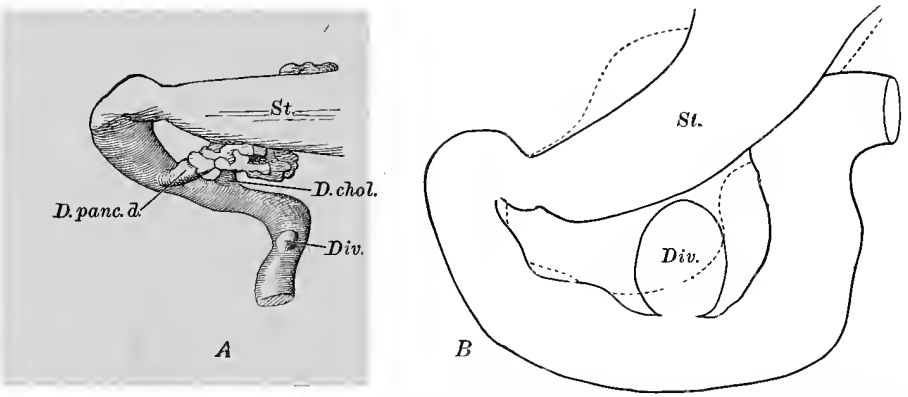

FIG. 285.—Diverticula of the duodenum. *A*, in an embryo of 13.6 mm. (Harvard Collection, Series 839). × 55 diam. (From a model by F. W. Thyng.) *B*, in an adult. (After C. M. Jackson.) In *B* the outline of the pancreas is dotted. *D. chol.*, common bile-duct; *D. panc. d.*, duct of the dorsal pancreas; *Div.*, diverticulum; *St.*, stomach.

ulum from a 13.6 mm. embryo is placed beside Jackson's sketch of a large diverticulum, 3.5 cm. deep, found in a man of 50 (Jackson, 1908), and the correspondence in location is striking. It is possible that some of the duodenal diverticula are congenital, although apparently no case has yet been recorded at birth (Fischer, 1901).

Occasionally a single diverticulum has been found in the jejunum or in the ileum, but more often there are multiple diverticula. They occur usually in old people, and differ from those of the embryo in their greater relative size and larger number, in occurring only near the mesenteric attachment, and in their distribution which includes the colon. Like the diverticula of the œsophagus, they have been found in relation with the blood-vessels, and have been attributed both to traction by the vessels and to pulsion along the path of the veins as they cross the musculature to enter the mesentery. Hansemann (1896) has produced them experimentally by distending the intestine with water. It is improbable, as stated by Elze (1909), that there is any genetic connection between such structures and the diverticula of the embryo.

Cysts derived from the intestine may be found at birth. Usually they are correctly ascribed to a detached Meckel's diverticulum, even when found within the mesentery (Hennig, 1880; Roth, 1881; Dittrich, 1885). These cysts are occa-

sionally very large (22 cm. long). Their walls include all the layers of the intestine and may contain aggregate nodules. The epithelium is sometimes smooth and ciliated, but it may exhibit more or less perfect glands and villi. In one of Roth's cases, there were two cysts in the abdomen and one in the thorax, and it is stated that they may have arisen *in loco* from the duodenum and œsophagus. In a pig embryo of 20 mm., Lewis and Thyng have figured a mesenteric cyst which had become detached from the intestine in the lower duodenal region, and it is possible that certain of the congenital intra-mesenteric cysts have a similar origin. The relation of intestinal diverticula and cysts to an accessory pancreas will be considered with the pancreas.

Several small oval cysts have been found by F. P. Johnson among the duodenal villi of a 7 months' embryo. They appear to be distended with mucus, derived from the small group of glands emptying into their basal portions. The epithelium which lines the cysts is separated from the surface epithelium by a thin layer of connective tissue. These structures resemble the cystic glands which Stöhr (1898) has figured in the vermiform process of a 5 months' embryo. The closure of the neck of the flask-shaped gland shown in Fig. 282 would apparently produce a similar structure.

THE DEVELOPMENT OF THE LARGE INTESTINE.

By FREDERIC T. LEWIS.

Early Development.—In a 10 mm. embryo the large intestine consists of an epithelial tube, an undifferentiated layer of mesenchyma, and, except along the mesenteric attachment and near the pelvic termination, a layer of peritoneal epithelium. The entodermal epithelium shows usually two rows of nuclei. Mitotic figures are limited to the row next the lumen. The lumen is circular, and, though minute in places, it is continuous throughout. There is a marked local dilatation of the lumen in the region of the cæcum, and a gradual enlargement downward in the rectal portion. The diameter of the colon is about equal to that of the lower portion of the small intestine, but it is less than that of the duodenum, the epithelium of which has begun to proliferate.

At 14.5 and 16 mm. the large intestine is still a round tube with a well-defined lumen, gradually enlarging from the colon toward the cloaca. At 22.8 mm. the lumen of the lower part of the rectum has become elliptical and the long axis is transverse. Passing upward the lumen gradually becomes circular. Near the cæcum the inner surface of the epithelium shows some irregularities due to the varying height of the cells. Here, in cross section, the lumen is stellate or polygonal, but the circumference of the epithelium is circular. Patzelt (1883) has described the same condition in cat embryos of 25 and 33 mm.

In a 37 mm. embryo the lumen of the greater part of the ascending colon is pentagonal, but the circumference is circular. Toward the right (or hepatic) flexure the lumen becomes round, and so continues into the descending colon. Then it assumes a

three-lobed form (in places four-lobed), but the circumference still remains nearly circular. After reaching the part of the rectum with a long transverse axis, the lumen shows additional lobes and the circumference becomes indented. Thus, in cross section, the lower part of the rectum shows five or six folds.

The transverse colon at 42 mm. is shown in Fig. 286, *A*. The cells at the bottom of the three outpocketings are lower than the others, and show a characteristic pearl or bud-like arrangement, suggesting the diverticula of the small intestine. They do not produce local pockets, however, but elongated ridges. Toward the rectum the epithelial irregularities are more marked. They are shown in longitudinal section in Fig. 286, *B* and in cross section in Fig. 286, *C*. Between the sheaf-like bundles of tall cells with superficial nuclei, there are concentric groups of short ones with

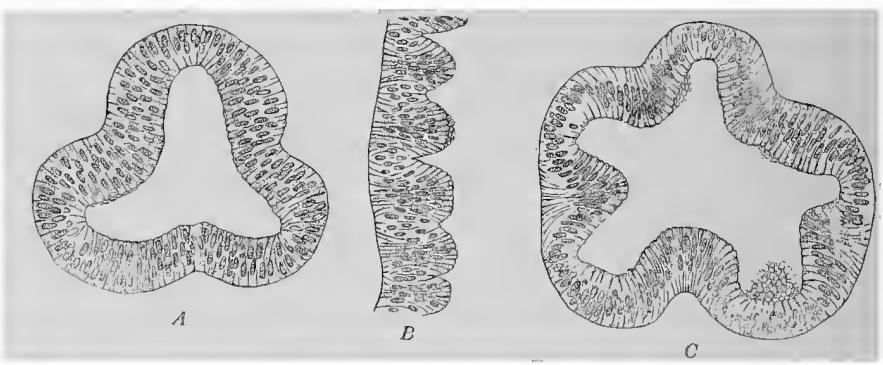

FIG. 286.—The epithelium of the large intestine in a 42 mm. embryo (Harvard Collection, Series 838). ×130 diam. *A*, cross section of the transverse colon. *B*, longitudinal section of the sigmoid colon. *C*, cross section through the upper part of the rectum.

basal nuclei. The latter appear to be growing outward, and by the shortening of the intervening cells the epithelium becomes folded. Thus in *C* there are three folds, but the places where two others will arise are clearly indicated, and lower down in the rectum five or six folds are found.

There is no solid stage in the development of the large intestine. The atresia described by Kreuter (1905) at the beginning of the fifth week has not been found by Forssner (1907). There are no diverticula. Small vacuoles are found at 37 mm. in connection with the nests of low cells, and similar vacuoles have been observed in the stomach, but these are never conspicuous as in the œsophagus. The expansion of the epithelial tube occurs slowly, so that at 37 and 42 mm. the large intestine is very much smaller than the adjacent coils of the jejunum and ileum, in which villi are conspicuously present.

Villi and Glands.—With the continued growth of the large intestine the outpocketings bifurcate, and, as seen in cross sections,

the number of elevations projecting toward the lumen increases. In a section of the transverse colon at 55 mm. there are five or six projections; at 73 mm. there are about ten; and at 99 mm. as many as twenty. A model of the transverse colon at 99 mm. shows that these elevations are true villi (Fig. 287). At their bases there are irregular epithelial clefts and pockets which give rise to the glands. The glands continue to grow downward, and they multiply through bifurcation. The cells at the bottom of the depressions are granular and dark, but the villi are covered with clear elon-

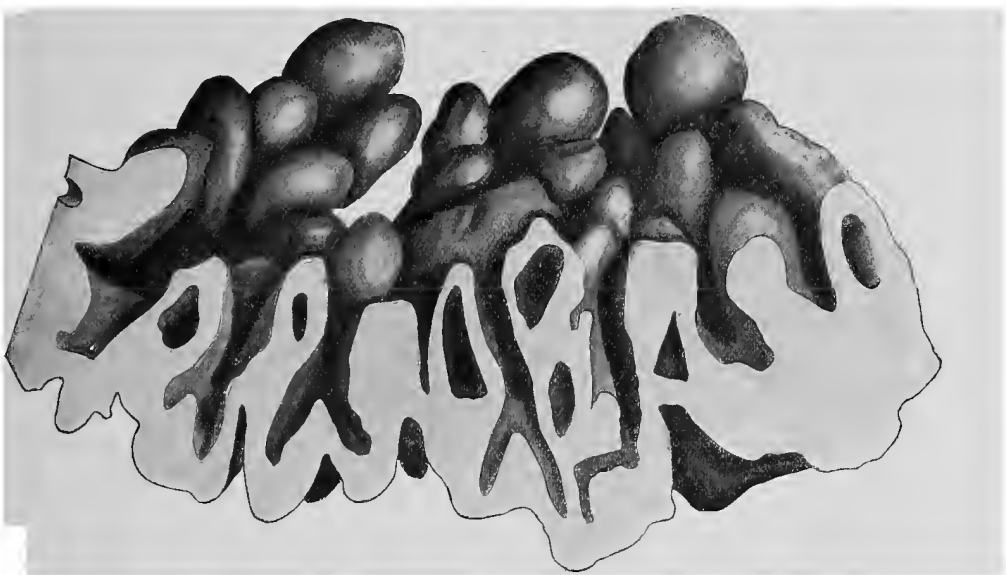

FIG. 287.—Model showing the villi of the transverse colon in an embryo of 99 mm. × 120 diam. (After F. P. Johnson.)

gated cells, apparently containing mucus. Patzelt found occasional goblet-cells in a 75 mm. embryo, and he notes that the cuticular border is distinct. The relation between the dark cells below and the clear cells above is similar to that seen in the stomach and small intestine.

Meckel in 1817 described the villi of the large intestine at 3 months as much lower than those of the small intestine, but quite as numerous. In the fourth month he found that they are not only considerably smaller, but less club-shaped and more scattered. By the eighth month the villi have gradually given place to very low, slightly indented longitudinal folds, which produce irregularities on the inner surface of the intestine. Kölliker (1861) stated that at the fifth month the villi begin to fuse from their bases upward, around the gland outlets, and that this process is completed in the seventh month. Brand (1877) described the development of septa between the villi, beginning below and extending upward, transforming the spaces between the villi into prolongations of the glands. At the sixth month the tips of the villi are reached by the septa. Patzelt (1883) states that he can confirm the observations of Kölliker and Brand regarding the disap-

pearance of the villi. But Hilton (1902) has found that the villi shorten and disappear as the intestine enlarges, without forming outer portions of the glands. This accords with Meckel's original description and is apparently correct. The gradual disappearance, whereby the villi become slight elevations, probably accounts for the discrepancy in determining the time of their extinction (Meckel, during the eighth month; Kölliker, in the seventh month; Brand, at the sixth month). Even at 240 mm. the villi are quite low.

The Outer Layers.—In embryos of 14.5 and 16 mm. the mesenchyma of the large intestine contains branches of the inferior mesenteric vessels. The circular muscle layer, which is present at this stage in the ileum, is still absent from the large intestine. It appears first in the rectal region and spreads upward. Thus at 22.8 mm. it is present only in the lower part of the large intestine, where it is in relation with branches of the pelvic sympathetic ganglia. At 42 mm. it is found throughout the colon. The longitudinal layer appears as a crescentic condensation along the mesenteric attachment of the transverse colon at 75 mm. In the transverse colon at 99 mm. the mesenteric tænia is still the most prominent part of the longitudinal muscle, but the other two tæniæ are indicated. There is probably a thin layer of longitudinal muscle in the intervals between the tæniæ. In the rectum at this stage the longitudinal layer is well defined. At 187 mm. the *muscularis mucosæ* is distinct in the rectum, but is apparently absent from the transverse colon. It is present there at 240 mm.

Lymphatic vessels are abundant along the mesenteric attachment of the rectum in early stages (37 mm.). At 120 mm. the lymphatic vessels in this region have extended into the submucosa, and lymph-glands are developing outside of the muscularis. At 187 mm. lymphoid tissue is present in the propria of the rectum, forming nodules and extending into the submucosa. Baginsky found developing nodules in the submucosa of the colon at 4 months. At birth the nodules are abundant.

The transverse folds of the rectum are seen in longitudinal sections at 120 mm. The haustra or sacculations of the colon, according to Meckel, are not present until the end of the fifth month and they first appear in the transverse colon. In this region they are distinct at 240 mm. Corresponding with the external indentation, which bounds the sacculation, there is a prominent internal fold of the mucosa. The *appendices epiploicæ* were found by Baginsky at 4 months. Meckel had said that they are distinct in the fifth month, although they contain quite as little fat as the omentum.

The Vermiform Process.—At 16 mm. the vermiform process is an epithelial tube surrounded by undifferentiated mesenchyma. Its lumen is clear-cut and round. At 55 mm. the lumen has become lobed, resembling that of the colon in earlier stages. The circular muscle is present as a well-defined layer, but the longitudinal

muscle has not yet appeared. At 120 mm. (about 4 months) villi are present, and between them there are bifurcating glands or pits. Brand (1877) found only villi at 3½ months, but at 4½ months the glands had appeared. Some of them showed "lateral outpocketings" which Brand thought were perhaps concerned with the later increase in the number of glands. At 120 mm. the *tunica propria,* because of its crowded nuclei, is quite distinct from the underlying submucosa, and the contrast between them is greater than in the adjacent colon. At 140 mm. Stöhr (1898) found small "groups of leucocytes" close beside blood-vessels, not only in the deep connective-tissue layer, but also within the villi. In the tunica propria they form compact masses of cells which are the beginnings of the nodules. At this early stage scattered leucocytes wander into the epithelium which covers the tips of the villi.

In the fifth month (170 mm.?) Stöhr has found that the *muscularis mucosæ* is indicated in the cæcum but is absent from the vermiform process. Villi are still present. The glands of the vermiform process vary greatly in diameter and length, and some of them extend almost to the circular muscle. At this stage Stöhr has described a degeneration of some of the glands, beginning with a characteristic thickening of the connective tissue which surrounds them. The goblet-cells at the neck of a degenerating gland first become flattened, and then give place to a solid epithelial strand. Later the strand ruptures, and the detached basal portion, after becoming cystic, undergoes involution. The last remnants of such a gland are small groups of epithelial cells, surrounded by thick connective-tissue capsules. Stöhr finds that degenerating glands are relatively less numerous at six months, and he infers that the degeneration may be limited to embryonic stages.

At 240 mm. both the muscularis mucosæ and the longitudinal muscle layer are present. The glands are branched and some of them are long enough to cause a local bulging of the muscularis mucosæ. Occasionally they appear to penetrate it. In this specimen detached glands were not found. The propria contains diffuse lymphoid tissue and five nodules, of which the two most highly developed are near the distal end of the vermiform process.

At birth the glands are still branched. The number of lymph-nodules has increased, and five were seen in a single longitudinal section of the distal third of a vermiform process 35 mm. long. Berry and Lock (1906) have stated that the lymph-nodules increase rapidly after birth, but these authors are in error in denying the presence of lymph-nodules at term.

Anomalies of the Large Intestine.—It is generally agreed that the sigmoid colon is relatively long and freely movable at birth.

Bourcart (1863) has determined its course and form in 150 cases. Frequently in the adult the sigmoid colon is excessively long, forming two or three very large coils. According to Frommer (1902), Curschmann found an elongated colon in 15 of the 233 bodies which he examined, and he regarded it as a persistence of the infantile condition. Concetti (1899) recognizes three types of congenital cases, which cause habitual constipation: 1, those with simple elongation of the descending and sigmoid colon; 2, cases in which, in addition to the elongation, the colon is dilated and its walls hypertrophied; 3, cases in which there is local dilatation of the lowest part of the colon, above which there is apt to be a region of compensatory hypertrophy. In the third group Concetti describes a case at 2 1-2 years, in which the longitudinal muscle was completely absent from the portion of the colon just above the rectum, and the transverse muscle was thinner than the muscularis mucosæ. The embryological factors which control the length of the colon are unknown.

Stenosis and atresia are less frequent in the colon than in the small intestine, but they present the same forms. They occur both as membranes and as complete interruptions of the intestinal tube, with blind ends more or less widely separated (Forssner, 1907). In the large intestine of the embryo there is ordinarily no occlusion such as occurs in the duodenum, and these cases are essentially abnormal. The same is true of the doubling of the cæcum and colon described by Lockwood (1882).

Diverticula of the colon are frequent, but apparently they are acquired late in life. Hansemann (1896) finds that they are not limited to the mesenteric attachments, but may occur on the convex side of the intestine, sometimes projecting into the appendices epiploicæ. Unlike the false diverticula of the small intestine with which they are sometimes associated, he states that the outpocketings of the colon often push the atrophic muscle before them and are "true dilatation diverticula."

Hedinger (1904) has described a case of congenital diverticula of the vermiform process. In the distal third of the vermiform process of a new-born child there were numerous outpocketings, which either only reached the muscularis or extended nearly through it so as to produce an uneven serous surface. Hedinger considers that in his case alone, the congenital origin of a diverticulum of the digestive tube has been established.

Contents of the Intestine.—When the glands of the digestive tract begin to secrete, their secretions together with desquamated and disintegrating entodermal cells are found in the intestinal tube. These become mixed with amniotic fluid, containing lanugo hairs and fatty material from the *vernix caseosa,* which has been swallowed. In early stages the fluid is yellowish in color, and at birth it is still light colored in the upper part of the intestine. Toward the rectum it gradually becomes dark brown or dark green, and is known as *meconium* (a Greek term for the juice of the poppy and for sepia). The color is due to bile pigments. Schenk (1896) states that in embryos of four months the meconium

appears as a bright yellow or pale greenish fluid, and that it fills the entire large intestine in embryos of five months. In later stages it becomes dark brown. But, according to Tourneux (1909), it does not pass the valve of the colon in embryos of five and six months; it is only from the seventh to the ninth month that it passes into the large intestine, where it becomes greenish brown. Bacteria are absent and there is no gas in the embryonic intestine.

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THE DEVELOPMENT OF THE LIVER.

By FREDERIC T. LEWIS.

Early Development of the Entodermal Portion.—In the embryo of 2.5 mm. which Thompson described (Fig. 236, p. 311), the liver is in a very early stage of development. It is a median ventral outgrowth of the entodermal tube, with thick walls which inclose a cavity in wide communication with the alimentary canal (Thompson, 1908). The latter presents a groove-like ventral border, but the liver appears as a well-defined cul-de-sac, the external form of which is shown in Fig. 288, A and B. Brachet (1896) and Swaen (1897) have described the liver as arising from a longitudinal groove.

In the slightly older Bremer embryo (4 mm.), the median hepatic diverticulum is still present, but there has been an extensive proliferation of the cells in its anterior and ventral walls. The proliferating cells have formed irregular masses and anastomosing cords. In places the nuclei are peripheral, so that there is a lightly staining protoplasmic core, but no lumen is present in these outgrowths. Ventral and lateral views of a model of the liver in this embryo are shown in Fig. 288, C and D. (A small nodular outgrowth of the digestive tube, shown in the figure, and a similar structure beyond the lower limit of the model, are not connected with the liver.)

The 4.9 mm. embryo described by Ingalls (Fig. 239, p. 314) is considerably older. The anastomising cords of hepatic cells have formed a large crescentic mass, Fig. 289, A, with wings extending backward on either side of the intestinal tube. This mass connects with an outpocketing of the intestine, which corresponds with the original hepatic diverticulum. Distally the diverticulum shows a rounded subdivision, or outgrowth, which gives rise to the gall-bladder and cystic duct. Toward the intestine, in the angle between the diverticulum and the duodenum, the ventral pancreas has developed.

In an embryo of 7.5 mm. the liver is much larger (Fig. 240, p. 316). The crescentic mass of anastomosing trabeculæ joins the elongated diverticulum by a short solid stem, the hepatic duct (Fig. 289, B). The diverticulum has become tubular, thus giving rise to the common bile-duct (*ductus choledochus*). Distally the gall-bladder and cystic duct are represented by a cylindrical prolongation of the diverticulum, which is nearly solid.

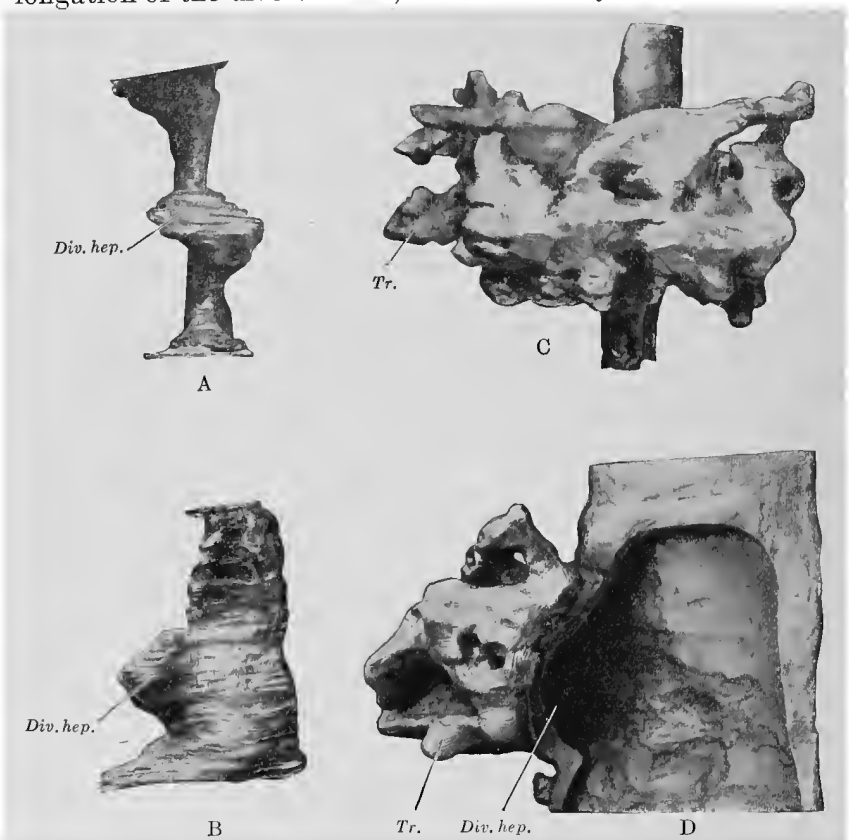


FIG. 288.—A and B, ventral and lateral views of the liver of an embryo with 23 pairs of somites (2.5 mm.), from a model by Peter Thompson. × 55 (?) diam. C and D, ventral and lateral views of the liver of a 4 mm. embryo, from a model by J. L. Bremer. × 135 diam. *Div. hep.*, hepatic diverticulum; *Tr.*, hepatic trabeculæ.

Before mammalian embryos had been satisfactorily studied, it was known that in the chick the liver arises from *two* outgrowths of the intestine, and Bischoff (1845), Remak (1855), and Kölliker (1861) believed that this would prove generally true for mammals. Although His (1885) found only single outgrowths in human embryos of 2–3 mm., Felix (1892) concluded that two are present. In addition to the "cranial hepatic duct" or diverticulum he found, in a single specimen, a "caudal groove" which he believed to be analogous with the posterior hepatic outgrowth in the chick. The embryo which he studied had been injured in the hepatic region. According to Felix, the caudal groove in man produces the gall-bladder and cystic duct, together with some of the hepatic trabeculæ, and it fuses with the cranial portion. Swaen (1897), in an embryo of 3.8 mm., found

the liver represented by a longitudinal groove, which forms a cul-de-sac anteriorly and becomes gradually lower until it disappears posteriorly. Other writers have described the cul-de-sac, or hepatic diverticulum, as consisting of an anterior *pars hepatica,* which gives rise to the trabeculæ, and a posterior *pars cystica,* which produces the gall-bladder (*cf.* Hammar, 1897). Thompson, following Maurer (1906), applies these terms to portions of the diverticulum shown in Fig. 288, A and B. Géraudel (1907), without describing young embryos, concludes that the bile-ducts and the hepatic trabeculæ are genetically independent; the former arise from the entoderm, and the latter from the mesoderm. This has been discussed and denied by Debeyre (1910). A bilaterally paired origin of the liver has been described in some vertebrates, but has not been found in man.

Certain investigators, following His (1885), recognize an early *compact stage* in the development of the liver, in which there are epithelial masses instead of anastomosing trabeculæ. It has been discussed whether the trabeculæ arise by epithelial outgrowths or by the breaking up of the solid masses through the invasion of mesenchymal tissue. The liver of the Bremer embryo is in the compact stage.

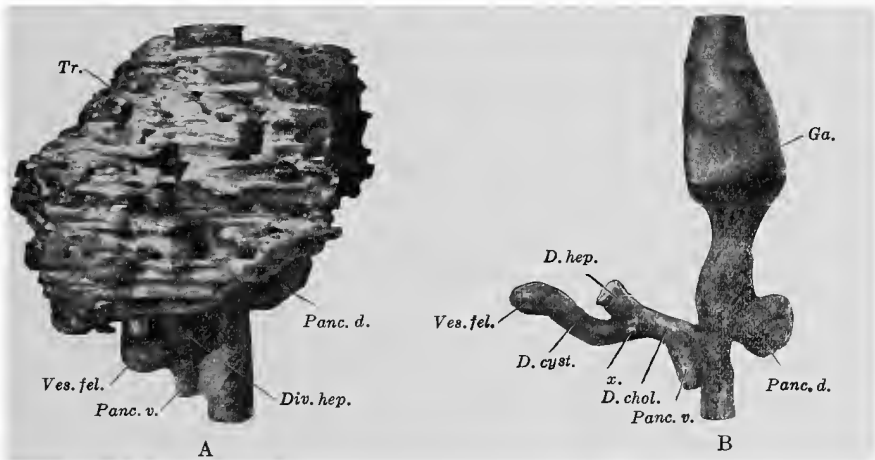


Fig. 289.—A, lateral view of the liver and pancreas of a 4.9 mm. embryo, from a model by N. W. Ingalls. × 65 diam. B, similar view of a model in which the hepatic trabeculæ are not included, from a 7.5 mm. embryo. Modelled by F. W. Thyng. × 50 diam. *D. chol.*, common bile-duct; *D. cyst.*, cystic duct; *D. hep.*, hepatic duct; *Div. hep.*, hepatic diverticulum; *Ga.*, stomach; *Panc. d.*, dorsal pancreas; *Panc. v.*, ventral pancreas; *Tr.*, trabeculæ; *Ves. fel.* (vesica fellea), gall-bladder; *x*, aberrant duct.

Relation between the Entodermal Portion and the Blood-vessels.—Von Baer (1828) described the hepatic outgrowths in the chick as arising in close relation with the veins. Similarly Janošík (1887) observed that "in birds, through constant ramification, new outgrowths form, which grow into the lumen of the omphalomesenteric vein, pushing the endothelium before them." But in a young human embryo he failed to find such an intimate relation between the liver and the veins. Swaen, however (in 1897), states that in human embryos "the cavities of these veins have probably been invaded by the hepatic trabeculæ and transformed into vascular ramifications and capillary networks."

Bremer (1906) described the liver shown in Fig. 288, C and D, as follows: "The liver cords are found to be growing into mesenchyma at a level ventral to the vitelline (or omphalomesen-

teric) veins; in this same mesenchyma, however, we find branches of the veins ramifying and forming plexuses, and in certain places these plexuses come into intimate relation with the liver cords."

With further growth the places of contact rapidly increase. As the trabeculæ ramify, new branches of the venous plexus extend between and around them, so that the cords of liver-cells are closely invested with endothelium. The process, therefore, is not a simple invasion of the lumen of the veins by the trabeculæ.

As the right and left wings of the liver extend dorsally, they encounter respectively the main trunks of the right and left omphalomesenteric veins, which are passing from the intestine to the heart. The hepatic trabeculæ surround these veins. The left omphalomesenteric vein soon loses its identity within the hepatic plexus, but the right vein remains as a distinct channel. These

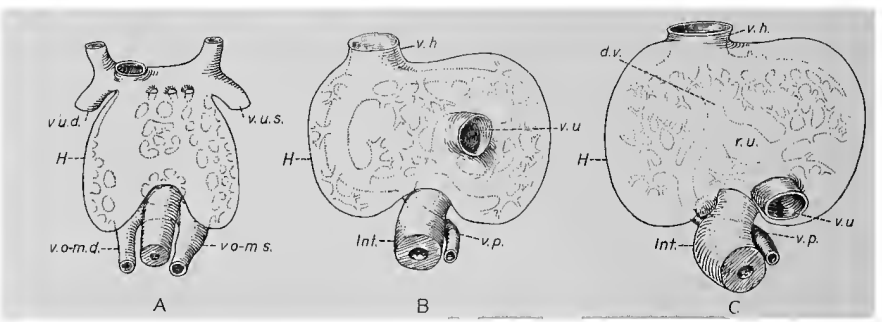


FIG. 290.—Semi-diagrammatic reconstructions of the veins of the liver (ventral views). (After Mall. A, embryo of 4.5 mm.; B, 6.5 mm.; C, 7 mm. *d. v.*, ductus venosus; *H*, liver; *Int.*, intestine; *r. u.*, recessus umbilicalis; *v. h.*, hepatic vein; *v. o-m. d.*, *v. o-m. s.*, right and left omphalomesenteric veins; *v. p.*, portal vein; *v. u.*, umbilical vein; *v. u. d.*, *v. u. s.*, right and left umbilical veins.

relations are shown in the diagram, Fig. 290, A, from an embryo similar to Ingalls' specimen. (For a reconstruction of these veins, see Ingalls, 1908.)

The further development of the large hepatic vessels may be considered briefly, since details are supplied in Chapter XVIII. In an embryo of 6.5 mm., Fig. 290, B, the two omphalomesenteric veins have produced a single vessel, which winds behind the intestine to enter the liver, the entering portion being a persistent part of the right vein. This is the *portal vein* of later stages. Within the liver the right omphalomesenteric vein can be followed continuously, and the left through a plexiform network, to the superior surface. Here a single vessel, the *hepatic vein,* conveys the blood to the heart. The hepatic vein is essentially the persistent outlet of the right omphalomesenteric vein.

Thus it will be seen that by intercrescence with the hepatic trabeculæ, the original omphalomesenteric veins have been resolved into an afferent portal vein, which empties into a network of branches, and an efferent hepatic vein, which drains these

branches. This purely venous type of circulation has long been described as a *portal circulation.* (In the liver it is the hepatic portal system; in the Wolffian body, the renal portal, etc.) It has also been described as a sinusoidal circulation (Minot, 1900; Lewis, 1904).

In addition to the blood from the intestines, received through the portal vein, the liver very early receives blood from the placenta, through the left umbilical vein. The pair of umbilical veins at first pass to the heart without entering the liver, but in some 4 mm. embryos the left umbilical vein already sends out branches which join the hepatic plexus. In the 6.5 mm. embryo, Fig. 290, B, one of these branches has become the chief outlet for the placental blood. At first the umbilical vein merges in the general plexus, but later it forms a large channel across the inferior portion of the liver (Fig. 290, C). Although it is a left vein, it gradually moves toward the median line, and the gall-bladder, which is morphologically median, is found on the right.

After birth, the portion of the umbilical vein extending from the umbilicus to the liver becomes reduced to a fibrous cord,—the round ligament (*lig. teres hepatis*). In the adult, a large branch of the portal vein within the liver extends toward this ligament and ends blindly. Rex (1888) has described this blind ending, as an appendage of the left branch of the portal vein, and named it the *recessus umbilicalis.* Mall (1906) has applied this term to a portion of the embryonic vessels, as indicated in Fig. 290, C. The vessel which appears as a continuation of the umbilical vein, passing from the portal to the hepatic (in later stages to the vena cava inferior), is the *ductus venosus.* Since the ductus venosus and the umbilical vein appear on the under surface of the liver, they will be further described with the surface markings.

As stated by Toldt and Zuckerkandl (1875), the capillaries of the liver in early embryonic stages are considerably wider than later, both absolutely and as compared with the glandular parts which they surround. Minot (1892), in describing the embryonic mammalian liver, noted that the "blood-channels are very large," and Schenk (1896) referred to the "lacunar vascularization" in the liver of batrachians. In 1900 Minot proposed the term *sinusoids,* in distinction from *capillaries,* for wide endothelial tubes fitted closely against the cells of the organ in which they are developed; those in the adult liver, which have become narrower, he distinguished as *capilliform sinusoids.* The intimate relation between the hepatic cells and the endothelium has long been known. Thus Hering (1871) recorded that "the secreting cells of the liver exhibit a peculiar arrangement, whereby there exists a much closer and more extensive contact between them and the capillaries than in other glands." In describing this relation in the embryo, the

perivascular tissue will be considered first, and then the cells which occur within it.

Perivascular Tissue.—The gross relation between the blood-vessels and the hepatic trabeculæ in a 9.4 mm. embryo is shown in the model, Fig. 308, p. 432. Along the upper surface of the model the liver is seen in transverse section. The histological features of such a section are shown in Fig. 291. In many places the endothelium has become separated from the hepatic trabeculæ, thus producing a perivascular space. The space is bridged by slender protoplasmic processes of the endothelial cells. These processes, together with the peripheral protoplasm of the endothelial cells, are directly transformed into connective-tissue fibres of a peculiar sort. Kon (1908) observed the transformation in embryos of four and five months, but Mollier (1909) declares that

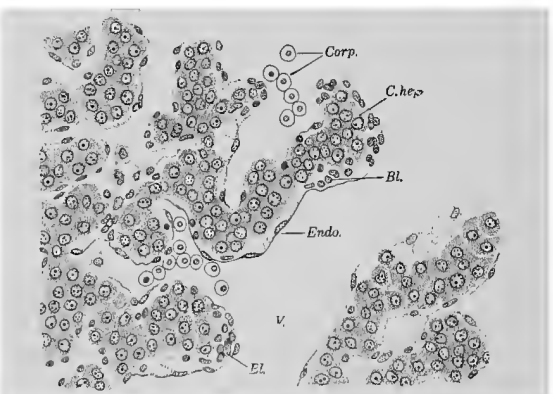


FIG. 291.—Section of the liver of a 7.5 mm. embryo (Harvard Collection, Series 256). × 120 diam. *Bl.*, blood-forming cells; *C. hep.*, cells of the hepatic trabeculæ; *Corp.*, nucleated blood-corpuscles; *Endo.*, endothelium; *V.*, branch of the portal vein.

it begins much earlier, since the fibres are clearly present at 30 mm.[15] As compared with the adult, Maresch (1905) finds that the fibres in embryonic livers are poorly developed, and that "not until birth can an abundant supporting tissue be demonstrated."

The nature of the delicate felt-work of perivascular fibres found in the adult has been discussed by Mall (1896) as follows: "Kupffer considers them to be elastic, while Ewald and Kühne consider them white fibrous. The fact that they are digested by pancreatin and yield but little gelatine when boiled excludes both views; and, since they seem to be identical with the reticulum of lymphatic glands, spleen, and mucous membrane, I shall retain for them the name reticulum."

Usually they are regarded as delicate strands of white fibrous tissue. Apart from the nuclei of the endothelium, no nuclei are found in relation with the fibres, as noted by His (1860) and abundantly confirmed.

[15] Mall found the network of fibrils in a pig embryo of 20 mm. *Amer. Journ. of Anat.*, vol i, p. 354, 1902.

Perivascular spaces, bounded on one side by the capillary wall and on the other directly by hepatic cells, with here and there a connective-tissue fibre stretched across, were described by Biesiadecki in 1867. He concluded that these spaces were preformed and not due to imperfect fixation. Hering (1871) recognized that, although the spaces are increased by shrinkage, they indicate a structural peculiarity. MacGillavry (1864) had injected these spaces through the lymphatic vessels, and also through the bile-ducts, but they do not normally open into either. They are interfibrillar tissue spaces, and are quite distinct from lymphatic vessels.

Blood-forming Cells.—In the liver of the 7.5 mm. embryo, in addition to the flattened nuclei of the endothelium and the round, coarsely granular nuclei of the hepatic trabeculæ, there is a third group consisting of small, darkly staining, and densely granular forms, occasionally somewhat indented, situated between the endothelium and the trabeculæ (Fig. 291). Frequently they occur in groups. The protoplasm surrounding them, in this specimen, is scarcely perceptible.

Toldt and Zuckerkandl (1875) designated these as *round cells,* in contrast with the *cuboidal* cells of the trabeculæ, and described them as follows:

"These cells are distinctly round, variable in size, sharply outlined, very finely granular, and clear; they never contain fat droplets, even when such are present in considerable quantity in the cuboidal cells, nor do pigment granules occur in them. The relatively large nucleus is generally distinctly outlined, yet not with so refractive a contour as in the cuboidal cells. It is of quite homogeneous consistency. Nucleoli are almost always visible, even two or three in a nucleus." These cells were observed in a 10 weeks embryo and in all the older ones examined. "Toward the end of embryonic life the number of the round cells, as compared with the cuboidal cells, strikingly decreases, but they are still present at birth, situated either singly in the wall of the gland tubes, or in groups by themselves, surrounded only by a capillary mesh." "After birth their number diminishes very rapidly, and even in the first weeks they seem to disappear entirely."

Toldt and Zuckerkandl mistook the round cells for young hepatic cells. The fact that they were not dislodged from the liver after the veins had been thoroughly washed out with salt solution confirmed their opinion that they were not the developing blood-corpuscles described by Kölliker. Kölliker (1846), from a study of one human and several sheep embryos, had concluded that "as the liver develops, the multiplication of corpuscles ceases elsewhere in the blood, and in its place, probably because all of the blood of the umbilical vein now flows into the liver, an active formation of blood-cells occurs in the hepatic vessels." Kölliker's communication is followed by a letter from E. H. Weber, who states that in the liver of the frog the corpuscles develop *outside* of the vessels, to which they may gain entrance by local absorption of the vessel wall. In 1874 Neumann described the corpuscles as occur-

ring in nests between the hepatic cells in human embryos of 8–9 months, and he thought that they arose endogenously in the protoplasm of certain elongated cells (presumably endothelial). Schmidt (1892) states that they arise through karyokinetic division of the endothelial cells and multiply by mitosis. Van der Stricht (1892) concluded that the cells described by Toldt and Zuckerkandl were young red blood-corpuscles. He observed that the capillary wall becomes discontinuous at the places where these cells appear to be imbedded in the trabeculæ, and therefore he considered that they came from the circulating blood.

In the perivascular spaces of the embryonic liver, not only are red corpuscles produced, but also leucocytes and giant cells such as are characteristic of red bone marrow. They are described in connection with the blood (Chapter XVIII). In early stages these cells are abundant, but, according to Nattan-Larrier (1904), after the fifth month giant cells and basophilic myelocytes are very rare, and at birth the nucleated red corpuscles remain almost exclusively. Lobenhoffer (1908) states that as blood formation in the liver diminishes, the capillary recesses become fewer and smaller, disappearing in the eighth month, but at birth, in almost every field, he found one or two blood-forming groups between the hepatic cells. He agrees with Schmidt that "the cells of the capillaries are capable of forming blood elements."

It is probable that the primitive blood-cells seen in the liver of the 7.5 mm. embryo are derived from the endothelium, but their possible origin from cells of the circulating blood must be considered (see Chapter XVIII).

In the adult, as shown by Kupffer (1876 and 1899), the endothelium is so perforated that its cells have become stellate. Mollier (1909) considers that the stellate condition is associated with blood formation and is most highly developed in the embryo. He believes that the endothelial cells and the blood-corpuscles both arise from a reticular syncytium, and, as the formation of corpuscles ceases, the syncytium becomes a closed endothelium with perivascular fibres. This change occurs first along the capillaries which are to become the main branches of the portal vein.

The Gall-bladder, Ductus Cysticus and Ductus Choledochus.—The solid stage of the gall-bladder, which occurs regularly in young human embryos, is presumably acquired with the elongation of the round diverticulum, such as is found at 4.9 mm. (Fig. 289, A). Both the gall-bladder and the common bile-duct have been recorded as solid in an embryo of 6.8 mm. (Piper, 1900) and in another of 6.75 mm. (Keibel and Elze, 1908). These are the youngest stages in which the solid condition has been observed. At 7.5 mm. (Fig. 289, B) there is a lumen in the common bile-duct, but the gall-bladder is impervious. Near the hepatic duct the lumen is subdivded, appearing in cross sections as two or three

minute pores. At 16 mm. there are irregular subdivisions near the hepatic duct, and the distal part of the gall-bladder is solid, but in both the cystic duct and the common bile-duct the lumen is single and well defined. Occasionally the common bile-duct has a double lumen in the midst of its course, as was noted at 14.5 and at 22.8 mm. (Fig. 292, B). In these cases the two cavities unite in a single lumen both proximally and distally.

As the gall-bladder expands it may present "intra-epithelial cysts," as recorded by Keibel and Elze at 18 mm., or the lumen may be bridged by epithelial strands, as in Fig. 292, A (29 mm.). At this stage the greater part of the gall-bladder has a clear-cut round lumen. Its wall shows two rows of oval nuclei, with mitotic figures in the inner row (22.8 mm.). In a 42 mm. embryo the tapering proximal part of the gall-bladder presents several rounded outpocketings, resembling the intestinal diverticula, some-

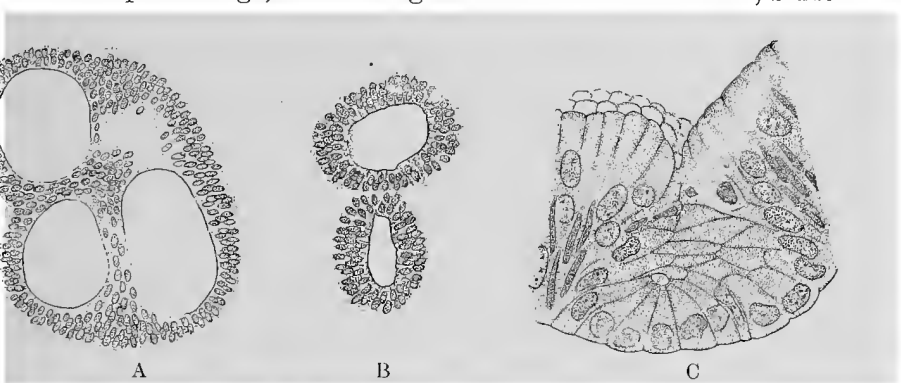


FIG. 292.—A, section of the gall-bladder of a 29 mm. embryo (Harvard Collection, Series 914). ×180 diam. B section of the common bile-duct of a 22.8 mm. embryo (Harvard Collection, Series 871). × 180 diam. C, epithelium of the gall-bladder, two weeks after birth. × 580 diam.

times sectioned so as to appear detached from the main tube. Similar pockets are apparently more definite and abundant in the sheep and pig than in man. The lining of the gall-bladder in a 78 mm. specimen shows numerous well-defined folds, such as are characteristic of all later stages. The development of the folds in the cystic duct, constituting the spiral valve, has apparently not been studied.

The epithelium of the gall-bladder of a child two weeks old, born prematurely at the seventh month, is simple and columnar, with distinct cell walls ending in terminal bars (Fig. 292, C). A broad clear border, or top plate, with radial striation, such as Virchow (1857) described in the gall-bladder of adults and children, could not be detected. The cells contain oval, pale, vesicular nuclei, together with more elongated and darkly staining forms, apparently due to compression. The dark nuclei may be scattered among the others or may form considerable groups. Occasionally

at the bottom of the depressions between the folds, a pearl-like group of cells is seen (Fig. 292, C), suggesting the buds of the intestine.

The developmnet of the "glands" of the bile-ducts has not been studied embryologically. These structures are generally considered to be epithelial pockets rather than true mucous glands. They formerly attracted much attention, culminating in a thorough study of them by Riess in 1863, for it had been supposed by Henle (1861) that these glands were the source of bile, and that the hepatic trabeculæ produced sugar. Riess states that they are most numerous in the hepatic duct, less numerous in the upper part of the common bile-duct and lower part of the cystic duct, and entirely absent from the lower part of the common bile-duct and upper part of the cystic duct; probably there are none in the gall-bladder. The largest of them are branched tubes with rounded terminations; the small ones are simple pockets, which give place, in the smaller branches of the hepatic duct, to rounded diverticula and swellings. Riess has noted that the glandular appendages of the bile-ducts are much less developed in children than in adults, and "in the earlier embryonic life they are perhaps wholly lacking."

The outer coats of the gall-bladder and cystic duct develop as follows: At 7.5 mm. the epithelium is surrounded by a layer of mesenchyma, and the entire structure is so imbedded in the under surface of the liver that it causes only a slight swelling of the peritoneal surface. Above and on the sides the mesenchyma is in direct relation with the hepatic trabeculæ, and it receives a few prolongations of the venous capillaries. Below it is covered by the peritoneal epithelium except on the left, where that layer is reflected to the abdominal walls in connection with the falciform ligament. In later stages the gall-bladder is separated from the hepatic trabeculæ on either side, and is attached to the liver only along its upper surface.

At 16 mm. the mesenchyma surrounding the gall-bladder is still undifferentiated, but at 22.8 mm. it forms two broad concentric zones, of which the inner is darker and more compact than the outer. At 29 mm. certain cells in the peripheral part of the dark zone form a third layer, which is thin and somewhat interrupted. As seen in later stages these cells are myoblasts, so that at 29 mm. all three layers of the adult gall-bladder are indicated. These are the mucosa, muscularis, and serosa. The layers become gradually less distinct toward the hepatic duct.

The vessels and nerves of the gall-bladder are branches of those seen at 10 mm. near the pyloric end of the stomach (Fig. 274, C, p. 370). Of these the hepatic artery is of special interest.

The Hepatic Artery.—At 10 mm. the hepatic branch of the cœliac artery can be followed to the hepatic duct. Later it extends along the hepatic and cystic ducts, but as the cystic branches develop first, the hepatic artery appears primarily as the artery of the gall-bladder. Thus, at 22.8 mm., the main stem lies in a wing-like fold of the tunica serosa of the gall-bladder, and other

branches follow the attached border of the gall-bladder, lying close to the hepatic trabeculæ. They connect with a capillary plexus in the mesenchyma, which empties at various points into the venous network among the adjacent trabeculæ. The cystic vein of the adult, which conveys the blood from the gall-bladder to the main trunk of the portal vein, is a later formation. Therefore three stages may be recognized in the development of the blood-vessels of the gall-bladder: in the first, the capillaries from the portal network extend into the mesenchyma around the gall-bladder; in the second, they are joined by the arterial capillaries and become efferent vessels; in the third, a single efferent vein, extending along the cystic duct and emptying into the portal trunk, is developed from the capillary system.

After the cystic branch of the hepatic artery has become established, mesenchyma develops around the hepatic duct and its ramifications, and branches of the hepatic artery appear in this mesenchyma. They form capillary plexuses, especially around the branches of the hepatic duct, and the blood passes from these capillaries into the subdivisions of the portal vein found among the adjacent trabeculæ. Veins comparable with the cystic vein, which collect the blood from the arterial capillaries and convey it to the main branches of the portal vein, have been described within the liver of the adult, but according to Mall (1906) they do not exist.

Certain branches of the hepatic artery reach the surface of the liver and ramify in the capsule. They either empty into the portal network beneath the capsule, or are drained by " branches of the hepatic vein which come to the surface of the liver and spread out between the meshes of the arterial plexus " (Mall).

The Hepatic Duct.—At 9.4 mm. the hepatic duct is a short stem connecting the great mass of hepatic trabeculæ with the common bile-duct (Fig. 308, p. 432). It is solid, or nearly so, in this specimen, but in a 10 mm. embryo it contains a lumen. The nuclei are crowded so that the duct stains deeply and contrasts sharply with the trabeculæ. Where it joins the trabeculæ the transition is so abrupt that it has led to the erroneous opinion that the two tissues are of different origin.

Although the hepatic duct in man is a single stem, there are certain mammals in which there are several ducts which pass from the trabeculæ to the cystic duct, or, in some species, to the gall-bladder (*cf.* Rex, 1888). Rudimentary additional ducts are common in human embryos. They may join the hepatic, cystic, or common bile-duct, but usually they occur very near the junction of the three. Thus, at 7.5 mm. (Fig. 289, B), on either side at this junction, there is a solid knob which does not quite reach the trabeculæ. In the same position there is a single outgrowth in

the 9.4 mm. embryo and also in the 10 mm. specimen. An aberrant duct with a lumen empties into the proximal end of the cystic duct at 14.5 mm., and the same embryo shows a detached nodule of epithelium beside the common bile-duct. A detached nodule containing a lumen was found at 16 mm. These structures may represent outgrowths of the original diverticulum which have contributed to the formation of the mass of trabeculæ and are now degenerating, or they may be abortive secondary ducts which have never reached the trabeculæ.

Within the liver of 9–10 mm. embryos the branches of the hepatic duct usually cannot be traced far, but there is marked variation in this respect. Frequently among the hepatic trabeculæ one or more very short ducts may be found which certainly do not connect with other ducts. They may blend with the hepatic trabeculæ at one or both ends. These detached ducts are lined with regular cuboidal or columnar epithelium and may show a clear-cut lumen. Such ducts were noted in embryos measuring 8, 9.4, and 10.2 mm., and, according to Elze (1907), in those of 7 and 11 mm. Lewis (1903) found similar detached cysts in the liver of a 12 mm. pig, and considered them to be cut off from the secondary hepatic ducts. Whether they are detached portions of the hepatic ducts is questionable. They may arise *in situ* by a transformation of the cells of the hepatic trabeculæ.

The Periportal Ducts.—In an embryo of 22.8 mm. (Fig. 293, A) the spread of the bile-ducts along the main branches of the portal vein has begun. The trabeculæ form cords extending along the surface of the periportal mesenchyma, and in them a lumen is formed. In places the cells on the mesenchymal side of the lumen are distinctly flatter than those toward the portal capillaries. As seen in the figure, the trabeculæ connect freely with these ducts. In a later stage (29 mm., Fig. 293, B) the mesenchyma has increased, so that it surrounds the ducts which were seen forming along its surface. Their epithelium has become regularly cuboidal or columnar. On the upper side of the vein in Fig. 293, B, the ducts are in the earlier stage of development.

The periportal ducts clearly form a plexus. The larger ducts, which have become surrounded by mesenchyma, are also plexiform, although with the enlargement of the liver their anastomoses become less numerous. However, the plexiform arrangement of the main branches of the hepatic duct, which was clearly seen in a single frontal section at 29 mm., persists throughout life, as has long been known.

In the adult, Kiernan (1833) found that an injection of the left branch of the hepatic duct returns by the right duct. "From this experiment . . . it appears that the right and left ducts anastomose with each other." Hering (1871) stated that there is

an anastomosis of the branches of the large ducts, and that the smallest ones sometimes appear to anastomose around the vein which they accompany (as stated by Riess), "but this requires further investigation." He described the connection between these ducts and the trabeculæ as formed by canals "bounded on one side by small epithelial cells and on the other by large hepatic cells." These transitional ducts, sometimes called the "canals of Hering," were observed in a child of 3 months.

Toldt and Zuckerkandl (1875) described them in an embryo of the tenth week as follows: "Those hepatic trabeculæ which are found in the immediate vicinity of the relatively very large portal branches, almost without exception are

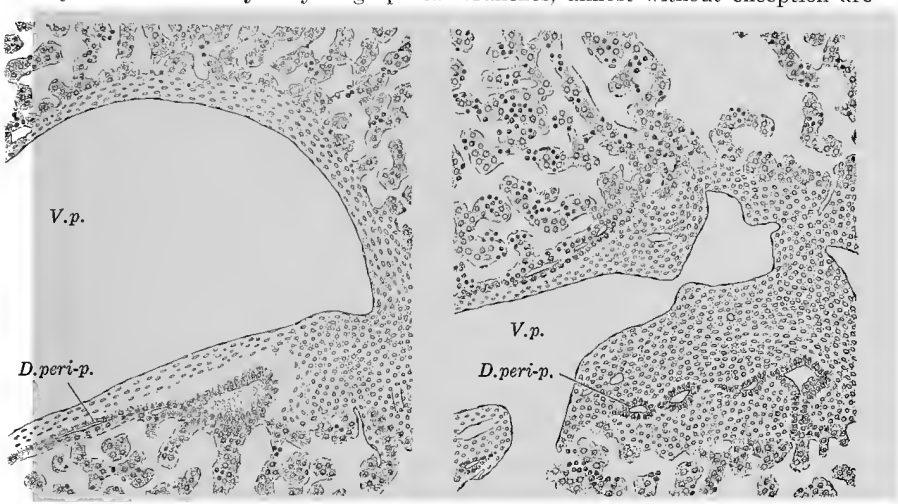


FIG. 293.—Sections showing the formation of the periportal ducts (*D.peri-p.*) around a branch of the portal vein (*V.p.*). A, from an embryo of 22.8 mm. (Harvard Collection, Series 871); B, from an embryo of 32 mm. (Harvard Collection, Series 913). × 185 diam.

perpendicular to the latter, so that in cross sections of a portal branch they show a radial arrangement, and in longitudinal sections they appear in parallel rows. They open into the ducts almost at right angles, and their cuboidal cells are inserted directly into the flat epithelium of the ducts."

The Bile-capillaries.—In an embryo of the fourth week Kölliker (1861) found the liver composed of solid trabeculæ. Remak (1855) had observed a similar condition in chick embryos, and had named the solid cords of cells "hepatic cylinders." Phisalix (1888), in describing a 10 mm. embryo, states that he agrees with Kölliker that there is no lumen in the primitive hepatic cylinders. This view is generally accepted. But Toldt and Zuckerkandl (1875) described the liver of an embryo of the fourth week, in which the tubular structure appears most distinctly. "That we have to do with tubes and not with solid cords of cells can be shown both in cross sections and frequently in longitudinal sections; the lumen is always bounded by so sharp an outline that

there is no question of an artificial separation of the cells." They find that in the slender tubes the lumen is bounded by three or four cells, in the larger tubes by still more.

Although in a 10 mm. embryo most of the trabeculæ are solid, there are some, scattered irregularly through the liver, which show a very distinct lumen (Fig. 294, *A*). The lumen is larger than that of the future bile-capillary and lacks the characteristic cuticular border. It is bounded usually by five or six cells and ends blindly in the adjoining sections. At 29 mm. the trabeculæ are extensively broken up by the nests of blood-cells, but those which are least disturbed often show a lumen. At 37 mm. the

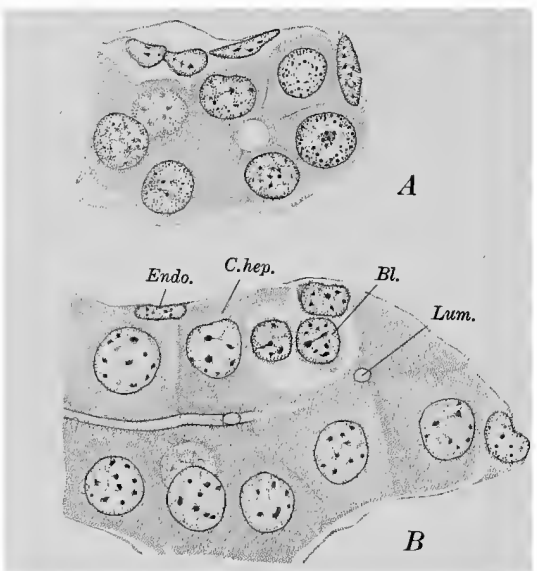


FIG. 294.—*A*, hepatic trabecula containing a lumen. From a 10 mm. embryo (Harvard Collection, Series 1000). × 1065 diam. *B*, bile-capillaries in a 44.3 mm. embryo (Harvard Collection, Series 1611). × 1065 diam. *Bl.*, blood-corpuscle; *C. hep.*, hepatic cell; *Endo.*, endothelium; *Lum.*, lumen of a bile-capillary.

lumen is more distinctly outlined, but it may still be bounded by as many as six cells. In a 44 mm. embryo, bile-capillaries with cuticular borders are abundant (Fig. 294, *B*). They occur in all parts of the liver, but appear to be most numerous near the peri-portal ducts, into which some of them empty. They extend axially through the trabeculæ, and where the latter branch, the capillaries branch also. Usually they are separated from the venous endothelium by an entire hepatic cell, but, as seen in the figure, nests of blood-cells sometimes approach very close to them.

Hendrickson (1898) studied the bile-capillaries with Golgi's method, and found them extensively developed at 50 mm. (Fig. 295). In his preparations they are somewhat more abundant

around the branches of the portal vein, but it could not be shown that they develop peripherally from the periportal ducts. They may arise within the trabeculæ as blind tubes, which later anastomose and join the ducts. In a Golgi preparation from an embryo of 100 mm., Hendrickson found numerous polygonal meshes made by the bile-capillaries. These may encircle a single cell within a thick trabecula, or they may run through trabeculæ which anastomose at both ends. Short lateral branches are seen in Hendrickson's preparations, but whether they represent axial capillaries, either ending blindly or passing out of the plane of section, or whether they are intercellular branches radiating from the axial capillary toward the venous endothelium, was not determined.

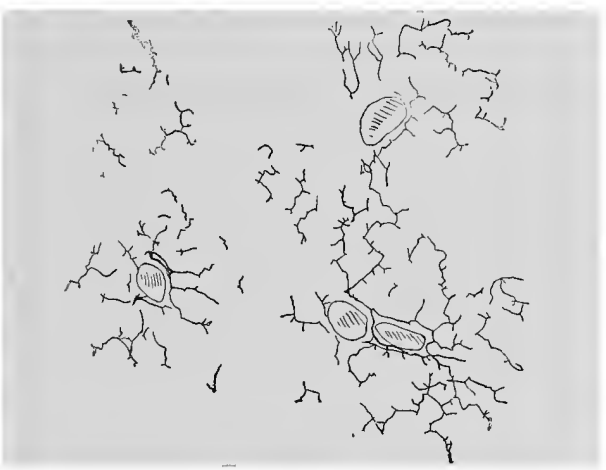


FIG. 295.—Golgi preparation of the bile-capillaries in an embryo of 50 mm. × 53 diam. (After Hendrickson.)

The number of hepatic cells bounding a bile-capillary is greater in embryos than in the adult. The capillary of the adult is usually a minute canal in the midst of the boundary between *two* adjacent cells, but occasionally it is surrounded by three or four cells; and von Biesiadecki, the discoverer of the human bile-capillaries, declared that five is the usual number,—rarely four. Von Biesiadecki studied only pathological specimens in which the bile-capillaries were distended. Hering (1871) was unable to find any capillaries bounded by five or more cells, either in the adult or at birth. At birth, however, in contrast with the adult, he found that the lumen of a bile-capillary is often surrounded by three or four hepatic cells, thus resembling the condition in certain amphibia. Toldt and Zuckerkandl (1875), who found three or four cells bounding the capillaries in an embryo of the fourth week, stated that in embryos of four to seven months the number

was "four to six or even more," but they included in their count the blood-cells lodged within the hepatic trabeculæ. Toward the end of fetal life they found usually three or four cells; and in the fourth and fifth years, "generally only two, but occasionally three and even four." The reduction from three or four to two cells, occurring shortly after birth, is accompanied, according to Toldt and Zuckerkandl, by a "stretching" of the trabeculæ, whereby they become longer and more slender, with their cells arranged in rows. They recognize the occasional persistence of three- and four-celled tubes, even after twenty years.

The Hepatic Cells.—In all stages the hepatic cells are characterized by large, very round nuclei, containing a coarse chromatic network, and surrounded by abundant, densely granular protoplasm. According to Toldt and Zuckerkandl, the diameter of the nucleus at birth is generally about 9.6 μ and in the adult about 8 μ, so that the nuclei of the adult are distinctly smaller than at birth. As a whole, however, the cells apparently increase in size. They multiply by mitosis. In a 10 mm. embryo the mitotic figures are abundant throughout the trabeculæ, but in later stages, according to Mall (1906), they are particularly numerous around the terminal (periportal) bile-ducts. Frequently the cell division is incomplete, so that a single cell may contain two nuclei. In early stages cell membranes are entirely lacking, and at 10 mm., although the cells readily separate from one another, the membranes are indistinct. Toldt and Zuckerkandl have noted that at five and six months the cells do not show the sharp outlines observed at birth. They find that at birth a portion of the cells, when isolated in salt solution, are irregularly cuboidal, but that most of them are somewhat elongated. The isolated cells of the adult vary in shape, but are more nearly cuboidal than at birth.

The hepatic cells always stand in close relation to the blood which contains absorbed nutriment. First the blood from the yolk-sac, then that from the placenta, and after birth the blood from the intestine passes directly to the liver and flows through its vascular network. Kölliker (1861) noted that the liver in the embryo is physiologically a very important organ, but that its significance is rather in producing chemical and morphological changes in the blood than in secreting bile. Fat appears in the hepatic cells before it is present in the subcutaneous tissue, as shown by Chipman (1902) for the rabbit. In the liver of human embryos Toldt and Zuckerkandl found fat droplets as early as the third or fourth month. Nattan-Larrier (1903) found that fat was forming in the fourth month, and that at birth certain hepatic cells were filled with large fat droplets, separated from one another by thin layers of protoplasm. In the liver of the rabbit, glycogen appears in the 22d day of gestation, six days after the formation

of fat, and it increases steadily and rapidly until birth (Chipman). Apparently the time of its appearance in human embryos has not been determined.

Kölliker found that the secretion of bile begins as early as the third month. He states that "from the third to the fifth month, material like bile is found in the small intestine, and in the second half of pregnancy it occurs also in the large intestine. . . . Until the sixth month the gall-bladder contains only mucus, but after that it contains bile."

Zweifel (1875) recorded that the intestinal contents of embryos of three months respond to the ordinary tests for bile acids and pigments. Toldt and Zuckerkandl observed yellow pigment granules within the embryonic liver beginning with the fourth or fifth month, but the granules were limited to the epithelial cells of the ducts, together with the adjacent hepatic cells. Even at birth they found that pigment granules are infrequent, and that the cells are clearer and more transparent than those of the adult.

Nerves and Lymphatics.—It has already been shown that the common bile-duct, cystic duct, and hepatic duct are very early surrounded by mesenchyma. Later the mesenchyma spreads along the ramifications of the portal vein, into the substance of the liver. Thus, in an embryo of the tenth week Toldt and Zuckerkandl found that the portal branches are surrounded by a considerable mass of connective tissue, and so can easily be distinguished from the thin-walled branches of the hepatic vein which are closely surrounded by the liver-cells. In the third and fourth month the difference becomes very striking. Ducts have formed at the periphery of the periportal tissue, and branches of the hepatic artery together with nerves and lymphatics have extended into it. The path by which the vessels and nerves reach the liver is shown in Fig. 274, B and C (p. 370); they enter at the transverse fissure or *porta* of the liver.

Little is known regarding the development of the nerves. Sympathetic fibres may readily be found at the entrance of the liver in embryos of 20–40 mm., but in the specimens at hand they can be traced no further than the primary division of the hepatic duct. They are associated with scattered clumps of nuclei, apparently ganglionic. In the adult the nerves form plexuses around the branches of the portal vein and hepatic ducts, and especially around the branches of the hepatic artery. In addition to the sympathetic nerves, there are fibres from the vagus, presumably entering from the pylorus.

The lymphatic vessels, which extend to the porta in a 42 mm. embryo, drain into the lower part of the thoracic duct. Later they grow into the periportal tissue, in which at birth they are conspicuously large. In the adult they extend as far as the smallest

ramifications of the hepatic ducts, and terminate in the connective tissue. Herring and Simpson (1906) find that the lymphatic vessels accompany the hepatic artery and its branches, forming networks around these vessels, as well as around the branches of the portal vein and bile-ducts. There are no lymphatics among the trabeculæ. Mall (1906) concludes that the great amount of lymph which flows from the liver is derived directly from the blood-plasma. It passes out between the stellate and endothelial cells, and flows through the perivascular reticulum to the periportal tissue, where it enters the lymphatic vessels.

There is another system of lymphatic vessels in the liver, which has not been studied embryologically. This includes the vessels which extend downward from the diaphragm, through the ligaments of the liver, to ramify in the capsule.

Lobules.—The great mass of hepatic trabeculæ is arranged in more or less definite lobules, which were discovered by Wepfer in the liver of the pig in 1664, and which have been familiar to anatomists since the time of Malpighi (see Kiernan, 1833). The liver was compared with a bunch of grapes. According to some anatomists its lobules were appended to the extremities of the portal vein, but Kiernan agreed with those who made the hepatic vein the axial structure. In the centre of each lobule he recognized a terminal branch of the hepatic vein. Between the lobules there are intervals, which Kiernan named *portal canals,* filled with connective tissue containing branches of the portal vein, hepatic artery, bile-ducts, nerves, and lymphatics. Three portal canals may be expected at the periphery of a single lobule. In the pig the connective tissue filling these canals spreads around the lobules, investing them with capsules, and thus making them conspicuous. In the human adult there are normally only indications of such capsules, and at birth they are wholly lacking. The portal canals then stand as isolated "boundary stones."

Kiernan recognized certain objections to describing the liver on the basis of these lobules, for he wrote, "The essential part of a gland is undoubtedly its duct; vessels it possesses in common with every other organ; and it may be thought that in the above description too much importance is attached to the hepatic veins." Recognizing this, Brissaud and Sabourin (1888) proposed the term *biliary* or *portal lobule* for the group of trabeculæ centred about a portal canal, leaving *hepatic lobule* for the structures described by Kiernan. Others also have considered that the portal lobule is morphologically the true unit of the liver.

As stated by Mall, "In all other glands we make the duct the centre of the structural unit. From this centre often the artery and the framework radiate. In the liver everything radiates from the so-called interlobular space,—arterial and portal blood-vessels, bile-duct, lymphatics, nerves, and connective tissue.

. . . Throughout my description I shall use the term portal unit, structural unit, or unit for the clump of tissue which surrounds each terminal branch of the portal vein. In order to avoid confusion, I shall use the term lobule in its old sense,—as the hepatic lobule,—for after much discussion carried on during two centuries, it has become well established."

Schenk (1874) stated that the embryonic liver, in a certain stage, represents a single lobule of the adult organ. This view was adopted by Toldt and Zuckerkandl, and defined by Mall (1906). Mall states that in a 4 mm. embryo "the single lobule is perfect; it is composed of a complete capillary network without an anastomosing vein through it."

Mall believes that the further development of the hepatic vessels is in accordance with the laws established by Thoma (1893). These are:

(1) An acceleration of the current leads to an enlargement of the lumen of a vessel, and a slowing of the current leads to its narrowing and final disappearance.

(2) An increase in the blood-pressure is the cause for new formation of capillaries.

(3) The growth in thickness of the vessel wall depends on the tension of the wall, which in turn is dependent upon the blood-pressure and the diameter of the vessel.

These laws apply to the liver, as shown in Fig. 290, B and C. In C a new and direct channel, the ductus venosus, has been formed across the liver, apparently by the enlargement of capillaries in which the current has been accelerated. At the same time the current becomes slower in the circuitous right omphalomesenteric vein, shown in B, which is reduced to capillaries in C. The liver then consists of two lobules, right and left respectively. The blood enters them from below, and is drained by the hepatic branches above. In an embryo of 11 mm. (Fig. 296) Mall finds that six lobules are indicated. These are obscure in the figure, since many of the enlarging capillary vessels have been drawn. It will be observed that the portal branches tend to alternate with the hepatic branches. "They are beginning to dovetail with each other." Thus the formation of a great number of lobules is suggested. The way in which this is accomplished is shown in Mall's diagrams, Figs. 297, 298, and 299. The single branches *d* and *a* in Fig. 297 become the main branches *d* and *a* in Fig. 299, and the successive orders of new branches *e*, *f* and *b*, *c* have arisen by the enlargement of capillary vessels. The lobules *b*, indicated by dotted outlines in Fig. 298, have become clusters of lobules in Fig. 299, and some new simple lobules, c^2, have appeared between them.

In this way the 480,000 lobules, which according to Mall's estimate are found in the liver of an adult dog, are produced from a single lobule. Regulated by Thoma's laws the main vascular stems develop in such a way that all the lobules are equally favored. "If fluids of different consistency are injected either

into the portal or hepatic vein, *all of the terminal veins fill simultaneously.*" Moreover, the final branches of the portal and hepatic veins are always as far from one another as possible. "At all times this distance is half the diameter of a lobule, and since this is in the neighborhood of one millimetre, the distance is about half a millimetre, the normal length of a capillary vessel."

The lobules at birth, according to Toldt and Zuckerkandl, differ from those of the adult, as follows: "In the child there are indeed vascular territories which show a certain independence. However, since they are drained by a group of terminal branches and not by a single venous root, they are not comparable with

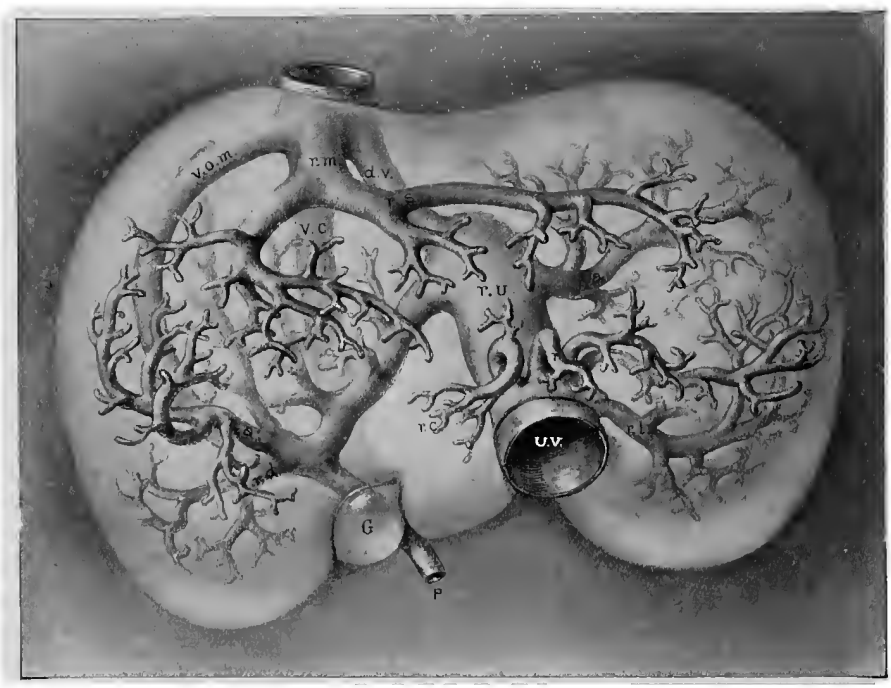


FIG. 296.—Ventral view of a reconstruction of the hepatic vessels in an embryo of 11 mm. × 25 diam. (After Mall.) The principal veins are—*d. v.*, ductus venosus; *p.*, portal vein; *r. m.* and *r. s.*, middle and left rami of the hepatic vein; *r. u.*, recessus umbilicalis; *u. v.*, umbilical vein; *v. c.*, vena cava; *v. o. m.*, omphalomesenteric vein.

the lobules of the adult. They correspond rather with a combination of the latter, and to a certain extent represent *lobules of a higher order,* from which gradually single portions will be detached."

The multiplication of lobules continues long after birth, and partly divided, compound forms were recognized in the adult by Kiernan.

Ligaments and Lobes.—The relation of the liver of a 4 mm. embryo to the body cavity is shown in dorsal view in Fig. 300. The model shown in the figure has three vertical cut surfaces,—the body wall on either side, and the mesentery, prolonged upward

as the mediastinal septum, in the centre. The ventral portion of the mesentery bulges laterally below, where the liver is growing into it, and then joins the septum transversum. The latter is the plate of tissue which forms the ventral surface of the model. Its position is so nearly vertical that it separates the pair of pleuroperitoneal cavities behind from the pericardial cavity in front. The pleuroperitoneal cavities are shown in the figure. Anteriorly they turn ventrally over the free margin of the septum transversum and empty into the median pericardial cavity.

Most embryologists, following His, state that the liver develops in the septum transversum, and as seen in median sagittal sections (Fig. 236, p. 311) this appears to be correct. The septum transversum, however, is early divisible into two parts, related to one another like the arms of a T. The transverse portion forms a part

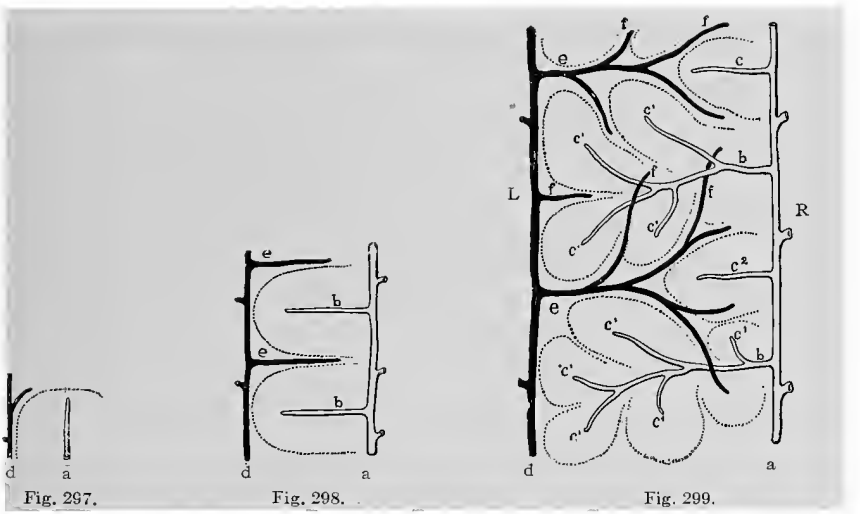


Fig. 297. Fig. 298. Fig. 299.

FIGS. 297, 298, and 299.—Diagrams of three successive stages in the formation of lobules. (After Mall.) *d*, branch of the portal vein; *a*, branch of the hepatic vein.

of the diaphragm. The median sagittal portion is the ventral mesentery, and it is in this subdivision of the septum transversum that the liver develops. The relatively very broad attachment of the mesentery to the diaphragm forms the falciform ligament of the liver, and the lateral bulgings indicate respectively the right and left hepatic lobes.

His (1880) recognized that in a 4 mm. embryo the tissue in which the liver develops is more or less independent of the septum transversum, and he named it the "Vorleber." Hertwig (1906), who states—following His—that the liver grows into the septum transversum, writes also that the liver develops in the ventral mesentery.

In the 4 mm. embryo (Fig. 300), each of the lateral lobes of the liver is prolonged upward by an irregular mass of tissue, which nearly fills the body cavity. Each mass is attached along its ventral border to the septum transversum, and thus it separates the medial pleural part of the body cavity from the lateral peritoneal part. But superiorly these cavities connect with one another and open into the pericardial cavity, as already noted. The

upward prolongations of the liver may be called the right and left coronary appendages. They are the anterior portions of the "Vorleber" of His, which were described in a 4 mm. embryo as containing a plexus of blood-vessels but no network of trabeculæ.[16]

They are certainly the *ventral pillars* bounding the pleuro-peritoneal opening, first described by Uskow (1883) and later, for human embryos, by Swaen (1897). Their relation to the dorsal pillars, which have been called the suspensory ligaments of the Wolffian body, have been discussed in Chapter XIII.

In an embryo of 9.4 mm. (Fig. 301) it is seen that the coronary appendages have fused with the septum transversum and the lateral body wall, thus shutting off the *superior lateral recess* of the peritoneal cavity (Swaen). The liver now presents a crescentic transverse attachment to the diaphragm, passing from one coronary appendage to the other; this attachment is the coronary ligament. Within its concavity, on either side, are the pleural cavities which communicate below with the peritoneal cavity.

A fundamental feature of the 9.4 mm. embryo is the presence of the *plica venæ cavæ* of Ravn (1889). This is essentially an attachment of the right lobe of the liver to the dorsal body wall, and it has developed downward from the right *ala pulmonalis*.[17] Through this attachment the right subcardinal vein anastomoses with the veins of the liver, thus giving rise to the vena cava inferior. The portion of the liver between the plica venæ cavæ and the ventral mesentery, or *omentum minus,* is the caudate lobe (of Spigelius). The caudate lobe joins the right lobe across the *foramen epiploicum* (of Winslow). Below the foramen, the portal vein and bile-duct are seen in section. In the lower part of the model the place where the left umbilical vein enters the liver is indicated by a fold. The gall-bladder is on the right of it.

In an embryo of 5 months (Fig. 302) the diaphragm has been completed in the way described in Chapter XIII. The œsophagus, not included in the preceding drawings, is seen passing through it. The thin lateral extensions of each coronary ligament (*ligamenta triangularia*) mark the position of the former appendages, and filling their dorsal concavity is the portion of the diaphragm which formed last, and which completes the separation of pleural and peritoneal cavities. The vena cava inferior now fills its plica, which has become broad. The lesser omentum is very thin except

[16] They were probably included by Lieberkühn (1876) among the "villi" which occur where the omphalomesenteric veins enter the heart, and which were said to be so related to the developing liver that they contained the first blood-vessels of that organ.

[17] *Ala pulmonalis* is the term introduced by Ravn for the developing mesodermal portion of each lung. The ala pulmonalis appears on either side of the fore-gut as a wing-like fold, which is flattened dorsoventrally and which has a free lateral margin. The caudal portion of each ala becomes a pulmonary ligament (*lig. pulmonale*).

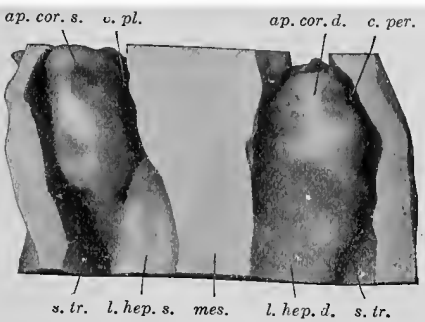


Fig. 300.

Fig. 301.

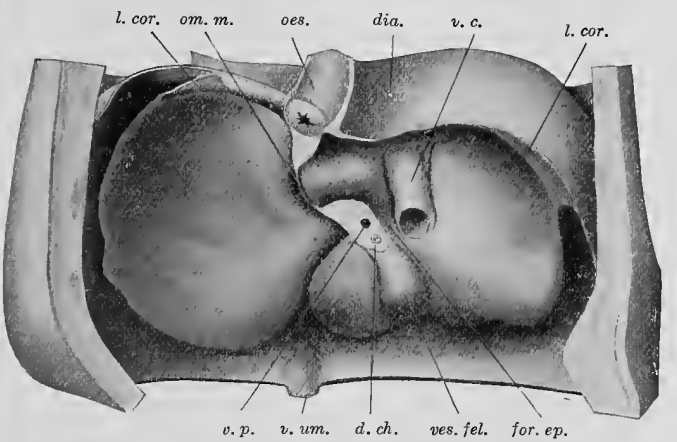


Fig. 302.

FIGS. 300, 301, and 302.—Dorsal views of the hepatic region. Fig. 300, model from a 4 mm. embryo (Harvard Collection, Series 714), × 66 diam.; Fig. 301, model from a 9.4 mm. embryo (Harvard Collection, Series 1005), × 32 diam.; Fig. 302, dissection of a 5 months' embryo, 220 mm. in length, × 1½ diam. *ap. cor. d.*, *ap. cor. s.*, right and left coronary appendages; *c. pl.*, pleural part of the pleuroperitoneal cavity; *c. per.*, peritoneal part of the pleuroperitoneal cavity; *d. ch.*, common bile-duct; *dia.*, diaphragm; *for. ep.*, foramen epiploicum; *l. cor.*, coronary ligament; *l. hep. d.*, *l. hep. s.*, right and left hepatic lobes; *mes.*, mesentery; *oes.*, œsophagus; *om. m.*, lesser omentum; *pl. v. c.*, plica venæ cavæ; *r. s.*, superior lateral recess of the peritoneal cavity; *s. tr.* septum transversum; *v. c.*, vena cava; *ves. fel.*, gall-bladder; *v. p.*, portal vein; *v. um.*, umbilical vein.

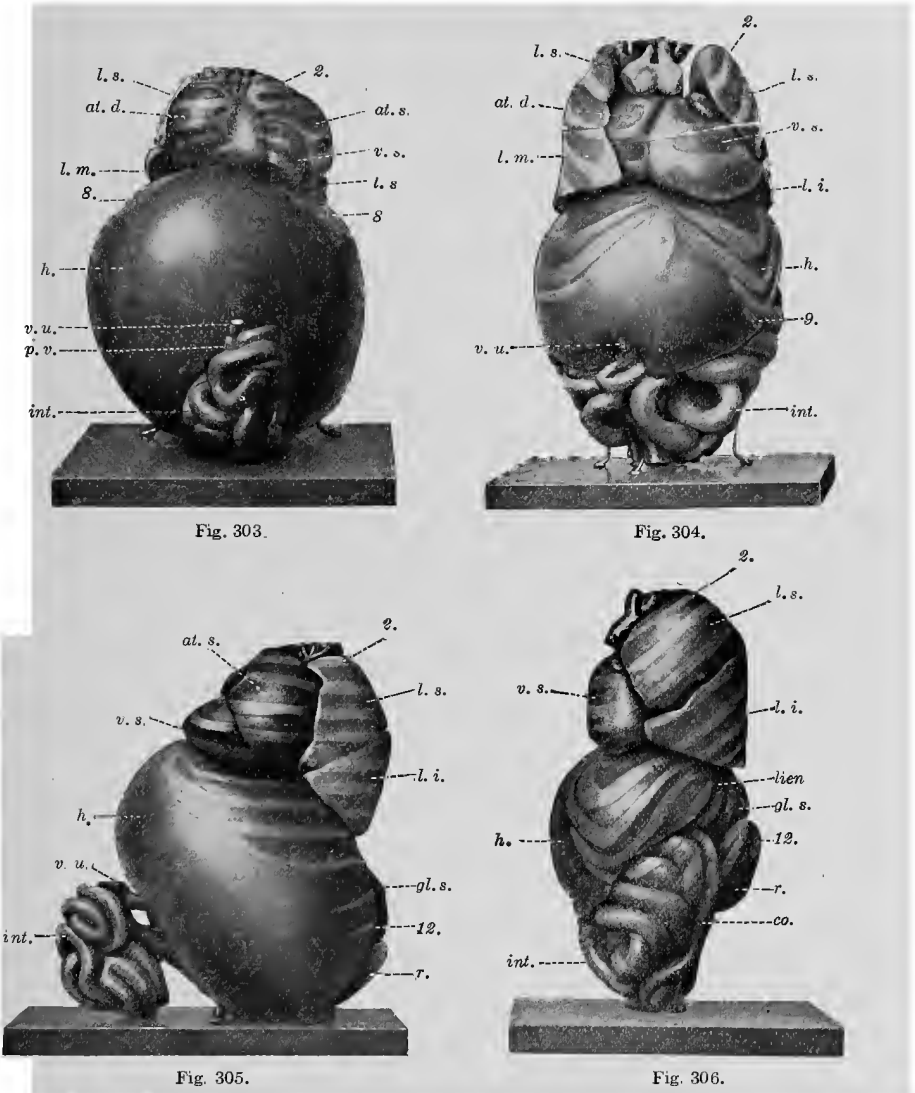
at the transverse fissure or porta; together with the gall-bladder it marks the true median plane of the liver. The umbilical vein is seen in the ventral abdominal wall, from which it passes to the liver along the free margin of the falciform ligament. It then lies in a deep groove on the under surface of the liver, and with the porta and the gall-bladder it bounds the quadrate lobe. Its extension, the ductus venosus, passes toward the vena cava at the bottom of the fissure of the lesser omentum.

In the preceding description the embryonic liver has been divided into right and left lobes, separated by the falciform ligament. Rex, after careful comparative studies of adult livers, declares that the only subdivision of the human liver which is a true lobe is the omental or caudate, but he admits that the recognition of the right and left lobes is justified by the distribution of the branches of the portal vein. Some embryologists have found this convenient. The absence of deep clefts, such as mark off the dorsolateral lobes in the embryonic liver of pigs and rabbits, is notable in the human liver. Nevertheless Swaen (1897) considers that corresponding lobes should be recognized, and accordingly he describes the human liver as composed of three lobes,—one median and two lateral. Mall (1906) states that each of the six primary lobules which he finds in an embryo of 11 mm. is to expand into a whole lobe, and Bradley (1908) shows the relation of six lobes to the three which he considers fundamental. Thompson (1899) has described the fissures and clefts which frequently appear on the under surface of the liver, especially of the right lobe. Certain of these were found with considerable regularity. The two most frequently met with, occurring respectively in 83 and 50 per cent. of the cases examined, were believed to form partial boundaries of a lobe which is well defined in the gorilla. The almost entire absence of lobes in the human liver has been emphasized by Rex.

The Liver as a Whole.—Except for a temporary decrease at birth, associated with the closure of the umbilical vein, the weight of the liver steadily increases. At the end of the second fetal month it weighs .2 gm.; at birth, 75 gm.; and in the adult 1500 gm. (Mall). But the volume of the liver, as compared with that of the body, reaches a maximum in a 31 mm. embryo, as determined by Jackson (1909). He found that in an 11 mm. embryo the liver is 4.85 per cent. of the total body volume, or approximately the same as at birth; in a 17 mm. embryo it is 6.9 per cent.; and at 31 mm. it is 10.56 per cent. (Figs. 303 and 305). In a 65 mm. embryo (Figs. 304 and 306) it has apparently decreased to about 5 or 6 per cent., which is the average for the remainder of the fetal period. In this specimen the liver, as indicated by its relation to the ribs, has acquired approximately its final position.

During its development, certain portions of the liver atrophy, while other parts increase. The most extensive degeneration is in the peripheral part of the left lobe. In the 31 mm. embryo the two lobes are still nearly symmetrical, and the left lobe extends between the spleen and the body wall (Fig. 305). At 65 mm. "the liver has partly retracted, so that it covers only the anterior portion of the external splenic surface " (Fig. 306). In the adult

any contact between the liver and spleen is exceptional. The decrease in the size of the left lobe is generally ascribed to pressure from adjacent organs. Pougnault (1905) notes that in cases of



FIGS. 303 and 305.—Ventral and lateral views of a model of the viscera from a 31 mm. embryo. × 4½ diam. FIGS. 304 and 306.—Similar views of a model of the viscera from a 65 mm. embryo. × 2 diam. (After C. M. Jackson.) *2, 8, 9, 12*, ribs; *at. d.*, *at. s.*, right and left atria; *co.*, colon; *gl. s.*, left suprarenal gland; *h.*, liver; *int.*, small intestine; *lien*, spleen; *l. i.*, *l. m.*, *l. s.*, inferior, middle, and superior lobes of the lung; *p. v.*, vermiform process and cæcum; *r.*, kidney; *v. s.*, left ventricle; *v. u.*, umbilical vein.

umbilical hernia the symmetry may be retained, and Jackson's models indicate that the decrease occurs when the intestines enter the abdomen. It may also be associated with the expansion of the gastric fundus. As a result of this degeneration, the left portion

of the coronary ligament (the *appendix fibrosa*) contains a network of anastomosing ducts, discovered by Ferrein and described by Kiernan as a "rudimental liver."

Both of these anatomists recognized similar tissue around the vena cava. Usually this vein occupies a fissure on the dorsal surface of the liver, but Kiernan states that the fissure is frequently converted into a canal, either by hepatic parenchyma or by a ligamentous band containing ducts and blood-vessels. He found that similarly the umbilical vein may be completely surrounded by hepatic tissue, or bridged by a band of the same structure as the *ligamentum venæ cavæ*. Hepatic trabeculæ may also invade the diaphragm, and at birth they have been reported as extending into the falciform ligament as far as the umbilicus. In all of these situations, and also near the expanding gall-bladder, the hepatic cells may degenerate, leaving aberrant ducts and blood-vessels. These have been studied through injections by Toldt and Zuckerkandl (1875). The marked variations in the form of the fetal liver have been tabulated by Ruge (1907).

Anomalies of the Liver.—The total absence of the gall-bladder, according to Meckel (1812), is not very unusual. In these cases the hepatic diverticulum has presumably developed normally, but has failed to produce the secondary subdivision which gives rise to the gall-bladder. Sometimes, in addition to the absence of the gall-bladder, there is no trace of the hepatic, cystic, and common bile-ducts. Kirmisson and Hébert have reported such a case in a child of one month, and they found two similar instances in the literature. These are probably due to obliterative processes which begin after the extra-hepatic bile-ducts have developed. Two gall-bladders may be present, perhaps produced by a double outpocketing of the diverticulum. Sometimes when the gall-bladder is single there are two cystic ducts, as in a case reported by Dreesman. The two ducts arose from the gall-bladder 1 cm. apart, and united before entering the common bile-duct. Fig. 292, B, indicates how such an anomaly may develop. Beneke (1907) has studied congenital atresia of the bile-ducts. Multiple hepatic ducts have been recorded, sometimes opening separately into the duodenum.

Congenital cysts of the liver generally arise from the ducts in the connective tissue, but they may occur within the hepatic parenchyma (Moschcowitz, 1906). Sometimes they attain very large size (Sänger and Klopp, 1880). The subdivision of the liver into multiple lobes is quite common, and the occurrence of accessory livers, more or less isolated from the central mass, is well known (Toldt and Zuckerkandl, 1875). An excessive atrophy of the left lobe, leading to its "entire absence," has been recorded by Kantor (1903).

DEVELOPMENT OF THE PANCREAS.

By FREDERIC T. LEWIS.

Historical Note.—The main duct of the human pancreas, figured by Wirsung in 1642, opens into the duodenum in common with the bile-duct. The regular occurrence of an independent accessory duct, opening into the duodenum somewhat nearer the pylorus, was recognized by Santorini in 1775. Meckel (1817) observed this accessory duct in several embryos. It was situated above and to the left of the bile-duct. Meckel mistook it for the only duct of the pancreas, and concluded, therefore, that "the bile and pancreatic ducts at first are quite separate from one another, but gradually they come together and unite." Kölliker (1879), in describing a rabbit embryo, stated that the pancreas is divisible into "two distinct glands which perhaps should be interpreted as an upper and a lower pancreas, such as are found in the chick." Not until 1888 was the similar condition observed in a human embryo. Phisalix then recorded that in a 10 mm. specimen the pancreas is represented by two separate outgrowths,—"one, superior and larger, the duct of which will become the accessory duct; the other, inferior and smaller, which corresponds with the canal of Wirsung." The upper gland is now known as the *dorsal pancreas* and the lower one as the *ventral pancreas.*

Early Development.—The two pancreases arise almost simultaneously shortly after the formation of the hepatic diverticulum, but, from the first, the dorsal pancreas is the larger. Both have been found in embryos of 3 and 4 mm. The failure of Fol (1884) to record a ventral pancreas at 5.6 mm., Mall (1891) at 7 mm., and Janošìk (1909) at 6.1 mm., must be attributed to imperfect description or to abnormal embryos. But the fact that Völker (1903) in a 3 mm. specimen, and Keibel and Elze (1908) in an embryo of 4 mm., describe only a dorsal pancreas, may indicate that the dorsal pancreas arises first. Bremer (1906), however, found only a ventral pancreas at 4 mm., represented by two knobs of intestinal epithelium, one immediately below the hepatic diverticulum (Fig. 288, D), and the other nearer the yolk-stalk. It is doubtful whether these intestinal outgrowths represent a normal stage in pancreatic development.

The dorsal pancreas is at first a "stomach-like" enlargement of the digestive tube. It is somewhat flattened laterally, and has a convex dorsal border which merges anteriorly with that of the intestine. Posteriorly the transition is more abrupt. The posterior part of the dorsal pancreas at 4.9 mm. is shown in Fig. 307, A. At 7.5 mm. (Fig. 307, B) the dorsal pancreas is separated from the intestine by a slight constriction, and the notch on the lower side is characteristically deeper than on the upper side. At 9.4 mm. (Fig. 308) the constricted part is prolonged into a short duct. The distal portion has also elongated, and its surface presents nodular swellings, which are the beginnings of branches.

The ventral pancreas in its early stages is lodged in the inferior angle formed by the hepatic diverticulum and the intes-

tine. It is a small epithelial mass, continuous above with the diverticulum, and uniting dorsally with the intestinal epithelium. This condition is seen in a series of four models made by Keibel and Elze, descriptions of which have not been published. They are from embryos of 4, *ca.* 4, 5.3, and 6.75 mm. respectively. The same condition is shown in Fig. 307, in embryos of 4.9 and 7.5 mm. In the latter the lower part of the ventral pancreas has become free from the duodenum. Subsequently it becomes entirely separate from the intestine, as in the 6.8 mm. embryo modelled by Piper (1900) and in the 8 mm. specimen modelled by Felix (1892). With the elongation of the bile-duct it becomes widely separated from the duodenum, as in the 9.4 mm. embryo (Fig. 308).

Hamburger (1892) found that the ventral pancreas in an embryo of 4 weeks had an independent opening into the duodenum, and concluded that its common outlet with the bile-duct is formed later. This has not been confirmed. However,

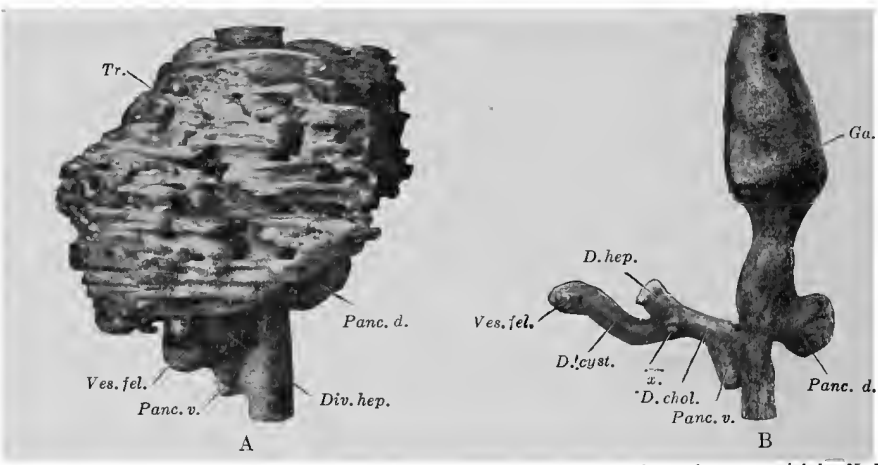


Fig. 307.—A, lateral view of the liver and pancreas of a 4.9 mm. embryo, from a model by N. W. Ingalls. × 65 diam. B, similar view of a model in which the hepatic trabeculæ are not included, from a 7.5 mm. embryo. Modelled by F. W. Thyng. × 50 diam. *D. chol.*, common bile-duct; *D. cyst.*, cystic duct; *D. hep.*, hepatic duct; *Div. hep.*, hepatic diverticulum; *Ga.*, stomach; *Panc. d.*, dorsal pancreas; *Panc. v.*, ventral pancreas; *Tr.*, trabeculæ; *Ves. fel.* (vesica fellea), gall-bladder; *x*, aberrant duct.

in the Bremer embryo the ventral pancreas may arise directly from the intestine, and in a 3 mm. specimen, according to Keibel and Elze, the ventral pancreas is an outpocketing found "just caudal to the bile-duct."

A pair of ventral pancreases are found in many vertebrates, and have been reported in a human embryo of 4.5 mm. (Debeyre, 1909). Felix (1892) recorded that in a section of the upper part of the pancreas at 8 mm., the lumen was toward the right side of the epithelial mass. He considered that the lumen belonged with a right ventral pancreas which had fused with a left ventral pancreas, and that the latter was represented by the solid left portion of the section. Jankelowitz (1895), in a 4.9 mm. embryo, found a single lumen below, which bifurcated above, sending its branches respectively to the right and left sides of the hepatic diverticulum. He considered that this indicated a fusion of right and left constituents. Ingalls (1907) studied the same specimen, and states that he is inclined to agree with Jankelowitz, although there is "only a suggestion of the paired condition." Keibel and Elze (1908) again examined this specimen, and they state that "it is very questionable whether two outgrowths are present; to us there appears to be only one."

A double lumen is often seen in the ventral pancreas of older embryos (6.8 mm., Piper; 7.5 mm., etc.), but this condition, as noted by Helly, may be observed also in the unpaired gall-bladder. It is associated with the formation of a lumen in a solid cord of cells.

Helly (1901) and Kollmann (1907) have figured a pair of ventral pancreases which have not fused. In Kollmann's 7.5 mm. embryo they are cranial and caudal in position, with the common hepatic duct between them. In Helly's 11 mm. embryo they are right and left. The left is much smaller and contains no distinct lumen. Helly believes that it degenerates without fusing with the right pancreas, and that "in embryos scarcely older than four weeks it has wholly disappeared." In other embryos between 7.5 and 11 mm. in length, including seven specimens in the Harvard Collection, the ventral pancreas appears as a single outgrowth. Moreover, a well-defined pair is not recorded in Keibel and Elze's extensive series. Therefore the specimens described by Helly and Kollmann are properly regarded as exceptional.

A paired dorsal pancreas, such as Stoss described in sheep embryos, has been sought for in man, but has not been found (Felix, Helly).

Relative Position of the Dorsal and Ventral Outgrowths.—Although the dorsal pancreas of most mammals enters the duodenum on the distal side of the bile-duct, that of man is normally on the proximal side, toward the pylorus, at all stages of development. In early stages the caudal border of the duct of the dorsal pancreas may be at a lower level than the cranial border of the hepatic diverticulum, as seen in Fig. 307 and in Keibel and Elze's models of the pancreas at 4 mm. Later there is an interval between them which varies in extent. Thus, from Keibel and Elze's model of a 5.3 mm. specimen the distance is found to be only 0.05 mm., whereas in a 5 mm. embryo figured by Tandler (1903) it is approximately 0.2 mm. The distance has increased to 0.5 mm. in a 22.8 mm. embryo (0.7 mm. in a 15 mm. specimen, Swaen), and in the adult, according to Letulle and Nattan-Larrier (1898), who examined 21 cases, it varies from 10 to 35 mm. (20 to 40 mm., Charpy, 1898).

Migrations of the dorsal pancreas in relation to the bile-duct have been described. His (1885) figured the dorsal pancreas on the pyloric side of the bile-duct in embryos of 5.7 and 10 mm., but at 11.5 mm. he placed it opposite the bile-duct, and at 12.5 and 13.8 mm. it is shown on the caudal side. This would necessitate a return to the pyloric side in subsequent stages. Thyng (1908) examined 18 embryos from 7.5 to 24 mm. in length, and failed to find a single instance of the caudal position figured by His. Janošík (1895 and 1909) and Völker (1902 and 1903) have held that the dorsal pancreas arises on the distal side of the bile-duct, and that it migrates anteriorly. This is denied by Helly (1904). Janošík's reconstructions (1909) begin with an embryo of 6.1 mm., in which the dorsal pancreas connects with the intestine "a little more distally than the bile-duct." This embryo, however, must be considered abnormal, since it shows "no trace of a ventral pancreas." In the next stage figured (8.7 mm.) the ducts are opposite. Doubtless the duct of the dorsal pancreas may occasionally open into the intestine caudal to the common bile-duct, as is the case in an embryo of 11.5 mm. in the Harvard Collection. Here, however, there is an abnormal persistence of the adjacent portion of the right omphalomesenteric vein.

Union of the Dorsal and Ventral Pancreases.—With the elongation of the bile-duct, which bends dorsally on the right side of the intestine, the ventral pancreas is brought into close relation with

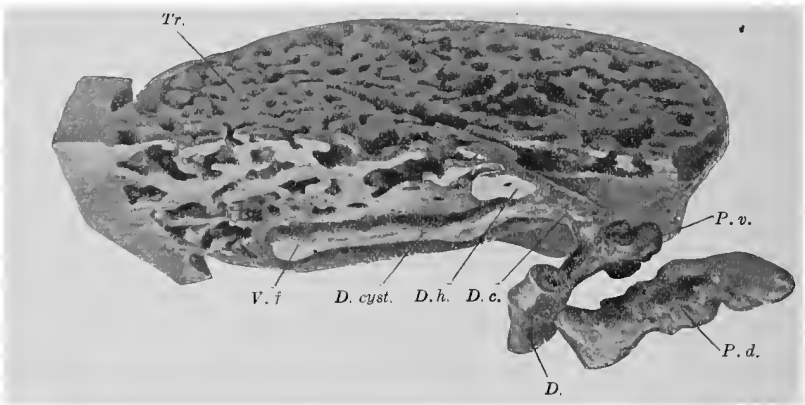


FIG. 308.—Model of a part of the liver and the pancreas of a 9.4 mm. embryo (Harvard Collection, Series 1005). × 50 diam. *D.*, duodenum; *D. c.*, common bile-duct; *D. cyst.*, cystic duct; *D. h.* hepatic duct; *P. d.*, dorsal pancreas; *P. v.*, ventral pancreas; *Tr.*, hepatic trabeculæ; *V. f.*, gall-bladder.

the dorsal pancreas (Fig. 308). Subsequently the ramifications of the two pancreases interlock, as shown in Fig. 309, from an embryo of 22.8 mm. In the model represented in the figure, the horizontal body and tail of the pancreas have been cut away at *x*. The

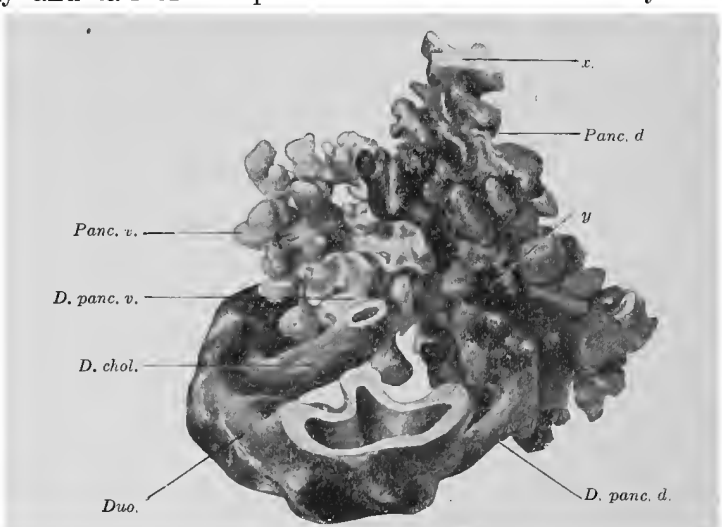


FIG. 309.—Model of the head of the pancreas of a 22.8 mm. embryo (Harvard Collection, Series 871). × 50 diam. *D. chol.*, common bile-duct; *D. panc. d.*, duct of the dorsal pancreas; *D. panc. v.*, duct of the ventral pancreas; *Duo.* duodenum; *Panc. d.*, dorsal pancreas; *Panc. v.* ventral pancreas; *x* and *y* are explained in the text.

pancreas at that point bends downward, forming the head of the organ, which in the adult terminates below in the uncinate process. The ventral pancreas forms a part of the head and more or less of

the uncinate process; the dorsal pancreas forms the remainder of these parts, together with the entire body and tail.

At 22.8 mm. the duct of the dorsal pancreas is a round stem, which passes into a flattened, plate-like duct, strongly curved upon itself. The cleft leading into its concavity is shown at *y* in Fig. 309. The convex surface of the flattened portion of the duct is beset with nodular branches, radiating in all directions. Distally the main duct again becomes round, and it may be followed as an axial structure through the tail of the gland. The duct of the ventral pancreas arises from the common bile-duct at some distance from the duodenum. It passes to the centre of a group of ramifications which nearly equal it in diameter. In this embryo, and in specimens of 14.5 and 16 mm., no connection could be found between the two pancreases. Moreover, the branches of either pancreas rarely anastomose among themselves.

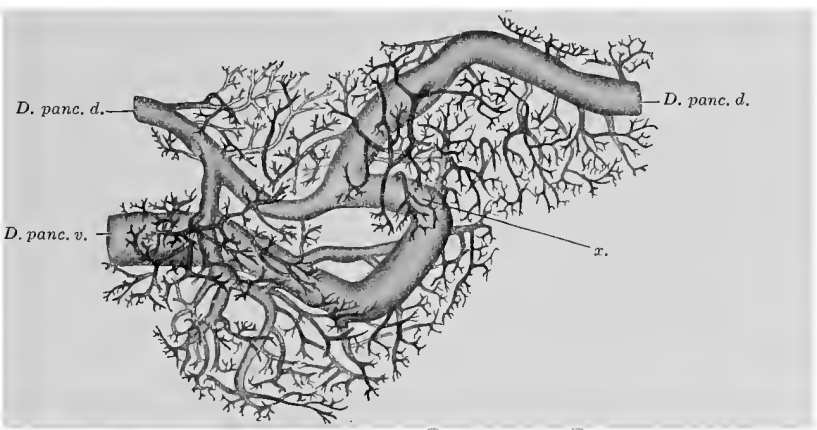


FIG. 310.—Corrosion preparation of the pancreatic ducts of an adult. Prepared by Dr. S. T. Mixter. × 1½ diam. *D. panc. d.*, duct of the dorsal pancreas; *D. panc. v.*, duct of the ventral pancreas; *x*, anastomosis between the pancreatic ducts.

In the adult the normal relations of the two glands are shown in the corrosion preparation, Fig. 310. In comparing this with Fig. 309, it will be noted that the duct of the dorsal pancreas appears to open into the duodenum at a higher level in Fig. 310 than in Fig. 309. This is associated with a shifting of the duodenum; in both cases the dorsal pancreas opens nearer the stomach than the ventral. In the adult the duct of the dorsal pancreas, shortly before entering the duodenum, receives a large branch which passes upward from the uncinate process. This branch is in front of the duct of the ventral pancreas. The latter, as in the embryo, lies at a deeper level, and is on the right side of the axis of the dorsal pancreas. The duct of the ventral pancreas forms a single large anastomosis with the duct of the dorsal pancreas, which is shown at *x* in Fig. 310. The continuous channel formed by the distal part of the duct of the dorsal pancreas, the anastomosis, and the duct of the ventral pancreas constitutes the "pan-

creatic duct" of the adult; the proximal part of the duct of the dorsal pancreas is the "accessory duct."

According to Hamburger (1892) the anastomosis between the dorsal and ventral pancreases has formed in a "six weeks' embryo." In a reconstruction of this specimen he shows that the distal end of an unbranched ventral pancreas has fused with the dorsal pancreas, which has a nodular surface but no branches. In a 14 mm. embryo Keibel and Elze (1908) found the pancreases "close together but not yet united." This is the largest specimen in their series in which the pancreases are separate, and an embryo of 12.4 mm. is the smallest in which they have united. At 14 and 15 mm. they are generally described as "fused." In such embryos the tubules interlock, and it requires a careful study of drawings of successive sections to determine whether there is a passage between the ventral and dorsal ducts. Ordinarily only a single anastomosis is produced, but Bernard (1856), in an abnormal adult specimen, has shown two connections. Charpy (1898) has found that the duct of the ventral pancreas may enter the dorsal duct at any point in its wall,—that is, on its superior, inferior, anterior, or posterior surface. Usually it appears to enter on the inferior surface. In one of the specimens figured by Charpy, the main duct draining the uncinate process passes upward to join the duct of the dorsal pancreas *behind* the duct of the ventral pancreas, instead of in front of it as in Fig. 310. This arrangement is abnormal and difficult to explain. Hasse (1908) has shown the normal relation of these ducts in the adult, but his inferences regarding their development are incorrect.

Vessels and Nerves.—The dorsal pancreas in early stages is lodged between the right and left omphalomesenteric veins. These vessels form a transverse anastomosis immediately caudal to the pancreas, and branch abundantly around it (see Ingalls, 1908, pl. 2). Later, as described in Chapter XVIII, portions of these veins give rise to the portal vein. The *vena portæ* reaches the inferior border of the pancreas in the notch between the body and head; it then passes behind the dorsal pancreas and curves forward, with the bile-duct, to enter the liver. In a 10 mm. embryo (Phisalix) the dorsal and ventral pancreases are completely separated by the portal vein; at 16 mm. (Fig. 311) they have come together and have partly surrounded the vein. The splenic branch of the portal vein develops early, and may be recognized in a 9.4 mm. embryo. It passes along the dorsal surface of the tail of the pancreas, which it drains. Some of its branches, and its opening into the portal vein, are indicated in Fig. 311.

Although the pancreas is at first in close relation with the portal vein, it does not give rise to a portal or sinusoidal circulation, and thus it differs strikingly from the adjacent liver. Its

afferent blood supply is from the splenic and hepatic branches of the cœliac artery, and from small branches of the superior mesenteric artery as it accompanies the portal vein across the inferior border of the pancreas (Fig. 311). At 37 and 42 mm. the pancreatico-duodenal arteries form a loop, which connects the hepatic and superior mesenteric arteries and supplies the head of the pancreas.

In a 42 mm. embryo lymphatic vessels are abundant in the connective tissue around the pancreas, but they do not extend among the tubules. Lymph-glands have not developed. They are present in close relation with the pancreas in a 99 mm. embryo, but they may arise in some much younger stage.

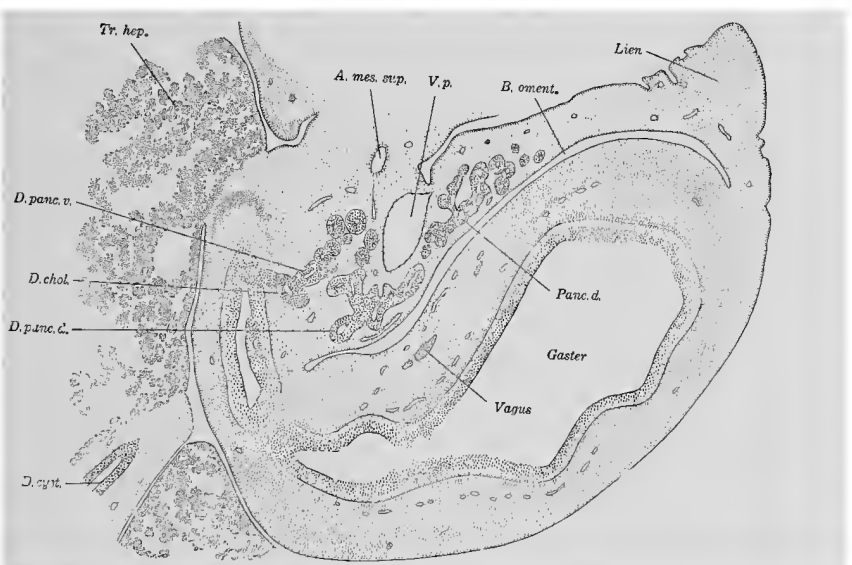


FIG. 311.—Section through the stomach, pancreas, and a part of the liver, from an embryo of 16 mm. (Harvard Collection, Series 1322). × 40 diam. *A. mes. sup.*, superior mesenteric artery; *B. oment.*, omental bursa; *Gaster*, stomach; *Lien*, spleen; *V. p.*, portal vein. (Other labels as in preceding figures.)

At 42 mm. the cœliac plexus of nerves sends branches toward the head of the pancreas, and some of them extend among the pancreatic tubules. Within the pancreas there are a few conspicuous groups of nuclei which, from their association with nerve fibres, are presumably ganglionic.

The Outlets of the Ducts.—In entering the duodenum the common bile-duct passes obliquely through the duodenal musculature, and is directed caudally. In its transit across the muscle, in embryos between 20 and 40 mm., it is joined by the duct of the ventral pancreas, and the pancreatic duct is always on its lower or caudal side (Figs. 309 and 311). At 22.8 mm. there is still no duodenal papilla at the outlet of the bile-duct, but Helly (1900) states that an elevation is present at 28.5 mm. In this embryo he

finds that sphincter muscles have developed around the bile and pancreatic ducts, but in specimens of 44 mm., in the Harvard Collection, the ducts are surrounded only by concentric mesenchyma and by the duodenal muscle through which they pass.

In the adult, according to Letulle and Nattan-Larrier (1898), the pancreatic duct may empty into the bile-duct, in the same way as in the embryo. More often the two ducts reach the duodenal surface independently, either at the base of an ampulla or at the summit of a nipple-like projection.

The duct of the dorsal pancreas, in embryos between 20 and 40 mm., has a longer course within the duodenal wall than the duct of the ventral pancreas. Consequently, although the branches of the ventral pancreas extend close to the outlet of its duct, they are almost entirely outside the duodenal musculature, whereas branches of the dorsal pancreas are regularly found in the submucosa. Helly (1900) states that an outpocketing of the dorsal duct within the wall of the duodenum is present in embryos of 12.5 and 14.5 mm. At 37 and 42 mm. distinct knobs and diverticula are present. Some of them branch and give rise to pancreatic tissue. According to Helly, this explains why true pancreatic tissue is so often found in the papilla of the dorsal duct (*papilla minor*) of the adult, but almost never occurs in the papilla of the ventral duct (*papilla major*).

The large pancreatic ducts, both within the duodenal wall and outside of it, give rise to diverticula and mucous glands. Helly has determined that they occur in both papillæ of an 80 mm. specimen, as very small outpocketings. In a 90 mm. embryo, and in all later stages, he finds that the mucous glands are easily recognized.

The Development of the Alveoli.—Kölliker (1861) described the pancreas of a four-weeks embryo as consisting of a simple wide and hollow duct, with branches, each of which has a lumen in its more slender proximal part, but terminates in a solid, pear-shaped bud. Similar buds arise in later stages, not only in the terminal branches, but also along the sides of the main ducts. The duct from a 42 mm. embryo shown in Fig. 312, A, presents early stages in their development. At *a* there is a group of cells with crowded nuclei and darkly staining basal protoplasm. At *b* a similar group is seen at the bottom of an outpocketing of the lumen, and at *c* there is a larger mass which causes a basal bulging. These structures apparently give rise to the darkly staining knobs which are abundant in the 42 mm. embryo and in younger stages. Three of them, from a 55 mm. embryo, are shown in Fig. 312, B. Often they appear to be solid, but sometimes a slender lumen may be found within them, as shown at *e*. Considered as terminal parts of the gland, these buds may be called alveoli. They contain central cells which apparently persist as the *central cells* of the

adult. The stalks of the alveoli become elongated, forming branches of the duct, and the alveoli subdivide. Thus in the adult, as seen in the model by Maziarsky (1902), the pyriform alveoli may be cleft nearly in two; some of them show lateral buds. The extension of the lumen between and into the secreting cells of the alveoli, which has been shown by the Golgi method to occur in the adult (Dogiel, 1893), has not been studied embryologically.

The Development of the Islands.—The youngest human embryo in which the islands of the pancreas have been observed is a specimen of 54 mm. (Pearce, 1903). None are present in embryos of 42 and 44 mm. in the Harvard Collection, nor in the head of a pancreas at 55 mm. Weichselbaum and Kyrle (1909) find none at 50 mm. They appear first in the distal part of the pancreas. Thus, Pearce found none in the head at 90 mm., and in an embryo "believed to be of the third month . . . numerous

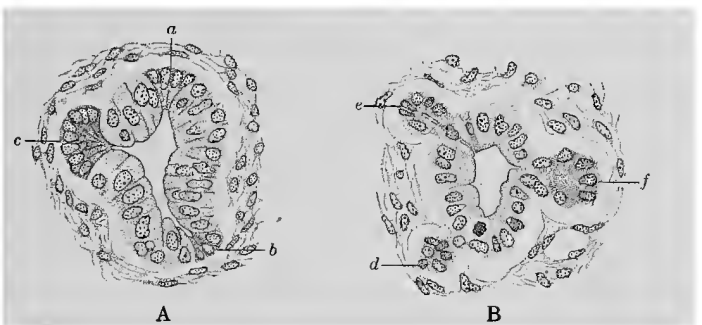


FIG. 312.—Sections of pancreatic tubules; A, from an embryo of 42 mm. (Harvard Collection, Series 838); B, from an embryo of 55 mm. × 350 diam. *a–e*, early stages in the formation of alveoli.

islands are scattered through the tail and body, while for the first time a few are seen in the head." Küster (1904) found them larger and more numerous in the splenic end in an embryo of the 17th week, and this accords with Opie's conclusion that in the adult the islands are almost twice as numerous in sections from the tail as in those from other parts.

The islands in an embryo of 99 mm. (Fig. 313, *b*) already resemble those of the adult. In sections stained with hæmatoxylin and eosin, they appear as pale areas, composed of anastomosing solid cords or rows of cells. Capillary blood-vessels extend among the cords, and their endothelium comes into close relation with the cells of the island. The presence of epithelial stalks connecting the islands with the ducts, as shown on the right of Fig. 313, has been observed by Pearce, Küster, and Weichselbaum and Kyrle.

The general structure of the islands, and of the glomeruli which they contain, is well shown in a model prepared by Miss Dewitt, from the pancreas of an adult. Miss Dewitt (1906) failed to find any arteries connecting with the vessels of the islands, contrary to Laguesse (1906) and others. She regards the blood-vessels of

the islands as venous, " with abundant capillary connections with the surrounding interalveolar capillary plexus," and describes them as sinusoids. In their development they are quite different from the portal sinusoids of the liver, but they resemble them histologically. Laguesse has described groups of red corpuscles as occurring normally between the endothelium and the cells of the islands.

An earlier stage of the islands than that shown in Fig. 313 has been described by Pearce. In a 54 mm. embryo he found them represented by small groups of from ten to fifteen cells, directly connected with the sides of the ducts. He described them as having round and lightly staining nuclei, with relatively abundant protoplasm which stains deeply with eosin. At this stage the islands are not penetrated by blood-vessels. Weichselbaum and Kyrle describe the islands in an 80 mm. embryo as solid buds, directly connected with the ducts, but composed of paler cells.

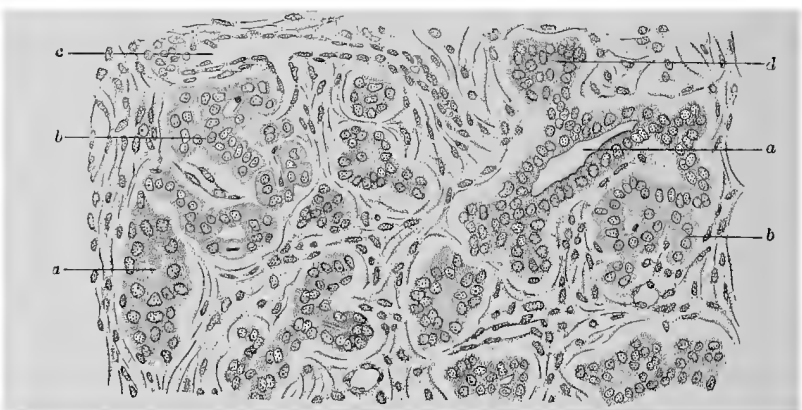


FIG. 313.—Section of the pancreas from a 99 mm. embryo. × 350 diam. *a*, pancreatic tubules; *b*, islands; *c*, blood-vessel; *d*, alveolar bud.

They are partly surrounded by capillaries. The difficulty of distinguishing these developing islands from the alveolar buds is apparent in sections and in the published figures. Laguesse admits this difficulty, but he concludes that certain formations in sheep embryos, apparently comparable with those seen in Fig. 312, are the first stages in the development of the islands.

In later stages the islands become detached from the epithelial tubes. Some of them have separated in an embryo of 130 mm. (Weichselbaum and Kyrle). Von Hansemann (1910) found them all detached at 210 mm., and concluded that the islands arise from mesenchyma; but in another embryo of the same length, and also at birth, Weichselbaum and Kyrle found that some islands are still in connection with the ducts. They believe that new islands may arise throughout life by budding from the ducts. The detached stalks of the older islands may be recognized in the small dark cells which have been described at the periphery of

certain islands. Occasionally they show a lumen, and pathologically they may give rise to retention cysts (Weichselbaum and Kyrle). Küster, in embryos of 24 and 32 weeks, has found stalks ending blindly in the islands.

Usually the islands are considered to possess "an anatomical identity as definite as that of the glomeruli of the kidney" (Opie), but some believe that alveoli may be transformed into islands and islands into alveoli. A review of the literature of this subject is presented by Laguesse (1906). Their embryological development does not accord with the idea that they represent a phase of glandular activity, and the presence of mitotic figures indicates that they are not degenerative structures.

The Pancreas at Birth.—In sections of embryos from 270 to 320 mm. in length, Weichselbaum and Kyrle find that the groups of alveoli are not only more compact than in earlier stages, but there is no longer such abundant connective tissue between them (*cf.* Fig. 313). Nevertheless the pancreatic connective tissue at birth, as compared with that in the adult, is relatively very abundant. It extends around individual alveoli, and forms broad septa between the clusters which are connected with the terminal ramifications of the ducts. These groups of alveoli, bounded by connective-tissue septa, become compact in the adult and constitute the lobules, which are ill-defined and may show secondary subdivisions.

"Islands are more numerous, as pointed out by Kasahara, in the pancreatic tissue of the fetus and of very young children than in that of the adult. . . . The organ being much smaller in the fetus, the same number of islands, though themselves smaller, are closer together and therefore appear more numerous in sections" (Opie). Küster likewise found that, in relation to the alveoli, the islands are decidedly more numerous at birth than in the adult. His measurements show no difference in the size of the islands, but Miss Dewitt finds that they are smaller, on the average, at birth than in the adult.

Concerning the position of the islands, Opie states that, "though an island is often situated in the centre of a more or less clearly defined lobule, no constancy of position is discoverable." Pearce considers that the islands at first lie free in the connective tissue, but that later, in the fifth and sixth months, "glandular elements surround and inclose the island, and it then occupies the centre of the lobule." But, as noted by Weichselbaum and Kyrle, here and there, at birth, an island occurs at the periphery of a lobule, or in the interlobular connective tissue near a duct. Moreover several may be found within a single lobule.

The cells of the islands at birth lack distinct outlines; they are crowded with fine granules which do not react to osmic acid (Stangl, 1901). Stangl states that fat appears in the cells of the

islands at the end of the first year, but this has been denied by Symmers (1909). The cells of the alveoli at birth show the zones characteristic of the adult. In the outer zone they sometimes contain small scattered fat drops (Stangl). Histologically no differences have been established between the dorsal and ventral pancreases, at birth or in preceding stages.

Anomalies and Variations.—The obliteration of the proximal end of the duct of the dorsal pancreas is probably not infrequent.

Charpy (1898) found the papilla minor closed in three-fourths of the thirty cases which he examined. Letulle and Nattan-Larrier (1898) state that the accessory duct is permeable throughout its extent, including the papilla minor, in only three out of twenty-one cases examined, and that usually it appears as a branch of the pancreatic duct. But Helly (1898) concludes that an open accessory duct is "by far the rule" (compare with Fig. 311), and Hamburger found it present in all of the fifty cases which he examined. In an embryo of 55 mm. Helly (1900) found, in place of a single papilla minor, two papillæ of nearly equal size, each of which contained a pancreatic duct. Letulle and Nattan-Larrier have recorded a similar case in the adult. The failure of the dorsal and ventral pancreases to unite, so that the duct of the dorsal pancreas persists as the main duct, opening at a normally situated papilla minor, has been figured by Charpy, and reported by Helly, Baldwin (1907), and others. In one of Helly's cases "an independent duct of Wirsung was not to be found." In a specimen figured by Bernard the duct of the dorsal pancreas persists as the main duct, although it has two small anastomoses with the duct of the ventral pancreas. As recorded in a previous section, the dorsal pancreas in an abnormal embryo of 11.5 mm. opens into the intestine lower down than the bile-duct. Charpy has figured an adult pancreas which shows this relation; in this case the ducts have not anastomosed.

Pancreatic tissue sometimes surrounds such adjacent structures as the portal vein, the bile-duct, and the intestine.

The encircling of the portal vein by a process of the dorsal pancreas has apparently not been observed in man, though characteristic of the rabbit and pig (Thyng). The common bile-duct occupies a groove in the head of the pancreas which is frequently converted into a canal of pancreatic tissue (see Helly, 1898). An annular pancreas, encircling the intestine, has been recorded by Ecker and by Symington (as cited by Thyng) and a case has been reported by Baldwin. An abnormal condition observed in a pig embryo of 12 mm. suggests that this anomaly may arise early in development, by an extension of the ventral pancreas dorsally on either side of the intestine.

Accessory pancreases are of frequent occurrence.

Among 150 autopsies, Symmers found three cases in which there were accessory glands of considerable size. Sometimes two occur in a single case (Opie, 1903). Gardiner (1907), who has reviewed the literature, finds that in nearly a third of the cases reported, the accessory pancreases are connected with the stomach. They occur also in the duodenum, jejunum, and ileum, and have been frequently found at the apex of a "true" diverticulum. These diverticula were at first considered to be remnants of the vitelline duct (Meckel's diverticula), but Neumann (1870) questioned this interpretation. Nauwerck (1893) reported a diverticulum 9 cm. long, tipped with an accessory pancreas, and situated 2.3 metres above the valve of the colon. In the same case he found another diverticulum, 3 cm. long, situated 80 cm. above the valve of the colon, and he regarded the latter

as Meckel's diverticulum. Hanau (Brunner, 1899) reports a duodenal diverticulum tipped with an accessory pancreas, and Weichselhaum (Gardiner, 1907) has described a similar pancreatic diverticulum of the stomach. It is evident that these diverticula are not vitelline remains, and yet it is not impossible that an accessory pancreas may be associated with a true Meckel's diverticulum. Wright (1901) has reported a case in which pancreatic tissue was excised from the umbilicus of a child of 12 years, who had an umbilical fistula since birth. The fistulous tract had apparently become separated from the intestine.

Accessory pancreases generally penetrate the muscularis, but they may be limited to the submucosa. The larger ones show lobules composed of typical pancreatic alveoli. Islands have been reported in numerous cases, including that of Wright. Sometimes, however, the islands are lacking, and the tubules may be duct-like rather than glandular.

The accessory pancreases develop from elongated epithelial buds, as observed in the wall of the stomach of a 19 mm. embryo. Lewis and Thyng (1908) have frequently found similar buds along the intestine of pig embryos of 10–20 mm., but not in human embryos. They usually become detached and degenerate. It is possible that accessory pancreases sometimes develop in relation with the embryonic intestinal diverticula described in a previous section.

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THE DEVELOPMENT OF THE PHARYNX AND OF THE ORGANS OF RESPIRATION.

By OTTO GROSSER, of Prague.

A. THE PHARYNX AND ITS DERIVATIVES.

The formation of the anterior part of the digestive tract has already been described at the beginning of this chapter, and it will be necessary to consider here only its further differentiation.

At first it is merely a short, tubular outgrowth of the yolk-sack, somewhat flattened dorsoventrally; the oral portion of its ventral wall, in the region of the pharyngeal membrane, rests on the ectoderm, and its rostral end projects somewhat beyond this membrane as Seessel's pouch (Figs. 314–316; see also the section of this chapter dealing with the development of the mouth cavity). Whether it presents further differentiations at the time of its first formation cannot be stated with certainty, but in the youngest human embryos that have been studied and in which it is already present the anlage of the first pharyngeal pouch is apparent (embryos of Krömer-Pfannenstiel and Dandy, Fig. 314).

In all Craniota there are formed bilaterally symmetrical lateral diverticula of the anterior portion of the digestive tract, which, pressing aside the lateral mesoderm of the head, come into apposition with corresponding invaginations of the ectoderm; the endodermal diverticula are termed *pharyngeal pouches* (also pharyngeal grooves, or inner branchial grooves or pouches), while the ectodermal invaginations are known simply as *branchial grooves*, or as ectodermal or outer branchial grooves (outer pharyngeal grooves, Hammar). By pressing aside the mesoderm the ectoderm and endoderm for a time come into contact and fuse, forming the *epithelial closing membrane*, which breaks through in all forms that have a branchial respiration; the branchial grooves and pharyngeal pouches thus become continuous and together form the *branchial clefts*. The formation of open branchial clefts occurs also in reptiles and birds, but not, under normal conditions, in mammals (see below). The pharyngeal pouches and branchial grooves are later again separated by the ingrowth of mesoderm or (sinus cervicalis) by the constriction of the branchial grooves from the surface and the subsequent modification of their epithelium. The number of pharyngeal pouches that are formed in succession on either side varies in the gnathostomatous Craniota from nine to five, the number in general diminishing with an increasing degree of organization.

Between the branchial clefts—that is to say, between the pharyngeal pouches and branchial grooves—are the *branchial* or *visceral arches*, each of which contains a skeletal rod, the cartilaginous branchial arch, its musculature, an aortic arch, and a nerve-trunk. The branchial arches are named in succession the mandibular, hyoid, and branchial arches proper, these last being numbered in succession from before backward. Behind the last branchial cleft lies the last branchial arch, the number of arches being one more than that of the clefts, an arrangement determined by the formation of branchial leaflets on both walls of the clefts. The first branchial cleft is also known as the hyomandibular cleft.

I. General Morphology of the Pharyngeal Pouches.

The anlagen of the pharyngeal pouches appear in succession and are formed earlier than the corresponding external branchial grooves, as was observed by Rückert and Piersol. In man the external grooves first become evident when the pharyngeal pouches have come into contact with the ectoderm,—that is to say, when the lateral cranial mesoderm has been pressed aside and the closing

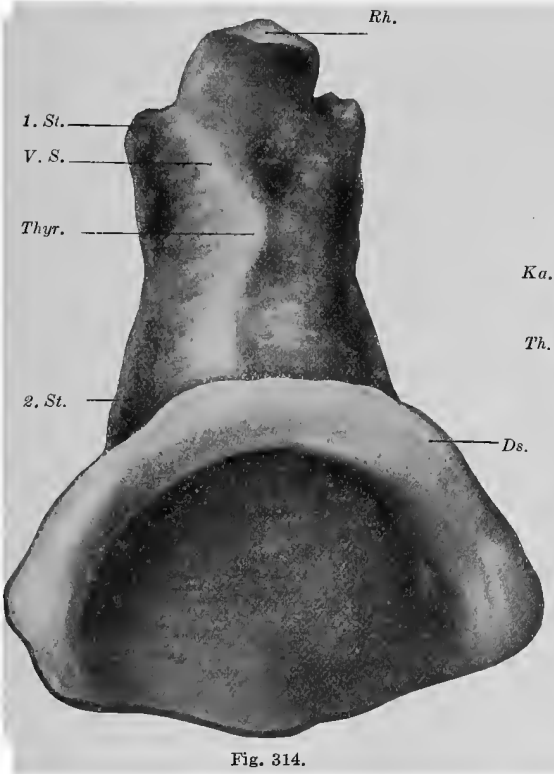


Fig. 314.

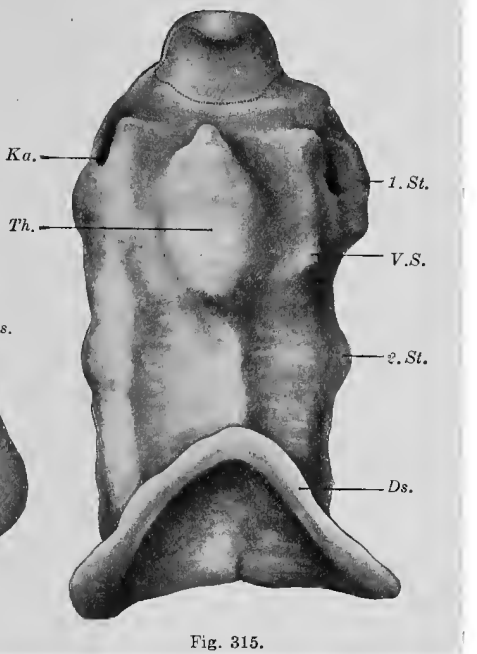


Fig. 315.

FIG. 314.—Pharynx of the embryo Klb (Krömer-Pfannenstiel; Normentafel, No. 3; 5–6 primitive segments, length, determined from the number of sections, 1.38 mm.). *Ds.*, yolk-sack; *Rh.*, pharyngeal membrane; *1., 2., etc., St.*, first, second, etc., pharyngeal pouch; *Thyr.* or *Th.*, thyreoid; *V. S.*, ventral pharyngeal groove. × 150. In all the models the epithelial lining of the cavity is represented, not the cavity itself.

FIG. 315.—Pharynx of the embryo Rob. Meyer No. 335 (9-10 pairs of primitive segments, length, determined from the number of sections, 1.70 mm.). *Ka.*, doubtful branchial anlage. The remaining lettering as in Fig. 314. × 150.

membranes formed (Fig. 316). At about the time of the formation of the two first membranes the closure of the neural canal in the brain region occurs, and there is an increase in the amount of the cranial mesoderm, whereby for the first time the transverse diameter of the skull notably surpasses that of the pharyngeal tube and opportunity is afforded for the formation of the external grooves (developmental period between the formation of the 10th and the 15th pairs of primitive segments).

The pharyngeal pouches grow out from the anterior part of the digestive tract not only directly laterally but also somewhat dorsally; moreover, a groove, known as the *ventral pharyngeal groove,* extends along the ventral wall of the pharynx from each pouch, and is recognizable even at its first formation (Figs. 314 to 317). While the surfaces of contact with the ectoderm, *i.e.,* the closing membranes, have at first a somewhat circular outline (Fig.

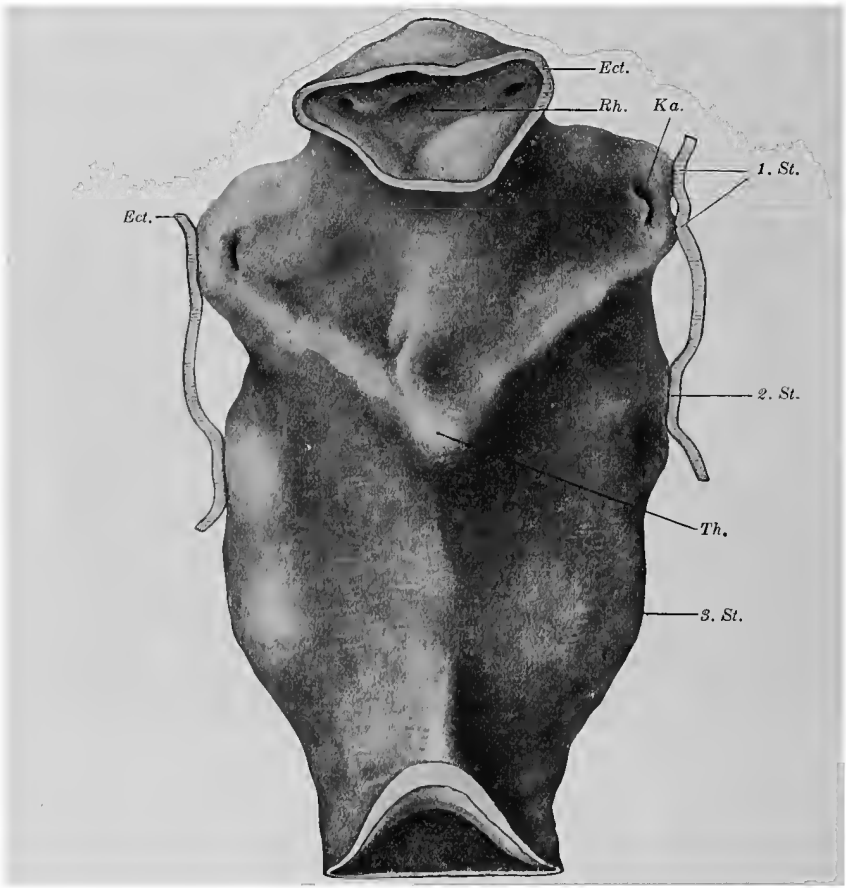


Fig. 316.—Pharynx of the embryo Hal$_2$ in the collection of the First Anatomical Institute, Vienna (about 15 pairs of primitive segments, length about 3 mm.). *Ect.*, ectoderm; *Ka.*, doubtful branchial anlage; *Rh.*, pharyngeal membrane, broken through in two spots. The remaining lettering as in Fig. 314. × 150.

316), they later elongate to a long, narrow strip, almost perpendicular to the axis of the pharynx (Figs. 317 and 318). By an increase in depth—that is to say, a lateral extension of the pouches (a process that depends upon an increase in the thickness of the intervening branchial arches)—these structures become sharply marked off from the principal lumen of the pharynx (compare Figs. 316 and 317). In a pouch which has thus become relatively

narrow and deep (Figs. 317 and 318) there is to be distinguished a cranial, a caudal, and an indistinctly delimited dorsal surface, a lateral edge, a dorsal and a ventral angle, and a ventral pharyngeal groove extending toward the mid-ventral line. By the formation of these grooves the branchial arches become marked

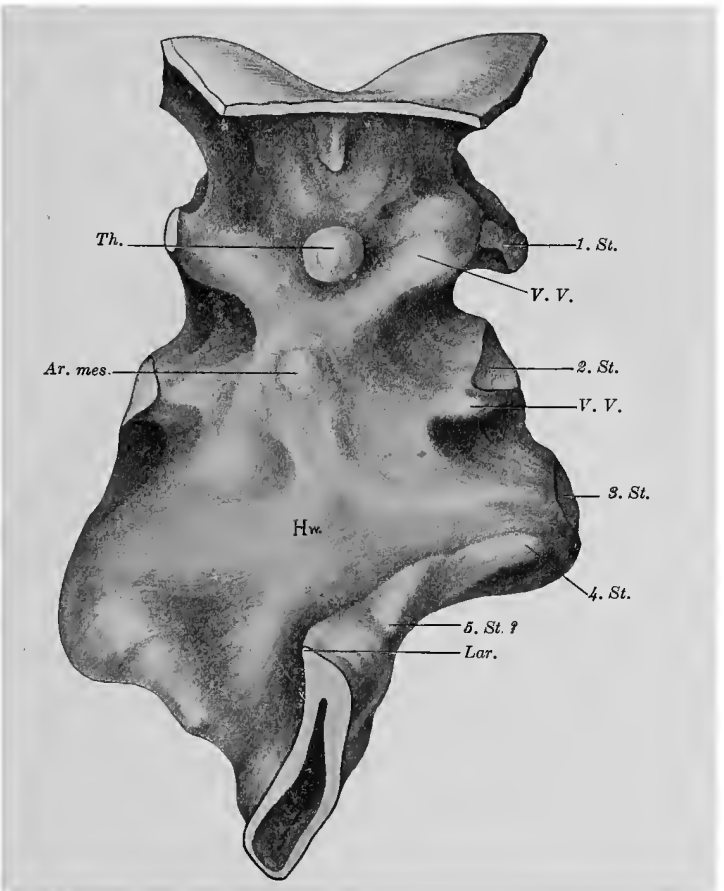


FIG. 317.—Pharynx of the embryo Rob. Meyer No. 300 (Normentafel No. 7, 23 pairs of primitive segments, 2.5 mm. vertex-breech length) seen from the ventral surface. The closing membranes of the gill-clefts are outlined in black. *Ar. mes.*, the somewhat depressed oral end of the area mesobranchialis; *Hw.*, heart swelling; *Lar.*, laryngotracheal groove; *V.V.*, ventral prolongations of the pharyngeal pouches. Other lettering as in Fig. 314. × 150.

out upon the ventral wall of the pharynx as elevations projecting into its lumen. The grooves (with, perhaps, the exception of the first) do not, however, at first reach the mid-line, and accordingly leave an area in that situation, known as the *area mesobranchialis* (His, 1885) (Figs. 317 and 319). In the caudal part of this lies the heart swelling (Fig. 317), but slightly marked in the human embryo. In the three anterior pouches, and later on also in the fourth, the dorsal angle grows dorsally a little beyond the region

of the closing membrane and so forms the dorsal prolongation (dorsal diverticulum) of the pouch (Born, Piersol, Hammar, 1902; Tandler, 1909).[18] Piersol terms the ventral angle, together with the lateral edge and the ventral groove, the *wing* of the pouch. By the continued deepening of the lateral parts of the ventral grooves a ventral prolongation of the pouch is formed, most distinct in the

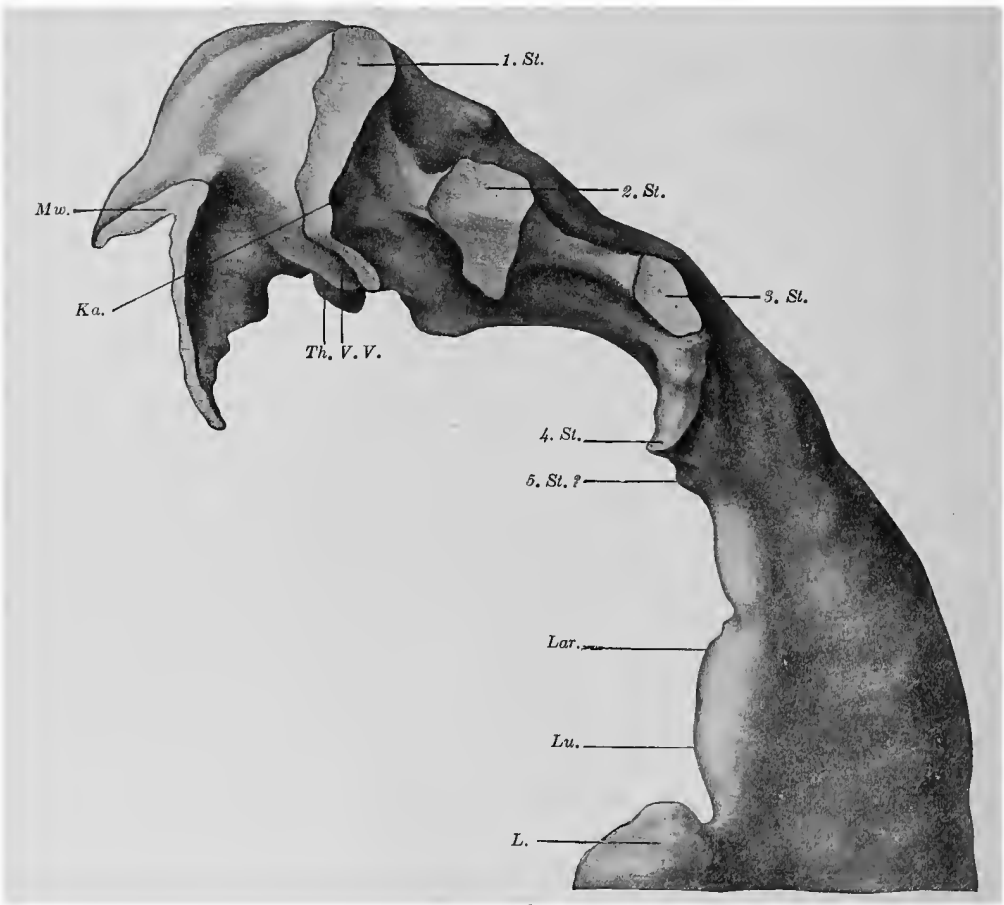


FIG. 318.—The model shown in Fig. 317 from the lateral surface. *Ka.*, doubtful branchial anlage; *L.*, liver; *Lar.*, laryngotracheal groove; *Lu.*, lung anlage; *Mw.*, angle of mouth. Other lettering as in Fig. 314. × 150.

second and third pouches (Fig. 319; indicated in Fig. 317); this is the *ventral prolongation* of Hammar (1902) and the *ventral diverticulum* of Fox (1908).

As a result of the elongation of the closing membranes and the formation of the dorsal and ventral diverticula, the dorso-

[18] H. Rabl (1909) does not recognize a dorsal diverticulum as of general occurrence in mammals, and ascribes to it, in any event, no special significance (in the formation of the epithelial bodies).

ventral diameter of the pharyngeal pouches increases much more rapidly in their lateral than in their medial portions, and a distinct delimitation of the pouches medially now becomes possible (Figs. 319 and 320). One may, with H. Rabl (1907 and 1909), term the at first uniformly broad pouches the *primary pouches* and the later stages, with the lateral portions broadened, the *secondary pouches;* the latter are connected with the pharynx by narrow connecting portions, the *ductus pharyngo-branchiales.* These ducts later become very distinct in the caudal pouches (third to the fifth) (Fig. 325).

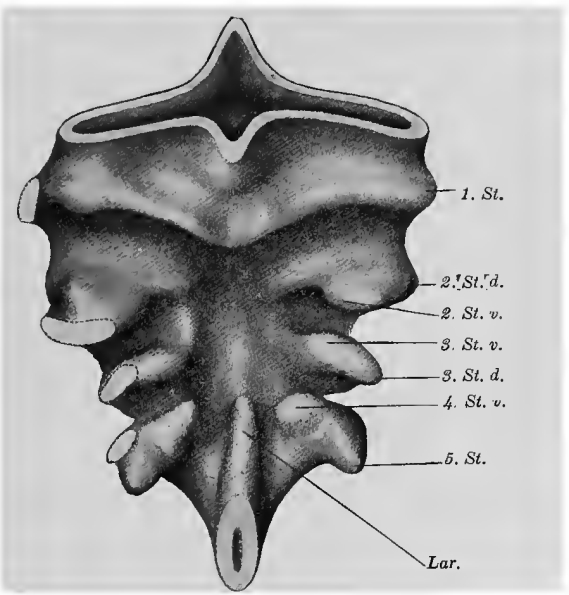


Fig. 319.—Pharyngeal pouches of the embryo Hal_2 of the First Anatomical Institute, Vienna (5.2 mm., about the same stage as No. 16 of the Normentafel). The closing membranes of the left side are outlined in black. The thyreoid has been omitted. (From a model in the Institute.) *Lar.*, anlage of larynx. Other lettering as in Fig. 314. × 50.

Just as the anlagen of the pouches appear in a cranio-caudal series, so, too, their enlargement takes place in succession in the same direction. Associated with this there is a dorsoventral flattening and a rather considerable lateral broadening of the pharyngeal lumen (Figs. 317 and 319), in such a way that the maximum broadening occurs opposite the first pouch, and caudal to the last pouch there is at first a diminution of the gut. The region in which the pouches occur practically represents the anlage of the pharynx (including the floor of the mouth). At the height of the development of the pouches the embryonic pharynx is strongly flattened dorsoventrally and convex dorsally and has a somewhat triangular outline, the base being directed orally and the apex at the point of union of the air- and food-passages.

Altogether *five pharyngeal pouches* are formed in the human embryo (Hammar, 1904; in 1889 His speaks of a rudimentary fifth pouch), and all of these reach the ectoderm.

According to Tourneux and Soulié (1907), a sixth pouch also occurs; this discovery has not, however, been thoroughly described. Tandler (1909) has described a diverticulum caudal to the fifth pouch (embryo shown in Fig. 320; indicated by the letters *Div.*), but he has left it open whether or not it is to be regarded as a rudimentary sixth pouch. Opposed to such an identification is the

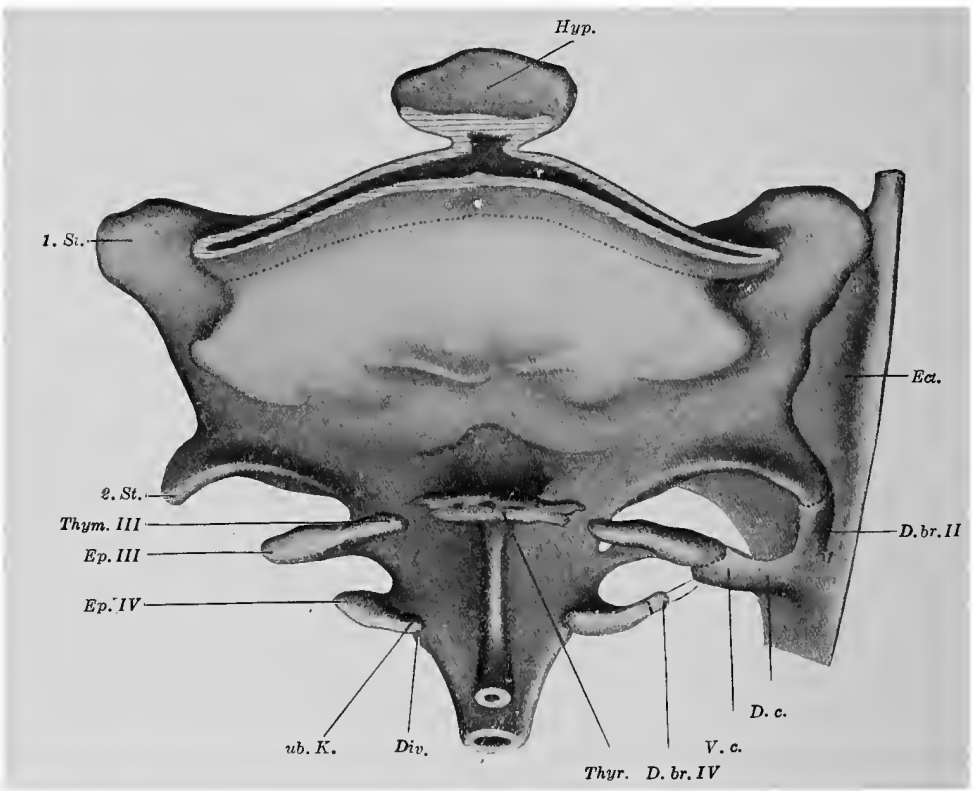


Fig. 320.—Pharyngeal region of the embryo BR (Normentafel No. 42, 9.75 mm. vertex-breech measurement), from the ventral surface. (From a model in the First Anatomical Institute, Vienna.) *D. br. II* and *IV*, ductus branchialis from the second and fourth branchial grooves; *D. c.*, ductus cervicalis; *Div.*, diverticulum (see text); *Ect.*, ectoderm; *1., 2. St.*, first and second pharyngeal pouch; *Thym. III*, thymus anlage of the third pouch; *Thyr.*, thyreoid; *ub. K.*, ultimobranchial body; *V. c.*, vesicula cervicalis. The approximate limit between ectoderm and entoderm is shown by a broken line. × 40.

fact that the ultimo-branchial bodies are associated with the fifth pouch, whereas in general they belong to the last formed pouch (the sixth in birds, according to H. Rabl, 1907). The diverticulum seen in Fig. 320 appears to be identical with that figured by Soulié and Bardier (1907) for an embryo of 6 mm. and designated as the fifth pouch, but it is certainly not identical with the fifth pouch of other authors.[19]

[19] Such diverticula are probably without significance and very transitory. H. Rabl (1907) has shown, without description, something similar in the duck in Fig. 6 of his paper. See also p. 454.

The available data regarding the appearance of the pouches are as follows: The first pouch appears shortly after or simultaneously with the separation of the anterior part of the digestive tract from the yolk-sac (Fig. 314, p. 447); it reaches the ectoderm at a stage in which there are ten primitive segments. In the embryo from which Fig. 315 was constructed the mesoderm has been pressed laterally by the pouch, but the ectoderm and endoderm have not fused to form a closing membrane. The second pouch, which is indicated quite early (Figs. 314 and 315), has formed its closing membrane at a stage with thirteen or fourteen primitive segments (compare also Fig. 316). At this time the third pouch is formed; it has reached the ectoderm in an embryo with twenty-three primitive segments (Figs. 317 and 318). Such an embryo also shows the anlage of the fourth pouch; this shows a certain amount of variability in its development, but it reaches the ectoderm in embryos of about 4 mm. in greatest length (thirty-five primitive segments). The rudimentary fifth pouch is perhaps already formed in the stage shown in Figs. 317 and 318 (p. 461); a closing membrane for the pouch is twice shown in the Normentafel in embryos of 5 mm. The pouch appears to be an appendage of the fourth (for details see later on).—In correspondence with the number of pouches, six branchial arches are to be recognized in the human embryo, of which, however, only four are visible from the surface. The fifth, in correspondence with the incomplete development of the fifth pouch, is at first very indistinct; its aortic arch, the fifth, is rudimentary and its nerve can only be distinguished transitorily (Tandler, Elze, Grosser). Its skeletal portion, which is included in the thyreoid cartilage, is, however, later of considerable size. The sixth arch is not bounded caudally by a pouch (see p. 446); its participation in the formation of the larynx is doubtful (see later).

Almost contemporaneously with the formation of the first pharyngeal pouch or only a little later there appears the *anlage of the thyreoid gland,* usually termed the *anlage of the median thyreoid;* the word median, however, now seems to be superfluous, since it probably represents the only anlage of the thyreoid tissue (see later, p. 468). The anlage is recognizable before the first pharyngeal pouch has come into contact with the ectoderm, as a prominence in the ventral wall of the pharynx (Figs. 314 and 315); it appears, therefore, much earlier than is shown in the Normentafel. It then becomes constricted to form a stalked vesicle (Figs. 317 and 318), and its stalk, whose lumen becomes obliterated, persists for some time as an epithelial cord. The thyreoid anlage belongs primarily to the medial region between the first two ventral pharyngeal grooves, that is to say, to the oral portion of what is later the area mesobranchialis. It is at first anterior to, not in, the region of the second branchial arch. The hollow stalk of the vesicle is the *thyreoglossal duct* (His).

Even before the obliteration of this duct the first ventral pharyngeal groove becomes prolonged medially and divides into two limbs, which unite in the median line with the corresponding ones of the other side and so enclose a median elevation, the *tuberculum impar* (Fig. 317). The opening of the thyreoglossal duct is situated at first upon the summit of the tubercle, but later it becomes shifted into the posterior boundary furrow or, according

to Ingalls (1907), in an embryo of 4.9 mm., into "the region of the second arch, immediately aboral to the tuberculum impar." Since the tuberculum belongs to the medial region (His, 1885), it is evidently not a derivative of a branchial arch.[20] When the arches are formed they are connected behind the tuberculum impar by a transverse elevation, a *copula*. This and the tubercle are for the most part taken into the anlage of the tongue, whose formation has been described in the portion of this chapter dealing with the development of the mouth. Behind the copula the mesobranchial area remains for some time but little altered; only a median groove, which replaces the heart swelling, becomes more marked (Fig. 319), and later the area is employed in the formation of the larynx (p. 476).

In addition to the embryos figured above, which have been kindly contributed by their owners, there are certain others that have been described which have important bearings on the early stages of the pharynx; these are the embryo Dandy (1910) with seven pairs of primitive segments, the embryo Pfannenstiel III (Normentafel, No. 6), which has been described by Low (1908), with thirteen or fourteen segments, and the embryo XII of Mall's collection, which has been described by Sudler (1901-02) and has fourteen pairs of segments. The embryos Klb and R. Meyer 300 have already been reconstructed by Kroemer (1903) and by Thompson (1907), but on a small scale and with very cursory descriptions. The embryo Dandy corresponds almost exactly with the embryo Klb, and the Pfannenstiel III and Mall XII embryos are almost exactly equivalent to the embryo Hal. In this the closing membrane of the first branchial cleft of the left side is not yet complete, but is divided into two parts by a strip in which there is no mesoderm, but where the two epithelia have not yet fused (Fig. 316). A similar condition occurs in the embryo Pfannenstiel III. Low has assigned the two portions of the closing membrane to two successive pharyngeal pouches, which is clearly an error and has led him to describe the first pouch as lying originally dorsal to the second, when, as the later development shows, he was describing merely the two angles of the first pouch.—Occasionally small irregular evaginations occur in connection with the pharyngeal pouches and the branchial grooves, as in the embryo shown in Fig. 319, on the dorsal side; they have also been observed and figured by Ingalls. Such are perhaps comparable to the embryonic intestinal diverticula described by F. T. Lewis and Thyng (Amer. Journ. Anat., vol. 7, 1907–8).

A remarkable observation has been made by the author in all young embryos with the first pharyngeal pouches well developed; these are the embryos R. Meyer 335, Hal$_2$, Pfannenstiel III (loaned for this purpose), R. Meyer 330, and also a somewhat pathological, young embryo from the collection of R. Meyer. In the region of the first pouch there projects ventrally (Figs. 315 and 316) or caudally (Fig. 318) from the closing membrane into the pharyngeal lumen an irregularly knobbed process filled with mesoderm. That it is an accidental structure or due to post-mortem changes seems to be excluded by the regularity of its occurrence (Low has figured, but not described it). It disappears quite early (in the oldest

[20] The account given above differs in many respects from that recently given by Kallius (Anat. Hefte, vol. 41, 1910) for the pig. Observations on a larger amount of human material than is at present available may show a necessity for some modifications of the statements made. Compare especially the development of the larynx described below.

embryo examined, Fig. 318, it is present only on the left side and is greatly reduced in size; in embryos of 4.25, 5.0, and 5.8 mm. and in those still older, it is wanting), and may perhaps be interpreted as a rudimentary internal gill. It would not be the first instance of a very ancient rudiment well developed in the human embryo. Similar structures have not yet been observed in other amniote embryos.

The thyreoid anlage in human embryos is at first exceptionally large, but seems to be subject to a certain amount of variation in form. Dandy describes a ventro-median pouch projecting from the union of the two first pharyngeal pouches —evidently the thyreoid anlage (compare Fig. 314), although he denies the occurrence of such a structure. In Fig. 316 it has a similar appearance, in Fig. 315 and also in the embryos Pfannenstiel III and Mall XII it has a much more distinct delimitation. The delimitation starts on the rostral side and appears later caudally; the separation from the obliterated thyreoglossal duct takes place, according to the Normentafel, in embryos of about 6 mm., occasionally, however, earlier or later. At this time the lumen of the anlage, which has usually become bilobed, has disappeared. For an account of the differentiation of the anlage see p. 468.

The closing membrane in the human embryo, as in those of mammals generally, remains imperforated (His); open branchial clefts do not occur. Perforation has, however, been frequently observed, most frequently in the case of the second pouch (Kölliker, Tettenhamer, and Hammar), which possesses the longest closing membrane (Hammar).[21] In this case perforation may be regarded as within the limits of variation, but in other pouches it is, as a rule, due to injury from handling, and such injuries assuredly also increase the percentage of cases of perforation of the second pouch.

After the closing membrane has become converted into an elongated strip (p. 448) the mesoderm again penetrates between the two epithelia of the membrane and the pouch once more becomes separated from the surface of the embryo. This process may be followed in its simplest form in the first pouch; in the more posterior ones it is combined with the formation and constriction off of the *sinus cervicalis* (C. Rabl, 1886 to 1887; *sinus præcervicalis,* His, 1885; compare vol. I, p. 69, *et seq.*).[22] This is formed by the mandibular and hyoid arches growing more rapidly than the other arches in all dimensions, but especially the transverse, while the growth of the branchial arches proper lags behind that of their surroundings, so that they come to lie in the floor of a depression, the sinus cervicalis, which is open laterally. The

[21] The closing membrane of the first pouch is, however, in early stages by no means so short as Born and Hammar have imagined (compare Fig. 318). But the degeneration of the ventral part of the membrane takes place very early in this pouch.

[22] Rabl has altered the name proposed by His, on the ground that the term "præcervicalis" implies a structure situated anterior to the neck region; His intended it to denote the ventral position of the sinus. Both terms are employed synonymously in the literature.

caudal edge of the hyoid arch later grows backward over the mouth of the sinus, forming an indistinctly delimited *operculum*, which is less developed in man (Hammar) than in other mammals; the sinus retains its connection with the exterior for a short time by means of the *ductus cervicalis* (*præcervicalis*), but finally becomes completely shut off so as to form the *vesicula cervicalis* (*præcervicalis*).[23] In man there persists at the surface only a shallow groove, the *sulcus cervicalis* (*sulcus præcervicalis*, Hammar; cervical groove, H. Rabl), which at first marks the boundary line between the head and the thorax. The vesicula cervicalis lies lateral to the third pharyngeal pouch (Figs. 320, 321, 325, and 326), and is connected by diverticula, the former external branchial grooves, with the second and fourth (and for a short time also with the fifth) pouches; these diverticula become drawn out into long canals, the ductus branchiales (II and IV) (Figs 320 and 321). The vesicula and the ductus exist only for a short time; their lumina vanish and the epithelial structure of the organs disappears.

With the sinus cervicalis are associated three cranial nerve placodes (branchial cleft organs of Froriep); they consist of intimate connections of the epithelium with the ganglia of the glossopharyngeus and vagus (see the chapter on the Nervous System). These placodes are also recognizable only for a short time and disappear with the other derivatives of the sinus.

From the time of His (1885) up to the present a number of authors have agreed in deriving the anlage of the thymus, either in whole or in part, from the epithelium of the sinus cervicalis. These results are hardly reconcilable, however, at least so far as man is concerned, with those of other authors (compare Hammar, 1910).—The fate of the sinus vesicle is, moreover, different in different mammals. While it disappears in man and in the cat at an early period and in the rabbit somewhat later, in the pig (Kastschenko 1887, Fox 1908) and in the sheep (Prenant) it persists for some time as a structure of considerable size, which Kastschenko has termed the *thymus superficialis*, but whose eventual fate is not yet certainly known. In the mole, according to the recent definite results of H. Rahl (1909), the thymus superficialis is actually formed from the vesicula cervicalis.—The third pharyngeal pouch seems also to vary in different species as to its lateral extension ventral to the sinus vesicle.—The duct-like remains of the second external branchial groove, Hammar (1903 and 1904), following C. Rabl (1886–7), has termed the *ductus branchialis*,[24] while he names the corresponding

[23] According to H. Rahl (1909) the term vesicula cervicalis is to be applied to the entire complex, including the two ductus branchiales (see above); Hammar uses the term vesicula præcervicalis only for the vesicular portion that is associated with the third pharyngeal pouch, this portion being approximately identical with the *fundus præcervicalis* (*cervicalis*) of His and H. Rahl, as well as with the *vesicula thymica* of Kastschenko and the *sinus vesicle* of Zuckerkandl.

[24] Fox (1908) has not been able to find this branchial duct in the pig, but, on the other hand, demonstrates the occurrence of a long pouch-like diverticulum of the second pouch. Differences apparently occur in different species in this respect also. The diverticulum in the pig may correspond with the thymus anlage of the second pouch described by Piersol (1888) and others in the rabbit; this structure has not yet heen observed in the human embryo.

duct of the fourth pouch the *ductus thyreo-cervicalis;* since, however, this latter structure, in my opinion, has nothing to do with the actual thyreoid anlage, the term ductus branchialis has been used above for both ducts, the numbers II and IV indicating the branchial grooves with which each corresponds.

The time of obliteration of the lumina of the ductus cervicalis and the ductus branchiales is subject to some variation (compare Figs. 320 and 321); according to the Normentafel it occurs in embryos of about 9 mm., and in those of 11–14 mm. the epithelial cord formed from the ductus cervicalis has disappeared, as has also the vesicula cervicalis a little later.—The first pouch has separated from the ectoderm in an embryo of 14 mm. (Normentafel, No. 54).

II. The Differentiation of the Pharyngeal Pouches; the Second Pharyngeal Pouch and the Tonsils.

Only for a short time do all the pharyngeal pouches have a relatively similar structure, differing essentially from one another only in that they diminish in size caudally (Fig. 319); they separate first into two groups, one of which consists of the first two pouches and the other of the remaining ones (Figs. 320 and 321). At the level of the first two pouches the pharynx rapidly increases in width, an increase that stands in relation to the development of the first arches as already described (p. 455). The succeeding pouches remain much less extensive, and from their epithelium a number of glandular organs develop.

By the increase in breadth of the pharynx the first and second pouches acquire a common pharyngeal opening (Fig. 320). The broadening occurs even before the separation of the pouches from the ectoderm; it practically corresponds to the *primary tympanic cavity* of Kastschenko or the *pharyngo-tympanic cleft* (lateral pharyngeal enlargement) of Piersol. Nevertheless, as is shown by the thorough study of the later development by Hammar (1902), the entire complex is not concerned in the formation of the anlage of the middle ear. Only the first pouch becomes transformed into the primitive tympanic cavity; its further development is described in another chapter. The second pouch gradually ceases to be an independent outpouching of the pharynx, its walls being taken up into the walls of that cavity, its dorsal angle only persisting as a slight evagination, which becomes pushed forward toward the point of connection of the first pouch with the pharynx, that is to say, toward the root of the primary tympanic cavity (Hammar) (Fig. 322). Between the derivatives of the first two pouches there now become interposed the palatine ridges, and they are thus definitely separated (Fig. 323), so that the fate of each may be readily determined. The dorsal angle of the second pouch becomes transformed into the palatine tonsil, and may, accordingly, at an early period, be termed the *sinus tonsillaris* (Hammar).

The development of the tonsil, which has been thoroughly studied by Hammar (1903), is associated with the appearance of a small elevation, the *tuberculum tonsillare,* which is situated on the ventral wall of the pharynx and projects into the sinus tonsillaris, lying practically opposite it (Fig. 323). Both structures lie on the lateral edge of the pharynx, and their derivatives are therefore to be found later side by side on the lateral wall of the pharynx. After the appearance of the tuberculum the palatine arches become evident, and the arcus palatoglossi cannot, therefore, be derived directly from the hyoid arches, as His (1885) thought, even although they lie oral to the tonsils. The tuberculum quickly flattens to form a fold, which surrounds the sinus tonsillaris

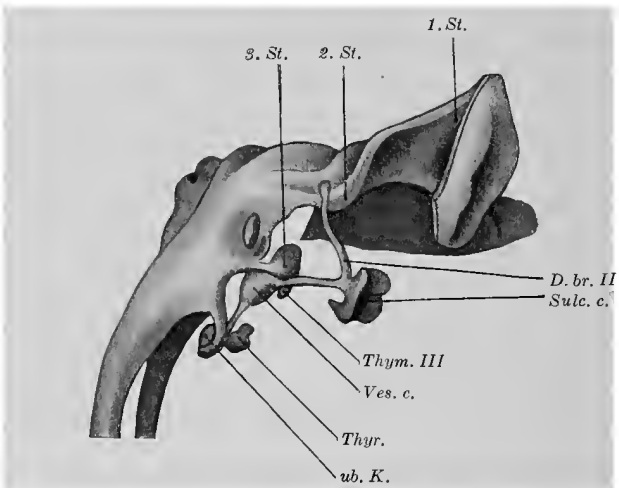


FIG. 321.—Branchial derivatives of an embryo of 11.7 mm. (nape-length), somewhat simplified. (After Hammar, 1903.) *Sulc. c.*, sulcus cervicalis (præcervicalis). The remaining lettering as in Fig. 320. × 21.

anteriorly and inferiorly and corresponds to the *plica triangularis* of the B.N.A. (His). The sinus itself becomes for a time divided by a plica intratonsillaris into two superposed recesses, and from the wall of the sinus tonsillaris epithelial processes grow out into the connective tissue of the mucous membrane; these processes are at first solid, but later become hollow by the degeneration of the central cells. Portions of the processes may be separated off, but these undergo degeneration. Around these epithelial processes there is formed, accompanied by abundant cell division, a lymphoid tissue, from which leucocytes penetrate into the epithelium. The plica triangularis, situated in front of the tonsil, is originally high, but it undergoes a progressive reduction which is continued even after birth and frequently results in the complete disappearance of the fold. The *plica retrotonsillaris,* which occasionally occurs in adults, belongs, according to Hammar, to relatively later devel-

opmental stages (fetuses of 190 mm. and upward). The *fossa supratonsillaris* (His) is formed from the upper recess of the sinus tonsillaris, with the assistance of the folds which surround the fossa.

Hammar has not confirmed the view that the recessus lateralis pharyngis (Rosenmülleri) is derived from the second pharyngeal pouch (His, C. Rabl, Kastschenko). The recess appears relatively late, but definite observations upon it are wanting.—The reduction of the ventral part of the second pouch begins in embryos with a length of somewhat over 8 mm. (Hammar; compare also Figs. 319 and 320), and in an embryo of 17 mm. only the dorsal angle of the pouch, lying near the entrance into the primary tympanic cavity, is to be found. The same embryo also has a recognizable tuberculum tonsillare. In one of 24.4 mm. the plica intratonsillaris can be seen, in one of 70 mm. the budding out of the epithelial processes

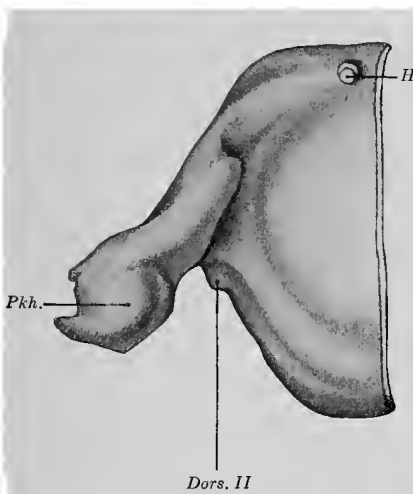


Fig. 322.

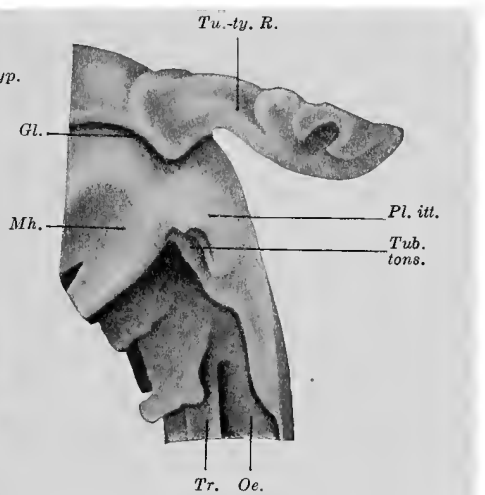


Fig. 323.

Fig. 322.—Dorsal view of the left half of the pharynx of an embryo of 21 mm. (nape-length). (After Hammar, 1902.) *Dors. II*, dorsal diverticulum of the second pharyngeal pouch; *Hyp.*, stalk of the hypophysis (cut); *Pkh.*, tympanic cavity. × 21.

Fig. 323.—Pharynx of an embryo of 24.4 mm. (nape-length), from the left side, somewhat simplified. (After Hammar, 1903.) *Gl.*, palatine ridge; *Mh.*, mouth cavity; *Oe.*, œsophagus; *Pl. itt.*, plica intratonsillaris; *Tr.*, trachea; *Tu.-ty. R.*, tubo-tympanic space; *Tub. tons.*, tuberculum tonsillare. × 12.

is beginning, and in one of 110 mm. the accumulation of cells in the connective tissue. Lymphocytes are first recognizable in embryos of 140 mm. and secondary nodules in one of 235 mm. By this time the tonsil has acquired its characteristic features.—The plicæ triangularis and intratonsillaris are rudimentary structures in man, but may play a part in the manifold modifications of the tonsils which occur in the mammalian series.—As is the case with other adenoid organs, so in that of the tonsils all observers are not agreed as to the origin of the leucocytes; yet their derivation from the epithelium (Retterer) has been, probably correctly, opposed by Stöhr, Kollmann, and Hammar. Stöhr's view that they migrate into the tonsillar tissue from the blood-vessels is replaced by Hammar by the assumption that they are autochthonous structures of the mesoderm.—Grünwald (1910) derives the tonsil from the ventral portion of the second pouch and regards it as equivalent to a thymus metamere. He finds in fetuses cartilaginous outgrowths from the second and third branchial arches included in the tonsillar anlage and serving it for support. The adenoid tissue is of mesodermal origin.

III. The Third to the Fifth Pharyngeal Pouches; the Branchiogenic Organs.

The importance of the three caudal pharyngeal pouches in the amniota lies mainly in the fact that their epithelium gives rise to a series of ductless glands; these are the thymus, the epithelial bodies or parathyreoids, and the ultimobranchial body (the so-called lateral thyreoid). Of these the first two are derived from the third and fourth pouches; the question of the development of the last is intimately connected with that as to the occurrence of a fifth pouch.

The thymus and epithelial bodies are formed in the lower vertebrates (with numerous pouches) from a series of pouches in succession; they are, accordingly, metameric (branchiomeric) organs, forming one of the characteristic products of a pharyngeal pouch and (together with the ultimo-branchial bodies) are collectively known as *pharyngeal pouch* or *branchial cleft organs* or as *branchiogenic organs.* Yet it must be left an open question, at least for the thymus (compare Hammar, 1910), whether this does not represent an originally unsegmented epibranchial organ. Epithelial bodies occur first in the tetrapodous vertebrates. Furthermore, they occur on all the pouches in none of the vertebrates, the anlagen being usually suppressed on certain of the pouches, namely the oral ones; in man they have not yet been described in the first two. According to my own observations, a circumscribed epithelial thickening may occur transitorily (embryo Hal. of the First Anatomical Institute, Vienna, with about 15 primitive segments) in the region of the dorsal wall of the first pharyngeal pouch, opposite the previously described invagination of the ventral wall (p. 454); the significance of this hitherto unobserved structure is, however, still in doubt.

A discussion of the historical development of our knowledge regarding the origin of these organs would lead us too far; one may consult on this subject the accounts given by Kohn (1900) and Hammar (1910). The actual explanation of the developmental processes has been principally due to the work of Kohn (1896) and Groschuff (1896). The very complicated nomenclature of the parts bears witness to our knowledge of the actual relationships having been acquired step by step; the embryonic anlagen were known in part much earlier (Remak, 1855) than the corresponding definitive organs, and they therefore received at first for the most part erroneous interpretations. For instance, the *glomus caroticum* has repeatedly been included in the series of branchiogenic organs and derived from the third pouch; it is, however, a derivative of the chromaffin system, a paraganglion (A. Kohn; see the chapter on that system), and the anlage seen by various authors was that of an epithelial body. Even in 1908 Fox, on historical grounds, termed the epithelial body of the third pouch the *glandula carotica,* although it has no other relation to the carotid than a transitory topographical one.[25] Such temporary topographic relations have also brought it about that the epithelial bodies derived from the third or fourth pharyngeal pouches have been termed glandules thymiques (Prenant) and glandules thyreoidiennes (Gley), as is usually done at the present time by French authors. The terms are historically intelligible,

[25] In some mammals an epithelial body is actually situated at the bifurcation of the carotid, as, for instance, in Echidna (Maurer), the sheep (Prenant) and Didelphys azara (Zuckerkandl); in the last the glomus caroticum is also recognizable.

but are unfortunate, since, apart from the possibility of confusion with the main glands and disregarding the histological and physiological similarity of all the epithelial bodies, the topographical relations are characteristic only for a definite stage of development, and the epithelial bodies in a long series of mammals, including man, are, on the one hand (when in normal position), all attached to the thyreoid and, on the other, are throughout genetically connected with thymus anlagen and also are frequently accompanied by small thymus lobes, so that both names might be applicable to each body. A similar criticism applies to the names *parathymus* for the derivative of the third pouch and *parathyreoid* for that of the fourth, employed by Groschuff (1896); the same author in 1900 names the bodies parathymus and distinguishes them according to the pouch from which they are formed as parathymus III and parathymus IV, names which have embryologically

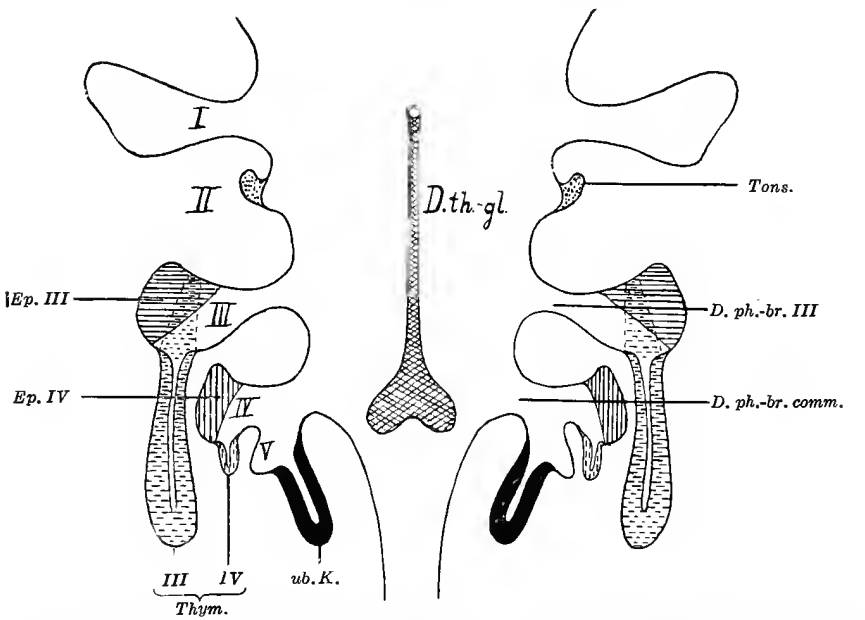


FIG. 324.—Schema of the branchiogenic derivatives in man, adapted from the schemata of Groschuff and Kohn. *D. ph.-br. III*, ductus pharyngobranchialis of the third pharyngeal pouch; *D. ph.-br. comm.*, ductus pharyngobranchialis communis of the fourth and fifth pouches (of the caudal pharyngeal pouch complex); *D. th.-gl.*, ductus thyreoglossus; *Ep. III* and *IV*, epithelial bodies of the third and fourth pouches; *Thym. III* and *IV*, thymus anlagen of the third and fourth pouches; *Tons.*, tonsil; *ub. K.*, ultimobranchial body.

a greater justification than the expression parathyreoid. Yet, at least for the adult condition in man, the name *parathyreoid,* proposed by the discoverer of the organs, Sandström, is quite characteristic, if one does not prefer the general name epithelial bodies, proposed by Kohn and borrowed from Maurer's description of the relations in amphibia. The very general term "glandules branchiales," used by Herrmann and Verdun (branchial glands, H. Rabl 1907), would also be strictly applicable to the other branchiogenic organs. The further classification of the epithelial bodies may probably be most satisfactorily based on the pouches from which they are formed, just as other metameric organs are grouped under a common designation and distinguished by numbers.

First of all, the development of the fifth pharyngeal pouch, which was long overlooked and whose existence was even denied,

must receive some further consideration (see above, p. 453). A thorough exposition of the question has been given by Tandler (1909), who, however, had for study no material showing the pouch with an epithelial closing membrane (compare in this respect Hammar in the Normentafel). The form of the pouch, as it makes its appearance, is extensively modified and complicated by the anlage of the ultimobranchial body. First of all (so far as our present knowledge extends) there appears on the fourth pouch, soon after its differentiation (embryo of about 3 mm., Hammar, 1902, Normentafel No. 11; compare also Ingalls, 1907, embryo of 4.9 mm., Normentafel No. 14), a process, directed ventrally and caudally,[26] which is longer than the ventral diverticulum of the third pouch of the same stage, but which, however, might readily be mistaken for such a diverticulum, as has apparently been done by earlier investigators and quite recently by Fox (1908). This process later becomes more distinctly separated from the fourth pouch, which then acquires a dorsal and a ventral diverticulum, the latter varying in extent (compare Tandler and Fig. 319). A lateral evagination of the caudoventral process reaches the ectoderm as a fifth pouch and forms a closing membrane; this, however, is perhaps not always formed and is at all events very transitory. A dorsal diverticulum is apparently not formed,[27] and after the degeneration of the actual pharyngeal pouch, which is directed toward the ectoderm, the caudoventral process becomes converted into the *ultimobranchial body*. The fourth and fifth pouches are, accordingly, intimately associated genetically, and the ultimobranchial body is the sole derivative of the latter. Both pouches possess only a common communication with the pharynx, a *ductus pharyngobranchialis communis* (compare p. 451), and the intimate connection of these last two pouches may be expressed by uniting them in the term *caudal pharyngeal pouch complex* (Figs. 319, 320, and 324).

H. Rabl (1909) finds in the mole a common anlage for the two pouches and names it the *caudal pharyngeal diverticulum*. In this case the fourth pouch is more rudimentary than the fifth.—That the ultimobranchial body does not make its appearance behind the series of pharyngeal pouches (as a *postbranchial body* according to Maurer), but is derived throughout the whole vertebrate series from what is in each case the last pouch, which has become rudimentary, was insisted upon by Geil, who is responsible for the term here employed for the structure. The body is identical with the *suprabranchial body* of van Bemmelen. The expression *telobranchial body*, which has been frequently employed recently, has been rejected by H. Rabl, since it does not express the relation of the structure to the *last* pharyngeal pouch.

[26] The structure in Figs. 317, 318, and 331 marked as a doubtful fifth pouch is perhaps merely an analogue of the diverticulum described on p. 452.

[27] Compare, however, p. 471 (Getzowa) as regards the occurrence of a corresponding epithelial body.

In the third branchial pouch the formation of the *thymus* is preceded by an elongation of the ventral diverticulum, which extends ventrally and medially (Figs. 319 and 320), and whose epithelium, consisting of closely packed cells, increases in height on the aboral wall of the diverticulum (Fig. 326). This thickening of the epithelium extends also upon the aboral and dorsal

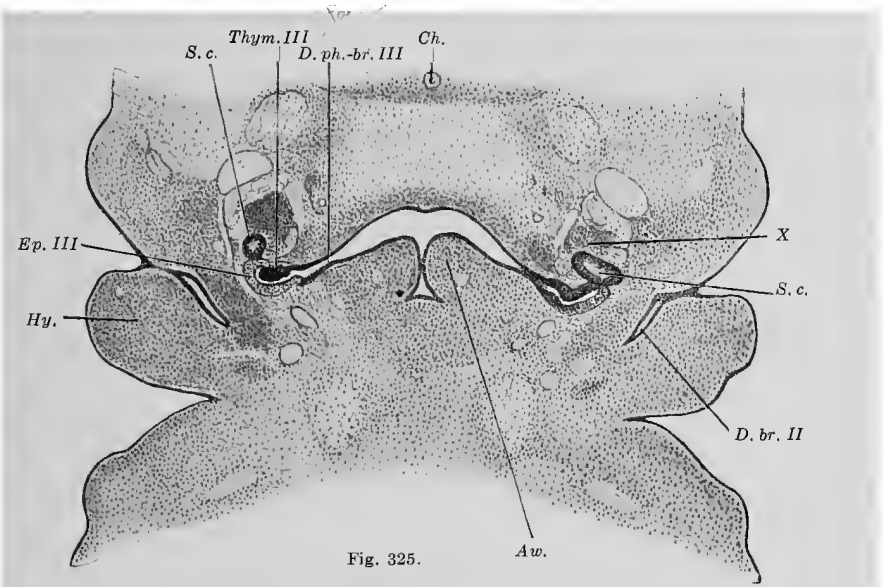


Fig. 325.

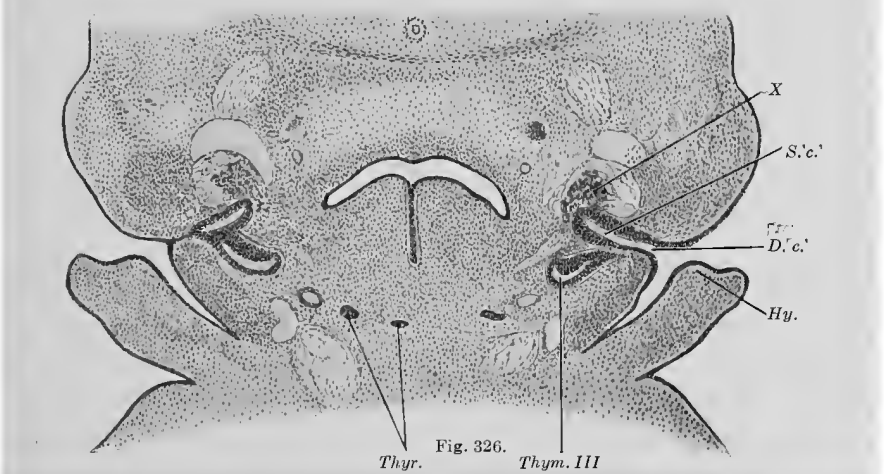
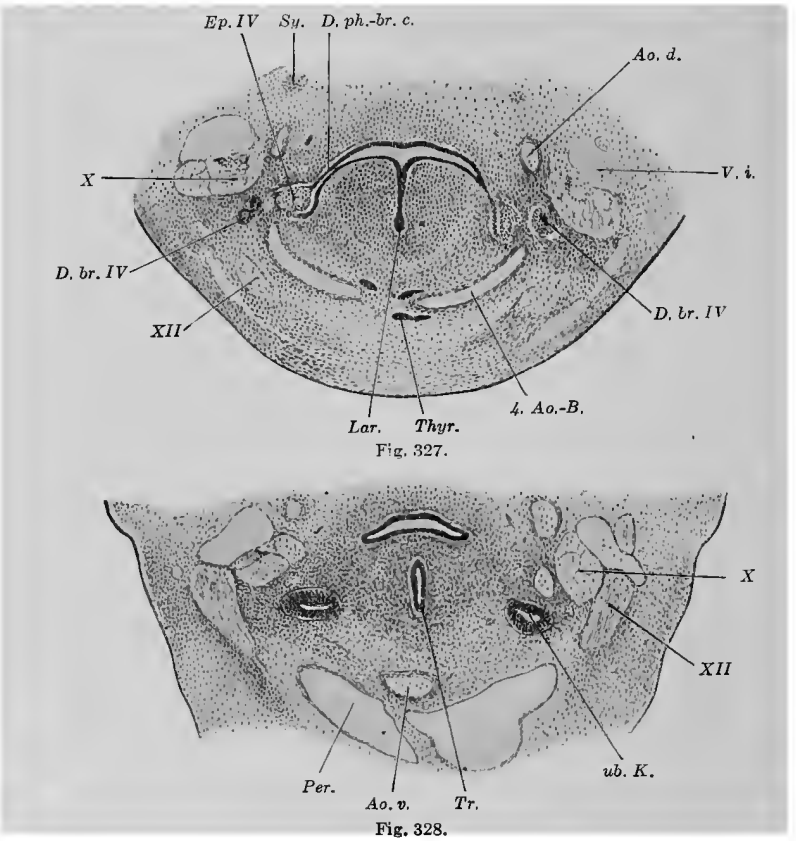


Fig. 326.

Figs. 325 and 326.—Two sections through the embryo BR (compare Fig. 320). Fig. 325 is through the point of communication of the third pouch with the pharynx, Fig. 326 through the sinus and ductus cervicalis. *Ao.-B.*, aortic arch; *Ao. d.* and *Ao. v.*, aorta dorsalis and ventralis; *Aw.*, arytenoid swelling; *Ch.*, chorda dorsalis; *D. br. II, IV*, ductus branchialis of the second and fourth external branchial grooves; *D. c.*, ductus cervicalis; *D. ph.-br. III*, ductus pharyngobranchialis of the third pharyngeal pouch; *D. ph.-br. c.*, ductus pharyngobranchialis communis; *Ep. III, IV*, epithelial bodies of the third and fourth pharyngeal pouches; *Hy.*, hyoid arch (operculum); *Lar.*, anlage of the larynx; *Per.*, pericardial cavity; *S. c.*, sinus cervicalis; *Sy.*, sympathicus; *Thym. III*, thymus anlage of the third pharyngeal pouch; *Thyr.*, thyreoid; *Tr.*, trachea; *ub. K.*, ultimobranchial body; *V. j.*, vena jugularis; *X.*, vagus; *XII.* hypoglossus. ×40.

walls of the pouch itself (Figs. 324 and 325), and simultaneously there begins on the oral and lateral walls of the dorsal diverticulum and of the pouch itself (Figs. 324 and 325) a proliferation of the epithelium, which very early shows itself, by its histological differentiation, to be the anlage of an epithelial body. The cells appear to be vacuolated, their plasma reticular and refractory to stains (chromatophobe). The cell boundaries are at first indistinct (compare also Maximow, 1909, p. 538).



Figs. 327 and 328.—Two sections through the embryo BR (compare Fig. 320). Lettering as in Figs. 325 and 326. × 40.

At the same time the medial portion of the pouch narrows to become the *ductus pharyngobranchialis III* (*connecting piece* or *duct, ductus thymopharyngeus* of Hammar), while the lateral portion becomes the secondary pouch of H. Rabl or, if the anlagen of the thymus and epithelial body be disregarded, the *remains of the pharyngeal pouch.* The formation of a large vesicle from the secondary pouch does not occur in the human embryo. The ductus pharyngobranchialis soon atrophies completely, so that the derivatives of the pouch become free. The thymus anlage becomes first

of all a thick-walled cylinder, at whose cranial end the cavity of the remains of the pharyngeal pouch is visible, while the sinus vesicle, which was in relation to the pouch laterodorsally, vanishes. Soon, however, the lumen of the thymus anlage disappears[28] and the *thymus cord* is formed. This thickens at its caudal end and so forms the *body of the thymus* (thoracic portion), while the uppermost portions become gradually thinner (cornu of the thymus, Groschuff; cervical portion) and come into connection with the epithelial body (Fig. 329). The entire anlage migrates caudally, the body more rapidly than the cranial end and the epithelial body, so that the cervical portion becomes more and more drawn out and finally vanishes. The migration usually takes place in front of (ventral to) the vena anonyma sinistra, frequently, however, behind it (Tourneux and Verdun). The epithelial

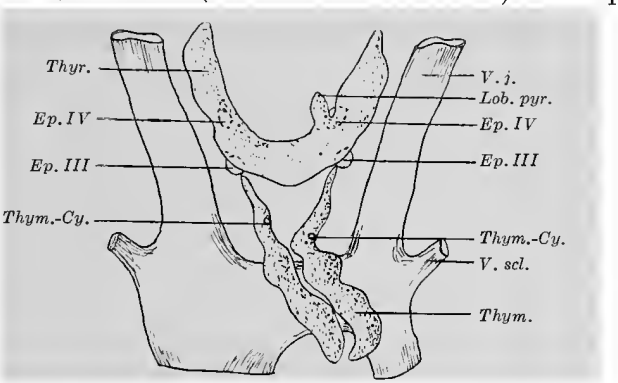


FIG. 329.—The branchiogenic organs of an embryo of 26 mm., somewhat simplified. (After Verdun, 1898.) *Lob. pyr.*, lobus pyramidalis; *V. scl.*, vena subclavia. The remaining lettering as in Figs. 325 and 330. × 20.

body, which as a rule becomes quite separated from the thymus cord, normally halts in its caudal regression at the lower pole of the thyreoid. If the cranial end of the thymus cord does not disappear completely, there occurs beside the epithelial body an *accessory thymus lobe* (A. Kohn). Frequently in older embryos there is associated with the epithelial body a cyst, probably derived from the remains of the pharyngeal pouch (Kürsteiner, 1899).

The thymus is from the beginning a paired organ and it remains so permanently; neither fusion of the two anlagen by transverse connections nor a complete division into several lobes occurs, according to Hammar (1910).—The thymus is first represented in the Normentafel as a short cylinder in an embryo of 5 mm.; the epithelial body, according to Tourneux and Verdun (1897) and Tandler (1909), appears as an epithelial thickening in embryos of 8 mm., and Tandler finds cell differentiation in the embryo represented in Fig. 325, Hammar, however, finding it earlier in an embryo of 8.3 mm. Nevertheless it is in some instances stated expressly in the Normentafel that the epithelial body is wanting in older embryos,

[28] The *thymus canal*, described by older authors as occurring in later stages, does not exist.

up to 11 mm. According to the Normentafel, the ductus pharyngobranchialis has disappeared in an embryo of 14.0 mm., but Hammar (1904) finds that this happens sometimes earlier and sometimes later (in embryos between 11 and 19 mm.). In an embryo of 12.5 mm. in the Normentafel the thymus has reached the pericardial cavity, and in one of 15 mm. the lumen is limited to the uppermost portion. The remains of the pharyngeal pouch are still to be seen, according to Hammar (1904), in an embryo of 24.4 mm.

According to Hammar (1911), there is a definite thickening of the wall of the thymus diverticulum while it is still cylindrical, situated dorsally in the more proximal portion and laterally in the more distal portion (compare Figs. 325 and 326); the thickening does not extend, however, to the tip of the diverticulum and accordingly cannot be regarded as the sole anlage of the thymus. The ends of the anlagen remain at first in close topographic relationship to the aortic arches, and their elongation corresponds to the increase in the distance between the third and fourth aortic arches and to the formation of the anterior surface of the neck. The elongation depends mainly on the stretching and not on the growth of the anlagen. During the elongation the anlagen, which have at first a more transverse position, come to occupy a position more nearly parallel to that of the body axis (as may be seen from Figs. 320 and 329). By the resulting rotation the dorso-lateral anlagen of the epithelial bodies are brought to the ventral side of the remains of the pharyngeal pouches. At the junction of the cervical and thoracic portions the aperture bend of the thymus anlage is formed, and, in addition, a heart bend and an aortic bend may also be distinguished.

The epithelial character of the thymus anlage continues plainly evident for a considerable time. In fetuses of about 50 mm. vertex-breech length one finds at the cranial end of the thymus anlagen and also in the cornua numerous closed vesicles with a high cubical epithelium (compare also Kürsteiner, 1899) and transitions from these to epithelial cords without a lumen. Cells arranged in an epithelium-like manner are generally distributed over the surfaces of the lobes of the body of the thymus. In fetuses of about the same stage of development (from 42 mm. onward), the centre of the anlage is beginning to appear clearer in sections—the differentiation of cortex and medulla is beginning. From now on the organ gradually assumes its characteristic appearance of being formed of small (''lymphoid'') cells. Hassall's corpuscles make their appearance in it in fetuses of from 60 to 70 mm. (Hammar, 1910).—The thymus grows not only throughout the entire period of embryonic life, but also through childhood, until puberty, and only at that time does its involution begin, a process which goes on but slowly in individuals with perfect health; during illnesses, however, an accidental involution may supervene and this explains the widely divergent statements of various authors concerning the condition of the postfetal thymus (Hammar, 1910).

According to Hammar (1911), the beginning of the "leucocyte infiltration" may be seen in fetuses of from 30 to 40 mm., and the formation of the medulla in those of 50 mm. The medulla appears at first in the central portions in the form of a longitudinal cord, extending later into the superficial boss-like anlagen of the follicles, which have appeared in the meantime; the formation of the

medulla is, accordingly, a continuous process, and for the most part it continues to be so later. In this manner the *tractus centralis* is formed, in whose composition, however, the cortical substance takes part later on. Since the boundary between the cervical and medullary portions is subject to functional modifications, the tractus centralis should not be termed the medullary cord, but preferably the *parenchyme cord.*

The histogenesis of the thymus is at present a very contentious question (compare Maximow, 1909; Hammar, 1910; and Stöhr, 1910), and cannot therefore be described in detail. Authors are agreed only as to the epithelial origin of the cellular reticulum and of the Hassall corpuscles. The chief elements of the organ, however, the small thymus cells, have been regarded either as immigrated cells and therefore as thymus lymphocytes (more recently especially by Maximow and Hammar) or as modified epithelial elements (among recent authors chiefly by Stöhr). According to Schaffer (1909), they must be regarded as lymphocytes, even if their epithelial origin be admitted. From the histological conditions and from their development in mammals, conclusive evidence is not at present to be drawn (compare Stöhr, 1910), but comparison and theoretical considerations undoubtedly speak in favor of their epithelial nature.

Little can be said concerning the histogenesis of the epithelial bodies. Even in the stage when they are epithelial thickenings their cells, as has been already mentioned, are characteristically differentiated; then the anlagen become split up by the epithelium growing out in the form of cords and probably also by the penetration of connective tissue between the cells, and the cell boundaries become distinct. The formation of different kinds of cells (compare the summary by Getzowa, 1907) occurs only in postfetal life. Lumina are not distinguishable in the epithelial bodies during embryonic life, but they may appear later. They may then become filled with a secretion, which shows the staining reactions of colloid, and such structures have hitherto continually led authors astray by causing the epithelial bodies to be confused with thyreoid tissue and to be regarded as young stages of it. Yet the acidophilous nature of a secretion is no indication of its colloid nature (Kohn, 1896); according the Erdheim (1904), any albuminous secretion, contained within a closed cavity, may assume the appearance of colloid.

According to H. Rabl (1909), the whole of the secondary pouch, except so much of it as is employed for the formation of the thymus anlage, is transformed into the epithelial body, even the wall opposite the original epithelial proliferation, since the connective tissue also penetrates the lumen of the pouch; at least this is the case in the mole. The other authors, who limit the extent of the anlage of the epithelial body to a greater degree than is done in the text, namely to the dorsal diverticulum or to the dorsal angle of the pouch, believe that the wall of the pouch itself degenerates; precise observations are, however, wanting.

The development of the *fourth pharyngeal pouch* follows essentially the same lines as that of the third; the ventral diverticulum is, however, much more feebly developed (Tandler, 1909), and it only occasionally undergoes a development into thymus tissue; when this tissue is formed, it remains in the neighborhood of the epithelial body, which is formed from the dorsal and lateral portion of the pouch, and, accordingly, again is not limited to the dorsal diverticulum. The development of the epithelial body resembles that of the third pouch; no difference in the structure of the two bodies is discernible. The anlage of the ultimobranchial body is a derivative of the *fifth pouch,* which projects caudoventrally from the fourth pouch in the form of a thick-walled cylinder (Figs. 320, 324, and 328). The common communication of the two pouches with the pharynx, the ductus pharyngobranchialis communis, diminishes in size and becomes constricted off from the caudal pharyngeal pouch complex, just as does the corresponding part of the third pouch. The complex then separates from the pharynx, the epithelial body becomes independent by the disappearance of the thymus anlage and of the remains of the fourth pouch, and the ultimobranchial body becomes an elongated vesicle with thick walls. The two structures (epithelial body and ultimobranchial body) usually remain close together, however, and migrate somewhat ventrally and caudally, thus coming into relation with the thyreoid anlage.

The thymus metamere of the fourth pouch was discovered by Groschuff; according to Erdheim (1904), its persistence is to be regarded as a rarity.—The ductus pharyngobranchialis communis, which has also been termed the lateral thyreoid anlage, has been named, with reference to its relation to the ultimobranchial body, the *ductus thyreopharyngeus.* This name must be rejected, for the reasons given with reference to the ductus thyreocervicalis (see p. 457); in addition it may be mentioned that an occasionally persistent thymus anlage is also present in connection with this duct, as well as with the ductus pharyngobranchialis III, the ductus thymopharyngeus of Hammar.

The thyreoid anlage (the middle or anterior thyreoid anlage of various authors), before its separation from the pharynx (p. 453), becomes bilobed with a divided lumen; at about the time when the thyreoglossal duct becomes broken it loses its lumen, and, undergoing a continuous displacement caudally, it develops into a broad structure composed of irregular cords of cells, disposed for the most part transversely. The derivatives of the caudal pharyngeal pouch complex apply themselves to the somewhat dorsally bent lateral portions of the anlage and become partly enclosed by it. This is the case with the ultimobranchial bodies, which then lose their lumina, but further than this they apparently do not always behave in the same manner. While in some cases they appear as compact bodies, in others they separate into an irregular group of small

cells with strongly staining nuclei (Grosser; see Fig. 330). In man, however, in normal development, no cell formations that can be referred to the ultimobranchial bodies are to be distinguished after a time (see also p. 471); up to the present no evidence has been advanced in favor of the widely accepted view that the bodies become converted into thyreoid tissue, and such a transformation is rendered highly improbable by the results of comparative investigation (see p. 471). The name *lateral thyreoid anlage,* which

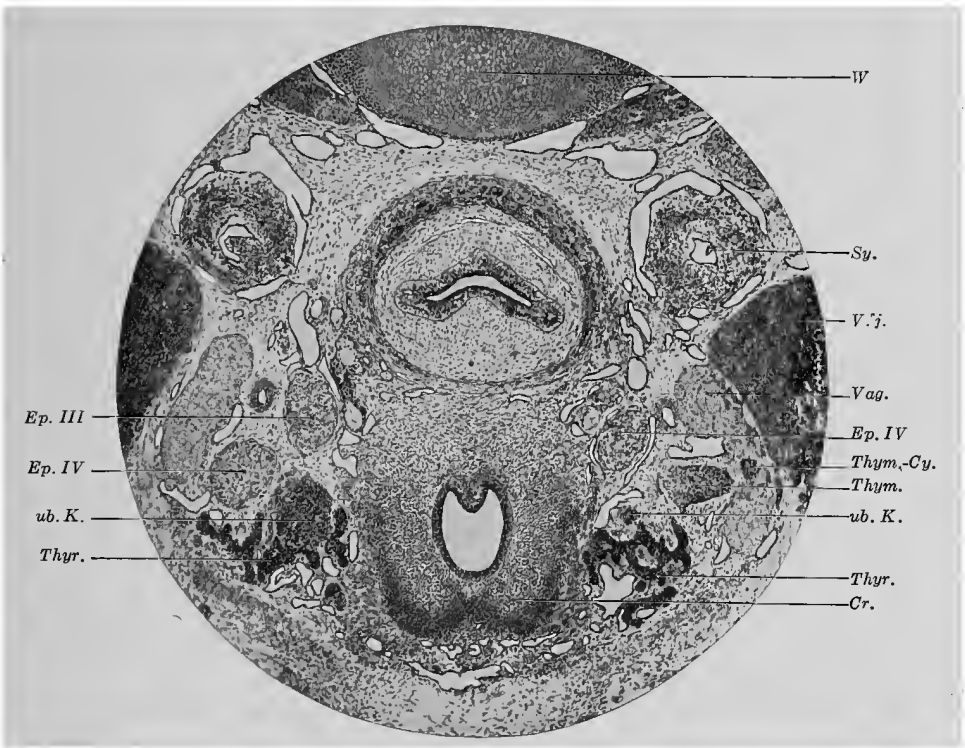


FIG. 330.—Section through the laryngeal region of the embryo Nat$_2$ of the First Anatomical Institute, Vienna (19.75 mm. vertex-breech length). *Cr.*, cricoid; *Ep. III, IV*, epithelial bodies; *Sy.*, sympathicus; *Thym.*, thymus; *Thym.-Cy.*, small cyst of the thymus; *Thyr.*, thyreoid; *ub. K.*, ultimobranchial body; *Vag.*, vagus; *W.*, vertebra. × 60.

has been applied to the ultimobranchial bodies, is therefore to be rejected (Verdun).

Toward the centre of the lateral lobes of the thyreoid there is to be found for some time (in fetuses of about 50 mm. vertex-breech length), as an expression of the more rapid growth of the lobes, a closer grouping of the thyreoid cords with a slighter development of the connective tissue; the differentiation of the cords takes place principally at the periphery. In this region there occurs in the stage mentioned the formation of lumina in the cell cords, which consequently appear beaded, and then the cords

become divided up into individual groups of cells, the anlagen of follicles, which in part possess a lumen before becoming constricted off, although for the most part the lumina appear later and successively, even forming to some extent in the first years of childhood.

According to the Normentafel, the (middle) anlage of the thyreoid shows indications of a bilobed condition in embryos of about 5 mm.; the occurrence of a lumen is variable. The thyreoglossal duct loses its lumen at a slightly earlier stage. It becomes drawn out to a long solid cord, which is broken in embryos between 6 and 7 mm.; it is occasionally distinguishable in later stages and remains of it may be found in embryos of 14 mm. In those of 8 mm. the anlage begins to separate into cords.—The ductus thyreoglossus, or its remains, occurs ventral to the hyoid bone and therefore between the derivatives of the first and second arches (His). The ultimobranchial body makes its appearance, according to Hammar, in embryos of 5 mm. as a cylindrical transformation product of the fifth pouch, or, it might be said, as an appendage of the fourth; the epithelial bodies IV, as well as the thymus anlagen, are defined in embryos of 8 mm. (Tandler, 1909), occasionally perhaps not until somewhat later (see p. 465). The caudal pharyngeal pouch complex separates from the pharynx in embryos of about 14 mm. (frequently only later, according to Hammar, 1904, in embryos over 18.5 mm. in length), and applies itself directly to the thyreoid. A little later, in embryos of somewhat over 15 mm., the lumen of the ultimobranchial body disappears. The small-celled proliferation of the ultimobranchial body, mentioned and figured above, can be perceived in two embryos in the collection of the First Anatomical Institute, Vienna (Nat. 1, with a length of 19.75 mm., and T. 1, with a length of 23 mm.); it seems also to have been observed by Tourneux and Verdun (1897) in an embryo of 19 mm. The denser grouping of the embryonic thyreoid cells in the lateral lobes of somewhat later stages (see p. 469), which these authors have also noticed, is not to be referred to the ultimobranchial bodies, as they have supposed. The (unpaired, middle) thyreoid anlage has been known since Rathke's time. That a derivative of the pharyngeal pouch region becomes associated with the thyreoid anlage in mammals was first observed by Wölfler (1880), and firmly established by Stieda (1881) and Born (1883); from the latter comes also the term *lateral* or *posterior thyreoid anlage,* which has been applied to the untimobranchial body, but which is rejected in the account given above.

In man the formation of the branchial derivatives is less completely and less easily followed than in many other mammals, as, for instance, the cat, but, on the other hand, more completely than in such a form as the rat. The differences which have been found in different species are partly to blame for the confusion which has long prevailed with regard to the development of these structures. Even in man the development of the individual organs has never yet been systematically followed throughout.

In correspondence with the extensive dislocation of the thymus, the epithelial body of the third pouch undergoes a much greater migration than that of the fourth, passing beyond it to come to rest at the lower border of the thyreoid. Consequently it appears as the *inferior epithelial body,* in contrast to the *superior* body of the fourth pouch situated at about the middle of the posterior (dorsal) surface of the thyreoid. This latter, in correspondence with the fusion that occurs between the ultimobranchial body and the thyreoid, in certain animals (rabbit, cat) regularly

and in man frequently becomes more or less enclosed within the thyreoid, and then appears as an *internal epithelial body,* with which the thymus IV may be associated as an *internal thymus lobe,* in contrast to the *external* one arising from the third pouch. Nevertheless all these conditions are very variable, and striking anomalies of position, as well as diminution and increase of number of the epithelial bodies, occur. Thus, that of the third pouch may remain even in man near its place of origin, not far from the division of the carotid (p. 460), or, on the other hand, it may descend into the thoracic cavity with the thymus. A diminution in the number of epithelial bodies is very difficult to demonstrate, on account of the possible occurrence of anomalies in position; increase, probably by division of the anlagen, was first observed by Kürsteiner and has since been repeatedly seen; Zuckerkandl has described a case in which there were eight, and Erdheim one with eight and one with twelve. The epithelial body III seems especially subject to division.

An internal epithelial body completely surrounded by the thyreoid is very rare in man, according to Getzowa (1907). According to the same authoress, cell cords of typical epithelial body tissue may occur in the interior of the thyreoid even when an external epithelial body IV is present. She is inclined to ascribe these cords to epithelial bodies of the fifth pouches, but embryological confirmation of this idea is as yet wanting.—The retrogression and atrophy of the cranial end of the thymus occasionally fails to take place, especially in connection with certain variations of the cervical nerves; a thymus lobe then occurs high up in the neck (Bien 1906 and 1907, Hammar 1910).

The ultimobranchial body in all vertebrates below the mammals is an independent structure which assumes a glandular character, produces alveoli and cell cords, but develops no colloid. In Echidna, according to Maurer, who has thoroughly studied the whole question, the body is also independent, but develops alveoli with colloid; nevertheless this material has been identified with that of the thyreoid only on the basis of its staining reactions. In all the higher mammals the body fuses with the middle thyreoid anlage, and its further history cannot then be followed with certainty. In many mammals a cyst can be found situated beside the internal epithelial body, surrounded by thyreoid tissue, and frequently finished with a ciliated epithelium and possessing mucous glands in its wall (*central canal* of the thyreoid of Prenant, *vésicule postbranchiale* of Herrmann and Verdun); furthermore there may be cell cords which extend into the interior of the thyreoid and vesicles, which are not always to be distinguished from undeveloped thyreoid tissue (Herrmann and Verdun 1899, Schaffer 1909). Similar rudiments occasionally occur in older human fetuses, of 55 to 65 mm. vertex-breech length, according to Herrmann and Verdun (1899). The cysts and glands have been derived by most authors from the ultimobranchial bodies themselves, yet some of them at least may represent the remains of the fourth and even of the fifth pharyngeal pouch (Groschuff, 1896). If this be the case, then only the cell cords and the small vesicles can be ascribed to the ultimobranchial bodies, these, however, occurring distinctly only in a few species (dromedary, sheep, cow, hedgehog, mole), as well as cysts whose epithelium is in a state of proliferation and is producing the cell cords (Herrmann and Verdun 1900). These authors also describe a case of an ultimobranchial body remaining independent in a camel one year of age; its structure was that of a gland, which was quite different from

the thyreoid but rudimentary, and consisted of coiled tubules, closed vesicles, massive cell columns, and cell spheres.

In thyreo-aplasia, the defect of the (middle) thyreoid anlage, the ultimobranchial body gives rise to no thyreoid tissue (Maresch 1898, Peucker 1899, Erdbeim 1904). In such cases one finds in addition to the epithelial body IV larger and smaller cysts, partly with contents which stain bright red with eosin; beside the cysts lie some lobes of serous or mucous gland tissue, and in one case Erdheim found immediately beside the cyst "a thin layer of small epithelial cells with dark nuclei." In any event these observations are opposed to the formation of thyreoid tissue from the ultimobranchial bodies; their significance is in harmony with the view stated above. The bodies are essentially rudiments, and one need not assume, as Erdheim has done, that only in thyreo-aplasia "the lateral thyreoid anlagen are also aplastic." In the atrophic thyreoids of cretins and idiots Getzowa (1907) observed cell masses and cords which likewise point to an occasional persistence of the ultimobranchial bodies in man. They correspond histologically with no other glandular tissue of the region, and are composed of large polyhedric cells rich in protoplasm and with large nuclei moderately rich in chromatin. In addition there were also small cysts which were not formed of thyreoid tissue. According to the same authoress, strumæ may arise from the parathyreoids or from the ultimobranchial bodies as well as from the thyreoid, whence the form variability of these tumors.

In general the so variable behavior of the ultimobranchial bodies throughout the whole mammalian series may be explained on the supposition that in the mammalia they constitute functionless rudiments (Herrmann and Verdun). Groschuff (1896) rightly sees, in the union of the bodies with the thyreoid, a condition that is confined to the mammalia, a process which essentially corresponds to the formation of an internal epithelial body or thymus lobe, but does not justify the derivation of tbe thyreoid from different anlagen.

The thymus of the mammalia is not directly homologous with that of the lower vertebrates, since in the latter it owes its origin to dorsal and in the former to ventral diverticula of the pharyngeal pouches. A harmonizing of the relations seems to Maurer to be made possible by the conditions in Lacerta, in which a transitory slender ventral process of the third pharyngeal pouch is formed, which occupies the same position as the thymus anlage of the mammalia, but is not transformed into thymus tissue, but atrophies. Further the extension of the thymus anlage upon the dorsal wall of the pharyngeal pouch itself may be mentioned in this connection.—The sometimes occurring differentiation of the ventral diverticulum of the fourth pouch into thymus tissue has never been followed directly, but has been assumed on account of the occasional occurrence of thymus lobes on the epithelial body IV.—In the rabbit the second pouch also gives rise to a transitory ventral diverticulum, that is to say, to a thymus anlage (compare p. 456, footnote).

The persistence of portions of the branchial system of cavities may give rise to branchiogenic fistulæ, cysts, and tumors (see especially Hammar, 1904). The region that corresponds to the outer opening of the ductus branchialis II and the ductus cervicalis is to be found at the anterior border of the m. sternocleidomastoideus. The second pharyngeal pouch corresponds to the tonsillar depression; the openings of the ductus pharyngobranchialis III and pharyngobranchialis communis are to be looked for near the larynx, about in the region of the sinus pyriformis, whence the n. laryngeus superior, as a branch of the fourth branchial arch, must pass between them. A fistula of the second cleft must lie, if the development of the vessels be normal, between the external and internal carotids and ventral to the glossopharyngeus and vagus; a fistula of the third cleft, between the common carotid and vagus, as well as between the glossopharyngeus and laryngeus superior; while a fistula of the fourth cleft must bend around the subclavian on the right and the arch of the aorta on the left, since these are derivatives of the

fourth aortic arch. The occurrence of these fistulæ is, therefore, very unlikely; the fistula of the second cleft is the only one that has hitherto been recognized with perfect certainty.—As to the persistence of the ductus thyreoglossus and the formation of median cervical fistulæ from it, the *résumé* of Erdheim (1904) may be consulted.

B. THE DEVELOPMENT OF THE RESPIRATORY APPARATUS

I. The Earliest Anlage.

The first anlage of the respiratory apparatus appears caudal to the pharyngeal pouches as a median ventral groove; the oral portion of this forms a ridge on the outer surface of the epithelial tube, but its caudal end is more rounded and hemispherical (Figs. 317, 318, and 331). In the region of the groove the epithelium is thickened. The ridge-like portion is the *laryngotracheal groove* and the rounded end the *unpaired anlage of the lungs.* These structures make their appearance very early, simultaneously with the last pharyngeal pouches and before the formation of the last two closing membranes, and show at first no connection whatever with the pharyngeal pouch region, except that the anterior end of the laryngotracheal groove extends just to the aboral part of the mesobranchial area. During the further development of the anlage the lungs grow much more rapidly than the remaining parts and form an unpaired, almost spherical vesicle (Figs. 332 and 333), which is in connection with the digestive tract dorsally and passes over into the tracheal groove orally.

The question as to whether the mammalian lung anlage is paired or unpaired has been answered in the latter sense almost unanimously by authors who have written since Kölliker's time, and may be regarded as definitely established for the human embryo by the observations of Blisnianskaja (1904) and Broman (1904) and the models figured here.[29] The view of most authors (compare Narath 1901 and Flint 1906), that the anlage is from the beginning asymmetrical, is not borne out by the models, since the asymmetry shown in Figs. 318 and 331 and limited to the laryngotracheal groove is produced by a torsion of the digestive tube at the boundary between the head and trunk, and is practically wanting in Fig. 332.

The unpaired character of the lung anlage marks the great difference that exists between the lungs and the gills. The unpaired anlage of the mammalia[30] is,

[29] Thompson (1907) ascribes a paired anlage to the embryo from which Fig. 331 is taken, but does not figure it, and this statement has been transferred to the Normentafel. That he has, however, made a mistake as to the position of the lung anlage is apparent from his own description and from a figure published later (1908); he identifies it in 1908 as the stomach anlage, while in 1907 he transfers the lung anlage to the region of the diverticulum doubtfully identified in Fig. 331 as a fifth pharyngeal pouch. The embryo has, however, no stomach anlage; probably also his model was made on too small a scale. Fig. 145 of Broman (1904) agrees essentially with my Fig. 331.

[30] A. Weber and his coworker Buvignier in several papers declare themselves in favor of a paired anlage for the mammals and for the homology of the lungs with the gills.

it is true, probably a secondary condition, for in other lung-breathing animals, and among these in the lowest Tetrapoda, the amphibia, the anlage is paired (Remak, Goette). Nevertheless even in these forms it is not to be homologized with a final (sixth or seventh) pharyngeal pouch, but is to be derived from a swim-bladder; probably this structure was originally generally paired, and has, as a rule, become permanent only unilaterally (Greil, 1905).

Two longitudinal grooves (*boundary grooves*) on the lateral walls of the anterior part of the digestive tract mark out at an early period a ventral respiratory from a dorsal digestive zone (Kölliker, Flint; compare Fig. 333 and the transverse section of the region in Fig. 317, where the left groove is already indicated).

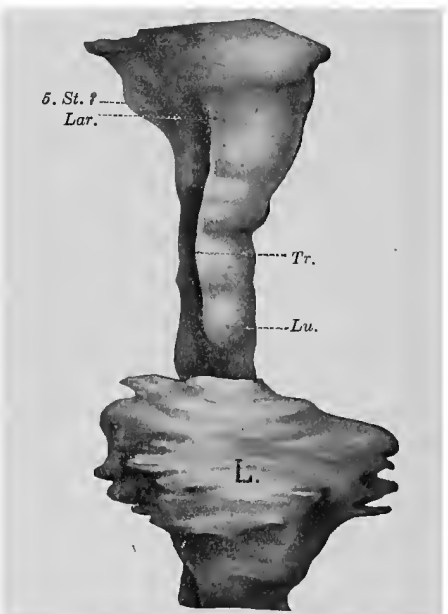


Fig. 331.—Anlage of the respiratory tract of an embryo of 23 primitive segments (Rob. Meyer No. 300, 2.5 mm.; compare Figs. 317 and 318). *L.*, liver; *Lar.*, laryngeal groove; *Tr.*, tracheal groove; *Lu.*, lung anlage; *6. St. ?*, doubtful anlage of the fifth pharyngeal pouch. × 150.

The unpaired anlage of the lung has, however, only a short existence; from it there develop laterally and caudally the two pulmonary sacks. The boundary furrows of the respiratory anlage at the same time begin to be more sharply defined, and first the lung anlage and then the tracheal groove become separated from the œsophagus by a septum that grows forward from below. Orally, however, the laryngeal portion of the groove encroaches more upon the mesobranchial area (p. 449) until it lies between the medial ends of the fourth branchial arches and later between those of the third. The respiratory apparatus now consists of the cleft-shape entrance of the larynx lying between the caudal

pharyngeal pouch complexes, of the relatively long and slender laryngotracheal tube,[31] and of the two pulmonary sacks.

II. The Trachea.

No striking modifications occur later in the tracheal tube. Its lumen is at first cylindrical (Fig. 341), but later, with the development of the membranous dorsal wall, it becomes heart- or horseshoe-shaped in transverse section (Fig. 330), and in older embryos (more than 30 mm. in length) the dorsal wall is always thrown into longitudinal folds. The *epithelium* undergoes no marked changes, except that it develops cilia. The *glands* appear at the close of the fourth month, almost simultaneously with the *elastic*

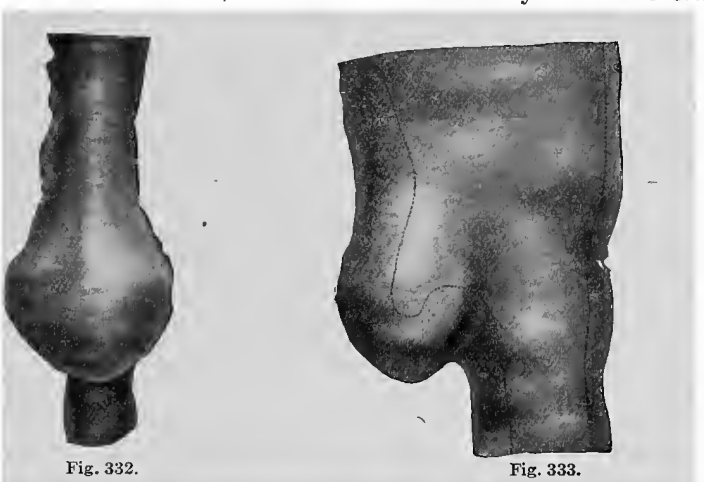


Fig. 332. Fig. 333.

Fig. 332.—Lung anlage of an embryo of 4.25 mm. vertex-breech measurement, from the ventral side. Embryo R. Meyer No. 399 of the Zurich Anatomical Institute (Stage I of Blisnianskaja). × 150.

Fig. 333.—The same model seen from the left side. The outlines of the lumen shown by the broken line. × 150.

fibres of the mucous membrane, and very soon become hollow; the formation of glands appears to continue throughout pregnancy. The *tracheal cartilages* make their appearance in the places where they are finally found; their anlagen are to be recognized as condensations of the tissue in embryos of 17 mm., and cartilage appears in embryos of 20 mm. The differentiation is always more advanced in the neighborhood of the larynx (Philip, Kölliker, cited by Merkel, 1902). *Musculature* occurs in the dorsal wall of the trachea before the rings become cartilaginous. (For further details see Merkel, 1902.)

[31] The occurrence of the œsophagotracheal septum and the anomalies that are occasionally associated with its formation have already been briefly discussed by F. T. Lewis in a preceding section of this chapter.

No evidence is furnished by human embryos nor yet by those of the Placentalia in general in favor of a derivation of the tracheal skeleton from that of the larynx, that is to say from the cartilago lateralis of the amphibia. In Echidna Göppert (1901) has found a union of the præchondral rings by paired præchondral cords and consequently their differentiation from a common anlage.

III. The Larynx.

The skeleton and musculature of the larynx have already been considered in the first volume of this Handbook; the differentiation of the entrance of the larynx and of the laryngeal cavity remains to be considered here.

The oral end of the laryngotracheal groove shortly after its formation becomes embraced by two swellings, the *arytenoid swellings* (Kallius; *crista terminalis,* His). They indicate also the caudal limits of the branchial portion of the intestine, characterized by its lateral widening. The caudal pharyngeal pouch complex lies at first craniolaterally to the swellings, which are at first actually only the somewhat more pronounced borders of

FIG. 334.—Entrance to the larynx of an embryo of 8 mm. (After Soulié and Bardier, 1907.) *Aw.*, arytenoid swelling; *Ep.*, epiglottis; *O. c. ph.-tr.*, orifice of the canalis pharyngotrachealis; *Pl. ar.-ep.*, plica ary-epiglottica; *3.*, *4. St.*, third and fourth pharyngeal pouches (their boundaries indicated schematically by dotted lines); *T. ar.*, tuberculum arytenoideum. × 30.

the oral end of the laryngotracheal groove (Kölliker, Soulié and Bardier). After the formation of the œsophagotracheal septum the swellings persist as the boundary of the laryngeal groove, and between them the groove deepens, its margins come into apposition, and its epithelium fuses, producing an obliteration of the cavity of the larynx (see below). At the time when the swellings lie almost parallel with one another, there may be distinguished, according to Soulié and Bardier (1907), at about their middle a thickening (arytenoid tubercle, bourrelet aryténoidien) and orally a narrower part, the later *plica ary-epiglottica.* By these the region of the laryngeal entrance becomes early delimited from that of the later interarytenoid notch. Anteriorly the swellings at first pass into the mesobranchial area and later they bend in this area in an arch-like manner to form a transverse swelling lying in front of the laryngotracheal groove. This, the *furcula* of His, is perhaps to be interpreted as the *copula region* of the branchial arches (see p. 454 and Kallius, 1910). This separates into the root of the tongue anteriorly and the *anlage of the*

epiglottis posteriorly (Hammar, 1902). In the median line the boundary furrow between these two structures is less deep than it is laterally, and there is thus formed the anlage of the *plica glosso-epiglottica media*, which, however, becomes more sharply defined only after birth (Kallius, 1897; Soulié and Bardier). The epiglottis lies at first between the fourth branchial arches; to what extent the third arches are concerned in its formation is still in dispute. A temporary median furrow would appear to indicate that it has a paired anlage, but this disappears very soon (Soulié and Bardier).

Whether the epiglottis is formed from a growth of the arches into the mesobranchial area (the view of the majority of authors; compare Soulié and Bardier), or as an elevation of this area itself, it being independent of the arches (His,

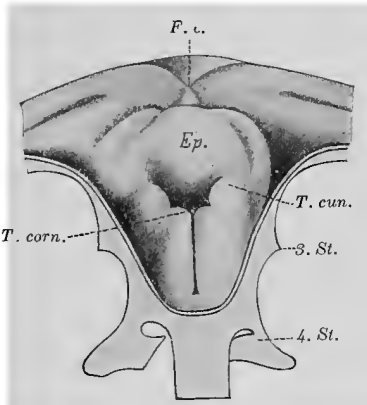


Fig. 335.

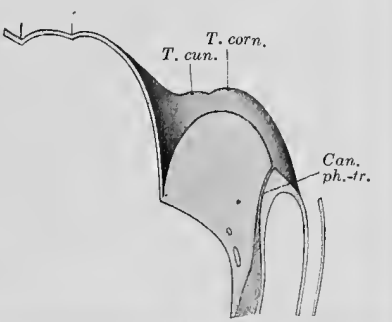


Fig. 336.

Fig. 335.—Laryngeal entrance of an embryo of 28 to 29 days (8–9 mm.). (After Kallius, 1897.) *Ep.*, epiglottis; *F. c.*, foramen cæcum; *3.*, *4. St.*, third and fourth pharyngeal pouches; *T. corn.*, tuberculum corniculatum. × 33.

Fig. 336.—Median section of the larynx shown in Fig. 335. (After Kallius, 1897.) *Can. ph.-tr.*, canalis pharyngotrachealis. The remaining lettering as in Fig. 335. × 33.

Hammar), is not yet definitely determined, and, furthermore, the first developmental processes of the entrance to the human larynx are not yet thoroughly known.—Kallius (1897), with His and others, derives the arytenoid swellings from the last (sixth) branchial arches (he names them the fifth, since the fifth pouch and the fifth aortic arch were at that time scarcely known). The manner of their formation contradicts this, however. The opinion of Kohlhrugge, cited by Kallius, that the ventriculus laryngis is a branchial pouch and therefore the caudal boundary of the arch mentioned, is untenable in view of the late appearance of the ventricle. At all events the material of the sixth arch, which is undoubtedly present (on account of its aortic arch), must pass continuously into that of the arytenoid swelling, since a separating sixth pharyngeal pouch is to be seen (see above, p. 446, 452).

Frazer (1910) comes to results which are in general quite similar, but, owing to the employment of a peculiar nomenclature, they are not easily compared with those of others. He also lays special stress on the identity of the arytenoid swellings with the last branchial arches, but later on allows also the ventral ends of the fourth arches to participate in the formation of the swellings. The epiglottis he derives principally from the third arch.

After the formation of the arytenoid swellings and the epiglottis the evolution of the larynx can be followed more thoroughly. The arytenoid swellings gradually become folded in the middle almost to the extent of a right angle, so that the caudal portions become parallel while the oral ones diverge more and more (Figs. 334 and 335). While this process is going on, they move forward and their oral portions apply themselves to the aboral surface of the epiglottis, with which the folds are connected by the plicæ ary-epiglotticæ. The aditus laryngis has thus assumed the form of a T-shaped cleft (Figs. 334 to 338 and 325); the horizontal limb of the T lies between the arytenoid swellings and the epiglottis, the vertical one between the aboral portions of the two swellings (interarytenoid notch). At this time, however, the cleft ends blindly, since the epithelium of the laryngeal entrance has fused (Figs. 326 and 327). At the points where each arytenoid

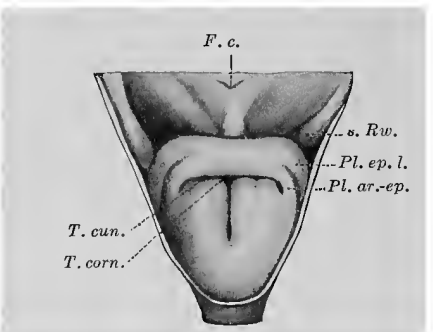


FIG. 337.—The entrance of the larynx in an embryo of 40–42 days (15–16 mm.). (After Kallius, 1897.) *Pl. ar.-ep.*, plica ary-epiglottica; *Pl. ep. l.*, plica epiglottica lateralis; *s. Rw.*, lateral pharyngeal swelling. The remaining lettering as in Fig. 335. × 15.

swelling is folded there is a tubercle, the *tuberculum corniculatum* of Kallius or the *tub. arytænoideum* of Soulié and Bardier. Lateral to this a second tubercle, the *tuberculum cuneiforme*, appears, according to Kallius, in embryos of 8–9 mm., but according to Soulié and Bardier, only much later, in fetuses of about 40 mm. (Compare Figs. 334–339.) Kallius finds also about this time the *plicæ epiglotticæ laterales*, extending from the anlage of the epiglottis toward two lateral folds of the mucous membrane of the pharynx (*lateral pharnygeal swellings*) (Fig. 337); Soulié and Bardier do not, however, perceive these folds (Fig. 338). In fetuses of about 40 mm. the fusion of the laryngeal walls becomes dissolved, the tubercles of the arytenoid swellings withdraw from contact with the caudal surface of the epiglottis, and the entrance of the larynx becomes oval (Fig. 339). Later, according to Kallius, the lateral plicæ epiglotticæ unite with the lateral pharyngeal swellings to form the *plicæ pharyngo-epiglotticæ*, probably as a result of the descent of the larynx; at all

events, these folds become very distinct later on (Fig. 340) and are even much higher in the new-born child than in the adult. The *plicæ glosso-epiglotticæ laterales* separate from these, according to Soulié and Bardier, in fetuses of more than 29/43 cm.

According to Frazer (1910), the cuneiform tubercle corresponds to the medial end of the fourth arch, the corniculate tubercle to that of the fifth. The transverse limb of the T-shaped laryngeal cleft represents a portion of the pharyngeal cavity, whose caudal boundary in the adult would be represented by the free edge of the true vocal cord and a line drawn from one tip of the processus vocalis to the apex of the arytenoid.

Kallius finds in the lateral plicæ epiglotticæ the similarly named, skeletonless portion of the epiglottis observed by Göppert in the lower mammals; the folds remain recognizable throughout life in the majority of the mammals, oral to the plicæ ary-epiglotticæ. The lateral pharyngeal swellings may be phylogenetic representatives of the plicæ palatopharyngeæ of the mammals (Göppert).

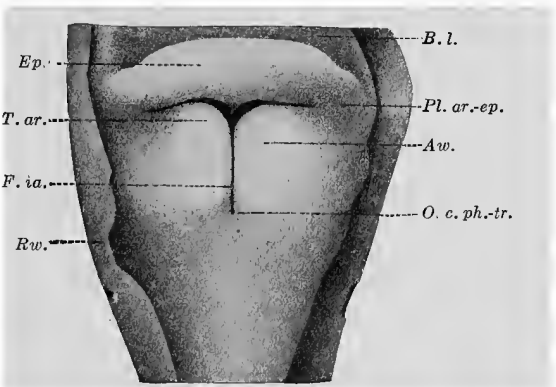


FIG. 338.—Entrance of the larynx of an embryo of 30 mm. From a dissection. (After Soulié and Bardier, 1907.) *Aw.*, arytenoid swelling; *B. l.*, base of the tongue; *Ep.*, epiglottis; *F. ia.*, fissura interarytænoidea; *O. c. ph.-tr.*, orifice of the pharyngotracheal canal; *Pl. ar.-ep.*, plica ary-epiglottica; *Rw.*, wall of pharynx. × 20.

The shape of the cavity of the larynx changes considerably during development. The cleft-shaped lumen of the laryngeal groove becomes obliterated, as has been stated, by the arytenoid swellings coming into apposition and by the fusion of their epithelium (compare Figs. 325–327). Nevertheless, this epithelial fusion, first described by Roth (1880), is in the beginning, at least, by no means complete (Fig. 336): on the one hand, there remains orally, between the arytenoid swellings and the epiglottis, a funnel-shaped cavity which usually ends blindly ventro-caudally; on the other hand, a fine canal persists in the epithelium along the posterior wall of the larynx, beginning at the interarytenoid notch and passing, with a gradual enlargement, into the tracheal lumen (embryo of 8–9 mm., according to Kallius; *canalis pharyngo-trachealis* of Soulié and Bardier; Figs 334–338). Frequently, however, even in this stage and also later, complete fusion occurs (compare the thorough account by Fein, 1903). The fusion extends

caudally beyond the region of the glottis,—that is to say, to the region of the vocal cords, and its lower boundary may correspond with the *linea arcuata inferior,* described by Reinke and occasionally perceptible even in the adult (Kallius). According to Soulié and Bardier, however, the fusion for a time extends downward as far as the region of the cricoid cartilage (embryos of 19 mm.). The fusion gradually dissolves in embryos between 17 and 40 mm. (Fein); indeed it perhaps begins somewhat earlier (Kallius), the solution showing itself at first as small spaces in the line of fusion. It results probably from a breaking down of cells. (Fein). Kallius mentions the incisura interarytænoidea as one of the places where the fusion persists for a long time, but Fein contradicts this statement.

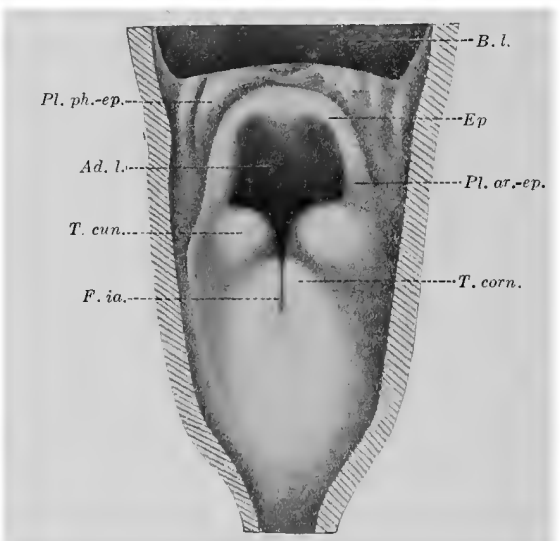


Fig. 339.—Entrance of the larynx of an embryo of 16/23 cm., male. From a dissection. (After Soulié and Bardier, 1907.) *Ad. l.*, aditus laryngis; *Pl. ph.-ep.*, plica pharyngo-epiglottica. The remaining lettering as in Figs. 335 and 338. × 6.

A satisfactory explanation of the epithelial fusion in the larynx has not yet been given. A difference from the epithelial fusions in other portions of the body exists in this case, in that an epithelial proliferation does not precede it; the epithelium is simply compressed between the mesodermal arytenoid swellings, its nuclei are arranged parallel to the mesodermic surface (Kallius). On account of its transitiveness it cannot be regarded as a protective phenomenon. Compare also V. Schmidt (1910).

The vocal cords are recognizable when the fusion is completely dissolved; the anlage of the *ventriculus laryngis* indicates their position. According to Soulié and Bardier, the anlage of the ventricle appears in embryos of 24 mm. as a solid epithelial bud, which acquires an independent lumen at the beginning of the third month; this later unites with the lumen of the larynx by its

epithelial stalk becoming hollow. Accordingly the ventricle has for a time the form of a spherical vesicle with a cylindrical stalk; but in a fetus of 44/57 mm. the typical form occurs. The ventricle makes its appearance earlier than the date Kallius assigns to it (middle of the fourth month); Hansemann (1899) finds it in an embryo of 27 mm. as a blind sack. The distinct delimitation of the vocal cords first occurs, however, in the middle of the third month (fetus of 37 mm., according to Soulié and Bardier); their epithelium differs from that of the surrounding regions, after stages of 45–50 mm., by the absence of cilia. Elastic fibres and a distinct musculature first appear at about the middle of pregnancy; yet at birth the free edge of the vocal cord is rounded and only assumes

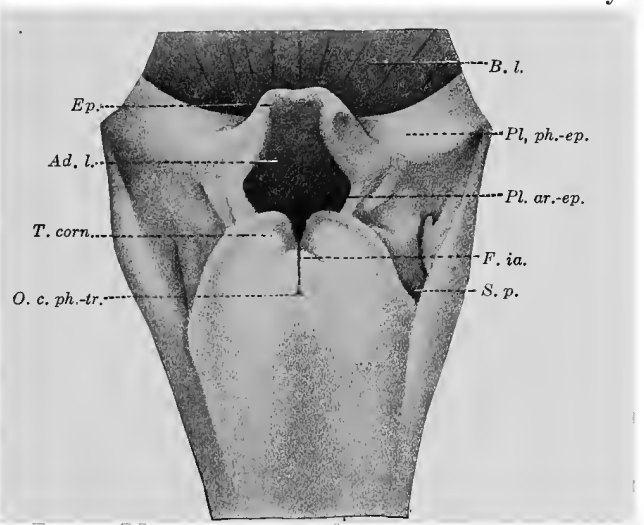


Fig. 340.—Entrance of the larynx of an embryo of 29/43 cm., male. From a dissection. (After Soulié and Bardier, 1907.) *S. p.*, sinus piriformis. The remaining lettering as in Figs. 335, 338, and 339. × 3.

its definitive form within the first six months of extra-uterine life. According to Frazer (1910), a præchondral "node" occurs imbedded in the ventral ends of each cord during the second fetal month; these disappear later.—The *plicæ ventriculares* form at first, after the formation of the ventricle, roundish elevations, in which glands appear in the fourth month. The ciliated epithelium with which they are covered is replaced by a squamous epithelium in the course of the first year.

The epithelium of the larynx caudal to the region of fusion rests at first close upon the cricoid cartilage (embryos of about 20 mm.; compare Fig. 330); later a rather thick layer of loose connective tissue becomes interposed between the epithelium and the cartilage (fourth month, according to Kallius). The cricoid cartilage at this time consequently grows more rapidly than its epithelial lining, but later again is equalled by it.

The entire larynx in embryos from about 8 mm. onward is proportionately large and only acquires its proper dimensions after birth (Kallius, Merkel). It is much higher in embryos and fetuses than in the adult, and in the fifth month projects into the pharyngonasal cavity, whereby the epiglottis rests upon the dorsal surface of the soft palate as in most mammals. At the time of birth the descent of the larynx is not yet completed; the glottis in the new-born child is at about the level of the disk between the second and third cervical vertebræ, while in the adult it is in front of the fifth vertebra. This relation, however, is subject to some slight individual variation (compare Merkel, 1902).

IV. The Lungs.

After the lung anlage has become paired two pulmonary sacks or vesicles are to be distinguished, and at first these appear to be symmetrical (compare Fig. 157 of Broman, 1904). Very soon, however, they become unsymmetrical, the right one becomes larger and bends caudally and dorsally, while the left at first has an almost transverse position (in embryos of 5 mm.; compare Fig. 341, and also Fig. 2 of Blisnianskaja and Fig. 170 of Broman). Each pulmonary sack ends in a swollen flask-shaped *stem bud.*

Our morphological knowledge of the arrangement of the bronchial system does not date further back than Aeby (1880), whose results, apart from the establishment of a special "eparterial" bronchial system, have been confirmed by later investigations. The account that follows is based especially upon the unsurpassed work of Narath (1901). Unfortunately, the number of human embryos studied by this author was very small, and the figures of Blisnianskaja (1904) that have since been published are rather incomplete. More recent investigations and figures of the development of the human lungs, especially in later stages, are wanting.

A short statement as to the nomenclature used in describing the branchings of the bronchi may be given. The stem bud is the anlage of the *stem bronchus,* which traverses the entire lung and from which branches or *lateral bronchi* are given off. These extend out in the four principal directions and are either direct or indirect lateral bronchi (bronchi of the first or second order; the latter also known as *accessory bronchi*); they are repeated at approximately regular intervals (Aeby). Each group of lateral bronchi given off, according to the principal directions at approximately the same level, constitutes one of the stories or tiers of the lung; they are perhaps genetically related (Narath). The most important and strongest lateral bronchi are those termed *ventral* by Aeby; they arise laterally and extend at first laterally, but later supply the ventral region of the lung and also in its oral portions pass more or less to the ventral side; they lie ventral to the main stem of the pulmonary artery. On this account Narath has retained Aeby's name for them, while other authors (His, Robinson, d'Hardivillier, Flint) term them *lateral* or *external bronchi.* Toward the end of the stem bronchus they pass more and more toward its dorsal surface; a line connecting their origins would therefore have a spiral course, an arrangement that is repeated in the other bronchi and in the course of the arterial stem. The second most important group is that of the *dorsal* bronchi, which arise orally to the corresponding ventral

bronchi from the dorsal surface of the stem bronchus, and are not infrequently represented by several branches in each lung tier. The apices of the lungs are supplied by *apical bronchi* (Narath); their significance is still disputed. The right apical is Aeby's *eparterial* bronchus, and in that author's opinion is a special element not represented elsewhere in the lung, while Narath regards it as the first dorsal bronchus (see below). In addition there occur *ventral* and *dorsal accessory bronchi* (lateral bronchi of the second order), whose importance is small and whose formation is quite irregular. The ventral ones have been regarded as direct outgrowths from the stem bronchus and have been termed by His and Flint, for example, simply *ventral bronchi,* in contrast to the lateral ones (Aeby's ventral). Among them one, the *infracardial bronchus,* is especially well developed and worthy of mention. Flint (and also d'Hardivillier) regard the dorsal accessory bronchi also as direct *medial* branches of the bronchus.

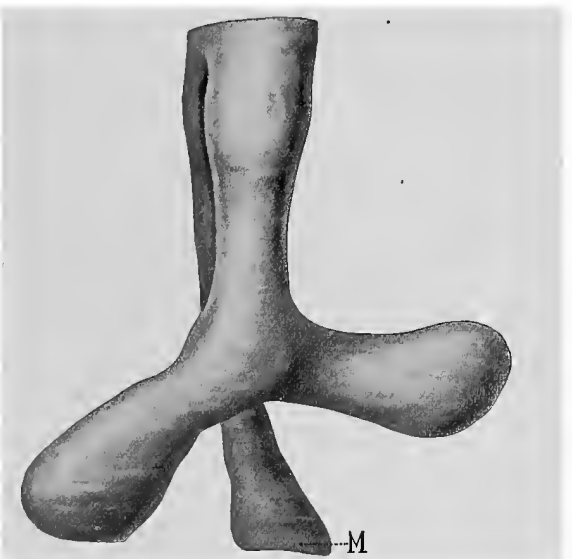


FIG. 341.—Epithelial lung anlage of the embryo Rob. Meyer No. 338 (Normentafel No. 18, 5 mm.), from the ventral surface. *M*, stomach. × 100.

The first lateral bronchus formed is the first ventral (lateral) one of the right side (Narath); yet the stage of the human embryo in which it is alone present has not yet been described.[32] Shortly after this laterally directed anlage and proximal to it there appears the smaller right apical bronchus and, in the left lung, the first ventral bronchus (Narath, embryo of 7 mm., Fig. 342). At the point of origin of the anlagen (buds) of the ventral bronchi the stem bronchus is distinctly bent medially. The anlage of the (right) apical bronchus is well separated from that of the first ventral bronchus in the stage represented in Fig. 342,[33] but it

[32] Perhaps Fig. 2 of Blisnianskaja (1904) represents such a stage. The text lacks a definite statement.

[33] Blisnianskaja describes a stage in which the right apical bud is seated on the ventral one.

flattens out toward the trachea. The right stem bronchus is markedly longer than the left. This stage corresponds approximately to the youngest figured by His (1887), but differs in form and proportion somewhat from His's figure.

An embryo of 11 mm. (Normentafel No. 45), whose bronchial tree almost exactly agrees with that shown in Figs. 343 and 344, had, according to Narath, on the right side the apical bronchus (*Ap.*), extending dorsolaterally and with three buds, the purely lateral first ventral bronchus (V_1) with two buds, the purely dorsal second dorsal bronchus (D_2) with two buds, the infracardial bronchus (*Jc*) between D_2 and V_2, directed ventromedially and with indications of buds, and then V_2 and V_3, both undivided, as is also the stem bud; on the left there is the first ventral bronchus, passing laterodorsally and having a strong

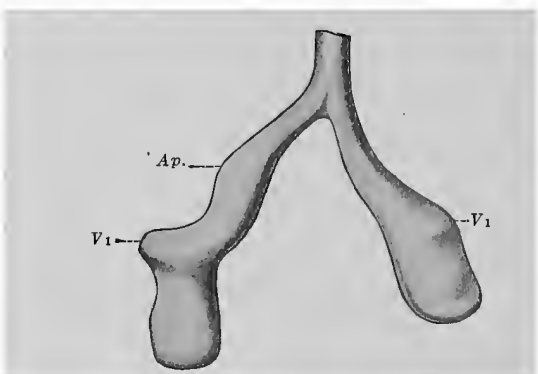


FIG. 342.—Epithelial lung anlage of the embryo Chr. 1 (Normentafe No. 28, 7 mm.). (After Narath, 1901.) Apparently the plates have been somewhat displaced in preparing the model; the right stem bronchus should descend more directly than the left (Narath). *Ap.*, apical bud; V_1, first ventral bud. × 100.

dorsal branch, the left apical bronchus; at the origin of this V_1 bends sharply ventrally. The ends of both show lateral buds. Then follow D_2 passing dorsally, V_2 passing laterally and having at its root what is perhaps the anlage of a left infracardial bronchus, and V_3, as well as the stem bud, which does not extend quite so far caudally as that of the right side.

In an embryo of 15.5 mm. Narath found in the right lung $Ap.—V_1—D_2—Jc—V_2—V_3$, and in the left $V_1—D_2—Jc—V_2—V_3—D_4—V_4$ and also a small bud which was perhaps an accessory bronchus from V_4. This stage, though slightly older than that shown in Fig. 345, is very similar to it. The left lung is at first decidedly more advanced in the development of its deeper parts, as His has pointed out. V_1 on the left side bears the strong, dorsally directed apical bronchus. The left infracardial bronchus, which has become interposed in the series, arises from the ventral side of the stem bronchus close to V_2 and already possesses three

buds. D_3 is wanting on both sides.—Altogether Narath finds in each lung from four to five ventral bronchi, a sixth rarely forming in the left lung; the dorsal bronchi are usually fewer, frequently only two on each stem bronchus. An infracardial bronchus occurs on the right side as a rule, but is rare on the left, and its presence there in the embryo just described must be regarded as an anomaly. Its suppression on the left side appears to be due to the position of the heart and pulmonary vein on the left side (Flint). Other ventral accessory bronchi appear only here and there. The infracardial bronchus belongs almost without exception to the second lung tier; that it may occur in the left lung has been shown by Ewart and Schaffner, while the bronchus thus described by Hasse is identical with the distal part of the main stem of the left V_1 (Narath). The apical bronchus of the left

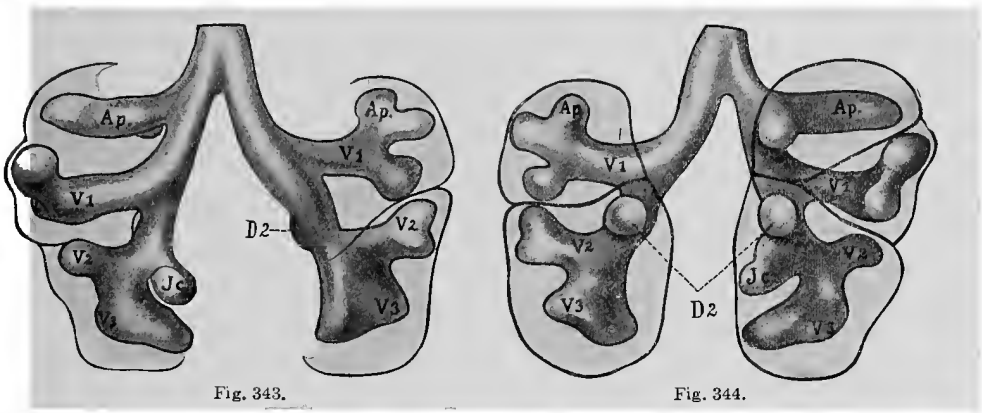


Fig. 343. Fig. 344.

FIGS. 343 and 344.—Reconstruction of the lungs of an embryo at the beginning of the fifth week, ventral and dorsal views. (After Merkel, 1902.) *Ap.*, apical bronchus; D_1, D_2, etc., dorsal; V_1, V_2, etc., ventral bronchi; *Jc.*, infracardial bronchus.

side, leaving variations out of consideration, arises even from the beginning from V_1, but in its branching it behaves throughout like the right apical, notwithstanding its smaller calibre (Narath).

The point of bifurcation of the trachea and the entire lung anlage migrates caudally during the course of development. In the embryo described by Ingalls (1904) (Normentafel No. 14, 4.9 mm.) the lung anlage lies at the level of the third cervical segment, but in one of about one month it is already at the level of the first thoracic vertebra, according to Blisnianskaja. From that time onward the recession proceeds more slowly, the level of the fourth thoracic vertebra being reached at birth. The bifurcation angle of the trachea at first diminishes (compare Figs. 341 and 342), but increases again later (for numerical data see Blisnianskaja).

The pulmonary arteries in the youngest stages that have been studied (7 mm.) arise, according to Narath, quite symmetrically

from the last aortic arch at the level of the larynx anlage, and course downward along the trachea, diverging somewhat caudally and dorsally, the left being a little more dorsal than the right. In the region of the stem bud the left artery lies laterodorsally, the right laterally. Later (embryo of 11 mm.) the right vessel bends ventrally to avoid the apical bud, distal to this again lying lateral and then laterodorsal to the stem bronchus, while the left lies at first laterodorsal and then dorsal (see also Fig. 345). Still later the recession of the heart influences the course of the arteries; these no longer run caudally alongside the trachea, but approach the lungs more and more from the ventral side, and accordingly become bent around the bronchial tree until its branches prevent a continuation of the process. The first of these branches is on both sides the first ventral bronchus, the right apical bronchus, being always situated dorsal to the artery, having no such effect upon it.

The pulmonary veins form at first a single stem opening into the atrium (see the chapter on the development of the heart). Narath observed it coming out of the angle of bifurcation of the trachea in an embryo of 7 mm. (Fig. 348). In an embryo of 11 mm. there was a main vein on each side, situated ventromedially to the stem bronchus, and opening into it a transverse vein from the first lung tier (compare also Fig. 345, from His). By the common stem being taken up into the wall of the left atrium, all four principal veins finally open directly into the atrium. The course of the veins is also influenced by the recession of the heart; the vein from the upper lung tier is forced to descend, the main stems become partly bent around the stem bronchus and their proximal portions pass transversely to the heart.

The situation of the pulmonary veins ventromedially to the stem bronchus is determined by the heart, according to Flint, and their position again explains the dorsolateral course of the arteries. Flint, however, ascribes to the arteries no importance in determining the arrangement of the bronchial branching. Ontogenetically they certainly have no such influence, since the first lateral bronchi are formed before the arterial stems appear (Narath).

A number of important questions cannot be settled from the study of human embryos, partly because the necessary material is not yet available and partly because the questions are not to be settled by what takes place in the highly modified human lung alone. The modification is due principally to the shortening of the trunk (G. Ruge); the human lung is exceptionally short and broad, and consequently the stem bronchus is so overshadowed in the adult lung by the very long and strong branches, especially by the ventral bronchi, that it was for a long time believed that the branching was of the dichotomous type. The available

embryonic material suffices to demonstrate the surpassing rôle of the stem bronchus during development; it also shows that the principal branches are formed not dichotomously but monopodially. The stem bronchus is throughout a continuous structure, whose undivided tip keeps on growing, while the lateral bronchi appear at some distance from it. Nevertheless, according to Narath, the stem bud always takes part in the formation of the lateral branches; the lateral bud always arises in its territory, and this is true not only for the stem bud, but also for the terminal buds of each lateral branch, and therefore for the entire branching. However, Narath did not study older stages with more than the fourth order of branches; for the later ones the

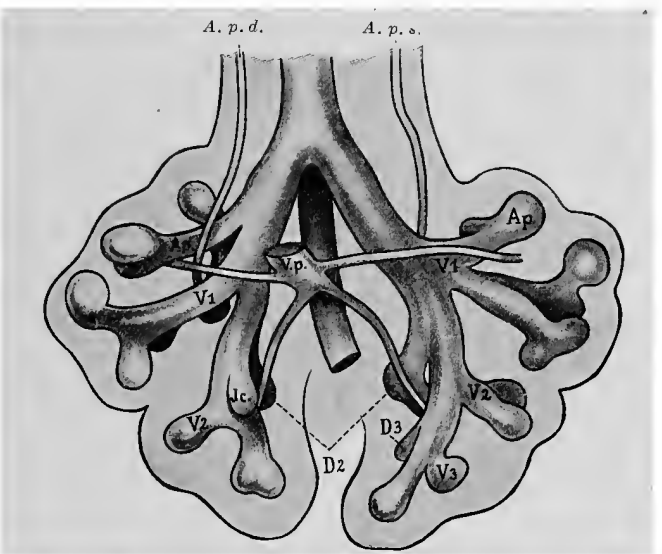


FIG. 345.—Anlage of the lung of embryo N (10.5 mm.), seen from in front with arteries and veins. (After His, 1887.) *A. p. d.* and *A. p. s.*, right and left pulmonary artery; *V. p.*, pulmonary vein. The remaining lettering as in Fig. 343. × 50.

occurrence of equal or unequal dichotomous divisions or of division even into three has been generally accepted (Kölliker, Merkel, Flint). These smaller branches, however, are so greatly under the influence of their surroundings that probably no very great importance is to be assigned to these departures from the main type. Indeed, such twigs, formed dichotomously, do not remain symmetrical (Flint). From Narath's conception of the branching certain further consequences relative to the significance of the stem bronchus follow. For only in the formation of the ventral bronchi does the stem bud participate, the dorsal bronchi and the ventral accessory ones, including the infracardial bronchi, arise from the stem bronchus frequently only after the formation of the corresponding ventral ones, or from the roots of the latter,

and, at least in some cases, proximal to these, so that they are separated by them from the stem bud. Narath assumes, on the basis of comparative observations, that all these bronchi are primarily branches of the ventral ones and that they have secondarily become displaced on to the stem bronchus. This view is accepted by Blisnianskaja, while d'Hardivillier and Flint, for example, advocate the equivalency of all branches passing off in the principal directions and deny a migration of them. According to this the stem bronchus as well as the stem bud possesses a capability for branch formation. Narath's conception of monopodial branching is, accordingly, somewhat different from that of the remaining authors; it is monopodial with acropetal development of the lateral buds. A final statement on this question can hardly be given here; indeed, it cannot be given on the basis of development alone.

As already stated, Aeby assigns a special significance to the right apical bronchus, which he terms the *eparterial bronchus*. Its development and comparative anatomy show, however, that it is the first dorsal bronchus; the "crossing" of the stem bronchus by the artery distal to it does not occur in the lower mammals and occurs late ontogenetically, being dependent on the degree of recession of the heart (Narath).[34] More difficult of explanation are the relations on the left side. Most authors (most recently Pensa, 1909) assume either a lack of the corresponding bronchus of the left side or (d'Hardivillier) its degeneration. According to Narath, who derives the dorsal from the ventral bronchi, the left apical bronchus is possibly a true dorsal bronchus which, from some cause or other, perhaps the course taken by the arteries (the aortic arches and the ductus Botalli, which, indeed, are generally made responsible for the asymmetry of the first lung tier), has not been able to migrate on to the stem bronchus and, on account of the course of the left pulmonary artery, then arises from the ventral bronchus far from its origin. With this explanation Blisnianskaja agrees. If this be the case, the upper lobe of the left lung is equivalent to the upper and middle lobes of the right. At all events, the idea of a special "eparterial" group of bronchi cannot be maintained.

In the embryonic lung the abundance of connective tissue is very striking; the intervals between the relatively widely sepa-

[34] Flint (1906) identifies the right apical bronchus, which arises from the trachea in the pig, as the first lateral bronchus (a ventral bronchus according to the nomenclature used here), and sees in it the sole representative of the first lung tier, which is completely wanting on the left side. However, the course of the arteries is not sufficiently established and, furthermore, the question is not to be settled by what occurs in the pig, which in this respect is certainly not a primitive form.

rated branches of the bronchi are filled with loose mesodermal tissue. This in the immediate vicinity of the epithelial tubes arranges itself concentrically around them and is here somewhat richer in cells than in the middle region between the bronchial rami (Fig. 346). With the progress of the bronchial branching the end buds become gradually smaller; in the fourth month they have, according to Kölliker (quoted by Merkel, 1902), a diameter of 0.18 to 0.27 mm., in the beginning of the fifth month they measure only 0.09 to 0.13 mm., with a maximum of 0.15 mm. At about this time the lobules appear as the result of an increase of the embryonic connective tissue in the intervals between the areas of the bronchioles; the lobules in a fetus of 20 weeks have an

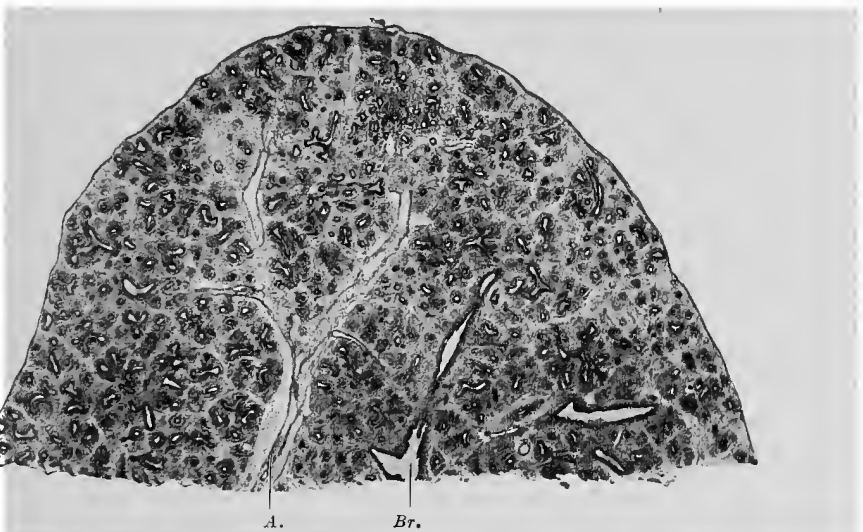


FIG. 346.—Section through the lower lobe of the right lung of a fetus of 100 mm. vertex-breech length taken at right angles to the dorsal surface. *Br.*, bronchus; *A.*, artery. × 20.

average diameter of 0.25 mm., according to Merkel (1902). At this stage of development the transverse sections of the larger branches are stellate, "the largest ones are lined by a ciliated epithelium. The cartilage plates in their walls do not extend beyond the first branches, nor do the gland anlagen. The muscles are distinctly recognizable from the surrounding mesodermic tissue." At the end of the sixth month the ends of the finer bronchi have a diameter of only 0.056 to 0.067 mm. and are very closely packed; they may already be termed alveoli (Kölliker). Their epithelium is low and the connective tissue in their immediate vicinity is still very rich in nuclei, although its quantity is on the whole greatly reduced. The cartilage formation extends in the sixth month far into the bronchial twigs, but the glands are still confined to the largest trunks (Merkel).

According to Kölliker (quoted by Merkel), the further development takes place in the following manner: "The formation of the air-cells and smallest lobes, beginning in the sixth month, is completed only in the last months of pregnancy, for while the air-cells of the mature fetus are scarcely greater than in the sixth month, and measure only from 68 to 135 μ, even in the lungs of new-born children who have already breathed the lobes themselves increase very markedly in size, so that the secondary lobes, which have a diameter of only 0.65 to 2.23 mm. in an embryo of six months, measure 4.5 to 9.0 mm. and over in the new-born child." The formation of new branches is, however, according to Merkel, scarcely to be followed in the later months, on account of the abundant foldings of the alveolar walls.

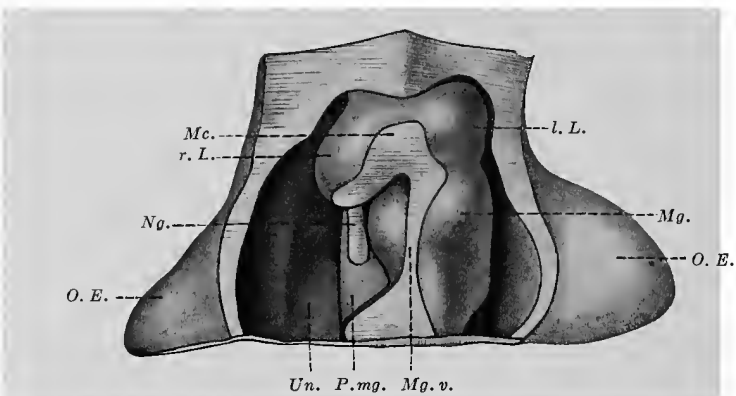


FIG. 347.—The mesodermal anlage of the lungs of an embryo of 5 mm. (Normentafel No. 20). (After Broman, 1904.) The epithelial anlage, according to Broman, is almost identical with that shown in Fig. 341, except that it is more asymmetrical and the left lung is directed even a little cranially. *r. L.*, *l. L.*, right and left lung; *Mc.*, posterior mesocardium; *Mg.*, stomach; *Mg. v.*, ventral mesogastrium; *Ng.*, accessory (mesolateral) mesentery; *O. E.*, upper limb; *P. mg.*, plica mesogastrica; *Un.*, mesonephros. × 35.

Elastic tissue is relatively late in making its appearance in the lung, according to Linser (1900), whose results, according to Merkel, agree essentially with those of Lenzi (1898). Already recognizable in the vessels in the third month, it appears at the beginning of the fourth month in the largest bronchi and increases slowly in amount; in the middle of the fifth month its fibres first appear in the alveoli, and in the seventh they occur free in the stroma. The tissue does not stain as deeply as it does later on, and is to be regarded as young, immature elastic tissue, which becomes mature a few weeks after birth under the influence of use. At this time, too, an enormous increase in the number of fibres takes place.—The pulmonary arteries, which possess the typical structure before birth, afterwards come to resemble the pulmonary veins, owing to a reduction of their tunica media, the elastic tissue in the walls of the veins becoming increased in amount.

The formation of the lobes of the lung was first considered by Aeby and was first worked out by Narath. Their development in the human lung has been described principally by Blisnianskaja, although some important figures of very young stages have been given by Broman (1904).

Aeby defines a lung lobe as follows: "A true lobe is never supported by more than a single lateral bronchus and therefore includes no portion of the stem bronchus." The "lower lobe" of the lung which contains the stem bronchus and most of the branches, without showing any corresponding markings on the surface, is termed by Aeby the "lung stem." Soon after the formation of the first lateral bud in the embryo, each bud becomes marked out upon the surface of the mesodermal anlage of the lung. This is a thick growth of mesoderm which projects on each

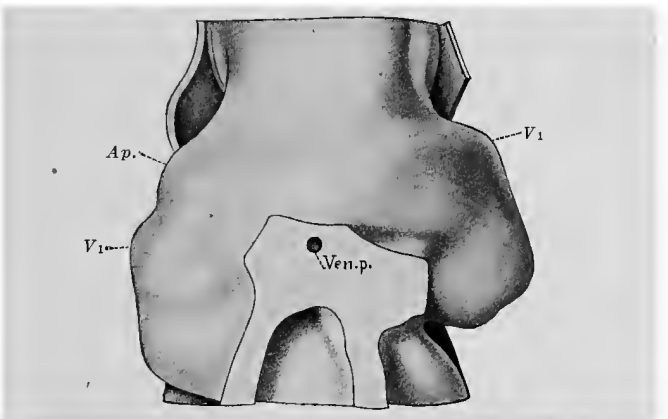


FIG. 348.—Mesodermal anlage of the lung of the embryo Chr. 1 (7 mm.; compare Fig. 342). (After Narath, 1901.) *Ven. p.*, pulmonary vein. The remaining lettering as in Fig. 342. × 100.

side into the cœlom (see Vol. I, Chapter 13) and surrounds the epithelial pulmonary sack, surpassing it in volume, however, many times. At first, before the development of the lateral bronchi, the surface of this anlage is smooth and rounded (Fig. 347; for still younger stages see Broman, Figs. 144 and 146 for a 3.4 mm. embryo, and Figs. 156, 158, 160, and 162 for a somewhat further developed embryo of 3 mm.); later it becomes almost mulberry-like, since not only the buds of the first lung tier (Fig. 348), but soon also those of the following tiers produce elevations on the surface (Figs. 349 and 350). Only the youngest part of the lung appears for a time as the lung stem in Aeby's sense. With the development of the buds the mesoderm over their tips gradually diminishes in quantity, although the branches continue to be imbedded in an abundant mesoderm. A series of lateral and a series of dorsal elevations are especially marked, and after these

the infracardial elevation. "Each primary elevation then becomes again divided into several secondary elevations[35] by the budding of the bronchial bud which it contains, and so the process goes on until the pulmonary wings become covered with fine granules. . . . With the growth of the lung these gradually disappear and the surface usually becomes smoother" (Narath). Only the first-formed furrows persist (Figs. 351 and 352), probably on account of the rapid and extensive growth of the first bronchi. Consequently in man only the first lung tier finally takes part in the formation of the lobes.

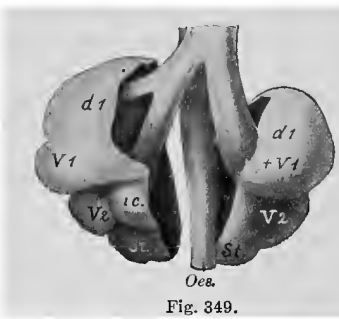


Fig. 349.

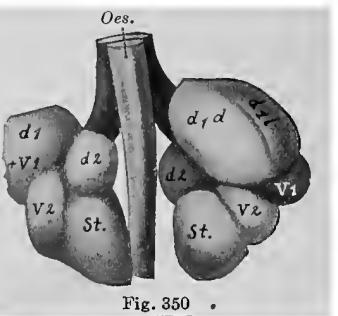


Fig. 350.

FIGS. 349 and 350.—Mesodermal anlage of an embryo of about 13 mm. seen from the ventral and the dorsal surface. (After Blisnianskaja, 1904.) *Oes.*, œsophagus. The remaining lettering (added by the present author) as in Fig. 342; in the right apical lobe (d_1) a subdivision into a dorsal and a ventral (*d* and *v*) portion is indicated. × 25.

Fig. 351.

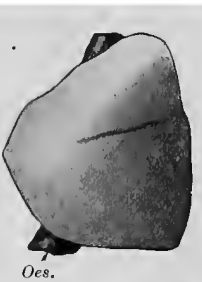


Fig. 352.

FIGS. 351 and 352.—Lungs of an embryo of about 17.5 mm. seen from the right and from the left. (After Blisnianskaja, 1904.) *Oes.*, œsophagus. × 12.

The arrangement of the lobes in animals and also a number of human variations, as well as the embryonic arrangement of the lobes, can be referred to a schema given by Narath (Fig. 353), in which the boundaries of the lung tiers (principal grooves) and those between the dorsal and ventral zones (accessory grooves) are shown as boundaries of the lobes. The most frequent variety is probably, however, the occurrence of a right *infracardial lobe,* which owes its existence to a similar process taking place on the medial surface and base of the lung. The lobes, as well as the bronchi, are, however, greatly reduced in man, in correspondence with the shortening of the trunk and the appoximation of the heart to the diaphragm (Ruge). As regards the corresponding pleural space see Vol. I, p. 547. The separation of a lobe from the right apex by the vena azygos is a

[35] To be seen in the upper lobe in Fig. 350.

variation that has nothing to do with the formation of the bronchial tree, but is rather to be explained as an adaptation of the lung to the space at its disposal (Narath, Bluntschli, 1905). The complete separation of portions of the lung, occasionally observed, is to be referred to disturbances in the early embryonic stages of development (Hammar, 1904).

Blisnianskaja has given some data regarding the evolution of the form of the lung as a whole. The form of the embryonic lungs is especially influenced by the great size of the heart; what are later the medial surfaces are first directed ventrally, and the

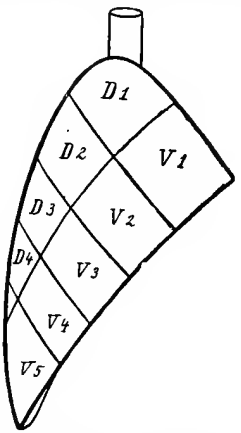


FIG. 353.—Schema of the lobation of the lung. (After Narath, 1901.) *D* and *V*, dorsal and ventral lobes.

lateral ones dorsally. The lungs are at first relatively more developed in what is later the dorsoventral (in the embryo approximately transverse) diameter than in the transverse (in the embryo almost sagittal) one, a condition that recalls what occurs in lower forms (apes). The same holds for the position of the base of the lung, which at first is much more sloped than it is later (compare Figs. 351 and 352). The lungs are drawn out almost to a point, which forms the lower and posterior pole. In the third fetal month they gradually assume the proportions seen in the adult.

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XVIII.

DEVELOPMENT OF THE BLOOD, THE VASCULAR SYSTEM, AND THE SPLEEN.

By C. S. MINOT, H. M. EVANS, J. TANDLER, and F. R. SABIN.

I. THE ORIGIN OF THE ANGIOBLAST AND THE DEVELOPMENT OF THE BLOOD.

By CHARLES S. MINOT.

Introduction.—The number of papers upon the development of the blood is large, but the majority of them have been written from the clinical standpoint and they often leave much to be wished for the scientific interpretation of the theme. To these clinical writings we owe a confusing nomenclature of the blood-corpuscles which, unfortunately, has become current in medical works, although it sins against every morphological principle. It unites forms which are morphologically different and separates forms which genetically and morphologically belong together, as is explained more fully in the note, p. 503, and in connection with the discussion of the development of leucocytes. Under these conditions it becomes unavoidable to discard almost entirely the current nomenclature and to replace it by a new one. The new nomenclature is in part taken over from others, in part proposed by myself. It at least corresponds to the morphological demands.

The following exposition is based chiefly on the investigations of four morphologists,—W. His, O. van der Stricht, J. Jolly, and F. Weidenreich,—to whom we are indebted for the greater part of our present comprehension of the problem of the blood. Of further importance is the just-published (March, 1909) memoir of Maximow (Arch. f. mikr. Anat., vol. lxxiii, p. 444), who studied the development of blood especially in rabbit embryos. Rückert and Mollier,[2] in Hertwig's "Handbuch," have given a detailed account of the early development of the angioblast in all classes of vertebrates. The value of this work is very high, and for that reason we regret very much that they have not included the cytomorphosis of the blood-corpuscles within the limits of their account. Although I am unable in many cases to adopt the point of view of the clinicians as my own, yet I have collected from their writings many data.

1. The Angioblast.—Comparative embryology teaches us that the first blood-vessels appear upon the yolk-sac collectively and at one time. They form a unit anlage, which we call briefly the angioblast, according to the suggestion of His. It must, however, be immediately mentioned that several investigators, like Maximow in his latest paper, derive the blood-vessels directly from the mesoderm of the embryo. In fact, we can assert the complete precocious independence of the angioblast from the mesoderm proper only as highly probable. The angioblast lies originally immediately upon the yolk and forms a network that can be recognized just after the first appearance of the anlage. The mesoderm, *sensu strictu*, forms a continuous layer which lies above the anlagen of the vessels and comes into direct contact with the yolk only in the gaps of the vascular network. According to the majority of observations the angioblast appears to be split off, in all vertebrates, directly from the yolk. It is very difficult to decide whether the

[1] To Professor Mall I am specially indebted, for he has had the kindness to lend me extremely valuable material from his embryological collection.

[2] Rückert und Mollier: Die erste Entstehung der Gefässe und des Blutes bei Wirbeltieren, Hertwig's Hdbch. vergl. Entw. Wirbeltieren, vol. i, p. 1910–1278.

angioblast is to be interpreted as belonging genetically to the middle germ layer or as a derivative of the entoderm. The views as to these interpretations are very divergent, but the fact remains that the angioblast becomes independent very early and is the first tissue of the embryo to exhibit an unquestionable differentiation and sharp limitation. It must be especially emphasized that the vascular anlagen do not develop in common with the mesoderm, or, if one prefers, with the remaining mesoderm. I incline strongly to the opinion that the mesoderm is formed first and that the angioblast, added later, forms itself, not through transposition and transformation of mesodermic cells already present, but from cells which separate from the yolk, or from the layer of yolk cells, and form a reticulate grouping of themselves between the middle and lower germ layers.

The angioblast probably maintains its complete independence throughout life. In other words, it is probable that the endothelium of the blood-vessels (and of the lymph-vessels) and the blood-cells at every age are all direct descendants of the primitive angioblast. Unfortunately, our present knowledge does not allow us to express an opinion on this point with absolute confidence. Thus, we find that Maximow (Arch. f. mikr. Anat., vol. lxxiii, p. 511–515) attributes the formation of new vessels and of new mesamœboids, not to the angioblast, but to the mesoderm proper. The most recent American observations speak against Maximow's view.

The differentiation of the angioblast in amniota may be summarized as follows: The network consists originally of cell cords, which soon become hollow. According to many observations the cavity may be bounded at first on its under side only by yolk. The angioblast cells transform themselves in part into endothelial cells, in part into new blood-cells. The endothelium arises from the peripheral layer of the cords; blood elements, on the contrary, from the more centrally placed cells. Only the endothelium forms an uninterrupted network; the blood-cells form scattered clusters, the so-called blood-islands. These consist of cells which are not separated by cell walls either from one another or from the neighboring endothelium. Very often, perhaps always, one finds the lumen of the vessel below (entad) the blood-islands, the cells of which hang down in a cluster from the upper surface of the vessel. In the majority of amniota, the blood-vessels arise in a limited space, which surrounds the embryo and covers only the upper surface of the yolk. This space is the *area vasculosa*. In man, however, the area covers the whole yolk from the start. The area vasculosa, studied in fresh specimens, can be recognized in many amniota by the red color of the blood-islands. This color corresponds to the beginning of the development of hæmoglobin. Soon the cells of the islands separate from one another and become free. They are the primary blood-cells, or, better, the primitive mesamœboids. Very often the first-formed cells are quite large; nevertheless, they possess the ability to wander out from the vessels, giving rise in this way to the giant wandering cells which one can observe in very young embryos, as, for example, those of the chick. The large primary cells become gradually smaller by repeated division until they reach the condition which I regard as the rejuvenated stage of the blood-cells, with which the cytomorphosis proper begins. The mesamœboids are round cells with relatively large nuclei, which are approximately round. The nucleus is surrounded by a thin layer of protoplasm which, on account of its slight thickness, has often been overlooked. The nucleus has a distinct reticulum, the nodes of which are thickened in part, forming so-called plasmasomes. The protoplasm is finely granular. Cells with these distinct characteristics occur in all vertebrates, but are restricted to early embryonic stages, and have not, up to the present time, been observed in adults. The cells in question multiply in the blood by mitotic division. Their bodies soon become larger, and thus arise colorless cells which continue to divide. Their descendants develop in different ways, in part retaining the embryonic habitus, and in part transforming themselves into red cells—erythrocytes. It must be further noted that in relatively late embryonic life the undifferentiated mesamœboids in part develop into genuine leucocytes.

The primitive mesamœhoids are the ancestors not only of all blood-cells, hut also, as Maximow has demonstrated, of other cell forms which occur in the connective tissue of the adult. Recent morphological investigators of the blood consider the conclusion secure that red and white hlood-corpuscles have the same origin, or, in other words, that they arise monophyletically. Especially illuminating are the investigations of Maximow[3] and Frau Dantschakoff[4] on this question.

The majority of emhryologists are of the opinion that the colorless mesamœboids remain throughout life in order to serve as a permanent source of both red and white hlood-cells. Since they can move freely, they can alter their distrihution in the hody. In mammals the multiplication of the primitive mesamœhoids during the earliest development occurs only in the yolk-sack; later it takes place in the circulating hlood; still later in the fetal liver and lymphoid organs; and, finally, in the marrow of hones, which serves as the permanent site of blood formation. Up to the present time no conclusive proof has heen hrought that the cells in question arise autochthonously in the liver or lymphoid organs or hone-marrow. Therefore, emhryologists incline to the opinion that we have to deal merely with the accumulation of immigrant cells. In other words, according to the present view all the cellular hlood elements are direct descendants of the primitive mesamœhoids. That this view is secure beyond all douht cannot, however, he asserted.

The development of human blood still awaits a thorough investigation. The observations at present available are in great part—though not exclusively—more or less incidental to other researches. We find data, first, in descriptions of the development of certain organs, especially the yolk-sack, the liver, and the bone-marrow; secondly, in more extended articles on blood development. The number of such articles is very large, but they are chiefly occupied with the phenomena as observed in various animals. Schridde has studied the blood development in nine young human embryos and has reached conclusions which cannot easily be brought into agreement with other apparently reliable observations. Unfortunately, his research is known to me only through his preliminary notice of 1907 (Verh. deutsch. pathol. Ges. für 1907, p. 360–365). Therefore a critical discussion of his work is excluded.

We possess at present two comprehensive memoirs, in which the previous literature—so far as it concerns the red hlood-corpuscles of vertehrates—is extensively considered and critically discussed. The memoir of Weidenreich[5] appeared in two parts, of which the first deals with the form and structure of red corpuscles, while the second describes the immature forms and the origin and transformation of the colored corpuscles. Weidenreich strives to give a unified summary of the results already ohtained. The memoir hy Jolly[6] offers us not only the results of an excellent comprehensive investigation of the cytomorphosis of the blood-cells, but

[3] Maximow: Arch. f. mikr. Anat., vol. lxvii, 1906, p. 680–757, and vol. lxxiii, 1909, p. 444–561; Folia Hæmatol., vol. iv, p. 611–626; Verhandl. Anat. Ges., vol. xxxii, p. 65–72.

[4] Wera Dantschakoff: Entwick. d. Blutes b. Vögeln, Anat. Hefte, vol. xxxvii, p. 471.

[5] Franz Weidenreich: Die rothen Blutkorperchen, I, Ergeb. anat. Entw. Ges., vol. xiii, 1905, p. 1–94; II, *ibid.*, vol. xiv, 1905, p. 345–450.

[6] J. Jolly: Recherches sur la formation des globules rouges des mammifères, Arch. Anat. microsc., vol. ix, 1907, p. 133–314.

also valuable discussions of previous investigations. The views defined by Jolly deserve special attention because they have been worked out very conscientiously. Since an exhaustive consideration of the development of the phenomena in animals lies outside the limits of our present undertaking, it seems suitable to recommend the memoirs of Weidenreich and Jolly as excellent sources for the reader who seeks exact literary data.

2. Origin of the Human Angioblast.—Our knowledge of the actual facts is here very defective. We do not yet know, by actual observation, how the earliest vessels arise in man. We know merely that the angioblast appears first on the yolk-sack, and that in almost the earliest stage known to us it already occupies the whole surface of the sack. The angioblast has genuine blood-islands and grows later into the embryo presumably by the formation of sprouts. The precocious development of the human angioblast is, in all probability, closely connected with the precocious independent development of the yolk-sack. A few of the more exact data may be presented. Graf von Spee[7] observed a few islands in the wall of the yolk-sack in an ovum of 9 mm. diameter, with an embryonic shield of 0.37 mm. The yolk-sack had a diameter of 1.84 mm. Its mesoblastic covering formed irregular bunches and projections, which were especially noticeable around the pole of the sack farthest from the embryonic shield. Each of these eminences corresponded to a blood-island situated between the mesoderm and the entoderm. Keibel[8] observed similar relations in an embryo of 6 mm. $\times$ 8.5 mm. (including villi). The vascular anlagen do not occur in the immediate neighborhood of the embryo, but begin at a line somewhat removed from it. The yolk-sack of an embryo of 1 mm. (Harvard Embryol. Coll., No. 825) comprises two territories: one of these I regard as the area pellucida, because it possesses a very thin entoderm and occupies the embryonic half of the sack; the other territory, which I regard as the area opaca, has a thicker entoderm and lies opposite the embryonic shield. It is to be noted, moreover, that the vascular formation is restricted to this second territory. This case, which up to the present is unique, renders it probable that in man also the formation of the angioblast begins in a true area opaca and then spreads out toward the embryo, as occurs typically in other amniota.

It is well known that in many amniota the earliest mesamœboids are relatively large. They probably arise directly by pinching off from the yolk (entoderm), and soon thereafter they are separated from the yolk, or entoderm, by the growth of the vascular endothelium around them, by which they become enclosed in a definitive vascular space. The large primitive mesamœboids, isolated in the manner described, multiply quite rapidly and become smaller. Meanwhile the circulation has begun, and at least a part of the mesamœboids leave their place of origin. The history

[7] Graf von Spee: Arch. f. Anat. u. Entwicklungs Ges., 1896, p. 8.
[8] Franz Keibel: Arch. f. Anat. u. Entwicklungs Ges., 1890, p. 255.

of the cells has not by any means become clear to us, for it still remains uncertain whether they all pass through the same transformations; but it is certain that many transform themselves into cells of very small size, with nuclei much smaller than those of the cells in the neighboring germ layers. Their protoplasm is minimum in man, so that the cell bodies form merely thin coverings for the nuclei. This process—multiplication of the nuclei and the retarded growth of protoplasm—is a general phenomenon in the earliest development of metozoa, and I have regarded it[9] as the rejuvenating process with which ontogeny must begin. If we accept this view, we may say that the mesamœboids rejuvenate much more rapidly than the other cells of the germ layers.

While we must admit that our knowledge of the earliest development of the blood in vertebrates is but little satisfactory, because it does not touch many essential points, we must add that the corresponding processes in man are, properly speaking, unknown to us.

The growth of the vessels into the embryo occurs very early. In embryo Klb.[10] (1.8 mm., 5–6 segments) the vessels have already passed into the embryonic body and lie between the visceral meso-

Fig. 354.—Three primitive mesamœboids from the yolk-sac of a human embryo of about 1 mm. Harvard Emb. Coll., series 825. × 1500.

derm and the entoderm. The same pathway between the germinal layers is followed, in all vertebrates, by the first vessels as they grow into the embryonic body. Schridde (l.c., p. 362) found in an embryo of 2.5 mm. a similar net of vessels. In human embryos of 8–10 segments the chief primitive vessels are present. They are of merely endothelial tubes.

3. The Primitive Mesamœboids of Man.—The cells in question have not yet been investigated accurately.[11] In the yolk-sack of the embryo mentioned above (H. E. C., No. 825) there occur cells which I regard as primitive mesamœboids, three of which are represented in Fig. 354. They are characterized by the largeness of their nuclei and the small amount of their protoplasm. The nuclei possess about the same dimensions as the nuclei in the neighboring mesoderm and entoderm. The karyoplasma forms a dense superficial layer and a very wide meshed net of fine threads in the interior, with a few thickenings of varying sizes and irreg-

[9] Minot: The Problem of Age, Growth, and Death, New York, 1908.
[10] Keibel: Normentafeln, Heft viii, p. 20.
[11] Compare Schridde; Verhand. deutsch. pathol. Ges., 1907, p. 360.

ular distribution. Not infrequently, however, there is a single main thickening centrally placed. The nuclei scarcely differ in structure from those of the neighboring tissues. The cell body is finely granulated, irregular in form, without a membrane, and is more deeply colored than the nuclei. I consider it probable that the cells are amœboid. Maximow [12] gives a detailed description of the primitive mesamœboids in the rabbit, to which the reader is referred because the author goes more into detail than is at present possible for the cells in man.

4. Cytomorphosis of the Erythrocytes.—The erythrocytes arise from the primitive mesamœboids, the cell bodies of which become laden with hæmoglobin and at the same time acquire a homogeneous appearance. Meanwhile the nuclei also undergo important alterations.

The development of the erythrocytes has been much studied. In the majority of the published papers one feels the lack of a scientific morphological interpretation of the observations, many authors being interested chiefly in clinical applications.

We can confidently distinguish four chief stages in the cytomorphosis of the red corpuscles, for which I propose the following designations:

1. *The mesamœboids,* the primitive or earliest colorless cells, which appear at first in the blood-spaces and arise chiefly, perhaps exclusively, by the breaking up of the blood-islands.

2. *The Erythrocytes.*—This term includes all red blood-cells which arise, probably exclusively, from mesamœboids. They are characterized by their content of hæmoglobin and the homogeneous appearance of their protoplasm. We can distinguish three stages in the genesis of the erythrocytes of mammals:

A. *The ichthyoid blood-cells,* the first form of the genuine erythrocyte, which occurs in all vertebrates and constitutes the permanent form in ichthyopsida. In the amniota, on the contrary, they represent a transitory stage of development. The cells in this stage are characterized by their content of hæmoglobin, their homogeneous appearance, and their granular nuclei.

B. *The sauroid blood-cells,* the second form of the genuine erythrocytes, which may be observed as the second stage in the developmental differentiation of the ichthyoids in all amniota. The cells in this stage differ from the ichthyoids by their smaller average diameter, and especially by their smaller, darkly staining (pyknotic) nuclei. The sauroids are atrophying cells. They represent the permanent form in sauropsida, the temporary form in mammals.

C. *Blood-plastids.*—These are erythrocytes which have lost their nuclei, and occur only in mammals.

Note.—"Mesamœboid" was originally proposed by me to designate the wandering cells which occur in the middle germ layer. The mesamœboid cells, which serve as the parent cells of the red blood-corpuscles, have been often confused with genuine leucocytes, and this has hindered the progress of hæmatology. The expressions "ichthyoid" and "sauroid" are in themselves not new, but the proposed application of them is new. The term "erythroblasts" has often been used in the sense of our ichthyoid cells, although in these we have to do with red blood-cells already differentiated. Current usage frequently restricts the term to the embryonic forms of the corpuscles in mammals. The mature red corpuscles of amphibia, for

[12] Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 464.

example, no one ventures to designate as erythroblasts, although they are homologous with the so-called erythroblasts of mammals. "Erythroblast" was introduced by Löwit to designate the colorless cells which, as the preliminary stage of red cells, are appropriately so called. For the regrettable misuse of the word the clinicians are alone responsible. "Normoblast" corresponds to the sauroid cell, but is not always applied with exactly the same meaning. The choice of the term is unfortunate: first, because it seems meaningless from the comparative standpoint, and therefore unavailable; and second, because even from the present clinical point of view it is without significance. The special stage of the "normoblast" is neither more nor less normal than the earlier and later stages. Further, since the stage in question is the permanent one in reptiles, the use of "blast" is unsuitable. "Erythrocyte" is a fitting name for all red blood-corpuscles whether they are nucleated or not, whether their nuclei are pyknotic or not. The effort of the clinicians to restrict this name to the non-nucleated blood-cells of mammals can hardly be justified. At the present day one would hardly expect that red cells with nuclei should not be recognized as erythrocytes but that they should change into erythrocytes by the loss of their nuclei. It does not appear scientific to call a cell κύτος only after it has become non-nucleated. Similar considerations apply against the use of the expressions "megaloblast" and "microblast." It may be pointed out that in all tissues variations in the size of cells are encountered, and if all these variations are to be specially named the result will be an unlimited confusion in biological nomenclature. I proposed, in 1890, to call the non-nucleated blood-corpuscles of mammals "plastids." At that time I was influenced by the hypothesis proposed by Ranvier, Schaefer, and others, of the intracellular origin of the red blood-corpuscles. In spite of the fact that the progress of our knowledge has compelled us to give up this hypothesis, we may still term the non-nucleated corpuscles plastids, since the word refers to the fact that they consist of cytoplasm. This renders it possible to ultilize "erythrocyte" as a collective term for any and all red cells, as is done in the present chapter.

The essential characteristic of erythrocytes is hæmoglobin, the formation of which may be initiated earlier or later during the development of the single cell. It has long been known that the deposit of hæmoglobin may begin in the blood-islands of the area opaca. This phenomenon appears clearly in the sauropsida and has also been recognized in various mammals. In man, on the contrary, if red blood-islands occur at all, they must break up very early; as indeed, according to Maximow,[13] occurs typically in mammals, which in that respect differ from the sauropsida. In the youngest stage yet observed, the free human mesamœboids do not have any hæmoglobin.

We must assume that in man also the primitive mesamœboids multiply, and that a part of them retain the primitive habitus. While this goes on, one observes the gradual disappearance of the forms with minimal protoplasm. At the end of the first month, and from then on to birth, we find colorless mesamœboid cells of the most varying sizes in the blood-spaces and in the blood-forming organs (Figs. 357 and 359).

[13] A. Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 461.

Note.—The genetic relations of these cells to one another have still to be accurately determined. In the sauropsida there arise at first very large cells. On the other hand, we learn that the youngest cells multiply and at the same time enlarge. Further, the question arises, Are the large cells in vertebrate embryos all ancestors of the smaller cells or not? We may assume that at least a part of the cells are such ancestors.

Now, while the embryonic blood formation is going on, we may observe, especially in younger embryos, that the erythrocytes differ much in size. In later stages, as in the adult, we find that the developing erythrocytes are much more uniform. From these relations we draw the conclusion that during the developmental period both larger and smaller mesamœboids transform themselves directly into colored corpuscles. But in this connection we must not forget that deductions are less conclusive than direct observations.

The appearance of hæmoglobin causes a diffuse coloration of the protoplasm, which at the same time loses its granular appearance and becomes optically homogeneous. Since cells may be observed with varying intensities of coloration, we conclude that there is a gradually increased hæmoglobin content of the cell.

Note.—Giglio-Tos maintains that in all vertebrates the hæmoglobin arises from special granules. Weidenreich (l. c., p. 406) declares that these granules are artefacts. According to his opinion, we must assume that the hæmoglobin appears diffusely in uniform concentration, without being demonstrable in the body of the cell by any special morphological structure. We cannot yet decide whether the hæmoglobin is an exclusive or partial product of nuclear activity, as some have supposed, or not.

The cell membrane is probably developed at the same time as the hæmoglobin. At least we observe that as soon as the coloration is recognizable the periphery of the protoplasm is bordered by a distinct line. How the membrane is developed is unknown. The nuclei undergo definite alterations during the formation of the hæmoglobin, in consequence of which the cells pass to the ichthyoid type. Unfortunately, these alterations have not yet been carefully investigated.

The accompanying pictures represent some of the corpuscles from the blood,—A, of an embryo of 4 mm. (Fig. 355); B, of 7.5 mm. (Fig. 356); and C, of 9.4 mm. (Fig. 357). In comparison with the earlier stage (Fig. 354) the diminution of the nucleus at once attracts attention.

The more intense nuclear coloration of the older cells is very noticeable. The wide, clear meshes of the nuclear reticulum can no longer be seen. On the other hand, the granules are more numerous, are more deeply colored, and more rounded than before. It is further to be pointed out that there is a striking increase of the cortical layer of the nucleus. These observations may easily

be repeated on other embryos. It seems probable that, together with the diminution of the nuclei, increase of the chromatin occurs. This fundamental question, however, cannot be decided on the basis of our present knowledge.

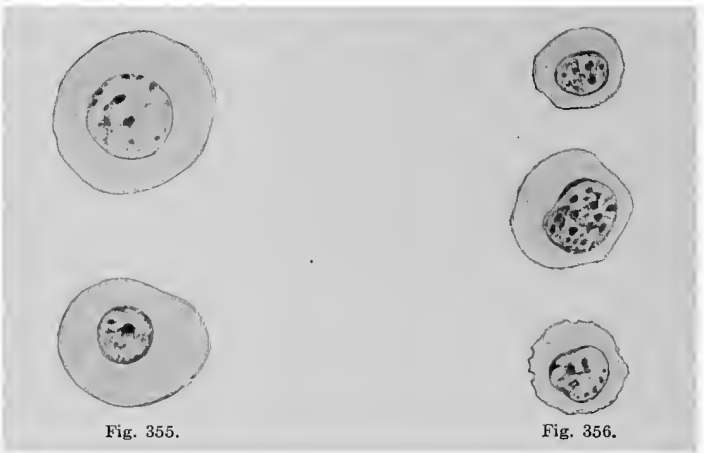

Fig. 355. Fig. 356.

Fig. 355.—Two blood-corpuscles of a human embryo of 4 mm. × 1500. Preserved with formalin, colored with alum-cochineal and orange G. Harvard Emb. Coll., No. 714.

Fig. 356.—Three blood-corpuscles of a human embryo of 7.5 mm. × 1500. Zenker's fluid, carmine coloration. Harvard Emb. Coll., No. 256.

In consequence of the changes above described, the cells reach the ichthyoid stage of their development. We have to deal not with the metamorphosis of single cells, but with a genuine cytomorphosis, since the cells continually multiply by division not only during the transformation of the mesamœboids, but also while in the ichthyoid stage. Evidently the cytomorphosis goes on through successive generations of cells.

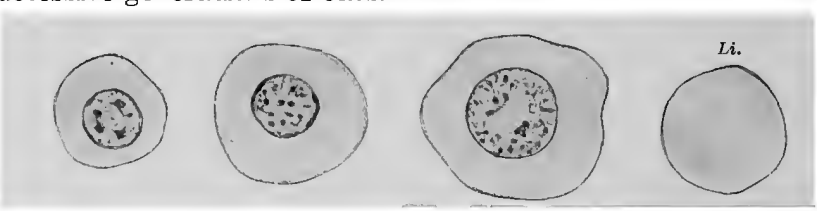

Fig. 357.—Three blood-corpuscles from a human embryo of 9.4 mm. × 1500. Müller's fluid, alum-cochineal and safranine. Harvard Emb. Coll., No. 259. *Li.* nucleus of liver-cell for comparison.

The multiplication of young blood-cells by division was ascertained by Remak in 1850, and since then has often been observed in many different vertebrates.[14] Mitoses of the ichthyoid blood-cells in the blood-vessels may be observed easily in well-preserved young human embryos. In embryos of 12 mm. the formation of

[14] J. Jolly has published an important paper on the division of blood-corpuscles in amphibia (Arch. d'Anat. microsc., vol. vi, 1904, p. 455). Jolly gives exhaustive consideration to the literature of the subject.

the blood in the liver has begun, and after this one finds either no or only exceptional mitotic red corpuscles in the blood-vessels of the body. The blood mitoses of man have not yet been studied in detail.

Bizzozero,[15] after repeatedly studying the multiplication of young erythrocytes, came to the conclusion that after very early embryonic stages the multiplication is accomplished exclusively by the division of cells already containing hæmoglobin, and in accordance with this view he denied the continued transformation of colorless cells (Löwit's erythroblasts) into colored cells. We cannot at present admit that Bizzozero was right.

The sauroid blood-cells arise by the transformation of single ichthyoids. Since, so far as is known at present, they do not multiply by division, they can increase in number only by the metamorphosis of the younger cells. The ichthyoid cells contain hæmoglobin and have a membrane, hence the further visible multiplications concern chiefly the nucleus. There occurs a steady diminution of the volume of the nucleus, and at the same time the framework of chromatin condenses and thickens; the granules or so-called nucleoli—of which the typical ichthyoid cell has several—become larger and merge with the condensed reticulum so as to become no longer observable (Weidenreich, l.c., p. 407), Fig. 358. The nucleus meanwhile becomes smoothly round, as in other mammals. In this condition it absorbs the usual coloring fluids so intensely that little or nothing can be seen of its structure (Fig. 358). Since the cell does not shrink with the nucleus, the hæmoglobin gains the space which the nucleus loses. In brief, the ichthyoid cell changes into the sauroid by pyknosis of the nucleus.

The "normoblasts" of Ehrlich are sauroid cells, but the sauroids vary much in size, a fact which Ehrlich has already pointed out (compare note, p. 504). He directed special attention to the larger and smaller forms, and was of the opinion that the extreme forms were genetically distinct. Weidenreich expresses himself positively against this opinion, justly, it seems to me. In fact, the mesamœboids in young embryos vary much in size (compare Fig. 354) and a similar unevenness prevails also among the ichthyoid cells (Fig. 357). It is further probable that the large mesamœboids, of which the majority form small cells by continual division, in small part at least develop hæmoglobin precociously and thus produce the so-called megaloblasts.

Variation of the erythrocytes is especially pronounced in quite young embryos (Kölliker, 1846) and diminishes rapidly with age. At the close of fetal life it is comparatively slight. A statistical investigation of the variations in man is much to be desired.

An observation which I have occasionally made may be interpolated here. Now and again one finds a human embryo in which the erythrocytes contain from one to three small rounded granules, which are yellowish brown and vary in size and form. They are highly refractile and have no resemblance to nuclear fragments.

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[15] G. Bizzozero: Ueber die Entstehung der rothen Blutkörperchen während des extra-uterinen Lebens. Moleschott's Untersuchungen zur Naturlehre, vol. xiii, 1888, p. 153–173, 1 pl.

These cells are especially numerous in an embryo of 6 mm. (No. 241 of Professor Mall's collection). Their significance is unknown to me.

Under pathological conditions granules may occur in the cytoplasm of erythrocytes which differ both from nuclear fragments and from the granules just described. They are unevenly fine granules, which take a basophile color. Naegeli[16] asserts that similar granules occur normally in the embryonic erythrocytes of several mammals (and also of man). I have been unable to confirm his statements.

The sauroid blood-cell changes into a blood-plastid by the loss of its nucleus. Since the change is imperfectly known in man, the following description is applicable rather to mammals in general than specifically to Homo. According to the original view of Kölliker[17] the nucleus was dissolved within the cell. According to the view of Rindfleisch[18] the nucleus is expelled. Both views have had many subsequent defenders. Jolly, l.c., gives an excellent exposition of the whole discussion. A more condensed review is given by van der Stricht.[19] Jolly reaches the conclusion that karyolysis may occasionally occur in young embryos, and is very

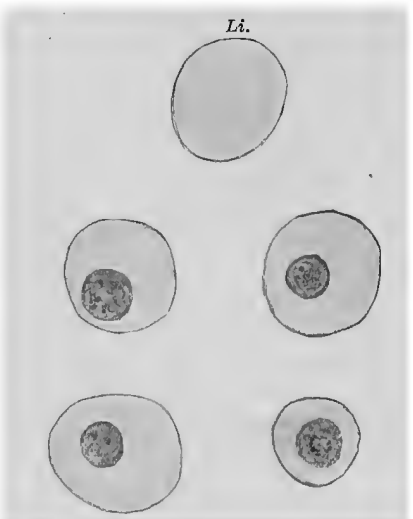

Fig. 358.—Four blood-corpuscles from a human embryo of 15.5 mm. × 1500. Coll. F. P. Mall, No. 390. *Li.*, nucleus of liver-cell for comparison of sizes.

rare, or does not occur at all, in older embyros and after birth. On the other hand, the expulsion of the nucleus is to be regarded as a normal process. The erythrocyte does not usually expel the whole nucleus at once, but in the form of single pieces which are driven out in succession.[20] Maximow,[21] however, reports that in young rabbit embryos the nucleus is expelled while still intact. It may happen that the part of the nucleus first expelled is larger than the part left behind. The expulsion may be easily observed in various phases; the phenomenon does not begin until

[16] Naegeli: Ueber basophile Granulationen der Erythrozyten bei Embryonen. Folia haematol., vol. v, 1908, p. 525.

[17] Kölliker: Ueber die Blutkorperchen eines menschlichen Embryo. Zeitschr. f. rationelle Med., vol. iv, 1846, p. 112.

[18] Rindfleisch: Ueber Knochenmark und Blutbildung. Arch. f. mikr. Anat., vol. xvii, 1880, p. 21.

[19] O. van der Stricht: Archives de Biol., vol. xii, 1892, p. 247.

[20] Man vergleiche Kostanecki, Anat. Hefte, vol. v, 1891, p. 315 and 317.

[21] A. Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 486.

the formation of blood has commenced in the liver. It occurs abundantly later in the bone medulla, but is rare in the blood-vessels of other parts of the body. Occasionally a pyknotic nucleus forms buds, which lead to the fragmentation of the nucleus and prepare for the expulsion. The expelled nuclei and nuclear fragments are, for the most part, eaten by phagocytes [22] and therefore almost never appear in the circulating blood. In passing, it may be mentioned that according to Afanassiew [23] the expelled nucleus becomes a blood-plate, an assumption which it has not been possible to affirm.

In young human embryos the blood plastids vary greatly; on the average they are larger than in later stages or in the adult. Maximow,[24] studying the rabbit, distinguishes the first erythrocytes as "primitive erythroblasts" and emphasizes the differences in their structure and that of later forms.

The early human plastids do not have the characteristic form of the definitive corpuscles, but retain a spherical shape. Gradually the cells of this type disappear, and at the same time appear

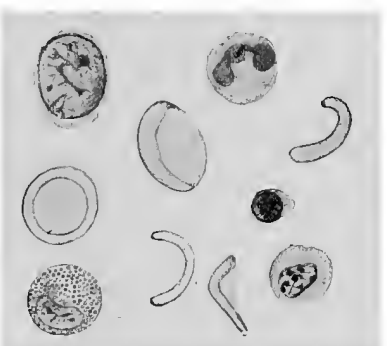

Fig. 359.—Blood-corpuscles from a blood-vessel of a human embryo of eight months. × 1500.

the small cup-shaped corpuscles (Fig. 359) which increase steadily in number. Meanwhile the nucleated erythrocytes gradually disappear from the blood, so that a little time after birth only the cup-shaped corpuscles are found in circulation.

We can observe, very early, disintegration of the erythrocytes, even of the primitive mesamœboids. Three sorts of disintegration are to be considered: 1, dissolving of the hæmoglobin and bursting of the corpuscle; 2, fragmentation; 3, vacuolization, with subsequent plasmolysis. Cells of the blood may die off in the most various stages of development. Their cytomorphosis closes with death. How far the death phenomena differ in the two cases is unknown. If the hæmoglobin is dissolved out, the erythrocyte remains as a round vesicle with or without a nucleus, as the case may be, with otherwise colorless contents and with a distinct

[22] O. van der Stricht: Arch. de Biol., vol. xii, 1892, p. 251.
[23] Afanassiew: Deutsch. Arch. f. klin. Med., 1884, p. 217.
[24] A. Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 471.

membrane. In the case of a plastid, the corpuscle swells by imbibition and assumes a round form. Although erythrocytes which have lost their hæmoglobin occur frequently in embryonic blood, yet, as might be expected, it is very rare to get sight of one in the moment of bursting. The fragmentation of the red corpuscles in the adult has long been known. It occurs also in fetal life, but has as yet been little studied in embryos. The disintegration by vacuolization has, so far as known to me, not been described hitherto,[25] and consequently may be treated somewhat more fully. So far as my observations go, this form of disintegration occurs only outside of the vessels.

Any embryologist can easily convince himself that all forms of blood-cells occur in the mesenchyma of young embryos. I have

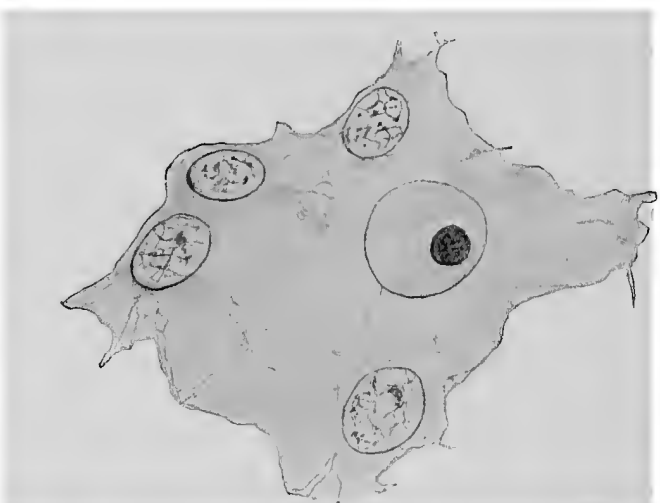

FIG. 360.—An erythrocyte lying free in the mesenchyma. × 1800.

observed this distribution not only in man, but also in the pig, sheep, rabbit, cat, etc. There are no exceptions. Generally speaking, the forms of the corpuscles in the mesenchyma are identical with those in the vessels of the same embryo. Fig. 360 represents an erythrocyte lying free in the mesenchyma in the neighborhood of the forebrain of a human embryo of 6 mm. The red cells are widely scattered, but occur most frequently near the vessels. Sometimes they lie singly, and sometimes there are several together. The primitive colorless cells show a similar distribution in the mesenchyma. They are the so-called "primitive wandering cells" to which attention has been directed by several

[25] We repeatedly find in the literature mention of wandering cells with vacuolated protoplasm, but they seem not to have been recognized as degenerating cells.

investigators, and especially by Saxer.[26] In my opinion, the conditions can be interpreted only on the assumption that all the free cells have wandered from the blood-vessels into the mesenchyma. I recognize no basis for assuming that we have to do with a progressive development in the mesenchyma, but this assertion is not equivalent to an absolute denial of such a possibility. It must be added that I have not yet been able to find evidence of the metamorphosis of mesenchymal cells into wandering cells. This metamorphosis has been especially emphasized by Maximow[27] and others, as a main part of their theories of the development of blood.

In older uninjured embryos we find that there are still mesamœboids, by no erythrocytes. How do the latter disappear? We can answer that in part, at least, by degenerative vacuolization (compare below). The majority, according to an hypothesis I have formed, are removed by the lymph-vessels. This hypothesis is merely the application to mammals of a discovery made by Eliot R. Clark. Clark[28] observed, in living tadpoles, that erythrocytes which had passed out from the blood-vessels were overgrown by sprouts developing from the lymph-vessels, and thus brought into the cavity of the vessel, in which they then moved along centripetally. In support of this hypothesis may be mentioned the fact that in the placental chorion of man—which, as is well known, has no lymph-vessels—erythrocytes occur in the connective tissue up to the time of birth.

It has long been known that strikingly large free cells appear in the mesenchyma of the chorion. They are pictured in my "Human Embryology."[29] Hofbauer[30] has recently again called attention to them. Grosser[31] mentions these cells—"*deren Bedeutung aber noch unklar ist.*" Renewed investigation has led me to the conclusion that we have to do with erythrocytes which have gotten into the mesenchyma and, remaining there, have swollen by imbibition and are undergoing degeneration by vacuolization of their protoplasm. Fig. 361 represents eight of the cells referred to, from the chorion of an embryo of 15 mm. *a* is an unquestionable erythrocyte, although it exceeds somewhat in diameter the average red cells in other vessels. *b* is also an erythrocyte, but distinctly larger. We can explain the appearance of these cells by the assumption of imbibition, in which the nucleus has

[26] Saxer: Anat. Hefte, vol. vi, 1896, p. 347.

[27] A. Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 502.

[28] E. R. Clark: Association of American Anatomists, Baltimore, 1909. See Anatomical Record, vol. iii, 1909, p. 183.

[29] Minot: Human Embryology, Fig. 190, p. 330.

[30] Hofbauer: Die menschliche Placenta, 1907.

[31] Grosser: Eihäute und Placenta, Wien, 1909, p. 224.

participated. Cells similar to *a* and *b* are easily found, but the majority of the cells in the mesenchyma have the habitus of *d* and *e* and exhibit the beginning of vacuolization. *f, g, h* are three cells which exhibit three stages of disintegration of the protoplasm. Since I have found similar cells in a considerable number of placentas, I draw the conclusion that they are constant and normal. I regard the interpretation of the pictures unattackable as proof of progressive degeneration. The cells *g* and *h* deserve special attention, because they look almost as though they were furnished with pseudopodia.

Now, we find similar denegerative appearances when we study the erythrocytes in the mesenchyma of the embryo. Hence we cannot avoid the conclusion that the corpuscles which have immigrated into the embryonic mesenchyma are subject to autolysis. I

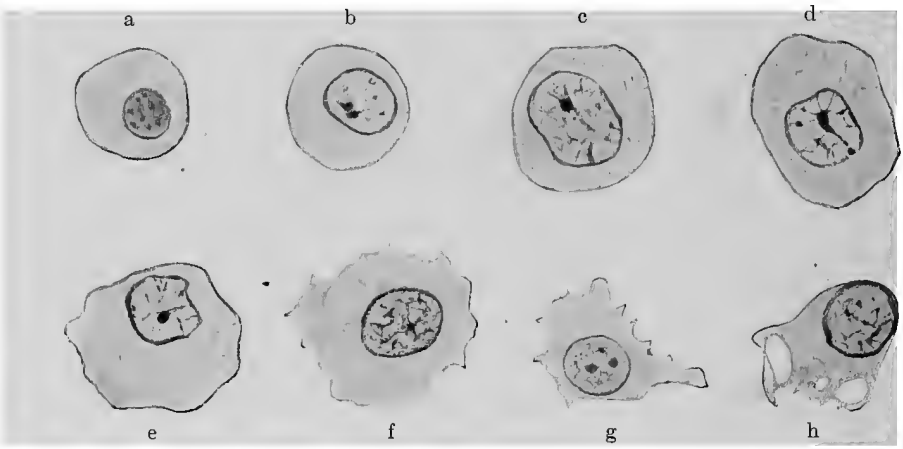

FIG. 361.—Red blood-cells from the placental chorion of a human embryo of 15 mm. Coll. F. P. Mall, No. 350. a, from a blood-vessel; b–h, from the mesenchyma. × 1500.

believe that I recognize among the degenerating cells the so-called pseudopod-bearing cells which Maximow and others have described. Important, also, is the observation that the mesamœboid cells may degenerate in a similar way in the mesenchyma.

5. HYPOTHESES CONCERNING THE FORMATION OF ERYTHROCYTES.[32]—According to Hayem,[33] the red cells are developed from blood-plates, which he further calls hæmatohlasts. Pouchet (1879), Arndt (1881), Poljakoff, and others have defended Hayem's hypothesis.

The intracellular origin of hlood-plastids has been asserted hy Ranvier,[34]

[32] A much more extended analysis of the subject is presented hy Jolly. Several older and often amusing hypotheses are mentioned by Feuerstack, Zeitschr. f. wiss. Zool., vol. xxxviii, 1883, p. 136.

[33] Das Hauptwerk Hayem's Du Sang erschein 1889. Darin stellte er die Ergebissne seiner früheren Untersuchungen zusammen.

[34] Ranvier: Du Développement et de l'accroissement des vaisseaux sanguins, Arch. de Physiol., vol. vi, 1874, p. 429–450.

Schäfer,[35] Minot, and others. This conclusion was drawn from the observation of degenerating capillaries, which retain in their cavities blood-corpuscles and fragments of corpuscles after they have lost their connection with the active vessels. Ranvier named the degenerating capillaries "*cellules vasoformatives.*" Vosmaer (1898) [36] made the true nature of these structures clear by his investigation of the embryonic great omentum. His discovery has been confirmed and extended by Renaut (1901), Pardi (1905), Jolly (1906), and others.

According to several hypotheses, the blood-plastids arise from the nuclei alone. Retterer [37] thinks they arise from the nuclei of connective-tissue cells. According to Hubrecht (1899), blood-corpuscles are formed in the placenta of Tarsius by the production of a colored mother cell which expels its nucleus, the nucleus becoming a red corpuscle. According to Poljakoff (1901) red disks are formed from the nuclei not only of connective-tissue cells, but also of leucocytes.

Since Neumann discovered (1869) nucleated red cells in the medulla of bones, there have been numerous hypotheses as to the method by which they changed into plastids. Many investigators have sought to recognize remnants of nuclei, or even entire nuclei, in the corpuscles after their transformation. In most of these cases one has to deal with artefacts.[38] Malassez (1881, 1882) lets the plastids arise as buds from the cytoplasm of red cells. According to Engel (1899) the red cell divides itself into a nucleated and a non-nucleated part; the latter is the definitive corpuscle. Janosik's hypothesis resembles that of Malassez. That the nucleus normally disappears by intracellular karyolysis has been a common opinion.[39]

An especially divergent account of the blood development in the yellow medulla of bone is given by Fr. Freytag.[40] He thinks that special cords arise by the degeneration of fat-cells. Into these cords blood-cells wander and there degenerate, their nuclei undergoing repeated fragmentation until they are broken up into small particles. The particles divide further until they become invisible, and these invisible remains of the nuclei he calls "nuclear units." These units gather to form new granules, the granules flow together and form genuine new nuclei, and finally new protoplasm is formed around each nucleus. The final member of the series is a new erythroblast. The author does not state how he has been able to follow the history of his invisible units, and does not show how he distinguishes the phases of evolution from those of involution of the blood-cells. Even if we admit the accuracy of these observations, they would still remain, in my opinion, without demonstrative value for the author's conclusions.

Our list of the hypotheses on the formation of the blood might easily be lengthened. Since, however, the hypotheses for the most part have only a passing interest, it is hardly worth while to go into greater detail. The reader will find further information given by Jolly.[41]

6. Cytomorphosis of Leucocytes.—The primitive mesamœboids (primary wandering cells of Saxer, Maximow, and others) are also parent cells of the leucocytes, according to the conclusion drawn by Jolly and Weidenreich. Both of these authors have not only studied the literature conscientiously, but have also

[35] Schäfer: Note on the Intracellular Development of Blood-corpuscles in Mammals, Proc. Royal Soc., vol. xxii, 1874, p. 243–245.

[36] Vosmaer: On the Retrograde Development of the Blood-vessels, etc., Versl. Akad. Wetensk. Amsterdam, vol. vi, 1898, p. 245.

[37] C. R. Retterer: Soc. Biol. Paris, 1901, p. 769.

[38] Compare the careful discussion of Jolly, l.c., p. 180–193.

[39] See especially Pappenheim, Virchow's Arch., vol. cxlv, 1896, p. 587, and vol. cli, 1898, p. 89; also His's Archiv, 1899, p. 214.

[40] Fr. Freytag: Zeitschr. f. allgem. Physiol., vol. vii, 1908, p. 131.

[41] Jolly, l.c., p. 180–193. An excellent, clear, conscientious review of the literature on the subject.

made extensive independent investigations. While I here adopt their conclusion, I must admit that I cannot venture to express a secure judgment in this question, based upon my own experience. In a meritorious memoir Saxer [42] (1896) appeared as a defender of the view that free wandering cells (leucohlasts) arise directly from mesenchymal cells. Since then several authors have expressed their agreement with this view: for example, T. H. Bryce [43] in his investigation of the development of the blood of Lepidosiren; and, recently, Maximow [44] in several articles, and also Weidenreich.[45] I have not succeeded in finding cell forms which can be unquestionably interpreted in favor of Maximow's opinion, although I have searched in numerous human and other mammalian embryos; and I must admit that the proofs which Maximow presents do not appear to me convincing.[46] Therefore I keep, at least for the present, to the conviction that all leucocytes have a unitary origin and develop from the primitive mesamœhoids.

A series of authors have defended the thesis that the first true leucocytes develop in the thymus from entodermal cells. Maurer [47] has maintained this thesis for teleosts, and it has heen asserted for man and other mammals by Hermann and Tourneux,[48] Prenant,[49], E. T. Bell,[50] and others. John Beard [51] has appeared as a specially eager defender. Stöhr [52] opposes the thesis. Bryce,[53] Stöhr, and Hammar [54] report that the true leucocytes first appear outside of the organ, and only secondarily, hy immigration, in the thymus. The small cells which really develop in the thymus are derived, according to Stöhr, from the epithelial cells and remain epithelial cells, not heing lymphoid elements (leucocytes) at all. The question is of fundamental significance, although *a priori* it is improhable that leucocytes have a douhle origin. For the present I am much inclined to agree with Stöhr, and we are thus hrought back to the statement at the heginning of this section—the leucocytes are derived from the primitive mesamœboids.

The transformation is manifested by two principal alterations in the microscopic picture,—1, the formation of special granules in the cytoplasm; 2, modifications in the form and structure of the nuclei.

We have to consider four principal types of leucocytes:

1. The young forms without granules (lymphocytes).

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[42] Fr. Saxer: Ueber die Entwickelung und den Bau der normalen Lymphdrüsen und die Entstehung der rothen und weissen Blutkörperchen, Anat. Hefte, vol. vi, 1896, p. 347–532, Taf. xv-xxii.

[43] T. H. Bryce: Histology of the Blood of the Larva of Lepidosiren, etc., Trans. R. Soc. Edinhurgh, vol. xli, 1904, p. 435–467.

[44] Maximow: l.s.c.

[45] Fr. Weidenreich: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 849–851, 857–858.

[46] I have heen able to convince myself that Maximow is a very trustworthy observer, for I have confirmed many of his new observations by comparison with the sections in the extensive embryological collection of the Harvard Medical School.

[47] Maurer: Schilddrüse und Thymus der Teleostier, Morph. Jahrb., vol. xi, 1886, p. 129.

[48] Hermann et Tourneux: Dict. encycl. sci. méd., 1887.

[49] Prenant: La Cellule, vol. x, 1894, p. 87–184.

[50] E. T. Bell: The Development of the Thymus, Amer. Journ. Anat., vol. v, 1905, p. 29.

[51] John Beard: Anat. Anz., vol. ix, 1894, p. 476–486; also Lancet, 1899.

[52] Philipp Stöhr: Ueber die Natur der Thymuselemente, Anat. Hefte, vol. xxxi, 1906, p. 407.

[53] J. A. Hammar: His' Arch. Anat., vol. lxxxiii, 1907, p. 83.

[54] J. A. Hammar: Zur Kenntniss der Teleostierthymus, Arch. mikr. Anat., vol. lxxiii, 1908, p. 1–68, Taf. i-iii.

2. The older forms with granules—

A. The finely granular (neutrophile of Ehrlich).

B. The coarsely granular (eosinophile of Ehrlich).

C. The degenerating (basophile of Ehrlich).

1. *The young forms* probably arise directly from the primitive mesamœboids, which have become smaller by repeated divisions. This origin of the lymphocytes was positively asserted in 1891 by O. van der Stricht[55] and Kostanecki,[56] and is now very generally accepted. The number of leucocytes is also increased by their own proliferation. The lymphocytes vary extremely as to size. The large cells are probably (1) genuine primitive mesamœboids, which by division produce the small leucocytes; (2) old cells, which have developed out of the small ones.[57] The following description is restricted to the small leucocytes, *i.e.*, to the cells to which exclusively Ehrlich[58] applies the term lymphocyte. Our cells have the following characteristics: first, they have very little protoplasm, which takes a basic color and exhibits no special granules; second, the colorable substance of the nucleus forms several little masses, often with distinct corners, which are united by threads and lie, for the most part, near the surface. The centrosome in the lymphocytes of amphibia has been studied by Flemming, Heidenhain, and Klemensiewicz. Weidenreich (Arch. f. mikr. Anat., vol. lxxiii, p. 818) found the human centres double and imbedded in a lighter colored oval court situated in the endoplasm close to the nucleus.

FIG. 362.—Four small lymphocytes from normal human blood. (After Weidenreich.)

The developmental history of these cells is still incompletely known to us. That they multiply by mitotic division of the lymph-glands was first demonstrated by W. Flemming.[59] Whence they come and how they or their mother cells get into the lymph-glands is still to be determined. It is also unknown how the highly characteristic nucleus is formed.

That the lymphocytes are preliminary stages of the granular leucocytes is positively asserted by Weidenreich.[60] As it is probable that he is right, lymphocytes

[55] O. Van der Stricht: Le développement du sang dans le foie embryonaire, Arch. de Biol., vol. xi, 1891, p. 19–113.

[56] K. von Kostanecki: Anat. Hefte, vol. i, 1892, p. 313.

[57] As concerns the nomenclature, see Weidenreich, Arch f. mikr. Anat., vol. lxxiii, 1909, p. 794.

[58] Ehrlich's application of the term "lymphocyt" in this restricted sense cannot be justified. Compare Weidenreich, Arch. f. mikr. Anat., vol. lxxiii, p. 797 ff.

[59] W. Flemming: Arch. f. mikr. Anat., vol. xxiv, 1885, p. 50.

[60] And by others before him. Compare W. H. Howell, Journ. of Morph., vol. iv, p. 144; C. Benda, Arch. Anat. Physiol., physiol. Abth., 1896, p. 347; and Weidenreich, Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 861.

are here regarded as the representatives of the young stage in the cytomorphosis of white blood-corpuscles. Unfortunately, the further development of these "young" cells is hardly better known to us than their origin.

The cells which have been recognized with certainty as becoming granular leucocytes are distinctly larger than the lymphocytes. If, therefore, they develop from the lymphocytes, we must say that during the process the protoplasm and the nucleus have both grown. The protoplasm retains its capacity of basic coloration; the nucleus retains—at least at first—its round form, has in its interior a coarse reticulum with some few thicknesses, and it stains deeply. Very often the centrosome can be seen in an eccentric position alongside the nucleus, and its occurrence is probably constant. Cells of this kind occur throughout life in the medulla of bone, and are well known to histologists under the inappropriate name "myelocytes." Out of such cells the three kinds of granular leucocytes are developed.

2, A. *The finely granular leucocytes* are much more numerous than the coarsely granular, and they represent the chief developmental series of the white corpuscles. The granules in man are "neutrophile," in the rabbit "pseudo-eosinophile," and in the guinea-pig "amphophile." According to Ehrlich, the coloration of the granules changes with the age or maturity of the cells. The clinicians, for diagnostic purposes, have occupied themselves industriously with the question of the coloration of granules and have founded a doctrine of the specific quality of the granules of leucocytes based on the coloration. Up to the present, however, the proof is entirely lacking that the coloration in this case has morphological meaning, or even that it allows a deduction as to the chemical specificity of the granules.[61]

The alterations in the nuclei during the cytomorphosis of the finely granular leucocytes are very striking. The alterations begin with an elongation of the nucleus (Fig. 363), which, however, remains a unitary structure while assuming a kidney-like shape and at the same time moving into a decidedly eccentric position. The convexity of the nucleus is directed to the exterior; the concavity is turned toward the centre of the cell. In the central part of the cell lies the centrosome. By the deepening of its concavity, the nucleus becomes sausage or horse-shoe shaped and at the same time grows more slender and longer, so that the two poles of the nucleus move toward the non-nucleated side of the cell and approach one another. In the next stage the nucleus appears divided into several small pieces, which are connected by thin short or long threads. The number of pieces is usually three or four, seldom five. The form and size of the pieces is extraordinarily variable. Uniting threads may start from any point on the surface of the pieces. During this transformation of form the nucleus elongates and becomes more bent, always curving around the centrosome. The nucleus further undergoes a pronounced pyknosis, so that when it reaches the lobate condition it exhibits no recognizable structure, but stains intensely and more or less uniformly. The alterations in shape are permanent and are not transitory consequences of amœboid movement of the nucleus. We have to deal with a genuine cytomorphosis: the nucleus never

[61] Compare Fr. Weidenreich: Arch. f. mikr. Anat., vol. lxxii, 1908, p. 308–319.

turns back in its course of development. The centrosome[62] has usually two centrioles which are round or oval and usually of the same size. A single centriole occurs rarely, and probably arises by the fusion of the two normal centrioles. The centrioles are surrounded by a small clear court of apparently homogeneous material, but which sometimes shows a radiate structure. When the disintegration of the cells begins, the centrosome can no longer be seen.

The formation of the fine granules in the protoplasm may begin either as soon as the nucleus assumes its eccentric position or not until it has reached the lobate form. The granules are small, more or less uniform, and of apparently round shape, and arise endogenously. The general attention of hæmatologists and clinicians has been directed to them by the invention by Ehrlich of a method of demonstrating them easily. They appear first at one or several points in the cytoplasm, and increase gradually in number until they occupy the whole body of the cells, with the

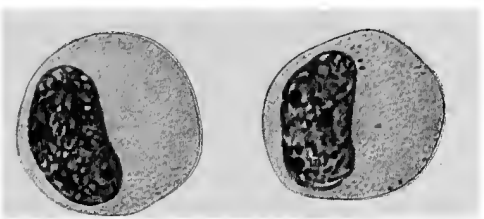


FIG. 363.—Finely granular (neutrophile) leucocyte with compact nucleus, a so-called myelocyte. From the circulating blood of a healthy adult. (After Weidenreich.)

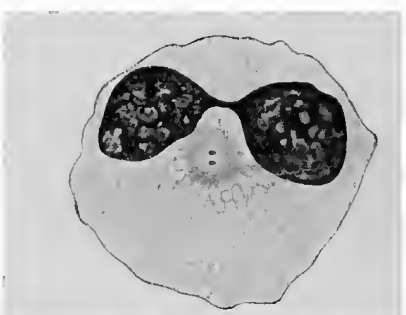
exception of the immediate neighborhood of the centrosome. Meanwhile the colorability of the intergranular substance diminishes. In a human embryo of three and one-half months the majority of "leucoblasts" in the bone medulla are without granules, but both neutrophile and eosinophile cells are present. During the fourth and fifth months the finely granular cells become more numerous.

2, B. *The coarsely granular leucocytes* (eosinophiles) develop at the same time as the finely granular, but are morphologically wholly different. The original round nucleus becomes eccentric and kidney-shaped, then more slender and longer, and bends around the centrosome, which takes a central position. Up to this point of its development it can scarcely be distinguished from the nucleus of the finely granular cell, but finally it assumes its permanent shape by forming two lobes (Fig. 364), which are united

[62] The fine research of M. Heidenhain upon the leucocytes of Salamandra (Festschr. f. Kölliker, 1892, p. 138) must be regarded as the starting-point of our knowledge of the centrosome of leucocytes.

by a strand varying in width and length. As a rule, the lobes are of unequal size, but the inequality is seldom striking. The lobes are in general round or oval and occasionally pear-shaped. They usually have very regular contours, but occasionally one sees a small projecting hump. The length of the uniting strand is very variable. Nuclei occur with shapes which do not exactly fit with this description, but they are extremely rare. The centrioles are similar to those of the finely granular leucocytes, and are also situated in a clear court of material, which, however, in the case of the coarsely granular cells, is surrounded by a darker, broader zone, which appears nearly homogeneous. The darker zone is often extremely distinct.

The eosinophile granules, according to Weidenreich,[63] are not endogenous structures, but are fragments of erythrocytes which have been eaten by the cells. He found that the erythrocytes break



364.—A coarsely granular leucocyte (eosinophile) with a bilobate nucleus. Highly magnified. From the blood of a healthy adult. (After Weidenreich.)

up into fragments in the hæmolymph glands of sheep and other mammals, and that the fragments break up into still finer granules, which retain their characteristic color reaction, and are taken up by the lymphocytes, in which they appear as the eosinophile granules. In the measure that the number of granules in the single cells increases, the nucleus passes through its metamorphosis. In the finely granular leucocytes, on the contrary, the granules arise sometimes earlier, sometimes later. A renewed investigation of the eosinophiles in man is very desirable.

2, C. *The degenerating leucocytes* correspond to the "basophiles" of Ehrlich's nomenclature. They are designated by Maxi-

[63] Fr. Weidenreich: Anat. Anzeiger, vol. xx, 1902, p. 196; also Verhandl. Anat. Ges., vol. xix, 1905, p. 79, and Arch. f. mikr. Anat., vol. lxxxii, p. 282 and 286 (extended discussion). The explanation adopted by Weidenreich had been previously proposed by Hoyer, Klein (Cbl. inn. Med., 1899), and Fuchs (*ditto*). Weidenreich's observations have been confirmed by Warthin and Th. Lewis. Zietschmann joins in the opinion of these authors.

mow [64] as "Mastleucocyten." [65] An apposite name for these cells is still lacking. As Maximow has demonstrated, we must distinguish strictly, morphologically and genetically, between "Mastzellen" and "Mastleucocyten." The Mastleucocyten make up a very small percentage of the leucocytes in normal human blood, but occur abundantly in many cases of pathological blood. The nucleus becomes first kidney-shaped and then of an irregular contour, as may be seen in Fig. 365. As the alteration continues, pieces of the nucleus pinch themselves off from the main mass, or else the nucleus assumes a highly irregular form and breaks up into single pieces. These alterations may be easily observed in leukæmic blood. No distinct internal structure can be recognized in the nuclei. The amount of chromatin must be increased, for the coloration of the nucleus is more intense than in other leucocytes. There is no centrosome. The granules are extremely variable in number, size, and form; in some cells there are only a few present,

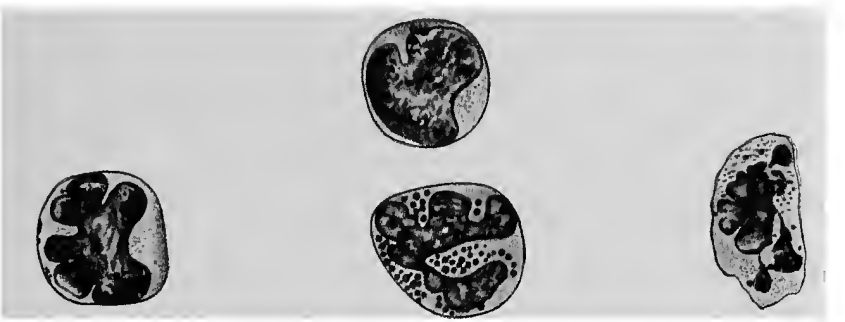


FIG. 365.—Degenerating human leucocytes (Mastleucocyten of Maximow). (After Weidenreich.)

in others they are abundant. The size varies also within a single cell. The form of the granules is often strikingly irregular; it may be angular, rounded, or elongated, or, in another case, the granules may be more uniformly rounded. They stain a dark blue violet with the Giemsa solution. The protoplasm loses its basophile reaction and appears vacuolated, especially in cells the nuclei of which have become irregular.

Note.—So far as known to me, Blumenthal [66] was the first to interpret these cells as degenerative, a view to which Pappenheim [67] and Weidenreich [68] have agreed. That this interpretation is correct is rendered probable by the above-given history of the cells.

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[64] Maximow: Ueber die Zellformen des lockeren Bindegewebes, Arch. f. mikr. Anat., vol. lxvii, 1906, p. 706.

[65] Die "Mastleucocyten" des Meerschweinchens und anderer Rodenten sind morphologische vollkommen verschieden von der hier zu berücksichtigenden *menschlichen* Zellen.

[66] R. Blumenthal: Ann. Soc. R. Sci. Méd. et Nat. Bruxelles, vol. xiv, 1905.

[67] Pappenheim: Atlas der menschlichen Blutzellen, 1 Lief., 1905.

[68] Fr. Weidenreich: Folia hæmatologica, vol. v, 1908, p. 135; also Arch. f. mikr. Anat., vol. lxxii, 1908, p. 252.

The multiplication of leucocytes is effected, as above stated, p. 515, by mitotic division,[69] which may often be seen in the young forms. As the cytomorphosis progresses, the mitoses become rarer. Blumenthal[70] and Renaut[71] have shown that the mitoses continue in the finely granular and eosinophile cells up to the stage of the kidney-shaped nucleus. In cells with lobate nuclei, mitoses have not been observed.

Amitosis of leucocytes has been described by several investigators. H. Pollitzer[72] has given a compilation of the recorded statements. Since the process has been observed only in nuclei which have become pyknotic, it is probable that we have to deal with a degenerative process which accompanies the downfall of the cells and plays no rôle in their normal multiplication. Yet authorities are not lacking to defend the hypothesis that the normal multiplication of leucocytes is by amitosis. Löwit[73] goes very far in this direction, for he asserts that the multiplication of leucocytes in the liver is effected only by amitosis, a view which Kostanecki[74] has shown to be completely untenable.

Disintegration of Leucocytes.—We may assume that leucocytes at the close of their cytomorphosis die and disappear. Death may befall a cell at any time, but accidental death is by no means comparable with the death which ensues at the close of the cytomorphosis of the cell. Our knowledge is still so incomplete that the following exposition can be regarded as tentative only. So far as the nuclei are concerned, we see that they break down by fragmentation, which begins with the rupture of the threads uniting the single lobes. Thus the cell becomes apparently multinucleated. After this the cells are often devoured by phagocytes; but if they remain free, the splitting up of the nucleus continues until some ten or fifteen fragments are produced, which possess a rounded form and lie irregularly scattered in the protoplasm. The nuclear fragments, or lumps of chromatin, are homogeneous and disappear by dissolution. During the degeneration of the nucleus the granular cytoplasm gradually disappears. Finally, the remnant of the cell breaks down and the fragments are eaten by phagocytes, or perhaps in part dissolved.

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[69] Discovered by W. Fleming, Arch. f. mikr. Anat., vol. xxiv, 1885, p. 50–91. Compare also O. van der Stricht, Verh. Anat. Ges. Göttingen, vol. vii, 1893, p. 81; and Jolly, Arch. d'Anat. micr., vol. iii, 1900, p. 168–228. The latter gives a detailed analysis of the previous literature.

[70] Blumenthal: Travaux Lab. physiol. Inst. Solway, vol. vi, 1904.

[71] J. Renaut: Arch. d'Anat. micr., vol. ix, 1907, p. 495.

[72] H. Pollitzer: Beiträge zur Morphologie und Biologie der neutrophilen Leucocyten, Zeitschr. Heilk. Abth. path. Anat., vol. xxviii, 1907, p. 277.

[73] Löwit: Sitz.-ber. Akad. Wiss., Wien, vol. xcii, 1885, 3 Abth.

[74] Von Kostanecki, Anat. Hefte, vol. i, 1892, p. 312.

The disintegration of leucocytes occurs in connective tissue, in exudates, and especially in the spleen and other lymphoid organs. Disintegration of the leucocytes also occurs in normal blood, but is rare.

7. Origin of the Blood-plates.[75]—We are indebted to the investigations of James H. Wright[76] for the recognition of the actual development of the blood-plates. He succeeded in making the process clear by the application of a new method of coloration.[77] According to Wright, the plates arise by the pinching off of the ends of slender processes of uninucleate giant cells (the megakaryocytes of Howell). After the application of Wright's stain, one can see in both the blood-plates and in the giant cells a narrow hyaline-blue border (ectoplasm) the edge of which is either smooth or finely dentate. The breadth of the border varies, yet is the same in the two structures. Its peripheral layer is capable of amœboid motion. The central portion of the blood-plate—as also the inner and by far larger portion of the cytoplasm of the giant cell—appears, after the same coloration, to be filled with more or less crowded granules of a red or violet tint. The majority of the giant cells—these observations refer chiefly to the bone medulla of various mammals—have a rounded form, while the minority exhibit forms of great diversity, which arise by the formation of pseudopod-like processes of variable length, width, and shape. In some cells almost the entire cytoplasm is absorbed in the formation of processes. We can observe, in these giant cells of a changed shape, that the red or violet granules of the internal substance of the cytoplasm extend into the processes and form in them an axial cord, which remains surrounded by a hyaline ectoplasm (Fig. 366). Occasionally a process extends into the cavity of a blood-vessel. Some of them lose the connection with the parent cell, and such free pseudopods have been observed by Wright not only in the blood-vessels of the medulla of bone and in the spleen, but also in the capillaries of the lungs. Now in some of these processes, the width of which corresponds to the diameter of the blood-plates, we can see that the granular internal substance exhibits constrictions. At other points the subdivision of the middle substance is complete, and we encounter a series of rounded segments having the diameter and other characteristics of the internal substance of the blood-plates. Each segment of the internal substance has a clear peripheral zone. A process thus

[75] Professor J. H. Wright has laid me under great obligations by reading the MS. of this section, and the value of the exposition has been much increased by his advice and additions.

[76] James Homer Wright: Die Entstehung der Blutplättchen, Virchow's Arch., vol. clxxxvi, 1906, p. 55–63; see also Journ. Morphol., vol. xxi, 1910, p. 263.

[77] Pathological Technique, by Mallory and Wright, 4th edition, 1908, p. 374.

modified is regarded by Wright as a chain of blood-plates which become free by the breaking up of the chain. Other processes occur which are so small that they probably produce only a single plate. That the giant cells really lose their protoplasm is proved by the occurrence of degenerating nuclei which are surrounded by little or no protoplasm.

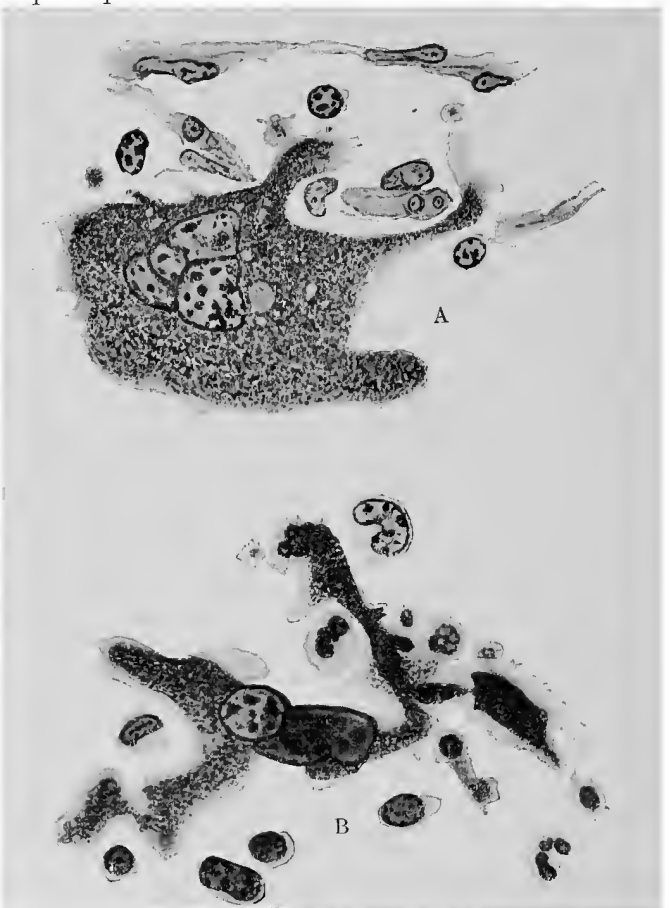

FIG. 366.—Giant cells with processes from which blood-plates arise. Alongside are blood-plates and a few leucocytes. A, from the spleen of a kitten; B, from the bone-marrow of a cat. Original drawings by J. H. Wright.

Two further facts deserve especial attention in discussing Wright's conclusions: first, that genuine blood-plates and genuine giant cells occur only in mammals; second, that the blood-plates first appear in the embryonic blood after the giant cells have been produced in the blood-forming organs.

Note.—A letter from Professor Wright enables me to add the following: There occur in the blood of mammalian embryos, before the development of blood in the liver has begun, together with a few blood-plates, a small number of cells which in their color reaction and in the structure of their protoplasm resemble the

giant cells of later stages, although in size they merely equal the red blood-corpuscles. Wright has observed the cleavage of these cells into blood-plates. They occur in the embryos of guinea-pigs of 4.5 mm., but were not found in a younger embryo. By his investigations of other mammalian embryos, Wright has convinced himself that the cells in question, which occur free in the blood, are identical with the giant cells of the blood-forming organs. He has found all possible transitions. According to Maximow[78] the giant cells in the rabbit and other mammals arise from the primitive mesamœboids (primary wandering cells), which would agree with Wright's conclusion.

8. The Composition of the Blood in Relation to Age.[79]—The distribution of the blood-corpuscles after the circulation has begun is probably always very unequal. This depends in part on the fact that the young blood-cells accumulate in special places, particularly those which serve as sites for the production of blood, concerning which see the following section. In the adult the percentage of the various forms of corpuscles differs according to the vessel. In embryos the relations are further complicated by the alterations which occur corresponding to the age.

The circulation of the blood begins extraordinarily early in man. The cytology of the blood at this moment is unknown to me.

In an embryo of 4 mm. I find large ichthyoid cells, as described on p. 505 and pictured in Fig. 355. Older cell forms are entirely lacking. Noteworthy is the extreme rarity of the primitive mesamœboids, a fact which does not correspond to my *a priori* expectations.

In an embryo of 7.5 mm. the cells are smaller on the average, but are still ichthyoid, Fig. 356, p. 506. They vary much in size, and may possess nuclei which indicate by their lessening diameter and deeper coloration the further cytomorphosis. In this case also I missed the primitive mesamœboids in the blood.

In embryos of 8–10 mm. the blood-cells are for the most part unquestionably ichthyoid, although their dimensions are extremely variable (Fig. 367). The younger types of cells are still extremely rare. One sees now and then accumulations of undifferentiated cells (Fig. 368) the protoplasm of which seems fused. Such clusters of cells adhere to the endothelium without being continuous with it.

Maximow[80] has observed similar clusters in the rabbit. According to his interpretation they arise by the proliferation of the endothelium. I am unable to

[78] Alex. Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 491.

[79] The principal work on this subject is that of Johann Jost (Arch. f. mikr. Anat., vol. lxi, 1903, p. 668), but he investigated only sheep and cow embryos. On p. 691 he gives curves of the percentages of corpuscles. His Metrocyten I are ichthyoid cells, his Metrocyten II are sauroids, and his Erythrocyten red plastids. Valuable data concerning the relations in rabbit embryos have been published by A. Maximow (Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 526–532).

[80] Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 517.

agree with him, because I find that there is no continuity of the protoplasm of the cells either in the rabbit or in man; also because mitoses of the endothelium in the neighborhood of the clusters are almost invariably lacking; and, finally, because the endothelial nuclei are differentiated while the nuclei of the cells of the clusters are not differentiated.[81] The clusters may be compared with blood-islands, and I regard the cells composing them as mesamœboids or primary wandering cells.

In all human embryos up to 12 mm. which I have had an opportunity of investigating, there occurs an active mitotic division of the red ichthyoid cells. Since the primitive cells are rare, we must conclude that the number of corpuscles increases chiefly by their own division during this period of development.

In embryos of about 12 mm. the blood formation is beginning in the liver, p. 528. At the same time the undifferentiated blood-cells become more numerous in the vessels, and the first cells of

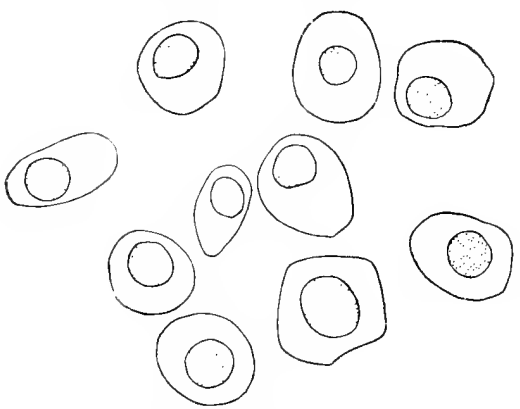

FIG. 367.—Outlines of erythrocytes of a human embryo of 8 mm. Harvard Embryol. Coll. No. 817.

the sauroid type appear. From this time on, the sauroid cells become constantly more numerous. The red cells are very variable. It must be further remarked that probably many erythrocytes are destroyed in the blood itself, so that we encounter the following cell forms: First, red cells of the round shape with a distinct membrane, but without hæmoglobin; second, similar cells collapsed; third, nuclei with remnants of a cell body; and fourth, free nuclei.[82] I have not observed expulsion of nuclei in very young embryos.

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[81] Compare Minot, "Age, Growth, and Death," Fig. 61, Nos. 5, 6, 7, 8. The nuclei of the cell clusters are all in the second stage in the figure referred to, and this stage immediately precedes the differentiation proper.

[82] The possibility remains that in these cases we have to do, in part at least, with the consequences of imperfect preservation. Still, I consider it probable that the break-down occurs normally in the manner indicated in the living blood.

In embryos of two months [83] the blood contains, 1, a minority of ichthyoid cells; 2, a large majority of sauroid cells which may be easily recognized by their pyknotic nuclei; 3, a considerable number of non-nucleated plastids, the formation of which occurs chiefly in the liver; 4, free erythrocyte nuclei, which are rare; and 5, mesamœboid cells of various appearance, some larger, some smaller, the largest equal in diameter the nucleated erythrocytes.

FIG. 368.—Endothelium and blood-cells from the lower part of the aorta of a human embryo of 9.4 mm. Harvard Embryol. Coll., No. 380. *Endo.*, endothelium; *A.*, collection of cells; *E.*, erythrocyte. × 1500.

Most of the mesamœboids retain their primitive character. Now and again, however, I found one with a kidney-shaped nucleus which probably was a mature granular leucocyte. Unquestionable "lymphocytes" I did not recognize.

[83] I have investigated seven embryos of about this age. In several the preservation of the tissues is pretty good, but in none is the preservation of the erythrocytes satisfactory. Therefore the statements given in the text possess only a preliminary value.

During the third month the young forms of the erythrocytes become steadily rarer and the ichthyoid cells almost disappear from the blood, while the blood-plastids become steadily more predominant.[84]

In a beautifully preserved embryo [85] of about eight months, I have found the following conditions: By far the majority of the corpuscles are thin disks without nuclei, many of them shrunken; the unaltered disks are convex on one side and concave on the other. In Fig. 369 two such are figured in optical section. Nucleated erythrocytes are extremely rare. Free dark nuclei and occasionally fragments of nuclei appear now and again. The colorless cells form distinctly a minority, but may be found everywhere. They are either primitive mesamœboids or young leucocytes, rarely leucocytes with lobed nuclei. The lymphocytes have the above described structure of the nucleus (p. 515) which is so

FIG. 369.—Blood-corpuscles from the vessels of a human fetus of eight months.

highly characteristic. The eosinophile leucocytes are very rare; they have for the most part a round or oval nucleus. Only by searching can one find an eosinophile with a kidney-shaped nucleus. The coarsely granular leucocytes are more numerous in the thymus and lymph glands.

It remains for the future to furnish satisfactory data concerning the composition of fetal blood and the changes it undergoes corresponding to age.

The percentage relations of the white corpuscles after birth have been investigated by Carstanjen.[86] I have put his chief conclusions in the form of a table. According to Carstanjen, the number of coarsely granular cells does not depend on the age, and, as far as they are concerned, only individual variations were

[84] For example, in an embryo of 29 mm. (Harvard Embryol. Coll., No. 914), although nucleated corpuscles are still numerous, the majority of the erythrocytes are without nuclei.

[85] I am indebted to Professor W. T. Councilman for this very beautiful material, preserved in Zenker's fluid, for which I here express my thanks.

[86] Carstanjen: Jahrb. Kinderheilk., 1900, p. 215 and 684.

observed. Very striking is the rapid increase of the young forms in the first days after birth. During the fifth year cells with lobate nuclei reach their maximum.

PERCENTAGE OF LEUCOCYTES IN THE BLOOD.

Young forms	Immediately after birth.	Twelve days.	First half year.	Second half year.	Two years.	Three years.	Four years.	Five years.
(Lymphocytes)	16.0	45.6	50.8	49.2	47.0	38.4	33.2	25.1
Finely granular cells with lobate nuclei	73.4	36.7	34.5	40.8	42.0	48.0	52.6	61.0

9. SITES OF BLOOD FORMATION.—Since it is highly probable that all blood-cells are descendants of the primitive mesamœboids, we must assume that these last seek out at different ages certain localities for their multiplication and transformation.[87] Of such sites of formation five are known with certainty: 1, the yolk-sack; 2, the blood-vessels of *young* embryos; 3, the embryonic liver; 4, lymph-organs; and 5, the medulla of bone.[88] The spleen may occupy a special position among the lymphoid organs, since nucleated erythrocytes occur in it during the fetal period. According to Neumann,[89] the erythrocytes are simply swept in with the blood current, and are not formed in the organ itself. Investigators are by no means agreed, however, in their opinions concerning the actual process. It would be out of place here to enter on an extended discussion, therefore we give only a short account of the phenomena which is necessarily of a somewhat preliminary character. As has been explained above, I cannot accept the opinion that the general mesenchyma serves as a site for the formation of blood. This opinion has been recently defended—perhaps correctly—by Maximow. In this connection mention must be made of the interesting observations of Pardi,[90] who studied the blood-cells in the mesenchyma of the omentum in rabbits.

1. *The Yolk-sack.*[91]—That the earliest blood-corpuscles arise in the wall of the yolk-sack has long been known, and has been asserted for man (compare above, p. 501).

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[87] E. Neumann (Virchow's Arch., vol. cxix, p. 393) still defended, in 1890, the idea that the hæmatoblasts arise in place in the medulla of bones, and that they are not immigrant elements.

[88] The significance of the medulla of bone for blood formation was discovered by E. Neumann (Cbl. med. wiss., 1868), and almost at the same time by G. Bizzozero (*ibid.*, 1869). Its discovery must be honored as the starting-point of the modern doctrine of blood development.

[89] E. Neumann: Arch. f. Heilk., vol. xv, 1874.

[90] F. Pardi: Eritrociti nucleati, . . . nel grande omento nel coniglio, Arch. Ital. Anat. Embriol., vol. iv., p. 370–386, Tav. liii–liv (1905).

[91] The conditions in the yolk-sack have been admirably described by Maximow, with special reference to the rabbit. See Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 457 and 476.

Further exact observations upon the hæmatogenic activity of the yolk-sac during its development are still lacking, both for man and for mammals in general. We can report only that during young stages there is a striking excess of the early stages of the erythrocytes in the blood-vessels of the yolk-sack, and that mitoses of the blood-cells are frequent.

2. *The Young Blood-vessels.*—As is well known, Remak[92] first discovered the multiplication of the blood-corpuscles in embryonic blood-vessels. We now know that this multiplication occurs by mitosis of both the mesamœboids and young erythrocytes. The mitosis in man can be easily observed in well-preserved material.

According to observations on mammals, the mitotic figures disappear from the circulating blood soon after the formation of blood in the liver is well started.

3. *Blood Formation in the Liver.*—That the liver serves as a site for blood formation in mammalian embryos, from soon after its first formation up to the end of fetal life, was first suspected by Prévost and Dumas[93] and later by Reichert and E. H. Weber.[94] Kölliker,[95] however, in 1846, gave the first definite proof of this important phenomenon, when he published his discovery that special cells occur in the fetal liver which change into erythrocytes. Although since then there have been many investigations[96] upon the fetal liver, the process of blood formation has not yet been completely cleared up. In these investigations there has been no lack of opinions which have later been recognized as untenable. Such, for example, is the opinion of Neumann, according to which the corpuscles arise endogenously; or the opinion of Foa and Salvioli, who derived the erythrocytes from hepatic giant cells.

The blood formation in the human liver begins in embryos of about 12 mm. in length.[97] At this time the hepatic cylinders are well developed, but are separated from one another by broad sinusoids. The endothelium of the sinusoids clings everywhere

[92] R. Remak: Ueber die Entstehung der Blutkörperchen, Med. Zeit., Ver. Heilk. Preussen, vol. x, 1841, p. 127. Compare also Canstatt, Jahresber., 1841, p. 17, and Remak's Untersuch. Entwicklungs Ges. Wirbelthiere, 1851, p. 22.

[93] Prévost et Dumas: Développement du Cœur et formation du Sang, Ann. Sci. Nat., vol. iii, 1824, p. 96–107, p. iv (le foie sanguifactif, p. 105).

[94] E. H. Weber: Zeitschr. f. rat. Med., vol. iv, 1846.

[95] Kölliker: Zeitschr. f. rat. Med., vol. iv, 1846.

[96] The following investigations may be mentioned: Fahrner: De Globuli sanguinis, Turici, 1845. Neumann: Berlin. klin. Wochenschr., 1871, p. 58; and Arch. f. Heilk., vol. xv, 1874. Foa e Salvioli: Arch. delle Sci. Med., vol. iv, 1880. M. B. Schmidt: Ziegler's Beitr., vol. xi, 1892, p. 199. The most exact investigations are those of van der Stricht, Archives de Biol., vol. xi, p. 19–113 and vol. xii, p. 235; and Maximow, Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 533–546. Both authors studied chiefly rabbits. Maximow gives a good review of previous results.

[97] This is according to my own observations and the statement of Schridde, Verhandl. deutsch. pathol. Gesellsch., 1907, p. 364.

closely to the hepatic cylinders. The broad blood-channels are clearly bounded; they contain blood-cells of varying appearance, but no true leucocytes, only mesamœboids and young erythrocytes (Fig. 370). Besides these there are also blood-cells so placed that they appear as part of the hepatic cylinders, and these last are the beginning of the development of the blood-producing centres in the liver.

From the stage of 12 mm. on, the number of the blood-cells which apparently are included in the liver cylinders increases rapidly. The blood-cells gather in little groups, which interrupt irregularly the hepatic cylinders. When colored sections are examined, these groups are conspicuous because the cells, in consequence of the progress of their development, possess nuclei of diminished size which stain very deeply. The nuclei of the liver-cells are much larger and more lightly colored, and their substance is not condensed, but forms a loose network. In earlier stages the sinusoids of the organ are separated from one another only by the cylinders consisting of liver-cells. In the region of the clusters

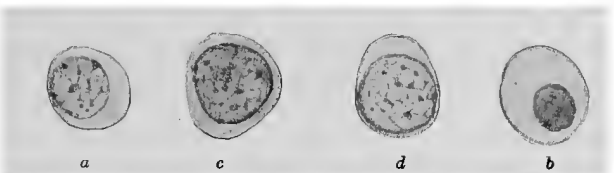

FIG. 370.—Blood-cells from a hepatic vessel of a human embryo of 11 mm. Coll. F. P. Mall, No. 353. *a*, *c*, *d*, primitive mesamœboids; *b*, erythrocyte. × 1500.

of erythrocytes, an examination of sections of the liver gives one the impression that the structure has remained essentially as before except that the hepatic cylinders now seem to consist in part of erythrocytes. Certainly the clusters of blood-cells lie outside the direct blood-channels through which the blood flows freely. It need hardly be said that the red cells are morphologically never parts of the hepatic cylinders.

The shape of the clusters of blood-cells is very variable. They may be sharply circumscribed, rounded, or elongated, and distinctly separated from one another; but quite as often they are extended into prolongations, by which the neighboring clusters may be united with one another, so that here and there we get a network with ample nodes. The size of the single clusters is very inconstant. In the third month it is not rare to find clusters in a section of which one can count fifty or more cells.

As regards the constitution of the cells in the blood clusters, we must distinguish the colorless cells from those colored with hæmoglobin. M. B. Schmidt estimated the number of colorless and colored cells to be approximately equal in a human embryo of nine and one-half months, and in his opinion this proportion holds true

for mature and nearly mature embryos. In earlier stages the colored corpuscles predominate.

The orginally colorless cells must be classed as mesamœboids, which must not be confused with true leucocytes. Nevertheless, they have been quite frequently loaded with this name. They can easily be distinguished from true leucocytes, although they are the parent cells of white corpuscles as well as of the red. Figure 369 represents some cells in the open blood-channels of the liver of an embryo of 11 mm. Such cells are numerous in the hepatic vessels

Fig. 371.—Hepatic cylinders of a human embryo of 11 mm. Coll. F. P. Mall, No. 353. The blood-cells with small nuclei lie apparently in the substance of the liver-cells, which have large nuclei.

at this time, although rare in the vessels elsewhere. Kostanecki [98] calls attention to the fact that the colorless cells lie usually, if not always, against the wall of the vessels. Mesamœboids with two nuclei alike in size are not rare.

The two chief forms of cells in the blood clusters are irregularly distributed. Often one sees in a single cluster nucleated elements, colored with varying intensity by hæmoglobin, alongside of uncolored corpuscles. Now and again a group consists of only colorless corpuscles, which usually lie so closely pressed together that they flatten one another and appear like a mosaic pattern.

[98] Von Kostanecki: Anat. Hefte, vol. i, 1891, p. 308.

Again, the boundaries between the cells disappear and the relatively large nuclei then lie closely crowded in a common protoplasmic mass. Such groups resemble those which occur in the blood-vessels of young embryos (Fig. 368). They are to be regarded as developing mesamœboids.

The colored cells differ much from one another. They vary within wide limits of size, in this respect contrasting with the non-nucleated plastids. There occur many cells which are so large that the nucleus alone equals the average volume of the plastids. Others, on the contrary, are less in diameter than a plastid. The content of hæmoglobin must be independent of the size of the cell and the amount of protoplasm; it now appears in the somewhat saturated color, as in the plastids, and again as a just-recognizable shade of yellow. Every intermediate condition occurs between these extremes. The cells containing the least hæmoglobin may display a light, granular protoplasm which, as the cells become more strongly colored, can no longer be seen. The optical homogeneity of the mature erythrocyte is generally known. The nuclei vary in their structure: first occur those of the ichthyoid type, which by their structure are clearly related to the nuclei of the colorless cells; second, nuclei of the sauroid type, which are smaller, and the substance of which appears darker and more homogeneous, allowing only a few indistinct granules and threads to be recognized in it. Every possible transition between these two nuclear types may be observed. The small sauroid nuclei belong to the cells richest in hæmoglobin. One may say that the higher the content of the cell in hæmoglobin, the smaller is the nucleus and the more condensed its chromatin framework.

We come now to the question of the relation of the above-described cells to the open sinusoids on the one hand, and, on the other, to the hepatic cylinders. Two opposing views are to be considered, since some defend the opinion that the clusters all lie in the vessels or in diverticula of the vessels, while others assert that a part of the cells are extravascular in position. Thus, M. B. Schmidt (l.c., p. 203), von Kostanecki,[99] and others assert definitely that the cell clusters are intravascular; O. van der Stricht,[100] on the other hand, reports that in mammals the young blood-cells lie in part outside of the vessels, between the hepatic cells, and that in older embryos the cells are clearly embedded in the mesenchymatous cells. So far as my observations go they fully confirm van der Stricht,[101] and the excellent observations on rabbit embryos

[99] Von Kostanecki: Anat. Hefte, vol. i, 1891, p. 308.

[100] O. van der Stricht, Arch. de Biol., vol. xii, 1892, p. 241.

[101] The conditions in the opossum embryo appear to me especially clear and unquestionable.

which Alexander Maximow [102] has recenly published appear to me to decide the question. Finally, and in favor of van der Stricht, since the vascular endothelium of young embryos allows the blood-corpuscles to pass through, we need feel no surprise that a migration of blood-cells occurs also in the liver.

By the shaking of sections, Schmidt has removed a portion of the blood-cells, and has then observed spaces which were simply enlargements of the sinusoids and which were enclosed on both sides by the cords of liver-cells. The liver-cells are pressed back, especially from the wider cavities, and are thereby reduced sometimes to mere strips of protoplasm; the endothelium is frequently still recognizable. In other cases, Schmidt saw the blood-cells situated between two liver-cells; the latter appeared hollowed out and as if eaten by the blood-cells (lacunar corrosion of Neumann). At other times it appeared to him as if the small blood clusters were embedded in a single liver-cell. In both cases he was unable to see the endothelium. Strictly speaking, therefore, the observations of Schmidt agree better with the conclusions of van der Stricht than with his own view.

Origin of the Cells of the Blood Clusters.—According to the prevalent view, as above stated, the clusters arise by the accumulation of cells which circulate in the blood. A fact in favor of this view is that from the first all the forms of cells occur in the blood clusters which at that time can be found in the blood. If we had to do with cells which arose *in loco*, we should expect that only young cells would appear at first, which later would differentiate themselves. Further investigations are necessary to give a final decision as to the origin of the cells.

M. B. Schmidt [103] has drawn from his observations the conclusion that the proliferation of the endothelium produces new young erythrocytes, which then multiply farther by mitosis. To me his argument is by no means convincing.

Investigations up to the present render it clear that a multiplication of erythrocytes occurs in the embryonic liver during a long period, the end of which is after birth. The cytomorphosis of the red cells in the liver is essentially, or exactly, the same as elsewhere during early stages of the embryo, and also as in the medulla of bone. The clusters yield, at least in part, immature corpuscles which enter the circulating blood, so that we must assume that these complete their cytomorphosis in the blood itself.

O. van der Stricht (l.c.), von Kostanecki (l.c., p. 313), and others report that in the liver of mammals lymphocytes are formed by the metamorphosis of primitive colorless cells.

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[102] Maximow: Arch. f. mikr. Anat., vol. lxxiii, 1909, p. 538.
[103] M. B. Schmidt: Ziegler's Beiträge, vol. xi, 1892, p. 212, 219.

Neumann was the first to prove that the blood flowing out of the liver contains more young erythrocytes and more mesamœboids than the inflowing blood. Later M. B. Schmidt found that in a nearly mature embryo the proportion of nucleated to non-nucleated cells was—

In the portal vein 1:38,
In the hepatic vein . . . . . 1:25.

4. *Formation of Leucocytes in the Lymphoid Organs.*—It is well known that the lymphoid glands, tonsils, the thymus, etc., all serve for the multiplication of lymphocytes. It is easy to observe the proliferations of the young leucocytes in the corresponding embryonic organs of man, yet the life history of the lymphocytes during embryonic development is almost unknown.

5. *Blood Formation in the Medulla of Bone.*—The medulla of bone [104] is a vascular, mesenchymatous tissue, which originally is merely a reticulum of branching cells, with relatively wide endothelial blood-vessels. A part of the cells become osteoblasts. In the adult condition the structure remains essentially the same, although the mesenchyma forms connective-tissue fibrils, multinucleated giant cells, and, later, fat-cells; the latter vessels become arteries and veins. Certain investigators assert that the cavities of the blood-vessels are in direct open connection with the spaces of the mesenchyma, but, so far as I know, the conclusive proof of the correctness of this statement is lacking.

The history of the fetal medulla in man has not yet been investigated, probably because fresh material is indispensable for such investigations. Hence it is that we can merely sketch the history in outline, and about as follows:

The medulla of bone arises late ontogenetically, since it does not appear until immediately before the commencement of ossification in each piece of cartilage, and therefore appears in different parts of the skeleton at different times.

Soon after its formation, there appear in it cells which we regard as primitive mesamœboids, and also young erythrocytes, young leucocytes, and young giant cells (megalokaryocytes); all three of which, according to the well-founded prevalent view, are developed from mesamœboids. The mesamœboids are called, inappropriately, "myelocytes," although as compared with the original medulla (mesenchyma) they must be regarded as foreign elements. Gradually the number of "myelocytes," as well as young red and white cells, increases. The cytomorphosis progresses toward maturity, that is, until the erythrocytes have lost their nuclei and the leucocytes have acquired their granules. When mature, the corpuscles under normal conditions pass into the blood stream, by which they are carried off in order to participate in the circulation until they break down. Probably the lymphocytes also pass in small numbers into the blood stream. Only under pathological conditions do nucleated erythrocytes or so-called myelocytes pass out

[104] C. M. Jackson: Zur Histologie und Histogenese des Knochenmarkes, Arch. f. Anat., 1904, p. 33–70.

in noticeable numbers into the circulating blood. This pathological condition has as yet been observed only after birth.

The number of blood-forming cells in the medulla increases slowly until birth, after which it mounts rapidly in the course of a few days. Incidentally occurs a diminution of the blood formation in the liver.

The distribution of the "myelocytes" and developing blood-corpuscles in the medulla has not been rendered clear by the existing investigations. The uncertainty is chiefly due to the fact that neither the course of the smaller vessels nor the structure of their walls is sufficiently known to us. The developing blood elements lie in part in the mesenchyma, in part in wide capillaries,—according to several investigations, made chiefly upon rabbits.[105] I may cite especially the work of O. van der Stricht and of Brinckerhoff and Tyzzer. The young forms are in excess in the mesenchyma. The young forms include the colorless mesamœboids, the ichthyoid erythrocytes, and the granular leucocytes with round or kidney-shaped nuclei. The cells in the vessels often cling closely crowded to the vascular wall, almost as if they were glued to it and to one another. In these vascular accumulations the sauroid erythrocytes and the mature granular leucocytes predominate. Since the number of the red plastids outside the active blood stream is never very great, we conclude that the plastids leave the medulla soon after their development.

II. THE DEVELOPMENT OF THE HEART.

By JULIUS TANDLER.

The earliest developmental processes of the heart, especially in so far as they concern the formation of the endothelium of the heart and vessels, are unknown in the human embryo, but probably one will not be far astray in assuming that the earliest anlage of the human heart is essentially similar to that of the mammalia. The earliest development of the heart is naturally associated with the first appearance of the vessels, but concerning this the following brief statement is all that is necessary here. According to the comprehensive investigations of Mollier, the preliminary

[105] Robert Muir: On the Relations of Bone-marrow to Leucocyte Production and Leucocytosis, Journ. Path. and Bacteriol., vol. vii, 1901, p. 161.

Muir and Drummond: On the Structure of Bone-marrow, etc., Journ. Anat. and Physiol., vol. xxviii, 1893, p. 125.

Rindfleisch: Arch. f. mikr. Anat., vol. xvii, 1880, p. 1–11 (describes the circulation).

W. H. Howell: On the Life-history of the Formed Elements of the Blood, Journ. of Morphol., vol. iv, 1890, p. 57.

E. Neumann: Ueber die Entwickelung rothen Blutkörperchen in neugebildetem Knochenmark, Virchow's Arch., vol. cxix, 1890, p. 385–398.

Freiberg: Experimentelle Untersuchungen über die Regeneration der Blutkörperchen im Knochenmarke, Inaug. Diss., Dorpat, 1892.

Bizzozero: Cbl. med. Wiss., 1881, and Moleschott's Unters. z. Nat.-Lehre, vol. xiii, 1888.

O. van der Stricht: Archives der Biologie, vol. xii, 1892, p. 199.

Brinkerhoff and Tyzzer: On the Leucocytes of the Circulating Blood of the Rabbit, Journ. Med. Research, vol. vii, 1902, p. 173.

to the formation of the heart in all craniote vertebrates is the appearance of a number of cells between the endoderm and mesoderm, at first in the distal portion of the head. These elements, known as *vascular cells,* are discernible much earlier in the amniota than in the anamnia, and are recognizable in mammalian embryos with two or three primitive somites. From these vascular cells there develops, however, only the cardiac endothelium, the remaining constituents of the heart wall, the myocardium and epicardium, being derivatives of the visceral cœlomic wall. The first aggregation of the vascular cells of the heart is paired and produces a bulging of the visceral lamella into the wide pleuropericardial cavity. This bulging portion of the wall, which, as already stated, gives rise to the entire heart wall with the exception of the endothelium, has been named by Mollier the *heart plate* or *cardiogenic plate.* The topical relation of the paired heart anlagen to one another, that is to say, the time when they come into contact, depends on the configuration of the fore-gut. If this is spread out flat at the time of the appearance of the heart anlagen, these are widely separated from one another; if, however, there is an early closure of the fore-gut ventrally, as, judging from stages already known, is undoubtedly the case in human embryos, then the paired heart anlagen are very close together from the beginning and their fusion takes place early. In the Spee embryo Gle (Normentafel[1] No. 2, primitive somites not yet visible) some scattered vascular cells occur in the region of the paired heart anlage.

On the closure of the fore-gut ventrally the hitherto symmetrical pleuropericardial cavities come together anteriorly and fuse in this region, the median partition between them, the *mesocardium anterius,* disappearing, while the *mesocardium posterius* persists for some time longer. The closely approximated but not yet fused endothelial tubes are now surrounded by a continuous *myo-epicardial mantle* (Mollier). Finally the two endothelial tubes come into contact, their partition wall disappears, and the unpaired heart cylinder is formed from the paired heart tubes. This stage of the development of the heart occurs in the Krömer-Pfannenstiel embryo, Klb (Normentafel No. 3, five to six primitive somites), a section of which, passing through the heart anlage, is shown in Fig. 372. The space which is seen between the myo-epicardial mantle and the endothelial tube, and which is probably filled with fluid *intra vitam,* is perhaps somewhat enlarged in this embryo by the collapse of the endothelial tube during preservation. The fusion of the endothelial tubes is shown

[1] By Normentafel is meant Keibel's Normentafel zur Entwicklungsgeschichte des Menschen.

only in a few sections: cranially and caudally from the section figured one still sees the paired ends of the endothelial tubes.

With the fusion of the paired anlagen to form an unpaired cylinder there begins a new period in the development of the heart, during which two processes take place simultaneously, namely, (1) the elongation and consecutive bending of the heart cylinder and (2) the differentiation of the heart into its individual parts. There is no doubt that both processes are the result of the functional elaboration of a primarily straight and simply propulsatory portion of the vascular system, that is to say, of the heart anlage. In the description that follows a division of the process into stages will be made; in the first stage the development of the heart wall will be followed from the condition of a simple straight cylinder, to which stage it has now been traced, up to the time of the primary atrial division. The *second stage* will extend from the development of the primary atrial septum to the degeneration of the septum primum and the development of the septum secundum, the *third* to the complete division of the heart, and the *fourth,* finally, to the acquisition of its definitive form.

The development of the mammalian heart from the stage in which it is a simple cylinder to the completion of its development has been made known by the fundamental work of Born. The observations of this author were made principally on the heart of the rabbit, but were frequently extended also to the human heart. Born has modelled some stages of the latter and has pointed out the slight differences that obtain in the development of the two hearts. Recently Hochstetter has written a comparative embryology of the vertebrate heart for Hertwig's Handbuch. The succeeding account of the development of the human heart follows closely the work of Born, yet the endeavor has been made to complete as far as possible our knowledge of the development of the human heart.

The bending of the heart cylinder begins by the portion exactly midway between the two fixed ends being thrown into a loop, which may be termed the ventricular loop and whose apex is towards the right. The cranial end of the heart cylinder is fixed at the point of emergence of the cylinder from the pericardium, that is to say, at the point of division of the truncus arteriosus into the aortic arches; the venous end, to which the umbilical and omphalomesenteric veins converge, is fixed by the septum transversum, developing immediately above the yolk-sack. Since the heart cylinder grows more rapidly than the fixed points separate from one another, its free portion becomes thrown into a loop. The two limbs of this loop are separated by an almost horizontal cleft, the interventricular, or better the *bulbo-ventricular cleft* (compare Fig. 373[2]). By this cleft the heart loop is sepa-

[2] I am indebted to Professor P. Thompson for the loan of this model.

rated into two portions, into a cranial limb, the *bulbar limb,* and a caudal one, the *ventricular.* The part situated immediately above the septum transversum widens later to form a cavity whose greatest diameter is transverse and whose left end communicates with the ventricular limb. This cavity represents the *atrial portion* of the heart, and the somewhat constricted portion by which it communicates with the ventricular limb is the *atrial canal.* The atrial portion lies dorso-caudal to the ventricular limb, which, on its part, is overlapped cranially by the bulbar limb. On the caudal wall of the atrium there opens the *sinus venosus,* which is greatly expanded in the transverse direction and whose cavity receives the blood from both venæ umbilicales, venæ omphalomesentericæ, and ductus Cuvieri. Consequently, simultaneously with its bending,

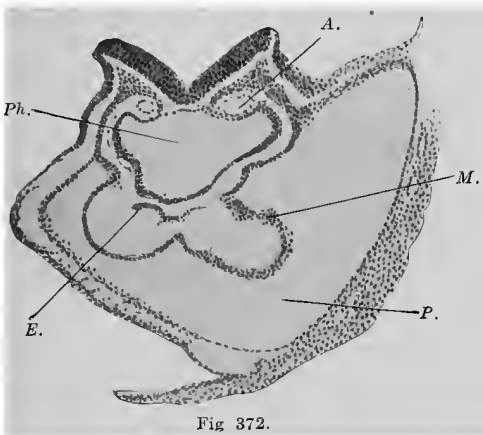

Fig 372.

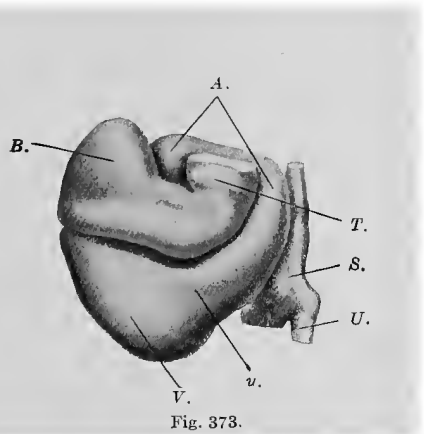

Fig. 373.

FIG. 372.—Section through the heart anlage of the Pfannenstiel-Krömer embryo Klb (Normentafel, No. 3, 5 to 6 primitive somites). *A.*, dorsal aorta; *E.*, endothelial tube; *M.*, myo-epicardial mantle; *P.*, pericardial cavity; *Ph.*, pharynx. × 100.

FIG. 373.—Model of the heart of a human embryo, No. 300 of Rob. Meyer's collection (Normentafel No. 7), 2.5 mm. greatest length. Modelled by P. Thompson. (After Thompson.) *A.*, atrium; *Au.*, region of the atrial canal; *B.*, bulbus cordis; *S.*, sinus venosus; *T.*, truncus arteriosus; *U.*, vena umbilicalis sinistra; *V.*, ventricular limb. × 50.

the heart cylinder becomes divided into its four portions. While the delimitation of the atrial portion from the ventricular limb is indicated by the constriction in the region of the atrial canal and that of the ventricular limb from the bulbus cordis by the constriction at the bottom of the bulbo-ventricular cleft, that of the sinus from the atrium is less distinct. Later, however, this delimitation is made clearer by a groove which constricts the floor of the atrium from the left and delimits the left portion of the sinus venosus from the left portion of the transverse atrial sac. By this the wide connection between the sinus and the atrium is narrowed and the sinus itself is divided into a transverse middle portion and two lateral portions communicating with this—the *transverse portion of the sinus* and the *left* and *right sinus horns.*

The changes that now take place consist in a relative change of position of the individual portions of the loop. The sinus with its sinus horns, which up to this time has been the most caudal portion of the loop, comes to lie on the dorsal side of the transverse atrial sack; at the same time the apex of the ventricular limb, which hitherto has looked towards the right, comes to be directed more caudally. This change of position of the bulbo-ventricular limb becomes clear by a comparison of the position of the bulbo-ventricular cleft of Thompson's embryo (Fig. 373)

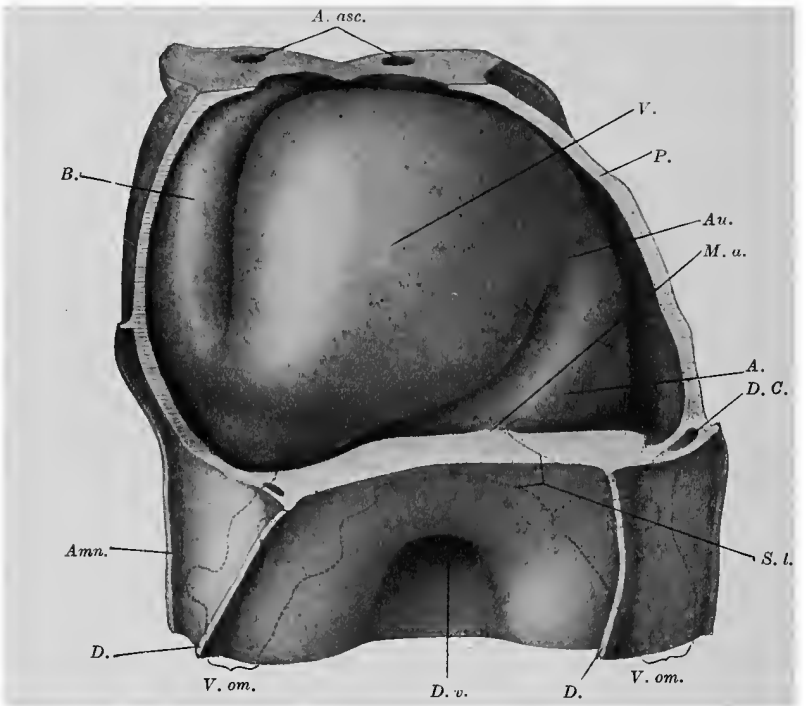

FIG. 374.—Model of the heart of the embryo Hal₂ of 3 mm. greatest length, 15 primitive somites. The property of the First Anatomical Institute, Vienna. Modelled by R. Weintraub. Seen from in front after removal of the anterior pericardial wall. The dotted lines represent the limits of the veins. *A.*, atrium; *A. asc.*, ascending aorta; *Amn.*, amnion; *Au.*, atrial canal; *B.*, bulbus cordis; *D.*, yolk-sack, cut at its margin; *D. C.*, ductus Cuvieri; *D. v.*, anterior communication of intestine with yolk-sack; *M. a.*, anterior mesocardium; *P.*, pericardium; *S. l.*, left sinus horn; *V.*, ventricular limb; *V. om.*, omphalomesenteric vein. × 150.

with that seen in Embryo Hal_2 (Fig. 374); in the former it is almost horizontal, in the latter almost vertical. By this change what was formerly the caudal limb of the loop becomes the left limb, and what was formerly the cranial one becomes the right. As this assumption of a vertical position by the ventricular limb progresses, the atrium rises so that it comes to lie in the dorso-cranial side of the ventricular limb and a continually increasing portion of it becomes visible in an anterior view. Moreover, by this change the atrium comes into contact with the basal surface of

the bulbar limb, which bends backward almost in a horizontal plane, and as the atrium continues to grow forward it becomes slightly constricted by the bulbus. The movement of the sinus venosus in a craniodorsal direction, already described, accompanies this change in the atrium, so that the sinus, which formerly opened at the base of the atrial limb, now opens into the posterior wall of the atrium. At the same time, by the recession of the entire heart, the direction of the sinus horns is altered, these being directed no longer upward and medially, but assuming at first a horizontal direction and finally opening into the transverse portion of the sinus from above and laterally; they form

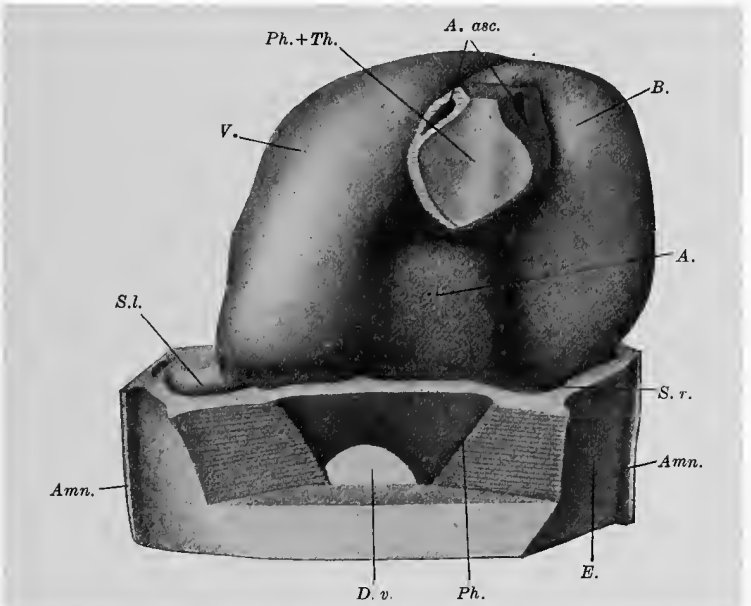

FIG. 375.—The model shown in Fig. 374 after removal of the pericardium, seen from behind. *A.*, atrium; *A. asc.*, ascending aorta; *Amn.*, amnion; *B.*, bulbus cordis; *D. v.*, anterior communication of the intestine with the yolk-sack; *E.*, ectoderm; *Ph.*, lateral wall of pharynx; *Ph. + Th.*, impression of the pharynx and the (median) thyreoid anlage on the pericardium; *S. l.*, reflection of the pericardium upon the left sinus horn; *S. r.*, right sinus horn; *V.*, ventricle. Lateral to *S. l.* the transverse section of the left ductus Cuvieri is to be seen.

with the transverse portion an arch which is no longer convex upward, but is at first convex anteriorly and later downward. The bulbus cordis participates in the relative change of position of the various parts of the heart to the extent that its distal end becomes more and more pushed toward the median plane as the ventricular limb becomes more vertical, and at the same time its distal bend becomes straightened out. In earlier stages this bend is quite sharp, but later the slightly curved bulbus passes gradually into the truncus arteriosus.

This topical modification of the heart is accompanied with changes of form, which consist partly in the progressive delimi-

tation of the four portions of the heart and partly in the further elaboration of each portion. Hand in hand with the change of position of the sinus there goes a diminution of the left sinus horn and a consequent retardation in the growth of the transverse portion of the sinus. The diminution of the horn is chiefly due to the obliteration of the left umbilical vein. The right half of the transverse part of the sinus is not greatly affected by the diminution, since in the meantime a number of hepatic veins have acquired openings into it. By the progressive constriction of the sinus from the posterior wall of the atrium from the left, the greatly narrowed opening of the sinus comes eventually to lie at the right posterior end of the transverse part of the atrium. The formerly transversely oval opening between the sinus and the atrium has been converted, by the developmental processes just described, into a longitudinally oval one, whose greatest diameter is placed sagittally and vertically. Toward the left it is bounded by the constriction described above, while on the right there is formed a vertical fold which, starting on the upper wall of the atrium, passes down the posterior wall beside the sinus opening to reach the lower wall. This fold is the first anlage of the *right sinus valve* (*valvula venosa dextra*).

The atrium changes its form to the extent that its two lateral extremities, enlarged in a balloon-like manner, project beyond the bulbar limb anteriorly and above, and it seems as if the right half decidedly surpasses the left in volume, at least the similar results of observations on several embryos of this stage point this way. The first division of the atrial cavity is due to the distal portion of the bulbus becoming lodged in its anterior upper wall. Corresponding with the blunt prominence projecting into the atrial cavity, produced in this manner, there develops, toward the end of the period now under consideration, a sickle-shaped fold, which extends at first over the posterior and later also over the anterior wall of the atrium, then gradually fading out. This is the anlage of the *septum primum.*

At about this same time the upper end of the right sinus valve thickens and projects into the atrial cavity as the first indication of the *septum spurium;* a slight groove on the outer surface of the atrium marks its position. Between this and the constriction produced by the lodgement of the distal end of the bulbus cordis, the cranial wall of the atrium is somewhat outpouched, forming the *intersepto-valvular space.* At the left end of the lower atrial wall is the entrance into the atrial canal, which at the beginning of this stage of development has a somewhat circular form, but at its end is transversely oval. At first this opening lies wholly to the left, associated with the abruptly descending left wall of the atrium, but later it shifts

as a whole to the right, so that its right end is finally situated at the middle of the atrial wall that is directed toward the ventricle. Corresponding to this change in the interior of the heart cavity a modification of the outer surface is naturally also visible. The atrial canal, which at first is visible on the left side of the heart, gradually comes to lie more and more deeply and vanishes towards the right, being overlapped from the left and above by the enlarging left atrium and from the left and below by the enlarging upper part of the ventricular limb. Hereby the atrial canal approaches nearer to the bulbo-ventricular cleft, until, finally, the depression bounding it on the left becomes continuous with the cleft and forms with it the *bulbo-auricular groove.* The ventricular limb, at this time, broadens in all directions and overlaps, especially on the left side, the circumference of the atrial canal. Its communication with the bulbus cordis, which at the beginning of this period was rather narrow, enlarges by the disappearance of the duplicature of the heart wall which is interposed between the ventricular and bulbar limbs, this duplicature being produced by the deep bulbo-ventricular cleft. In this process there is naturally no degeneration of heart substance, but merely a difference of growth to the disadvantage of the part under consideration. This lagging behind of the portion intervening between the bulbus and the ventricle shows itself on the outer surface of the heart by the bulbo-ventricular cleft becoming gradually shallower and gradually shortened in the caudocranial direction. The enlargement of the communication produces a common ventricular cavity, involving the transition portion, that is to say the caudal part, of the bulbo-ventricular limb. This becomes divided into two portions in its cranial part by the projection of the heart wall into the interior at the bottom of the bulbo-auricular cleft. This ridge-like projection, whose cranial portion was rather plump so long as the auricular canal lay entirely to the left, becomes sharper with the shifting of the atrial canal toward the right, and finally becomes a sharp-edged fold, which, as already stated, subdivides the cranial portion of the ventricular loop in the sagittal direction. To the left of this *bulbo-auricular ridge* lies the entrance to the atrium in the form of a well-defined atrial canal, to its right is the bulbus cordis, gradually diminishing in size as it is followed away from the ventricle. At the base of the common ventricular cavity there begins at this period the formation of a sagittally placed elevation, the first anlage of the *interventricular septum.*

The histogenetic processes which take place during the developmental period that has so far been followed are as follows. At first the distance between the endothelial cardiac tube and the myo-epicardial mantle is very great throughout the whole extent of

the heart anlage, and during life it seems to be filled with a serous fluid, since it is occupied in sections by a clot-like, fibrous mass, entirely destitute of cells and staining feebly with hæmatoxylin (Fig. 376). The *endocardium* consists of a layer of endothelial cells with large nuclei, while the myo-epicardial mantle is composed of several layers of cells, which have more of a syncytial character, at least their boundaries are distinguishable only rarely and sporadically. It is, however, difficult to determine how far this indistinct delimitation of the individual cells is due to the preservation or staining, since none of the embryos I have had for study were

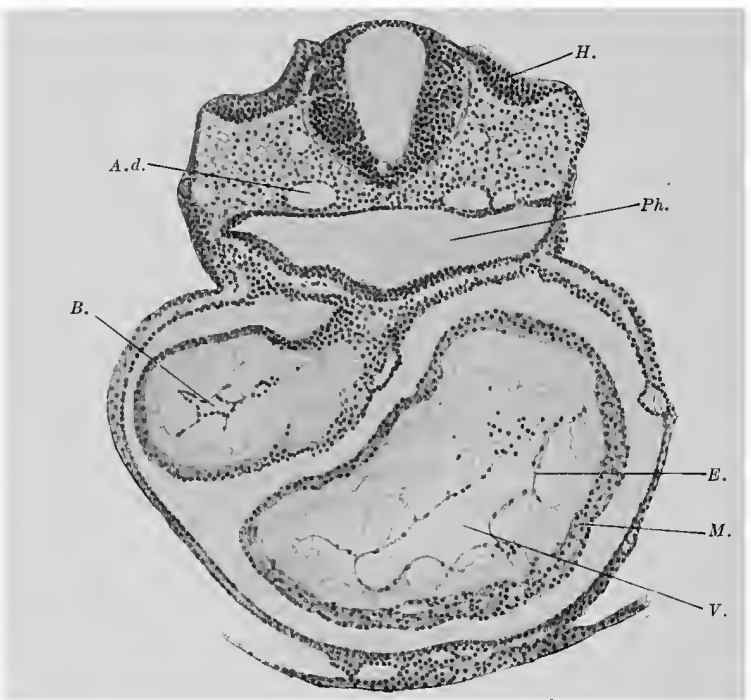

FIG. 376.—Transverse section through the embryo Hal₂. *A. d.*, descending aorta; *B.*, bulbus cordis; *E.*, endothelium of the cardiac tube; *H.*, auditory pit; *M.*, myo-epicardial mantle; *Ph.*, pharynx; *V.*, ventricle. × 100.

stained with iron-hæmatoxylin. The space which at first exists between the endocardium and the myo-epicardium diminishes later in an irregular manner; it disappears first of all in the sinus and then in the atrium, so that in these regions the endocardium is in contact with the muscle mantle in early stages. In the region of the impaired ventricular cavity the apposition of the two layers occurs somewhat later, while throughout the circumference of the atrial canal and in the bulbus the apposition does not take place within the limits of the period now under consideration. In these regions there are formed in the space between the two

layers the so-called *endocardial thickenings* or *endocardial cushions*. In place of the absolutely cell-free, fibrous coagulum there occur in these regions sporadic stellate cells with relatively small nuclei, the staining with hæmatoxylin becomes decidedly stronger, and the whole tissue reminds one forcibly of the type of tissue seen in the Whartonian substance.

The myo-epicardial mantle differentiates to the extent that in the region of the ventricular loop and in that of the bulbus its superficial layer is formed by a continuous row of cells, the *epicardium,* while on the atrium and sinus, so far as the latter has a free surface, no such differentiation can as yet be said to occur. But the ventricular limb takes precedence over the atrium in the differentiation of the myocardium itself, as well as in that of the epicardium. In the ventricle one sees not only an increase

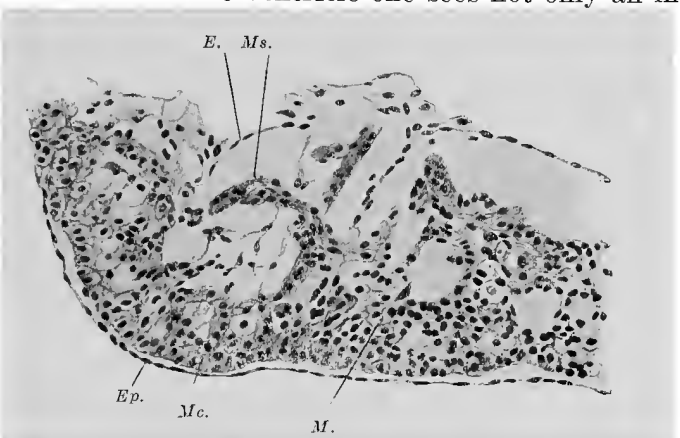

FIG. 377.—Section through the ventricular wall of the heart of embryo Hal2, 3.5 mm. greatest length, in the collection of the I. Anatomical Institute, Vienna. *E.*, endothelial cells; *Ep.*, epicardium; *M.*, myocardium; *Mc.*, cortical and *Ms.*, spongy portion. × 150.

of volume in the myocardium, but also its further differentiation and finally the appearance of trabeculæ. These first appear at the base of the common ventricular cavity as projecting elevations, which gradually become more and more undermined, until finally, surrounded on all sides by the closely apposed endocardium, they traverse the ventricle more or less free. The elaboration of the trabecular network proceeds from the base toward the atrial canal on the one hand and toward the bulbus on the other, and at the close of this period one can speak of two portions in the cardiac musculature, an *outer cortical* and an *inner trabecular* or *spongy* portion (Fig. 397). The latter is of considerable thickness, but the corticalis forms only a thin layer and a difference in the degree of differentiation of the two portions is also perceptible. At the beginning of the period under consideration the entire myocardium stained deeply with eosin and the individual cells were rich in

protoplasm, but at this stage the spongy portion is composed of cells poor in protoplasm; at least these cells in well-preserved embryos stain feebly with eosin. On account of their poverty of protoplasm the boundaries of the individual myoblasts are more distinct than formerly. In the region of the trabecular myocardium there now appear in the otherwise feebly-stained cell-bodies fine, strongly eosinophile muscle fibrils, which do not confine themselves to individual cell territories, but traverse several cells. None of this fibrillar structure is yet to be seen in the cortical layer. The atrial myocardium, which, so far as its differentiation is concerned, behaves like the cortical layer of the ventricle, shows a discontinuity along the line of attachment of the posterior mesocardium, muscle substance being completely wanting in early stages along this narrow zone (area interposita of His). The right sinus valve in its early stages is a duplicature of the myocardium, at least it may be seen that embryonic connective tissue occurs between the two muscle lamellæ. No boundary exists between the atrial and ventricular musculature, the former passing into the latter on all sides at the atrial canal. The myocardium is continued distally to the line of attachment of the pericardium, that is to say, to the region of transition from the bulbus to the truncus. Later this limit becomes less definite, as the distal portion of the bulbar myocardium apparently vanishes, a process by which the truncus arteriosus undergoes an elongation at the expense of the bulbus, and this at the time when the myoepicardial mantle is not yet differentiated at the distal end of the cardiac tube. This explains the difficulty which exists in determining the limits of these two portions of the efferent tube.

The endocardial thickenings in the atrial canal, mentioned above, may be described, in accordance with the form of the atrial canal itself, as an *anterior endocardial cushion,* situated on the anterior wall, and a *posterior* one on the posterior wall. On the small lateral borders of atrial canal the endocardium lies fairly close upon the myocardium. In the region of the bulbus a ring of endocardial tissue, at first of almost uniform thickness, replaces the space filled with fluid that is present in the earlier stages, and in this ring the following changes take place. In the proximal part of the bulb, the *ventricular part,* the endocardial thickening becomes especially strong along two spirally arranged regions, while in the intervals between these its development is retarded, and there are thus formed the proximal bulbar swellings, which, according to Born's method of nomenclature, may be termed the *proximal bulbar swellings A* and *B.* The distal portion of the swelling *A* lies on the left side of the bulbus, and as it descends it passes more and more toward the front, until, finally, at the proximal end of the bulb, it extends down toward the common ven-

tricular cavity on the anterior wall. The proximal swelling *B* in its distal part lies on the right wall of the bulb and passes thence downward on the posterior wall to disappear in the posterior wall of the ventricular cavity, just as the swelling *A* does in the anterior wall. In the oldest embryos belonging to this period of development one sees already that the most proximal parts of both bulbar swellings are undermined by trabecular musculature ascending from the apex of the ventricle. In the distal or *truncus portion* of the bulb the endocardial ring is also in process of differentiation to the extent that in a series of sections one sees endocardial thickenings projecting toward the lumen to form the *distal bulbar swellings*. Distally the endocardial thickenings

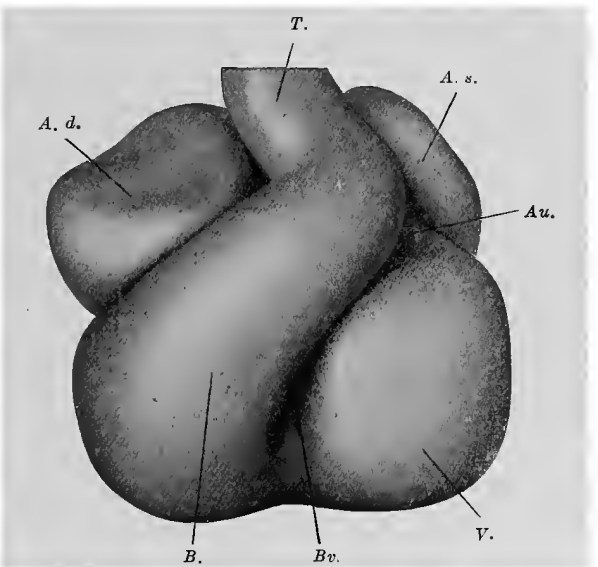

FIG. 378.—Model of the heart of the embryo Hal$_2$ of 5.2 mm. greatest length. In the collection of the I. Anatomical Institute, Vienna. Modelled by W. von Wieser. Seen from in front. *A. d.*, right atrium; *A. s.*, left atrium; *Au.*, region of the atrial canal; *B.*, bulbus cordis; *Bv.*, bulbo-ventricular cleft; *T.*, truncus arteriosus; *V.*, ventricle. × 100.

become gradually lower, until finally they pass over into the closely apposed endothelium of the truncus at the region where externally the indistinct boundary between the bulbus and truncus may be perceived. The projecting spur, the future septum aorto-pulmonale, which projects between the two halves of the system of aortic arches, *i. e.*, between the future systemic and pulmonary aortæ, does not at this stage reach the line at which the pericardium is attracted to the truncus arteriosus.

In the *second stage* of development of the heart there is an approximation of the external form to the final condition, but the more important part of the progress is in connection with parts in the interior of the heart. As regards the external form, the

change in the relative position of the various parts proceeds, the atrium gradually reaching a higher position, while the apex of the heart is carried so far caudally that, as is shown by a side view, it comes to lie caudal to the atrium. At the same time the opening of the sinus shifts completely to the dorsal wall of the atrium. The formerly slight constriction of the cranial wall of the atrium, produced by the bulb and the truncus arteriosus, now becomes a deep groove, and the lateral parts of the atrium on either side of this groove have enlarged so much that they begin to embrace the bulb as the anlagen of the auricular appendages (Fig. 378).

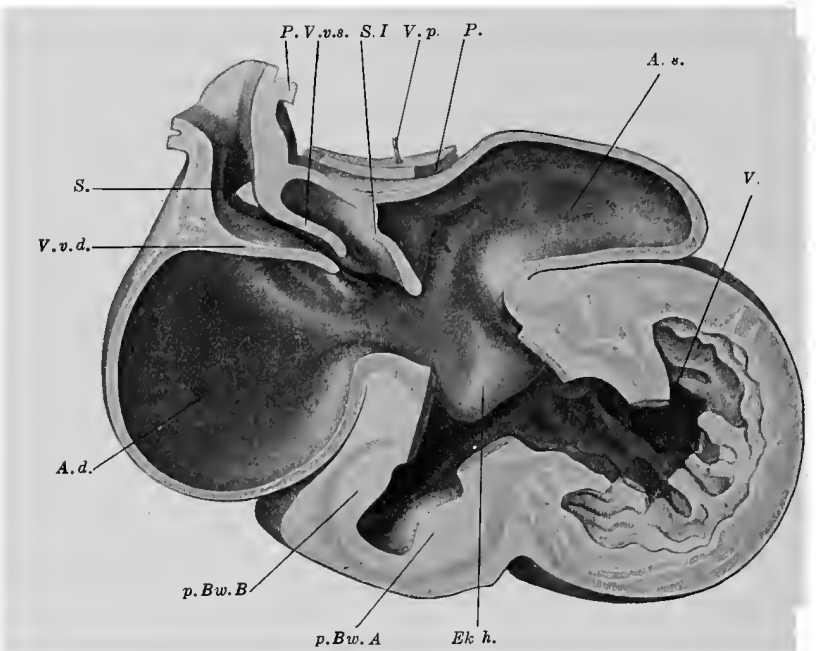

FIG. 379.—Model of the heart of embryo H_6 of 6.5 mm. greatest length. In the collection of the I. Anatomical Institute, Vienna (Normentafel No. 27). Modelled by J. Tandler. The lower half of the model divided transversely, seen from above. *A. d.*, right atrium; *A. s.*, left atrium; *Ek. h.*, posterior endocardial cushion of the atrial canal; *P.*, pericardium; *p.Bw.A*, proximal bulbar swelling A; *p.Bw.B*, proximal bulbar swelling B; *S.*, sinus venosus; *S. I.*, septum primum; *V.*, ventricle; *V.p.*, vena pulmonalis (with sound inserted); *V.v.d.*, right valvula venosa; *V.v.s.*, left valvula venosa. × 100.

The posterior surface of the atrium also shows a shallow furrow, which corresponds to the œsophagus. To the right of the broad deep atrial furrow for the reception of the bulbus cordis, the groove corresponding to the attachment of the septum spurium, already described, has greatly deepened, so that a portion of the posterior wall of the right atrium projects in a dome-like manner, forming the spatium intersepto-valvulare. This is bounded below by a short transverse furrow, which separates it distinctly from the region in which the right sinus horn opens. The left sinus horn has emancipated itself from the pericardium to

the extent that at first it remains in connection with it only by a small band, resembling a mesentery, but in later stages this also vanishes and all connection between the sinus horn and the pericardium disappears. Similar conditions occur also in the transverse part of the sinus, except that in this region they occur somewhat later. The right sinus horn continues to enlarge without interruption and at the same time gradually ascends on the posterior atrial wall and is absorbed into the atrium, with the exception of its caudal portion, into which the transverse part of the sinus opens, and of its blind cranial end which is elevated in a

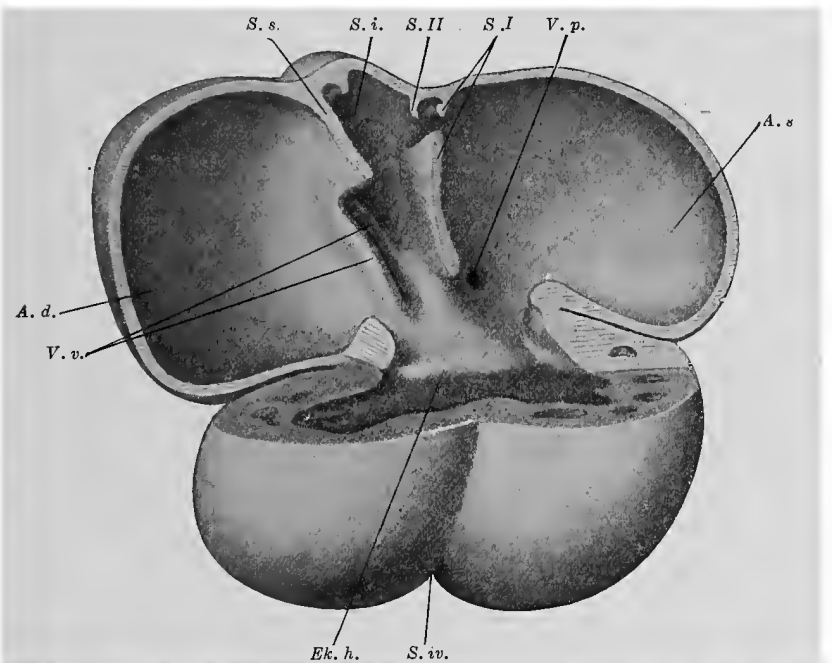

FIG. 380.—Model of the heart of embryo La of 9 mm. greatest length. In the collection of the I. Anatomical Institute, Vienna (Normentafel No. 37). Modelled by J. Tandler. The atrial portion of the model hae been divided frontally and the whole ie viewed from in front. *A.d.*, right atrium; *A.s.*, left atrium; *Ek.h.*, posterior endocardial cushion of the atrial canal; *S.I*, septum primum; *S.II*, septum secundum; *S.i.*, spatium interseptovalvulare; *S.iv.*, sulcue interventricularis; *S.s.*, septum spurium; *V.p.* vena pulmonalis; *V.v.*, right and left valvula venosa. × 75.

dome-like manner and is separated from the spatium interseptovalvulare by the groove already described (compare Fig. 380).

The changes taking place in the interior of the atrium may be described as follows (Fig. 379). The septum I, which grows downward from the posterior upper wall of the atrium and is at first quite low, becomes higher, and its ends, drawn out in a sickle-shaped fashion, extend so far forward along the lower and upper walls of the atrium that they reach the margin of the atrial canal. At the same time the free edge of the septum becomes remarkably thickened and bounds, together with the plane of entrance of the

atrial canal, the primary narrowed opening of communication between the two atria, the *foramen ovale I.* Its line of origin, however, becomes gradually thinner and thinner, and finally there is formed, either directly at the line of origin of the septum on the posterior upper wall of the atrium or immediately below it, a dehiscence, the *foramen ovale II,* which rapidly enlarges. The septum I then gradually separates from its line of attachment and becomes a ribbon-like structure with fluted margins, traversing the atrium from behind and below forward and upward. In such hearts (compare embryo La, Wal, Figs. 380, 381, 382) the original line of attachment of the septum I appears as a slight elevation on the dorsal wall of the atrium, and immediately to the right of

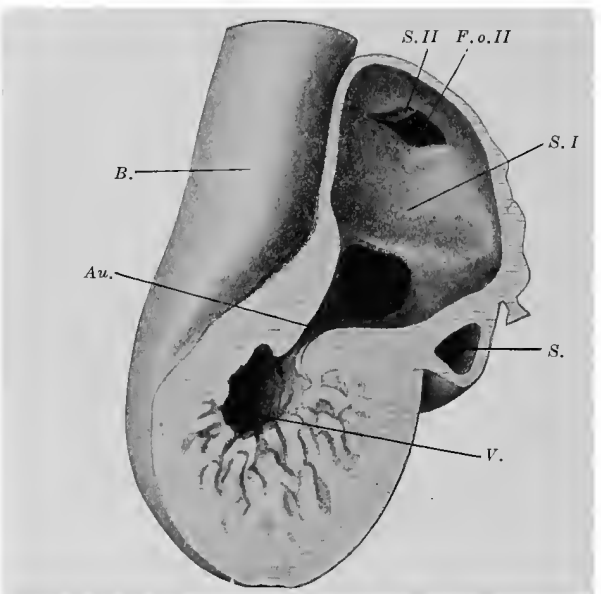

FIG. 381.—Sagittal section through the model shown in Fig. 380, the section passing to the left of the septum I. Seen from the left. *Au.*, atrial canal; *B.*, bulbus; *F.o.II*, foramen ovale II; *S.*, sinus venosus; *S.I*, septum primum; *S.II*, septum secundum; *V.*, ventricle. Below the septum primum and above the atrial canal is the foramen ovale I.

this the elevation of the septum II begins; the further history of this may conveniently be described in the third period of development. In the first period the right sinus valve was the only one present, the left (*valvula venosa sinistra*) being scarcely indicated, but now the latter is strongly developed. The two valves lie one on either side of the slit-like opening of the sinus, which is directed from above and outward, inward and downward (Fig. 379). The left one unites on the cranial wall of the atrium with the thickening of the right valve, which has already been described, and forms with it a large distinct septum-like structure which passes over the cranial wall of the atrium on to the anterior wall and is

the *septum spurium* of His (Fig. 380). Caudally the two valves behave differently, in that the right one gradually flattens out on the floor of the atrium, while the left one extends toward the sickle-like end of the septum II, which is growing backward on the floor of the atrium, and later unites with it.[3] The space between the left valvula venosa and the anlage of the septum II is outpouched dorsocranially to form the spatium intersepto-valvulare. To the left of the septum I, in the angle between the posterior and lower

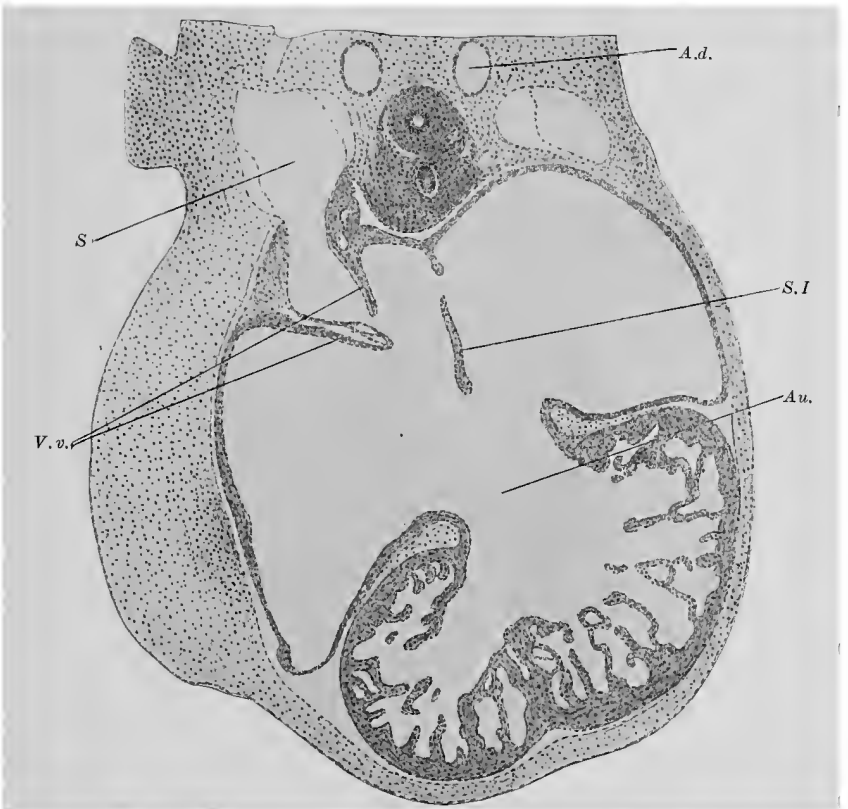

FIG. 382.—Transverse section through the heart region of the embryo Wal of 8 mm. greatest length. In the collection of the I. Anatomical Institute, Vienna. *A.d.*, descending aorta; *Au.*, atrial canal; *S.*, sinus; *S.I*, septum primum; *V.v.*, valvulæ venosæ.

walls of the atrium and in the region where externally the posterior mesocardium is still attached, is the opening of a vessel coming from the lungs, the single *vena pulmonalis* (Figs. 379, 380). In a section through the model of a heart at this stage (Fig. 380) one sees how distinctly the atrium has become separated from the ventricle by the deepening of the atrioventricular groove,—that is to say, how greatly the atrium and ventricle have become ex-

[3] The details of this process will be described with the next period of development.

panded beyond the outline of the atrial canal. Changes in the position and form of this canal have also taken place. As regards its position it is to be noted that it has made such progress in its shifting toward the right that it has already come to lie in the centre of the floor of the atrium. If in the model of a heart at this stage one looks from the ventricle into the atrium through the atrial canal, one sees that the septum I is directed exactly toward the centre of the transverse diameter of the canal (Figs. 379, 380). As the result of this further shifting toward the right the bulbo-atrial ridge, already described, becomes still more prominent and simultaneously with the shifting other changes take place in the canal. In correspondence with the bulging of the ventricle beyond the circumference of the canal, which has already been noted, and, further, in correspondence with the continued undermining of the endocardial cushions by the musculature, the endothelial swellings project freely some distance further into the ventricular cavity. Both the anterior and the posterior swellings become modified in such a way that their lateral extremities become more elevated, while their central parts remain somewhat flatter; consequently one may distinguish in each endocardial cushion a middle straight portion and two lateral elevations or *tubercles.* The shape of the atrial canal in transverse section thus comes to resemble the figure formed by two T's placed base to base (⊢⊣). This peculiar modification of the atrial canal is completed relatively quickly; small endocardial thickenings also appear on the lateral margins of the canal in later stages.

In the ventricular limb on the convexity of the common ventricular cavity,—that is to say, at the point where in the earlier stage the ventricular limb passed into the bulbus,—a constriction appears, extending over the ventricular surface of the heart and gradually becoming shallower as it is traced upward. This *interventricular groove* (Fig. 380) marks externally the separation between the right and left ventricle and divides the blunt apex of the heart into two portions, so that at this stage the right and left ventricle each has its own apex. The portion belonging to the left ventricle is, however, greater than that pertaining to the right one. Corresponding to this external groove, the interventricular septum, already seen in the earlier period as a rounded ridge, becomes more prominent, but just as there is externally an asymmetry in the two ventricles, so too in the interior the subdivisions of the ventricular cavity are by no means equal at first. This inequality of the ventricles is later partly compensated for by a broadening of the right one, but a slight asymmetry persists in that the interventricular septum is so placed that its prolongation would not cut the middle of the atrial canal but the right tubercules of the endothelial cushions.

The most proximal portion of the bulbus has enlarged considerably and has been taken up into the ventricle, and at the same time the greater part of the bulbo-ventricular cleft has disappeared. Processes having an important bearing on the entire subdivision of the heart take place in the bulb during this period of development. Attention has been called to the fact that already in the first period endocardial thickenings develop in the bulbus; these were termed the proximal bulbar swellings A and B, and, as their name indicates, they are situated in the proximal half of the bulbus. They have, as has also been stated, a spiral course around the inner surface of the bulbus, yet they have grown more distally, so that the swelling A, beginning distally on the left posterior wall, passes thence to the left, to finally disappear proximally on the right anterior bulbar wall, as this ascends from the

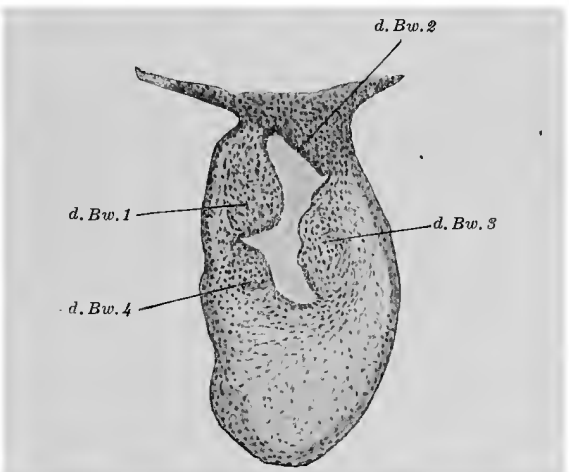

FIG. 383.—Section through the bulbus cordis of the embryo He. The section cuts the bulbus obliquely to its long axis, and consequently the line of attachment of the pericardium is also cut. *d.Bw. 1–4*, distal bulbar swellings 1–4.

common ventricular chamber without any sharp delimitation from it. The swelling B begins distally on the anterior wall of the bulbus and passes thence over the right wall to the posterior one, where it disappears at about the same level as swelling A, at the junction of the bulbus and ventricle. The conditions at the proximal ends of the bulbar swellings will be described in detail later on. In earlier stages an endocardial thickening occurred around the whole circumference of the bulb in its distal portion, and a differentiation of the distal bulbar swellings had not yet taken place. In the period now under consideration these are developed; but it may be said that they do not present the regularity of form and occurrence that obtains in the birds and reptiles. To demonstrate the extent of the proximal and distal bulbar swellings it is convenient to divide the bulbus into a proximal

ventricular and a distal truncus portion; these subdivisions can only be temporary, however, since the bulbus during this period of development undergoes a continuous and rather rapid shortening at both ends. Its central end is gradually taken up into the right ventricle, while the truncus arteriosus elongates heart-ward at the expense of its distal end. In this shortening bulbus the proximal bulbar swellings occupy the proximal half and the distal swellings the distal half; yet this delimitation is not quite accurate, at least for the distal bulbar swellings 1 and 3, to be described below, since these gradually pass over into the proximal swellings A and B. Four distal bulbar swellings can be distinguished, and starting with the right distal one and proceeding to the left and backward they may be denoted by the numbers 1–4. When fol-

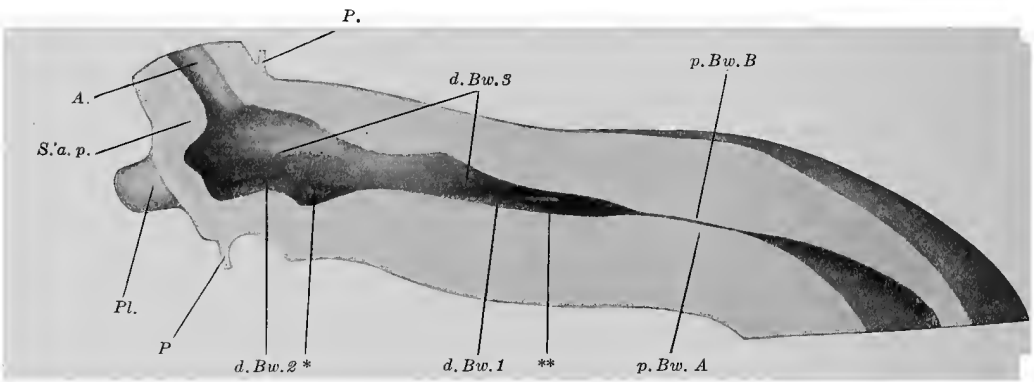

FIG. 384.—Model of the bulbus cordis of the embryo H_8, divided longitudinally. The left half of the model is shown. *A.*, aorta (4th aortic arch); *d.Bw. 1–3*, distal bulbar swellings 1–3; *P.*, attachment of pericardium; *p. Bw. A, B*, proximal bulbar swellings A, B; *Pl.*, pulmonary artery (6th aortic arch); *S.a.p.*, septum aorto-pulmonale; *, point at which the sound in the lumen of the pulmonary artery disappears, being covered by the fusion of the distal bulbar swellings 1 and 3, forming the *distal bulbar septum;* **, point at which the sound again appears in the common lumen. Proximally the aorta and pulmonary artery are separated by the two proximal bulbar swellings coming into contact to form the *proximal bulbar septum.* The subdivision of the common efferent tube is produced distally by the septum aorto-pulmonale, in the middle region by the distal bulbar septum and proximally by the proximal bulbar septum. Between these three portions of the partition there are two points of communication, in which the ends of the sound are visible.

lowed proximally they are seen to run downward on the bulbus walls in a clock-wise spiral. They do not project equally into the lumen of the bulbus, but swellings 1 and 3 are strongly developed while 2 and 4 are weaker. Swelling 1 lies distally on the right wall of the bulb and passes gradually backward and to the left, swelling 3 begins above on the left wall and passes to the right anterior one as it descends; thus it is possible for them to pass over into the proximal swellings A and B in later stages, since swelling A passes distally on to the left posterior and swelling B on to the right anterior wall of the bulbus. The swellings 2 and 4 have a position between swellings 1 and 3, swelling 2 passing from above and behind downward and to the left and swelling 4 from above and in front downward and to the right.

In addition to these two sets of bulbar swellings the *septum aorto-pulmonale,* in so far as it is a derivative of the truncus wall, must be considered in connection with the subdivision of the efferent tube. The partition between the sixth and fourth pairs of aortic arches, which in earlier stages reached to the line of attachment of the pericardium, grows proximally in this period of development and extends into the portion of the efferent tube that is already intrapericardial. At the same time a continually increasing portion of that part of the truncus which was originally outside the pericardium is brought within its territory by the elongation of its walls at the expense of those of the bulbus. The processes by which this change of the walls is brought about will be described later. Three factors, accordingly, take part in the subdivision of the efferent tube, the septum aorto-pulmonale and the distal and proximal bulbar swellings. At the beginning of the second period of development—in embryro H_6 (Fig. 384), for example—these three portions are still distinctly separated. The septum aorto-pulmonale ends bluntly, and with its prolongations are associated the distal bulbar swellings 1 and 3, which for a certain distance still project but little into the lumen, so that in this region the aorta and pulmonary artery still remain in communication; more proximally the two swellings are in contact and consequently separate the two arterial tubes. They terminate immediately below this region of contact and are still distinctly separated from the proximal swellings A and B. At this point the more or less broad, single lumen of the proximal half of the bulb begins, and the proximal swellings, which project extensively into the lumen of the bulb, gradually flatten out. In the succeeding stages of this period the septum aorto-pulmonale reaches the point of union of the distal bulbar swellings 1 and 3, so that the aorta and pulmonary artery become separate throughout the entire extent of the distal half of the bulb; yet even in this stage the limit between the septum aorto-pulmonale and the *distal bulbar septum,* as the union of the distal bulbar swellings 1 and 3 may be termed, may be recognized by the differences in the histological structure of the two partitions and of the walls of the truncus and bulbus.

As regards the tissue differentiation in this period two distinct processes may be recognized: first, the differentiation of the myocardium, and, second, the continued development of the endocardial thickenings. The differentiation of the muscular tissue proceeds more rapidly in the ventricle than in the atrium. In the latter the tissue occurs in the septum I and also in the two sinus valves, the myocardium of these latter being a single structure and no longer appearing as a duplicature projecting into the atrial cavity. It is continued as a strong bundle into the septum spurium, and,

in addition, there are present some muscular ridges projecting into the lumen of the atrium, the first anlagen of the *musculi pectinati.* The right sinus horn, the transverse portion of the sinus, and even the left horn possess a musculature, and in the walls of the atrial canal the atrial musculature at all points is continuous with that of the ventricle. In this two portions may again be recognized, a peripheral cortical and a central trabecular layer, the latter being everywhere more differentiated than the former. In sections in which the trabecular musculature is cut longitudinally (Fig. 385) it may be seen that the fibrillæ have become quite long and occupy the entire breadth of the prismatic cells; correspondingly the boundaries between individual cells are

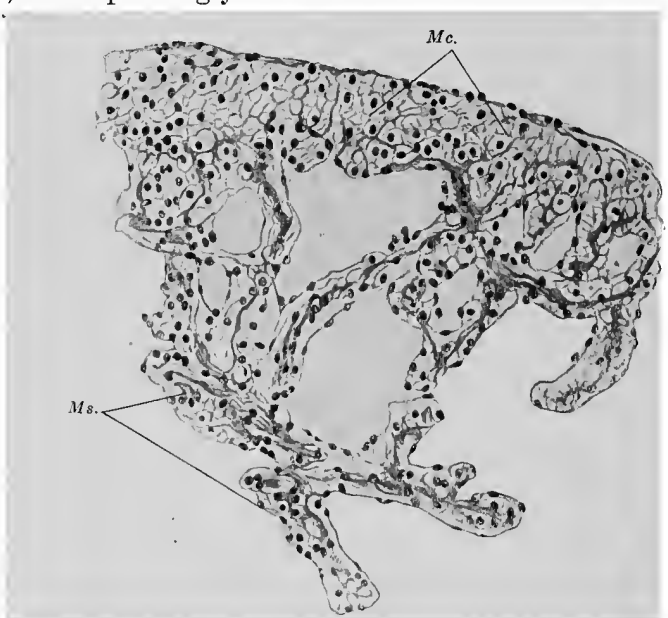

FIG. 385.—Section through the wall of the ventricle of embryo H₈ (Normentafel No. 27). *Mc.*, cortical substance; *Ms.*, spongy substance. Muscle fibrillæ are distinctly visible in the spongy substance. × 150.

still quite distinct where they are in contact by their lateral surfaces, while in those places where their bases are in contact the boundaries have vanished, at least it is impossible to say, on account of the extensive development of the fibrillæ, to what extent these belong to one cell or the other. In transverse sections through trabeculæ the cell boundaries are therefore plainly visible, but at the same time the greater part of the cell body is already occupied by fibrillæ. In sections of the cortical portion one can see that only the peripheral portions of the cells are occupied by very fine fibrils, the central portions being free from them and poor in protoplasm. While the development of the cortical substance in the proximal part of the bulbus keeps pace with that

of the ventricle, the musculature of the distal part is less differentiated. The myocardium of this portion surrounds the bulbus tube as a distinct muscle layer and extends peripherally as far as the distal bulbar swellings can be traced, the layer, however, gradually becoming thinner distally and the differentiation of the myo-epicardial mantle less pronounced, until finally it appears not only as if a further differentiation of it had not occurred, but even as if degeneration had taken place. All those parts of the efferent tube in whose lumen the partition is formed by the septum aorto-pulmonale are destitute of myocardium.

The cardiac endothelium rests smoothly on the subjacent tissue in all parts of the heart and, as in earlier stages, consists of a single layer of flat cells with relatively large nuclei. The endocardial thickenings have the following distribution: in the atrium the free, thickened edge of the septum I is provided throughout its entire length with a small endocardial thickening, whose anterior and posterior prolongations extend as far as the corresponding endothelial cushions of the atrial canal and fuse with them. Consequently the foramen ovale primum is completely surrounded by an endocardial thickening. The shape of the endothelial cushions of the atrial canal has already been described, but it may be remarked that the masses of tissue now stain more deeply with hæmatoxylin and their nuclei are more abundant. The endocardial swellings on the narrow sides of the atrial canal have also been described already. The most important change that occurs in the atrial endothelial cushions is their undermining by the trabecular musculature of the ventricle. In earlier stages the slope of the endothelial swellings toward the ventricular cavity was a gradual one and they did not overhang the ventricle; but now, partly by the downgrowth of the endocardial cushions and partly by the undermining of their attachment, they project freely into the lumen of the ventricle with sharp edges. The undermining is brought about by the continued extension of the trabecular network, which may be followed as far as the attachment of the anterior and posterior endocardial swellings. In the atrial canal itself the cortical and spongy substances are not yet differentiated and as a single sheet pass over into the atrial musculature. The lateral endocardial thickenings have not yet been affected by the undermining process.

The proximal bulbar swellings are bounded externally in their upper parts by the muscle ring of cortical substance; if, however, they are traced proximally they show a change at about the level of the atrial canal, in that there develops between the endocardial thickenings and the cortical substance of the bulb a system of trabecular musculature, which is at first thin and composed of scattered trabeculæ, but increases gradually in thickness toward

the ventricle. Here also the endocardial swellings become undermined by trabeculæ, and in places where the bulbar swellings have ceased for some time to be distinguishable in the model as elevations directed toward the ventricle, one sees as final prolongations of them, endocardial thickenings on the surface of the trabecular network which looks toward the lumen of the ventricle. These conditions show, moreover, the extent to which the progressive absorption of the bulbus into the ventricle has advanced in given cases. Histologically the bulbar swellings differ from the endocardial cushions principally by being somewhat poorer in cells. The distal bulbar swellings are similar in structure to the proximal ones, but the septum aorto-pulmonale is quite different. Here one finds a connective tissue which is very rich in cells with large nuclei and which does not differ from that of the rest of the wall of the aorta and pulmonary artery. This tissue also does not stain diffusely with hæmatoxylin. Where the septum aorto-pulmonale ends—that is to say, where it passes over into the distal bulbar swellings 1 and 3—the histological character of the wall alters, a very delicate ring of but slightly differentiated myocardium making its appearance.

At the conclusion of the period of development just described the subdivision of the heart into the right and left halves has advanced so far that the anlagen of almost all portions of the cardiac septum have appeared and the individual cardiac cavities communicate only by more or less wide openings. In the succeeding *third period* of development the subdivision is completed, with the exception of that of the atria, which, as is well known, only becomes perfect *post partum.* But this period, which includes embryos from about 10 to 20 mm. vertex-breech measurement, and extends from the fifth to the eighth week of fetal life, shows not only the completion of the subdivision of the heart but also the almost complete development of the valve apparatus. At the close of the period the outer form of the heart and the subdivision of the ventricular cavity and bulbus are complete, but only in the next and last period is the final development of the interior of the atrium accomplished and the histological differentiation of the heart then reaches its completion. This period extends to the close of fetal life and, indeed, is not quite completed at birth.

Beginning with the changes that take place in the sinus during this period, it is seen that simultaneously with the gradual retrogression of the left sinus horn, the right one sinks more and more to the level of the posterior wall of the atrium, until finally it no longer is seen rising above the posterior surface of the atrium when the right atrium is viewed from behind. This, however, is not due to a fusion of the atrial and sinus walls, but to the absorption of the sinus walls into the posterior atrial wall by the flat-

tening out of the furrows bounding the sinus and by the passive stretching of the sinus wall, which lags behind the rapidly growing atrium, so that both the transverse and vertical diameters of the sinus are enlarged. Thereby the opening of the superior vena cava (ductus Cuvieri), which has appeared in the meantime, is shifted from the posterior to the upper atrial wall, and similarly the inferior cava is shifted to the inferior wall. The portion of the sinus wall situated between these two vessels becomes at the same time part of the posterior wall of the atrium, and this exogenous portion of the atrial wall is delimited from the parts in its neighborhood by the line of attachment of the two sinus valves. While the right sinus valve is still very high at the close of this period, the left one lags behind in its development and undergoes a modification to be described later.

With this absorption of the sinus wall into the posterior wall of the atrium there occurs a change in the opening of the transverse portion of the sinus into the right sinus horn. This transverse portion, the continuation of the left horn, opened hitherto into the left lower angle of the right sinus horn immediately beside the opening of the inferior vena cava. By the absorption of the sinus the opening is brought to the level of the posterior atrial wall, and with it the spur-like elevation between it and the right horn, representing the former bend of the transverse portion toward the right horn. This *sinus septum,* that seems to arise from the posterior wall of the atrium, now grows so far toward the right that it reaches the valvula venosa dextra and divides this into two portions,—a shorter portion in front of and below the line of meeting of the two structures, and a longer portion behind and above, passing upward over the posterior wall of the atrium and disappearing in the septum spurium. When the last period of development is being considered it will be seen that from the former portion the *valvula Thebesii* is formed and from the lower part of the latter portion the *valvula Eustachii.*

The foramen ovale I closes at the end of the preceding period by the fusion of the free edge of the septum I with the endocardial cushions of the atrial canal, but the foramen ovale II still forms a wide communication between the two atria on account of the feeble height of the septum II. Later this septum increases in height and there is in consequence a narrowing of the foramen ovale II. But in addition another change occurs in the circumference of the foramen, dependent upon a change in the direction of growth of the two septa. This change is as follows: at the beginning of this period the free edge of the septum I, directed toward the foramen ovale II, in the natural position of the heart (the plane of the foramina atrio-ventricularia almost frontal), looks backward and upward; gradually, however, its lower pro-

longation extends backward and upward, at first over the posterior wall of the atrium and finally over the upper wall, while the upper prolongation lags behind in its growth, so that now, with the heart in the same position, the free edge of the septum looks forward and upward. At the beginning of this period the septum II is still low, and its free edge, directed toward the foramen ovale II, looks forward and downward in the natural position of the heart. Later the septum becomes higher and at the same time its anterior prolongation grows forward and downward over the upper wall of the atrium, until finally the free edge of the septum looks backward and downward. The two septa have thus altered their relative positions to the extent that the posterior prolongation of the septum I on the left side has grown past the line of attachment of the septum II, and the anterior prolongation of the septum II has similarly on the right side grown past the line of attachment of the septum I. The left sinus valve now also takes part in the formation of the circumference of the foramen ovale II in the following manner: the outpouching of the right atrium, the spatium intersepto-valvulare, described in the preceding period of development and situated between the left sinus valve or the septum spurium and the septum atriorum, continually lags behind in its growth. Consequently the prominence produced by the spatium on the posterior wall of the atrium also disappears and the valvula venosa sinistra gradually approaches the septum atriorum, and, finally, there remains of the once extensive spatium intersepto-valvulare only a small cleft-like recess, which is closed below by the fusion of the lower end of the left sinus valve with the lower prolongation of the septum secundum. Later, while the destruction of the spatium intersepto-valvulare is taking place by the fusion of the valvula venosa sinistra with the septum I, the upper and middle portions of the left sinus valve vanish more or less completely, but the lower part, persisting on account of its union with the septum II as described above, elongates its free border backward and upward, and so completes later the *limbus Vieussenii,* which is formed from this free border.

In the earlier period of development the single quite short *pulmonary vein trunk* opens close to the line of attachment of the septum atriorum. Later there is an absorption of this short trunk into the posterior wall of the atrium, so that the right and left pulmonary veins open into the left atrium by two separate openings. The portion of the atrial wall between the two openings has therefore been formed by an originally extracardial portion of the pulmonary veins, and later it increases rather rapidly in breadth, so that the two pulmonary veins become separated more and more.

The changes in the form of the atrial canal have been followed

to the time when the canal is a slit so narrow in the frontal direction that its central portion is a mere cleft, while its lateral extremities represent the places in which the atrio-ventricular valves will develop. At the beginning of the present period of development the opposed edges of the slit fuse throughout their whole extent, where the marginal tubercles, that have already been described, occur. In this way the single atrial canal is divided to form the two *atrio-ventricular orifices,* which are separated by the entire width of the zone of fusion. The septum primum rests upon this zone of fusion.

The subdivision of the ventricular cavity has progressed by the ventricular septum becoming higher, so that only a small opening, the remains of the *foramen interventriculare,* exists between its upwardly concave margin and the under surfaces of the endocardial cushions, which, in the meantime, have fused. The anterior end of the ventricular septum, which if prolonged would come into relation with the two right tubercles of the endothelial swelling, passes without interruption into the remains of the bulbo-atrial ridge, while the posterior prolongation applies itself directly to the right tubercle of the posterior endocardial cushion.

Before the processes which lead to the final closure of the foramen interventriculare are described it will be necessary to consider in detail the subdivision of the bulb, since the two sets of processes not only take place simultaneously but also show a causal dependence. After the fusion of the distal bulbar swellings 1 and 3 the lumen of the aorta contains one half of each bulbar swelling 1 and 3 and the whole of the swelling 4, while the pulmonary artery has the other halves of swellings 1 and 3 and the entire swelling 2. The external groove between the aorta and pulmonary artery, which was present in earlier stages only in the distal portion, has now become prolonged proximally and has deepened, so that the two vessels have almost circular lumina.

While the peripheral portions of the distal bulbar swellings flatten out and finally disappear, their most proximal portions, which have come into relation with the proximal swellings A and B, not only retain their former height but increase in size and begin to be hollowed out in their distal slopes. Thus there are formed in each vessel three plump folds directed distally, the first anlagen of the *semilunar valves.* The pouch-like cavities between these folds and the walls of the vessels gradually increase in size, partly by the folds becoming thinner and partly by the outpouching of the corresponding portions of the walls of the vessels, and the evaginations so formed are the anlagen of the *sinus Valsalvæ.* A complete separation of the aorta and pulmonary artery has thus been accomplished, and the semilunar valves develop, as has just been described, from the lower ends of the

distal bulbar swellings. Proximally the proximal bulbar swellings A and B, which have increased in height in the mean time, fuse to form a short septum, the proximal septum bulbi, which extends toward the ventricle from the line of the semilunar valves. This septum lies in the same plane as the septum between the aorta and pulmonary artery, which was formed by the fusion of the two distal swellings 1 and 3, but it becomes replaced by the tissue of the septum aorto-pulmonale as the wall of the truncus arteriosus elongates proximally at the expense of the wall of the bulbus. The proximal septum thins out rapidly as it is traced downward, and, in the natural position of the heart, it extends from the right above

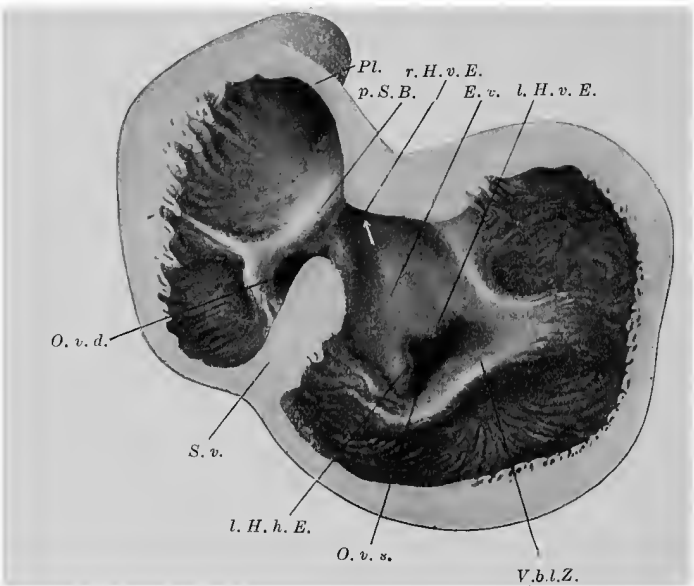

FIG. 386.—Model of the heart of embryo S_2 of 14.5 mm. greatest length (Normentafel No. 58). In the collection of the I. Anatomical Institute, Vienna. Modelled by J. Tandler. The model has been divided transversely midway between the atrio-ventricular groove and the apex of the ventricle and the upper half is shown from below. *E.v.*, the two endocardial cushions fused; *l.H.h.E.*, left tubercle of the posterior cushion; *l.H.v.E.*, left tubercle of the anterior cushion; *O.v.d.*, right ostium venosum; *O.v.s.*, left ostium venosum; *Pl.*, pulmonary artery; *p.S.B.*, proximal septum bulbi; *r.H.v.e.*, right tubercle of the anterior endocardial cushion; *S.v.*, septum ventricularum; *V.b.l.Z.*, lateral cusp of bicuspid valve. The arrow points to the orifice of the aorta. × 44.

and behind to the left down and forward, and consequently does not lie in line with the sagittally placed septum interventriculare, but forms with it a sharp angle, open upward and backward (Fig. 386). The proximal septum bulbi has a free border that is concave downward, and its anterior prolongation, the bulbar swelling A, becomes continuous with the anterior prolongation of the upwardly concave septum interventriculare, while its posterior prolongation, the swelling B, deviates to the right of the right tubercle of the anterior endocardial cushion and becomes greatly broadened and flattened; the posterior prolongation of the septum interventriculare, however, runs toward the right tubercle of the posterior endo-

cardial cushion. If one follows the margin of the foramen interventriculare, beginning with the posterior prolongation of the septum bulbi, it is found to be a spiral ridge, that runs first upward along the free concave border of the proximal septum bulbi, passing anteriorly into the edge of the septum interventriculare, then along this downward and backward and finally upward again, to terminate at the right tubercle of the posterior endocardial cushion. The opening so bounded unites not only the two ventricles, but also leads upward and to the right into the pulmonary artery and to the left and upward into the aorta. It becomes closed in the following manner: the proximal septum bulbi grows downward and reaches the septum interventriculare. The right ends of the endocardial cushions, which have fused in the meantime, undoubtedly participate in the fusion of the two septa, but the extent of their participation cannot be exactly determined, since the entire circumference of the foramen interventriculare is surrounded by endocardial growths which pass into one another. Since from the very beginning the septum interventriculare tends toward the right tubercles of the endocardial cushions, and since the final closure of the foramen interventriculare takes place in the region where they occur, it follows that the right atrio-ventricular orifice lies immediately adjacent to the point of closure, while the left one is separated from it by the entire breadth of the fused endocardial cushions. A further complication is introduced by the fact that the closure of the foramen takes place with the aid of the prolonged septum aorto-pulmonale, so that the right portion of the circumference of the aorta comes to lie at the very point of closure. Consequently the *septum membranaceum,* which is formed at the point of closure, forms a constituent of the wall of the *conus arteriosus aortæ.*

Since the septum atriorum is attached to the endocardial cushions much further to the left than the septum interventriclare. the portion of the fused cushions between the attachments of the two septa, when it later comes to lie in the planes of the septa, does not separate ventricle from ventricle, but the sinus arteriosus aortæ, *i. e.,* the left ventricle, from the right auricle, and it may therefore be termed the septum atrio-ventriculare (Hochstetter). The distance between the semilunar valves and the point of final closure of the foramen interventriculare is still relatively great, so that the aorta, and especially the pulmonary artery, arise from the ventricles as elongated cones. The inner surfaces of the cones are smooth, trabecular musculature not having yet developed in their walls. With the closure of the foramen interventriculare the final subdivision of the ventricular portion of the heart is completed.

The *histological changes* occurring during this period may be

described as follows: The left sinus horn possesses far distally a muscle mantle that is interrupted by the openings of certain cardiac veins. The differentiation of this musculature, as well as of that in the region of the atrial wall which has been formed by the absorption of the right sinus horn, lags far behind that of the rest of the atrium. In the regions of the septum I and the septum II, as well as in the sinus valves, musculature is present, but it has made no especial progress in differentiation. In the portions of the atrium which represent the auricular appendages trabeculæ have developed, more apparently on the right side than on the left. In the small area of the left atrium, which was formed by the absorption of the pulmonary trunk, no musculature is evident

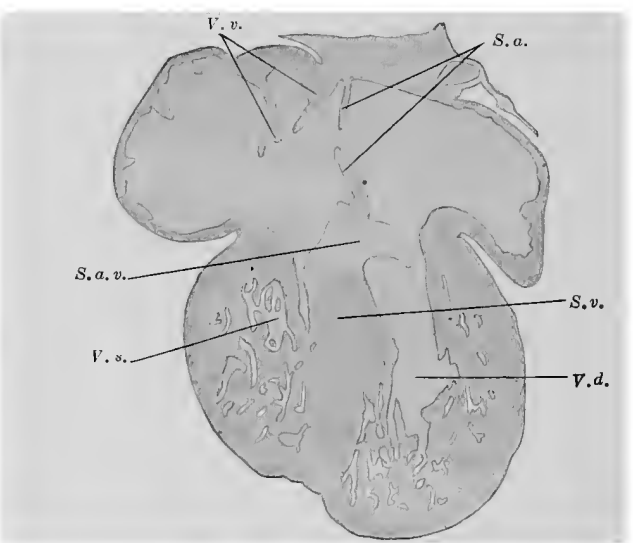

FIG. 387.—Section through the heart of embryo Mi of 16.75 mm. greatest length. In the collection of the I. Anatomical Institute, Vienna. Semidiagrammatic. *S.a.*, septum atriorum; *S.a.v.*, septum atrioventriculare; *S.v.*, septum ventriculorum; *V.d.*, right ventricle; *V.s.*, left ventricle; *V.v.*, valvulæ venosæ.

at this period. As to the ventricular musculature it may be noted in the first place that the wall of the left ventricle undoubtedly surpasses that of the right in thickness. The difference depends, however, especially on the cortical substance. The trabeculæ are exceedingly numerous and almost fill the entire cavities, yet they are not so uniform in thickness and differentiation as in the earlier stages, but trabeculæ conspicuous by their strength and advanced differentiation occur in both ventricles. These trabeculæ, from their topography and from their relation to the valves, are to be identified as anlagen of the *musculi papillares*. While, at the beginning of the period under consideration, the cortical substance was relatively thin, at the end of the period it has become greatly developed and its fibrillar structure has made further progress.

In longitudinal and transverse sections through the cardiac musculature the individual muscle-cells show distinct cell boundaries on their long sides, but pass into one another on their short sides without any delimitation, a condition that was present to some extent in the earlier period of development, but has now become general. To this extent it is proper to speak of a *cardiac syncytium* at the end of this period.[4] At the same time the myocardium shows a further differentiation in that the individual rows of muscle-cells have already become arranged to form muscle bands, just as one sees them in the adult heart.

While up to the present the atrial and ventricular musculatures were continuous around the atrial canal, one now sees these two portions of the musculature lose their continuity. In earlier stages there was along the line of the atrio-ventricular groove an aggregation of embryonic connective tissue, which was wedge-shaped in section, the edge of the wedge being directed inward. In later stages this wedge gradually becomes prolonged toward the cavity of the heart and cuts so deeply in between the atrial and ventricular musculature throughout the entire circumference of the atrio-ventricular groove that the direct continuity of the atrial and ventricular cortical substance is interrupted. Thus the original continuous cortical musculature is divided into two portions, a sinus-atrial portion and a ventricular portion, while the trabecular parts are still in continuity at the anlagen of the valves.

The changes in the form of the endocardial thickenings occurring in the atrial canal and in the bulbus have already been described. The following points may be noted as regards their texture. The plump semilunar valves, formed from the proximal ends of the distal bulbar swellings, do not yet show any special differentiation of their tissue, at least their diffuse staining has not appreciably diminished, although the nuclei of these portions of the endocardial swellings are perhaps somewhat more closely set than formerly. The part of the *septum aorto-pulmonale* that follows, *i. e.,* the proximal septum bulbi, still shows all the characteristics of endocardial growths, as do also its prolongations, the remains of the bulbar swellings A and B. If one follows the bulbar swelling A, one sees the tissue characteristic of such swellings fade out at the free edge of the septum interventriculare and pass posteriorly without interruption into the fused endothelial swelling. The tissue of the posterior bulbar swelling becomes

[4] The old discussion concerning the boundaries of the cardiac muscle-cells cannot be considered here. As has already been described, the fibrillæ pass beyond the cell territories, a condition which may justify the term syncytium. The condition described above is not, however, sufficient for the settlement of the question, since the staining of the objects (hæmatoxylin-eosin) is not suitable for final conclusions.

greatly broadened and in part passes medially into the tissue of the endocardial cushions and into the endocardial thickening on the free edge of the interventricular septum, and in part it passes laterally toward the lateral circumference of the right atrio-ventricular orifice and may be followed for some distance toward the apex in the posterior wall of the ventricle.

When the closure of the interventricular foramen is completed, nothing can be determined as to the origin of the various parts contributing to the closure from their texture, the entire region being occupied by an endocardial tissue, relatively poor in cells and staining diffusely with hæmatoxylin, and which at the very spot of the future septum membranaceum undergoes rather soon a further development; it loses its diffuse staining with hæmatoxylin and at the same time becomes richer in cells. The anlagen of the valve cusps, which arise from the anterior and posterior endocardial cushions, as well as from the endocardial thickenings at the lateral ends of the atrial canal, lag behind the region just described in their differentiation (Fig. 387). These anlagen are plump and their undermined borders are connected with the trabeculæ of the ventricles. This connection is quite distinct where especially strong trabeculæ, the anlagen of the musculi papillares, come into connection with definite portions of the valves. In such places it is possible to follow muscle bundles ascending from the cortical substance through the entire length of the papillary anlage to the valve. The muscle bundles on the atrial surface of the valve anlagen which have been described as passing toward the ventricles are apparently continuous with the ventricular bundles just described; at least no boundaries between the two could be made out. Thus the valve cusps are for a time a series of plump elevations, consisting partly of endocardial growths and partly of musculature; a differentiation into actual musculi papillares, chordæ tendineæ, and valve flaps cannot be distinguished at this stage.

In addition, the degenerated processes which occur in the region of the bulbus cordis are of interest. At the beginning of the period under consideration the undermining of the proximal bulbar swellings by the trabecular myocardium has not extended very far. The older the embryo, the more the trabecular tissue grows toward the line of attachment of the semilunar valves. On the other hand, one sees the cortical substance, which formerly surrounded the bulbus far distally, gradually receding, the recession being accompanied by a simultaneous change in the structure of walls of the derivatives of the distal part of the bulbus, the aorta and pulmonary artery. The typical wall of the two arteries extends gradually proximally, until finally this typically layered wall, destitute of myocardium, may be followed to near the semi-

lunar valves. The part of the bulb immediately distal to the valve zone thus becomes surrounded by a common myocardial layer, so that in this stage of development the future bulbus aortæ is surrounded for a considerable distance by cardiac musculature. Toward the end of the period this portion of the musculature is so far degenerated that the relation of the aorta to the musculature is almost that which obtains in the heart of the child.

In the following period of development the parts of the heart that have been already elaborated undergo a further modelling and are slightly altered, but one sees nowhere any extensive transformations of the constituent parts of the heart. The same is true also with regard to the further histological differentiation.

As regards, first of all, the sinus portion of the heart, one sees that, in consequence of the apposition of the left sinus valve to the septum atriorum, the latter comes to represent the medial boundary of the sinus area, while the lateral boundary is formed by the derivatives of the right sinus valve or of the septum spurium. It is therefore necessary to consider first the extensive modifications of the right sinus valve (Fig. 388). As was noted in the account of the preceding period of development, this broad valve, which projects markedly into the lumen of the atrium, is divided by the apposition of the sinus septum into two parts, an anterior inferior (ventral) and a posterior superior (dorsal). The dorsal portion of the valve is continued without interruption into the septum spurium, which formerly served as a common stay for the two valvulæ venosæ, and later it undergoes further modifications. The portion of valve corresponding to the posterior wall of the atrium, which was also originally high, gradually flattens and forms a prolongation of the ridge-like elevation of the septum spurium on the upper wall of the atrium, carrying it over this wall backward and downward. This small ridge, which forms the persistent lateral boundary of the original sinus area, consists in its upper portion of the rudiment of the septum spurium and in its posterior inferior portion of the rudiment of the right sinus valve, the *crista terminalis* of His.

The lower part of the dorsal portion of the sinus valve remains high and bounds the opening of the inferior vena cava laterally, as the *valvula venæ cavæ Eustachii.* Frequently one may actually speak of an increase in the surface of this portion, but the valve presents great variation in its height, development, and form. In accordance with its development the valvula Eustachii is continuous above and behind with the crista terminalis and in front and below it ends at the border of the transverse portion of the sinus, *i. e.,* the *sinus coronarius cordis.*

The ventral, much smaller portion of the right sinus valve bounds the opening of the sinus coronarius, that has been formed

from the transverse portion of the sinus, and eventually becomes the *valvula Thebesii.*

Since the atrial septum must furnish until birth a means of communication between the two atria, a final closure of this portion of the heart cannot occur during embryonic life. In the developmental period under consideration the septum I increases in height more rapidly than its surrounding parts increase in extent; the communication between the two atria thus becomes somewhat narrowed, but, on account of the oblique position of the septum I, it continues to be wide enough to allow free passage of the blood from the right atrium into the left. The oblique position of the septum I is not determined by any special mode of growth of the

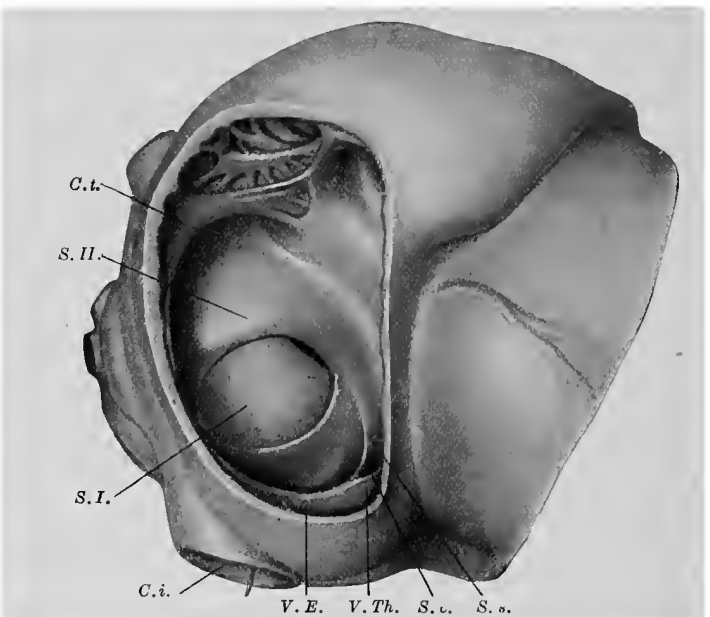

FIG. 388.—Model of the heart of an embryo of 310 mm. greatest length. Modelled by Born. *C. i.*, vena cava inferior, in which a sound is placed; *C. t.*, crista terminalis; *S. I*, septum primum; *S. II*, septum secundum; *S. c.*, opening of coronary sinus; *S. s.*, sinus septum; *V. E.*, valvula Eustachii; *V. Th.*, valvula Thebesii.

septum, but is produced mechanically by the greater pressure of the blood in the right atrium. The septum I, *i. e.*, the valvula foraminis ovalis Vetteri, only attains its definitive position when the blood pressure becomes equal in the two atria, and then only does it have an opportunity for fusing with the septum II and so bringing about the final separation of the two atria.

Before mentioning the changes that take place in the ventricles and the valve apparatus, a few words are necessary as to the modifications that now occur in the left atrium. By the absorption of the originally single pulmonary vein trunk, these veins are now represented by two stems, and at the same time a new portion,

corresponding to the distance between the two pulmonary orifices, has been added to the atrial wall. This portion continues to increase in breadth, and at the same time the absorption of the two pulmonary vein stems progresses until these have been taken up into the atrial wall as far as their first division. As a result the originally single openings of the right and left venæ pulmonales become again divided, so that on either side there is an upper and a lower pulmonary vein orifice. The portion of the atrial wall between each pair of pulmonary veins was likewise originally a part of the wall of the veins. It will thus be seen that the participation of the pulmonary veins in the formation of the wall of the left atrium is quite extensive.

The anatomical changes occurring in the ventricular portion of the heart during this period can be briefly described. The valve apparatus alone undergoes further elaboration in that the differentiation of the *valve cusps,* the *chordæ tendineæ,* and the *musculi papillares* makes further progress and the formal differentiation of the semilunar valves increases.

The *histological differentiation* of the heart approaches its conclusion during this period. The principal changes occur in connection with the valve apparatus, but before this is described it will be necessary to consider briefly the remaining portions of the heart. And, first of all, it may be noted that even in the latest fetal stages the development of the sinus musculature lags behind that of the rest of the atrium.

While the part of the right sinus valve which becomes the valvula Eustachii continues to lose its musculature, that of the crista terminalis continually increases. The rudiment of the left sinus valve still shows traces of musculature in later stages of fetal life, as, for instance, in a fetus of 150 mm. vertex-breech length. The originally thin margin of the limbus Vieussenii thickens by the development of strong muscle bundles in it.

The portion of the left atrial wall lying between the openings of the pulmonary veins was destitute of musculature in the earlier period of development, but in this period it acquires a complete muscle layer. The differentiation of the musculi pectinati takes place more rapidly than that of the remaining portions of the atria.

The greater thickness of the cortical substance of the left ventricle continually increases (Fig. 389), and the fibrillæ of this layer become more and more abundant until the difference between the cortical and spongy substances which obtained at the beginning of the period now under consideration gradually disappears. In this period also loose subepicardial connective tissue appears on the surface of the heart along the lines of the vessels and nerves.

The semilunar valves become thinner, their connective tissue

loses its succulent character, becoming fibrous and tendinous, and finally presents the characteristic appearance seen in the child.

While in the earlier period the endocardial portion of the atrio-ventricular valves greatly surpassed the muscular, at the beginning of the present period the trabeculæ which pass from the spongy substance of the ventricle toward the valves increase greatly, and at the same time the central portions of the valves come to project further into the lumen, owing to the growth of their peripheral portions. In accordance with this process the trabeculæ of the spongy substance, which originally were almost immediately in contact with the cortical substance in the neghborhood of the atrio-ventricular orifices, separate from the corticalis more and more and pass centrally. In this stage also not one free-ending trabecula could be found as an indication of a secondary union between the valves and the papillary muscles. At this time also

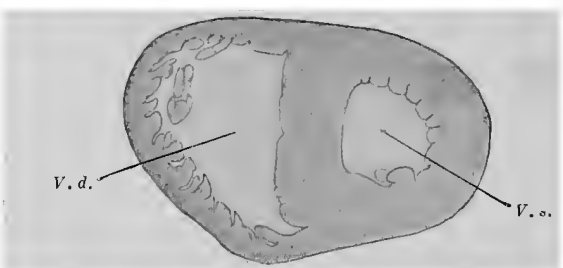

FIG. 389.—Section through the heart of an embryo of 165 mm. greatest length. *V. d.*, right ventricle; *V. s.*, left ventricle. The difference in the thickness of the two ventricles is apparent.

the musculature on the atrial surfaces of the valves becomes greatly developed, so that, in comparison with later stages, it actually seems as if the valves were exclusively muscular in structure, with the exception of the purely endocardial marginal portions which are directed toward the lumen. Later the musculature degenerates, at first in the valve areas, and connective tissue takes its place, standing in intimate connection with the connective-tissue wedge which was described as occurring in the earlier stage of development and which separates the cortical substance of the atria from that of the ventricles. Still later one sees that the peripheral portion of the ventricular valve musculature degenerates, at first at the surface and then more deeply, giving place to connective tissue and so becoming transformed into *chordæ tendineæ*. In later stages accordingly one must distinguish between a connective-tissue *valve* (the *secondary valve* of Bernays), *chordæ tendineæ*, and *papillary muscles*. The free margins of the valves at certain points retain for a longer time the characteristic structure of the endocardial thickenings, while in other points they are converted into typical connective tissue. These thickenings represent the *noduli Albini*.

APPENDIX.

The developmental history of the *atrio-ventricular system* is at present practically unknown. The time allowed for the completion of the present article did not permit a thorough study of the question and a satisfactory solution of it, and I shall therefore state the results of my observations briefly.

In a human embryo of 19.75 mm. one sees at the upper border of the septum musculare, close to the lower surface of the not yet completely differentiated endothelial swelling, a triangular area, which occupies the tip of the muscular septum and is distinguishable even under a low magnification by its special staining properties. Its nuclei are dark and the cell bodies stain faintly with eosin. It is not unlike a sympathetic ganglion, but its cells are less numerous. This structure corresponds in position with the stem of the *His bundle,* and it already possesses a right and left prolongation, which are the right and left limbs of the atrio-ventricular system.

An embryo of 28.5 mm. shows a similar condition at the same region, but the two limbs have become longer and the cells larger. A similar aggregation of cells is to be seen in the region of the septum atriorum, immediately above the septum membranaceum.

In the study of the development of the bundle of His the following point is of importance.

The conducting system may either be a persistent connection between the atrial and ventricular musculatures situated in the posterior wall of the heart, in which case it would represent an ancient connection between the two parts of the heart, or it may be a new development which has been formed only after the completion of the septum, in other words only secondarily. If the latter be the case, the conducting apparatus of hearts without a septum is quite a different affair from that of hearts which possess a septum. Furthermore the conduction of stimuli in hearts which possess a septum must be a different affair before the development of the septum—that is to say, before the development of the bundle of His—from what it is later on.

So far as my observations go, I incline to the view that the His bundle does not represent the persistence of an ancient atrio-ventricular connection. This view has also been expressed by Retzer, who has supplied some data as to the development of the atrio-ventricular system of the pig.

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III. THE DEVELOPMENT OF THE VASCULAR SYSTEM.

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1. General.

We shall consider here, first, the more general questions concerning the development of the vascular system, and, secondly, the special development of the vascular system in human embryos.

In recent years studies on the vascular system of the higher vertebrates have opened up new and profitable fields and have given us a better conception of the method by which the blood-vessels grow and become transformed in the general growth of the embryo.

In the following account I shall confine myself to the history of the chief vascular trunks only,[1] for here our knowledge now stands on a firm footing, and any laws which we may discover as applicable in these instances may safely be taken as of general worth.

The two fundamental questions involved in the development of the vascular system are—

1. What is the origin of the blood-vessels in the body of the embryo?

2. What is the primitive form of the vessels in any area, and the manner of change from this to that of the adult?

These two aspects of the subject thus concern themselves with the problem of the cellular antecedents of the endothelium, on the one hand, and with the principles governing the architecture of the vascular system, on the other.

To the former problem it is still impossible to give any decisive answer, but to the latter I trust the reader will see that a flood of new light has come.

[1] There exist few accounts of the development of peripheral vessels, but mention may be made of the work of Mall, Flint, Miller, Sabin, and Fuchs.

1. Human embryos, as will be mentioned further on, have contributed little information on the origin of the cells forming the vascular system, and indeed after a wealth of observations on other animals this question is still a very open one, having met with a decisive answer in no case.

In embryos of the higher vertebrates the first cells which can be identified as standing in any relation to the vascular system are in the form of localized thickenings of the extra-embryonic mesoderm[2] lying next the endoderm of the yolk-sac. These constitute the so-called vascular anlagen, and typically undergo a gradual differentiation from a nest of indifferent cells into two more definite cell types, blood-cells on the one hand and endothelium on the other. The endothelial cells enclose the former, and, continuing to divide, produce vascular sprouts and thus extend themselves into new areas. While this differentiation of the earlier anlagen is progressing, new anlagen are formed by the mesoblast, but eventually a time is reached when this latter process ceases, and subsequently in the history of the embryo all endothelium is derived from that of pre-existing vessels. That this is the case in older embryos and in the adult has been verified by many observations. It is important, then, to distinguish vessels which have arisen through the sprouting of the endothelium of other vessels in contrast to vessels whose endothelium has been contributed directly from the neighboring mesoderm. Even on the yolk-sac these latter vessels which arise *in loco* are not numerous, for they only occur at the site of the so-called anlagen, and the main mass of the vitelline capillary plexus arises from the extension and frequent anastomoses of these primary vessels.

It is a question now whether the early blood-vessels in the body of the embryo itself are not formed by an ingrowth of the vitelline capillaries, or whether, on the other hand, the embryonic stems, or at least a part of them, do not arise *in situ* from the mesoderm of the body. Both of these positions have been defended, the name of His (1900) being identified with the former idea and that of Rückert and Mollier (1906) especially with the latter.

In the birds it has been possible to establish beyond all doubt that most of the aorta descendens is formed from the medial margin of the vitelline capillary plexus (Vialleton 1892, His 1900, Evans 1909; see Fig. 390). The frequent early connections of this vessel with the same plexus in mammals makes it highly probable that a similar origin obtains here (Türsting, 1884). For the head portion of the aortæ, on the other hand, conflicting accounts are given. His described it as arising from a continued growth of the same extra-embryonic capillaries which formed the vessel in its lower course, but which were restricted to a capillary chain growing headward, eventually turning ventrally over the blind end of the head-gut and fusing with the cephalic portion of the heart tube. On the contrary, Rückert and Mollier have given various details of what they consider the local origin of the aorta in this locality from the mesodermal cells of the lateral plate of the mesoderm and from the splanchnic mesoderm. It is not possible then to state positively that the yolk-sac anlagen are the only source of the endothelium of the body vessels, for the earliest of these latter may themselves

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[2] Although lying in the mesoderm, these anlagen may have actually arisen from the entoderm. This is the view taken by Ruckert (1906), who has been the last to subject the question to a special study. On the other hand, most investigators, beginning with Kölliker's early work on the rabbit (1875), have emphatically denied any entodermal participation here, and affirmed that the blood islands of mammalian embryos are to be looked upon as special localized proliferations of the mesoblast. Robinson (mouse) and Heape (mole), Janosik (marmot, pig), Fleischman (cat), Keibel (guinea-pig, man), and Van der Stricht (rabbit and bat) may be mentioned.

be primary vascular anlagen in the sense of being directly derived from neighboring mesoderm. Another possible source for the endothelium of the vessels of the head is constituted by the paired anlage of the heart (C. Rabl, 1887).[2a]

After the establishment of the aorta it is possible to satisfactorily deny the further local origin of any of the subsequent vessels of the embryo, since these can all be demonstrated to arise from capillary sprouts of true vascular

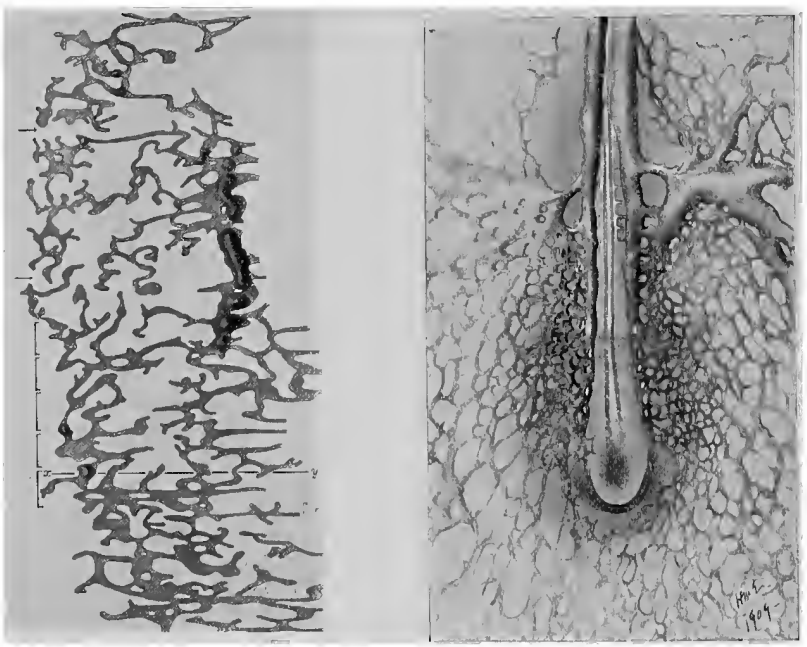

Fig. 390*a*. Fig. 390*b*.

Fig. 390*a*.—Ventral view of the left side of a rabbit embryo of five somites, showing the vascular plexus from which the left heart and aortæ are derived. The heart is already indicated as an especially enlarged member of the mesh. This is not yet true for the aorta; the arrows indicate two places where the aorta is as yet unconnected into a longitudinal plexus. The brackets show the position of the five somites. (After J. L. Bremer.)

Fig. 390*b*.—Ventral view of posterior portion of an injected chick embryo of 20 somites, showing the formation of the lower aortæ from a capillary plexus continuous with that of the yolk-sac.

endothelium, just as is the case in every locality where the development of vessels has been carefully studied in the living animal, *e.g.*, the tail of the living frog larva.

The various claims for a local origin of blood-vessels relatively late in the growth of the embryo have gradually been successfully disproved. It will be remembered that the appearances known to many observers as Ranvier's "vaso formative cells" were supposedly instances in which a local origin of blood-vessels occurred relatively late in the growth of the embryo. Recently Vosmear (1898) has shown

[2a] Since the above was written, Bremer (1911) has demonstrated that in the head of rabbit embryos of five somites, the aorta is represented by a distinct plexiform angioblast coterminous with the vitelline angioblast. These facts make it highly probable that the extra embryonic endothelium has grown into the body in this region just as can be demonstrated in successive stages for the more caudal portion of the aorta of the chick.

that the vessels in question were isolated secondarily after having clearly arisen from other vessels, and Clark has observed the same phenomenon in the living frog larva (personal communication). (See also Renant, 1901, 1902.)

It would seem that a mere histological analysis, even though on perfectly fixed material, would not suffice to settle the question of the delicate connection of embryonic vessels. These collapse so readily that the most perfect of the usual methods of study will not suffice to disclose them. On the other hand, injections of the vascular systems in young embryos show a wealth of capillaries and interconnections not hitherto demonstrable, and it would consequently seem unwise to overvalue any negative evidence in this respect given by uninjected embryos.

It is evident, then, that, while it is probable that the only source for the endothelium for the blood-vessels is comprised in the cells of the vascular anlagen, it is nevertheless possible to prove that this source is comprised in the endothelium of the first intra-embryonic vessels (aortæ and cardinal veins), however these may have arisen. Injections of the embryo after these early stages and subsequent exploration with the microscope show no vessels unconnected with the general system, and lead us to be certain that new vessels in any area arise exclusively as offshoots from the older ones. This doctrine of the specificity of the endothelium has met many apparent confirmations in the histogenesis of new growths, for there also, as in normal development, Rabl's dictum is doubtless true, "Endothelium only from endothelium."

2. Concerning the development of the form of the vascular system, two positions have been taken,—one, that the arteries and veins grow out as single trunks to their respective territories, the other, that the first vessels in any area are capillaries usually in the form of a typical plexus from which secondarily arteries and veins arise.

It will be seen that a correct conception of the actual truth here affects vitally our ideas even of the factors concerned in development as a whole; for it is difficult to see in the blind outgrowth of single trunks to their future territory anything but a teleological design or hereditary predestination. On the other hand, the adherents of the idea of a capillary plexus ancestry for vessels view the vascular system as functioning from the beginning, and the formation of arteries and veins as only an expression of the functional adaptation of these plexuses to a beating heart.

The immense number of vascular variations in the adult, which seem to take every conceivable direction, and the occurrence of arterial and venous anastomoses, early led the Swiss anatomist Aeby (1868) to suppose that the vascular system, arteries as well as veins, existed originally in the form of a uniform mesh-work of vessels, in which, so to speak, a competition took place for supremacy, and, the victors being the only trunks remaining, we obtained the dendritic branched appearance of the adult vascular system. Occasionally the primitive net was retained, and in these instances we saw retia mirabilia, or merely anastomoses between vessels.

In the case of variations the theory was most convenient, for the hypothetical uniform net furnished the possibility for a vessel to course in practically any direction. At a loss for a better explanation, Krause (1876) adopted the Aeby hypothetical plexus to account for the vast range of blood-vessel variations which he recorded in his well known chapter in Henle's Handbuch. But until recently Aeby's ideas have met with no other favorable reception. Indeed they were strongly opposed by the careful work inaugurated by the rise of a more exact comparative anatomy, in which C. Gegenbaur and his pupils are to be mentioned. Extensive comparative investigations soon showed that there was to be observed everywhere a remarkable constancy in the number and position of the vascular trunks and their relation to other structures (muscles, nerves).

Ruge's (1883) epoch-making work in this field demonstrated clearly that when variations occurred they tended to group themselves into quite definite types, which could be explained by the over-development of normally inconspicuous

vessels, " collateral stems " or aberrants. Thus the old conception of the outgrowth of single trunks was only strengthened, for there could be considered present in anomalies only an unusually strong outgrowth of a normally small trunk. Moreover, another authority in this field, F. Hochstetter, took occasion to denounce the Aeby-Krause idea. In his study of the developing vessels in the early limbs, Hochstetter declared he could find no instances of an indifferent condition of the vascular system anywhere in the limb buds, and that consequently " die Hypothese Baader's und Krause's als vollkommen unrichtig bezeichnet werden muss." [3] (Hochstetter, 1891, p. 42.)

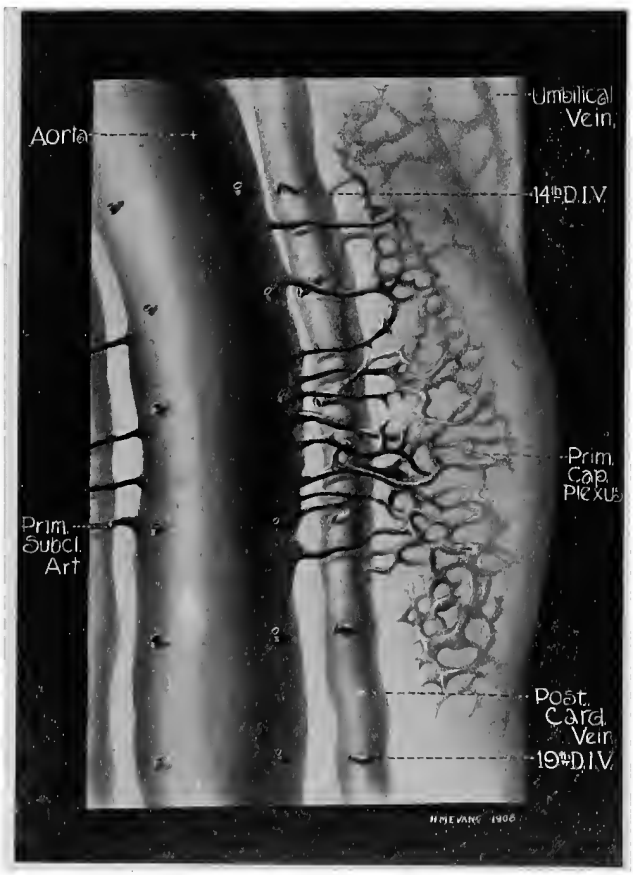

FIG. 391.—Injection showing the profuse outgrowth of primary subclavian capillaries into the early wing bud of a chick 60 hours old. 14th D. I. V., fourteenth dorsal intersegmental vein.

In 1894 R. Thoma published the results of a study he had been conducting on the ancestry of the vascular trunks present in the chick's yolk-sac. Thoma set himself the task of solving how it came about that arteries and veins were

[3] This statement was at least partially justified by the simple conditions Hochstetter saw in the vessels of the limbs and tail of Triton, for here the vascular trunks are remarkably simple and suffer a more or less direct transformation into arteries and veins. That such simple conditions do not apply to the limbs of higher vertebrates (birds and mammals) the studies of Göppert (1910) and myself (1909) will demonstrate.

differentiated in this locality. Early stages showed him only an indifferent network of vessels in which no predominate trunks could be distinguished, and he was able to secure successive preparations showing the gradual formation of arteries and veins from this capillary net. The elaboration of these larger supplying and draining vessels represented merely a functional adaptation of the net to the demands of the circulation and a fortuitous location with regard to the aortæ or the venous ostia of the heart determined the use and enlargement of certain channels of the net to become arteries and veins respectively.

Thoma's ideas did not at first attract the notice they deserved. Nevertheless, Mall (1908) indicated that they were applicable in the development of the

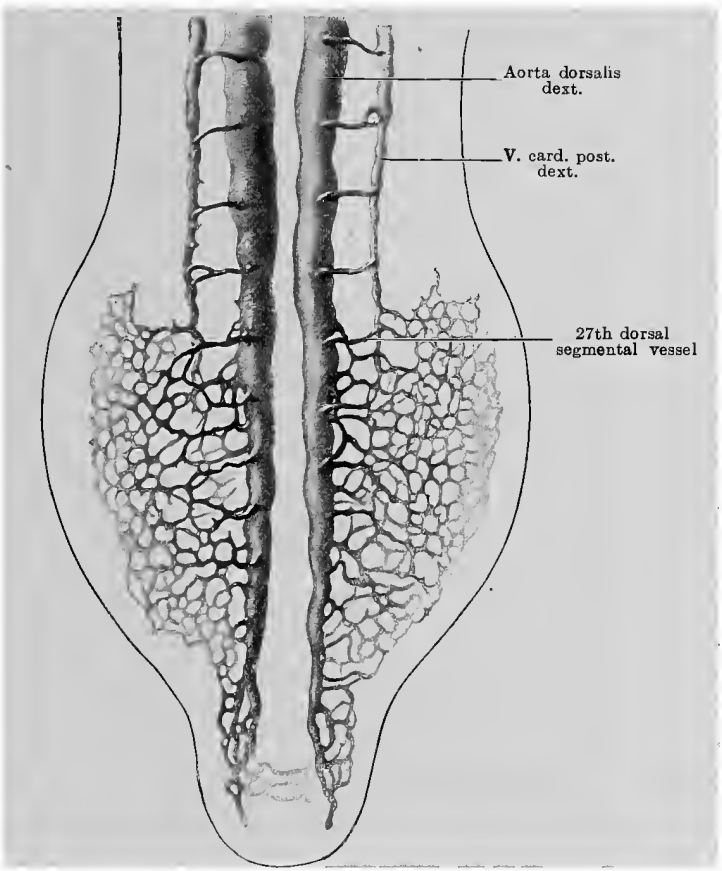

FIG. 392.—Injection into the early leg buds of a chick of 32 somites, showing the capillary plexus.

body's vascular system no less than in the extra-embryonic area vasculosa, and in succeeding years he and his pupils repeatedly furnished evidence that such was indeed the case. Flint's (1903) study of the submaxillary gland and more recently of the lung (1906) showed that a capillary net always existed at the periphery of the growing vascular tree, and Mall (1906) instanced the same phenomena in the division and growth of the lobules of the liver. It may be noted that Zuckerkandl (1894) had reported an exactly similar phenomenon in the development of the median artery of the arm, for the early stages in the history of this vessel were represented by a chain of capillaries accompanying the median nerve.

In 1903 E. Müller reported the results of a study of the development of the vessels in the human arm. His reconstructions showed that in some instances what is undoubtedly a true arterial plexus may exist in the region of the axillary artery.[4] These appearances were quite impossible to harmonize with the old idea of the outgrowth of single vascular trunks and led Müller consequently to dispute this prevailing notion.

Four years later H. Rabl published the results of his study of the early vessels in the wing bud of the duck, and showed clearly that many of these could be detected in arising from parts of a capillary plexus. Rabl also established the origin of the secondary subclavian artery, which characterizes the birds, from a chain of capillaries which grows caudally from the third aortic arch to join the plexus of the wing bud.

Above all, now, the admirable study of the vessels in the developing arm of the white mouse which E. Göppert has recently published shows clearly the development of the successive branches of the subclavian artery "auf der Grundlage eines capillaren Netzes," and I cannot doubt but that in the further growth of the vascular system, in the various regions of the body, we will be able to observe these facts again and again.

Very recently methods of injecting living embryos so that the delicate vascular system is completely filled and yet extravasations avoided, have yielded a wealth of facts on the development of the vessels. *The revelations due to such preparations have enabled us to see the capillary precursers of some of the more fundamental vascular trunks of the body.*

Thus, if injections of chick embryos are made just preceding and during the time in which the limb buds are beginning to be elevated from the body wall, it is possible to trace the earliest vascularization of the limbs. Such preparations show that a series of capillaries springs from the lateral aortic wall opposite the limb eminence, and, anastomosing together, form a typical capillary plexus in the early limb tissue. The preservation and enlargement of one of these many aortic offshoots constitute the subclavian and sciatic artery respectively (Figs. 391 and 392).

Still other large vessels in the body can be traced to a similar stage in which there exists only a simple capillary plexus, out of which the main vessel arises through the utilization of a single channel in the mesh and the coincident atrophy of the remainder. Thus, in the early stages the head of the embryo possesses as its only vessels a delicate plexus of capillaries which arise at many points from the aortæ and more caudally are connected with the vitelline vein. Eventually with the circulation through this primary head capillary plexus, arteries and veins are formed from some channels in the mesh, and it is exactly in this way that the main stems of the internal carotid artery and jugular veins are formed (Figs. 393, 394, 395).

The pulmonary arteries are represented at first by a capillary plexus which arises from the sixth aortic arches and grows caudally on to the lung bud (Fig. 396).

In the chick it is easy to see that the gut arteries are earliest represented by a plexus of capillaries which arise from the ventral aortic wall.

With all these instances, however, of an early plexiform anlage for many

[4] A fact which has more recently been confirmed for the mouse by the important researches of Göppert (1909) in the same territory. The exact significance which Müller would attach to this axillary plexus must be disputed, as also his contention for its constant occurrence. It must be considered merely one of the instances where the circulation has for a time taken equally favored paths through a preceding capillary plexus and thus formed for us for a time several anastomosing embryonic arteries rather than a single one, which is normally the case.

vessels, we are forced to admit that some of the primary vessels of the body are not preceded by such stages, but from the very first occupy a definite position and consist of only a single endothelial tube. The most striking example of this

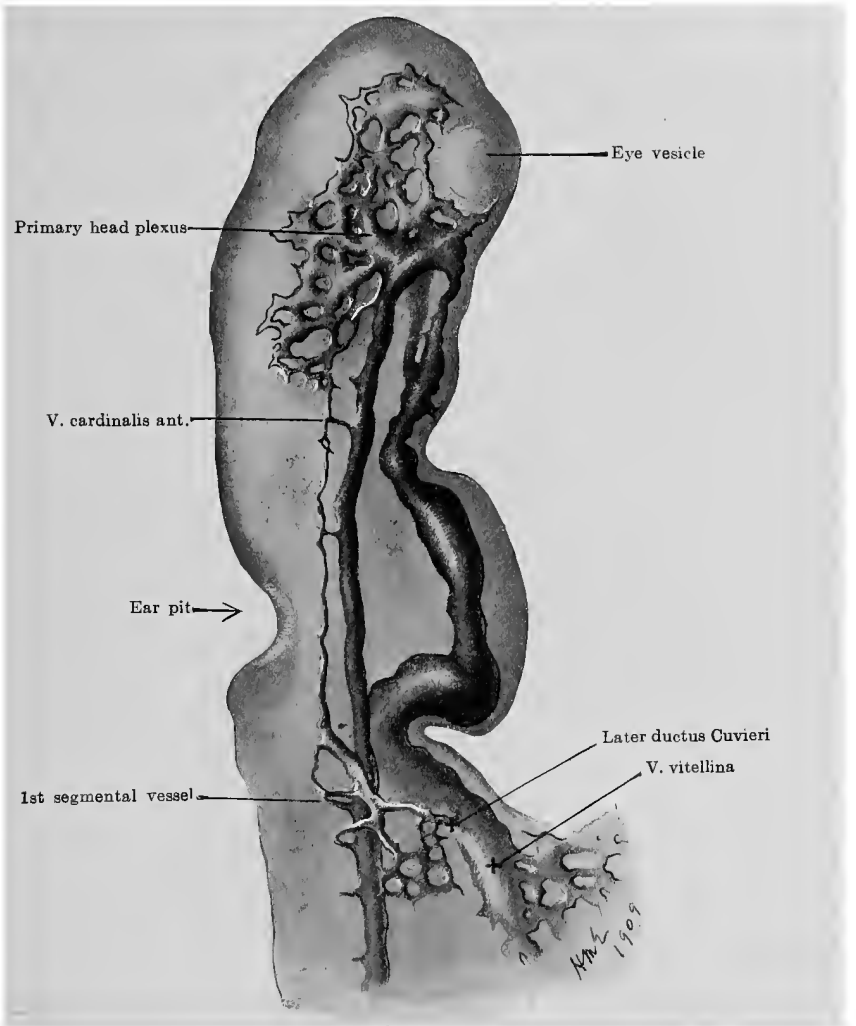

FIG. 393.—Lateral view of head of an injected chick of 15 somites, showing the primary capillary plexus here. The plexus takes origin from the convexity of the first aortic arch, and is continued posteriorly as a slender capillary chain which eventually joins the main vitelline vein near the junction of the latter with the heart. This slender capillary chain has arisen at several points from the dorsal aorta on each side, and two of these points of origin are still preserved opposite the region of the hind-brain. The delicate capillary path from head to vitelline vein is destined to form the anterior cardinal vein.

is furnished by the dorsal segmental arteries, which, as is well known, arise from the aorta at strictly intersegmental points and are usually distinctly single vessels.

The sharply limited definite positions of such great vessels as the aortæ and umbilical veins are also phenomena which have been known for a long time

and which seem unquestionably due to inheritance. However, even in these cases, an exacter study shows that these vessels do not develop at first as merely simple tubes. When, for instance, we turn to a consideration of the aorta, we can see clearly that in the chick the lower part of this vessel is merely the exaggerated medial margin of the vitelline capillary plexus, which has invaded the embryonic tissue (Fig. 390). This is also exactly the condition which may be seen in human embryos of corresponding age, for here also the caudal part of the aorta is

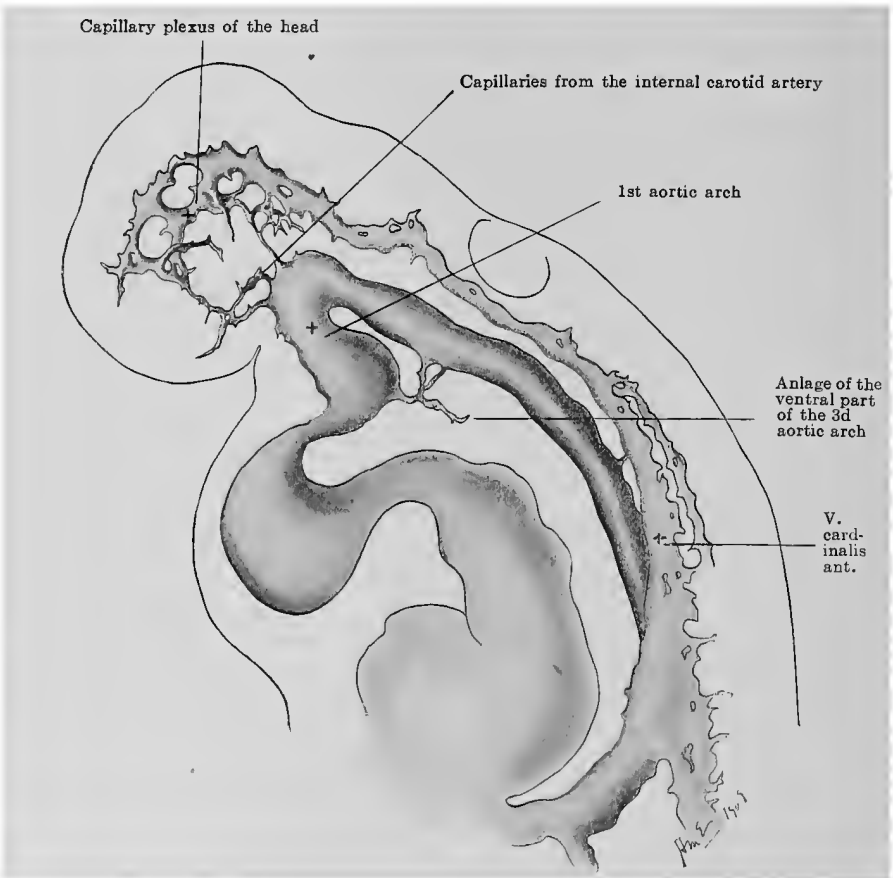

FIG. 394.—Lateral view of injected pig embryo of 5.7 mm. length, showing the capillary origin of the a. car. int. × 80.

only a part of a general plexus of vessels which lie in the gut wall and continue to grow caudally. The dorsalmost members of this plexus straighten out longitudinally and form the aorta dorsalis while the connections of the latter with the plexus become the primitive vitello-umbilical complex of arteries. Inasmuch as in embryos of 6 somites these conditions occur opposite the future 7th and 8th somite (*i. e.*, cervical somite 5), it is hence apparent that all of the aorta which exists later below this level has emerged from this preceding stage. There is little doubt but that the cephalic portion of the aorta has also an identical development, although less study has been given the appropriate stages. Türstig (1884) long ago showed that this was at first not a single vessel but a narrow meshwork of vessels

(Fig. 397), and that the single aortic tube came about only secondarily by the enlargement of one channel of the narrow mesh or by the fusion of several capillaries in some places. In the latter instances he described very clearly remnants of the old partition walls between the individual preceding channels in the form of cross-strands joining the ventral and dorsal aortic wall. Recently, Bremer (1911) has demonstrated the plexiform endothelial anlage of the entire cephalic portion of the aortæ in rabbit embryos of five somites. Lingering remains of the several capillary channels which constitute the aorta in its earliest stages are occasionally

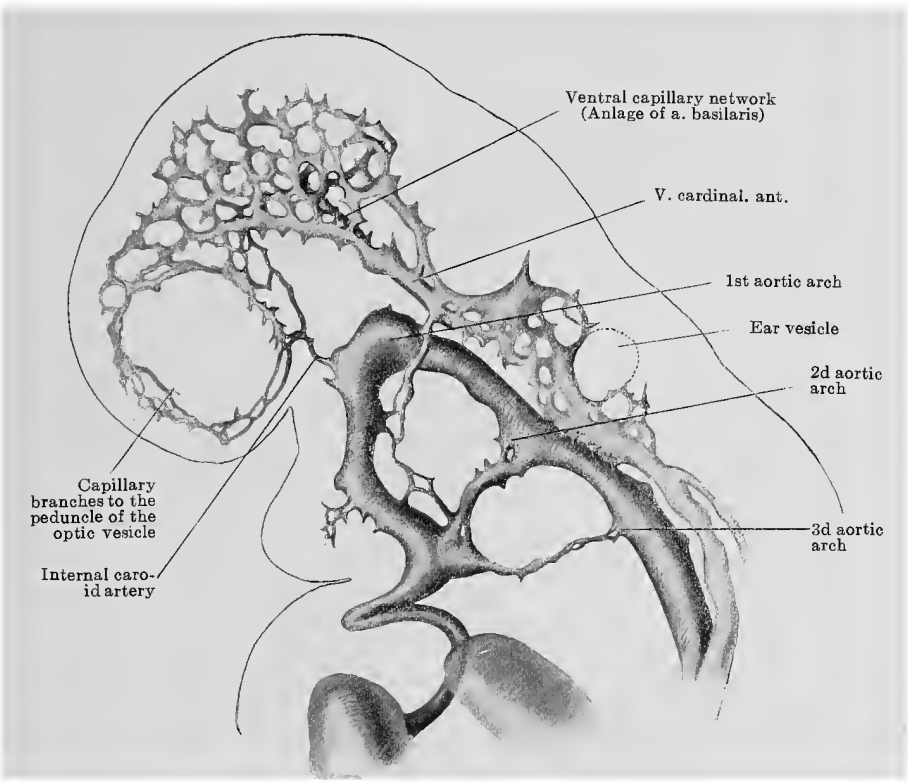

FIG. 395.—Lateral view of injected pig embryo measuring 6.5 mm. The injection was made while the heart was still beating and shows the extent of the primary capillary plexus in the head. × 80.

seen in somewhat older specimens, where it is not uncommon to find the aorta splitting into two or three vessels to reunite again, a fact which I can confirm as occurring now and then in the human embryo with from 6 to 8 somites (Embryos Pfannenstiel-Kroemer, Eternod, Graf Spee).

The aortic arches are similarly formed by narrow chains of capillaries which quickly give way to the employment of a single channel in the mesh, though in some instances remains of the earlier plexiform condition persist. I figure here the first aortic arch in a young duck embryo (Fig. 398).

It is only natural that the studies which have previously been made on the vascular system have usually revealed only the chief stems and have consequently led us to suppose that these stems grew out as such, for the usual methods of reconstruction of uninjected embryos can not hope to reveal more than the

chief trunks in any area. I present, for example (Figs. 399, 400), an embryo of about the same degree of development as Elze's (1907) shown in Fig. 420. His is from an unusually good reconstruction, mine from an injected specimen. It may be well to note that in the area here figured the reconstructed figure gives the appearance of the anterior cardinal vein growing forward and dorsally to constitute the future superior sagittal sinus; but the injected embryo shows clearly that this structure is beginning to be formed by the enlargement of the medial dorsal margin of the capillary mesh here, somewhat as the lower aortæ represent the enlarged medial margin of the vitelline net.

Most important of all, then, is the fact that the injections show us that the vascular system is not merely growing in an irregular fashion to obey an impulse given by heredity, but that it constitutes a connected and functioning whole.

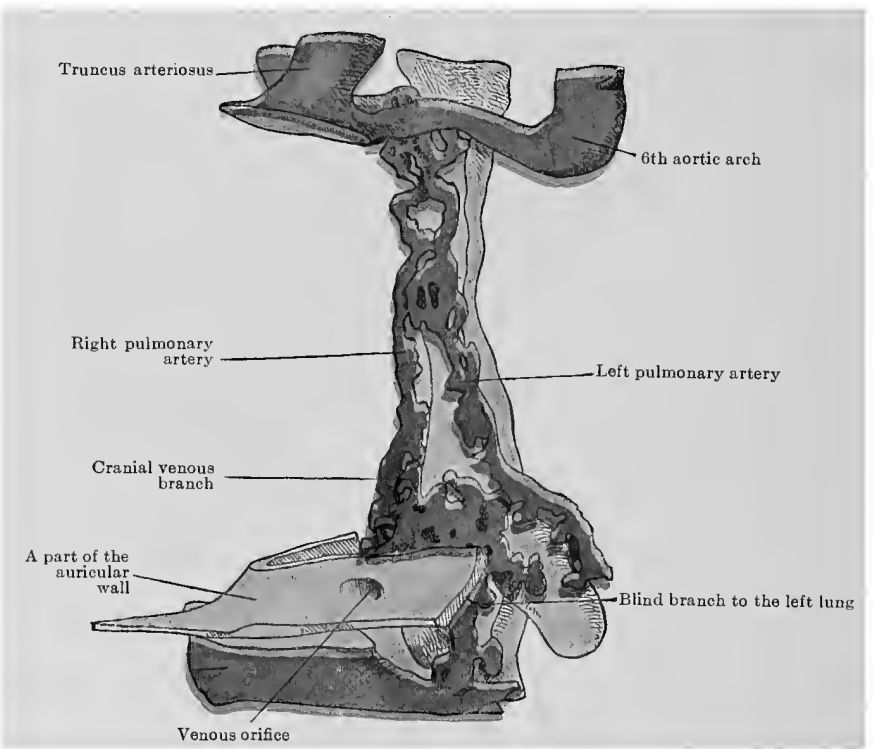

FIG. 396.—Pulmonary vessels in a guinea-pig embryo 21 days old. (After Fedorow, 1911.)

If now we assemble the remarks which have just been made it is evident that we may state generally that *arteries and veins do not grow out as such, but that the blood-vessels tend always to be laid down in a multiple capillary anlage rather than in single trunk-like forms, and that this is true even where the position of the vessel is apparently predetermined by inheritance. In many areas, however* (e. g., *the head and the limbs*), *we have more typical plexuses from which, through the secondary enlargement of some channels in the mesh and the coincident atrophy of others, arterial and venous vessels develop.*

These facts are in accord with what we know to be the manner of development of blood-vessels in areas which are open to direct observation in the living animal. I refer, for example, to the studies which have been made ever since the time of Schwann on the tail of larval amphibia, where the transparency of the tissue

enables one to see the various structures in their growth and to prove for himself that new vessels are formed by endothelial buds and that the latter in turn form plexuses. It is only necessary to refer here to the classical observations of Kölliker (1846), Remak (1850), Billroth (1856), Stricker (1865), Golubew (1869), Arnold (1871), Rouget (1873), Bobritzky (1885), Clark (1909), and others. Clark, in a piece of careful work on the tadpole, has now proved that we can thus actually watch the outgrowth and transformation of the primary plexus in an area so large that we may note that what are at one time parts of the most peripheral members of the capillary plexus are actually later used to become the arterial pathways for capillaries which have extended far more peripheralward.

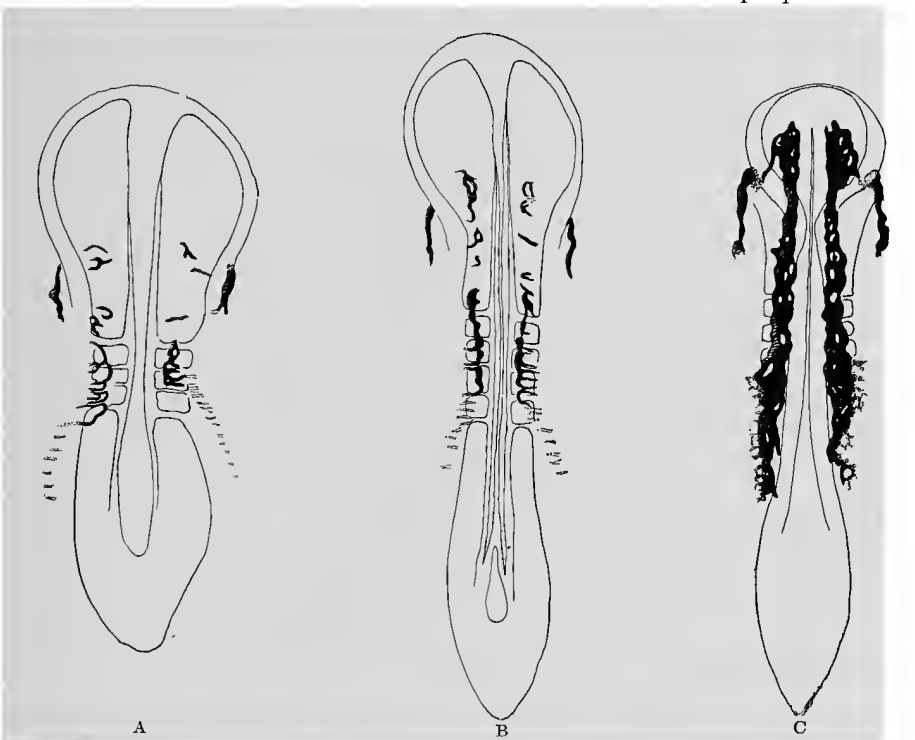

FIG. 397.—Graphic reconstructions of the blood-vessels present in three stages of early rabbit embryos, showing the formation of the aorta. (After Türstig, Schriften herausgegeben von der Naturforschen-Gesellschaft an der Universität Dorpat, I, 1884.) A, B, and C, embryos possessing 3, 4, and 7 somites respectively.

I may also point out that this method of blood-vessel formation and growth has also been demonstrated in all cases where it has been carefully studied in the adult,—e. g., in the vascularization of granulation tissue, new growths, etc.

The cause of the early appearance of vessels in a multiple capillary form is consequently to be found in the view that this represents the fundamental method of vascular growth, and that larger vessels only come into existence secondarily when the number of capillaries induces an increased supply of blood. Such an event leads to the enlargement of certain fortuitously situated capillaries into arteries and veins. The larger vessels are to be considered in the light of servants of the capillaries, for which they are but the delivering and draining pipes. *Consequently the cause for the rich vascularity of a tissue cannot be sought in its possession of larger vessels, but rather in the influences which have brought about a more abundant growth of capillaries in it.*

It may be noted now that, in addition to the method of capillary sprouts and plexuses, the blood-vessels in some special regions may be looked upon as arising in an essentially different way. I refer to the invasion of large venous trunks by certain tissues in such a way that the trunk becomes broken up into a great number of smaller vessels which now nourish the tissue in question. The fundamental point here is that we have capillaries interposed in a strong venous stream instead of between arteries and veins. The best examples of this are furnished by the invasion of the vitelline veins by the liver tissue, which thus breaks these vessels up into portal and hepatic systems, and the invasion of the posterior cardinal veins by the mesonephric tubules, creating a transient renal-portal system (F. T. Lewis, 1904). The vessels formed in this way are markedly irregular and often

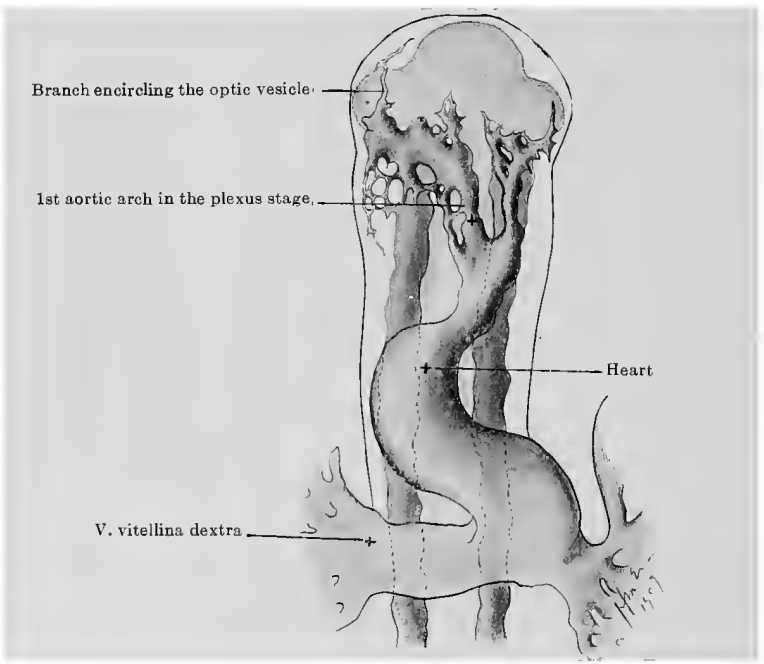

FIG. 398.—Injection of a duck embryo possessing 13 somites, made while the heart was still beating. Viewed ventrally.

much larger than normal capillaries. So striking in fact is the picture produced by vessels which have arisen in this way and so many are the points of difference with the usual capillary plexuses that Minot (1900) has designated them sinusoids.

It will be necessary now to refer briefly to the capillary plexuses occurring in the development of the embryo and the relation of these to the tissues. It may be stated first of all that no one has been able to verify the exact conception of Aeby, according to which a homogeneous mesh of vessels pervades all the tissues of the body. This is, indeed, almost as far from the truth as is the existence merely of isolated arterial and venous channels. *All recent work has shown that definite vascular and non-vascular areas exist in the embryo,* and that the capillaries grow from a vascular area into an adjoining non-vascular one. Thus, in the beginning the entire embryonic body is non-vascular, and after the formation of the aortæ we can recognize vascular centres or areas from which the capillaries continue to spread into areas which are as yet non-vascular. But the capillaries do not spread evenly in their growth from centre to periphery, thus invading

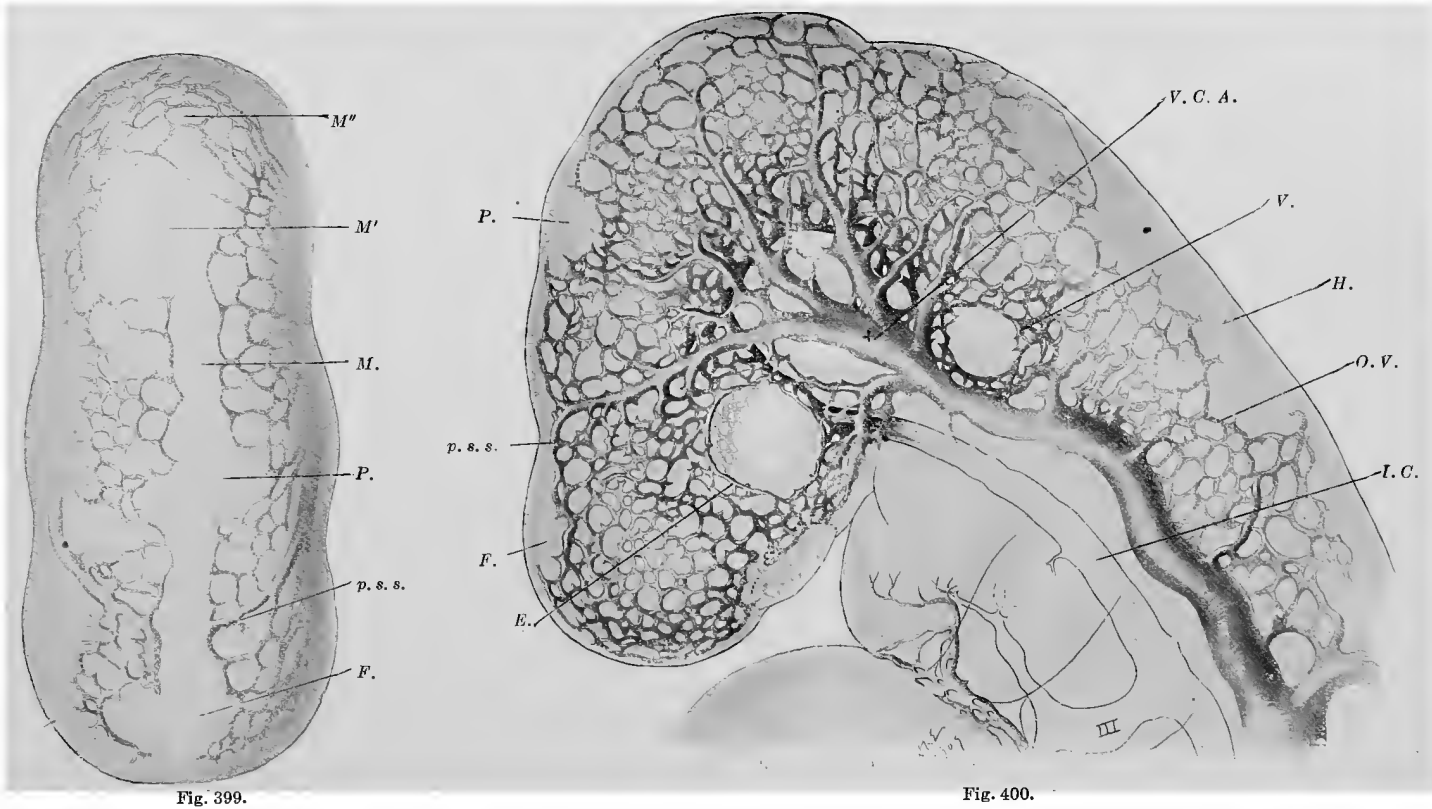

Fig. 399. Fig. 400.

FIGS. 399 and 400.—Mid-dorsal and lateral views of the head of an injected pig embryo 7.5 mm. long. *I. C.*, internal carotid artery; *V. C. A.*, v. cardinalis anterior *p. s. s.*, primitive superior sagittal sinus; *E.*, *V.*, and *O. V.*, margins of capillary plexus surrounding the eye, fifth nerve, and otic vesicle; *F.*, non-vascular area over the fore-brain, *P* just in front of the mid-brain, *M* and *M'* over the mid-brain, and *H* over the hind-brain; *M''*, capillaries bridging the caudal part of the mid-brain.

quite uniformly an ever-widening zone, but, on the contrary, are apparently governed, even from the beginning, by the nature of the tissues, some attracting them early and others relatively late. Thus, the central nervous system is early supplied by a close capillary net; other areas in the embryonic tissue are apparently inimical to capillary growth, and these constitute distinctly limited non-vascular zones. Of these are to be mentioned those early condensations of the mesenchyme which represent pre-muscle and pre-cartilage masses. We are not improbably dealing here with the question of a chemical stimulant or "tropism" for endothelial proliferation, and may consider some tissues as possessing marked angiotactic properties in contract with a corresponding lack of them in others. It will be recalled that some tissues—*e. g.*, the articular cartilages and cornea—remain non-vascular in the adult.

All the branches of an artery do not necessarily arise from the same primitive capillary plexus which gave birth to the main stem. Assuredly many branches have emerged with the parent trunk in this way, but, on the other hand, repeated instances can be given of the origin of branches from an embryonic artery after it has become an independent tube. I should assume then that the delay in the elaboration of stronger arterial coats enables the embryonic artery of more naked endothelium to respond to a stimulus and send out branches. The most fundamental example of this is furnished by the main branches of the aorta, for, although the aorta itself arises from a narrow strand of capillaries (Türstig), it becomes a large unbranched tube functioning for the vitelline and chorionic capillaries long before it again sprouts out branches. It is true, however, that when these branches arise, they themselves are first in the form of capillaries and often constitute a plexus—*e. g.*, that nourishing the limb buds. All this, then, is paramount to stating that the vascular system does not grow merely at its end bed,—*i. e.*, the capillary area—and for a time during the development of the vascular system this fact must be conceded.[6]

We find, then, in the development of the embryo, that the Aeby idea of a uniform all-pervading capillary plexus anlage for the vascular system is far too crude and inexact for the facts, but that the vessels even from the beginning take definite positions and relations to the tissues, and that consequently the main vascular stems which come out of them cannot, as a matter of fact, course in every possible direction.

However, there was still a precious kernel of truth in the old idea. The vessels arise from plexuses which, if not all-pervasive, still have frequent connections with other plexuses. More important still, a functional rôle is played by the plexuses and the vessels supplying and draining them, and we cannot doubt but that hydro-dynamical grounds often determine which parts of an original

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[6] The ability of an embryonic artery to sprout out capillaries is, however, eventually lost, and in late fetal life, as in the adult, capillary sprouts occur almost exclusively at the peripheral or true capillary bed. In general, then, it may be held that the origin of a vessel from any of the largest arteries assigns it to a quite early embryonic appearance. This may be the underlying cause for the fact that vasa vasorum seldom arise from the vessel which they supply, for by the time an arterial wall becomes elaborated enough to need a proper nourishment of its own, the main vessel may have lost the power to send out direct sprouts.

It must be remembered that even the smaller arterioles and pre-capillary vessels of the adult are highly differentiated structures in which muscle and elastic elements occur so that their inability to directly sprout capillary branches is in no contrast with the possession of this power by even the largest of the embryonic arteries, for the latter structures have a greatly simplified histological structure, differing less from the capillaries themselves.

plexus shall be converted into larger trunks. This gives the possibility of variation not only in the exact position of a single trunk but also in the territory supplied by it, for by means of its capillary union with the area of its fellow trunk it may successfully displace the latter.

Repeatedly in the history of the vascular system we find areas which are primitively supplied by many smaller vascular trunks secondarily supplied by a single large one, and this seems certainly due to the fact that the constant presence of a functioning capillary bed enables the successful artery to annex neighboring fields. Whereas in the intestine we have originally a row of vessels which go to the gut wall and yolk-sac, these later give way to three large permanent trunks (aa. cœliaca et mesentericæ), and whereas in the arm bud a row of delicate arterioles nourish the limb, soon fewer, and eventually a single artery possesses this field. This story is repeated over and over again in the vascular system from centre to periphery. It occurs first in the history of some of the main stems, as I have just indicated, but it occurs repeatedly afterwards as the more peripheral vascular tree is gradually developed.[7]

All these facts now enable us to understand better many peculiarities of the adult vascular system. Above all, can we appreciate better now a reason in the frequent occurrence of vascular variations, for we see clearly the possibility for channels other than the normal ones to obtain possession of a field. Again, there sometimes occur in embryonic vessels, and more rarely in adult ones, cases of "inselbildungen" where a chief stem is for a short distance reduplicated. See, for instance, the inselbildungen at the origin of the aortic arch[8] in Fig. 421, or the condition of the a. hyaloidea in Fig. 430. These phenomena are difficult to explain on the basis of our old notions of the outgrowth of naked vascular stems, but appear now as cases in which an arterial stream has for a time retained two paths instead of a single one through its preceding capillary net.[9] We cannot, however, carry this analogy further and proclaim that all instances of anastomosis and of plexiform vessels in the adult are survivals of embryonic conditions, for many of the latter are clearly secondary formations.[10]

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[7] Witness, for example, the history of some of the arm vessels. Göppert (1909) has shown that many branches which are at one time present on the dorsal side of the chief arterial stem are later replaced by a single artery arising in their middle, the a. interossea dorsalis. (Compare his Figs. 7 and 8, Taf. viii, with Figs. 9 and 10, Taf. ix.)

[8] This is doubtless due to the tendency of the aortic arches, in common with other vascular trunks, to be formed at first from true capillary vessels which are fundamentally multiple rather than single. Thus I have seen repeated instances in injections of the chick and pig where not one but two or three capillary sprouts are sent out by the dorsal aorta into one of the visceral arches, though only one of these vessels persists to constitute an aortic arch.

[9] Backman (1909) has recently discussed the view here advanced.

[10] It could be thought, for instance, in cases where an artery was resolved into a rete mirabile that we had a survival of the primary embryonic net here. That we may err, however, in such an interpretation is clear from the research of Tandler (1906), who showed that the retia mirabilia occurring at the base of the skull in many artiodactyls does not really represent an incomplete resolution of the primitive plexus of the a. carotis interna, but comes from a later series of capillary sprouts which arise directly from the naked carotid stem and plexify. It is, then, likely that many of the "wundernetze" which constitute the arterial channels in some mammals—*e. g.*, edentates and prosimians, are specialized secondary formations. The extensive subcutaneous venous plexuses of the limbs and body wall of man are also clearly secondary formations. (See beyond.)

But it is to the general conception of the developing vascular system as a connected and functioning whole, which recent studies and especially injections have given us, that a better notion of the formation of variations will accrue. The fact that the arterial current has formed its path from the capillaries, and with the shiftings of growth may form new ones through this mesh, is of the greatest significance. Thus, a chief vessel may channel a new way through the capillary paths connecting two of its branches, the old stem atrophying, and so come to acquire new relations, for instance, to neighboring nerves, as Göppert has recently proved. (See Göppert, 1909, pp. 376–379.)

Vascular variations, however, do not occur in an infinite number of ways, because the developing arteries and in fact even the capillary plexuses have definite relations to the tissues. But even with these relations, the tendency to a lingering plexiform type in the main stem and the constant occurrence of the capillary mesh, any part of which may, as it were, be called into service,—all this gives sufficient choice in the selection of a permanent channel to cause the usual variations which are so frequent in the adult.

Exactly what hydrodynamical factors are concerned in the development of arteries and veins from the primary indifferent net which we have seen to exist, are not yet well known.[11]

Knower's experiments certainly demonstrate that normal vascular development is dependent on the heart beat.

With our present ideas on the mechanical advantages enjoyed by a well-established channel, it might appear all the more remarkable that prominent embryonic vessels are not oftener retained, for example the median artery as the chief stem in the lower arm. But it is probable that continued studies on the manner of vascular development will only strengthen the conviction that the eventual dominance of secondary channels is due to the utilization of an actually better path by the blood when we consider the entire territory to be supplied. The path which the blood takes is dependent from the beginning on the demands of the tissues. Strong growth, which, so to say, sucks the blood in another direction, must play a prominent rôle in development, and so it may come about that a straight path is actually exchanged for a circuitous one. But this indeed is the whole course of vascular growth, for longer and longer paths are chosen by the developing arterial tree, and we are forced back to the conclusion that the growth and demands of the peripheral or capillary portion of the system exercise a determining influence on the architecture of its main stems, both in embryo, fetus, and adult.

Comparative.—In accordance with a similarity in the general anatomy of vertebrate embryos, we find also a remarkable agreement in the plan of their chief vessels. They furnish us with the opportunity of comparing accurately the vessels

[11] The minor differences in the angles at which vessels arise may greatly favor or hinder their acquisition of a large part of the current in a contest of trunks supplying the same field. (Hess, 1903.) We also know, of course, that two distinct types of vessels are differentiated according as they stand in relation with the supplying or draining system, for in the former case we have always small independent thick-walled vessels and in the latter a greater number of large, anastomosing, and thin-walled ones. The measurements made by Mall and his pupils indicate that arterial blood is delivered to the capillaries in the various organs through a much smaller-calibred system than the veins must possess to drain it. Nevertheless an actual rôle of the circulation in adapting the architecture of the vessels needs to be investigated. (Since this was written Oppel, 1910, has published his extensive discussion of this phase of the subject, and the reader is referred to it.)

of various vertebrates. This has been possible chiefly through the mass of splendid comparative researches which we owe to Hochstetter. The reader should consult, for this stand-point, Hochstetter's various researches and his more general presentations. He will see there that we now possess for many vessels a fundamental vertebrate plan. The first and most brilliant example of such homologies was furnished us by the work done on the homologies of the aortic arches and the vessels derived from them. Rathke's (1843) work on the arches in the mammalia is a classic.

Late Changes.—Finally, we may remark that the history of the development of the vascular system hardly ends with the establishment of the chief trunks, since the position of many embryonic vessels is far removed from their adult one. A remarkable shifting or wandering process must consequently take place. The studies of W. His gave us a classical example of this in the caudal displacement of the heart and of the great vessels in connection with it, and Mall first called our attention to the cervical position of the intestinal vessels which later shift into the abdomen. These great changes are usually accomplished by the time the human embryo is twenty millimetres in length and finally other, less momentous displacements occur.[12]

2. Development of the Human Vascular System.[13]

A. The origin of the vascular system.
B. Description of the vascular system present in early human embryos.
C. The development of the arteries.
D. The development of the veins.

A. Origin of the Vascular System.

The question of the source of the cells which form the vascular system still remains, as it has for a long time, one of the most disputed problems of mammalian and indeed of general vertebrate embryology. The question has met no undisputed solution for the case of any vertebrate, and here, in contrast to the dearth of human material, we can possess a wealth of all the necessary stages. When such fundamental questions as the genetic relation between extra-embryonic and embryonic vessels, and indeed even the method of origin of the former—the well-known vitelline vascular anlagen—are still unsettled, and when we consider the paucity of these earlier stages which should be necessary for the determination of this question in man, a speedy solution of the problem in human ontogeny is expected by no one.

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[12] Such, for instance, as that of the upper thoracic aorta on the columna vertebralis. Whereas in embryos of 20 mm. the upper aa. intercostales find their interstitia intercostalia at the same level, in the adult, as is well known, they must course upwards to reach their interspaces.

[13] When completing the present account of the development of the human vascular system, I had access to six young embryos in the possession of Professors Kollman, Eternod, R. Meyer, Strahl and Felix. These were studied in the laboratory of Professor Wiedersheim in Freiburg i. B. To all of these gentlemen I wish to express my sincere thanks. Four very valuable embryos in the collection of Graf Spee were studied in his institute in Kiel, for which great privilege I am deeply indebted.

If, then, we posses no safe generalizations with which to interpret the few observations possihle on human embryos, we are also still further retarded hy certain peculiarities of the early history of the primate embryo which affect profoundly the vascular system. The presence of an early vascularized belly stalk and chorion distorts the entire sequence of the usual development of the vessels and furnishes us at once in embryos astonishingly young with highly specialized and characteristic phenomena. These latter facts are now beyond douht and I shall present them briefly helow. Here only it need he remarked that the early history of the human vascular system has not enahled us as yet to make any statement as to the exact cellular origin of the endothelium in man. The only facts in the human emhryo's history which may he hrought into relation with this important question seem to point clearly to a mesodermal source for the primary hlood-vessels. These are:

1. The abundant vascularization of the early chorion, where apparently any rôle of the entoderm can he excluded.[14]

2. The early vitelline vascular anlagen which cause a characteristic "hummocking" of the yolk-sac wall lie in the mesodermal coat of the latter and are sharply separated from the entoderm.

3. The earliest vascular cells within the body of the embryo (in the Graf Spee emhryo "Glaevecke") are certainly in more intimate relation with the mesodermal than with the entodermal cell layer.

B. Description of the Vascular System Present in Early Human Embryos.

EMBRYOS WHICH AS YET POSSESS NO MESODERMIC SOMITES.

It is certain that long before any vessels are present in the body of the human embryo, and at a time so early as considerably to precede the formation of any somites, typical "vascular anlagen" are found scattered over the ventral pole of the yolk-sac.

In those mammals which, like the rahhit, possess a vitelline vascular area of the limited circular form, hounded hy a marginal sinus, which characterizes the lower vertehrates, it is probahle that the vascular anlagen first form in a ring-like row around the horders of the future area vasculosa, as Van der Stricht has described for the rahhit. But in the primates (and presumahly in all other mammals in which the yolk suffers a complete overgrowth by the area vasculosa,—*e.g.*, carnivores and artiodactyls) the vascular anlagen are most irregularly scattered, covering at an early date the whole ventral surface and soon all the yolk-sac.

These vascular anlagen or blood islands, as in other vertebrates, appear as nodular swellings of the wall of the yolk-sac, and consist microscopically of circumscribed cell clumps lying between the mesoderm and entoderm. The cells of these clumps very early show a differentiation into centrally lying blood-cells and a row of peripheral bounding cells,—the endothelium. The best-developed, and hence earliest, of these anlagen are situated more ventrally, the younger nearer the body of the embryo, *in very*

[14] It may perhaps he mentioned that those who, like Hubrecht (1908), consider that a considerahle part of the early mesohlast has really come from the entoderm will dispute the ahove statement.

early stages they can be shown to be concerned in the formation of the vessels in the belly stalk (aa. umbilicales), *and these vessels belonging to the placental circulation, are so exaggerated in development as to precede the appearance of vessels in the embryonic body proper.* Furthermore, as Eternod discovered, when, later, the vascular trunks of the embryo proper make their appearance (the aortæ and vv. umbilicales), they are already connected with the chorionic capillaries through the precocious aa. umbilicales

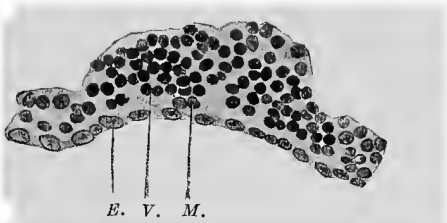

FIG. 401.—Section of a vascular anlage in the wall of the yolk-sac in the human embryo 2 mm. long shown in Fig. 408. *E.*, entoderm; *V.*, vascular cells; *M.*, usual mesoderm cells.

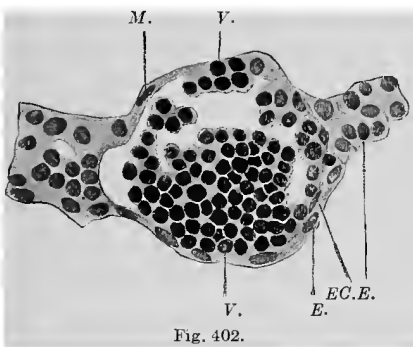

Fig. 402.

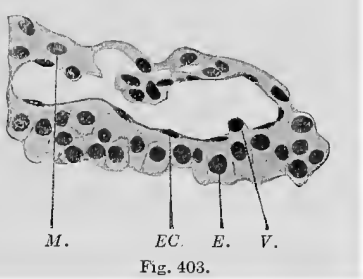

Fig. 403.

FIG. 402.—Section of a more advanced vascular anlage from the yolk-sac of the same embryo as shown in Fig. 401. *EC.*, endothelial cell.

FIG. 403.—Section of a well-developed vessel from the same yolk-sac.

and vv. chorioplacentares, and so it comes about in the human embryo that an umbilical circulation exists in embryos so young that the mesoderm is as yet unsegmented into somites.

The embryos which I have been able to examine with respect to their early vessels constitute, together with that so fully described by Eternod, the following series, given in order of their probable age.

Designation of embryo.	Length of embryonic shield.	Collection.	Literature.
Von H(erff).	.37 mm.	Graf Spee	Graf Spee, Arch. f. Anat. u. Phy., 1896.
Frassi, NT. 1	1.17 mm.	Prof. Keibel	Frassi, Arch. f. mik. Anat., Bd. 70 u. 71.
Glaevecke...	1.54 mm.	Graf Spee	Graf Spee, Arch. Anat. u. Phy., 1889, 1896.
Eternod....	1.3 mm.	Prof. Eternod	Eternod, Anat. Anz., Bd. xv, No. 11, 12, 1898.

For further descriptions of the embryos themselves the reader is referred to Chapter IV of the present work, where this has been done by Prof. Keibel. Here we need be concerned only with remarks on what blood-vessels are present.

The embryo von Herff, the youngest, and probably only consisting of the region of the primitive streak, possesses abundant vascular anlagen scattered over the entire ventral and part of the lateral surfaces of the yolk-sac, reaching often to the angle of junction of the yolk-sac with the embryonic shield. Whereas in general those of the anlagen whose development seems most advanced are more ventrally situated, there exist also many not widely separated from the embryonic body, in which an evident differentiation into endothelium and blood-cells has come about. In the belly stalk and chorion of this embryo there are, as Graf Spee has described, highly characteristic strands of spindle cells, which often consist of a double row of nuclei and, again, may enclose a distinct lumen. These cells appear to keep to themselves, and to constitute a single unified but widely branched tissue which grows oftenest in strands frequently anastomosing among themselves. This tendency to constitute a distinct tissue element different from the connective tissue, together with the histological appearance of longer oval nuclei and more deeply staining cytoplasm, suggests strongly that we may be dealing here with endothelium, a conviction strengthened by the typical vascular appearance given in those instances where the cells surround a distinct lumen.[15]

The embryo Frassi, which now, besides the primitive streak region, shows a considerable embryonic area in front of this (the two being separated by a typical canalis neurentericus) also exhibits many evident blood-vessels. Not only have we here again an abundance of well-differentiated vascular anlagen on the ventral walls of the yolk-sac, but *in many of the sections through the belly stalk vessels can be recognized* (one of these being especially large), *and this is also the case in the chorion.*

The embryo Glaevecke of Graf Spee (*NT.* 2) *contains, besides many yolk vascular anlagen and chorionic vessels seen in the preceding stage, the first vascular cells within the body of the embryo itself.* In the region of the heart these constitute a true typical endothelial anlage for that organ (Fig 404), but also further caudalward there can be recognized many cell strands clearly isolated and different in character from the endoderm and mesoderm between which they lie; they thus occupy the typical position for, and present the typical appearance of, early vascular cells[16] (Fig. 405). At first lying about half-way between the point of insertion of the yolk-sac and the mid-line of the body, they gradually shift lateralward, and before the neurenteric canal is reached occur quite exclusively only at the

[15] If such an interpretation be correct we must have a remarkable growth of the endothelium in the chorionic membrane of young human embryos, for there occurs here no coincident development of blood-cells, as is typically the case in the vitelline anlagen. These cells of the chorion (Spee's so-called spindle-cells) are present in relatively great numbers and, so far as I am aware, cannot be distinguished from similar cells in still younger embryos (*e.g.*, that recently demonstrated by Fetzer [1910]), where we are quite unable to distinguish vascular beginnings on the yolk-sac proper. The above suggestion, however, appears to me forced on one who now takes up the study of a series of progressively slightly older stages, such as we have in the embryos here dealt with, where difficulty would be experienced in separating these cells from those which gradually are concerned in the formation of undoubted vessels.

[16] Concerning the origin of these intra-embryonic vascular cells, it can only be said that the histological appearances are inconclusive, and one may often see what might be taken for a genetic connection of the cells with the intermediate mass of the mesoderm as Mollier (1906) has reported in reptilian and avian embryos. On the other hand, however, the series of sections does not permit one to exclude the strong possibility that these cells constitute a connected unit which could have invaded the embryonic body from the splanchnopleure of the yolk-sac.

lateral margins of the embryonic area and very near the insertion of the yolk-sac. In the area behind the neurenteric canal these cells apparently retreat to the upper margin of the yolk-sac proper. This parallels the condition found in this area in the younger embryo von Herff. Finally, as the allantois is given off, these vascular anlagen can be traced into vessels which in the belly stalk lie at first on either side of and soon below the allantoic diverticulum; they are consequently in the position typical for the umbilical arteries and doubtless represent the anlagen of these vessels in the belly stalk.

We turn now to the embryo described by Eternod (1898) and in which we have the earliest circulatory conditions in the human embryo. However, a considerable gap exists between the stages which we have just been considering and that depicted by Eternod, for in the latter case a system of vessels are now present

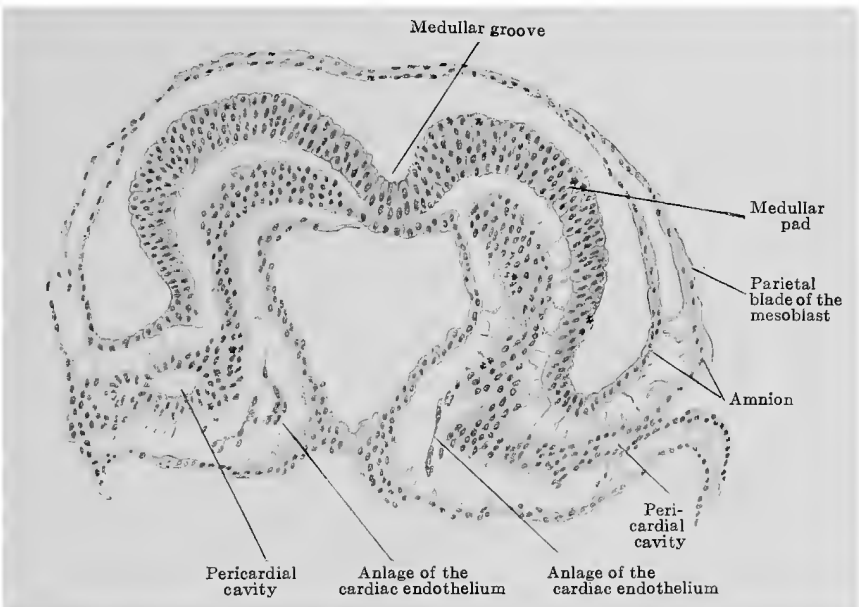

FIG. 404.—Cross section of the human embryo Glaevecke (collection of Graf Spee), taken just in front of the anterior intestinal portal, showing the vascular cells constituting the anlage of the endothelium of the heart. × 113.

coursing through the body of the embryo,—the aortæ and umbilical veins. Exactly how these first vessels are formed in man is as yet unknown. The umbilical veins, the heart, the aortæ and umbilical arteries, and, finally, the chorionic capillaries, form the simple vascular cycle here present (Fig. 406).[17]

The Eternod embryo measures approximately 1.3 millimetres in length and has also as yet no indication of mesodermic somites. It shows an anteriorly placed heart, the short aortic end of which, doubtless representing the future bulbus

[17] As yet, though there are many vessels on the yolk-sac, particularly on its ventral surface, no evidence for a vitelline circulation exists, for no connections between these capillaries and the aortæ can be traced. This, the most revolutionary result of Eternod's study, appears to place man unique among mammals in the ontogenetic precedence of the umbilical over the vitelline circulation, for in the mammalia generally, as is well known, the yolk-sac circulation is always primary.

aortæ and aorta ventralis, gives off the aortic arch [18] which sweeps up on each side to the primitive aorta. The aortæ course dorsal to the head-gut and on either side of the notochordal plate, and at last turning down sharply into the belly

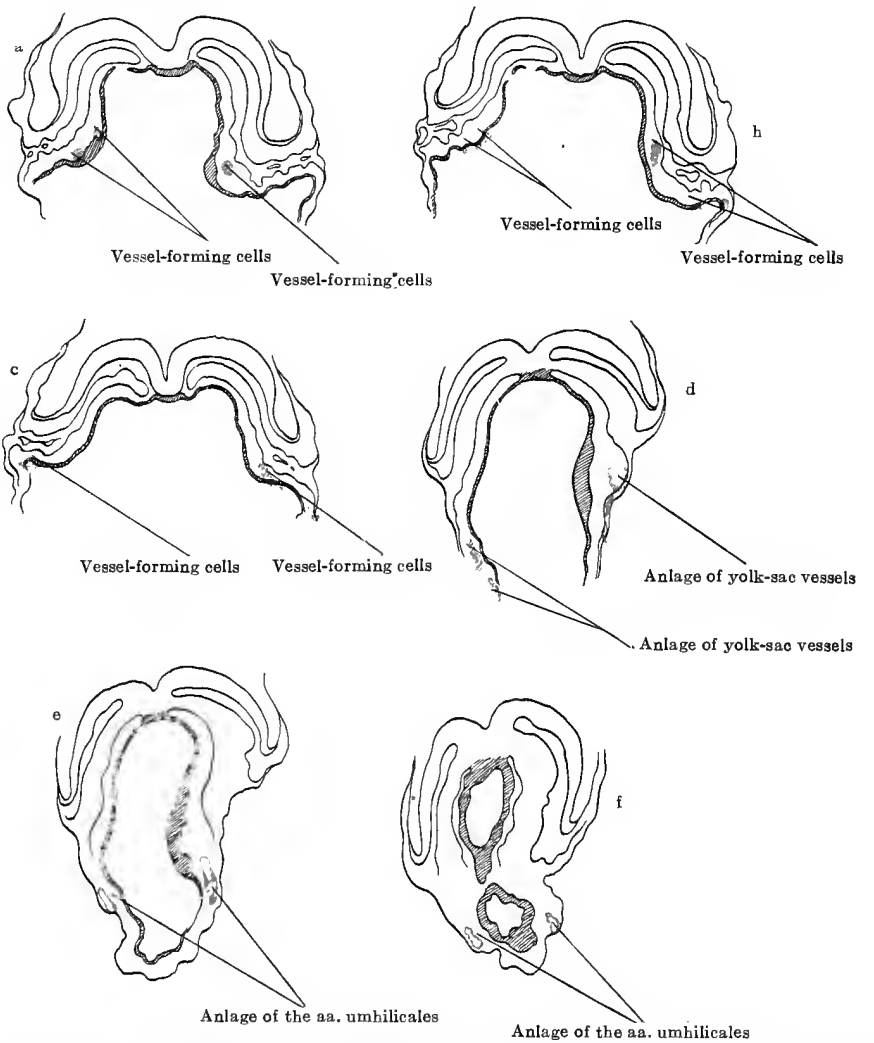

FIG. 405.—A series of sections through the human embryo Glaevecke, showing the earliest intra-embryonal vascular cells and the anlage of the aa. umbilicales in the belly stalk.

stalk, run out onto the chorion without having given any branches into the tissues of the embryo. The umbilical veins (vv. umbilicales primitivæ), which collect the blood from the extensive chorionic vessels (vv. chorio-placentares), unite

[18] It is certain that we are not dealing here with three aortic arches and that the picture given by Eternod is somewhat schematized, the small irregular vessels here likely being persisting strands of a capillary plexus. (See Fig. 398 of a duck.)

in the belly stalk into a single trunk (v. umbilicalis impar), but again part as the embryo proper is reached, and course in the body wall on either side near the attachment of the amnion. Just as they begin their embryonic course, each umbilical vein receives a large tributary from the capillary plexus of the yolk-sac,

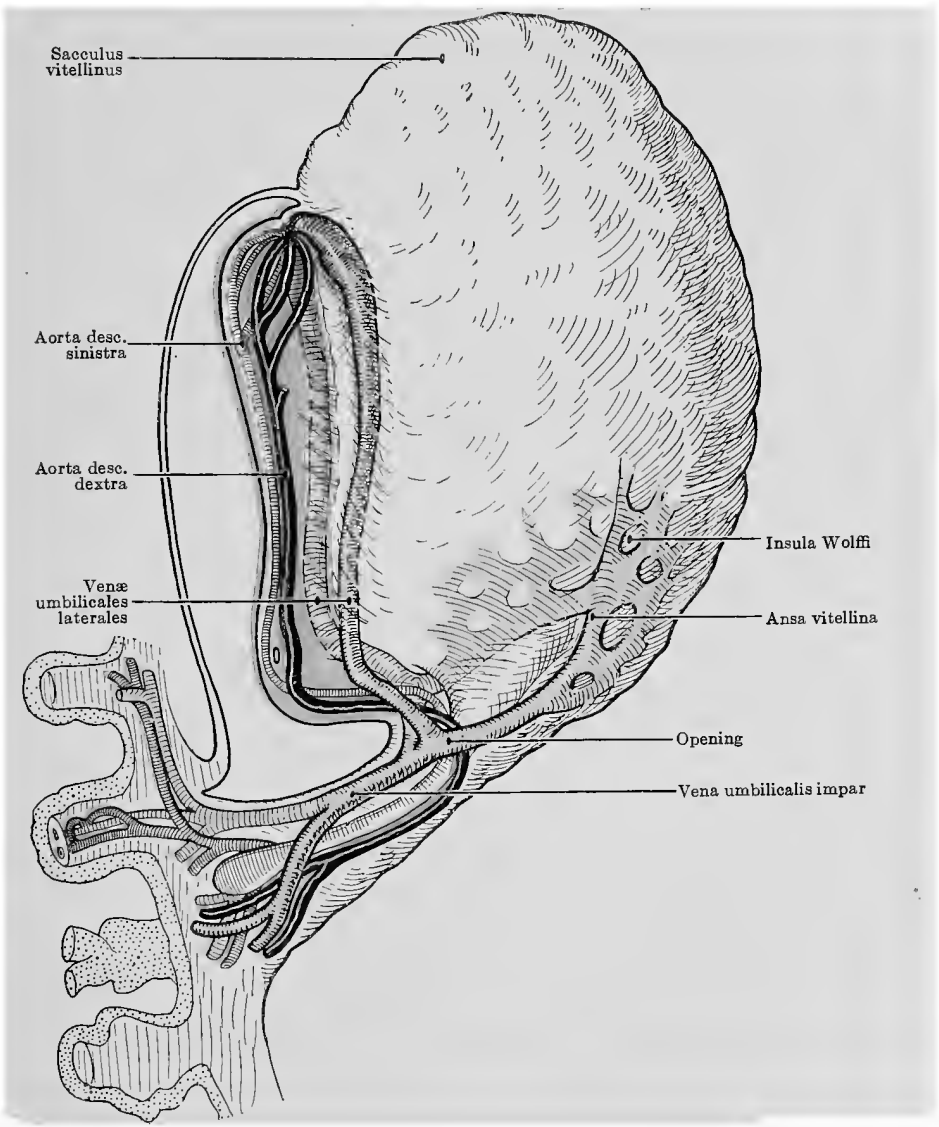

FIG. 406.—Lateral view of the vascular system in a human embryo 1.3 mm. long, without somites. (After Eternod, from Kollmann, Handatlas der Entw. d. Menschen. 1897 ' ig. 512.)

and these two tributaries anastomose with one another on the wall of the yolk-sac so that a venous ring is produced enclosing the allantois (ansa vitellina). The significance of this is unknown. This connection of the vitelline vessels with the umbilical vein gives the possibility of an early drainage of the yolk-sac in that

direction were any aortic afferents traceable to the vitelline plexus. But at a time when such afferents clearly supply the vitelline plexus, the true vitelline veins are formed, so that at the time when we are first able to affirm the possibility of a complete vitelline circulation it is supplied and drained, as in all mammals, by its own system of vessels.[19]

EMBRYOS POSSESSING FROM SIX TO EIGHT SOMITES.

Unfortunately, we possess as yet no human embryos belonging to the interesting period in which the first five somites are formed, but for stages only shortly after this several excellently preserved and trustworthy specimens are now known. I base what can be said about the vascular system at this stage chiefly on the study of the following four embryos:[20]

Designation of embryo.	Number of somites.	Collection.	Literature.
Pfannenstiel-Kroemer NT. 3	5–6 somites	.....	Keibel-Elze, 1908. Felix, 1910.
Graf Spee embryo....	6–7 somites	Graf Spee	Graf Spee, 1887. Kollmann, 1889, 1907 (Figs. 187 and 188).
Mall No. 391.	7–8 somites	Prof. Mall	Dandy, 1910.
Eternod's embryo....	8 somites (the 8th not completely separated)	Prof. A. C. F. Eternod	Eternod, 1896, 1899, 1904, 1909. Kollmann, 1907 (Figs. 183 and 184)

The most striking change which has occurred in the vascular system of these embryos is found in their possession of the first branches of the aorta. The majority of these aortic branches go to the yolk-sac (aa. vitellinæ primitivæ), and, though at present appearing as almost frank lateral branches (Figs. 407 and 444), in later stages are shifted so as to come off more ventrally.

The primitive vitelline arteries form an irregular series of connections between the aortæ and the vitelline capillary plexus which has arisen out of the early yolk anlagen. They are not, as

[19] Eternod has pointed out that in the Selenka specimen of Hylobates the vitelline plexus is also shown in connection with the chorionic vessels by means of two stems which surround the allantoic tube in reaching the belly stalk, and in the latter they fuse to a single large vessel (v. umbilicus impar) which can be traced into the chorionic vascular tree. The ansa vitellina may consequently be a characteristic primate structure, but it is impossible in the light of present knowledge to assign to it any significance. It is quite possible that these vessels merely represent a persisting connection of the vitelline and chorionic vessels indicating a primitive common anlage.

[20] The manuscripts of Dandy and of Felix were generously placed at my disposal by their authors and were of much service during the study of the embryos concerned.

a rule, at first segmentally arranged. Cephalad they may extend as far as the first intersegmental cleft, as Dandy (1910) first showed. In the Pfannensteil-Kroemer embryo the first of these appear opposite the third somite on the left, and in the Eternod embryo between the third and fourth somite on the right. Occurring generally so frequently as to be opposite each somite thereafter (though they occupy no constant position with regard to the somite mass), when the unsegmented mesoderm is reached they are found in far greater numbers, and eventually resolve the termination of the aorta itself into a plexus of capillary-like vessels not unlike that to be seen in injections of chick embryos.[21] With

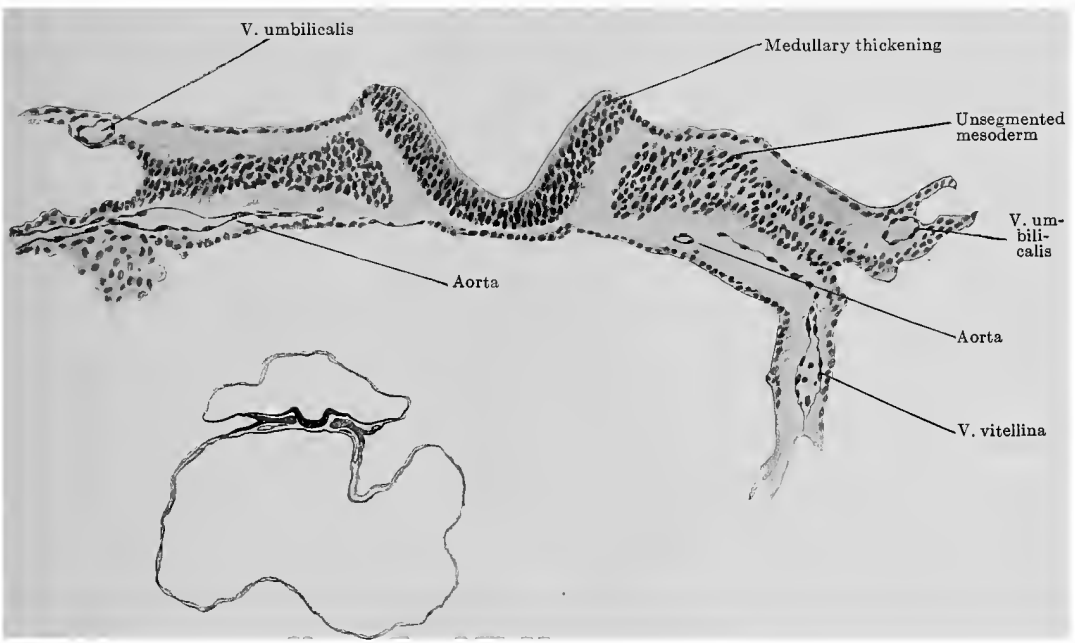

FIG. 407.—Cross section of a human embryo with six somites (NT. 3), in the region caudal to the last somite, showing the delicate aortæ and their vitelline branches.

this plexus, as Felix (1910) has shown, and as I can confirm, the umbilical artery is in connection and so by these multiple roots takes its origin from the aorta. It is by means also of the farther caudal growth of this plexus that the aorta is continued caudally and the a. umbilicalis wanders caudalward through a considerable distance. *These facts establish clearly that the umbilical artery is*

[21] Felix (1910) is unable to follow the aorta throughout its entire extent in the first of the above embryos (NT. 3), indicating his belief that it is not present in some places (see his account, p. 603). I am not able to agree with his account, nor with his statement concerning the intestinal vessels (p. 606)—"cranialwärts öffnen sich seine Gefässe teilweise frei in die primäre Leibeshöhle"!

merely a modified vitelline vessel; for a considerable time its roots of origin from the aorta are indistiguishable from the row of primary vitelline arteries.

Headward the vitelline plexus is connected on each side with the heart by two primitive vitelline veins, which receive the umbilical veins which have coursed in the somatopleure and then turn in sharply from their lateral position to gain the heart; in doing

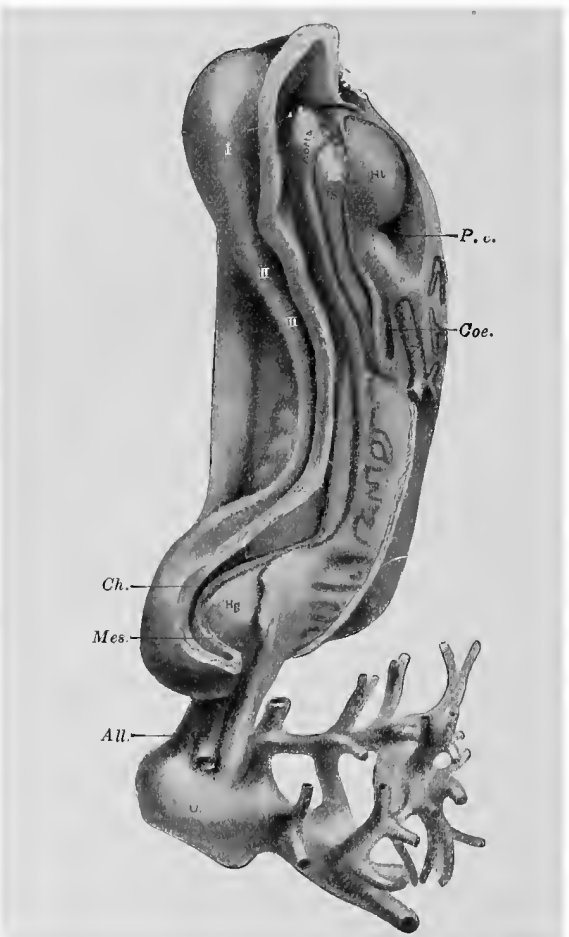

FIG. 408.—Dorsa view of model of human embryo possessing 7–8 somites, being the same embryo shown in Fig. 23 B (ante, p. 32). Portion of ectoderm of right neural plate is removed, showing thickness of wall and its relation to deeper structures. The three primary cerebral vesicles are indicated. (After Dandy.) *All.*, allantois; *Ch.*, chorda; *Coe.*, cœlom; *Fg.*, fore-gut; *Hg.*, hind-gut; *Ht.*, heart; *Mes.*, mesoderm; *P. c.*, pericardial cœlom; *U.*, umbilical arterial sinus; *V.*, umbilical vein. (Mall, No. 391.)

this they traverse the bar of mesoderm which intervenes between the pericardial cavity and the yolk-sac wall and which is destined to constitute the septum transversum of His. Their course here hence resembles entirely that taken by the terminal portions of

the primitive vitelline veins in other very early mammalian embryos (*e.g.*, the rabbit), and I present here in lieu of a more detailed description a series of accurate tracings of their course (Fig. 409).

Besides the vitelline circulation, which is thus well established

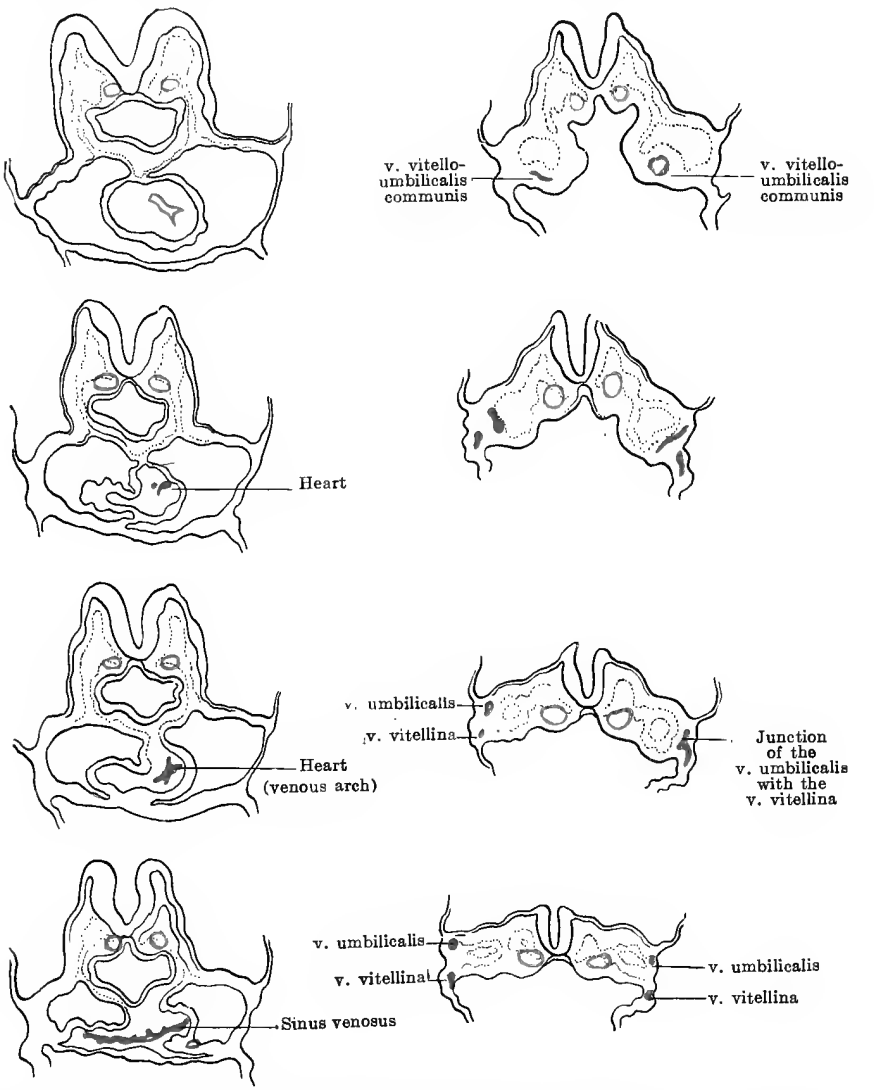

FIG. 409.—A series of sections through the human embryo with 7–8 somites (shown in Fig. 408), showing the relation of the chief venous stems to the heart.

in these embryos, other vascular channels are beginning to be formed; these constitute the first endothelial sprouts to be sent out into the tissues of the embryo proper; arising dorsally from the aorta, they lay the anlage for the *a. carotis interna* in the region

of the fore- and mid-brain, whereas farther caudally they form a series of *presegmental* and *segmental dorsal offshoots of the aorta.* In all cases these tiny vessels are directed to the sides of the neural tube, which consequently, neglecting the primitive gut and yolk-sac, must be considered the first embryonic tissue to receive vessels; this occurs, in fact, before the nervous system is in the form of a tube, for it is, in the first of these embryos, a widely open furrow. Each vessel, having reached the side of the medul-

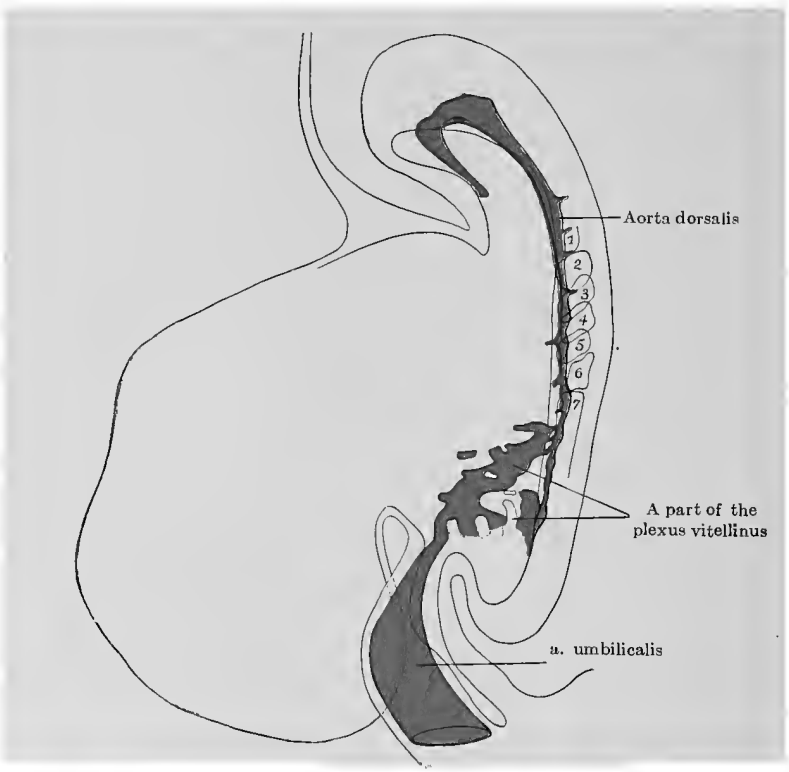

FIG. 410.—Reconstruction of the arterial system of a human embryo with 6 somites (NT. 3), seen from the left. (Modified after W. Felix, 1910.)

lary furrow, divides T-like and can be traced a short distance caudally and cephalically. It is by the anastomosis of these branches that in older embryos (those of 15 somites) a longitudinal vessel is established at the sides of the hind-brain and the neural tube caudal to it (*v. capitis medialis*). The *dorsal segmental arteries* have long been known, for they occupy accurately the interspaces between the somite masses; some four of them are already present in the Eternod embryo with 8 somites, and, since these are progressively smaller in size cephalo-caudally, their outgrowth from the aorta quite certainly proceeds in this sequence.

EMBRYOS POSSESSING FROM THIRTEEN TO FIFTEEN SOMITES.

Designation of embryo.	Number of somites.	Collection.	Literature.
Bulle, NT. 5	13–14 somites	Prof. Kollmann	Kollmann, 1889, 1907.
Pfannenstiel III, NT. 6	14 somites	.....	Keibel and Elze, 1908 Low, Jour. Anat. and Phys., 1908. Felix, 1910.
Graf Spee No. 52.....	15 somites	Graf Spee	

In human embryos which possess some fifteen somites we not only have an increased number of dorsal segmental arteries (eleven

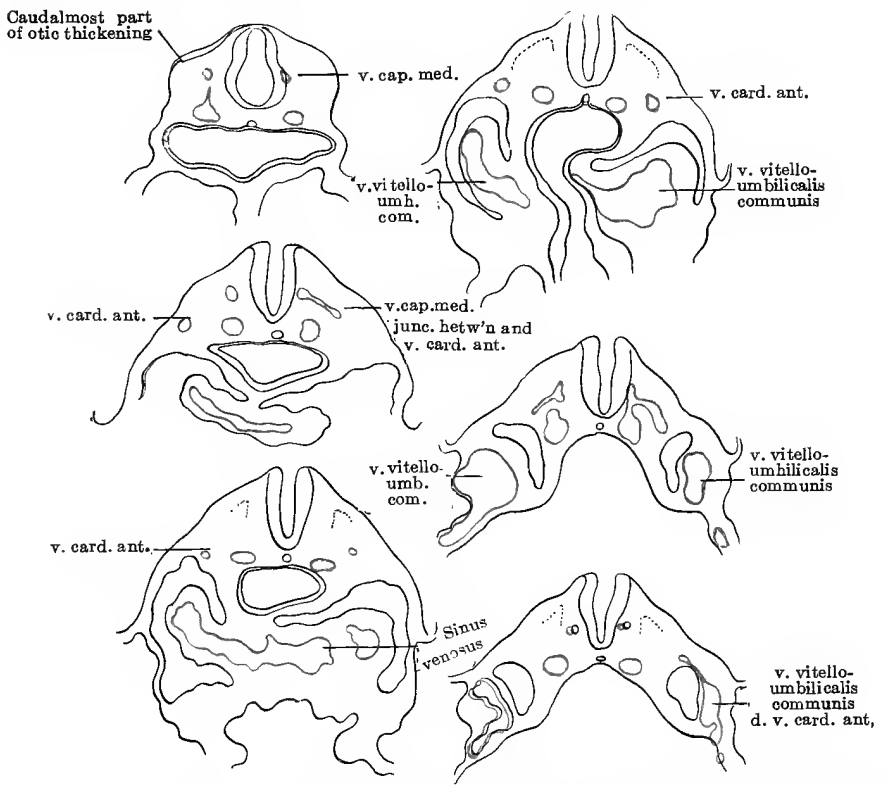

FIG. 411.—A series of cross sections through a human embryo with 15 somites (collection of Graf Spee, No. 52), showing the course and relations of the primitive head vein (v. capitis medialis et v. cardinalis anterior) and the relation of the chief venous stems to the heart.

in the embryo with fifteen somites) and of the primitive vitelline arteries, but also another set of aortic branches which I shall designate as the *primitive lateral branches of the aorta*.[22] These

[22] Grafe (1905) was, I believe, the first to see these vessels, describing them in the posterior portion of a chick embryo of about sixty hours; but their cephalic extension was shown by Williams (1910), who described them in the first two intersegmental clefts.

vessels take origin from the lateral aortic wall, often from its ventro-lateral angle, and course obliquely upward and outward in the space between the somite and the intermediate mesodermic mass; here I have seen them anastomose with the cardinal vein; they are also often connected with the dorsal segmental arteries by direct cross anastomoses in the loose mesoderm of the intersomitic clefts.

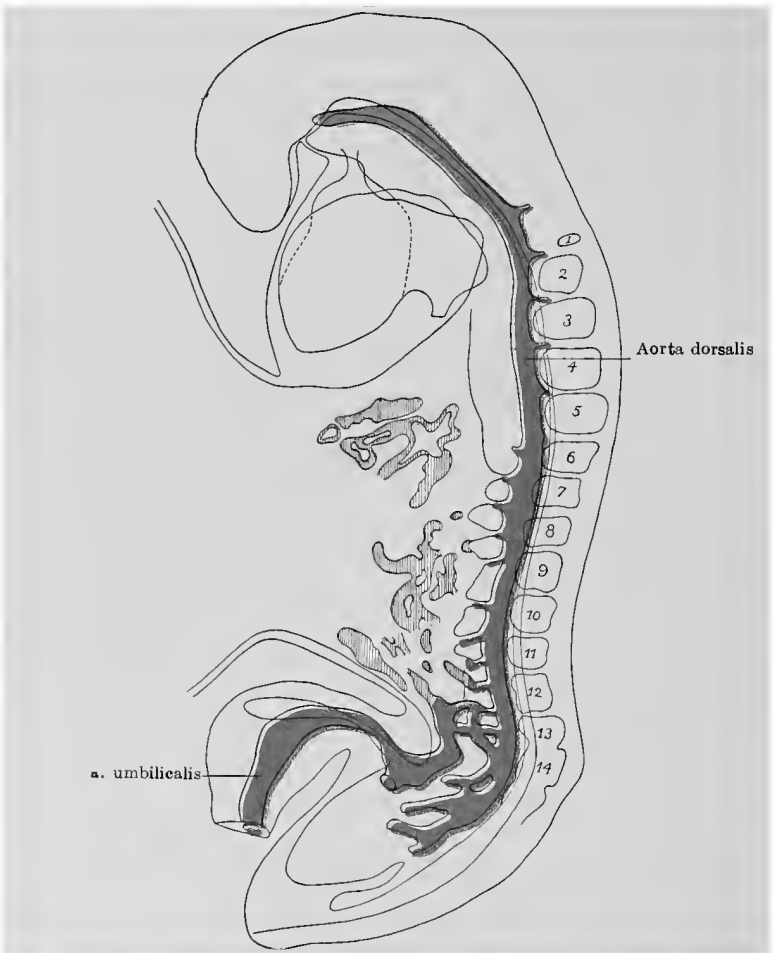

Fig. 412.—Reconstruction of the arterial system of a human embryo with 14 somites (NT. 6), seen from the left. (Slightly modified, after W. Felix, 1910.)

The primitive vitelline arteries in the area opposite the first five somites have atrophied, but the series of these vessels begins from here caudally to form a continuous row unrelated apparently to metamerism and finally, in the unsegmented area, giving way, as in the younger embryos, to a plexus from which the umbilical artery takes origin.

The first venous channels of the embryo proper—the vv. cardinales anteriores—are found at this stage, and in the Graf

von Spee embryo with 15 somites can be traced clearly from the region of the optic vesicles, cephalically, to their opening into the common vitelline and umbilical vein, caudally. These veins, as Grosser (1907) has shown to be probable for all vertebrates, in man also possess two different and distinct topographical relations, for in their cephalic course they lie close to the sides of the neural tube, constituting the *v. capitis medialis,* whereas more caudally—*i.e.,* in the region beginning with the first mesodermic somite—they take up a lateral position between the somite and the cœlomic mesoderm where they may be designated the true vv. cardinales

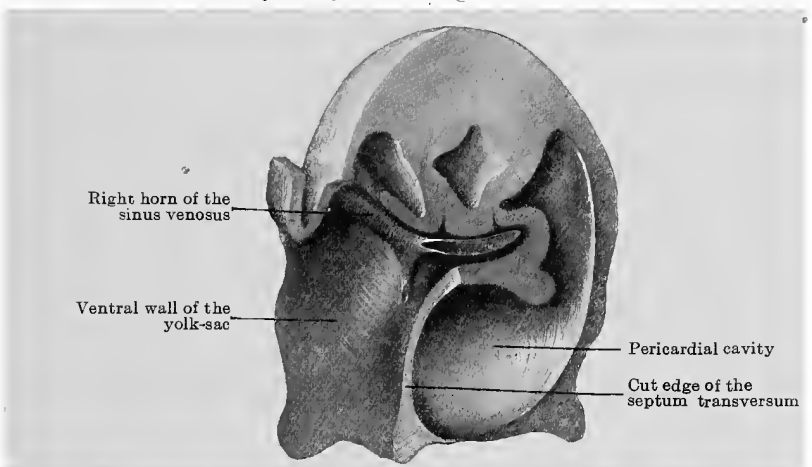

FIG. 413.—Sinus venosus and septum transversum in a human embryo with 14 somites (NT. 6), viewed from above. The right half of the septum has been removed to show the sinus venosus contained therein. (Drawn from the model by Dr. Alex. Low.)

anteriores. Opposite the third somite the vessel finally joins the common vitello-umbilical vein by coursing dorsal to the cœlomic cavity in this region (Fig. 411). The v. capitis medialis receives several (four) direct dorsal offshoots from the aorta, so that it really appears as a longitudinal neural anastomosis of these pre-segmental dorsal arteries; it turns out rather sharply somewhat in front of the first somite to constitute the true anterior cardinal, which is again formed apparently by a laterally-situated longitudinal anastomosis of loops formed by the dorsal segmental vessels; to it also the primitive lateral branches of the aorta are joined.[23]

[23] This history of the formation of the anterior cardinal vein in man is thus identical with that which has been previously found in the chick (Evans, 1909), in which latter embryo Williams has recently described the same phenomena in a careful account of the region about the second somite. It is consequently probably significant that the picture furnished by the endothelial cells constituting the first dorsal segmental vessel in the Eternod embryo shows a marked lateral wandering of the endothelium (Fig. 439). This probably should be accounted the first stage in the formation of the anterior cardinal in man.

The vitelline veins still behave in all essentials as in the younger stages; they receive the umbilical veins when quite lateral in position, and the common veins receive the anterior cardinals, turning in sharply to constitute the sinus reuniens (Fig. 411).

EMBRYO OF TWENTY-THREE SOMITES.

In stages which are intermediate between those which have just been described and embryos possessing limb buds, the *posterior cardinal veins* develop. This has already occurred in the embryo with twenty-three somites (Robert Meyer, 300, N.T. 7),

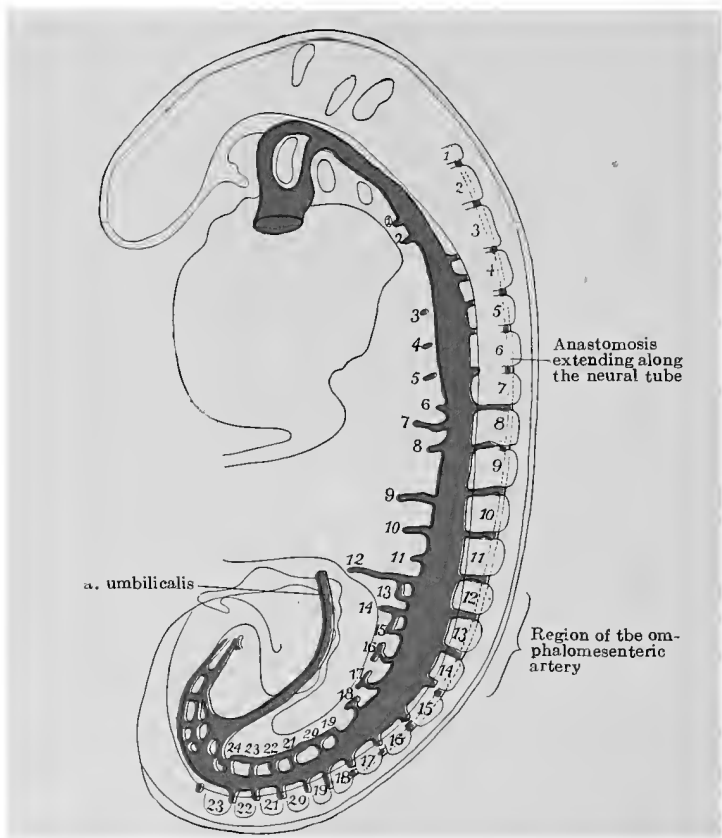

Fig. 414.—Reconstruction of the arterial system of a human embryo with 23 somites (NT. 7). (After W. Felix, 1910.)

which has no indication as yet of limbs. It is probable that lateral loops of the dorsal segmental arteries are instrumental in the formaton of these veins, as is the case with the anterior cardinals.[24] At this stage the dorsal segmental vessels form in the

[24] This method of formation of the posterior cardinal veins appears fundamental. Raffaele (1892) and Hoffman (1893) described it for selachian embryos and Grafe (1905) and the writer have indicated it in the case of the chick.

tissue of the intersomitic clefts large well-marked vascular arches or loops, one limb of which is against the neural tube while the other joins the cardinal vein (Fig. 436). At this stage also the primitive lateral branches of the aorta form an extensive system, and at many levels we are able to find all three systems of branches occurring together and segmentally arranged.

The row of vitelline arteries is by no means exclusively segmentally arranged; nevertheless there is a symmetrical disposition in that these vessels occur in pairs, so that in the region in

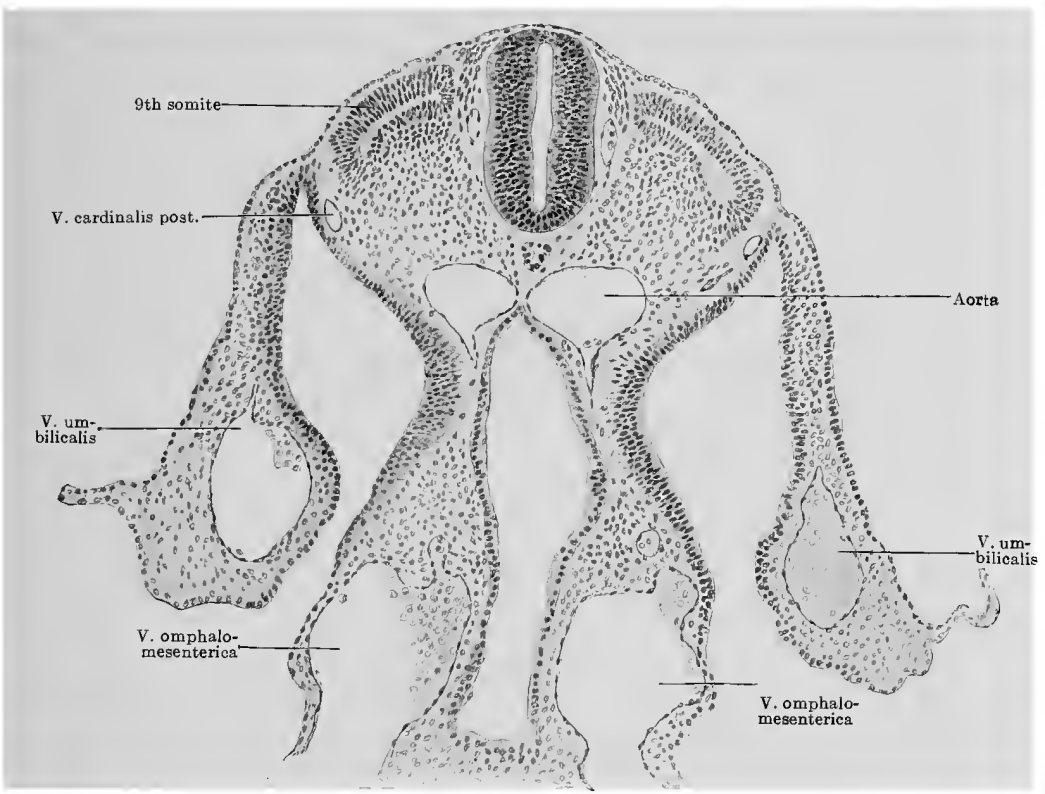

FIG. 415.—Cross section of the human embryo with 23 somites, shown in Fig. 414, taken through the region of the 9th somite, showing paired aa. vitellinæ.

which the two aortæ primitivæ have fused to a single median aorta we can observe that two vessels arise from the ventral surface of the aorta and course each on its corresponding side of the gut, which possesses as yet no mesentery (Fig. 415). When later an intestinal mesentery is formed, these vessels course for a time side by side, but eventually are completely fused to a medial ventral trunk, or it is possible that one member of the pair gains the ascendency and its fellow atrophies.

In the posterior region of the body we find not only the posterior cardinal vein, but a new one, lying ventral to the former and near the cœlomic epithelium. This vein, the v. subcardinalis (F. T. Lewis, 1902), has probably arisen by sprouts from the posterior cardinal trunk, as Graefe has shown for the chick; at any rate the presence of a large number of anastomoses between these two vessels speaks strongly for this view. In the region of the mesonephros the subcardinal vein occupies a characteristic position ventral to the Wolffian duct, but at levels above this region, where we have as yet, according to the view of Felix, only the pronephric anlage, the vein is also found, and in the same position, *i.e.*, ventral to the chief duct, as Fig. 416 will show. There also

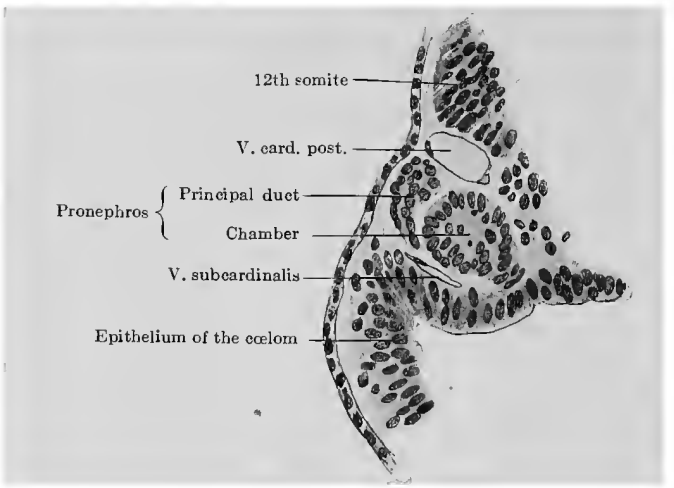

FIG. 416.—Section showing the position of the v. cardinalis posterior and the v. subcardinalis in a human embryo with 23 somites (NT. 7), taken in the region of the 12th somite.

occurs in embryos of this age another vein medial to the pronephros, and it has probably arisen as a longitudinal anastomosis binding together vascular offshoots from the posterior cardinal veins and also the primitive lateral branches of the aorta.[25]

EMBRYO OF 4.9 MM. LENGTH (35 SOMITES, N.T. 14).

By the time the embryo reaches a length of 5 millimetres several important changes in the vascular system have occurred. The embryo described by Ingalls (1907) and shown in Figs. 417, 418 will serve to illustrate this stage.

It will be noted that four complete aortic arches are present, and that another pair—the sixth or pulmonary arches—are being

[25] One finds in this embryo pictures which very much resemble that given by Grafe in his table 11, Fig. 7, for a chick of 71 hours.

formed by both ventral and dorsal endothelial sprouts. The third pair, the carotid arches, are by far the largest of the series, while the first are already very much reduced. The aortic root on each side now appears to continue toward the head beyond the location of the first arches. This, the *internal carotid artery,* is doubtless the trunk representing the very early capillary sprouts which the first arch sent toward the brain. It courses headward lateral to the hypophysis and bending dorsally anastomoses with a long branch—the a. vertebralis cerebralis—given off from the first of the dorsal segmental arteries here present (in this case the hypoglossus artery). At the optic cup the internal carotid gives off the *a. ophthalmica* as its first branch, and somewhat beyond this a very large branch (a. cerebri ant. et med.) which courses forward between eye and brain; other smaller branches are given off to the mid-brain region, and the carotids then sweep backward to join the cerebral vertebrals, which they furnish with their main volume of blood, although later the stem of origin of the latter vessel gives it most of its blood. The *first cervical dorsal segmental artery*[26] anastomoses with the hypoglossus, and consequently the path is already furnished for this stem to take over the cerebral vertebral when the hypoglossus yields the current and atrophies. Excluding the hypoglossus vessel twenty-seven dorsal segmental branches arise in pairs from the aorta and sacralis media artery,—*i.e.,* the full number of cervical, thoracic, and lumbar vessels and the first two sacral segmentals. The umbilical arteries, though they later shift to the last lumbar level, arise here opposite the third lumbar segmentals, the remaining lumbar arteries at this stage consequently arising from the a. sacralis media. The aa. umbilicales course medial to the Wolffian ducts, but at the prominent bend which they make in turning upward are in connection with capillaries lying lateral to the Wolffian duct, which ultimately gain a connection with the aortic wall and completely displace the medial roots of origin of these arteries. *The subclavian artery* arises from the seventh dorsal segmental pair.

Most interesting are the ventral branches of the aorta, for these no longer form a uniform row of vessels, but reflect a beginning differentiation of the gut. Consequently there are retained, besides many smaller ones, three chief branches, to correspond to the stomach-pancreas region, the vitelline-duct region, and the colon respectively (*a. cœliaca, a. omphalomesent., et a. mesent. inf.*). The middle of these three stems, which is also by far the largest, since it drains yolk-sac as well as gut, takes origin from

[26] I refer to the segmental artery cranial to Hochstetter's "first cervical artery," naming that artery the first cervical which courses with the first cervical nerve, as do Mall, Tandler, and Broman.

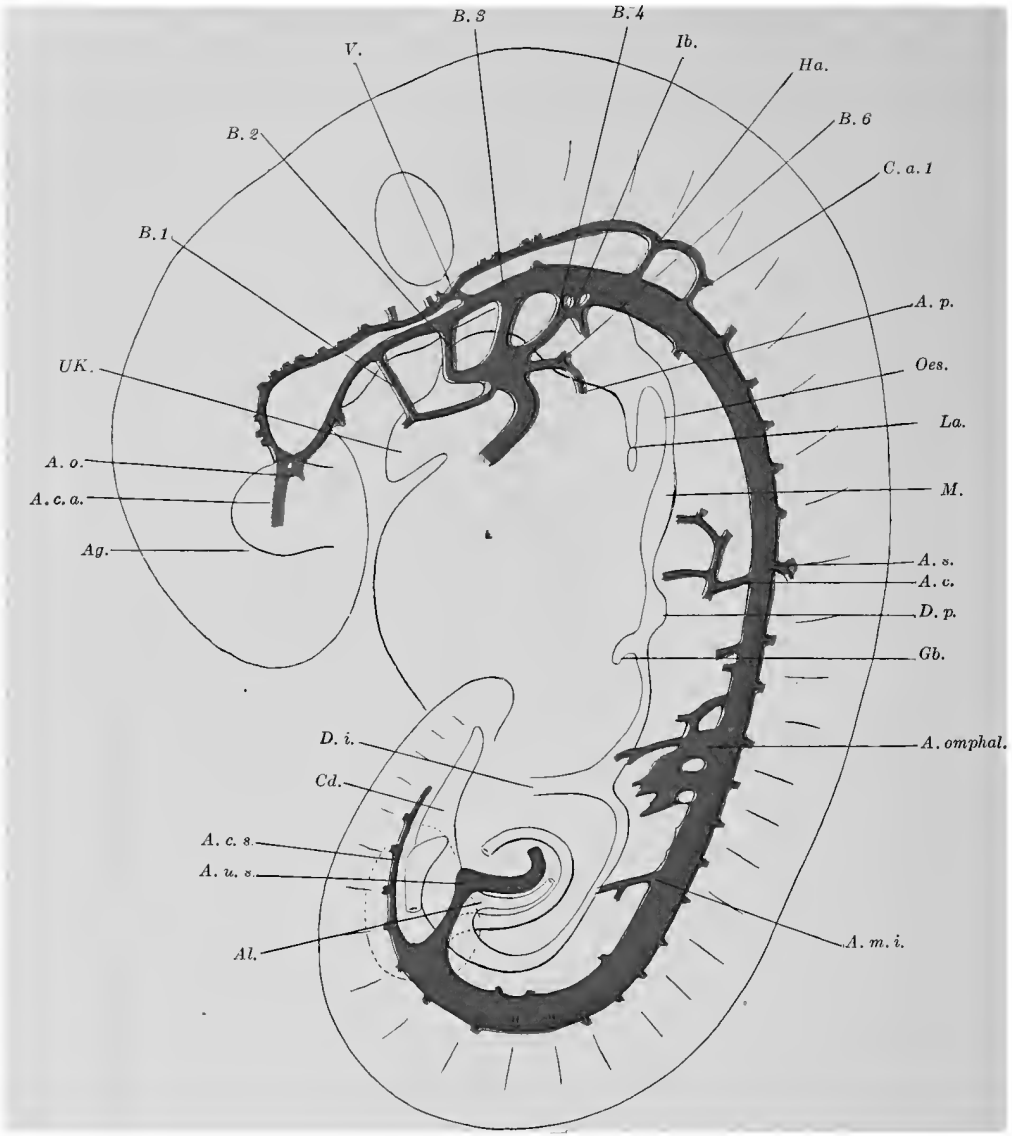

FIG. 417.—Reconstruction of the arterial system in a human embryo 4.9 mm. long, lateral view. (Aftsr Ingalls, Arch. f. mik. Anat., Bd. 70, p. 530, 1907.) *A. c.*, a. cœliaca; *A. c. a.*, a. cerebralis ant.; *A. c. s.*, a. caudalis sin.; *Ag.*, optic vesicle; *Al.*, allantois; *A. m. i.*, a. mes. inf.; *A. o.*, a. ophthalmica; *A. omphal.*, a. omphalomesnterica (with thres roots); *A. p.*, a. pulmonalis; *A. s.*, a. subclavia; *A. u. s.*, a. umb. sin.; *A. v.*, a. vertebralis; *B. 1,2,3,4,6*, aortic arches; *C. a. 1*, first csrvical artery; *Cd.*, caudal intestine; *D. p.*, dorsal pancreas; *D. i.*, ductus vitello-intsstinalis; *Gb.*, gall-bladder; *Ha.*, hypoglossus artery; *Ib.*, insslbildung; *La.*, lung anlags; *M.*, stomach; *Oes.*, œsophagus; *T. a.*, truncus arteriosus; *UK.*, lower jaw; *V.*, questionable union betwesn the a. vertebralis and a. car. int. (N. T. 14.)

the aorta by four distinct roots. It will be noticed that all these branches are much above their location in the adult, as can be seen by comparing them with the dorsal segmentals opposite, and it is not indeed until the embryo attains a length of from 16 to 20 millimetres that their definitive position is reached.

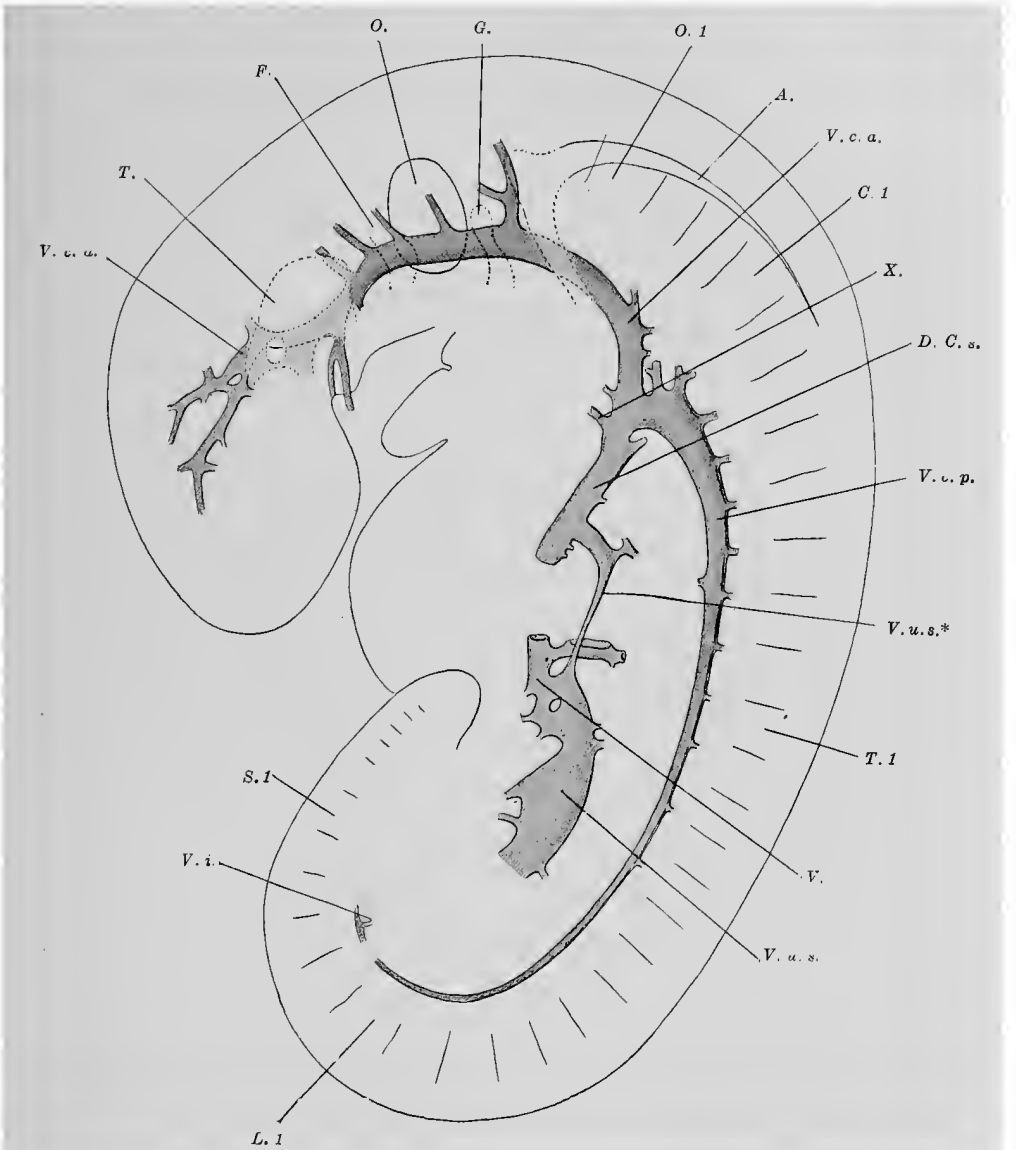

FIG. 418.—Reconstruction of the venous system of the embryo shown in Fig. 417. *A.*, fibres of the accessorius; *C. 1*, first cervical segment; *D. C. s.*, ductus Cuvieri sin.; *F.*, facialis; *G.*, glossopharyngeus; *L. 1*, first lumbar segment; *O.*, ear vesicle; *O. 1*, first occipital segment; *S. 1*, first sacral segment; *T.*, trigeminus; *T. 1*, first thoracic segment; *V.*, union of the left umbilical vein with the liver circulation; *V. c. a.*, v. card. ant.; *V. c. p.*, v. card. post.; *V. i.*, v. ischiadica; *V. u. s.*, v. umb. sin.; *V. u. s.**, remains of the original circulation to the sinus venosus; *X.*, linguo-facial vein.

Irregularly arising, lateral branches of the aorta go to the mesonephros.

In contrast to the earliest stages, the venous system of the embryo proper is now well developed, and one sees the well-

known fundamental pattern of the two cardinal veins on each side uniting to form the ductus Cuvieri which then joins the umbilical. The *anterior cardinal* can be seen beginning in two strong efferents in the head region, the first of which doubtless represents the ophthalmic vein. Passing medial to the ganglion of the fifth nerve, the main vein next receives a tributary from the hypophysis region, and continues caudally on the lateral side of the acusticofacial ganglion, the auditory vesicle, and the ganglion of the glossopharyngeus, but medial to the vagus ganglion; just before reaching the latter nerve, it receives a prominent tributary from the dorsal region (v. cerebri post., Mall), although smaller tributaries have joined it all along its previous course. Before joining the ductus Cuvieri, several venules run into it, which, from their position and correspondence with the veins of other mammalian embryos, can be recognized as the segmental veins belonging to the first cervical and the several occipital segments. The *ductus Cuvieri* receives on each side a slender venule, which drains the capillary plexus in the first visceral arch. This vessel crosses from the latter into the ventral body wall (here constituted by the membrana reuniens over the front of the heart) and runs in this to open into the ductus (*v. linguo-facialis,* F. T. Lewis, 1909).

The *posterior cardinal* vein begins at about the level of the third lumbar segment, and courses in the tissue dorsolateral to the Wolffian body. It receives the dorsal segmental veins, which do not become appreciable structures until about the level of the fifth thoracic segment. The seventh cervical segmental vein receives the vessel from the arm bud (the *subclavian vein*), although this afterward shifts up to the anterior cardinal vein. The *v. subcardinalis* can first be recognized at about the level of the seventh thoracic somite, and empties into the posterior cardinals at the level of the sixth cervical one. They drain the Wolffian body at this stage, but later acquire greater significance inasmuch as they are incorporated in the formation of the inferior vena cava. The *umbilical veins* are already sending their main mass of blood into the liver, but with their old connections with the sinus venosus still evident. This uppermost and superficially lying part of the umbilical vein receives tributaries from the arm buds, and this source of blood delays their atrophy (Evans, 1909). The vessels from the lateral body wall also drain into the v. umbilicalis along all of its course until the liver is reached, so that the vein forms at this time an important drainage channel for the entire lateral body wall. The *vitelline veins* empty their blood directly into the liver sinusoids, the blood from the left omphalomesenteric vein being collected by a short trunk which enters the left horn of the sinus venosus (*v. hep. sinistra*); but the right and larger one possesses a wide passage through this organ to the right horn of the

sinus venosus. The two vitelline veins are anastomosed on the ventral, then on the dorsal, and again on the ventral sides of the duodenum, forming thus two venous rings around the gut (His).

EMBRYO OF 7 MM. LENGTH (40 SOMITES, N.T. 28).

The vascular system present in an embryo measuring 7 millimetres begins to be complex enough to demand detailed descriptions for many areas, so that with a brief presentation of the chief features here, we may leave this account of the early vascular system as a whole and turn to the explicit history of the various vessels. The main blood-vessels in an embryo of this length (7 mm.) are well known to us through the papers of Mall (1891),

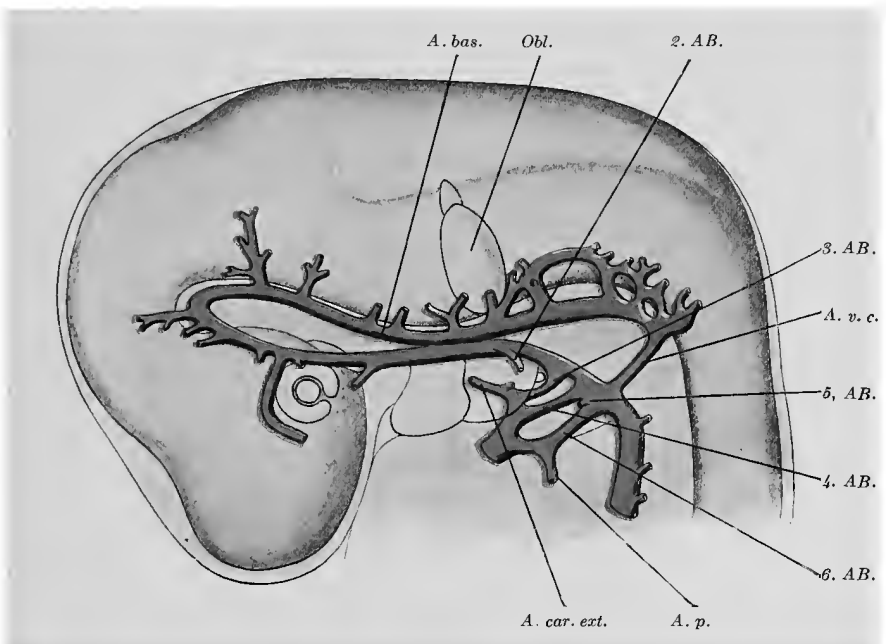

FIG. 419.—Profile reconstruction showing the arterial system of the head and neck in a human embryo 7 mm. long. (N.T. 28.) (After Elze, Anat. Hefte, Bd. 35, Heft 106, Taf. 16, Fig. 3.) *2, 3, 4, 5, and 6 AB*, aortic arches; *A. bas.*, a. basilaris; *A. car. ext.*, a. carotis externa; *A. p.*, a. pulmonalis; *A. v. c.*, a. vertebralis cerebralis; *Obl.*, ear vesicle.

Piper (1900), and Elze (1907); the latter's figures are here reproduced and his description largely followed (Figs. 419 and 420).

Three complete aortic arches exist, the third, fourth, and sixth. The first pair, already very weak in the preceding embryo (4.9 mm.), are now entirely atrophied, but both dorsal and ventral end pieces of the second arch are recognizable, the dorsal remnant, in fact, being destined to constitute the trunk of origin of the *stapedial artery* (Tandler, 1902). The upper end of the sixth arches sends out, between these and the fourth pair, a small vascular frag-

ment, which perhaps represents the persisting upper end of a previous transitory fifth arch. The *aorta ventralis* in the area of the first and second arches now constitutes the *a. carotis externa* which reaches into the region of the upper jaw. The *internal carotid* artery, after giving off the dorsal rudiment of the second arch, courses headward to give off in the region of the hypophysis

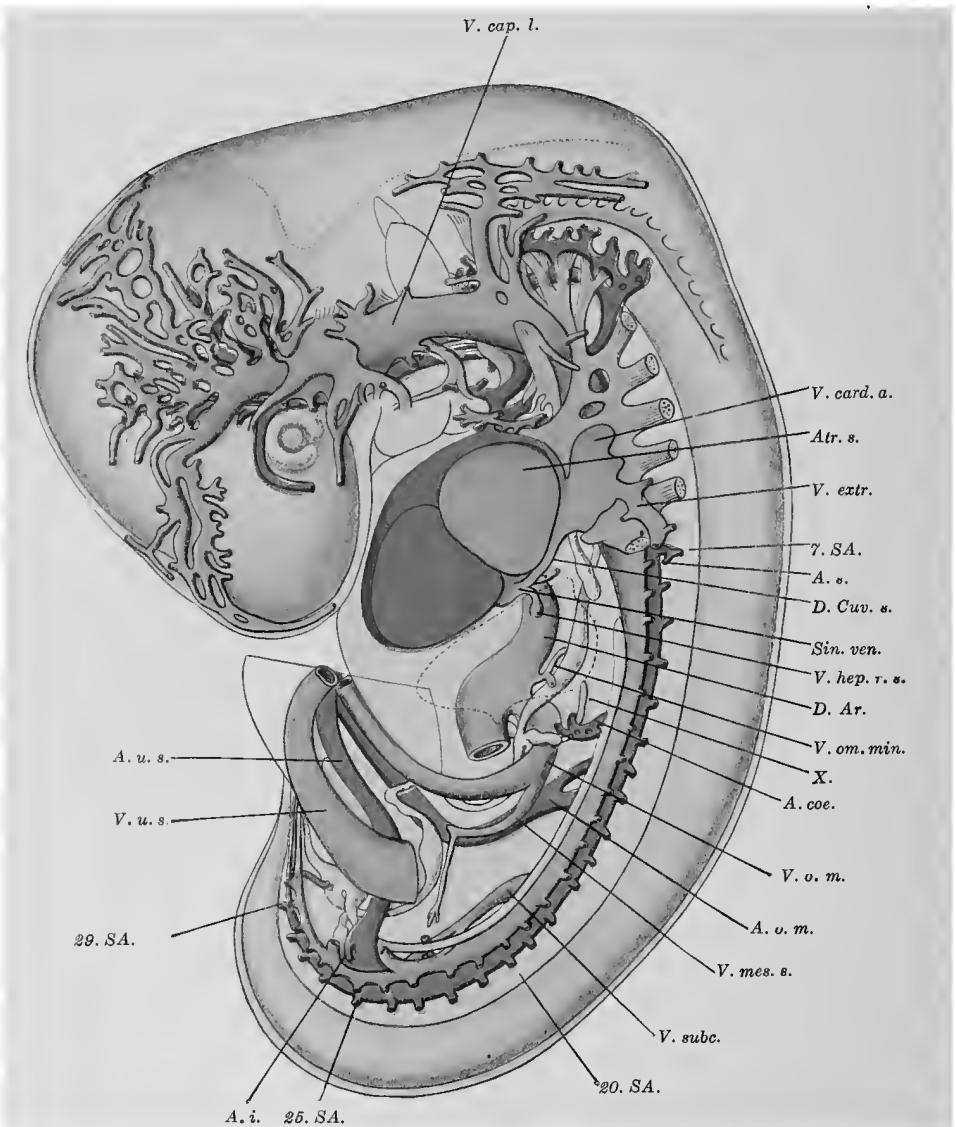

FIG. 420.—Profile reconstruction of the same embryo, showing general arterial and venous system. (After Elze, Taf. 15, Fig 2.) × 26.5. *A. coe.*, a. cœliaca; *A. i.*, a. iliaca; *A. s.*, a. subclavia; *A. o. m.*, a. omphalomesenterica; *Atr. s.*, atrium sinistrum; *A. u. s.*, a. umbilicalis sin.; *D. Ar.*, ductus venosus Arantii; *V. card. a.*, v. cardinalis anterior; *V. cap. l.*, v. capitis lateralis; *V. extr.*, extremity vein; *V. hep. r. s.*, v. hepatica revehens sinistra; *V. o. m.*, v. omphalomesenterica; *V. om. min.*, v. omenti minoris; *V. mes. s.*, v. mesenterica superior; *V. u. s.*, v. umbilicalis sin.; *V. subc.*, v. subcardinalis; *D. Cuv. s.*, ductus Cuvieri sin.; *7, 20, 25, 29 SA.*, segmental arteries; *Sin. ven.*, sinus venosus.

a branch which courses toward the brain beneath the optic cup, then above this, a small branch to the latter (*a. ophthalmica*), and dorsal to the eye, a large branch which apparently supplies the main portion of the fore- and 'tween-brain (a. cerebri ant. et med.). After giving off other branches to the lateral side of the 'tween- and mid-brain, the artery ends in its *ramus communicans posterior* which appears to continue the main trunk into the *basilar artery*. The *a. vertebralis cerebralis* now arises from the *first cervical segmental artery,* and the preceding *hypoglossus vessel* has entirely disappeared. The stem of the first cervical vessel, however, has been shifted cranially until it is now opposite the sixth aortic arches, whereas earlier even the hypoglossus artery arose relatively further caudad. The two cerebral vertebral vessels unite in the mid-ventral plane to form the *a. basilaris,* which extends from the area opposite the vagus nerve to the vicinity of the oculomotor nerve, where it splits into the two posterior communicating rami which connect it with the internal carotids. Both the cerebral and the basilar arteries send off many branches to the hind-brain, some of the branches of the former anastomosing dorsal to the emerging fascicles of the twelfth nerve, so that these fibres appear to go through arterial fenestræ. The full number of cervical, thoracic, and lumbar *segmental arteries* exist and all but the last sacral. The *umbilical arteries* come off the aorta at the level of the last lumbar segments, and now course lateral to the Wolffian ducts and send each a small branch into the posterior limb (a. ischiadica). The ventral branches of the aorta have been reduced to three main trunks: the *a. cœliaca* arises opposite the fourth thoracic artery; the *a. omphalomesenterica* is two-rooted, its upper root coming from a level slightly above the fifth thoracic artery, its lower one opposite the sixth; while the *a. mesenterica inferior* arises opposite the second lumbar vessel.[27]

The veins show several important changes. The proportionately great growth of the head gives a great drainage area for the *anterior cardinal vein,* which is consequently much increased in size. Its foremost tributary is the paired primitive *sinus sagittalis superior* on the top of the fore-brain. These are the only tributaries to reach the mid-dorsal plane, with the exception of a very short partly paired one on the roof of the mid-brain.[28] Sev-

[27] A ventral vessel is seen arising from the sacralis media beyond the level of the fourth sacral segmental vessels and supplying the end of the gut where it goes over into the cloaca. Branches of this type from the sacralis media are seen in injections of other mammalian embryos, namely the pig, where they are more numerous and reach further headward.

[28] Considerable interest should attach to these mid-dorsal veins of the mid-brain, inasmuch as Grosser (1901, p. 322) has demonstrated a pair of veins in this locality in bat embryos where they are retained, in fact, in the adult as the *v. longi-*

eral tributaries from the first two visceral arches reach the main trunk, while behind the ear vesicle the posterior cerebral (Mall) vein has grown to great proportions. The anterior cardinal, proceeding caudally, surrounds the vagus by a venous ring and then goes under the hypoglossus to join the posterior cardinal trunk. The *linguo-facial vein* (F. T. Lewis) is now no longer a tributary of the *ductus Cuvieri,* but joins the cardinalis anterior.

The *posterior cardinal vein,* receiving the same number of *dorsal segmental tributaries* as is sent out from the aorta and sacralis media artery, drains also the marginal vein of the leg bud and along its entire length receives efferents from the Wolffian body; but the *axillary vein* now reaches the ductus Cuvieri and will soon indeed be a branch of the anterior cardinal trunk. The *subcardinal veins* (not illustrated) exist from the level of the tenth thoracic segment caudally and are in frequent communication with the corresponding posterior cardinal. The *umbilical veins* can no longer be traced to the ductus Cuvieri on either side, and the superficial portion of the primitive vein is only represented by several small stems draining from the body wall into the main trunk just before it plunges into the liver. The left umbilical is by far the larger of the two, and the same is true for the *vitelline trunks;* the right vitelline indeed has atrophied practically completely, and its previous large pathway through the liver has given way to many sinusoidal paths, whose supplying or portal stem may be called the *ramus arcuatus* while the corresponding draining or hepatic venule is the *v. hepatica dextra.* The *v. hepatica sinistra* still opens independently into the sinus venosus. The main mass of the umbilical blood takes a direct path through the liver in the ductus venosus (Arantii), which receives several small veins from the caudal end of the stomach (Magenvene, Hochstetter, 1893; *v. omenti minoris,* Broman, 1903). From the liver capillaries a slender vessel grows out into the caval mesentery, the anlage of the *v. cava inferior.*

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tudinales mesencephali, apparently homologous with this vein in reptiles (Grosser and Brezina, 1895). Grosser attributes the disappearance of these veins in other mammals to the great overgrowth of the cerebral hemispheres, which, as is well known, are notably small in the Chiroptera. He also calls attention to the fact that Salvi (1897) probably saw the same structure, if we may judge from the descriptions in his paper on the development of the meninges in Cavia and Lepus. Attention may here be called to the fact that the primary head capillary plexus in pig embryos halts in its spread along two parallel mid-dorsal lines in the mid-brain as well as fore-brain, and, just as the medial margin of the former plexus comes to constitute the primitive paired sinus sagittalis superior, so also in some embryos an exactly similar condition transitorily exists on the top of the mid-brain. So that from the careful description of Grosser and the less satisfactory references of Salvi this evidence may now be added to indicate quite clearly, I think, that a condition resembling the reptilian v. longitudinalis mesencephali exists transitorily in all mammalian embryos, including man.

C. Arteries.

DEVELOPMENT AND FATE OF THE AORTIC ARCHES.

Since the human embryo, like that of all other vertebrates, possesses a row of definite gill bars or visceral arches, separated distinctly, externally by clefts, internally by entodermal pockets or pouches, so also its primitive vascular system is in conformity with this fundamental plan, and strong branches connecting the dorsal and ventral aortæ—the aortic arches—each course in a visceral arch (Fig. 421). It has been known for a long time that in all vertebrates above the fishes,—*i.e.*, in the amphibia, the sauropsida, and the mammalia—the number of these arches is five

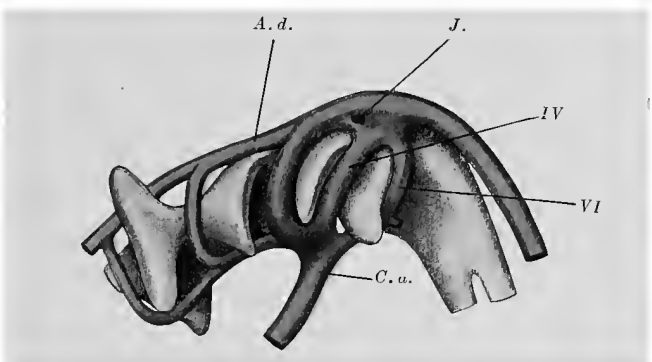

FIG. 421.—Model of the pharynx and aortic arches in a human embryo 5 mm. long. (After Tandler, Morph. Jahrb., xxx, 1902, Taf. v, Fig. 17.) *A. d.*, aorta dorsalis; *C. a.*, conus arteriosus; *J.*, island; *IV*, fourth aortic arch; *VI*, sixth aortic arch.

Within the last three decades, however, it has gradually been shown that in reality six arches exist in these classes, the fifth aortic arch being everywhere an exceedingly transitory vessel.[29]

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[29] In 1886 Van Bemmelen for the first time described a transitory aortic arch found between the systemic and pulmouic arches in embryos of birds and reptiles. A year later Boas (1887), in welcoming this discovery, pointed out its importance in the comparative anatomy of vertebrates. He recalled (Morph. Jahrb., Bd. 7, 1882: Bd. 8, 1883) that in amphibian larvæ, as well as in Ceratodus, Polypterus, and Amia, the four aortic arches which occur occupy the third to the sixth visceral arches, the pulmonic artery being given off in each case by the last pair, *i.e.*, by the aortic arch of the sixth gill-bar. It hence appeared evident that the pulmonic arch was the sixth and not the fifth of the series in all vertebrates, and Boas now predicted the discovery of a transitory fifth arch in the embryos of mammalia, the only remaining class in which it had not as yet been seen. Two years later Zimmermann, as is well known, reported the presence of a fifth arch in embryos of man, the rabbit, and the sheep. Tandler's careful paper, following in 1902, reported traces of the arch in the rat and two very clear examples of it in man, for which he furnished the first figures published. Lehman has described what were

Zimmermann (1889) was the first to indicate that there was any tendency to the formation of a fifth arch in man, reporting the separation of the fourth arch into two distinct vessels in a seven millimetre human embryo.

In his article on the development of the head arteries in mammals, Tandler (1902) described two very clear cases of a human fifth aortic arch, neither of which, it may be noted, corresponded to Zimmermann's description, for in both cases the fifth arch took origin from the aorta ventralis and joined the dorsal portion of the pulmonary arch. A diverticulum of the fourth endodermal pouch (postbranchial body) separated the fifth and sixth arches, whereas the fourth pouch lay between the fifth vessel and the fourth arch. Since then other observers (Elze, 1907) have reported the partial presence of this vessel in the same situation. The question of the existence of a true fifth aortic arch was soon seen to involve the identification of the postbranchial body as the fifth branchial pouch. Hammar (1904), now, had described an embryo of 5 mm. (N.T. 20), in which five pouches were present, the fifth fusing with the ectoderm of a fifth branchial cleft in the manner typical for these structures. Elze (1907), aware of Hammar's report, and finding a fifth ectodermal cleft opposite the post-branchial body in an embryo of

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interpreted as vestiges of the arch in the rabbit and gave a distinct instance of it in the pig. It is important that in some of these cases—*e.g.,* in Tandler's (man) and in Lehman's (pig)—we had also to do with what was apparently a fifth pharyngeal pouch. This structure, the so-called postbranchial body, is not new. It had been known to appear behind the fourth pouch but soon to grow into the latter, with which it had a common opening into the pharynx and of which it now appeared to be a diverticulum. It seemed highly significant also that in the cases which have just been enumerated the fourth pouch pointed towards the ectoderm between the fourth and fifth arches, while the postbranchial body occurred between the fifth arch and the sixth. The whole picture of these interrelations, in short, pointed strongly to their all being serial true branchial structures. In 1906 F. T. Lewis indicated that the very general acceptance of this interpretation was probably caused by the weight of comparative considerations. He called attention to the ordinary conception of a vessel which could be called an aortic arch having a definite course from the ventral to the dorsal aorta, and emphasized that a fifth arch of this completeness had never been seen, except by Zimmermann in the rabbit, where subsequent investigators (Lehman, Lewis) have not been able to confirm him. This fact must be admitted, for even in Tandler's clear cases the accessory arch does not join the dorsal aorta, but instead fuses with the pulmonary arch before this ends dorsally. Locy has emphasized that it seems generally true that the fifth arch is in some way connected with the last pair, in some of the lower classes, in fact, the pulmonic arch appears to have split,—*e.g.,* Lacerta (Peter). Other reports have recently come in affirming fifth aortic arches in other mammals,—Soulié and Bonne (1908) in the mole, Coulter (1910) for the cat, and Reinke for the pig,—(Note on the Presence of the Fifth Aortic Arch in a 6 mm. Pig Embryo, Anat. Record, vol. 4, No. 12, December, 1910) and the evidence is too unanimous to cause doubt that vascular rudiments in the position of a fifth arch occur generally in the mammalia.

7 mm. (N.T. 28), felt no hesitancy in identifying the postbranchial or ultimobranchial body as the fifth branchial pouch. Finally Tandler (1909) has examined a considerable number of embryos bearing on this point and brought together all that has been ascertained about the fifth arch. His conclusions seem to put the question at rest and to show that in man, very transitorily, in embryos from five to ten millimetres in length, a true fifth arch exists (Figs. 422 and 423, A and B), springing from the truncus aorticus just before the fourth arteries are given off, and coursing dorsally in what is sometimes a distinct fifth gill bar to open into the sixth arch close

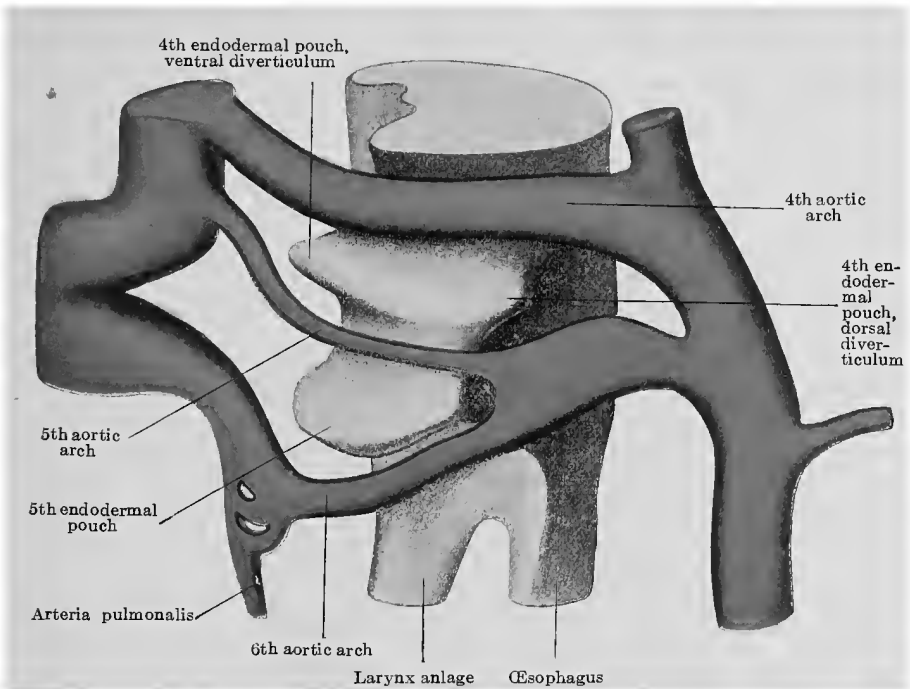

FIG. 422.—Model of the pharynx and aortic arches of a human embryo 7 mm. long. (After Tandler, 1909.) (Embryo Hs of the I anat. Lehrkanzel, Vienna.)

to its upper end. In relation with it is a special transitory branch of the vagus nerve (ramus posttrematicus, Elze),[30] in front of it is the fourth entodermal pouch, and behind it the postbranchial body (fifth pouch). The latter is indeed in early stages apparently only a caudal ventral division of the fourth pouch. It is later

[30] Ramus posttrematicus der IV Schlundtasche," "R. posttrematicus V," or "R. posttrematicus II des Vagus," given off by the N. laryngeus superior shortly after its departure from the ganglion nodosum and described by Elze (1907) and Tandler (1909) in embryos from 7 to 9 mm. in length. It is usually absent in later stages, although Grosser (1910) believes he has identified it in an embryo 19¾ mm. (crown-rump), passing through the foramen thyreoideum.

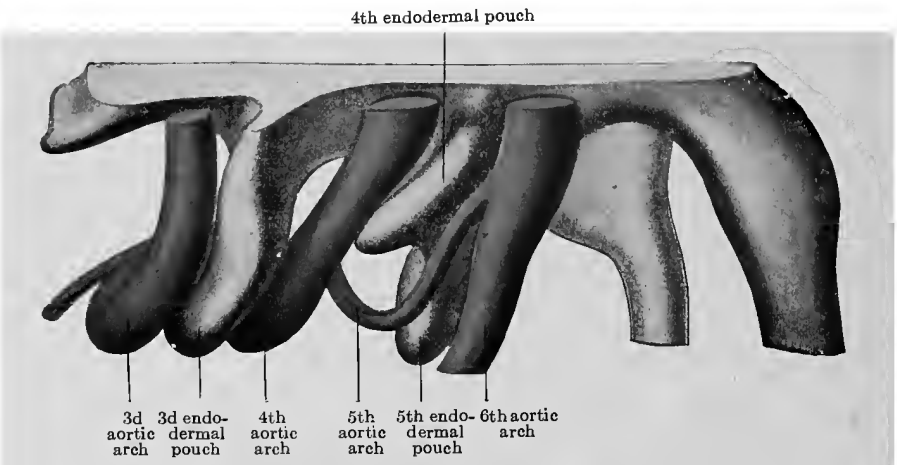

Fig. 423 A.

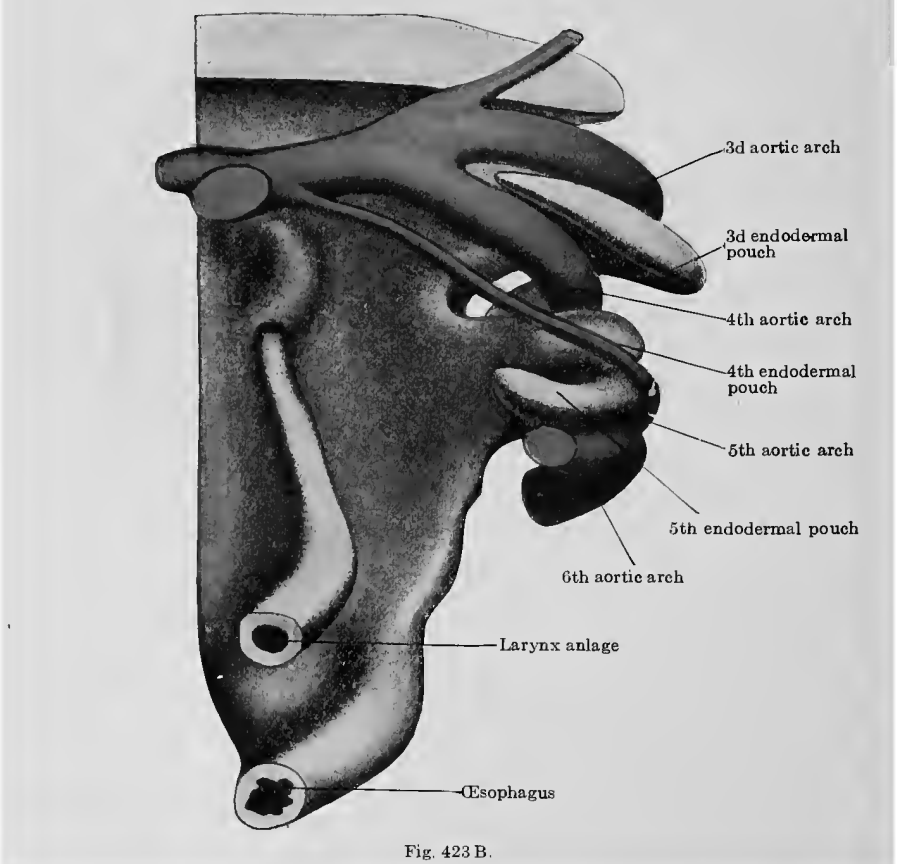

Fig. 423 B.

FIG. 423 A and B.—Model of the pharynx and aortic arches of a human embryo 9 mm. long (NT. 37). (After Tandler, 1909.)

incorporated in the thyroid gland (Tandler, 1909, Grosser, 1910), although apparently not contributing true thyroid tissue (Grosser).

The only certain facts which have been established in the metamorphosis of the human arches into the trunks of the permanent vascular system have been incorporated in the diagram of Fig. 424. As far as their actual arch portions are concerned, the first two aortic arches are commonly lost, but the third and left fourth arches are retained, becoming the root portion of the internal carotid and the arcus aortæ respectively. On the other hand, both the ventral and dorsal aortæ beyond the position of the third arches are preserved, the former to furnish the stem of the external carotid, the latter the second part of the internal carotid

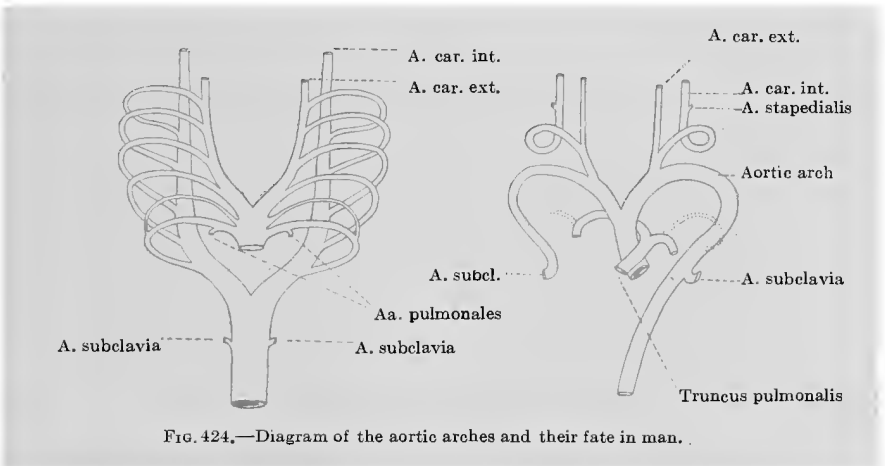

FIG. 424.—Diagram of the aortic arches and their fate in man.

artery; whereas the ventral aorta between the third and fourth arches becomes the stem of the a. carotis communis. The corresponding part of the dorsal aorta disappears, so that now all of the internal carotid blood courses by way of the ventral stem. The sixth arch is lost on either side beyond the origin of the corresponding pulmonary artery, but on the right its proximal portion, between the truncus and the a. pul. dextra, persists and is the root portion of the adult right pulmonary artery. On the left side, however, this proximal portion of the pulmonic arch is apparently incorporated as part of the truncus pulmonis, and the adult a. pul. sinistra consequently is merely the exact analogue of the embryonic vessel (Bremer).[31]

[31] This subject forms one of the few instances in which a correction is necessary in the conception originally given us by Rathke in his epoch-making monograph on the "Aortenwurzeln und die von ihnen ausgehenden Arterien der Saurier." Rathke, as is well known, represented the right and left pulmonary arteries both coming each from its respective arch in lizards and birds, but for the snakes among

This, then, is the general outcome of the arches, although we are now in the possession of some facts concerning the fate of the first two arches about which nothing hitherto has been known.

Before proceeding to consider details of the changes undergone by the various arches, mention may be made now of several kinds of shifting or growth displacements which affect these vessels and which make it easier to understand the relations which characterize the chief trunks derived from them in the adult. In the first place, as His clearly showed, the place of insertion of the aortic truncus into the anterior pharyngeal wall, whence it is split up into the arches, moves gradually lower down, so that, while at first the arches go off horizontally and even more caudally placed from the truncus, they soon course in an ascending direction from

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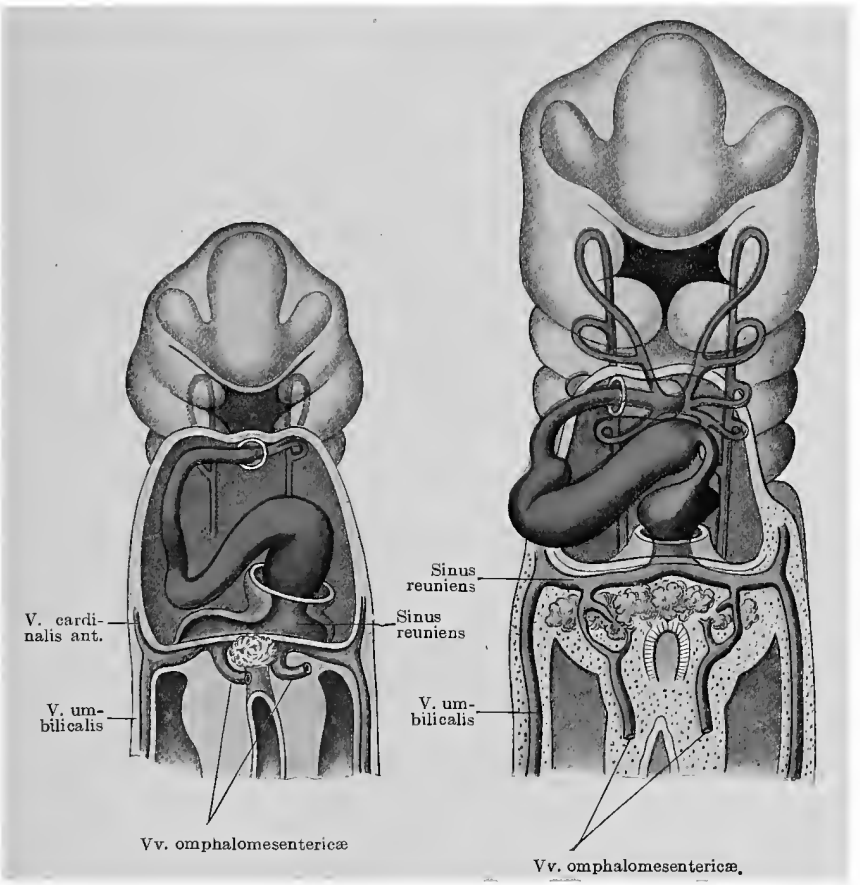
the reptilia and for the mammalia he showed the two vessels arising from only a single arch, in the snakes the right one and in the mammalia the left one. Rathke's ideas were founded on appearances given by embryos which have passed the earliest stages of origin of the pulmonary artery. His first showed that the earliest human pulmonaries came each from its respective arch, as in the lacertilia, and Bremer has proved that this is a general fact for all the mammalia, and suggested the high probability of its general occurrence, at least in earlier stages, in all air-breathing vertebrates. Bremer's studies have included man, the rabbit, cat, dog, pig, opossum, sheep, guinea-pig, cow, and deer, and, as a result of them, he distinguishes two methods for the formation of the adult pulmonary stem in mammals. In the method occurring most generally (man, cat, dog, rabbit, sheep, cow, deer, and opossum) the original symmetry is disturbed by an absorption of the proximal part of the left arch into the truncus pulmonalis, so that the left pulmonary artery now rises from the bifurcation place into left and right arches while the right artery comes off its usual distance from this bifurcation place. With the destruction of the distal part of the right arch up to the point of origin of the a. pul. dextra and the eventual atrophy of the corresponding part of the left arch, the adult plan is reached, and this therefore means that we must consider the left pulmonary artery as representing only the original embryonic one, but the right pulmonary vessel has also as its most proximal part the right pulmonic arch. A second method followed in the evolution of the adult mammalian pulmonaries is exemplified by the pig and guinea-pig, in both of which forms the two early pulmonary arteries are joined in a general capillary plexus, the anastomosis enabling one root to serve as a common stem, which in the pig happens to be the left original artery and in the guinea-pig the right. Consequently, in the former animal the blood to both lungs must first traverse the proximal parts of the left arch and left original artery, and in the latter animal the corresponding parts on the right side. Sakurai (1904) has declared that the left artery in the deer moves toward the right past the bifurcation of the truncus pulmonalis to the right arch, but Bremer questions his interpretation, and the case here must rest till an examination of more abundant material in the stages implicated. In the meanwhile, Bremer's work has shown the incorrectness of the conventional diagram in which both definitive pulmonaries are shown as sharing equally the proximal parts of the sixth arches, for in no mammal is this true. Man and most of the other members of the class have a right a. pulmonalis which is of this nature, but an a. pul. sinistra, which is merely the original pulmonary artery of that side, the corresponding proximal part of its arch having been assimilated in the truncus pulmonalis.

the caudally placed root stem. These changes have been described as a " moving down " of the insertion place of the truncus, and are doubtless due to the same phenomena of unequal growth which cause the apparent rapid descent of the heart from its earliest position at the end of the fore-gut. This change takes place in a regular and characteristic way, as Figs. 425, 426, 427 clearly indicate. Originally, when only two arches exist, the truncus may



Figs. 425 and 426.—Reconstruction of the aortic arches in two human embryos, measuring 2.15 mm. and 3.2 mm. respectively. (After W. His, Anat. mensch. Embry., iii, Leipzig, 1885, p. 186, Fig. 119, and Atlas iii, Taf. ix, Fig. 12 and 15.)

be described as splitting to send on either side of the gut an ascending and descending limb—the first and second arches respectively. Soon the full complement of arches is present, and the downward progression of the aortic truncus with respect to the gill bars now gives a different arrangement of its arches from the parent stem. Both of the first two arches arise together from an ascending stem, while the third arch courses back practically horizontally from the truncus and the last two come off together from a descending

stem. Next an exaggeration of the length and importance of the common ascending stem for the first two arches (the stem which will later constitute the external carotid trunk) occurs and a truly ascending course for the third arch, although the latter has not yet been incorporated in the larger ascending trunk (Fig. 426). In the next changes which take place, the third arch has been carried up in the general ascending trunk (now the common carotid trunk),

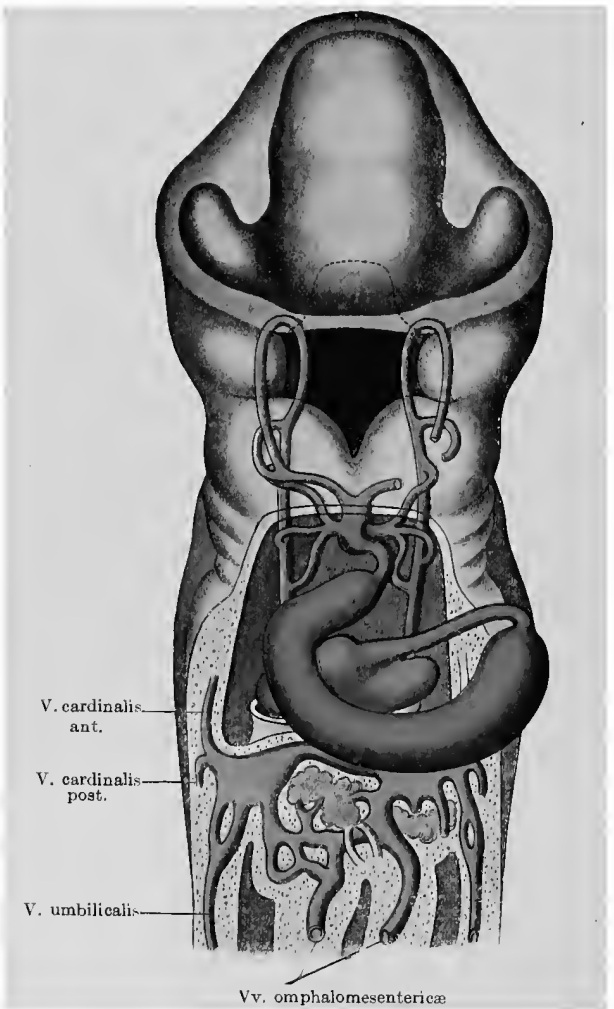


FIG. 427.—Reconstruction of the aortic arches in a human embryo 4.2 mm. long. (See Figs. 425 and 426.)

whereas the fourth tends to course more nearly horizontally. Eventually even the fourth and sixth arches come to have an ascending course.

At the same time that these changes in the arrangement of the arches have been taking place, another of a more general nature has transpired, for not only the heart but the whole system

of arches also has moved down toward the thorax. A reliable criterion of this general dislocation is furnished by the relation of the arches to the dorsal segmental arteries, for the latter have a fixed relation to the somites of the dorsal body wall. Before the stage of five millimetres, all the series of dorsal segmental arteries, including the hypoglossus artery, are considerably below the junction place of the sixth arch with the dorsal aorta. By the stage of seven millimetres this place corresponds to the first cervical dorsal segmental, by the stage of nine millimetres to the second vessel, and by the time the embryo has reached eleven and a half millimetres to the sixth or even the seventh cervical segmental, from which trunk the subclavian and vertebral arteries arise (Tandler). This relation is at last almost that of the adult, where the subclavian comes off the transverse portion of the aortic arch.

At the stage of seven millimetres, a splitting of the truncus begins, proceeding from above downward and separating the fourth arches, with the system lying above them, from the sixth ones. The latter then come to have an independent common trunk, —the truncus pulmonalis,—and this, as is well known, is exclusively connected with the right heart, whereas the truncus aorticus is similarly in relation with the left.

Still another growth change in the arrangement of these vessels is to be mentioned. We left the last three arches in a markedly ascending course. Such a course obtains for the pulmonic arches so long as they persist, but after the division of the truncus the systemic truncus elongates much, pushing, as it were, the proximal portions of the third and fourth arches again upward and giving them a horizontal or even slightly descending course (Tandler).

The dorsal part of the right fourth arch now atrophies beyond the origin of the subclavian stem, and this whole segment now constitutes but a branch of the persisting *a. anonyma.*

A. Carotis Interna and its Branches.—It has already been emphasized that the earliest branch of any of the arches consists in that given off by the dorsal part of the first arch toward the embryonic mid-brain. This persists and is of increasing importance, and when the atrophy of the connecting portion of the dorsal aorta between the third and fourth arches results, it constitutes, together with this part of the dorsal aorta and third arch, the internal carotid artery. The internal carotid, then, consists of three morphologically different portions,—a proximal or root portion derived from the third arch, an intermediate portion consisting of the original aorta dorsalis from here to the first arch, and an end portion which is the earliest branch of the first arches and is the chief supply of the brain.[32]

[32] Injections of very early bird and mammalian embryos show that the trunk of the internal carotid artery extending from the first arch distalward is

It is to be noted that, besides the larger internal carotid which is given off from the end of the first arch, the aorta dorsalis also sends several smaller branches toward the hind-brain before the region of the primitive segments is reached, and, when, at length, the latter territory is reached, the dorsal segmental vessels. Those dorsal branches which are in front of the segmental area are very transitory, and attract our interest chiefly because they represent the first vascular sprouts sent out by the dorsal aorta into the tissues of the embryo in this region and, directed toward the sides of the medullary tube, are directly responsible for the formation of the v. capitis medialis.[33]

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represented at first by the outgrowth of a plexus of capillaries from that arch (Figs. 393, 394). This plexus spreads over the sides of the early mid-brain first, then over the fore and hind-brains (Fig. 395). Soon out of the several capillary stems of origin from the first aortic arch, one is chosen to become the artery and the remainder perish. Gradually the plexus of capillaries invades the ventral surface of the brain and tends to halt there on either side of a narrow mid-ventral non-vascular strip. In the meanwhile the continuation of the main arterial stem is being evolved out of this plexus in such a way that the carotid, after giving off an a. ophthalmica, appears to have two terminal branches anterior and posterior. The latter connects up with the medial ventral margin of the capillary mesh on each side, and so there come to be in the midventral region two long parallel vessels, the continuation of the posterior terminal branches of the two carotids. This conversion of the medial margins of the ventral capillary mesh here is analogous to the formation of the aortæ from the medial margins of the vitelline capillary plexus. It will be shown that in the spread of the capillary plexus over the spinal cord an exactly similar phenomenon takes place,—that is, the capillaries halt along two parallel lines on either side of the midventral plane. In the cord region also these two plexus margins are converted into two transitory longitudinal arteries, furnished at every segmental point by blood from the segmental arteries and connected headward with the same vessels supplied by the carotid arteries. The whole structure from head to tail has been called by Sterzi the tractus arteriosus primitivus; by De Vriese the primitive anterior spinal arteries. It will be evident from all this that this primitive midventral vessel is the earliest arterial anastomosis between the carotids and dorsal segmental vessels. The second of the dorsal segmentals is the hypoglossal artery, and that part of the anastomosis between it and the carotid is of the greatest importance, for it, according to De Vriese, is the a. vertebralis cerebralis of His; at any rate it is destined to form the basilar artery in the region beneath the hind-brain. Thus the basilar artery is primitively paired and gets its chief supply of blood from the carotids, for the hypoglossal artery cannot figure greatly. Gradually the double basilar is replaced by a single vessel, which is really formed through the development of anastomoses between the two parallel trunks permitting the original left vessel to persist in some areas and the right one in others. This is also what happens as regards the anterior spinal artery. Very soon after the unpaired basilar is produced, its lower source of blood exceeds its upper in importance, and when the cerebral vertebrals are taken over by the cervical vertebrals, the latter vessels are the main supply of the basilar.

[33] These pre-segmental branches of the aorta have, of course, another interest, inasmuch as we may be dealing with evidences of a segmentation of the head in front of the occipital somites. Be this as it may, Tandler (1902) has seen a remarkable row of these vessels in the rat, where they seem to arise at regular intervals.

As soon as the region of the somites is reached the dorsal aortic branches are strictly segmentally arranged,—*i.e.,* they course between successive somites. The pair between the first and second somites, however, early atrophy, and the pair situated between the second and third somites and which are in relation with the hypoglossus nerve remain somewhat longer and, as the so-called *hypoglossus arteries,* constitute the first of the series. In embryos of five mm. length (Tandler 1902, Ingalls 1907) the hypoglossus can be seen giving off a long longitudinal cranial-coursing branch, which headward anastomoses with the a. carotis interna on each side, thus making two long arterial arches. This branch of the hypoglossus artery is the *a. vertebralis cerebralis.* Later, as has been mentioned, the a. vertebralis cerebralis is taken over by the first cervical segmental artery, and the hypoglossal artery atrophies, and still later, as was first shown by Hochstetter (1890), an anastomosis between the first seven cervical segmentals (*aa. vertebrales cervicales*) enables the seventh of these vessels to act as the origin for the vertebral artery. De Vriese has pointed out that in all early embryos the carotid, after giving off the ophthalmic artery, may be considered as dividing into two terminal branches, anterior and posterior, the latter of which turns round to anastomose with the a. vertebralis cerebralis and is by far the more important of the two. When the cerebral vertebrals fuse to a *basilar artery* beneath the hind-brain, the two posterior terminal branches of the carotids consequently join each other in this trunk. This is the condition of the arteries in the head in embryos measuring nine millimetres (Fig. 428). Here the ophthalmic artery is not illustrated, but the carotid is seen splitting into its two terminal trunks, a small anterior and a strong posterior, the latter continued into the basilar. The anterior terminal trunk immediately gives off the *anterior chorioidal artery* and proceeds as a prominent vessel on the side of the fore-brain, encircling the optic cup from above and meeting its fellow of the opposite side just behind the olfactory pit. This vessel is the *a. cerebri anterior,* and gives off many rami to the cerebral vesicle, which are later represented by a single

(Compare his Fig. 8, p. 302.) De Vriese (1905) mentions their appearance in the rabbit (see her Fig. 28, planche 16), and for the area in front of the hypoglossus vessel mentions two as being more constant, one at the level of the otic vesicle and the other near the gasserian ganglion. In the human embryo Kroemer-Pfannenstiel (N.T. 3), with six somites, I have found two of these vessels on the left in front of the first somite, and in the Eternod embryo, with eight somites, one behind the region of the first aortic arch, just in front of the second pharyngeal outpocketing; whereas in the Spee embryo No. 52 there are on each side, although not paired, four of these pre-segmental dorsal branches of the aorta. Finally, Ingalls in his 4.9 mm. embryo distinguished clearly four of these vessels on the left side. The relation of these vessels to the cranial nerves or visceral arches awaits demonstration.

trunk, the middle cerebral. The posterior terminal branch of the carotid gives off many branches to the sides of the mid-brain, and these later are also represented by a single trunk, the posterior cerebral. In the next succeeding stages we see an increase in the

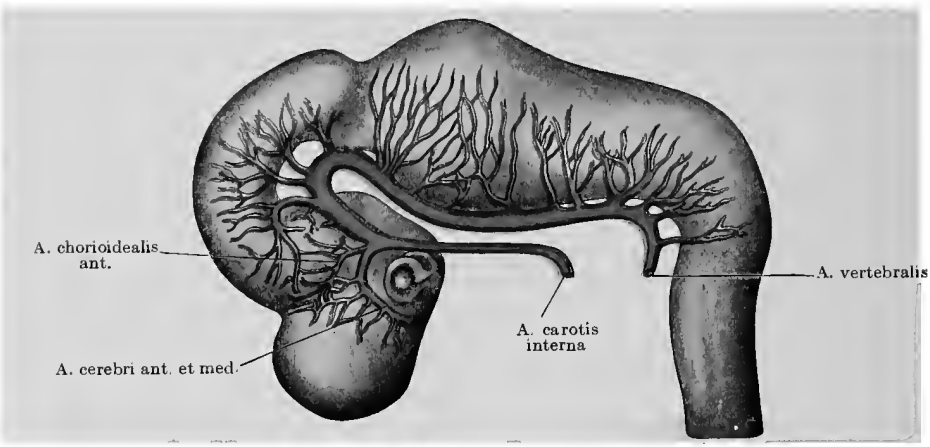

FIG. 428.—Graphic reconstruction of the arterial system in the brain of a human embryo 9 mm. long. (After Mall, Amer. Jour. Anat., vol. iv, Plate I, Fig. 4.) (Mall No. 163.)

importance of the anterior chorioidal artery (Fig. 429), but it is remarkable that single large stems representing either the middle or posterior cerebral artery are very late in appearing. Mall is

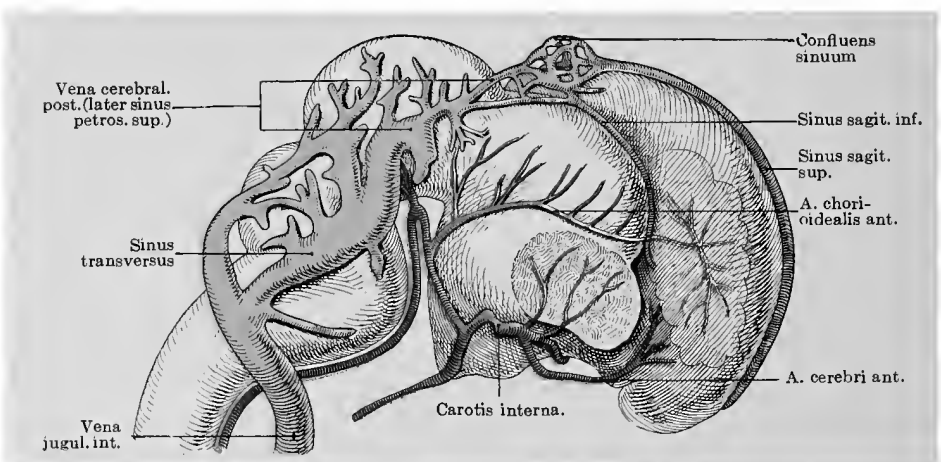

FIG. 429.—Graphic reconstruction of the vessels of the brain in a human embryo 38 mm. long. (From Kollmann, after Mall.) (Mall No. 145.)

of the opinion that we must consider the last-mentioned artery as being represented originally by all the small branches which come off from the carotid between the third and fourth nerves behind and the middle cerebral in front. In older embryos (48 mm. long) these

many branches are represented by a large mesencephalic artery and a small true posterior cerebral (Mall); in older fetuses the latter branch absorbs the former.

The *ophthalmic artery* is the first branch of the internal carotid to develop. In embryos measuring seven millimetres it can be seen to course toward the eye, dividing in its mid course into the *a. ciliaris longa temporalis* and a common trunk, afterwards splitting into the *a. ciliaris longa nasalis* and the *a. hyaloidea.* The latter artery pierces the optic cup, courses through the vitreous body, and reaches the posterior surface of the lens in capillaries. The arrangement and size of these branches of the ophthalmic are such that the a. ciliaris longa temporalis appears as the continuation of the main stem, and this is true up to the stage of 20 millimetres at least. The ciliary arteries supply a capillary plexus representing the *chorioidea.* Dedekind (1908) has reconstructed this simple vascular scheme in an embryo measuring 19 millimetres (Fig. 430 and 431). The hyaloid artery is noted by Dedekind as turning into an arterial plexus before being resolved into the capillaries constituting the tunica vasculosa lentis. Here, then, is another instance of several paths being used by the arterial blood before the reduction to a single path. The hyaloid artery serves as the later *a. centralis retinæ,* but no retinal vessels are present till late. The researches of O. Schulze (1892) had indicated the same fact in other mammals. Versari (1903) has stated, indeed, that the human embryo reaches 120 millimetres in length before the retinal vessels are formed. In an embryo of 33.4 millimetres Dedekind has recorded the *a. lachrymalis, aa. ethmoidales,* and *a. nasofrontalis.*

We have as yet only an incomplete record of the development of the eye vessels in man, but Versari has furnished important observations on older stages (beginning with 22 mm.). In the splendid paper by Schultze the older stages in many mammals were beautifully portrayed, and some of the eye vessels in human fetuses of the sixth and eighth months shown. However, only Fuchs's careful study in the rabbit can lay any claim to completeness.

Fate of the Second Aortic Arches.—As a rule, no trace of the first arch is seen in embryos of 7 millimetres and only the dorsal and ventral ends of the second arch are evident. Tandler (1902) has recently declared that in man and other mammalian embryos the dorsal parts of the second arches become the root portions of the *stapedial artery* on each side.[34]

The a. stapedialis persists throughout life in some mammals,—*e.g.,* the rat,—but normally atrophies in man. At the height of

[34] Although the recognition of an embryonic artery piercing the mammalian stapes dates back some thirty years (Salensky, 1880), no one had before established the relation of this vessel to the aortic arches.

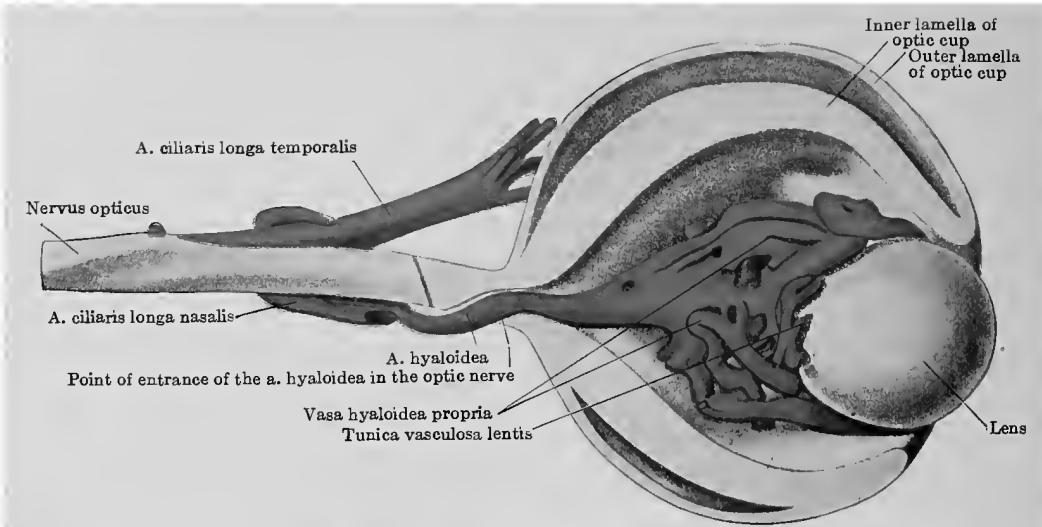

FIG. 430.—Left eye of a human embryo 19 mm. long, opened through a horizontal section. × 66. (After Dedekind, 1908.)

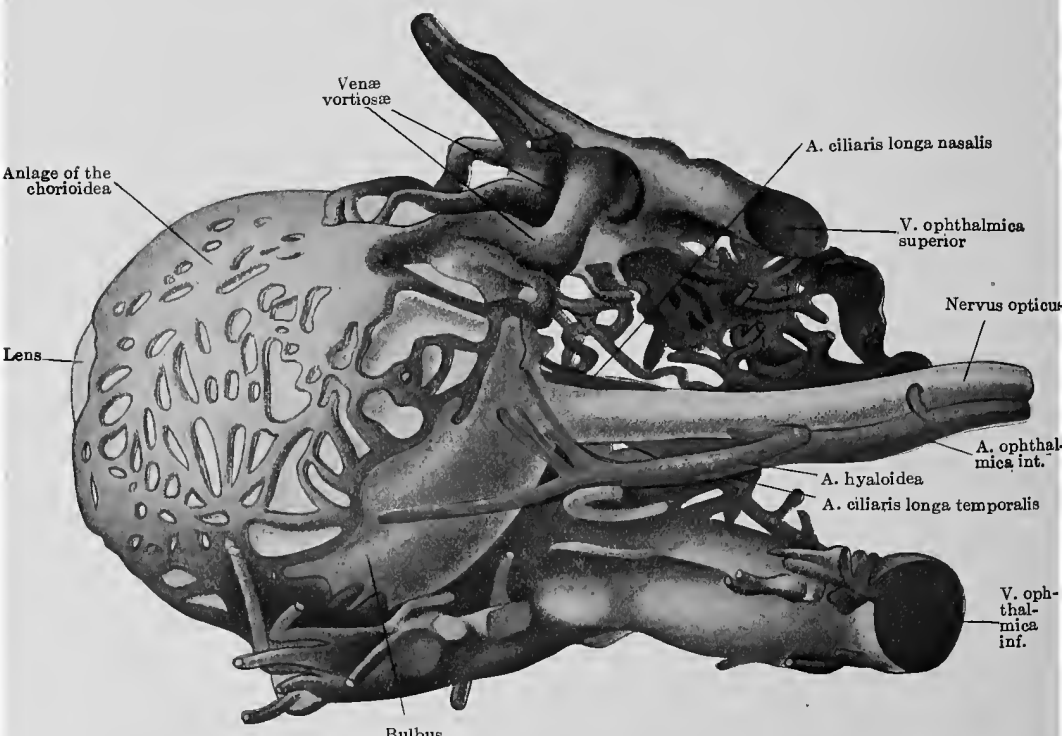

FIG. 431.—Left eye of the same embryo seen from the temporal side. × 66. (After Dedekind, 1908.)

its development it possesses, after piercing the anlage of the stapes, three branches, which follow the three divisions of the fifth nerve; these are the *supra-orbital,* the *infra-orbital,* and the *mandibular rami,* respectively. The first of these (ramus supra-orbitalis) leaves the main stem, shortly after the stapes is passed, so that the infra-orbital and lower-jaw rami have a common stem (Fig. 432). The infra-orbital division of this stem passes behind the third division of the fifth nerve to gain the second division, which it follows. Later (in embryos of 15 to 17 mm.) the external carotid artery anastomoses with the common trunk for the infra-orbital and mandibular rami, just at the point where these vessels are given off. The infra-orbital ramus gains the outer side of the third branch

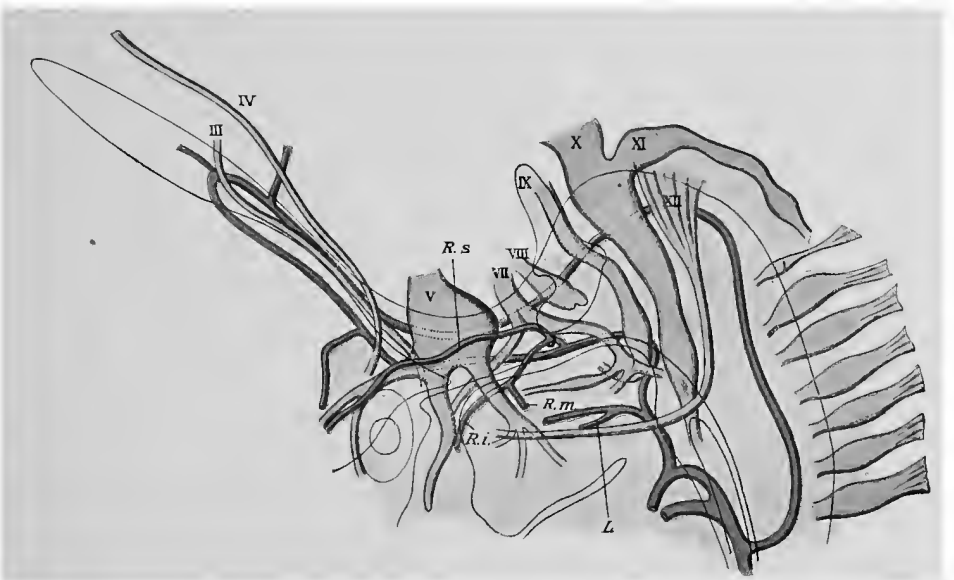

FIG. 432.—Profile reconstruction of the head vessels and nerves in a human embryo 12.5 mm. long. (After Tandler, Morpb. Jahrb., xxx, Taf. v, Fig. 21.) *R. s.*, *R. i.*, *R. m.*, ramus supra-orbitalis, infra-orbitalis, and mandibularis of the a. stapedia; *L.*, a. lingualis of the a. car. ext.

of the fifth nerve by the development of an arterial loop around the nerve and the atrophy of the medial limb of the loop. Soon the original common trunk of the infra-orbital and mandibular rami (which lies above the point of the anastomosis with the external carotid) becomes surrounded by the auriculo-temporal nerve and we can recognize in it the future *a. meningea media.* Now the stapedial atrophies from its origin to its division place into the three rami, and consequently these branches are then all supplied by the a. carotis externa, the stem of supply for the supra-orbital branch being the old common stem for the two lower branches, in which the flow is now reversed; this is, as has been said, the middle meningeal artery, whereas the ramus infra-orbitalis is the *a. infra-*

orbitalis of the *internal maxillary,* and the ramus mandibularis, the *a. alveolaris inferior.* This is clear from the diagrams in Fig. 433.

The place of origin of the stapedial artery and its relation to the stapes identify it accurately with the second visceral arch, but its territory of supply, when its three typical rami are developed, is entirely in the province of the first arch. This becomes intelligible when we know that these rami are later acquisitions of the stapedial, that primarily they arose from the first arch, and were later added to the a. stapedialis. Such, at any rate, is the case in the rat, as Tandler was able to show that the blood supply of the jaws (upper and lower) came originally from the dorsal part of the first arch. To the stem supplying the jaws, a supra-orbital vessel was added, and then from the stapedial vessel an anastomosis with this common stem developed, whereby the three branches went

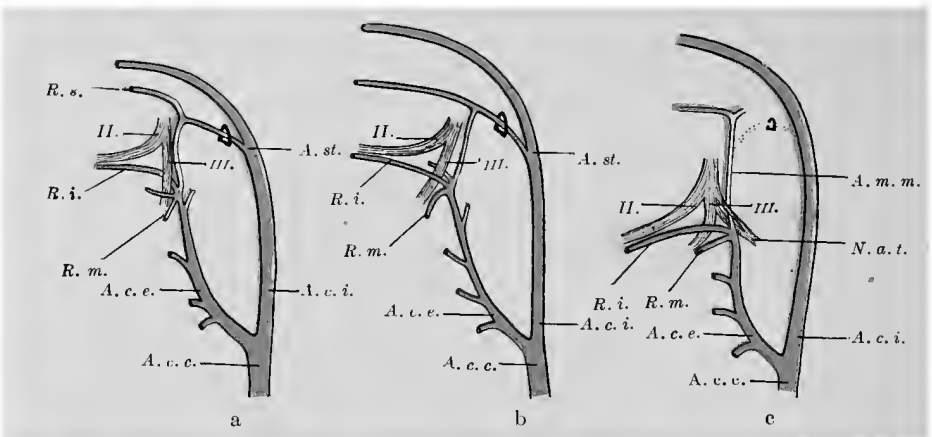

Fig. 433.—Schemata showing the fate of the a. stapedialis in the human embryo. (After Tandler, 1902.) a represents the conditions present in a human embryo 17 mm. long, b those in one 19 mm. long, and c those in one 23 mm. long. *II.*, second branch of the trigeminus; *III.*, third branch of the trigeminus; *A. m. m.*, a. meningea media; *A. c. c.*, a. carotis communis; *A. c. e.*, a. carotis externa; *A. c. i.*, a. carotis interna; *N. a. t.*, nervus auriculotemporalis; *R. i.*, ramus infra-orbitalis; *R. m.*, ramus mandibularis; *R. s.*, ramus supra-orbitalis.

to the a. stapedialis. This early history of the three stapedial branches has not as yet been secured in man, but the facts at present known make it none the less certain that the stapedial artery here has gained the territory of the first arch only secondarily. In man the three branches of the stapedial, instead of being derived from the dorsal end of the first arch, are probably derivatives of the ventral portion of that arch and the aorta ventralis.[35]

[35] It has been known since the time of Rathke that in many adult reptiles an artery exists which pierces the columella. The same reptiles possess another artery which supplies the upper jaw and courses with the vidian nerve. It would be of the greatest interest if embryological observations here should establish the origin of the vidian-accompanying artery from the first aortic arch and the columella-piercing vessel from the second arch, like the stapedial of mammals. Evidence that this may be true is furnished by an interesting variation found by Grosser (1901) in a young mammalian embryo (bat). Here the infra-orbital branch of the stapedial artery was not a member of the usual trunk, but an independent branch of the carotis interna, having a definite relation to the vidian nerve, just median to which it coursed. If these homologies, which were suggested by Tandler, are established, then

A. Carotis Externa.—The trunk of this vessel may be considered the aorta ventralis from the origin of the third arches cranialward. His indicated that the *lingual artery* was among the first of its important branches to develop, and at 17 millimetres (N.T. 65) Tandler identified the *superior thyroid, lingual,* and *external maxillary* arteries. These vessels are, in fact, present at 14 millimetres, when the *internal maxillary* is also being evolved from the anastomosis of its trunk of origin with the stapedial (Fig. 434). At this stage one also sees a prominent branch of the carotis externa coursing dorsalward. This is the *a. occipitalis,* having the

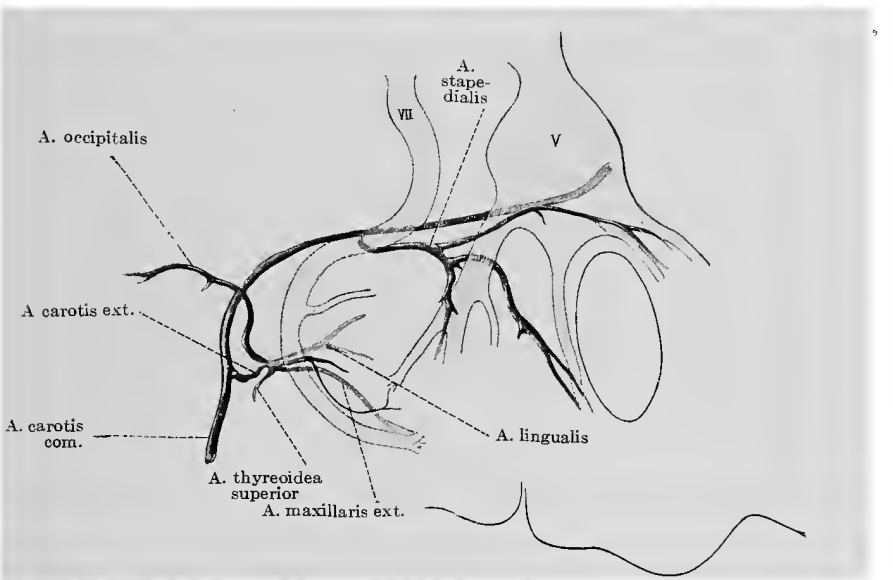

Fig. 434.—Graphic reconstruction of the face vessels in a human embryo measuring 14 mm. (No. 144, Mall collection.)

position and typical relations of this vessel to the muscle masses. Its proportionately great development in these early stages is probably to be explained by its importance as a meningeal vessel.

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1. The territory of the first aortic arches in all the higher vertebrates is supplied at first by vessels coming from that arch. The stem for these vessels or one of them may course with the vidian nerve.

2. The territory of the second arch possesses a vessel normally related to the columella (or stapes).

3. The second vessel (stapedial) remains in its original state in the reptiles mentioned, but in the mammals usually annexes the branches developed from the first arch.

4. In adult mammals the stapedial artery secondarily surrenders these branches to the external carotid and atrophies, or, in the cases where is persists, at least loses its mandibular ramus to the external carotid artery (rat), and in some cases also its infraorbital one (bat).

At 15.5 millimetres, the chief superficial branches of the carotis externa are evident, the *a. auricularis posterior* and *a. temporalis superficialis.*

Nothing is known of the development of the coronary arteries. Tandler has noted their beginnings in a 17 mm. embryo (N.T. 65).

The only observations known to me (1904) on this subject are the fragmentary ones of Martin (1894) and those of F. T. Lewis (1904). Lewis has called attention to the fact that the heart of early embryos is nourished by diverticula of the ventricular lumen which course between the muscular trabeculæ—sinusoids of Minot, the chief method of nourishment of the myocardium in the lower vertebrates. Later the coronary system supervened and there was a great regression of the extensive sinusoidal system characteristic for the preceding stages. Lewis records the coronary arteries being first recognizable in rabbits of 14 days and 18 hours.

Variations.—The variations in the great vessels arising from the aortic arch have been known for a long time and could be explained satisfactorily on an

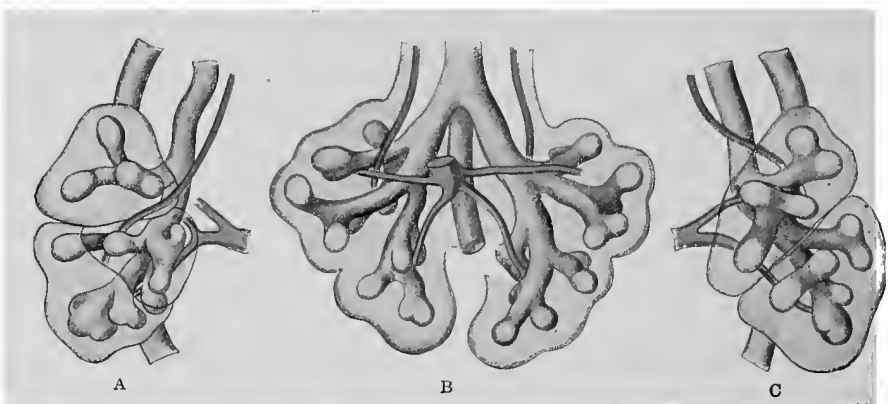

FIG. 435.—Reconstruction of the lung anlagen and their vessels in a human embryo 10.5 mm. long. (After His, 1887.)

embryological basis ever since the work of Rathke. They have been classified by Krause, for instance, and by so many, following him, that it will not be necessary to consider them here. De Vriese's work has shown the morphological character of the posterior communicating artery,—*i.e.,* this vessel represents the original caudal continuation of the posterior terminal branch of the carotid. Consequently, cases in which the posterior cerebral arteries appear to be supplied by strong posterior communicating vessels, represent merely a retention of normal embryonic conditions, whereas the complete atrophy of the posterior communicating is an exaggeration of normal development. Islands in the course of the basilar are readily intelligible from the original paired nature of this vessel.

Comparative.—In the fish, amphibia, birds, and reptiles the internal carotid arteries are the sole source of supply for the brain, or nearly so, since the vertebrals are unimportant. The carotid in these classes divides into its anterior and posterior terminal branches, and the latter are continuous down the spinal cord with the anterior spinal artery, having formed the basilar in the region of the hind-brain. This is the simple scheme represented in early mammalian embryos.

The development of the main vessels in the early lung is known to us from the observations of His (1887). His showed

that the two *pulmonary arteries* are from the first asymmetrical, in that the right vessel passes in front of the so-called eparterial bronchus, whereas the remainder of its course, like the entire extent of the opposite artery (a. pulmonalis sinistra), is behind the bronchial tree (Fig. 435). The pulmonary veins, on the other hand, are placed ventral to the bronchial system, and this relation persists throughout life, giving us arteries separated everywhere from veins by the corresponding divisions of the bronchial tree.[36]

Flint (1906) has followed the developing vessels in the lung of the pig, more completely than has been done in the case of any other mammal. The pulmonary veins are reported by most observers as growing out of the sinus venosus before the development of the pulmonary arteries (see also Federow, 1910). In this connection, Flint has suggested that the early appearance of a drainage channel ventral to the pulmonary anlage and the ventral projection of the anlage from the walls of the foregut combine to favor the mechanical establishment of arterial paths dorsal to the organ. These early relations are only repeated in growth, and hence may be regarded as fundamental in determining the architectural interrelations of bronchial and vascular trees in the adult organ. In relation with this is the fact that the eparterial bronchus receives a ventrally placed arterial supply, and that here, consequently, the veins and arteries are accompanying vessels. It seems hardly necessary to refute the error of Aeby (1880) and others who attempted to make the arrangement of the arteries responsible for the form of the bronchial tree. As Flint has emphasized, the arteries are mere passive followers of the bronchi in development, and arise secondarily from the capillary mesh which enveloped a newly formed diverticulum of the bronchus.[36]

THE BRANCHES OF THE AORTA.

As has been seen from the preceding description, the history of the development of the arterial system in the human embryo shows that at first two long channels exist—the descending aortæ—which course through the entire length of the embryonic body and emerge in the belly stalk without having sent off any branches into the tissues of the embryo. The aortæ and their system of branches, then, do not develop like many other vessels of the body, but pursue an elongated unbranched course over an area into which later they are destined to send out a copious supply of arteries. When, as development proceeds, capillaries are finally sent into the embryonic tissues, these sprout from the aorta, dorsally at strictly inter-segmental points, often ventrally and laterally also at such points, but in the case of these vessels usually more irregularly.

The segmental position is strictly observed only in the case of the dorsal branches. These from the first course only in the planes between the primitive segments. The ventral branches, however, are often found arising at more fre-

[36] Since the above went to press I note that Pensa has given us reconstructions of the pulmonary arteries in two human embryos, 11.5 and 25 mm. long respectively. Antonio Pensa, "Osservazioni sulla morfologia e sullo sviluppo della arteria pulmonalis nell' uomo." Boll. della Soc. Med. Chir. di. Pavia Comunicazione fatta nella seduta del 8 Aprile, 1910. Pavia, 1910.

quent intervals from the aortic wall, while the lateral branches, except the earliest stages, depart furtherest from a segmental alignment. Both ventral and lateral branches, however, show a tendency to adhere to the segmental plan.[37] Recent investigations on mammals and birds indicate that the branches supplying the limb arise from the aorta at multiple irregular points as a typical capillary plexus (see beyond), but are later segmentally arranged, as is the case in the earliest stages yet seen in man.

The aortic branches fall into three groups or rows, a dorsal row, a lateral row, and a ventral row. At first the dorsal segmentals supply only the central nervous system (the spinal cord and its ganglia), the lateral row, only the Wolffian body, and the ventral row, only the primitive intestine.[38] But of these branches, those which are at first purely neural in their area of distri-

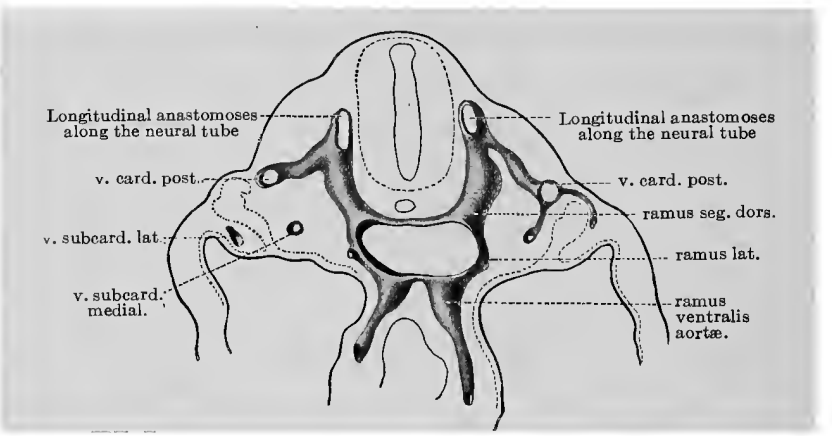

FIG. 436.—Reconstruction to show the branches of the aorta in a human embryo with 23 somites (NT. 7). The reconstruction was made from six successive sections in the mid-thoracic region.

bution come eventually to supply also the body wall with its muscles and skin, and those at first purely nephric to supply also the adrenals and the sex glands; the gut branches which persist,

[37] I am aware that Broman, for instance, bases much of his discussion of the position of the ventral branches and their changes on the supposition of their being primarily segmentally arranged. This, however, is not the case, as my experience with embryos of from six to twenty-three somites clearly proves. Many of the ventral branches are unquestionably as far as possible from a segmental alignment, so that the most which can be said here is that a segmental influence is evident, but expresses itself imperfectly. Later, however, there is a marked agreement with the segmental plan, so that we have conditions analogous to what occurs in the limb buds where stages of a more irregular row of primitive limb arteries are succeeded by those in which these vessels are segmentally arranged.

[38] Felix (1910), chiefly on comparative grounds, assigns the primitive function of the intestinal arteries to the supply of the pronephros. There seems, however, little evidence for this in human ontogeny, where these arteries are from the first truly intestinal vessels and where the pronephric rudiments are not in relation with these but with the primitive lateral branches of the aorta.

however, supply, as they do in the embryo, the alimentary tract, the organs derived from it (liver, pancreas), and the spleen.

It is interesting to note that Mackay (1889) constructed a hypothetical schema classifying the branches of the aorta in a similar way, some twenty years ago. The main features of Mackay's classification are thus substantiated by development, for, though he confused some secondary with the primary characters of these vessels, he recognized that there were three kinds of them, naming them, from the influence of adult anatomy, the parietal, the intermediate, and the visceral branches.

The ventral branches arise first, owing to early importance of the vitelline circulation, the dorsal branches quickly after them, and, after an interval, the lateral branches. Although Eternod (1898) did not find any of these branches in his embryo of 1.3 mm.

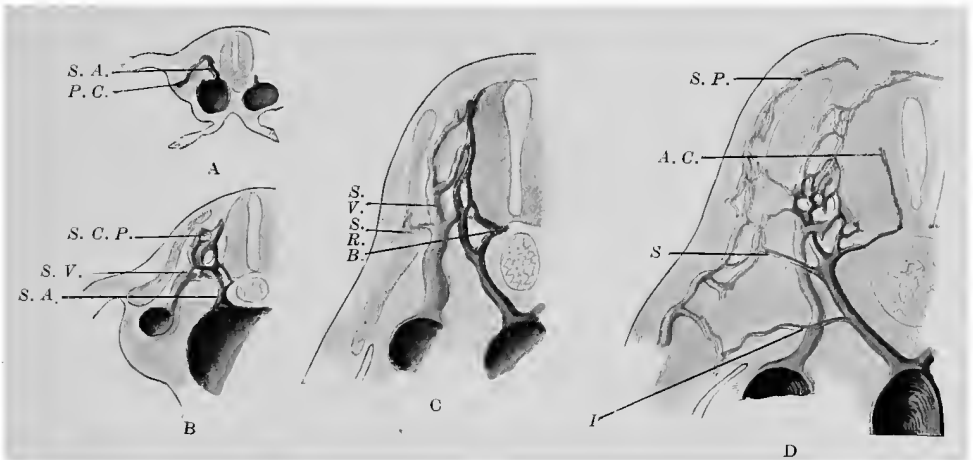

FIG. 437.—Cross sections of injected chick embryos showing the development of the dorsal segmental vessels. A, cross section of a chick of 50 hours (24 somites), showing the 15th dorsal segmental vessels; B, a chick 60 hours old; C, 78 hours old; and D, 116 hours old: all in the neighborhood of the 20th segmental vessels. *S. A.*, dorsal segmental artery; *P. C.*, posterior cardinal vein; *S. V.*, dorsal segmental vein; *S. C. P.*, spinal ganglion's capillary plexus; *R. B.*, ventral radicular branch of the segmental artery; *S.*, first extra-myotomal or skin branch of the segmental artery; *A. C.*, a. centralis; *S. P.*, superficial capillaries without the myotome; *I.*, probable intercostal artery.

length, many of the ventral branches and two of the dorsal series occur in embryos with six somites (N.T. 3), while in an embryo with thirteen somites (N.T. 6) many distinct lateral branches can also be recognized. Both ventral and dorsal branches grow out before the primitive aortæ fuse, and consequently when this occurs an accurate apposition of the two aortæ permits these branches to come off in pairs from the single aorta descendens.

DORSAL SEGMENTALS (Neural Segmentals, "Segmental Arteries" (of many authors), Interprotovertebral Arteries (P. Albrecht), etc.).—The dorsal segmental branches of the aorta have often been referred to as the parietal or body wall segmentals, and, inasmuch as they furnish the large well-known intercostal and lumbar arteries, their segmental nature is preserved and recognizable

in the adult. These later branches of the dorsal segmentals (*i.e.*, aa. intercostales et lumbales) so far outstrip the primary trunks in growth that in the adult they themselves become known as the branches of the aorta, and the original dorsal segmentals merely

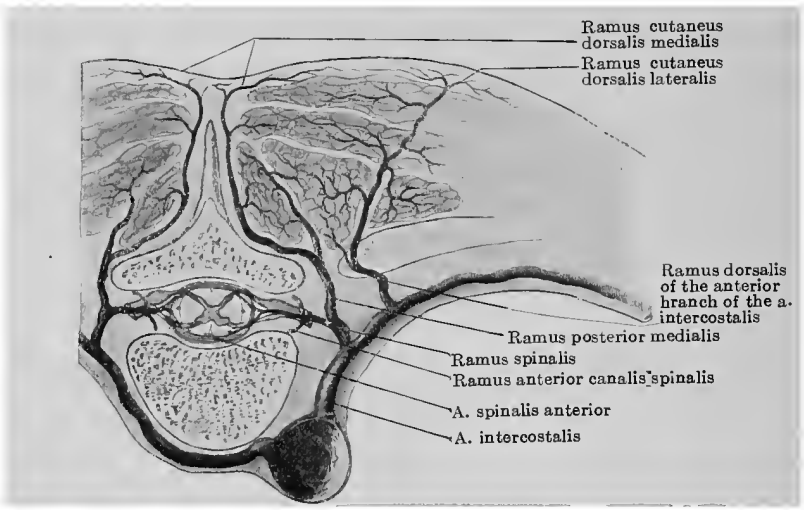

FIG. 438.—Diagram of the behavior of a typical dorsal segmental artery in the human adult. (Founded on Toldt, Spalteholz, Sterzi, and Grosser.)

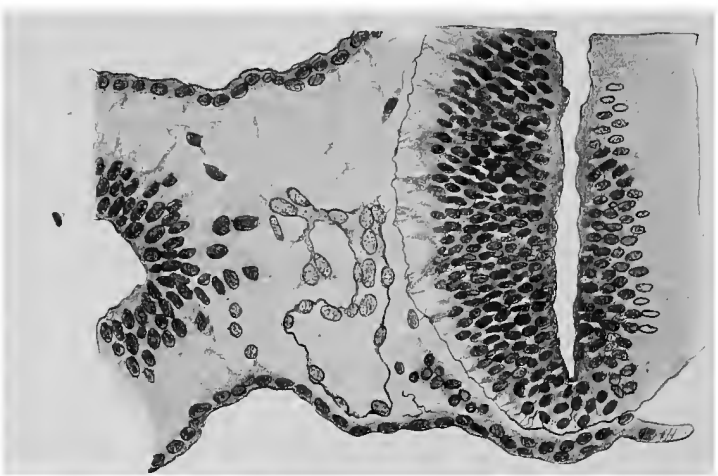

FIG. 439.—The first dorsal segmental artery in a human embryo with 8 somites. (Collection of Professor Eternod, *vide* p. 594.) The endothelium is seen growing in the loose tissue of the first intersegmental cleft.

as their posterior branches (rami posteriores). The course of development, however, shows clearly that the reverse is actually the case.

The dorsal segmentals begin to grow out from the aorta at about the time that the embryo possesses six somites (Fig. 410). The number of dorsal segmental arteries increases rapidly, and in

embryos in which the extremities are recognizable, almost the whole series is present. The first pair of these vessels between the first and second somite early atrophies, although they are still clearly evident in embryos of 14 and 15 somites (N.T. 7 and embryo Graf Spee No. 52).[39]

The second pair constitute the vessels which are known as the hypoglossus arteries. These remain in embryos of five mm. in length, but shortly thereafter also atrophy, so that the first cervical pair—*i.e.,* the arteries between the third and fourth somite, which course with the nn. cervicales 1—are next the first of the series. As Hochstetter long ago showed for the rabbit, and as is evident for man from the Normentafel of Keibel and Elze, the whole upper six of the cervical dorsal segmentals atrophy and the seventh only is permanent as the trunk of origin of the *vertebral* and *subclavian arteries;* this also functions as the root of origin for the eighth cervical and first (or first and second) thoracic arteries by its strong *a. intercostalis suprema,* so that the next permanent dorsal segmental behind the seventh cervical is the second or third thoracic one.

The following table shows the number of dorsal segmental arteries present in several young embryos.

Designation of embryo.	Number of somites.	No. of dorsal segmental arteries.	Probable identity of the dorsal segmental arteries.
Pfannenstiel-Kroemer, NT. 3	6	2	O_1, O_2.
Eternod	8	4	O_1, O_2; C_1, C_2.
Pfannenstiel III, NT. 6	13–14	6	O_1, O_2; C_1–C_4.
Graf Spee No. 52	15	11	O_1, O_2; C_1–C_8; T_1.
Rob. Meyer 300, NT. 7	23	21	— –?; C_1–C_8; T_1–T_{12}; L_1.
Broman, NT. 11	ca 30	23	— O_2; C_1–C_8; T_1–T_{12}; L_1, L_2.
G. 31, NT. 14	35	29	— O_2; C_1–C_8; T_1–T_{12}; L_1–L_5; S_1–S_3.
Chr. 1, NT. 28	40	29	— —; C_1–C_8; T_1–T_{12}; L_1–L_5; S_1–S_4.

In their simplest form the dorsal segmental arteries consist of single capillary loops which extend from the aortæ to the venæ cardinales posteriores (Fig. 437, A), yet numerous other capillaries soon sprout out from these loops; and the aortic end of the original capillary loop becomes the dorsal segmental artery and the venous end the dorsal segmental vein.

Inasmuch as the dorsal segmental arteries constitute at first the arterial supply of the spinal cord, their history belongs to that of the blood supply of the cord.

[39] The first pair of the dorsal segmental arteries is not generally referred to. Hochstetter (1903), for instance, states that the first pair of these arteries courses with the hypoglossus nerve, as a result of the embryos which he, Zimmermann (1890), and Piper (1900) had studied. These embryos were so old that the first pair of the segmental arteries had already atrophied.

With the exception of the brief account by His (1886), this subject has not been followed in detail in man; on the other hand, the main facts in the history have been ascertained for the birds (chick) and the mammalia (sheep, pig) by a series of injections, and the brief description given is based mainly on these.

The single capillary loops which constitute the early dorsal segmentals approach the spinal cord near its ventrolateral angle and the ventral part of its lateral surface. In succeeding stages these loops give off delicate sprouts, which reach the cord at the area mentioned and anastomose with corresponding capillary sprouts given off by the adjacent segmentals, thus forming a longitudinal chain of

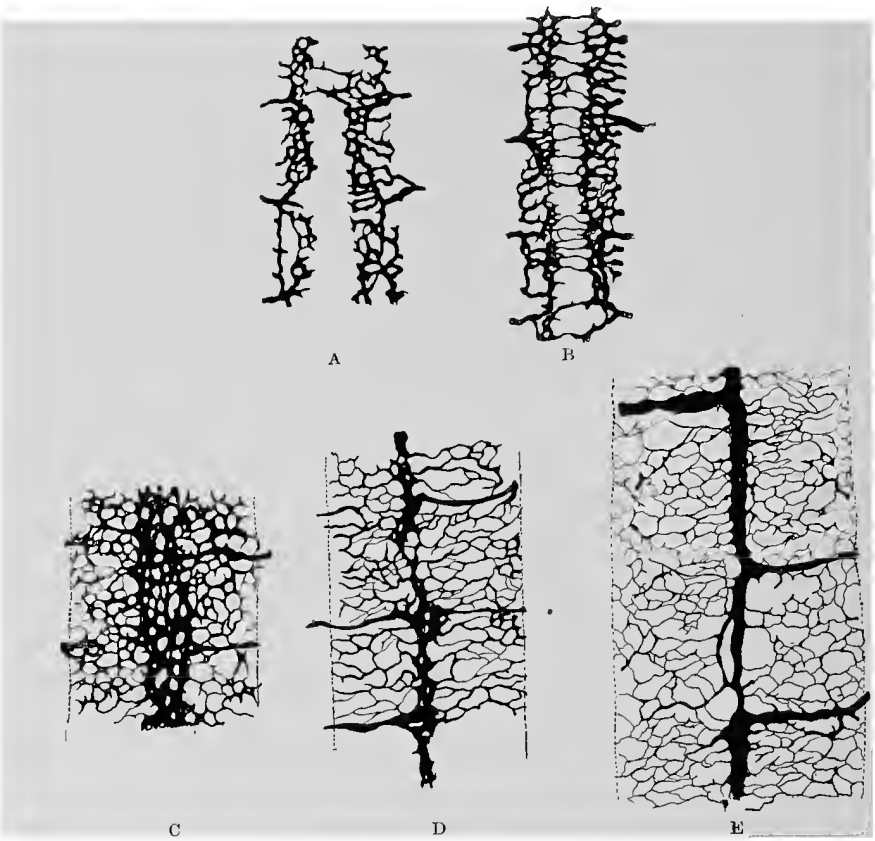

FIG. 440.—Successive stages in the development of the anterior spinal artery in the pig. The embryos were injected and the cord dissected in the region of the first three thoracic segments. A, an embryo 8.5 mm. long, B 9 mm. long, C 14 mm. long, D 15.5 mm. long, and E 28 mm. long.

capillaries on the lower lateral surfaces of the cord. These capillaries soon increase, growing over the spinal ganglia and forming a close plexus over the lower lateral surfaces of the cord, which extends dorsally as far as the under edges of the ganglia and their roots. Ventrally this plexus extends to the ventrolateral margin of the cord. Along the latter line sprouts begin to grow ventrally, and the earliest and more important of these, occurring near the chief trunks of the dorsal segmentals, represent the future *aa. radiculares ventrales*. As yet no capillaries have extended beyond the myotomes. Such are the conditions which occur in mammalian and human embryos until a body length of six or seven millimetres is reached. In the succeeding stages the blood stream in the segmental artery em-

phasizes in each case two main branches out of the many capillaries, an upper or dorsal and a lower or ventral branch. The upper branch courses just ventral to the spinal ganglion and the dorsal nerve roots, joining the general plexus that more intimately invests the cord just ventral to the line of emergence of the dorsal roots,—*a. radicularis dorsalis;* the lower branch courses ventral to the ventral roots, extending on to the ventral surface of the cord,—*a. radicularis ventralis.* In the next changes which occur the most striking feature is the behavior of the capillaries on the ventral surface of the cord. The plexus which had previously begun to extend there advances from both margins until a line is reached on each side corresponding to the lateral limits of the bodenplatte; along this line they halt temporarily in their spread, thus producing a peculiar and highly characteristic vascular pattern which leaves the middle third of the ventral surface—beneath the bodenplatte—devoid of vessels but its outer thirds covered with a close net. The medial margins of this net are soon somewhat enlarged, constituting two parallel longitudinal vessels, the *primitive anterior spinal arteries* (*tractus arteriosi primitivi*). Very soon delicate transverse capillary bridges cross the middle area which was previously non-vascular (Fig. 440). Some capillary sprouts arising from these primitive anterior spinal arteries push into the substance of the cord and course dorsally, ending usually within the gray matter of the ventral horns. These are the future *aa. sulci* (Adamkiewicz), or *aa. centrales.* This stage of double anterior spinal arteries was first seen in the human embryo by His (1886). It is probably most definite and typical for human and mammalian embryos from 9 to 11 mm. in length. His's observations showed it well marked in the human embryo of 10.9 mm. and still apparent in one of 13.8 mm.

The anterior radicular arteries contribute directly to the anterior spinal on each side, and the latter vessel is really to be viewed as merely a particularly prominent anastomosis between these aa. radicales ventrales. In like manner, in later stages, a strong arterial anastomosis develops between the posterior radicular arteries and is known as the *posterior spinal artery.*

To return now to the general development of the dorsal segmental vessels and their system of branches, we find, at the stage which we are considering, these vessels each possess two chief branches, the anterior and posterior radicular arteries, which are concerned respectively in the formation of the longitudinally coursing anterior and posterior spinal arteries, and which as development proceeds become separated more and more from the cord itself by the formation of the meninges, which (in the adult) they must pierce before reaching the cord.

But besides these two branches of the dorsal segmentals, another soon develops which sprouts out beyond into the skin. This is the representative of the trunk which later gives off both the muscular and cutaneous rami; the former do not as yet exist, so that the vessel may be said to be the *ramus cutaneus dorsalis medialis* (ramus posterior medialis of Grosser, Fig. 438). Below this another branch of the dorsal segmental now extends out ventral to the anlage of the rib. This, the intercostal sprout, represents the *ramus anterior* of the adult vessel. Its future great growth makes it the chief portion of the final vessel, but embryology shows plainly that the posterior ramus is the parent, and, again, that of the branches of this posterior ramus, the spinal branch is the primary or parent one and others (rami cutanei et musculares) secondary branches of it. *From their origin to the point of division into posterior and anterior rami, then, the intercostal and lumbar arteries represent the original dorsal segmentals, but beyond the latter points they are entirely new and secondary formations.* One may compare the above figures of the dorsal segmentals of embryos with the schema which I give in Fig. 438 to represent the adult.

Mall (1898) has shown that in the 16 mm. embryo anastomoses connect all the intercostal and lumbar arteries among themselves

as well as with the subclavian above and the femoral below. In this way, then, arise the *a. epigastrica inferior* and the *a. mammaria interna,* and along with the rectus, nerves, and ribs shift later into the mid-ventral line (Fig. 441). He thus explains the formation of the superior intercostal artery: "The descent of the heart into the thorax on the inside with the descent of the arm over the clavicle on the outside of the body causes great tension on the upper intercostal arteries, and favors the new formation of blood-vessels in

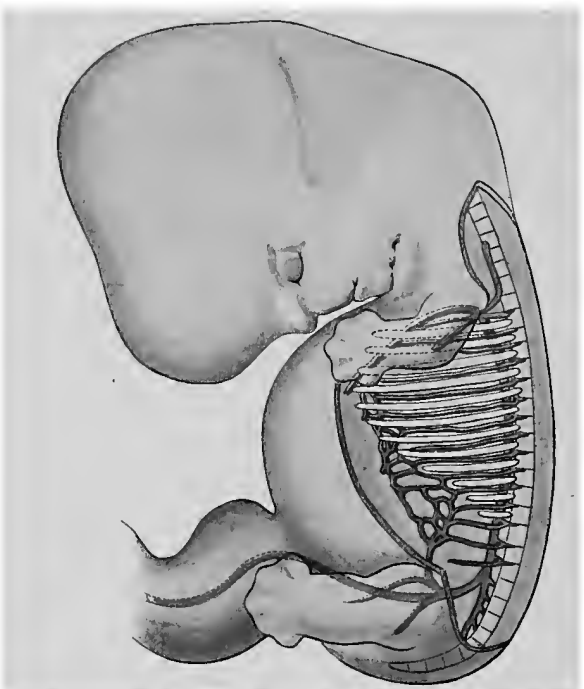

FIG. 441.—Arteries of the trunk in a human embryo 16 mm. long, showing the formation of the internal mammary and deep epigastric arteries. (Mall collection, 43.) (After Mall, Johns Hopkins Hospital Bulletin, 1898.)

a more direct line. This is the reason why the main branch of the superior intercostal is a secondary and direct artery from the subclavian." Whereas the first two intercostals passed dorsal to the sympathetic chain originally, they now pass ventral to it.

Concerning the development of the *muscular rami* which belong to the dorsal segmentals little is known.

The *cutaneous rami,* though at one time thought to develop equally and symmetrically (Manchot, 1889), do not do so, as Grosser (1905) has recently been able to show. In fact, the segmental symmetry of these vessels is quite completely destroyed in the adult.

It is entirely probable that in the early stages of development the twigs which represent the blood supply of the skin are arranged perfectly symmetrically and

segmentally. They doubtless correspond accurately with the segmental cutaneous nerve branches. Both, passing out from their source, find their territory of distribution opposite them and at the same level. But the skin does not keep its relation with the skeleton, but shifts over it, dragging, as it were, its nerves and vessels with it. Thus it happens that in the adult the segmental vessels and nerves no longer supply the skin area opposite them. Since in the thoracic region this shifting is chiefly caudalward, the cutaneous nerves all supply territories lying below their points of emergence from the intervertebral foramina. The arteries, however, though tending to follow the same law, also acquire new connections with the skin territories secondarily opposite them, and accordingly also supply besides their own proper segmental area territory which originally belonged to the adjoining more cranial segments. Such a departure probably does not obtain in the nervous system, where we may perhaps rely on the innervation of a skin territory to reveal its primary segmental position. In the case of the vascular system the departure is doubtless due to the tendency of a blood current to take the shortest possible path—a fundamental law in the development of the vessels. Some others accomplish this shorter path by the employment of anastomoses normally existing between the various cutaneous rami, and so come to course not only downward with the nerve of their own original segment, but also directly outward with the cutaneous nerves of contiguous upper segments and emerge with the latter into the skin. The original segmental skin arteries of these more cranial segments thus vicariously supplied may no longer play any rôle in the supply of the skin and in this way the number of actual skin vessels is reduced. Another cause, besides this shifting and secondary assumption of a shorter path, operates to disturb a primary segmental symmetry in the skin vessels. This also is fundamental in the development of the vascular system—the tendency of favored vascular channels to annex contiguous ones. Such a tendency is shown to a remarkable degree in cases of certain twin embryos, where we appear to have a contest between the two hearts. In the skin plexus the favored channels supplying this net enlarge at the expense of others, and this may result in the complete assumption of the territories of some three original skin rami by the vessel originally belonging to only one. It is probable that this tendency would operate in the absence of any shifting of the skin even though it is encouraged by the latter, for it is unlikely that exactly equal conditions should obtain in the case of supply of all the segmental skin areas, and a disproportion once established is rapidly exaggerated. This is without doubt the reason why both the posterior rami (rr. cutanei dorsales mediales et laterales) of a particular vessel seldom persist, usually the medial rami alone persisting in the upper segments and the lateral rami in the lower ones.

The further history of the anterior spinal artery may be briefly given here.[40]

His (1886) had noticed that in the human embryo of 18 mm. the single anterior spinal artery of the adult was finally present, and indicated that its definitive singleness was attained by a medial dislocation and fusion of the two primitive trunks, a process typified, for instance, by the well-known fusion of the two aortæ. This view has never rested on any embryological evidence, Kadyi (1889), Hoffmann (1900), and others merely accepting it tentatively, following His. Although such a fusion seems to be actually the case in the elasmobranchs (Sterzi, 1904), in the higher vertebrates, and especially in all the mammalia, a

[40] Sterzi has pointed out that the condition of paired anterior spinal arteries or a "tractus arteriosi primitivi," is never developed in the mammals to the degree seen in the birds. In the latter class they form large, much stronger and less transient trunks,—*e.g.*, lasting from the third to the twelfth day in the chick. It is interesting to note that this condition is definitive in the cyclostomes.

series of more elaborate changes must occur before the single vessel is formed. These changes do not involve a fusion process, but consist essentially in the selection of one of the possible paths offered by the primitive vessels and a plexus which has sprung up between them. The single definitive vessel may thus be unilateral, median, or even oblique in origin (Sterzi, 1904, Evans, 1909). In the first case the adult vessel represents one of the original primitive paired vessels, in the other cases it is formed from the median plexus which connects the two primitive vessels.[41a]

The single anterior spinal begins to be formed in human embryos when a length of about 15 to 16 mm. is attained. The irregular, "vacuolated" character of the young primitive trunk (Fig. 440, E) betrays its origin from the original plexus, as elsewhere in the developing vascular system.

Variations.—The studies of Kadyi (1889), Burrows,[41b] and others show that the form of the adult anterior spinal artery often bears the stamp of its method of origin, being median in some areas but in very many others truly right or left sided. In some areas it even retains its original plexus character (circuli arteriosi medullares), and in others consists of two strong parallel trunks which again unite, —*e.g.*, Kadyi (1889), Taf. 3, Fig. 11.

His stated that the double aa. sulci were later shifted together in the midline, but this does not rest on evidence differing from that for his statement of tho fusion of the anterior spinals. Usually, indeed, the aa. sulci or centrales are distinctly separate in man, even in the adult (Kadyi), thus disclosing their original paired origin from the primitive anterior spinals: a thing which Kadyi first discovered in man, Hoche (1899) in the rabbit and dog, and Sterzi has recently shown from many other instances to be the general mammalian plan.

Even in those rare instances in which some of the aa. centrales have a common trunk, this does not arise from fusion of the two original ones, but from the development of an anastomosis between these and the persistence of only one of the two penetrating trunks below the level of the anastomosis, as is normally the case in the birds (Sterzi). (Vide Sterzi's figure, page 311.)

The aa. centrales are evident in chick embryos of the 96th hour and in sheep embryos of about 6 mm. In human embryos of 10–11 mm. they form two distinct rows of delicate vessels which enter the cord at the margin of the primitive ventral sulcus and, anastomosing on each side among themselves, produce two vertical or dorso-ventral planes of capillaries. These two rigid planes of capillaries form a striking picture of the internal circulation of the cord at this time.

[41a] Sterzi was the first to show that the anterior spinal artery usually seen in the adult is only formed after the appearance of a series of anastomoses between the two parallel primitive trunks. The final vessel, according to him, may in some regions be derived from the left primitive vessel and in other regions from the right one, according to chance. The development of the anastomoses between the two primitive vessels permits the branches of that one destined to perish to be taken over by its more successful neighbor. Probably the usual anterior spinal is thus really unilateral in origin. At the same time, however, another plan may be followed in some areas. The anastomoses between the two primitive anterior spinals may become so large and numerous as to completely destroy in places the paired character of the arterial channels of the ventral cord surface and in such areas the cord is nourished by a rather wide median arterial plexus, from which later an exactly median vessel can emerge (Evans).

[41b] Burrows, M. T., unpublished observations.

This is the earliest method of blood supply of the cord in all the higher vertebrates, a sole exception being made for the urodelous amphibia, in which the first cord vessels penetrate from the lateral surfaces (Sterzi).

The further development of the cord vessels is as follows: Some time after the entrance of the aa. centrales into the cord, other vessels also penetrate it from the lower lateral surfaces opposite the level of the dorsal margins of the anlagen of the ventral gray columns (*aa. peripheric*æ). For a while, although both these ventral and lateral penetrating vessels exist, the dorsal two-thirds of the spinal marrow is still non-vascular. The whole lateral sides of the cord and its ganglia are quickly covered with the capillary plexus, but few if any sprouts have ventured on to the dorsal surface (7 mm. pig embryos). Thus the cord presents the remarkable condition of a close capillary investment everywhere save on its upper surface, which is as yet non-vascular. However, this surface is now rapidly covered, at first by delicate transerse capillaries which bridge the gap just as they do at first between the primitive anterior spinals. Gradually then a close mesh is formed here. The gray matter of the cord is better and better supplied by secondarily arising penetrating arteries, which may arise as far dorsally as just beneath the posterior nerve roots (sheep embryos of 10½ mm.). Eventually the aa. peripheric*æ* exceed in importance the original aa. sulci, an event which occurs not only in man, but also in the rodents, artiodactyls, perisodactyls, and carnivores, in all of which the peripheral penetrating arteries come ultimately to supply the greater part of the cord substance. In the chiroptera and insectivores, on the other hand, the original ventral segmentals remain always the chief arterial supply of the cord. The white matter of the cord is always supplied late, it remaining practically non-vascular in sheep embryos until a body length of almost 50 mm. is reached. Gradually there develop on each lateral half of the cord four longitudinal anastomotic chains; the first to arise and more important of these forms at or just medial to the line of exit of the posterior roots (sheep, 50 mm.). This is the posterior spinal artery of descriptive anatomy (*tractus arteriosus postero-lateralis* of Kadyi), and corresponds to the *tractus arteriosus lateralis* of most mammals. Next, a similar but weaker anastomosis develops along the line of exit of the ventral nerve-roots (*tractus arter. ventro-lateralis*) (tractus arteriosus antero-lateralis, Kadyi). Finally, anastomotic arterial chains are established dorsal to the dorsal roots (*tractus arteriosus posterior,* Kadyi), and opposite the ligamenta denticula (*tractus arteriosus lateralis*), the latter being peculiar to man and the apes. Of the various longitudinal venous trunks which develop, the order of establishment is similar to that for the arteries, the ventral, lateral, and finally dorsal appearing successively.

Anomalies of the Dorsal Segmental Arteries.—As regards their manner of origin from the aorta, the dorsal segmental arteries show two main types of anomaly. They may (1) either disappear completely on one or both sides, their branches being taken over by the adjacent cranial or caudal segmentals, or they may (2) fuse with the vessel of the opposite side into a single median stem, a process normal to the ventral segmentals (*vide infra*).

Examples of the first type of anomaly are not infrequent in man, Krause having recorded cases in which as many as four interstitia intercostalia were supplied by a single intercostal artery. It is interesting to note that such a condition occurs on one or both sides in the normal development of certain fish, amphibia, and birds. The second type of anomaly in which the two dorsal segmentals of one and the same segment fuse to a common stem is also common in man. Ernst has recorded a remarkable case in which all the intercostal and lumbar arteries arose in this way,—*i.e.,* for each segment from a single median trunk. Broman has found this second type of anomaly occurring in instances in the early embryo (13 mm.), and advances the notion that it occurs through an actual fusion rather

than through the atrophy of one of the pair.[42a] Many years ago Krause emphasized that the two places in which this anomaly was commonest were in the lowest intercostal and lowest lumbar regions, and Broman suggests that this is connected with the fact that the aortæ first fuse in the lower thoracic region and that a marked fusion process, normally bringing the roots of the two common iliacs together, occurs in the lower lumbar region. Common stems are normally produced in the case of some or all the dorsal segmental pairs in some mammals,—Lepus (Ernst), Halichœrus (Hepburn).

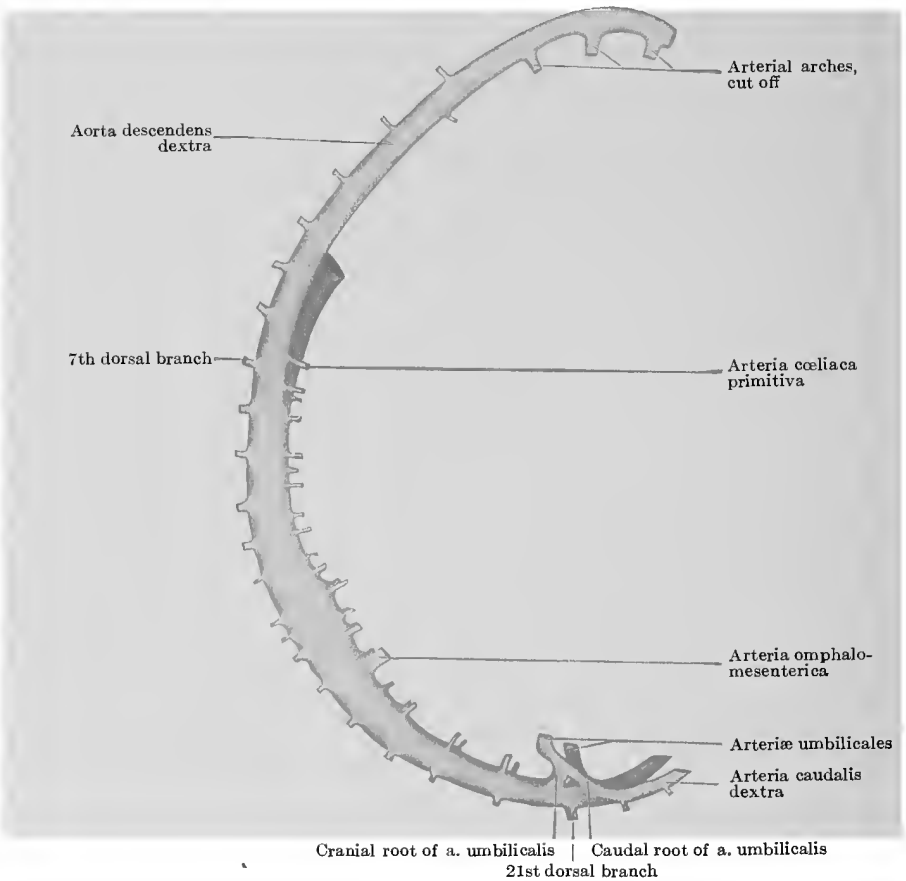

FIG. 442.—Reconstruction of the aorta and its branches in a human embryo 3.4 mm. long. (After Broman, 1908.)

THE VENTRAL SEGMENTAL ARTERIES. (Gut Segmentals, Yolk Segmentals, "Visceral Circle" [Mackay]).—The first branches to be given off by the aortæ, if we except the precocious and immense umbilical arteries, are those which course on to the primitive gut and the yolk-sac. Here the primitive *aa. vitellinae* were first seen in the human embryo by Mall (1897).

Bischoff (1842) has usually been given credit for the discovery of the row of yolk arteries given off by either aorta; his observations were made on the rabbit.

[42a] But see Hochstetter, 1911.

Von Baer (1827), however, had preceded him, for in his "de ovi mammalium et hominis genesi epistola" (Fig. VII a) he shows some six or seven pairs of yolk-sac arteries in a young dog embryo.

When the two aortæ have met and fused, opposite ventral arteries are quite accurately matched, as is always the case with the dorsal segmental arteries, so that from the now single aortic tube there go off at many places pairs of ventral or gut arteries which are also often accurately segmentally (*i.e.*, intersegmentally) placed.

It should be mentioned, though, that, while this is the case for most of the aorta's length, in its most cranial portion the ventral branches have perished before the aortic fusion has taken place, so that a condition of paired ventral vessels from the single aorta does not ever come about in this region,—*i.e.*, in the territory of the occipital and six upper cerical segments.

The most cranial lying ventral branches are very transitory, and the very first of them have entirely escaped notice until recently. In the Mall embryo No. 391 (Dandy, 1910) possessing seven somites, the ventral or gut branches extend as far forward as the first intersegmental cleft (Fig. 408). By the time the embryo possesses fourteen somites (2.1 mm., Mall, 1897, Pfannenstiel III, N.T. 6) the most cranial ventral branches appear in the region of the fourth and fifth somites. In the embryo with twenty-three somites (Robert Meyer, No. 300, N.T. 7) the ventral vessels opposite the next three caudally lying somites are also in degeneration, so that the vessels near the beginning of the eighth somites constitute the first of the functioning series.

In the Broman embryo of 3 mm. (N.T. 11) (Fig. 422) the ventral vessels opposite the 7th cervical dorsal pair constitute the most cephalic of the series, and this pair is probably the most cranial of the ventral branches to persist long enough for fusion of the aortæ to occur in their neighborhood.[42] By the time the embryo attains a length of five millimetres, all of these ventral pairs have given place to single median stems (Fig. 443). Broman (1908) believes this to take place first in the middle of the unpaired aorta and to have proceeded cranially and caudally from this point. In a human embryo of five millimetres which Tandler (1903) has described, all of the ventral pairs have "fused" and there exists a complete series of unpaired or median ventral segmentals from the seventh cervical to the second lumbar segments inclusive. Broman (1908) describes these vessels as representing in each case a fusion of the original segmental pairs, and not, as has been supposed (Thane, 1892, and others), persisting right or left members of the original pairs; but it is possible, as

[42] Whether the œsophageal arteries which Broman and I have seen in quite young embryos are remains of these cephalically lying original vitelline vessels or entirely new sprouts does not permit of determination.

Felix remarks from his study of the embryo of 23 somites, that this is often not the case, since here occasionally right members of the ventral pairs were already larger. The question is an open one.

Broman has attempted to explain the normal fusion of the ventral segmentals, in contrast to the persistence of the paired condition which the dorsal segmentals

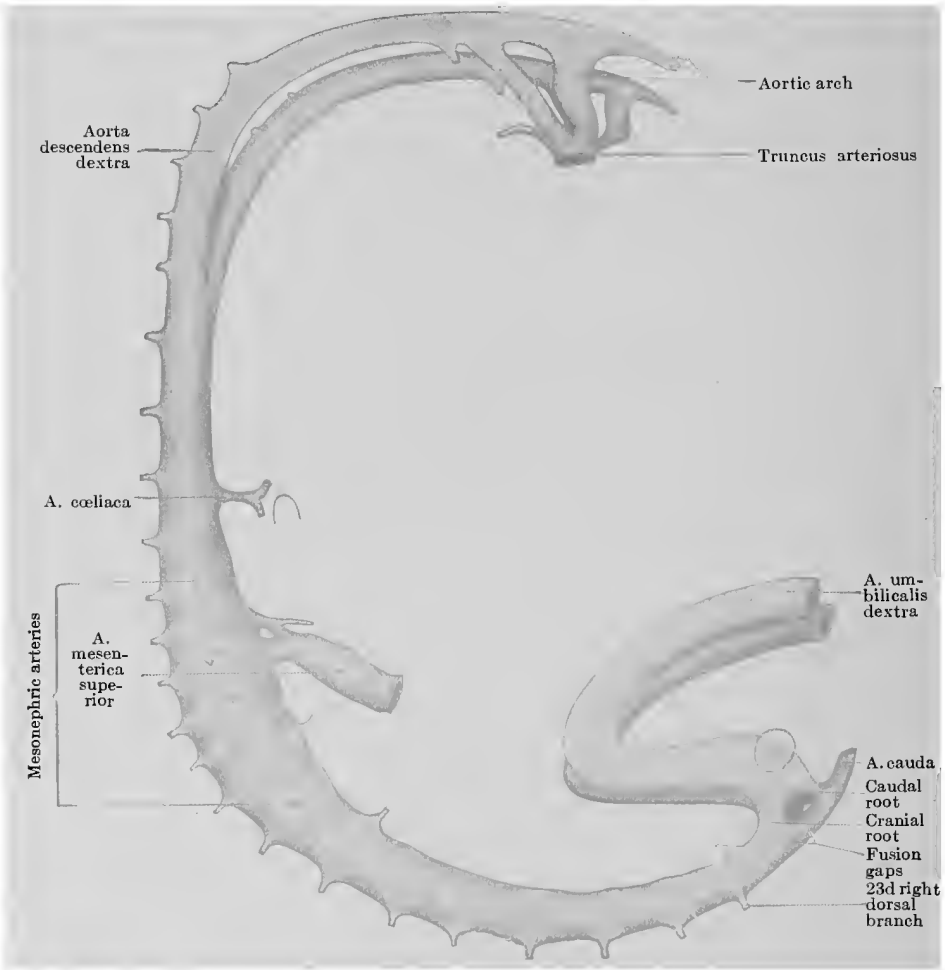

FIG. 443.—Reconstruction model of the aorta and its branches in a human embryo 5 mm. long. (After Broman, 1908.) The cranial end of the right mesonephros and the position of the metanephric anlage are indicated by dotted lines.

exhibit, by affirming that the ventral vessels are from the very beginning placed nearer each other than are the two dorsal stems. This statement, of course, will not hold, as can be seen from the study of younger embryos than were at his disposal (Fig. 444). The coalescence of the ventral segmentals is doubtless connected with those forces which pull the intestine farther away from the aortic wall to produce the dorsal mesentery.

It is quite possible that the seventh pair of ventral segmentals remain longer than those above them just because they function as one of the roots of the cœliac artery. At the stage of five millimetres, although the series of mid-ventral segmentals may be uninterrupted, some of the members of the series are already much exaggerated over the remainder and enable us to recognize them as forming the cœliac and omphalomesenteric arteries respectively (Fig. 445). The former vessel arises by two roots from the seventh and eighth ventral segmentals and, coursing ventrally, forks, the two branches being traceable forward toward the portion of the alimentary canal from which later the stomach and liver are respectively derived. The omphalomesenteric artery is by far the largest of the ventral series, and, while its main trunk is the con-

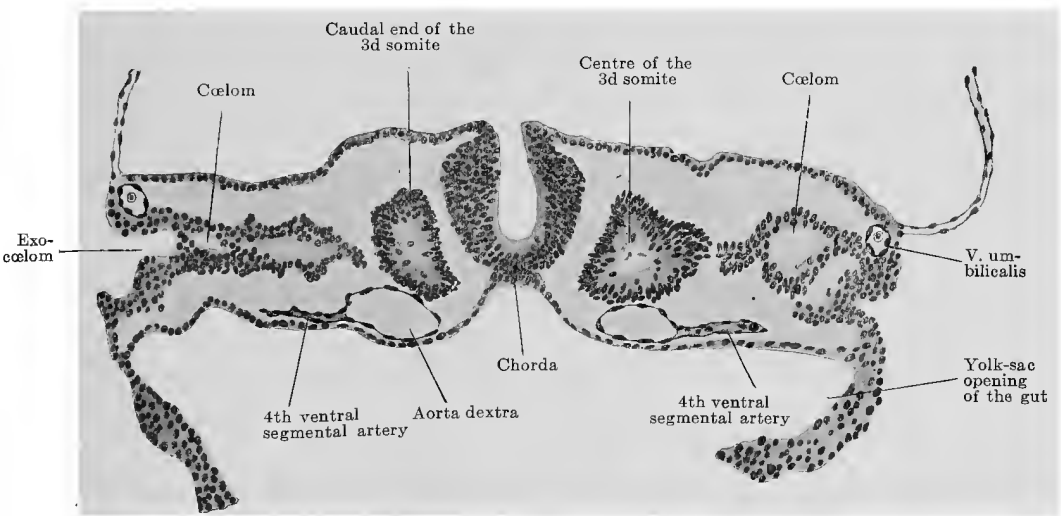

FIG. 444.—Cross section of a human embryo of 7 somites, showing the primitive ventral (segmental) branches of the aorta. The yolk-sac is so spread out that these branches appear as lateral derivatives of the aorta, although later ventral. (After a drawing kindly placed at my disposal by Dr. Walter E. Dandy.)

tinuation of the thirteenth segmental vessel, the four ventral segmentals cranial to this also share in giving origin to it, for they are connected with this artery by a series of longitudinal anastomoses. As can be seen from Fig. 445, the omphalomesenteric artery splits on reaching the intestine and surrounds the latter at its junction with the ductus omphalo-entericus, with an arterial ring, before proceeding on its way to its final field of distribution on the yolk-sac. Fig. 446 shows conclusively that the left limb of this ring has atrophied, since the artery now passes entirely on the right side of the gut.

Anomalies.—Sometimes a considerable part of the old omphalomesenteric artery persists in those rare cases of the most primitive type of Meckel's diverticulum. In such cases what is undoubtedly the original artery courses beyond the gut and its diverticulum to the umbilicus, and a determination of on which side of the

gut the vessel courses will disclose whether the right or left limb of the early arterial ring has persisted. All of the more advanced types of the diverticulum, in which the process is merely supplied by an unusually strong vessel but in which the old trunk cannot be identified with certainty, must be inadmissible for the determination of this point, for the diverticulum is a healthy functioning pocket of the bowel and as such could have secondarily attracted for its supply branches from the vessels of either contiguous wall of the intestine.[43]

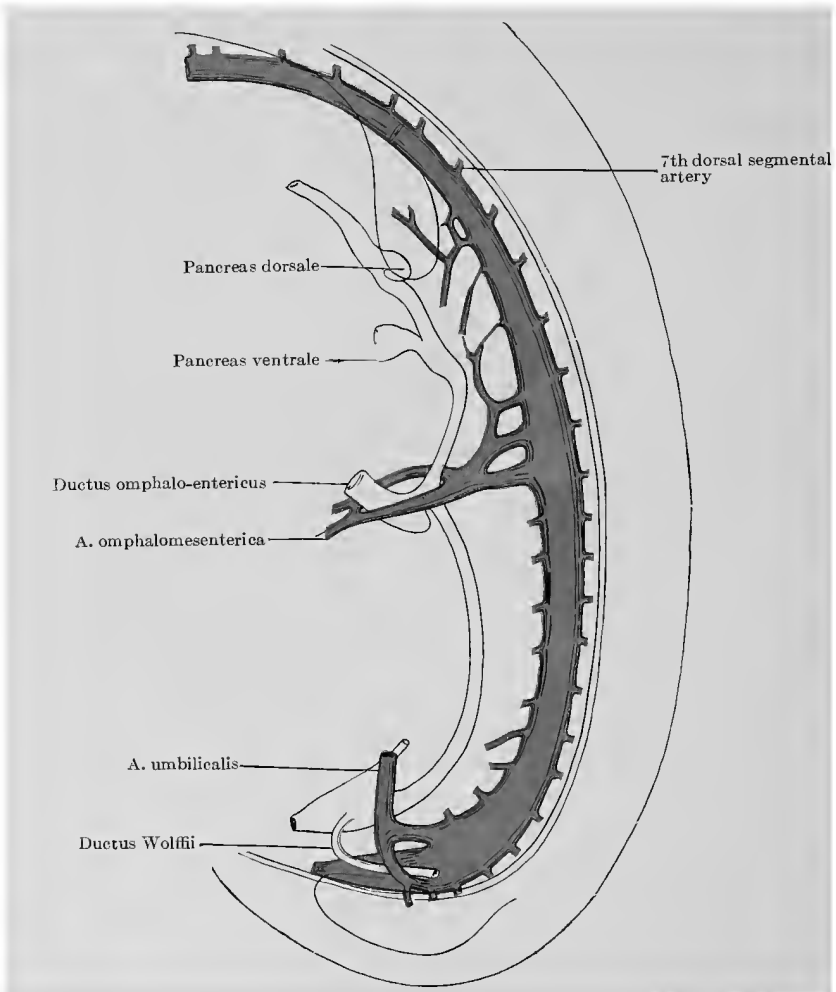

FIG. 445.—Sagittal reconstruction showing the aorta and its branches in a human embryo of 5 mm. (After Tandler, Anat. Hefte, Bd. 23, p. 192, Fig. 1.)

Opposite the lower colon, no one of the ventral segmental arteries is especially enlarged above its fellows, and the equal part which all of them play in the nourishment of this part of the bowel

[43] It is of interest to note that Allen (1883) some years ago pointed out that remnants of both the a. and v. omphalomesenterica are normally found in the newborn of the cat, dog, and guinea-pig in a strand of tissue which reached the navel.

prevents us from identifying any one of them as the a. mesenterica inferior. Nevertheless, in an 8 mm. embryo the latter artery is apparent as the 20th ventral segmental (Broman, 1907).

In the succeeding stages in the life of the embryo, the vessels which we must recognize as the cœliac, superior mesenteric, and inferior mesenteric respectively are all found at successively lower levels on the aortic wall, a fact which is to be correlated with the descent of the intestinal viscera (their territories of distribution) into the abdomen. This highly interesting phenomenon, the so-

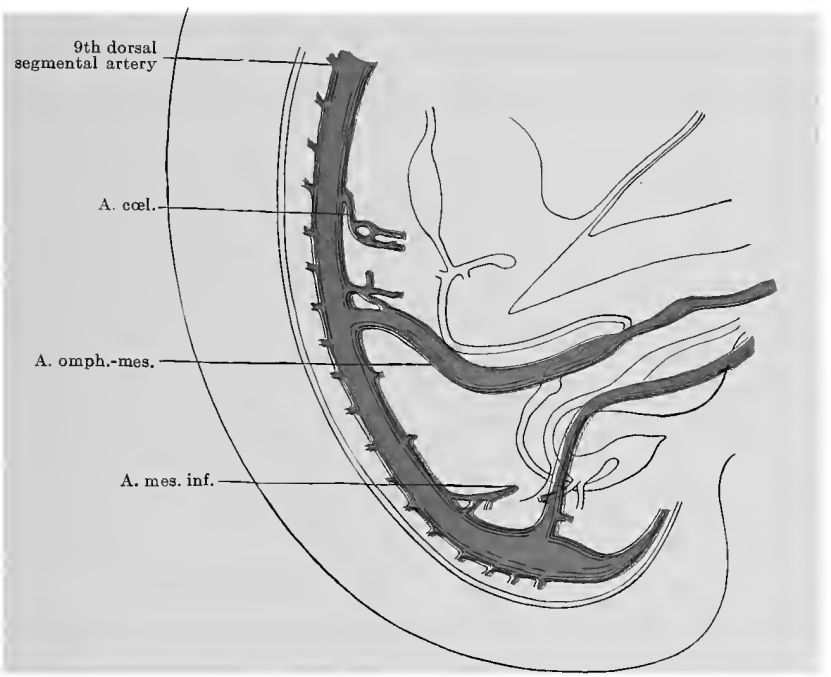

Fig. 446.—Sagittal reconstruction showing the aorta and its branches in a human embryo measuring 9 mm. (After Tandler, Anat. Hefte, Bd. 23, p. 197, Fig. 2.)

called "caudal wandering" of the visceral arteries, was first discovered by Mall (1891), and has since been abundantly confirmed and extended by the studies of Tandler (1903) and Broman (1908). The subjoined table shows the position of these vessels in a number of human embryos during the time of their migration (p. 648).

The cœliac artery thus wanders from the seventh cervical to the twelfth thoracic segments, a displacement of some eleven segments, and the superior mesenteric artery almost equally as far (ten segments, second thoracic to first lumbar); whereas the inferior mesenteric artery wanders through but three segments (twelfth thoracic to third lumbar). The great change which the levels of origin of the first two vessels undergo, in contrast to the slight one of the third, is readily intelligible from the proportion-

ately great dislocation which the upper part of the alimentary tract undergoes. All of these vessels usually attain their adult levels by the time the embryo is 17 mm. long.

This shifting of the intestinal arteries is not produced by a displacement of the aorta on the vertebral column, but is an actual

	Length of embryo.	Position of a. cœliaca.	Position of a. mes. sup.	Position of a. mes. inf.	Observer.
1	4.9 mm...	C. 7.....	T. 1, 2, 3, 4.....	.....	Ingalls.[44]
2	4.5 mm...	Betw. C. 8 and T. 11.....	T. 2 and T. 3.....	.....	Broman.
3	5 mm....	C. 7 and C. 8.....	T. 1, 2, 3, 4, 5....	.....	Tandler.
4	5 mm....	C. 8 and T. 1.....	T. 4 and 5.....	.....	Broman.
5	6.75 mm..	T. 2.....	T. 5 and 7.....	.....	Keibel and Elze.
6	7 mm....	T. 5.....	Betw. T. 5 and 7.	L. 1.....	Elze.
7	8 mm....	T. 2.....	T. 4, 5, 6.....	T. 12.....	Broman.
8	9 mm....	T. 4.....	T. 5, 6, 7.....	T. 12.....	Tandler.
9	9 mm....	T. 4.....	T. 6, 7.....	L. 1, 2.....	Tandler.
10	10 mm...	T. 8.....	T. 9, 10.....	L. 2.....	Broman.
11	10.3 mm..	Betw. T. 7 and T.8	T. 9, 10.....	Betw. L. 1 and 2..	Broman.
12	11 mm...	T. 6, 7, 8.....	T. 8, 9.....	L. 3.....	Broman.
13	11.7 mm..	Betw. T. 7 and 8..	T. 9.....	Betw. L. 1 and 2..	Broman.
14	11.7 mm..	T. 9.....	T. 10.....	L. 2.....	Broman.
15	12.5 mm..	T. 8.....	T. 10.....	L. 2.....	Tandler.
16	13.2 mm..	T. 8, 9.....	T. 10, 11.....	L. 2.....	Broman.
17	14 mm...	T. 10.....	T. 10, 11.....	L. 2.....	Broman.
18	14.5 mm..	T. 9, 10.....	T. 11.....	L. 2.....	Tandler.
19	14 mm...	T. 10.....	T. 11.....	Betw. L. 1 and 2..	Author.
20	14 mm...	T. 11.....	T. 12.....	L. 2.....	Tandler.
21	15.5 mm..	T. 11.....	T. 12.....	L. 2.....	Author.
22	16 mm...	T. 12.....	T. 12.....	L. 3.....	Broman.
23	16.2 mm..	T. 11.....	T. 12.....	Betw. L. 2 and 3..	Broman.
24	16 mm...	T. 11 (lower part).	T. 12 (upper part)	L. 2.....	Author.
25	16 mm...	T. 12 (upper part)	T. 12 (lower part).	L. 2 (lower part)..	Author.
26	17 mm...	T. 12.....	L. 1.....	L. 3.....	Tandler.
27	19 mm...	T. 12.....	L. 1.....	L. 3.....	Broman.
28	19 mm...	T. 12 (lower part).	L. 1.....	L. 3.....	Author

shifting of these ventral branches when compared with the dorsal branches of the same trunk.[45]

[44] "Zwischen dem fünften und sechsten Rumfganglion findet sich ein bis an den Darm verfolgbares Gefäss, das vielleicht als a. mes. inf. anzusehen ist." (Ingalls.)

[45] The exact manner in which this wandering of the gastro-intestinal vessels is accomplished has not as yet been established. Undoubtedly one possible method in early stages is by means of the anastomoses which connect the ventral vessels. This, however, will only account for very early shiftings, for the studies hitherto made show that very soon there may not be a single other vessel between the points of origin of the three chief vessels (*e.g.*, Tandler's embryo K.S.). Consequently other methods have been called on to explain this caudal wandering. These are—

1. That it takes place through the formation of special non-segmental anastomoses between the wandering arteries and the aortic wall below them, with the ensuing atrophy of the older roots. The chief evidence in favor of this view consists in the frequent presence of non-segmental roots of origin for these vessels. The original roots being all supposedly segmental, any non-segmental position for the vessel is explained by the acquirement of secondary non-segmental roots. Such a view overlooks the fact that even in the beginning non-segmental ventral branches are present (see, for instance, the vessels in Broman's Fig. 1, page 646).

Regarding the development of the peripheral branches of these arteries in man almost nothing is as yet known.[46] Tandler has identified the a. pancreatico-duodenalis superior in an embryo 13 mm. long (N.T. 57). At 15.5 mm. (Mall's collection, 390) the cœliac axis possesses the following branches: *a. phrenica inferior, a. gastrica sinistra* with *œsophageal rami, a. hepatica* with its a. cystica (strongly developed), *a. pancreatico-duodenalis superior,* and *a. lienalis* (Fig. 447).

Interest attaches to the development of the ventral branches which the adult aorta is known to send to the œsophagus, especially as to whether these also are descended from the early segmental branches. Some of these aa. œsophageales have moreover been identified in relatively early stages, but they are apparently new formations.[47]

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2. That it takes place through an active ventral wandering, by which it is understood that the caudal wall at its junction with the aorta bulges itself out, while the cranial wall at a corresponding place is taken up by the aortic wall. There is no evidence for this view.

In discussing the subject it is to be pointed out that the cœliac and superior mesenteric arteries have their roots in an uninterrupted chain of anastomosing vessels, and there is no *a priori* reason why the vessel functioning as the superior mesenteric in one stage may not subsequently be used as the cœliac channel. As the area of distribution of one of these vessels shifted caudally, the blood stream could adapt itself to a more direct path by the employment of these anastomoses which enable it to come from successively lower segments of the aortic wall.

It seems to me most probable, however, that the identity of the three main vessels is established permanently very early, and that the great shifting is due to an entirely different phnomenon,—namely, to the unequal growth of dorsal and ventral walls of the aorta. Attention may be called here to the remarkable shifting undergone by the fourth aortic arch, for instance, compared with the dorsal segmental vessels, and yet the arches have not been thought to climb down by special secondary roots, etc.

[46] Fransen has studied the branches of the a. mesenterica inferior in two human fetuses between the eighth and ninth month. The six chief branches which he finds going off from this artery he interprets not as the usual branches of the third order, but as original ventral segmentals from the aorta and sacralis media, which subsequently became united through a longitudinal anastomosis (the ascending and descending rami of the a. mesenterica inferior), whereas the root portions die. There is nothing embryologically to establish this claim. These lower ventral segmentals do not exist long enough to leave a permanent trace in the mesenteric plexus. Like the earliest limb vessels they are usually of a capillary nature. The establishment of the inferior mesenteric artery rearranges the whole vascular pattern of its territory of distribution, and the six branches to which Fransen refers came out of this plexus.

[47] In an embryo of 4.5 mm. Broman has identified three of these vessels rising from the right aorta opposite the third and fourth dorsal segmental vessels, and reports them in embryos of 10.3 and 14 mm. I have myself seen them in embryos of 10 and 14 mm. *In the embryo of* 15.5 *mm.* shown in Fig. 447 they are shown as delicate twigs opposite the sixth and seventh thoracic segments, and have been seen in this location or slightly lower in five other embryos measuring from 19 to 23 mm. (Numbers 229, 368, 108, 57, and 382, Mall's collection). In the older of these embryos they were represented by a fairly strong vessel opposite the eighth thoracic segment.

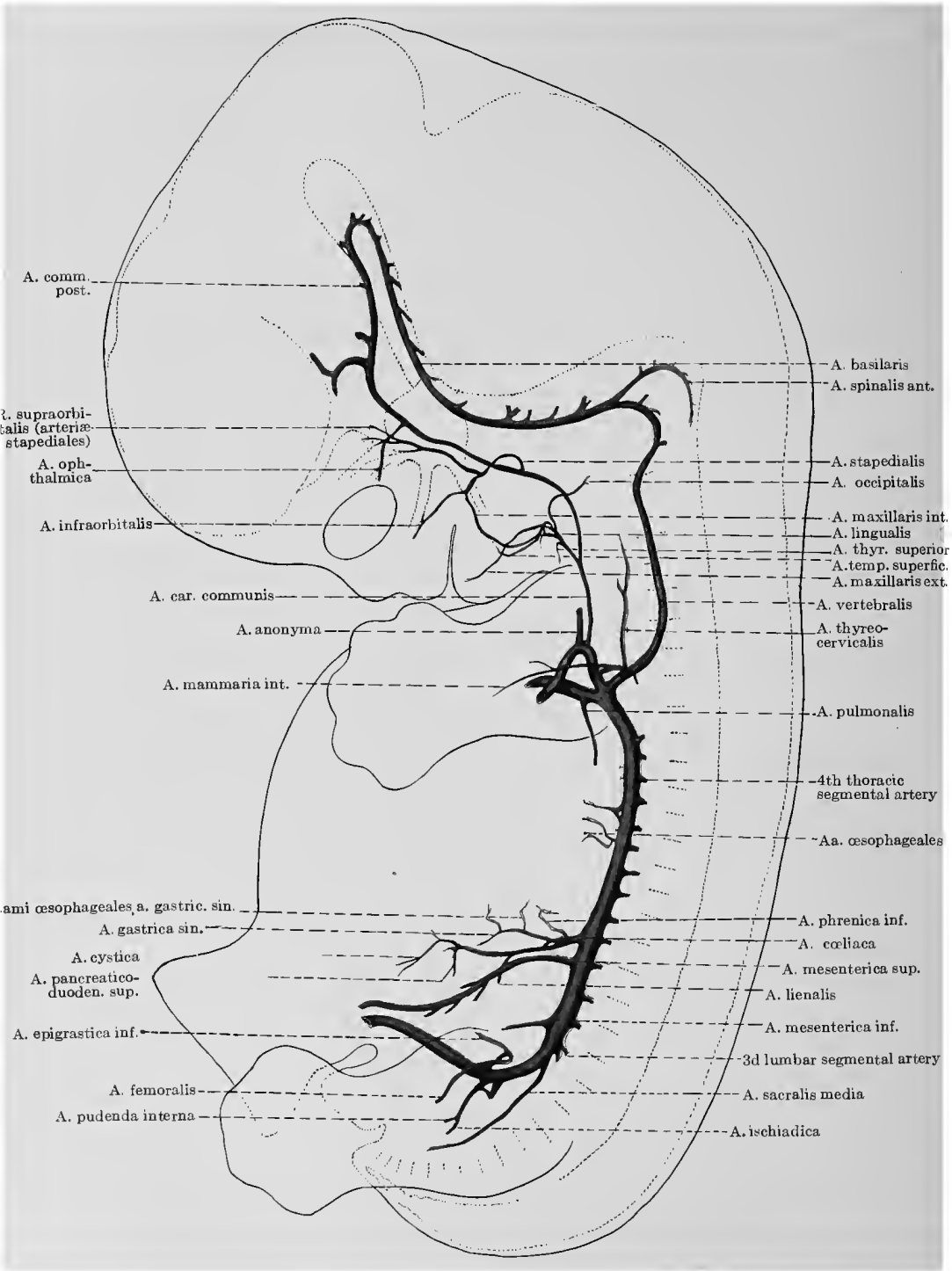

FIG. 447.—Graphic reconstruction of the arterial system of a human embryo 15.5 mm. long, which had been injected while the heart was still beating by Mr. Broedel. The embryo was subsequently cut into a series of sagittal sections. (No. 390, Mall collection.)

As far as I know, nothing has been ascertained concerning the development of the bronchial arteries. In the embryo of 15.5 mm. (Fig. 447) three ventral branches of the aorta are seen to constitute aortic vasa vasorum.

The main branches of the mesenteric arteries are formed very early and can be identified in mammalian embryos well under 10 mm. in length. From the time of the earliest existence of the ventral segmentals, the gut is supplied with capillaries, and in the early embryo these form a close plexus in the tissues of the simple intestinal tube.

The earliest capillaries plexify in a fairly definite plane which corresponds to the future submucosa. This tunic—the so-called "tunica vasculosa" of the older anatomists—contains, as is well known, the chief plexus of intestinal vessels in the adult; there the chief vessels of the intestinal wall are found, and it is from them chiefly that the muscular rami and all of the mucosal rami are derived. This fact finds a better comprehension from the history of the vascularization of the gut wall, for in the submucosa the earliest and hence oldest vessels are found. From this layer of vessels, with the progressive development of the muscularis and the mucosa, there sprout out the rami which nourish these tunics. When the first villi are formed they receive simple capillary loops and sprouts; from the capillary plexus of the older villi, the villous arteries and veins are formed. The increase in complexity of the proper intestinal vessels proceeds from above downward, just as does the development of the intestinal walls and especially the villi; the vessels of the small intestine much precede in complexity those of the large bowel, and the latter portion, for a long time smaller in girth, remains supplied only with a single, simple, submucosal net at a time when the small gut has manifold muscular and mucosal rami.

Anomalies.—The cœliac and superior mesenteric arteries sometimes arise from a common trunk—the so-called "cœliaco-mesenterica," Rathke. This is an entirely normal condition in the Anura, some of the Chelonia and Lacertilia, and some of the Mammalia (Phocæna [Cuvier], Talpa [Tandler], Echidna [Hyrtl], etc.). The formation of such a trunk has been interpreted as due to the approach and fusion of the cœliac and superior mesenteric arteries (Howes, Klaatsch, Fransen, etc.). Tandler (1904), however, has studied the embryonic development of Talpa, in which this occurs as a part of normal development. He finds a strong longitudinal anastomosis between the various early segmentals of the cœliac and superior mesenteric group. Only one of these early segmentals remains as the permanent trunk, and it has as its chief cranial branch a longitudinally coursing vessel, which is doubtless the old longitudinal anastomosis between the segmental series, the cranial members of which have now degenerated. From this longitudinal vessel the gastric (sinistra), hepatic, and splenic arteries are later distinguished as arising. The main part of the permanent trunk is the omphalomesenteric channel; in this way, then, the anastomosis enables the latter vessel to take over the branches which usually belong to the cœliac. Tandler has applied these findings to explain also the anomalous occurrence of an a. cœliaco-mesenterica in man. If his schemata are interpreted liberally as signifying any mesenteric anastomoses by virtue of which one vessel can take over the whole or part of its neighbor, they deserve to stand as the most reasonable and plausible explanation for these anomalies. It is significant that it is always the stronger vessel—the a. mesenterica superior—and never the weaker cœliac which performs the annexation, a fact in conformity with our general ideas of the method of development of the vascular system. Tandler in fact recognizes a general anastomosis between the branches of aorta in this

region, constituting, as it were, a general cœliaco-mesenteric complex. Normally there occurs a later separation of the cœliac and mesenteric systems. Broman, on the other hand, thinks that from the earliest time at which they can be recognized these two vessels with their multiple roots are entirely separate; this is because the human material hitherto explored has not revealed a complete chain of anastomoses between the two vessels, as it has in Talpa. The limitations of method of attack here make it probable that these vessels can not always be seen and that future researches will show them present. If they are not present, another method of formation of a truncus cœliaco-mesentericus may be the correct one; this is the active outgrowth of a wandering root from the cœliac which attaches itself to the superior mesenteric rather than the aorta (Broman).

The rather commoner, longer anastomoses between the cœliac and upper mesenteric arteries are doubtless more secondary developments from the plexus in the primitive mesentery. (In this category are to be placed the cases reported by Aeby, Bühler, Fawcett, Tandler, Thane, Toldt, and others.) The superior mesenteric artery has also been reported as taking over the field of the inferior mesenteric (Fleischmann, 1815), but this is doubtless an anomaly of the greatest possible rarity, because the lower vessel is initially so far removed from the superior one as to be from the beginning a far more effective supply for the bowel which is opposite it.

Lateral Branches. (Nephric Segmentals, Intermediate Arteries (Mackay), etc.).—Mention has already been made of the occurrence of primitive lateral branches of the aorta in human embryos of 15 and 23 somites (see Fig. 436). The relation of these vessels to the lateral branches of the aorta present in embryos of 4 to 5 mm., and which are now clearly concerned in the supply of the Wolffian body, is not clear, and will not be so until intermediate stages are possessed. I shall discuss here only the latter arteries, which we may designate simply as lateral branches of the aorta or the mesonephric arteries.

His (1880) first observed multiple branches of the aorta supplying the mesonephros in a seven millimetre embryo, and Mall (1891) emphasized the tendency of these to be segmentally arranged in early stages.[48] Broman has recently given a more extended account of them and their fate in a series of embryos, and I follow him.

At first, when the Wolffian bodies are relatively small, the number of mesonephric vessels is correspondingly small and these

[48] Tandler has confirmed this tendency for a segmental arrangement of the mesonephric arteries, but the studies of Broman, Ingalls, Elze, etc., show that many non-segmental arteries exist either from the beginning or as a result of shifting of original ones and we must admit that the metameric arrangement of the Wolffian body arteries is soon completely lost. Hochstetter has called attention to the fact that the mesonephric vessels in Selachians are described as coming from the segmental body wall arteries (Dohrn), and in Amphibia as being true segmental offshoots of the aorta (Semon). He is of the opinion that the corresponding vessels in amniotes were also segmentally arranged in correspondence with segmental mesonephric glomeruli, each of which had its own artery. Actual observations on amniote embryos which will support this have not yet been made.

come from only the middle portion of the aorta (2d to 8th thoracic segments); but when, at the end of the first month, the mesonephros reaches its greatest development, it receives many direct branches from the aorta at levels cranial as well as caudal to the original ones. The following table will indicate this:

Length of embryo.	Level of origin of mesonephric arteries.	No. of mesonephric arteries on each side.	Observer.
5 mm.	2d to 8th th. segments	7	Broman (1908).
5 mm.	1st to 12th th. segm	13	Tandler (1903).
7 mm.	8th cerv. to 12th th.	14	Mall (1891).
8 mm.	8th cerv. to 12th th. segm.	20	Broman (1908).

The last vessels added to the series appear to grow out from the level of the first lumbar to second lumbar segments in embryos of 10 millimetres. These indeed are destined to persist in the adult representatives of these arteries, for all the remainder atrophy by the time the embryo is from 16 to 19 mm. long. When the sex glands and the adrenal arise, they are supplied by branches from many of the neighboring mesonephric arteries.

Gradually the sex gland loses all but a single one of its many arteries, and this is the branch from the mesonephric vessel opposite the second lumbar segment. The atrophy of the Wolffian body permits the entire blood stream in this artery now to supply the sex gland, and thus the a. spermatica interna appears to be a direct branch of the aorta (Hochstetter for mammals, Broman for man).[49]

The branches of the mesonephric arteries to the adrenal gland are originally many (6 at least), and come off from the higher members of the series,—*e.g.*, in a 10 mm. embryo, from the mesonephric arteries arising from the sixth to eighth thoracic segments. But eventually, with the relative descent of the adrenal, it acquires branches from the Wolffian body arteries at lower and lower levels. At last in 16 mm. embryos the adrenal arteries are branches of three mesonephric vessels near the first and second lumbar segments.[50] With the atrophy of the Wolffian body, these three adrenal arteries persist and consequently take over the entire blood current, thus appearing as three independent branches of the aorta. Before the adult state is reached, the upper and lower members of the series of three adrenal vessels acquire important secondary con-

[49] Along with this goes the fact that the recognizable rudiments of the Wolffian body in the adult—the epididymis or epoophoron—are naturally supplied by the sex gland artery.

[50] It is to be noted that at this stage these are at last the only mesonephric arteries existing, with the exception of the very last member of the series—that of the second lumbar segment—which sends a branch to the sex gland.

nections, for the latter comes to supply the permanent kidney (*a. renalis*), [51] and the former the diaphragm (*a. phrenica inferior*). These secondary fields for the upper and lower adrenal vessels soon exceed in importance their adrenal territory, and so, in the adult, we only speak of the upper and lower adrenal arteries as small branches of the large renal and inferior phrenic vessels, though embryologically the reverse is the case. The a. renalis soon takes a descending course, and only in the second half of fetal life does it appear transverse.[52] Luna (1908) has shown that the a. phrenica inferior does not surpass its adrenal branch in size until about the seventh embryonal month.

As a result of all observations hitherto made, it may be stated that the permanent kidney in mammalian embryos certainly does not receive any large and readily appreciable arterial supply until its definitive position is reached. Hochstetter has stated that the vv. renales also wait such a time for their development. These facts, however, can not be taken to mean that the renal anlage possesses no circulation during the important early period of its development. For it can be shown, even from ordinary histological sections, that the kidney during this time possesses many small vessels in its walls, and Broman (1907) has recently traced connections between these and the posterior cardinal veins, on the one hand, and with the efferent Wolffian body veins, on the other.[53]

This is not the only source of blood for the early metanephros, for injections of mammalian embryos (pig) indicate that its capillaries receive arterial blood from the a. sacralis media (Fig. 448) and inferior mesenteric artery. (See Jeidell, 1911.)

Variations.—Supernumerary renal arteries have been known for a long time (Macalister [1883] records a case of seven), but until the embryology is accurately known explanations for their occurrence will be highly speculative, as they have been in the past. From the time of Meckel onward, there have been observers willing to postulate a hypothetical "splitting" of the usual single renal artery to explain this! (*e.g.,* Kolster, recently). However, other observers have stated their belief

[51] Hochstetter declares the a. renalis of other mammals to be a direct secondary outgrowth of the aorta, and the same history was described by Hill for the pig. The subject is worthy of reinvestigation in very early injected embryos.

[52] Broman explains this by a descending course of the a. suprarenalis inferior at the time the a. renalis supplants it. Formerly these vessels were transverse, but after the closure of the diaphragm he thinks the latter successfully prevents any upward extension of the adrenal, and that adrenal growth from now on consequently pushes down its lower pole together with the a. suprarenalis attached there.

[53] From such a finding Broman concludes that the post-cardinal venous blood flows to the kidney and is drained out again into the vv. revehentes of the Wolffian body; this would furnish a renal-portal system for the early metanephros comparable with the renal-portal system so well known in the case of the mesonephros, and in accord with similar observations made some years ago by Hochstetter on the metanephros of reptiles.

in the derivation of supernumerary aa. renales from Wolffian body vessels, and Broman's derivation of the normal a. renalis from this source makes this explanation of multiple renals the most plausible. The abnormal origin of the renal artery in common with other trunks is of some interest, inasmuch as we can now explain a large number of these embryologically. The inferior phrenic, adrenal, and sex-gland arteries being derivatives of the original mesonephric vessels, all combinations in the origin of the former vessels may be expected. Thus the origin of the a. spermatica interna from the a. renalis is not uncommon, the common origin of a. renalis and a. suprarenalis inferior is normal, and the other adrenal vessels may likewise come from the renal. It is now possible, in view of new observations on the earliest blood supply of the metanephros, that certain types of origin

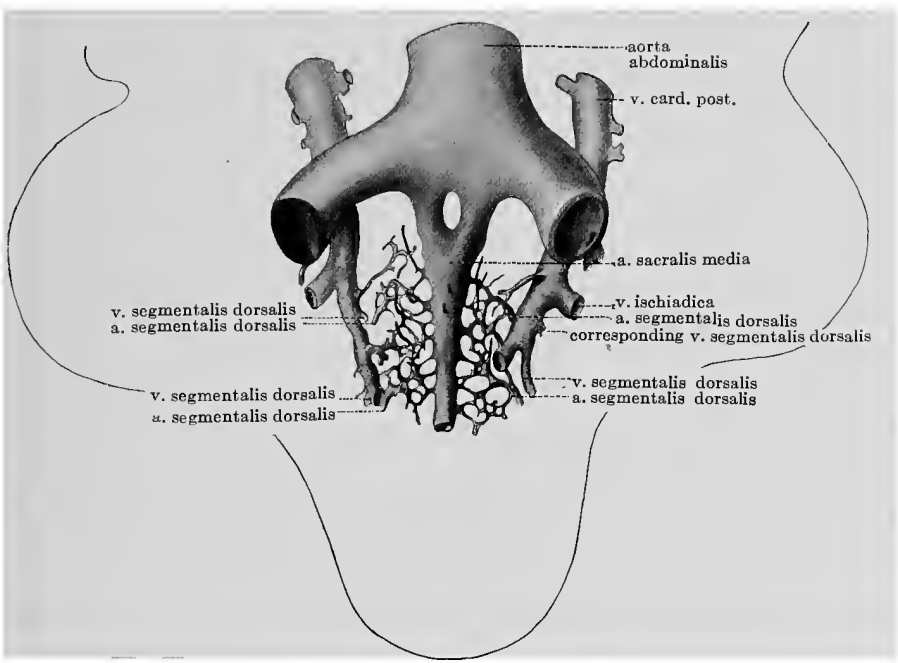

FIG. 448.—Arteries to the permanent kidney in a pig embryo 14 mm. long, after an injection of the living embryo. The arteries in question are the small upwardly-directed branches which arise from the a. sacralis media and the lateral plexus formed by the a. sacralis media. The same plexus is seen to give rise to the aa. segmentales dorsales on each side.

of the renal artery from lower sources—*e.g.*, from the a. mesenterica inferior or a. sacralis media—represent the retention of its first vascular connections when the gland was pelvic in position. There still remain, of course, many remarkable anomalies of all these arteries which indicate entirely secondary shiftings or connections,—*e.g.*, the origin of the a. spermatica interna from certain lumbar arteries. Broman has emphasized that the mesonephric arteries may come off at variable points from the lateral aortic circumference, many of them, in fact, being ventrolateral derivatives. It is easy to understand how, in the latter cases, in further growth the mesonephric artery may come to be incorporated with a contiguous ventral branch of the aorta. The most common instance of this is afforded by the common origin of cœliac and inferior phrenic arteries.

END BRANCHES OF THE AORTA (Caudal, Lower Limb, and Pelvic Arteries).—In all vertebrates in which the hind limbs are im-

portant, the aorta does not appear to go over insensibly into the a. caudalis, but is rather drained of most of its blood by the mighty iliac branches, which we have come to speak of, in addition to the caudal vessel, as the end branches of the aorta. The simplest arrangement of the aortic end branches is that seen in man, and involves merely a tripartite division into the two common iliacs and the a. caudalis (a. sacralis media).[54] In many mammals, including man, later shifting makes the sacralis media appear as a dorsal derivative of the aorta and not as its direct continuation,—*e.g.*, in the human adult it almost constantly arises cranialward from the "bifurcation place" of the aorta.[55]

In the human embryo we have seen that the tremendous importance of an early placental circulation has "pushed forward" the development of the umbilical arteries so that they much precede of course the appearance of limb arteries.

Studies on early embryos show that the umbilical artery is relatively farther cranial in position than it subsequently comes to be,—*i.e.*, it appears to wander caudally. We have seen that the primitive umbilical arteries possess many roots of origin from the aorta which are in fact only the caudal members of the general vitelline series (aa. vitellinæ).[56]

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[54] Hochstetter has shown that in some mammals, although this plan is originally followed, there subsequently occurs a disappearance of the common iliac vessels, so that the external and internal iliacs arise separately from the aorta (cat). Hochstetter in 1903 felt inclined to explain this as due to a splitting of the aa. iliaca communes, Broman (1908), by a fusion of the umbilicals down to the point of origin of the external iliacs. Very recently now, Hochstetter (1911) has subjected the matter to a careful restudy, and comes to the conclusion that the cat's truncus hypogastricosacralis comes through a wandering upward of the origin of the a. iliacæ externæ from the wall of the a. iliacæ communes to that of the aorta; a similar thing apparently occurs as regards the a. iliolumbales which wander from the external iliacs to the aorta.

[55] Young has attempted to maintain that the umbilical arteries really represent the original continuations of the aortæ which have fused only down to the point of origin of these vessels. He goes over into a hypothetical and poorly founded realm in declaring that the aortæ thus bend around into caudal arches comparable with the aortic arches. He explains the a. sacralis media as a secondary branch, being much impressed with its dorsal origin from the aorta at a point cranial to the iliacs rather than at the exact division place. Nevertheless in development the sacralis media goes off at the point of origin of the a. umbilicales, and in addition behaves like the aorta in its position, dorsal segmental branches, etc. Broman explains the definitive origin of this artery cranial to the division of the aorta into its iliacs by assuming that the last part of the aortic stem is formed by a secondary fusion of the aa. umbilicales for a short space at their proximal ends. No evidence exists for this view, and if relative growth differences cannot completely account for the apparent cranial shifting of the sacral artery, we must assume a true wandering to have taken place.

[56] In this connection it is of interest that in some mammals the omphalomesenteric artery first appears to take origin from the umbilical by a stem which leaves the

In very early stages this caudal migration of the umbilical artery is unquestionably brought about by the caudal growth of the aorta itself together with its intestinal branches, the whole forming a plexus with which the umbilical arteries are constantly in relation and by means of which the blood to them gradually flows in more and more caudally placed ventral branches. Thus, in the Kroemer-Pfannenstiel embryo of 6 somites (N.T. 3), these vessels arise at about the level of the future seventh or eighth segment, —*i.e.*, the fourth cervical somite. In embryos measuring less than 4 mm. the artery is almost at the level of the first lumbar vessels. It is probable that the single or at most double roots which the a. umbilicalis possesses at this stage are its final ones which belong to the original vitelline series. These roots, however, are themselves displaced or "wander" caudally, so that in embryos of 5 mm. they are found at or slightly below the level of the third lumbar vessels.[57] They do not, however, constitute the definitive roots of these arteries, for, as Hochstetter (1890) some years ago showed for rabbits, the umbilical arteries of mammals next gain a more laterally placed root of origin from the aorta by the development of an anastomosis with the posterior limb arteries, whose origin from the aorta now becomes the root trunk of the umbilical artery, the original ventral umbilical root now atrophying. Hochstetter showed clearly that both ventral and lateral roots for the umbilical may exist for a short time coincidently (*e.g.*, in rabbits of eleven days, two hours), and so form an arterial ring enclosing the Wolffian duct and cœlomic cavity, lateral to which the secondary roots and medial to which the primary roots course. Such a condition can be seen in human embryos of about 5 mm. (N.T. 16) as Keibel and Elze (1908) first reported and as may be seen from

latter vessel and courses cranially toward the place where later strong arterial connections with the aorta enable the proper omphalomesenteric artery to displace it. Those are the conditions seen by Ravn (1894) in the rat and mouse, and I can report an almost similar phenomenon in early embryos of the pig. Here injections show that there exists for a time (7.5 to 9 mm.) a strong arterial route for the omphalomesenteric artery which arises from the a. umbilicalis and courses cranially to join the former vessel. These phenomena were quite unintelligible before we were aware, as we now are, that the entire vitelline-umbilical complex of vessels is originally one and the same system.

[57] Broman has explained this caudal "migration" of the umbilical arteries by the successive development of "wandering" roots by virtue of which the artery acquires lower and lower connections with the aorta. As evidence of this he points to the double-rooted condition in which the artery may be found. This coincides with his explanation for the descent of the gut arteries. It is to be pointed out that many embryos do not show these multiple roots, and the appearance, even when found, is possibly merely an instance of inselbildungen. Disproportionate growth of the two aortic walls may again be responsible for this dislocation, or we may have to do with an actual active caudal migration of an individual trunk.

Felix's Fig. 449, drawn from the Keibel embryo. In the embryo of 7 mm. (N.T. 28) only the secondary root is found, and the vessels are at their permanent location (at or slightly below the level of the fourth lumbar dorsal segmentals).[58] In embryos of this age, then, the strong umbilical arteries are found giving off, shortly after their origin from the aorta, a distinct branch, which courses somewhat downward and outward to the posterior limb, where it goes over into a capillary plexus. This is the primary artery of the limb, the *a. ischiadica,* and, while originally reaching the limb

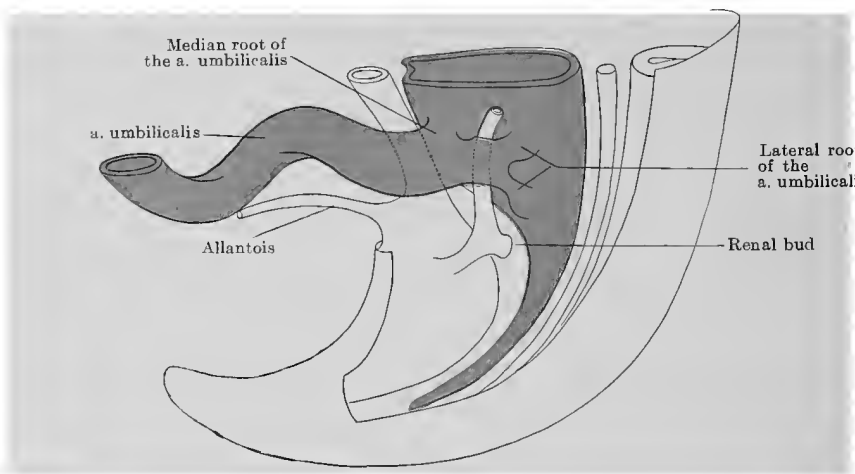

FIG. 449.—Reconstruction of the a. umbilicalis in a human embryo 5.3 mm. long. (Collection of Professor Keibel, No. 1420.) The umbilical artery is seen to arise from the aorta by three roots, a visceral and two parietal. (After Felix, 1910.)

tissue without piercing the lumbar-sacral nerve plexus, at length the ventral growth of the latter makes this necessary in embryos of 9½ mm. (Elze, 1907).

Soon there also arises, from the upper side of the umbilical artery, the second vessel to the limb, *a. femoralis,* and we may now designate the umbilical trunk from the aorta to the femoral branch, the *common iliac,* for what is at first merely a femoral soon gives off the a. epigastrica inferior and other branches and consequently

[58] According to the investigations of Hochstetter (1911), they have, indeed, wandered to a position farther caudalward than that in which they are normally found in the adult, for in embryos of this age (6.5 to 10 mm.) the fifth lumbar arteries still usually arise from the division place of the aorta, whereas in later embryos, as in the adult, the aortic bifurcation is "pushed up" to lie opposite the fourth lumbar vessels, so that the aa. lumbales V can no longer be found coming from the aorta directly but are given off by the a. sacralis media. The latter vessel appears to wander cranialward independently, and so comes to arise from the dorsal wall of the aorta rather than at its exact division place; it may even be found giving rise to the aa. lumbales IV.

comes to be the *a. iliaca externa* of the adult. The remainder of the umbilical trunk together with its a. ischiadica constitutes the definitive *a. hypogastrica.* Now the ischiadica is soon not merely that vessel, for in the 15.5 mm. embryo it gives off a prominent *a. pudenda interna* (Fig. 447). The root portion of the ischiadica from umbilical to this division place is consequently probably the great anterior division of the a. hypogastrica in the adult, and after the origin of the internal pudic comes to be the *a. glutea inferior* before at last the a. comes nervi ischiadici is reached. We are still without any series of observations on the development of the pelvic vessels.

EXTREMITY VESSELS.

For no portion of the vascular system do we stand in such need of a series of well-verified observations as we do in the case of the embryology of the extremity vessels. This field is of profound interest, too, from two stand-points: first, because the developmental history ought to furnish us with a key for the explanation of the many anomalies which the limb vessels show and which have formed the basis for classic studies on the variation of the vascular system (*e.g.,* Baader 1866, Ruge 1883, etc.); and, secondly, because enough has already been learned to indicate that the first arterial tree in the limb recapitulates in a striking way the simpler conditions which are definitive for some of the lower vertebrates (Zuckerkandl, 1894). The subject gains added interest also from another aspect, for from a closer study of the extremity vessels, Müller (1903) and De Vriese (1902) in recent years have been led to advocate the idea of a capillary plexus ancestry for vascular trunks, in contrast to notions which had previously prevailed. Subsequent research has confirmed this general idea, extending it in some places and restricting it in others, as has already been mentioned. However our exact knowledge of the development of the subclavian tree is still scanty, and there is an even greater dearth of observations in the case of the lower limb.

Arm.—The earliest channels of an arterial source into the anterior limb buds are doubtless capillaries which arise directly from the lateral aortic wall at many points and anastomose profusely in the early limb tissue.

This stage has yet to be described for man, but may be shown clearly by injections of embryos of the chick and duck (Fig. 391). That it also obtains in the mammalia has been recently indicated by the reconstructions made by Göppert (1908) for the early subclavians in white mice (Fig. 450). Thus, as many as eleven of these earliest subclavians have been seen in the birds and five in the mammalia (Göppert). The capillary plexus which is formed by the anastomoses and further extension of these delicate vessels into the tissue of the limb is uniformly distributed in the blastema of the latter, save in a definite marginal

zone which constitutes a narrow non-vascular shell of mesenchyma lying beneath the ectoderm. The plexus is drained into the posterior cardinal and umbilical veins through a series of small venules, and later, after the survival of only a single subclavian artery, the well-known marginal vein of Hochstetter is established.

Very soon after the outgrowth of these early multiple subclavians, changes occur which involve a disappearance of those vessels not arising at intersegmental points, so that the arrangement retained consists of two or more subclavian arteries which are located exactly opposite the dorsal segmental vessels in this neighborhood and are hence "segmental subclavians." In the mammalia, including man, one of these segmental subclavians is always opposite the seventh cervical dorsal segmental vessel (according to Hochstetter's method of counting, the sixth), and others

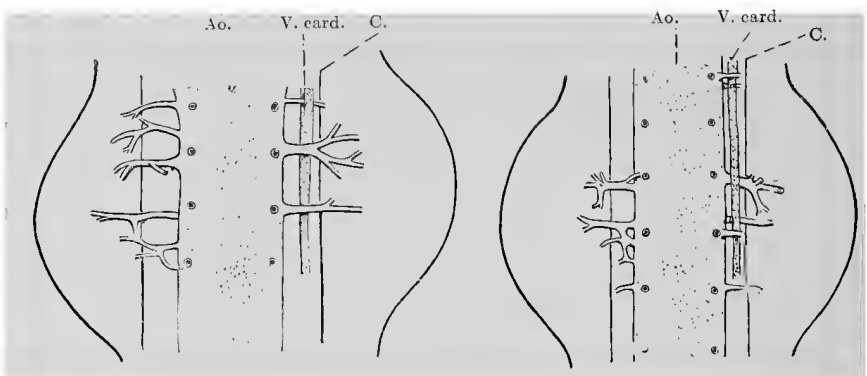

FIG. 450.—Reconstructions of the arterial system in the arm buds of embryos of the white mouse, 8 days old. (After Göppert, Verh. d. anat. Gessell., Vers. 22, Anat. Anz., 1908, p. 94, Figs. 1a and 1b.)

may have persisted at segmental points above or below this.[59] Very soon after the establishment of strictly segmental subclavians, these vessels are incorporated in common stems of origin with the dorsal segmental vessels, so that they no longer appear as direct lateral derivatives of the aorta, as was the case earlier, but become strong side branches of the dorsal segmentals.

All the stages just mentioned, however, are passed over by the time the human embryo attains a length of five millimetres, for at this stage only a single member of the early subclavian series remains to constitute the definitive subclavian artery, the vessel of

[59] Thus, three segmental subclavians have been seen in the rabbit and mouse, and several cases of two segmental subclavians reported for man. The human embryos 16 and 17 of the N. T. possess subclavians from the sixth and seventh segments. Embryo 148 in Mall's collection has segmental subclavians from the seventh cervical and first thoracic segments. These observations show the possibility of four segmental subclavians in man,—*i.e.*, from the last three cervical and first thoracic segments.

the seventh segment. It forms now the sole supply of the capillary plexus formerly nourished by multiple vessels and, after a short course to the root of the extremity, is soon resolved into a "spray" of many capillaries. As Müller (1903) has shown, the main stem of the artery at this stage, while tending to be a fairly strong trunk, centrally located, often shows island-formations in its course, and eventually, before the true capillaries arise, becomes quite plexiform in character (Fig. 451).[60]

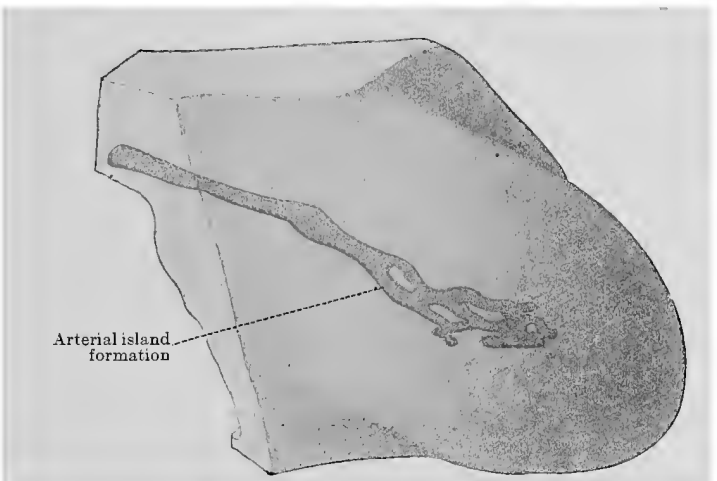

FIG. 451.—Arm bud of a human embryo 5 mm. long, showing central arterial net. (After Müller, Anat. Hefte, Bd. 22, Taf. 25–26, Fig. 1.)

In the next stage which has been described, that of a 7 mm. embryo in the excellent study by Elze, but little change has occurred. No inselbildungen happen to occur into the proximal course of the artery, nor, apparently, is there any plexiform condition of the artery before the capillaries are given off.

In an embryo of 8 mm. Müller found the subclavian giving off a branch just before the ventral nerve mass was penetrated; this branch continued for a short distance still medial to the ventral nerve, eventually plunging obliquely through the latter and joining the main stem, which has kept along the lateral side of the nerve; from this arterial loop, the main stem continues along the lateral

[60] Within the tissues of the limb, then, the central arterial channel is not everywhere in the form of a single tube, but is rather constituted by an axial arterial plexus from which the capillaries are given off. The same character for this central nourishing channel of the early limb can be demonstrated by injections of the vessels in other mammalian embryos, and may be correctly taken to indicate that for a time the arterial current employs several instead of a single channel out of many available channels open to it by reason of the pre-existing general capillary mesh.

side of the nerve, and other fine vessels are given off to course just ventral to the dorsal nerve mass of the limb, as well as ventral to the ventral nerve.

This is evidently the condition occurring still in the 9.5 mm. embryo which Elze (1907) has carefully reconstructed, although the branch of the subclavian given off to continue mediálly along the ventral nerve does not anastomose with the main vessel, which, as in the previous stage, continues along the lateral side of the ventral mass, especially along the m. medianus; a more dorsally directed branch can be followed along the radial nerve (Figs. 452 and 453).

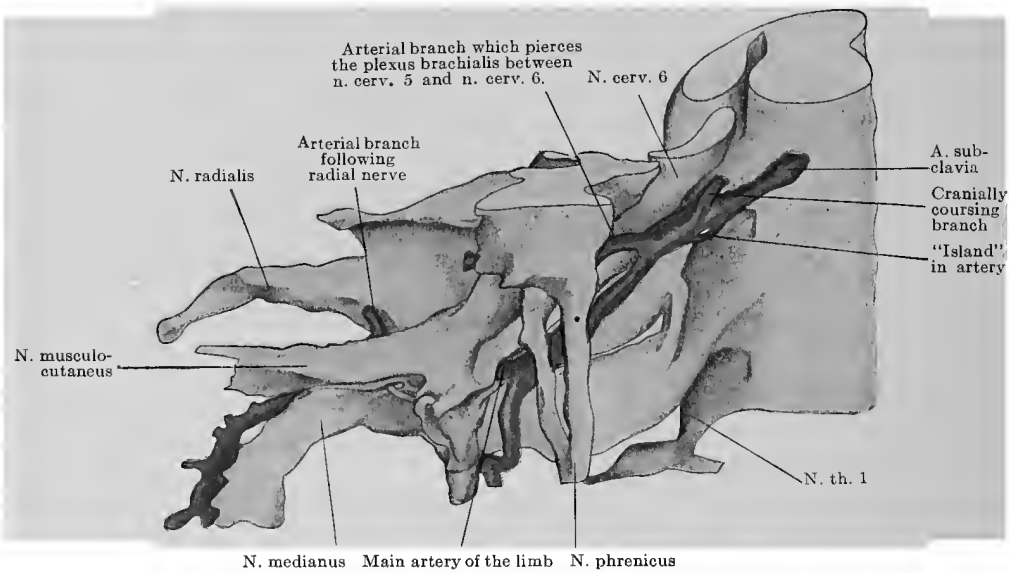

FIG. 452.—Reconstruction of the arteries and nerves of the right arm of a human embryo 9.5 mm. long, viewed ventrally. (After Elze, Anat. Hefte, Bd. 35, Taf. 17–18, Fig. 3.)

Some years ago Leboucq (1893) reported that in human embryos of about this age (7 to 11 mm.) the primary vessel of the limb coursed in the forearm between the anlagen of the radius and ulna, and represented the a. interossea volaris. Zuckerkandl had been led to expect this fact by comparative-anatomical studies which indicated that the interossea volaris was the oldest trunk in the lower arm, as well as by embryological observations on other mammalian embryos. His studies, constituting the first researches on the development of these vessels, remain of fundamental value.

Comparative.—Zuckerkandl (1894) thus described the condition of the vessels in the fore limb of rabbit embryos 8.9 mm. long, in which the skeleton was just indicated by mesodermal thickenings. The brachial artery, after accompanying the median nerve in a typical way in the upper arm, is continued in the

forearm as a stem lying next the skeletal anlagen, covered by the flexor pre-muscle mass. Just below the elbow, the artery gives off a branch which goes through to the dorsal side of the forearm (a. interossea dorsalis). As the main artery continues to go distally, the median nerve turns away from it to become superficial, leaving its internal interosseus branch to accompany the axial vessel, which may thus now be called the a. interossea volaris. As the main part of the median nerve leaves the stem artery it is supplied by the latter with an accompaniment of fine vessels which continue with it along its entire superficial course to the palm, where they constitute a superficial palmar plexus. The axial artery itself divides at the distal end of the forearm into a ramus volaris, which breaks up to constitute a delicate deep volar plexus next the skeletal anlagen, and a strong ramus dorsalis which supplies the back of the hand. In rabbits somewhat older the fine vessels

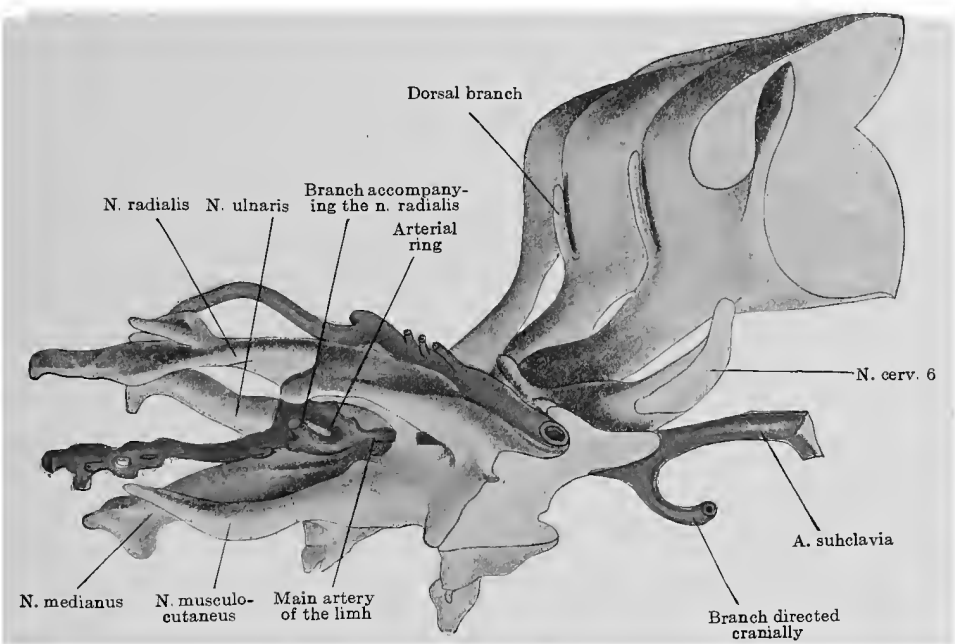

FIG. 453.—Vessels and nerves of the same arm (Fig. 452) shown from above. (After Elze, Anat. Hefte, Bd. 35, Taf. 17–18, Fig. 4.)

along the main median nerve constitute an artery large enough to begin to dispute the field with the interossea volaris, the a. mediana, while the ulnar nerve has a small accompanying vessel, a. ulnaris. Essentially the same conditions are shown in an 11 mm. cat embryo.

De Vriese has found that in the human embryo of 10 mm. the chief nerve trunks are all accompanied by capillary vessels,[61] and has chosen to represent these as already constituting arterial

[61] Injected mammalian embryos show that this is partially true, although the poor material with which De Vriese worked has justly led to the conviction that perineural spaces were confused with true capillaries, a fact which the illustrations accompanying her research leads us to suppose.

pathways. It is doubtful whether these should all be given the valuation which she has set on them, and it must be left to future research to modify or confirm the conception of an already quite complicated arterial system which her description gives us.

The author recognizes at this early stage the a. n. interossea dorsalis, a. n. radialis, a. n. ulnaris, a. n. mediani, and a. n. interossea volaris, the last of which constitutes the continuation of the axial stem and divides just above the carpus into dorsal and palmar branches, which are themselves in communication by means of a small a. perforans carpi. Four vascular planes are distinguished in the hand, two palmar and two dorsal.

In an embryo measuring 11.7 mm. Müller has reconstructed the chief arterial system of the limb, and, inasmuch as the nerves and the anlagen of the humerus, radius, and ulna were evident, homologized the vessels present with those occurring in the adult (Fig. 454).

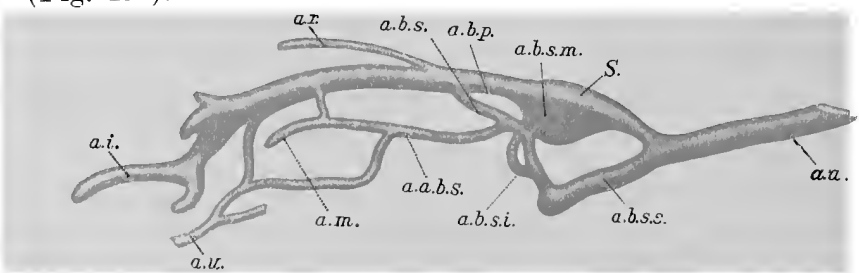

FIG. 454.—Reconstruction of the arteria system of the arm in a human embryo 11.7 mm. long. After Müller, Anat. Hefte, Bd. 22, Taf. 25–26, Fig. 9.) *a.a.*, a. axillaris; *a.b.s.s.*, a. brachialis superficialis superior; *a.b.s.m.*, a. brachialis superficialis media; *a.b.s.i.*, a. brachialis superficialis inferior; *S.*, widening of the arterial tube after it has passed through the ventral plexus plate; *a.b.s.*, distal part of the a. brachialis superficialis; *a.b.p.*, a. brachialis profunda; *a.r.*, a. radialis; *a.i.*, a. interossea; *a.m.*, a. mediana; *a.u.*, a. ulnaris; *a.a.b.s.*, a. antibrachii superficialis.

The subclavian perforates the brachial plexus in the usual manner from its ventral side, but the strong branch which, as in previous stages, is given off just before the penetration of the plexus to continue on the medial side of the latter, sends an anastomosing branch through the ventral nerves to join the main vessel. This anastomosing branch joins the main stem at or near the origin of the radial artery from the latter, and on its course toward the chief trunk splits into other branches, as the figure shows. Two of these branches also run into the main trunk, one by piercing the median nerve, the other by going under the same, while another branch courses along volar to the median to anastomose eventually with the median artery branch of the main stem again. In the other limb of the same embryo three strong perforating branches join the part of the main artery medial to the ventral nerve mass with the stem lying lateral to the same. So that in both limbs we are dealing with a rather plexiform condition of the axillary artery.[62]

[62] Great interest attaches to the arterial plexus formed by the three vessels which penetrate the brachial plexus in this embryo, for it again indicates the employment by the arterial stream of several rather than a single channel from the pre-existing capillary plexus. This transitory plexus axillaris arteriosus of Müller has also been seen in other mammals (Göppert in the mouse). It by no

The main vessel pursues a general course along the radial border of the median nerve to become in the forearm the *a. interossea volaris*. In its upper-arm portion it gives off, in addition to the *a. mediana*, a small vessel which joins a chain of capillaries lying in front of the radius anlage (identified by Müller as the *a. radialis*). Another branch of the main stem joins correspondingly small vessels lying along the ulnar nerve, and constitutes the a. ulnaris.

In his embryos of 14 mm. Müller has identified the a. profunda brachii, the a. mediana, a. interossea vol., a. radialis, and a. ulnaris.[63] The main vessels in a 16.2 mm. embryo may be seen at a glance from Fig. 455, in which the lower-arm and hand areas have been omitted.

Mention has already been made of the fact that if, for example, the point of union of the sixth aortic arch with the aorta dorsalis be taken as a fixed point, the subclavian artery appears to wander upward. Whereas in the embryo of 4.9 mm. the a. subclavia is some eight segmental spaces below this point, in the embryo of 7 mm. it is but six spaces below it, and in the embryo of 11½ mm. it is opposite the sixth arch.

The a. mammaria interna and the a. thyreo-cervicalis are conspicuous stems in the embryo of 15.5 mm. (Fig. 447). The a. thyreo-cervicalis courses for some distance in the wall of the jugular lymph-sac in this embryo, and, as McClure has observed the same thing in embryos of the cat, the relation is probably of general significance.

In reviewing the facts hitherto acquired concerning the history of the arm vessels, one must be struck with the need of more careful

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means constitutes an invariable intermediate stage in the development of the arm vessels, but, as Müller himself has shown, may occur on one side of the embryo, while the opposite axillary is composed of but a single trunk. Such phenomena may be expected to occur somewhat more frequently in the developing vascular system than in the adult, inasmuch as the increasing blood current exercises a more definite choice to the elimination of multiple paths, but that they may persist even here is shown by the occasional presence of islands in the course of adult arterial trunks.

[63] In two 14 mm. embryos Müller has found the main artery splitting into two branches which surround the median nerve and fuse again, and is consequently of the opinion that we have here a retention of the arterial paths ventral to the median nerve shown in the previous stage. That this has been the case is strengthened by the fact that the two limbs of the brachialis meet again at the place of origin of the a. radialis which is quite an exact correspondence with the place of opening of one of the anastomosing channels shown in Fig. 454. In one of these embryos the artery lying ventral to the median nerve is the larger of the two, while in an older embryo (W. P. 20.5 mm.) it is the persisting one. It seems reasonable to suppose that we are dealing here with instances of a so-called superficial brachial artery, which, as is well known, lies on the volar side of the median nerve, while the normal brachial is dorsal to the latter.

studies here.[64] The reconstructions of Müller and Elze are our sole possessions in this field. Viewed from a more general stand-point, however, the history of the arm vessels in man certainly confirms the conclusions arrived at some years ago by Zuckerkandl in his studies on the general morphology of these vessels, for *in man also the primary artery is an axial stem from shoulder to hand and in the forearm constitutes the later a. interossea volaris.* There is also a very general agreement among all observers in the important rôle played by the embryonic a. mediana.[65] However, there is as complete an agreement in the recognition that at first the volar interosseus is the chief lower-arm vessel, and no support whatever for the idea of Janosik who speaks of the mediana in that primary rôle.

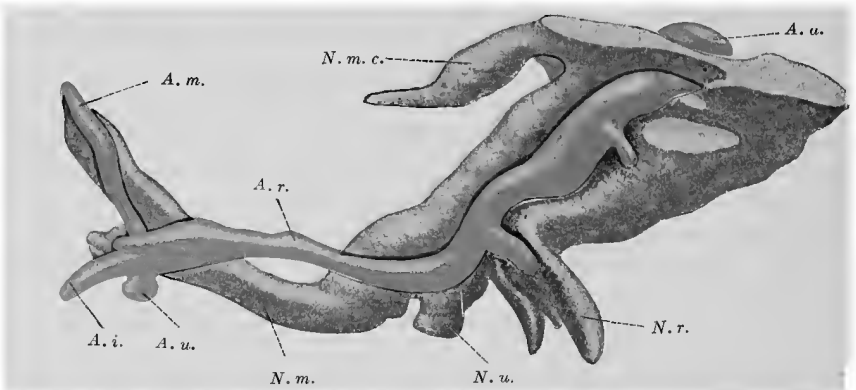

FIG. 455.—Reconstruction of the nerves and arteries of the arm in a human embryo 16 mm. long. (After Müller, Anat. Hefte, Bd. 22, Taf. 27–28, Fig. 6.) The vessel accompanying the radial nerve is the a. profunda brachii (a. nervi radialis of De Vriese). *A. a.*, a. axillaris; *A. i.*, a. interrossea; *A. m.*, a. mediana; *A. r.*, a. radialis; *A. u.*, a. ulnaris; *N. m.*, n. medianus; *N. m. c.*, n. musculocutaneus; *N. r.*, n. radialis; *N. u.*, n. ulnaris.

Comparative.—The a. interrossea volaris with a. perforans carpi is the chief vessel of the forearm in the adult in amphibia, reptilia, and in Ornithorhynchus among the mammalia (Zuckerkandl). It is also apparently the plan in the embryos of all the mammals. (Zuckerkandl, rabbit, cat; Hochstetter, Echidna; Grosser, bats; De Vriese, calf.) In very many mammals the chief definitive arterial stem is the a. mediana (marsupials, edentates, most carnivores, bats, etc.). In the primates its territory is taken over by the ulnar. A vessel accompanying the ulnar nerve, hence an a. nervi ulnaris, occurs in adult amphibia and reptiles and apparently constantly in the embryos of mammals. In the adults of the latter class the artery is not, as a rule, important and may be lacking entirely (most ungulates). A vessel which can be designated the radialis is not of general occurrence till the mammals are reached, and in the majority of these is a superficial radial. It comes to possess its deep volar territory in the higher mammals, but its proximal end is still superficial (really the superficial brachial here) in many of the primates, as Bayer has well shown.

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[64] Very recently Göppert (1910) has supplied us with the history of the development of the arteries in the arm of the white mouse, an account which is by far the most complete we possess for any mammal.

[65] The observations of De Vriese even indicate that this vessel is not finally displaced from the hand until the embryo reaches almost 30 mm. in length.

Variations.—Many of the variations of the arm vessels must remain uncertain in origin until we possess a well verified series of observations on their embryology. There can be no doubt, however, that Müller has demonstrated the manner in which a superficial brachial may arise, for arterial channels are retained on the ventral side of the median nerve in most of his specimens. It may be pointed out, also, that cases of persistence of great median or even volar interosseus arteries (Baader) are unquestionably survivals of embryonic conditions, and we may have all possible degrees of variation in the part taken by these vessels in the supply of the hand (Schwalbe and others). Krause pointed out that high origins of the radial or ulnar arteries usually involved a superficial course for the proximal part of these vessels, a fact which may be explained by the retention of a brachialis superficialis inferior. Attention may also be called to the very ingenious series of schemata which Müller has constructed to explain the lower-arm arterial anomalies, but until more is learned of the normal history here, we can not venture to present satisfactorily founded diagrams for anomalies.

Arteries of the Lower Limb.—In human embryos measuring from 5.5 to 7 mm. and shortly after the umbilical arteries have acquired their secondary, more lateral, stems of origin from the aorta in the neighborhood of the fourth or fifth lumbar segments, there can be seen going out from these vessels on either side, a small artery which penetrates the tissues of the posterior limb bud (Fig. 420). When the nerve-plate for the lower limb grows out farther, it surrounds this vessel, so that the extremity artery appears now to pass through it, just as is the history with the subclavian artery and the brachial plexus. Later the ischiadic nerve joins this vessel and it may consequently be identified as the *a. ischiadica.*[66]

Probably injections of earliest stages here would show that the a. ischiadica is really only the exaggerated member of a series of vessels, which originally supply the limb tissue, as is the case with the upper limbs.

This vessel (a. ischiadica) forms a central or axial nourishing channel for the early leg bud, just as is the case with the subclavian and early arm bud. Leboucq (1893) first called attention to the fact that the primitive blood supply of the hind limb consisted in a single axially-coursing artery, the a. ischiadica, which, as soon as skeletal elements could be recognized, continued to course in the lower-leg region between the anlagen of tibia and fibula, and ended chiefly as a strong branch which perforated the interspace between the elements of the first tarsal row, to reach the dorsum of the foot. Lately De Vriese[67] has confirmed this.

[66] It is to be noted that in mammalian embryos, where the history of the leg vessels has been followed more carefully, the a. ischiadica is primarily a branch of the aorta, and its proximal portion serves later as the stem of origin for the umbilical artery when the latter abandons its ventral roots (Hochstetter, 1890). The origin of the a. ischiadica from the aorta has not yet been observed in man.

[67] De Vriese has considered the history of the leg vessels in man. I will not, however, detail her account, for reasons given above in the account of the arm vessels.

It may be well to refer here to the important previous observations of Zuckerkandl (1894-95), who described the leg arteries in a rabbit embryo of 7.7 mm. somewhat as follows: The a. ischiadica is continued in the lower leg as a strong axial vessel next to the skeleton. It sends two perforating branches towards the side of the limb, the upper of which probably corresponds to the a. tibialis ant., while the lower supplies the dorsum of the foot. The distal end of the axial vessel supplies the depths of the sole. Fine vessels accompany the posterior tibial nerve in its lower course, and in embryos of 13.5 mm. these constitute a distinct artery, a branch of the axial vessel. The further history in this animal disclosed the a. saphena (from the a. femoralis) taking over the posterior tibial trunk.

The supremacy of the a. ischiadica in the supply of the extremity is soon disputed by the appearance of a new vessel, the a. femoralis, which in the embryo of 15.5 mm. (Fig. 447) is already the chief vessel in the limb. The femoral soon gains all the branches of the a. ischiadica in the territory of the lower leg (*e.g.*, tibialis posterior et anterior), by anastomosing with the ischiadica near the knee; we know the a. ischiadica of the adult only as the stem portion of the a. glutea inferior.[68]

This ontogenetic history of primary and secondary vessels for the human leg is closely paralleled by the vessels found in an ascending vertebrate series, as Zuckerkandl showed.

Comparative.—The a. ischiadica is the chief vessel of the thigh in the adult for amphibia, reptilia, and the birds, yet the femoral in the latter class may attain quite an area of distribution, and in some (*e.g.*, Spheniscus) even behaves as in mammals by taking over the chief rami of the a. ischiadica and constituting the chief limb vessel (Hochstetter). On the other hand, among the mammalia the atrophy of the ischiadica is the rule. Yet it may persist in part, as, for example, forming the a. tibialis anterior of bats (Grosser, 1901).

The appearance of an a. ischiadica in the embryos of all mammals was indicated by the observations of Hochstetter and Zuckerkandl. The chief lower-leg portion of the a. ischiadica in adults in the amphibia, reptiles, and birds behaves exactly as it does in the early stages of the embryo of man, namely, courses between the tibia and fibula and supplies the dorsum of the foot by means of a large perforans tarsi. Other stages in the ontogeny of man's leg vessels are found definitive in various mammals, *e.g.*, the stage in which a distinct superficial plantar arch or plexus exists, as well as a deep one. This is the case in most apes, as Popowsky has shown, and is lost in the anthropoids, where, as in man, the lateral plantar artery is larger than the medial and the deep plexus practically the only one present.

Much interest attaches to the *saphenous artery.* The earlier work of Zuckerkandl emphasized the very general occurrence of this vessel in all the mammalia,[69] and led him to declare it the oldest (phylogenetically speaking) branch of the

[68] According to Hochstetter's (1891) investigations on mammals the a. comes n. ischiadici does not appear to be a relic of the old ischiadica, although this assumption is made by most authors. De Vriese describes the lower leg portion of the original axial artery (a. n. interossei cruris) as becoming the a. peronea of the adult, giving over all of its important branches in the territory of the foot to the a. tibialis anterior.

[69] With the exception of Bradypus bidactylus, Lemur catta, and man, in which it is much atrophied.

femoral. In its lower portion this artery usually takes over the dorsalis pedis artery, or the primary tibialis posterior, or both, in which latter case it constitutes the chief or only vessel for the supply of the foot. The vessel retains its importance in the primates,—*e.g.,* in Cebus, where it supplies the entire foot. Popowsky has recalled the anomalous occurrence of this vessel in man and reported two interesting cases in which the a. saphena was large, in both cases anastomosing with the posterior tibial artery and in one case in addition with the dorsalis pedis. He has again called attention to the frequent great development of this vessel in the monkeys, where, even in the anthropoids, it supplies the dorsalis pedis. Popowsky, evidently much influenced by this, states his belief that this vessel must play a prominent rôle in the development of the leg arteries of man. There is no evidence, however, that such is the case. The work of De Vriese indicates there is apparently no necessity for the recapitulation of a stage in which the saphenous functions as the chief artery of the lower leg. In the reworking of this field, nevertheless, great interest will attach to the re-examination of the embryonic importance of this vessel, for the reasons above given.

Variations.—Dubrueil, Krause, Ruge and others have described cases in which the a. ischiadica was the chief vessel of the limb in man, which is quite evidently a survival of embryonic conditions. The occurrence of an a. saphena magna, following the saphenous nerve, has already been mentioned, the first case having been observed by Zagorsky in 1809. Normally this vessel probably reaches the lower third of the leg, for in well-injected subjects I have traced it this far, as Hyrtl first did. Krause and more recently Salvi report cases where an artery accompanies the n. cutan. suræ lat. This corresponds to an embryonic vessel seen by De Vriese at the peroneal side of the leg in the 13 mm. embryo, but it usually disappears entirely. Cases in which the a. peronæa instead of the tibialis ant. supplies the dorsum of the foot are not rare, and represent again the embryonic picture where the axial artery behaves normally thus. Most interesting are cases in which a perforans tarsi persists, joining the dorsalis pedis with the deep plantar vessels. In the adult also a superficial plantar arch occasionally occurs, as Krause, Gegenbaur and others mention.

D. The Development of the Veins.

1. The venous types.
2. The ground-plan of the young venous system.
3. Transformations of the vv. umbilicales et vitellinæ.
4. Transformations of the vv. cardinales anteriores.
5. Transformations of the vv. cardinales posteriores.
6. The development of the veins of the body walls.
7. The development of the veins of the extremities.

1. THE VENOUS TYPES.

In the adult, as has been recognized for a long time, the veins tend everywhere to follow the arteries,—*i.e.,* the majority of the veins are vv. comites. In the embryo, however, it is possible to satisfy one's self that this is not the primary arrangement, for, if one studies carefully the developing vessels in any area, it will be seen that the earliest arterial and venous trunks are separated from one another so as to stand in reciprocal relation as regards the general capillary bed. Should this primary separation of

arteries and veins be perpetuated as the vascular trunks continue to grow, we have the plan which obtains, for instance, in the circulation of the brain or lung, where larger arterial and venous vessels instead of coursing together are arranged so as to stand opposite one another. As a rule, however, as development proceeds the main vascular stems are found coursing together,—*i.e.*, the veins are true vv. comites. *We have to recognize, then, two types of veins, primary and secondary veins,* primary veins standing opposite or alternating with the arteries and trunks, secondary ones coursing in company with the corresponding arteries.[70] Venæ comites, which are, then, always later formations, may arise either as a result of shifting of primary trunks in growth or entirely *de novo*.[71] Splendid examples of the persistence of primary veins are furnished by the great subcutaneous veins of the limbs and trunk (v. basilica, v. saphena, v. thoraco-epigastrica). These are in fact remains of the early border veins of the extremities and of very early body wall trunks and it may hence appear more reasonable why they possess no corresponding accompanying arteries.

2. THE GROUND PLAN OF THE YOUNG VENOUS SYSTEM.

If now one turns to the details of the developing venous system in man, it will be recalled that the remarkable precocious development of the chorionic circulation gives us the *vv. umbilicales* at stages much earlier than obtain in the mammalia generally. In embryos of 6 somites (N.T. 3) we can also trace clearly the *vv. vitellinæ* and it can be seen that in their terminal portions the umbilical veins join the heart by receiving the vitelline veins and coursing now as a common *vitello-umbilical trunk*.[72] At the margins of the anterior intestinal portal, this vessel turns inward, courses in the mesial wall of the pleuropericardial passage, and in the mesodermic tissue ventral to the foregut anastomoses with its fellow of the opposite side to constitute the sinus venosus. The latter is at first situated in front of the first somite (Mall embryo 391, with seven somites), but in the fifteen somite embryo (Graf Spee No. 52) is opposite the body of the first somite, and in the twenty-three somite embryo (N.T. 7) is opposite that of the sixth (Thompson, 1908). In this last stage there open into the sinus

[70] Even though their peripheral portions, of course, always exhibit a primary separation from the arteries.

[71] The primary circulation schema and the secondary birth of venæ comites may be seen beautifully in such an expanded flat area as the area vasculosa of the chick (cf. Popoff), but no less clearly, for example, in the extremities, where the primary border vein drains all the blood from the central artery, whereas secondarily venæ comites arise (Hochstetter, 1891).

[72] This common vitello-umbilical vein of man corresponds really to the end portion of the vitelline veins of other early mammalian embryos in which always umbilical veins secondarily appear later (*e.g.*, rabbits).

the anterior and posterior cardinal veins by means of a ductus Cuvieri, but earlier, when the sinus lies more cranialward, the anterior cardinal vein joins the common vitello-umbilical vein (embryo of fifteen somites). The intermediate stages are not known in man.

At twenty-three somites, then, we have present the four pairs of veins (the vv. cardinales anteriores et posteriores, the vv. umbilicales, and the vv. vitellinæ), which form an entirely symmetrical venous ground-plan, characteristic not only for man but for all the vertebrates. This ground-plan of the venous system remains in embryos which are approximately a centimetre long, and its existence in man has been known to us since the classical descriptions of His (1880 to 1885).

It will be convenient to study the development of the adult venous tree as a modification of each of these primitive systems. The proximal ends of the umbilical and vitelline veins enter into special relations with one another in the region of the liver, and with the further growth of the liver bud are converted into the two venous trees of that organ, the vv. hepaticæ and vv. portæ. On account of the early inauguration of these changes, they may be described first.

3. THE TRANSFORMATION OF THE UMBILICAL AND VITELLINE VEINS.

Mention has already been made of the fact that the vitelline veins are first interrupted in their course to the sinus venosus by the growth of the liver bud, which in embryos from three millimetres on in length, begins to cause the interposition of many smaller vessels (sinusoids of Minot) in the venous current through the liver. The early stages in this process can be seen in the figures supplied us by His (Figs. 425 and 426), where both vitellines have as yet a fairly direct path through the liver region and open on either side into the sinus venosus. Very soon, however, the left v. omphalomesenterica is more effectively cut up into nourishing liver capillaries (sinusoids), although these still drain into the left horn of the sinus venosus by way of the old opening there of the original vein, which hence constitutes a primitive v. hepatica sinistra (Fig. 456).

This persists as late as in embryos of 7 mm. (Elze).

The umbilical veins next gain connections with the liver sinusoids and eventually lose completely their early superficial course in the region between liver and heart, a fact first noted by H. Rathke (1838).[73] The umbilical blood is now poured into the liver channels, the largest of which is the old direct path of the right omphalomesenteric to the corresponding horn of the sinus venosus. In the mean time the two vitelline veins have anastomosed with

[73] Cited after His, Anat. Mensch. Embryonen III, S. 210 (1885).

each other by cross connections, which go, first ventral, then dorsal, and again ventral, to the gut tube and so form two venous rings around the duodenum, as may be seen from Fig. 456.[74] The middle or dorsal of these anastomoses receives the vein from the intestine, the true mesenteric vein.

His pointed out that the usual fate of these venous rings involved always the atrophy of certain limbs and the persistence of others in such a way that an S-shaped course is now described

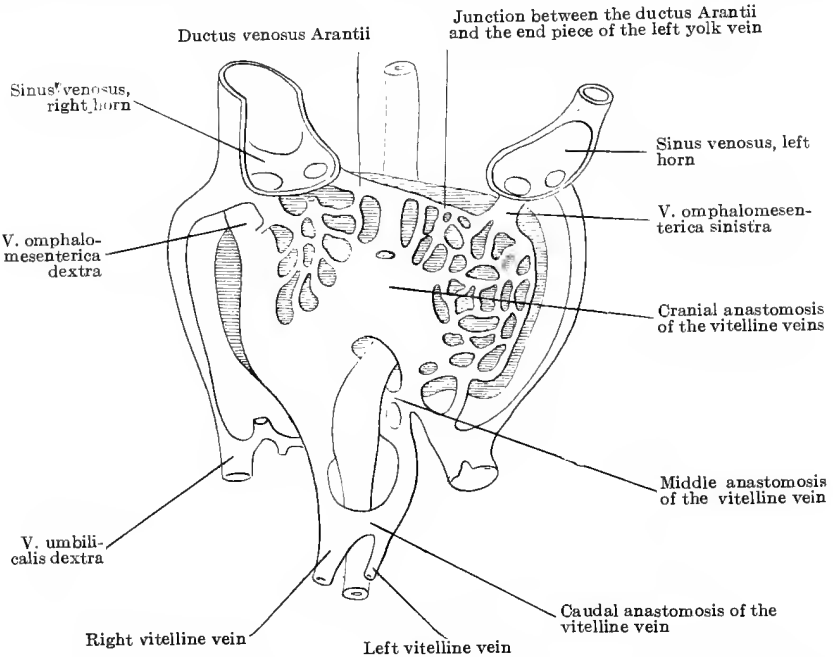

FIG. 456.—Schema of the liver circulation in a human embryo 4.9 mm. long (NT. 14). (After Ingalls, 1907.

by a common vitelline trunk in reaching the liver. It is important to note that during this time the left umbilical vein has effected a direct connection with the cranial venous ring and that the right umbilical atrophies. The right vitelline vein also disappears, so that by the time the embryo is 7 millimetres in length the main source of blood for the liver comes from the left vitelline and left umbilical veins.[75] The liver end of the former vessel is the old S-shaped common vitelline trunk, and where it becomes dorsal to the gut, consequently the place corresponding to the early dorsal venous anastomosis,—the middle one of the three,—it receives the

[74] The researches of Hochstetter make it probable that these venous rings (first seen by His in the human embryo) are of very general occurrence among the mammalia.

[75] The umbilicalis dextra still connects with the liver sinusoids in the 7 mm. embryo (Elze).

mesenteric vein. Somewhat further headward and after it has turned around the right side of the gut to become ventral to it, and at a place corresponding to the former cranial venous ring, this, now the omphalomesenteric trunk, receives the left umbilical vein. For a time the chief channel for all this blood through the liver is the intrahepatic course of the former right vitelline vein (Mall) (Fig. 458). Soon the development of an anastomosis (already indicated in Fig. 456) enables the vena hepatica sinistra to lead its blood also into the right end of the sinus venosus, near the opening of the right vitelline trunk (secondary v. hepatica sinistra), while the former multiple afferents of the left omphalo-

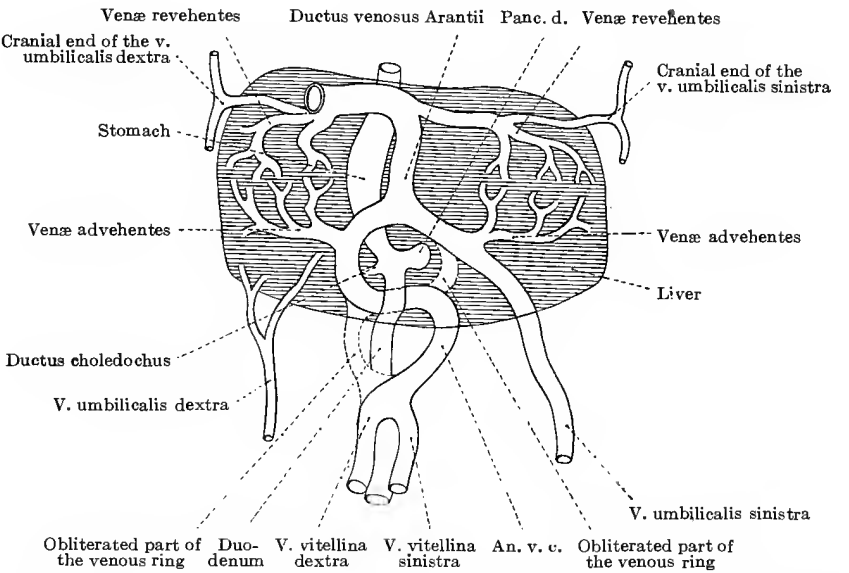

FIG. 457.—Schema of the liver circulation in the human embryo at a later stage than that shown in Fig. 456. (After His, from Marshall.) Panc. d., pancreas dorsale; An. v. c., annulus venosus caudalis.

mesenteric into the left lobe of the liver are now reduced to a single larger supplying trunk, the ramus angularis (Mall).

When, with the growth of the right lobe of the liver, the intrahepatic course of the right vitelline becomes shifted so as to constitute a somewhat circuitous route, a new direct one to the sinus venosus is formed; this is the *ductus venosus Arantii*. Mall's researches show that the former intrahepatic course of the right vitelline does not completely atrophy without a trace, but leaves representatives in the form of its end, which drains into the sinus venosus, and its first portion, which leaves the umbilical vein, for these are now incorporated as parts of the supplying (portal) and draining (hepatic) systems of the liver, and become respectively the ramus dexter venæ hepaticæ and the ramus arcuatus (et descendens) venæ portæ. At this stage, then, we have for both of

the two main divisions or lobes of the liver, portal or supplying and hepatic or draining trunks; on the left, the ramus angularis venæ portæ, the blood from which is drained into the ramus sinistra venæ hepaticæ, on the right, the ramus arcuatus of the portal vein, opposite to which stands the ramus dexter of the hepatic (Mall) Fig. 459).

In an embryo 11 mm. long two trunks have been added to both the supplying and draining systems, and four units or lobes may be described as being present. To the portal system have been added the right and left arborizations of the recessus umbilicalis (Rex, 1888), to the hepatic the ramus medius and vena cava inferior (Fig. 460). Now the middle and left hepatic veins both

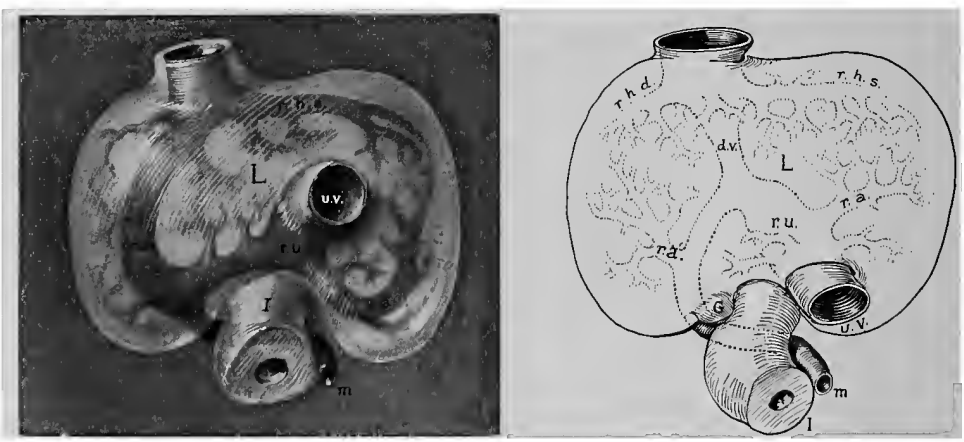

Fig. 458.—Semidiagrammatic reconstruction of the veins of the liver of a human embryo 5 mm. long, (Mall No. 80.) (After Mall, 1906.) *L.*, liver; *u. v.*, umbilical vein; *v. o. m.*, right omphalomesenteric vein; *r. h. s.*, ramus hepaticus sinister; *r. u.*, recessus umbilicalis; *r. a.*, ramus angularis; *m.*, mesenteric vein; *I.*, intestine.

Fig. 459.—Semidiagrammatic reconstruction of the veins of the liver of a human embryo 7 mm. long, (Mall No. 2.) (After Mall, 1906.) *L.*, liver; *u. v.*, umbilical vein; *m.*, mesenteric vein; *r. u.*, recessus umbilicalis; *d. v.* ductus venosus; *r. a.*, ramus arcuatus; *r. h. d.*, ramus hepaticus dexter; *r. h. s.*, ramus hepaticus sinister.

divide, and consequently by the stage of 26 millimetres we find six collecting trunks, the upper and the lower right hepatic (the latter a branch of the inferior cava), the right and left media, and the upper and lower left hepatics. Correspondingly six supplying trunks exist, for the right portal branch splits into a ramus ascendens as well as ramus dexter, and, in addition to the ramus angularis, we have also the left arborization of the recessus umbilicalis and two other prominent branches of this trunk, one of which may be identified as its right arborization (Fig. 461). Mall has pointed out that these six primary lobules of the liver correspond with the six lobes to be recognized in the morphology of the adult mammalian liver (Rex).

It has been pointed out that at the stage of 4.9 mm. the dorsal anastomosis between the vitelline veins receives the *mesenteric vein* draining the intestine. After the S-shaped common vitelline vein

is formed out of these anastomoses and after the right vitelline vein has atrophied, the left vitelline becomes the sole efferent from the yolk-sac and receives the mesenteric vein at the earlier point of union of the latter with the dorsal anastomosis. From here on to the liver then this vein is properly the omphalomesenteric vein, but in most of its course it has been free from the mesentery, crossing the cœlome independently of the latter. On the other hand, the omphalomesenteric artery, which supplies both gut and yolk-sac, courses in the mesentery. The artery is directly trans-

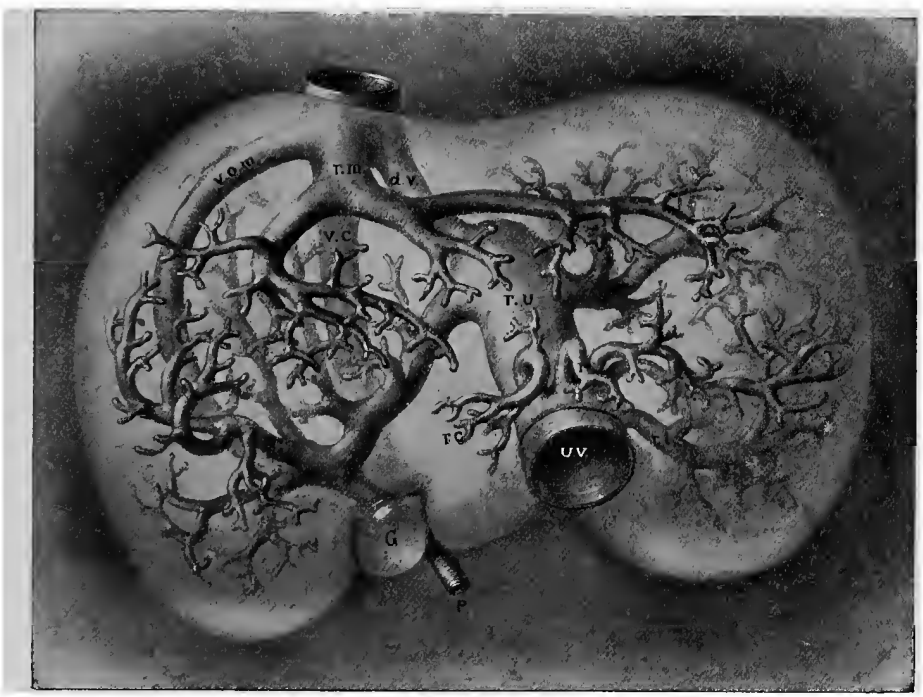

FIG. 460.—Reconstruction of the vascular system of the liver of a human embryo 11 mm. long. (Mall No. 109.) (After Mall, 1906.) *u. v.*, umbilical vein; *p. v.*, portal vein; *r. a.*, ramus angularis; *r. u.*, recessus umbilicalis; *r. d.*, ramus descendens; *r. a.*, ramus arcuatus (possibly ramus ascendens); *r. c.*, right arborization of the recessus umbilicalis; *r. l.*, left arborization of the recessus umbilicalis; *d. v.*, ductus venosus; *v. c.*, vena cava; *v. o m.*, omphalomesenteric vein; *r. m.*, ramus medius; *r. s.*, ramus sinister.

formed into the superior mesenteric artery, but its accompanying vein (v. mesenterica superior) is a secondary channel which has arisen to drain the gut wall and it alone, the yolk-sac drainage going by way of the former left vitelline vein. Only a small part of the vitelline vein is incorporated in the *vena portæ* of the adult, namely, that part proximal to where the mesenteric vein is received.[76]

[76] It was Luschka (1863) who first pointed out that the vitelline vein does not persist in the v. mesenterica superior, although this is largely true for the corresponding artery. Dexter (1902) and Lewis (1903) for the cat and pig, and Bonnot and Seevers (1906) in the case of man, have called specific attention to this fact.

4. THE TRANSFORMATION OF THE ANTERIOR CARDINAL VEINS.

The *anterior cardinal* vein suffers profound modifications, for it and its derivatives come to form the sinuses of the dura while its proximal portion constitutes the great internal jugular trunk of the adult. We have already seen that in human embryos of 15 somites the *anterior cardinal* or, better, the *primitive head vein* can be identified from the region of the fore-brain to its opening into the common vitello-umbilical vein opposite the third somite, and that it can be divided into a longer portion lying in front of the region of the somites and a shorter portion in the segmental

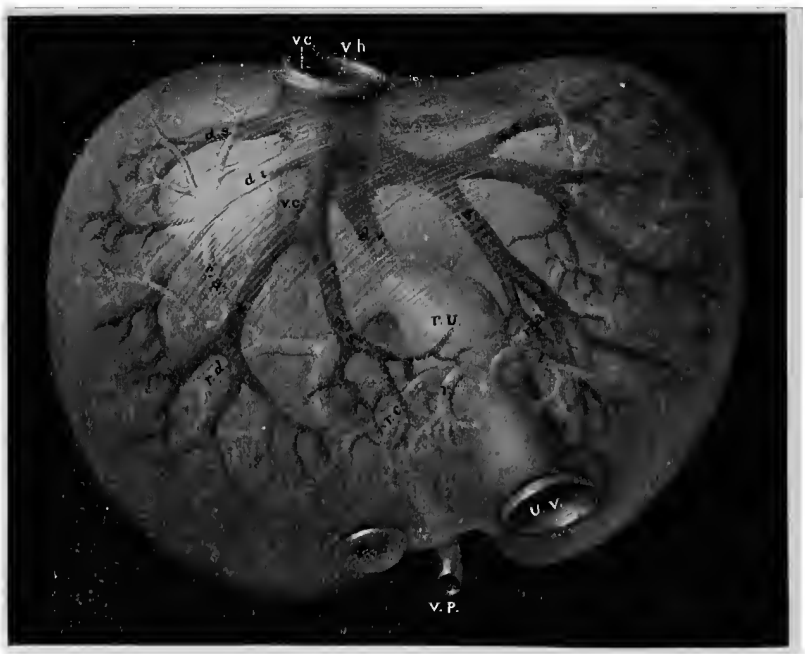

FIG. 461.—Reconstruction of the vascular system of the liver of a human embryo 24 mm. long. (Mall No. 6.) (After Mall, 1906.) *u. v.*, umbilical vein; *v. p.*, vena portæ; *r. u.*, recessus umbilicalis; *r. a.*, ramus arcuatus; *r. d.*, ramus descendens; *r. a.*, ramus angularis; *r. c.*, right arborization of the recessus umbilicalis; *r. l.*, left arborization of the recessus umbilicalis; *v. h.*, vena hepatica; *d. v.*, ductus venosus; *d. s.*, vena dextra superior; *d. i.*, vena dextra inferior; *m. d.*, vena media dextra; *m. s.*, vena media sinistra; *s. s.*, vena sinistra superior; *s. i.*, vena sinistra inferior; *v. c.*, vena cava.

area; the former portion lies close at the sides of the hind-brain and should be known as the v. capitis medialis (Grosser, 1907); the latter is situated more laterally and is the true cardinalis anterior.[77] Both portions of the primitive head vein are in fre-

[77] Grosser first separated these two portions of the primitive head vein, which occur in all vertebrates, and called attention to the fact that only the caudal part is homologous with the posterior cardinal and hence merits the name cardinalis anterior. He remarks that the cardinals are probably especially related to the segmental excretory system and that the anterior cardinal is likely evidence of the former cephalic extent of this.

quent connection with the aorta by means of numerous small direct branches, the v. capitis medialis by means of dorsal presegmental arteries, the true cardinalis anterior by means of the dorsal segmental arteries as well as by direct lateral branches of the aorta. Later all of these aortic offshoots atrophy, and the chief source of the blood drained by the primitive head vein is supplied by the a. carotis interna. When the anlagen of the cranial nerves first appear, they are found lateral to the vena capitis medialis, but in later stages, as Salzer (1895) first showed, the vein is gradually shifted lateral to the nerves by the formation of channels which course on the outer side of the latter, and the *v. capitis lateralis* thus produced gives us a secondary, wholly lateral, head vein.

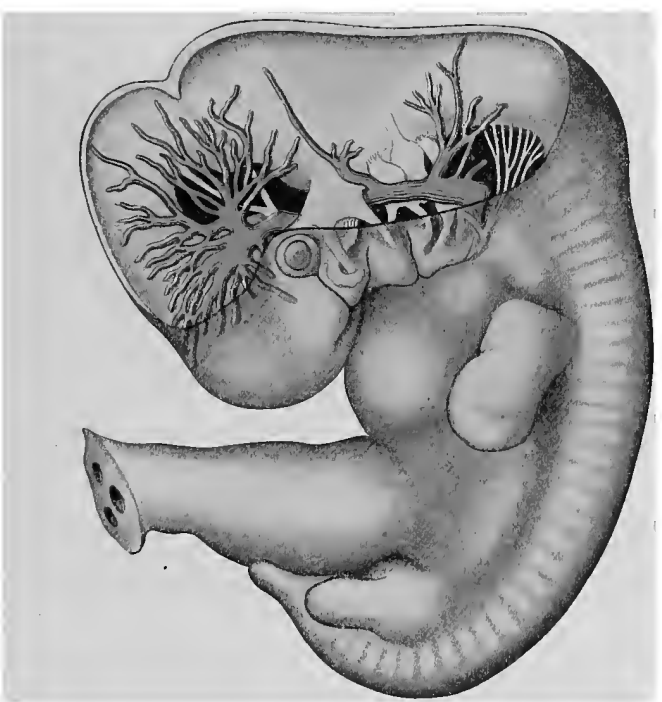

FIG. 462.—Reconstruction of the veins of the head in a human embryo 9 mm. long. (Mall No. 163.) (After Mall, 1905.)

The development of vascular sprouts which enable the medial head vein to begin to circumvent the ganglia of the cranial nerves occurs early. In embryos 3 mm. in length (Broman, NT. 11) it has shifted lateral to the acustico-facialis, the otic vesicle, and the glosso-pharyngeus. This position we saw it had retained in the embryo of 4.9 mm. (NT. 14). When the sixth nerve can be identified, it also is medial to the vein. Next the tenth nerve is surrounded by a venous ring and the lateral path around this nerve chosen, to the elimination of the medial one. Such a ring around the vagus may be seen in 7 mm. embryos (Fig. 420) or, again, may not be formed when a length of 9 mm. is reached (Fig. 462). Gradually a similar loop forms around the Gasserian ganglion (Fig. 463). From the fifth nerve caudalward to the twelfth, then, the medial head vein has become the v. capitis lateralis.

The v. capitis medialis in the region of the fifth nerve is retained to become the sinus cavernosus of the adult (Mall), but otherwise the early medial head vein leaves no trace of its existence. The v. capitis lateralis is entirely without the skull, or, more accurately, leaves the skull with the seventh nerve to empty its blood into the internal jugular vein, and so it takes no part in the formation of the permanent head sinuses, although its chief tributaries do so, as Mall has shown in the following way. At the stage of which we are speaking, the v. capitis lateralis possesses three main tributaries, the anterior, middle, and posterior cerebral veins respectively (Mall). The first of these drains the eye (v. ophthalmica) and cerebral hemispheres as well as mid-brain; its most cephalic extension courses on either side of the mid-dorsal

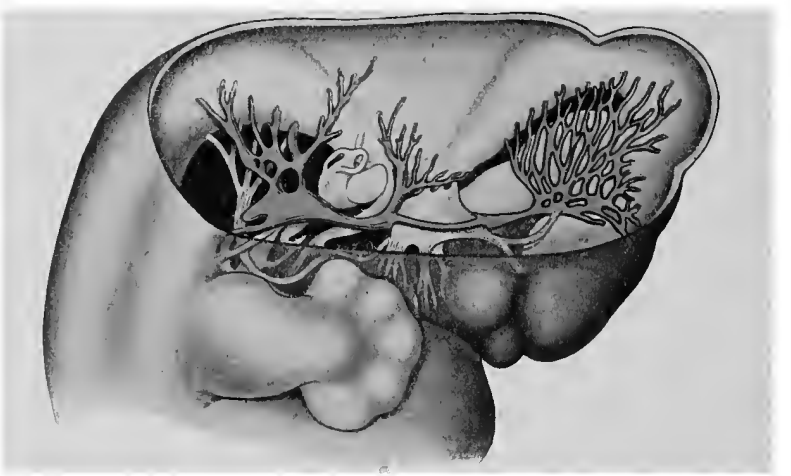

FIG. 463.—Reconstruction of the veins of the head in a human embryo 11 mm. long. (Mall No. 109.) (After Mall, 1905.)

line in the region of the fore-brain and constitutes the anlage of the *superior sagittal sinus,* thus primitively paired. The middle cerebral vein drains the anterior part of the hind-brain (cerebellum) and joins the main trunk between the fifth and seventh nerves. Since the v. capitis lateralis leaves the skull in company with the seventh nerve, it is apparent that through this foramen the venous blood of the fore-brain, mid-brain, and cerebellum is drained. The last tributary of the lateral head vein joins it behind the otic vesicle, leaving the skull through the embryonic jugular foramen (v. cerebralis posterior). This posterior cerebral vein drains the remainder of the hind-brain (medulla) and first portion of the cervical cord. As the anterior cerebral vein extends forward to the top of the cerebrum, so also the posterior cerebral reaches the mid-dorsal region of the hind-brain (Fig. 464).

Now anastomoses develop between these three primitive cerebral veins and the v. capitis lateralis atrophies, so that not only

the hind-brain blood but that of the entire brain is drained out through the foramen jugulare, and the old anterior exit with the n. facialis disappears.[78]

The anastomoses which develop between these three primitive brain veins begin the changes that convert these to the head sinuses. The blood from the sinus sagittalis superior is no longer returned by way of the anterior cerebral vein, but courses dorsally by means of a new anastomosis which links it to the upper end of the cerebralis media. Very soon, though, an anastomosis is carried still further caudally, so that the blood now enters the posterior cerebral vein, which leaves the skull through the jugular foramen. This last and most important anastomosis forms the

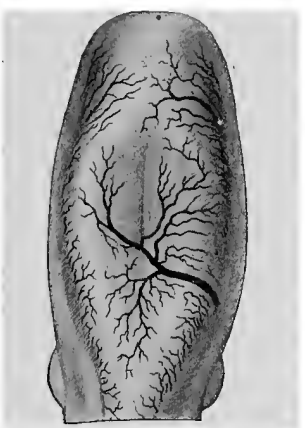

FIG. 464.—The right vena cerebralis posterior (Mall) draining the roof of the hind-brain in a human embryo 11 mm. long. (Mall No. 353.) Injection preparation. (After a sketch kindly placed at my disposal by Mr. Max Broedel.)

major portion of the *lateral sinus,* and in the fetus of 33 mm. is a large channel which has completely supplanted the old v. capitis lateralis. This great channel is gradually shifted backward in later stages by the growth of the cerebral hemispheres. The

[78] Salzer and Mall call attention to the fact that in all probability Kölliker mistook this exit of the v. capitis lateralis from the skull as a drainage of the early head by the external jugular vein, and hence thought that he had confirmed Luschka, who believed that this was the case and that only secondarily did the internal jugular drain the brain. Luschka fancied that the foramen jugulare spurium, to which he first called attention, represented this primary exit of the skull drainage. The internal jugular, however, is from the first the only vein of the brain, and this is true also after the skull begins its development. The external jugular vein is an entirely secondary channel much later to develop. It is of interest to note that Hochstetter has shown that in the adult of Echidna the blood of the anterior part of the brain is drained by the persisting part of the v. capitis lateralis, which leaves the skull with the facialis and thereafter joins the internal jugular trunk. In Ornithorhynchus also, as Hochstetter has shown, the same vein exists, but it is only supplementary here to the vein traversing the foramen jugulare.

original cerebralis media is probably incorporated to form the superior petrosal sinus, but the inferior petrosal sinus is a later formation.[79a]

The *v. jugularis externa* is a secondary venous channel which in man, as in the mammals generally, appears relatively late (embryo of 16 mm., F. T. Lewis, 1909; see also Schawlowski, 1891). We possess as yet no connected history of the vein for man.

The reader will find the mention of some stages in the development of this vein in the guinea-pig given by Salzer (1895) and in the hat by Grosser (1901).

We have seen that in early embryos the floor of the branchial region is drained on each side by a vein which originally joins the duct of Cuvier but is soon a tributary of the anterior cardinal.[79b] Lewis (1909) has traced this vein in a series of embryos, and believes it can be recognized as the *linguo-facial vein* of the adult, where it usually belongs to the external jugular trunk. Its transfer from the internal to the external jugular appears after the stage of 16 mm.

The proximal ends of what were originally the anterior cardinal veins do not continue to open into the heart separately,—*i.e.*, by means of two ducts of Cuvier, formed by the union of anterior and posterior cardinal veins on each side. Only the right opening persists, and this is possible by the development of a great anastomosis between the anterior cardinals (Fig. 478) which enables the left vein to conduct all its blood into the right one. The anastomosis becomes the v. anonyma sinistra,[80] and that portion of the right anterior cardinal between the opening of the v. anonyma sinistra and the right subclavian vein is known as the v. anonyma dextra, whereas the lower portion of the right anterior cardinal and the right ductus Cuvieri becomes the vena cava superior. The original portion of the left anterior cardinal below the transverse anastomosis becomes the end portion of the v. hemiazygos accessoria, the remainder of which is constituted by the left posterior cardinal; of the left ductus Cuvieri only the proximal portion is preserved as the sinus coronarius (Marshall, 1850).

[79a] Grosser (1907) has shown this to be homologous with the inferior jugular vein of fishes.

[79b] The reader is referred to the recent study of the development of these veins made by J. Markowski (1911). (Markowski, Ueber die Entwicklung der Sinus durae matris und der Hirnvenen bei menschlichen Embryonen von 15.5–49 mm. Scheitel-Steiss länge, Bull. de l'Acad. des Sciences de Cracovie, Juillet, 1911.)

[80] Schawlowski (1891) and Anikiew (1909), from fragmentary observations on human embryos, conclude that veins draining the thymus gland are concerned in the formation of this anastomosis (v. anonyma sinistra).

5. TRANSFORMATIONS OF THE POSTERIOR CARDINAL VEINS.

We have seen that the posterior cardinal veins form two long symmetrical drainage channels which receive dorsally segmental afferents[81] (vv. intercostales et lumbales) and ventrally many small tributaries from the Wolffian bodies, and that, when the hind limbs develop, their chief afferent—the fibular border vein—also opens into the posterior cardinal.

Gradually, now, two veins arise to assist in the drainage of the mesonephros. These are the vv. subcardinales (F. T. Lewis, 1902), and have already been noted in the preceding accounts of several embryos (*vide* pp. 604, 612). They lie on the ventral surface of the mesonephros on each side, and each of them is not only connected at either end and at many other points with the corresponding posterior cardinal vein, but also joins its fellow of the other side by means of cross anastomoses across the front of the aorta. The latter communications are soon confined to one large connection just below the origin of the a. mesenterica superior and at the level of the future vv. renales.

Although for a time the subcardinal veins can only thus be considered accessory and tributary to the posterior cardinals, the right subcardinal acquires another highly important connection headward with the vascular system of the liver (the hepatic half),[82] and it is afterward possible for a great part of the blood from the hind end of the body to stream directly into the heart by means of the common hepatic vein (v. hepatica revehens communis).[83] This connection inaugurates a profound change in the drainage of the legs and lower trunk, the end result of which is the substitution of a single large channel—the vena cava inferior—in place of the earlier multiple and symmetrical veins.

For the details of this change we are indebted mainly to the investigations of F. Hochstetter and of F. T. Lewis on the rabbit. A complete account for man,

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[81] It may again be emphasized that in the beginning the posterior cardinals receive more of the cervical segmental veins than later. These, with the exception of the first, drain into the v. cardinalis posterior, but with the descent of the heart and great vessels, the cervical veins become tributaries of the anterior cardinal.

[82] It is of interest to note that Davis (1910) has demonstrated open connections between the subcardinal veins and the portal system in early embryos of the pig, but these reach their maximum and are obliterated before the vena cava is formed.

[83] Hochstetter thus names the trunk passing from the liver to the heart and formed, as we have already seen, from parts of the hepatic, umbilical, and omphalomesenteric veins. It has been pointed out that some of the blood from the lower limbs and tail can stream through the sinusoidal vessels of the Wolffian body and join the vena cava, thus giving us a partial renal-portal system for the mesonephros of mammals. Yet in mammalian embryos we must grant Hochstetter's remarks that the characteristic renal-portal system of Sauropsida is only approached.

founded on a satisfactory series of human embryos, is still lacking. I shall accordingly content myself here with a brief presentation of the essential facts won from other mammalian embryos and of the probable history in man. This is the more justifiable also, since we possess many scattered observations, on such human material as has been at hand, by Hochstetter, Zumstein, and Kollmann, among others.

The exact manner in which the cardinal system is tapped by the hepatic was pointed out by F. T. Lewis (1902) and more recently by D. M. Davis (1910). The latter observer has shown that the capillaries on the ventral surface of the Wolffian body proliferate in a cephalic direction, fusing with capillaries which surround the œsophagus (peri-œsophageal plexus) and which course also on the

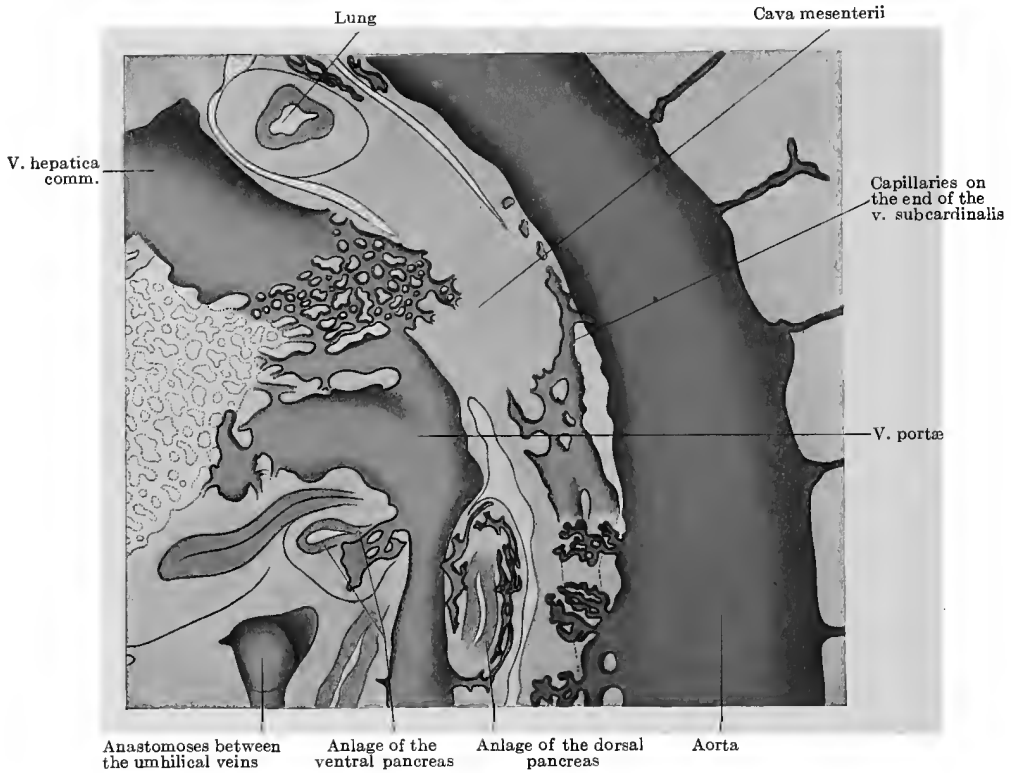

Fig. 465.—Sagittal section through a pig embryo 8 mm. long, showing the hepatic and subcardinal capillaries approaching one another to form the vena cava inferior. (After Davis, 1910.)

wall of the stomach. Thus the drainage territory of the subcardinal vein is extended headward. On the right side, beyond the anterior limit of the Wolffian body, this skirmish line of capillaries grows in the connective tissue of the caval mesentery which has also been invaded by hepatic capillaries in advance of liver cells. Soon hepatic and subcardinal capillaries meet and fuse, and for the first time a vascular path is offered from the right subcardinal to the common hepatic vein (Fig. 465). Inasmuch as both subcardinal and cardinal veins are in frequent connection, this new path diverts much of the blood stream of the lower posterior cardinal, which formerly went to Cuvier's duct, through this new channel. Thus in the posterior cardinal veins we may now be said to have two blood streams, for the current in the lower part of both veins turns ventrally into the upper right subcardinal vein by virtue of the great anastomoses between cardinals and sub-

cardinals, whereas in that part of the posterior cardinals above the level of the Wolffian bodies the blood goes upward to the ductus Cuvieri. This leads to a more or less complete separation of the two portions of the posterior cardinal vein. The upper portions of these veins are transformed into the system of the azygos and hemiazygos veins of the adult; the lower portions undergo still other changes.[84] For a while, although disturbed by the migration of the permanent kidneys,[85] they remain quite symmetrical, and so the vena cava appears double in the region below the great anastomosis above mentioned.[86] Eventually, however, only the lower segment of the right posterior cardinal persists to constitute the peripheral segment of the single adult vena cava inferior, for the left vein atrophies[87] in virtue of anastomoses between the two cardinals which enable the right channel to drain satisfactorily all the blood. The chief of these anastomoses (the transverse iliac vein) enables the blood from the left pelvic region and the left limb to drain practically entirely into the right cardinal. In this way the transverse iliac vein constitutes the terminal portion of the left common iliac, which has hence a morphological value different from the terminal part of the right v. iliacus communis.[88] Anastomoses also enable the left lumbar veins to be carried across the vertebral column to open into the right lower cardinal (cava), whereas the upper great anastomoses between the cardinals remains as the proximal part of the left adult renal vein. It is only necessary to add that the subcardinal veins below the level of the great transverse anastomoses atrophy, while that portion of the left vein above this level functions as the proximal part of the left adrenal vein. It hence goes into the renal vein (which represents in part the original great trans-anastomoses), rather than into the vena cava directly, as the right adrenal vein does.

The vena cava inferior, then, is a composite vessel, and is formed, from the liver downward, of parts of the following veins: right hepatic vein, connecting vein in the caval mesentery, right upper subcardinal vein, and right lower posterior cardinal.

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[84] These lower portions of the posterior cardinal veins persist symmetrically in some mammals and so form a vena cava which is double below the level of the vv. renales (Echidna, Edentates, Cetacea).

[85] As the anlage of the permanent kidney ascends from the pelvis to its permanent position, it appears to push in between the aorta and the posterior cardinal vein and to displace the latter ventral- and lateralward. A more direct collateral venous path is developed going dorso-medial to either the ureter or the kidney anlage, which may for a time be thus surrounded by a venous ring. (Vide Hochstetter, 1893; Zumstein, 1887 and 1890; Grosser, 1901; Lewis, 1902.)

[86] An arrangement which may persist in those well-known anomalies in which we have a double cava below the kidneys.

[87] Hochstetter states that the lower left cardinal obliterates up to the point of reception of the spermatic (ovarian) vein, and that consequently the end portion of this lower left cardinal is represented in the most proximal part of the left spermatic vein of the adult. The opinion that part of the left cardinal is represented by the ascending lumbar vein (Lewis, Bryce) is disputed by him, on the ground that the latter has a more lateral position. He assigns the origin of this vein to secondary anastomoses which establish a chain between the thoracic and iliac region. It is of interest to note that the atrophy of the left lower cardinal is not the only method by which a single adult cava is produced in the region below the kidneys. In some mammals this is attained apparently by a true fusion of the two cardinals dorsal (Ornithorhynchus) or ventral (most Marsupials) from the aorta (Hochstetter).

[88] Which is probably only the proximal part of the early v. ischiadica.

The upper portions of the posterior cardinal veins are undoubtedly concerned in the formation of the vv. azygos and hemiazygos.[89] Here again, though, we possess as yet no accounts for the embryo of man. The arrangement of the veins in question in the adult shows that normally in further growth an asymmetrical development of these two veins occurs. This, nevertheless, is not

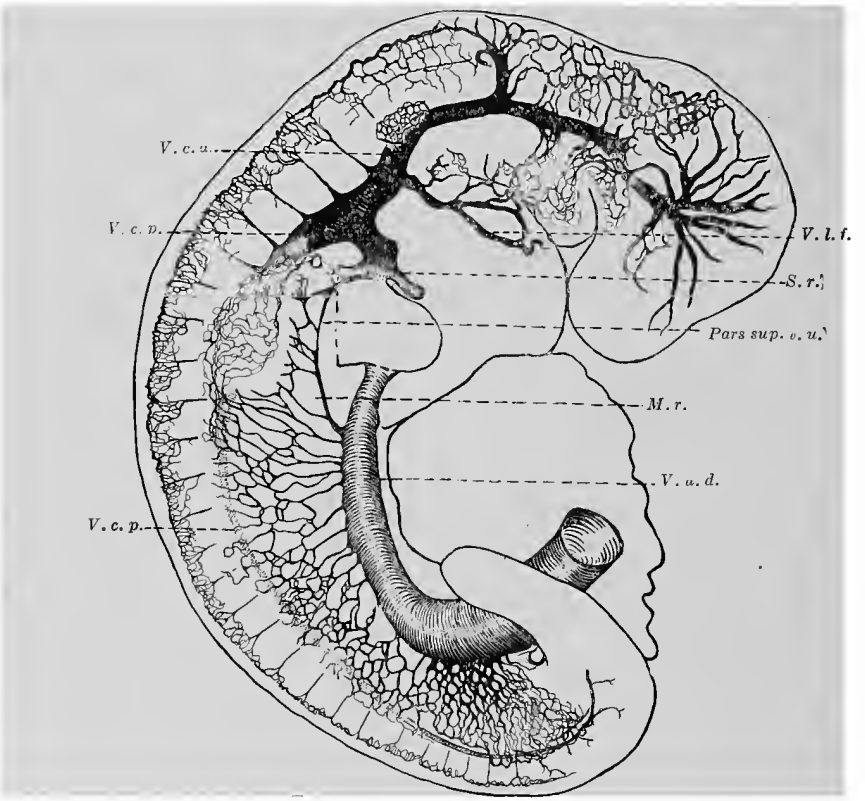

FIG. 466.—Injection of a pig embryo 8 mm. long, showing the extensive system of transverse body-wall tributaries to the umbilical vein. (After Smith, 1909.) *V. l. f.*, vena linguo-facialis; *S. r.*, sinus reuniens; *Pars sup. v. r.*, pars superior v. umbilicalis; *m. r.*, membrana reuniens; *v. u. d.*, vena umbilicalis dextra; *V. c. a.*, v. cardinalis anterior; *V. c. p.*, v. cardinalis posterior.

usually so extreme as is the case, for instance, with the rabbit, where the right vein alone persists. In man, as is well known, the left trunk is only interrupted, for, while the lower portion joins

[89] In all accounts hitherto given us, the upper portions of the original posterior cardinal veins have been described as entirely separated from their lower portions by the great deflection of the venous blood current due to the appearance of the inferior cava, and this "separation" occurs at such a level (*e.g.*, the eighth thoracic segment, rabbit) that these upper portions of the posterior cardinals must be subsequently extended to the end of the thoracic region to constitute the azygos of the adult. They are, in fact, described as actually "growing down" secondarily. Hochstetter (1903, p. 604) comments on the conditions he found in a 15.5 human embryo, in which the adrenal glands destroyed the symmetry of the posterior

the right vein (v. azygos) by means of one or more large cross anastomoses, its upper portion, the so-called v. hemiazygos accessoria, continues to Cuvier's duct.[90]

Information on the exact details of the transformations effected in these venous channels in various mammals should be sought in the papers of Hochstetter, Zumstein, Lewis, Grosser, McClure, Gosset, Parker and Tozier, Van Pée, Beddard, Soulié and Bonné.

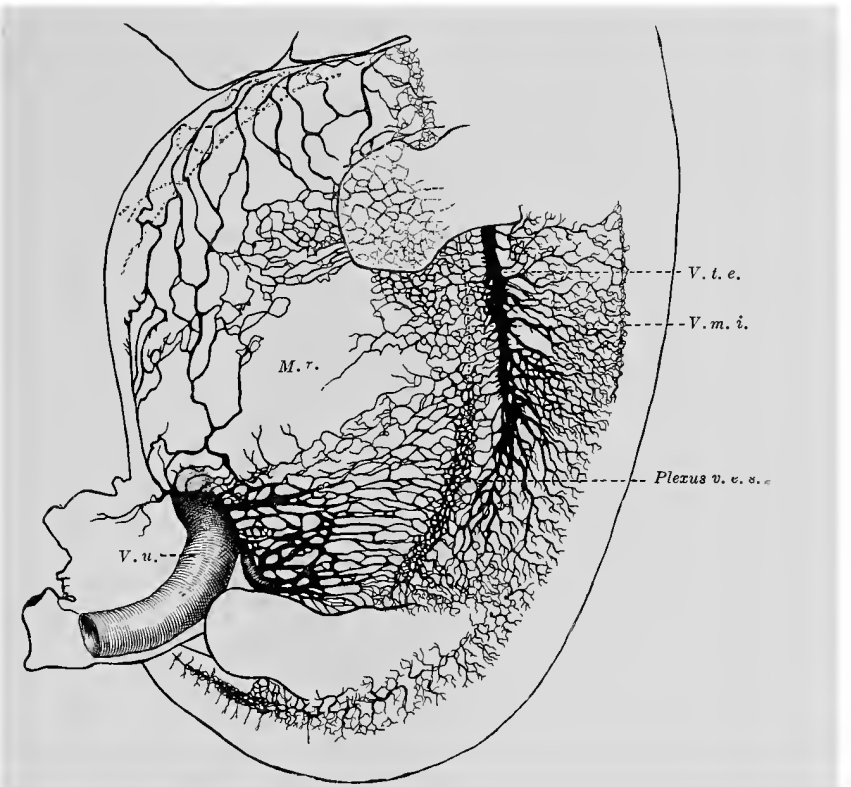

FIG. 467.—Injection of a pig embryo 18 mm. long, showing the superficial body-wall veins. (After Smith, 1909.) *Plexus v. e. s.*, plexus of superficial epigastric vein; *V. m. i.*, v. mammaria interna; *V. t. e.*, v. thoraco-epigastrica.

6. THE DEVELOPMENT OF THE VEINS OF THE BODY WALL.

We have seen that in young embryos the body walls are drained into the umbilical vein by an extensive system of tribu-

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cardinals: "Auch hat dieses Organ (die Nebenniere) das Kopfende der Urniere, welches sich somit schon sehr stark retrahiert hat, so weit lateralwärts abgedrängt, dass ein Zusammenhang der v. azygos und hemiazygos mit den Venen dieses Organs nicht mehr bestehen kann. Der geschilderte Befund lässt bedeutende Zweifel darüber aufkommen, ob die v. azygos und hemiazygos beim Menschen in ihrer Totalität als Reste der hinteren Kardinalvenen aufzufassen sein werden."

[90] But exceptional cases in which an entirely symmetrical doubled schema is preserved are by no means uncommon in man, and in some mammals, on the other hand, this is a normal course of development,—*e.g.*, Echidna (Hochstetter).

taries. There is no doubt, then, but that we must regard the *v. umbilicalis* as the primary drainage channel for the body wall.[91] Its domain here is next disputed by the appearance of the *v. thoraco-epigastrica,*[92] which forms on the lateral body wall just caudal to the arm bud. Proximally, the thoraco-epigastrica unites with the *primitive ulnar vein* to constitute the *v. subclavia,* which, as Hochstetter (1891) first showed, at first courses dorsal to the brachial plexus and subclavian artery to enter the *v. cardinalis anterior* (embryo of 10 mm., F. T. Lewis, 1909), but in slightly

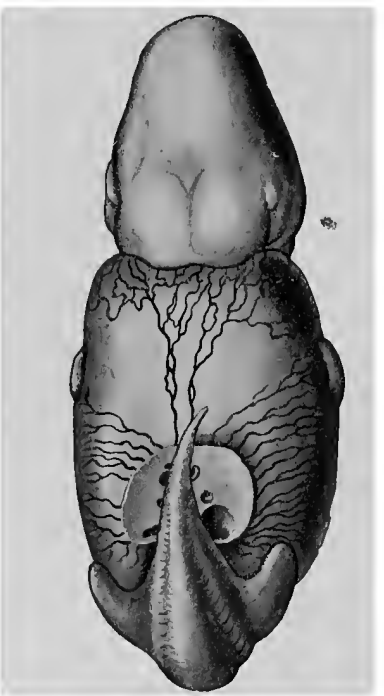


FIG. 468.—Injection of a pig embryo 15 mm. long, showing symmetrical mid-ventral veins draining the plexus situated in the membrana reuniens over the heart.

older embryos possesses also an opening ventral to these structures, so that in the latter stage (embryo of 11.5 mm., F. T. Lewis, 1909) the a. subclavia and plexus brachialis are enclosed in a venous ring, only the ventral limb of which will persist.

[91] Since the complete system of these veins has not yet been figured for human embryos, I present here three figures to show their extent in another mammal (the pig). Miss Smith's figures (Figs. 466, 467) have been secured from injections of living embryos, and I supplement them by a figure to show the plan of mid-ventral drainage (Fig. 468). Here one remarks that the membrana reuniens over the upper portion of the heart territory is drained by two parallel mid-ventral veins which eventually join the v. umbilicalis. (In some instances they also end by branches which sink in directly to the vessels of the liver.)

[92] Homologous with Hochstetter's "Seitenrumpfvene" of the lower vertebrates.

Owing to the fact that at first the lateral body walls greatly exceed in extent the dorsal and ventral surfaces, their chief drainage channels, the *vv. thoraco epigastricæ,* are the most important body-wall veins until relatively late (embryo of 50 mm). What proportion of the body-wall drainage they still *control* in an embryo of 35 mm. can be seen from Fig. 473. At this later stage, however, the more ventrally lying veins begin to play a significant rôle, among which are to be mentioned the *superficial epigastrics* and the perforating branches of the *vv. mammaria internæ* and *intercostales.* In embryos of 50 mm. injections show that the territories of these latter veins have grown very appreciably, yet there do not occur as yet any appreciable anastomoses, such as produce here the great venous plexus well known in the adult (Fig. 472).

7. THE DEVELOPMENT OF THE VEINS OF THE EXTREMITY.

We lack as yet any thorough-going account of the development of the extremity veins in man. Nevertheless, the researches of

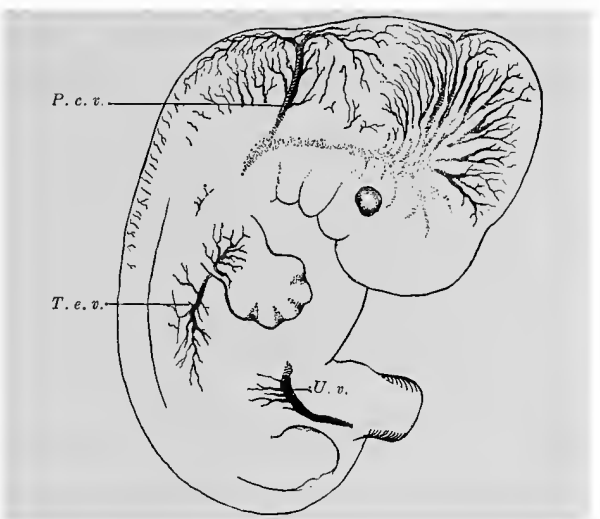


FIG. 469.—Injected human embryo 11 mm. long, showing some of the chief superficial veins. (From a drawing by Mr. Max Broedel.) (Mall No. 353.) *T. e. v.*, thoraco-epigastric vein; *P. c. v.*, posterior cerebral vein; *U. v.*, umbilical vein.

F. Hochstetter (1891) on the extremity veins of Amniotes and the scattered observations which have been made on the human embryo, together with some others which will be presented here, enable us to outline the essential facts in this field.

The first veins of the limb bud in man, as in other mammals and in the chick, are small direct vessels which drain the early capillary plexus of the limbs into the posterior cardinal and umbilical veins. These venules thus constitute two sets—a dorsal series, which are the tributaries of the posterior cardinal vein,

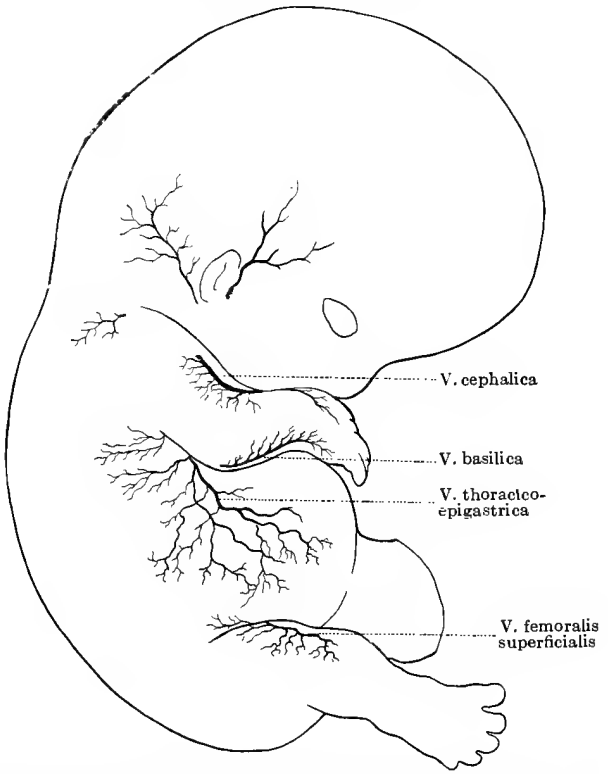


FIG. 470.—Injected human embryo 20 mm. long, showing some of the chief superficial veins. (Mall No. 349.) (After drawings kindly placed at my disposal by Mr. Max Broedel.)

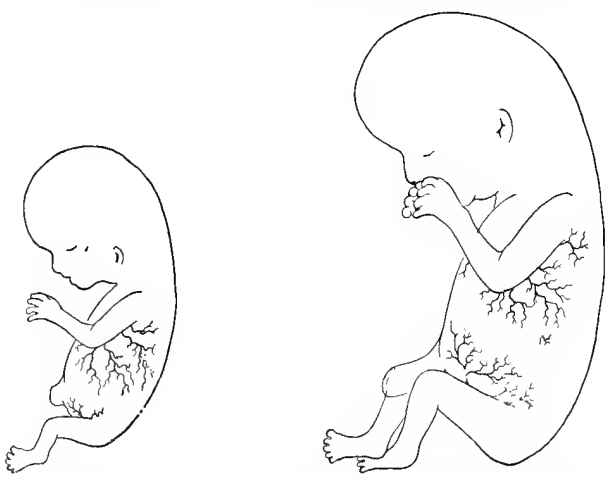


FIG. 471.—Injection showing the thoraco-epigastric and superficial epigastric veins in a human embryo 35 mm. long. (Mall No. 449.)

FIG. 472.—The same in an embryo 50 mm. long. (Mall No. 458.) The relative growth of the lower vein is evident. No anastomoses between the two systems are yet present.

and a ventral series, the tributaries of the umbilical vein. Such are the conditions in human embryos under five millimetres in length.

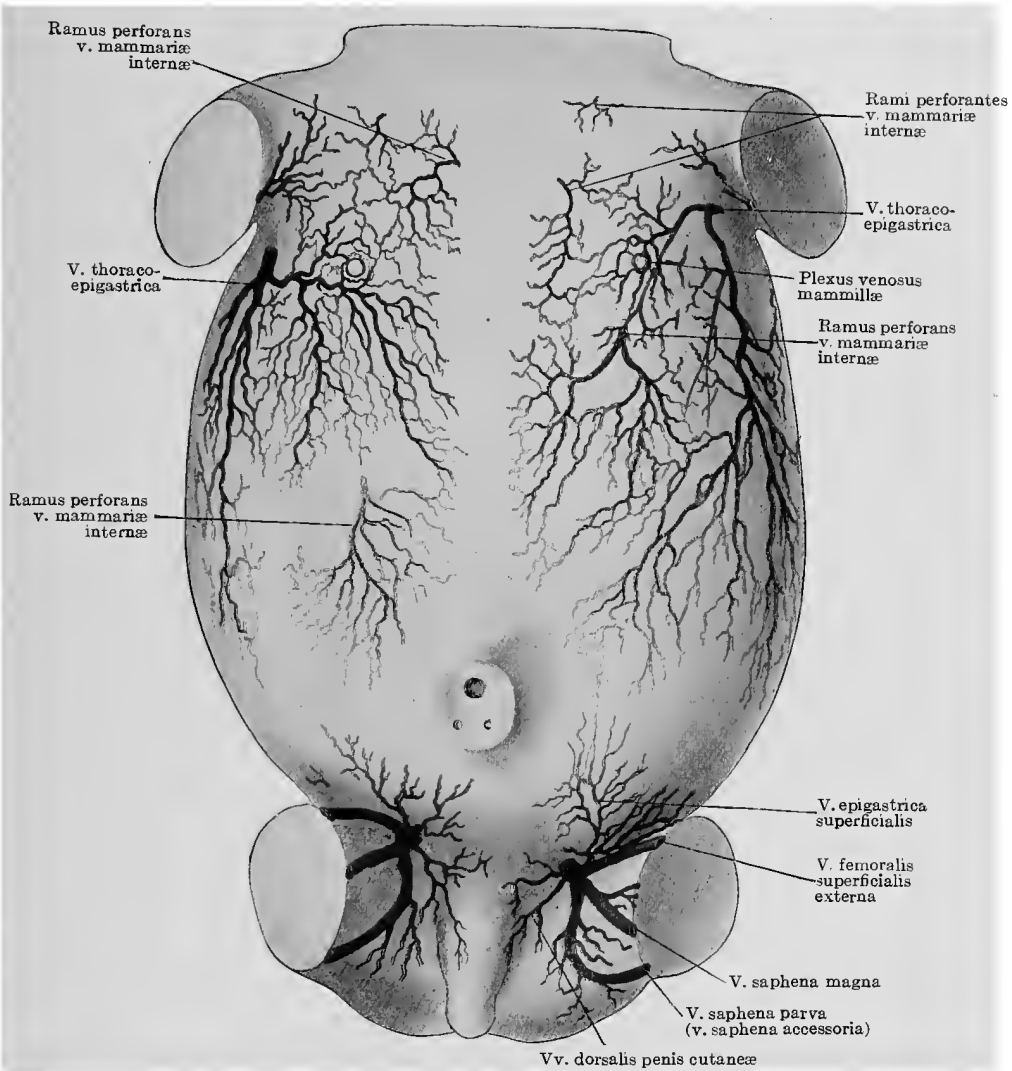


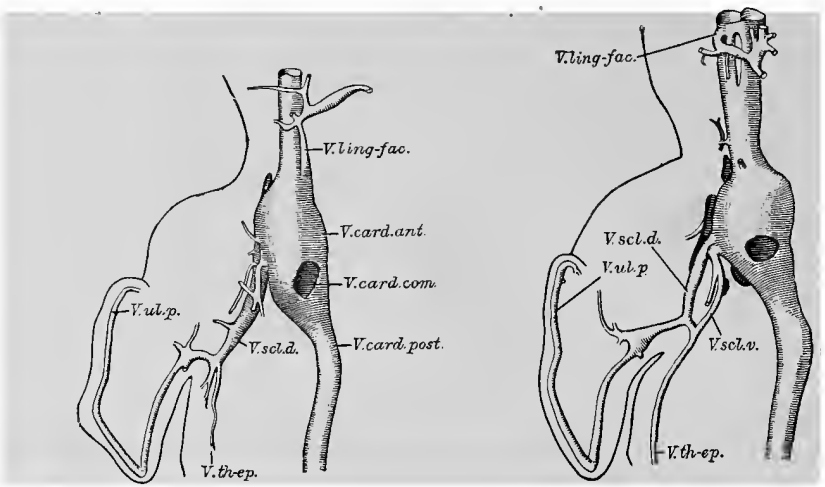
FIG. 473.—Body-wall veins of a human fetus 35 mm. long. (Mall No. 449,) The specimen was secured alive through the kindness of Dr. Thomas Cullen and injected through one of the aa. umbilicales.

But there is soon established in both limbs (in the anterior limb first and later in the posterior) a *border vein* which surrounds the paddle-like extremity,[93] a vein which Hochstetter has shown to be characteristic for the limb bud of all the amniota. The

[93] The observations of Lewis and Grosser have indicated that both radial and tibial border veins are extremely transitory; Grosser, in fact, was not able to find a tibial border vein in the bat; however, Bardeen figures this clearly in his study of the leg bud of a 11 mm. human embryo (Amer. Jour. Anat., I, 1901, PI. IV, Fig. D, p. 36).

Injections of the limb buds of pig embryos show that the border vein is constructed out of the peripheral margin of the capillary plexus of the limb.

upper (radial and tibial) portions of these border veins are quite insignificant, but the lower (ulnar and fibular) ones are relatively large [94] and constitute the chief channels of drainage of the extremities. Moreover while the *radial* and *tibial border veins* completely atrophy, the *ulnar* and *fibular veins* persist, their peripheral portions constituting the *basilic* and *small saphenous veins* of the arm and leg respectively. Proximally the *ulnar border vein* constitutes the definite *branchial, axillary,* and *subclavian vein.* For a considerable time this is the only important venous channel in the arm, and, although its proximal portion still functions as the



FIGS. 474 and 475.—Reconstructions of the veins of the right arm in two human embryos 10 and 11.5 mm. long respectively. (After F. T. Lewis, 1909.) *V.card.ant.*, vena cardinalis anterior; *V.card.com.*, v. cardinalis communis; *V.card.post.*, v. cardinalis posterior; *V.ling.fac.*, v. linguo-facialis; *V.scl.d.*, v. subclavia dorsalis; *V.scl.v.*, v. subclavia ventralis; *V.th.ep.*, v. thoraco-epigastrica; *V.ul.p.*, v. ulnaris prima.

chief vein in the adult limb, its distal superficial territory is soon greatly exceeded by the development of the *v. cephalica.*

In embryos of ten millimetres and under, the proximal portion of the *ulnar border vein,* after receiving the *thoraco-epigastric vein* from the lateral body wall, drains into the *posterior cardinal* or *common cardinal vein* by taking a course dorsal to the brachial plexus and subclavian artery (Fig. 474, F. T. Lewis). Shortly after this stage, however, a venous path is also found ventral to these structures, and after a short time, during which the brachial nerves are enclosed in a venous ring (Fig. 475), the dorsal path finally

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For some reason the limb capillaries will not approach very close to the ectodermal covering of the limb bud, but leave a narrow sub-ectodermal zone of mesenchyme non-vascular; hence the marginal vein which is formed from the "frontier line" of these capillaries follows faithfully the boundary of the rim.

[94] Hochstetter observed in living embryos that the direction of blood flow for practically the entire extent of the border vein of the upper limb is from before backward, *i. e.,* into the ulnar extremity.

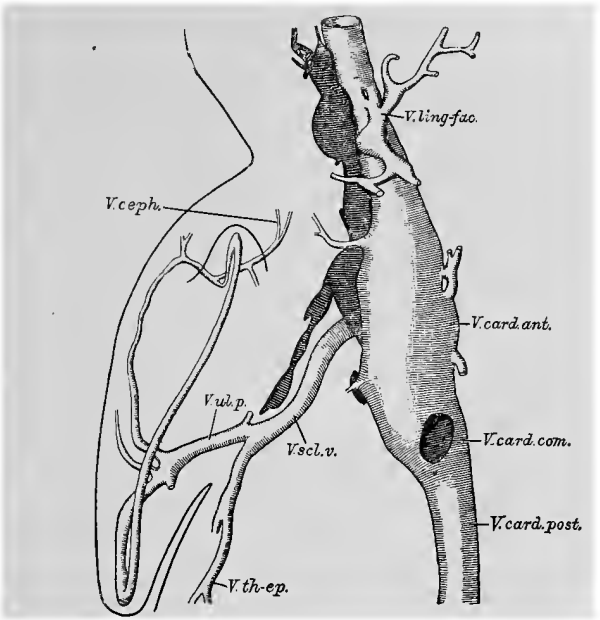


FIG. 476.—Reconstruction of the veins of the right arm in a human embryo 16 mm. long. (After F. T. Lewis, 1909.) *V. ceph.*, v. cephalica. For other abbreviations see Figs. 85 and 86.

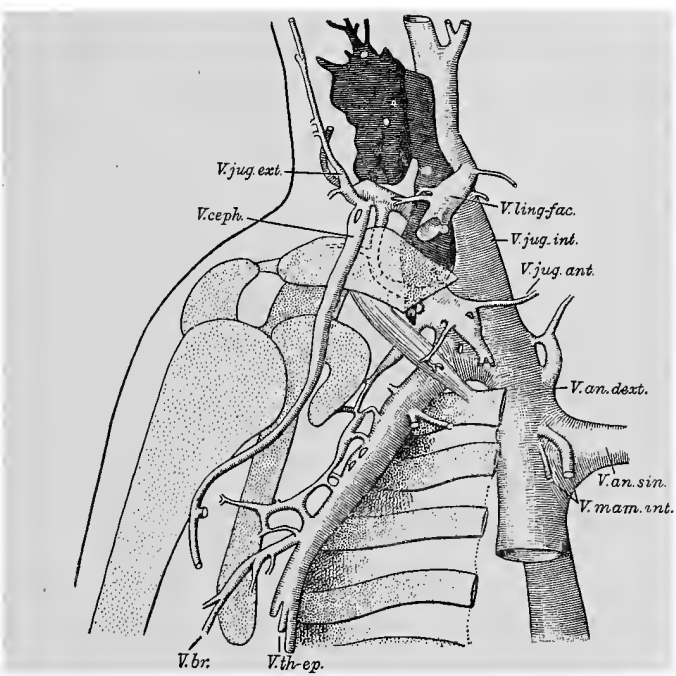


FIG. 477.—Reconstrnction of the right shoulder region in a human embryo 22.8 mm. long. (After F. T. Lewis.) Ribs, clavicle, scapula, and humerus have been stippled and the subclavius muscle has been drawn. *V. an. dext.*, v. anonyma dextra; *V. an. sin.*, v. anonyma sinistra; *V. br.*, v. brachialis; *V. ceph.*, v. cephalica; *V. jug. ant.*, *V. jug. ext.*, *V. jug. int.*, v. jugularis anterior, externa, et interna; *V. mam. int.*, v. mammaria interna.

atrophies. Moreover, while the *subclavian vein* at first opens into the *posterior cardinal,* it eventually is found joining the *duct of Cuvier,* and in still older embryos (16 mm.) the *anterior cardinal* or *jugular vein,* a phenomenon to be associated with the descent of the heart and main vessels into the thorax.

The *cephalic vein* is entirely secondary, and appears first in man, as in the rabbit (Fig. 469),[95] as a small vessel which collects the blood from the outer side of the hand plate and fore-arm anlage and flows into the radial end of the ulnar border vein near the elbow.[96] Very soon this vein can be traced upward along the

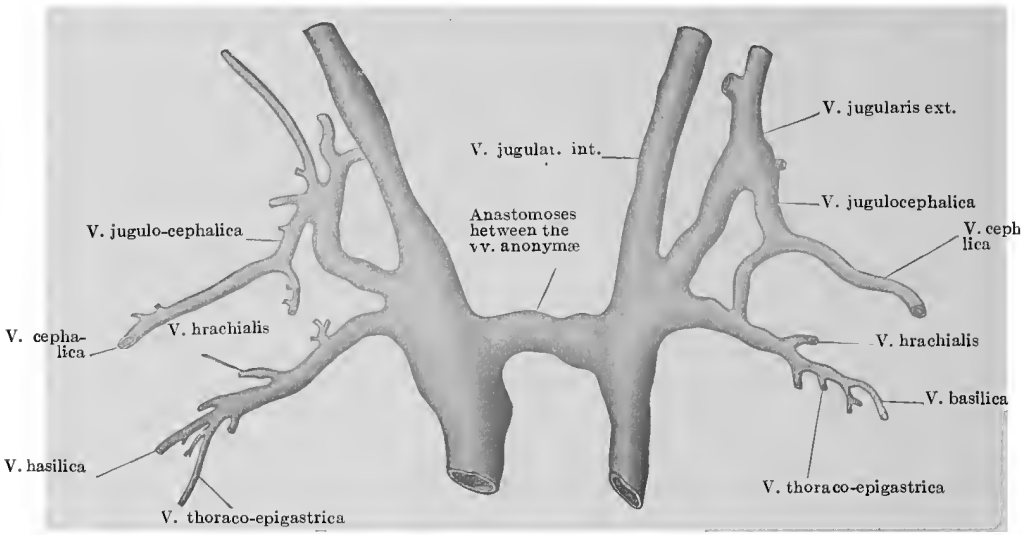


FIG. 478.—Reconstruction of the relations of the great veins of the arms and neck in a human embryo 20 mm. long. (Mall collection, No. 349.)

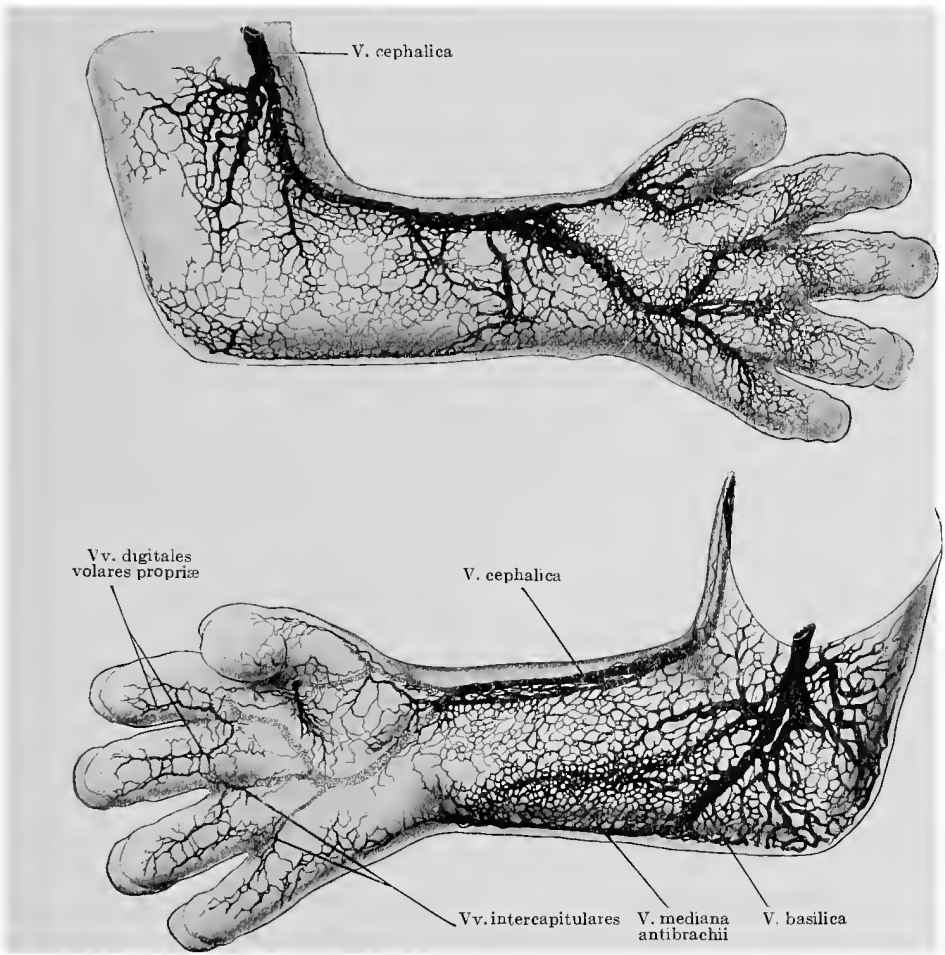
radial side of the upper arm (Figs. 476, 477), and in an embryo of 22.8 mm. Lewis has shown that the cephalic vein now joins the external jugular, an arrangement which is true for the embryo figured in Fig. 478, but in which there is also now present a connection between the cephalic and the subclavian veins which is to function as the definitive proximal ending of the cephalic vein in man. This earlier drainage channel of the cephalic into the external jugular vein may persist (*jugulocephalic vein*), as has been noted for many years in descriptive human anatomy.

The cephalic vein at the stage last mentioned has become the chief superficial vein of the arm, for, with the breaking up of the

[95] Compare with Hochstetter's figure 2 a, Taf. III. Morph. Jahrb., 1891, for the rabbit.

[96] This connection of basilic and cephalic veins has nothing to do with the v. mediana cubiti, which is a late connection and formed long after the primitive junction of the two veins has disappeared and they have existed as two independent channels. (See beyond.)

border vein by the outgrowth of the digits and the formation of interdigital veins, we have a transferral of the latter veins to the system of the v. cephalica, which now, collecting its blood from the back of the hand, courses along the radial border of the forearm and arm entirely distinct from the *ulnar border vein* (the *v. basilica,* Fig. 479). As is well known, in the adult these two great veins are connected in a wide-meshed plexus. A complete injection



FIGS. 479 and 480.—The superficial veins of the right arm in a human fetus 35 mm. long. From an injection. (The specimen is the same as that shown in Fig. 473.)

of the arm veins in an embryo 35 mm. long shows that even at this stage there are not yet formed the many connections between basilic and cephalic veins which constitute the well-known venous plexus of the dorsum mani and the forearm. It is thus possible to state that the great subcutaneous venous plexuses of the extremity are not partial remains of a primary embryonic more

extensive plexus, for the only primary plexus existing here is again a general capillary mesh, and the larger venous connections which characterize the adult are clearly secondary formations. In the arm figured, one may see the earliest veins of the volar surface of the forearm, and, especially clearly, the method of formation of the *v. mediana antibrachii* through the enlargement of parts of the general capillary mesh (Fig. 480).

In the posterior limb bud it has already been mentioned that the superficial portion of the *fibular border vein* persists, for it can be identified in a series of embryos (15.5, 20, 23, and 26 mm. long) and seen to constitute the *v. saphena parva.* The

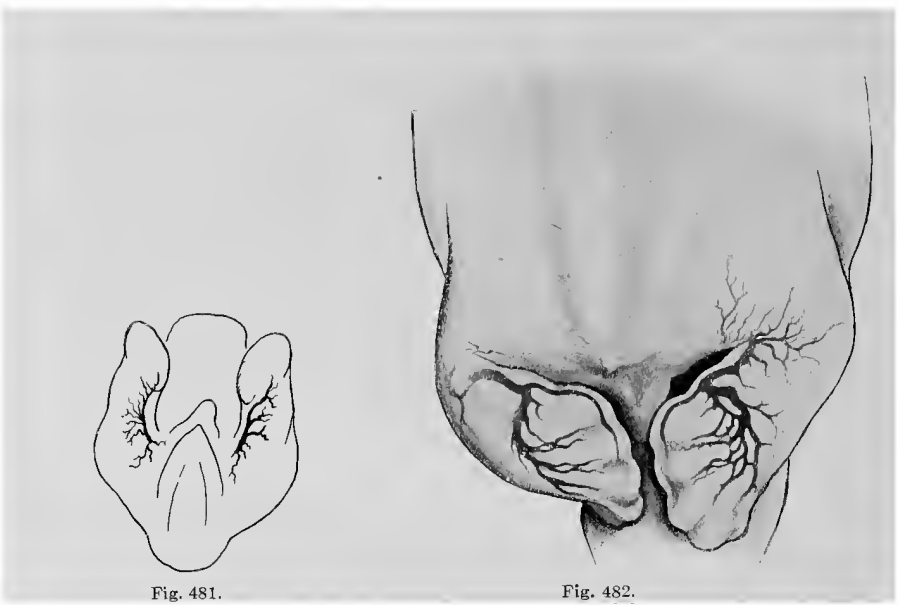


Fig. 481. Fig. 482.

Fig. 481.—The fibular border vein in a human embryo 15.5 mm. long. (Mall collection, No. 390.) (After a sketch kindly placed at my disposal by Mr. Max Broedel.)

Fig. 482.—The fibular border vein in an injected human embryo 21 mm. long. (Mall collection, No. 460.) The vein is seen to drain the dorsum of the foot by a distinct venous arch; the proximal portion of the original border vein can be recognized.

deep portion of this vein accompanies the sciatic artery and nerve in the region of the thigh and through the foramen ischiadicum into the pelvis; it is hence the *v. ischiadica.* It joins the *posterior cardinal vein,* of which it constitutes the chief radicle, for the caudal vein (*v. sacralis media*) is inconspicuous. At a later stage (Fig. 485) the vein formed from the union of the *femoral* and *great saphenous veins* joins the proximal portion of the *ischiadic vein* just before the latter ends in the *v. cardinalis posterior.* In human embryos measuring 10 mm. or less, the *ischiadic vein* constitutes the chief drainage channel of the lower limb, but in its superficial extent the vein is soon exceeded by the *v. saphena magna,* a secondary channel, and in its deep territory by

the v. femoralis, which has developed along the permanent artery (a. femoralis) of the limb (the v. ischiadica in the adult being important only as a collateral path for the blood). The early

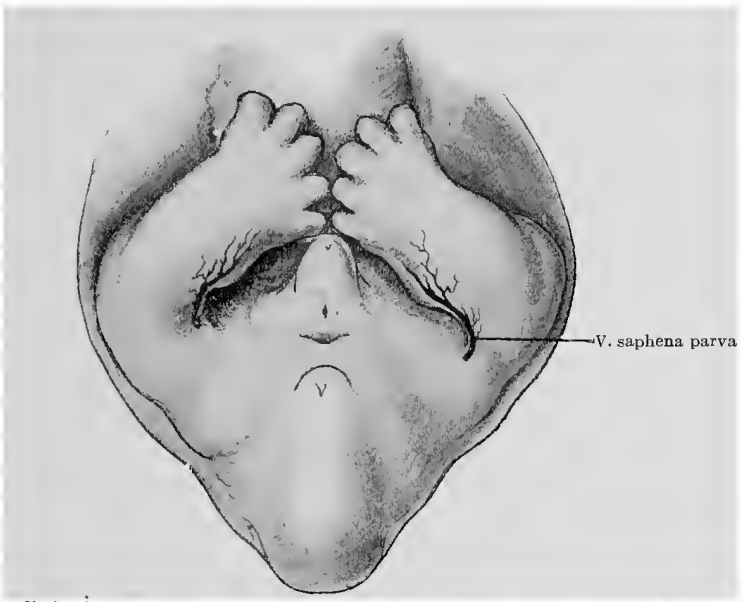


FIG. 483.—The fibular border vein (v. saphena parva) in a human embryo 23 mm. long (Mall No. 462) at a time when toes and heel are clearly evident.

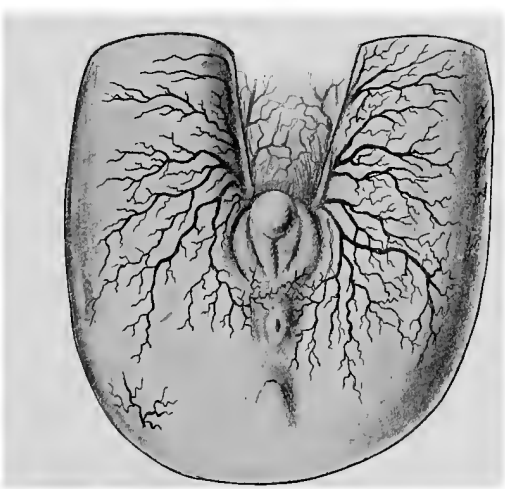


FIG. 484.—Drainage of the perineum and bnttocks into the v. saphena magna, in a human fetus 50 mm. long. (Mall No. 458.) (From an injection by Mr. Broedel.)

development of the v. saphena magna in man is not known, but at the stage of 23 mm. it already constitutes the chief superficial vein of the leg.

In embryos of 24 and 25 mm. length, anastomoses on the inner side of the thigh have begun to direct the blood stream in the

saphena parva to the *v. saphena magna*, and in an embryo measuring 35 mm. and in three embryos of approximately 50 mm. in

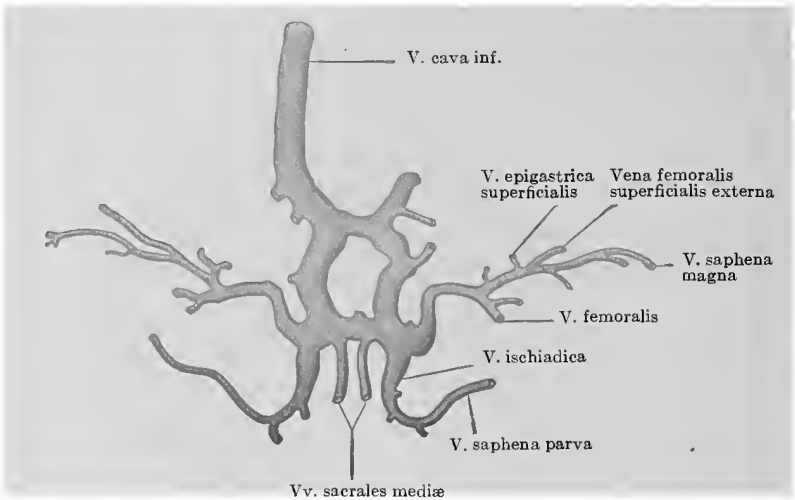


FIG. 485.—Reconstruction of the chief veins of the pelvis and lower extremities in a human embryo 20 mm. long. (Mall collection, No. 349.)

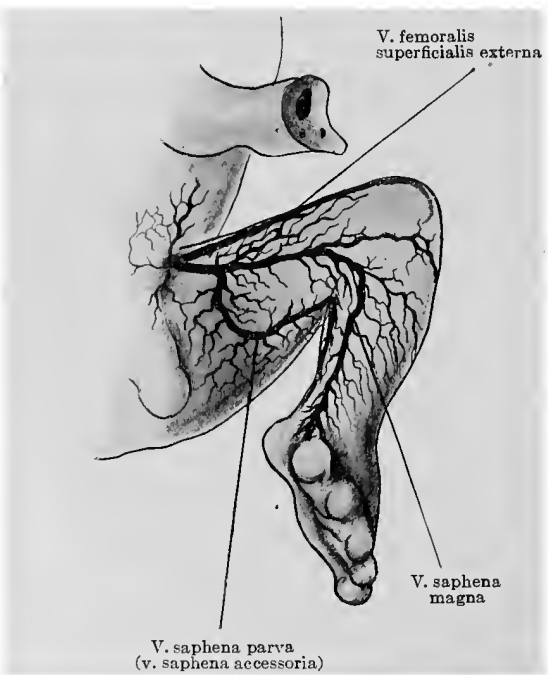


FIG. 486.—The superficial veins of the leg in a human fetus 35 mm. long. (After an injection of the living embryo; secured through the kindness of Dr. Thos. Cullen.) (Mall, No. 449.)

length, I have found this connection a constant feature, practically all the blood of the lower leg vein (*v. saphena parva*) going

into the greater saphenous channel.[97] In the youngest of these embryos the *saphena parva* continues up the inner side of the thigh before joining the *saphena magna* (a condition which has been observed as a variation in the anatomy of the adult for a long time), but in all the other cases the small saphenous vein pours its blood into the v. saphena magna near the knee. Eventually the *v. saphena parva* joins the deep vein (*v. femoralis*) in this neigh-

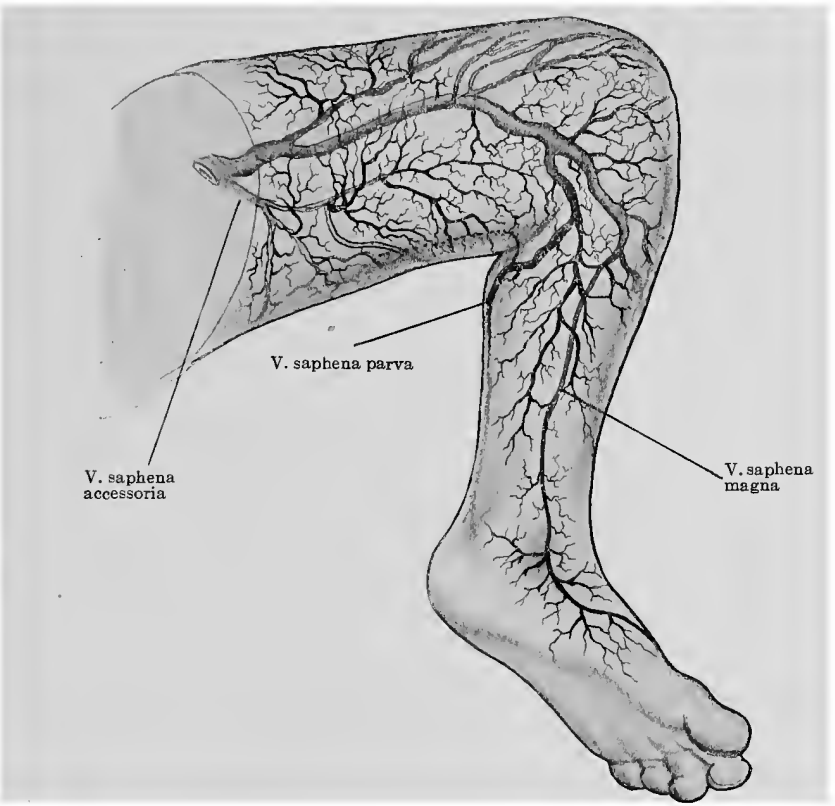


FIG. 487.—The superficial veins of the leg in a human fetus 50 mm. long. (After an injection by Mr. Broedel.)

borhood, as is well known to be its definite normal ending, although in a great percentage of cases the connection here with the *saphena magna* is also retained to form a subsidiary channel (*e.g.*, Quain's Elements of Anatomy, 10th Ed., Vol. II, Part II, p. 538, London 1894.)

[97] Whether we are dealing here with a general fact or not is impossible as yet to decide. If such is not the case, it must be remarked as unusual that I have found the six lower limbs of the three embryos measuring fifty millimetres to be absolutely indentical in this respect. I note also that Bardeleben refers to a similar arrangement of the saphenous veins. "Ferner mundet bei jenen (d. h. Feten) die v. saphena parva, welche der basilica homolog ist, in die saphena magna" (Bardeleben, 1880, p. 604).

In the development of the leg, the proximal portion of the extremity is for a while buried, as it were, in the tissues of the embryo, and only in embryos of some 20 mm. in length, and in those older than this, can we speak of a cutaneous surface belonging to the inner side of the thigh. Consequently the *saphena parva* is in the position to drain the early venules which come from the neighborhood of the perineum and buttock (if we may yet speak of the latter), as Fig. 481 will show. With the "pushing out" of the thigh, this is no longer possible,[98] for the proximal end of the *saphena parva* is carried out with the knee, and the *saphena magna* is now the direct and natural channel for this blood. In embryos measuring 50 mm. in length the vessels draining the back of the buttocks into the *saphena magna* constitute a large and prominent system (Fig. 484).

As Bardeleben first indicated and as has been shown by the work of Hochstetter and of Lewis, the limb veins which are true accompanying vessels to the arteries are the last to develop.[99]

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[98] Except, of course, in those cases in which, as in Fig. 486, the saphena parva continues up the inner side of the thigh.

[99] Mention may here he made of the occurrence of a prominent "superficial external femoral" vein which drains the front and outer side of the thigh and joins the saphena magna near the fossa ovalis (emhryos of 23 and 35 mm.). It is relatively large in these emhryos, hy far the greatest tributary of the saphena magna. The vein is recognized as common in the adult (*e.g.*, Quain, Spalteholz, Piersol, etc.). In the 35 mm. emhryo it was remarkahle that on both sides the vein hegan suddenly hy deep roots in the region of the knee—the latter streamed from the vascular plexus surrounding the cartilage of the lower end of the femur and turned out sharply to the skin.

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IV. THE DEVELOPMENT OF THE LYMPHATIC SYSTEM

By FLORENCE R. SABIN.

Recent work on the development of the lymphatics has given us a new conception of the general morphology of the system as a whole. It has related the lymphatics to the vascular system and separated them from the system of tissue spaces. The study of human embryos [1] has sharpened this conception and made it possible to go a step farther,—namely, dividing the development of the system into two stages. The primary stage consists of a series of isolated lymph-sacs, which are clearly derived from the veins, and which become united into a system through two agencies,—(a)

[1] Many of the facts concerning the development of the lymphatic vessels in human embryos have been obtained from the study of the Mall collection.

by the thoracic duct, which connects these sacs with each other, and (b) by the formation of a secondary opening into the veins at the jugular valves. The secondary stage involves the peripheral growth of lymphatic vessels which sprout from the endothelial lining of these sacs and spread out over the body. The invasion of the body is gradual, and in certain areas never takes place, as, for example, the central nervous system and the skeletal muscles. Since this new conception is not wholly accepted,—in fact, since most of the texts on anatomy and zoölogy describe the lymphatics as arising out of tissue spaces,—the evidence for the conception presented here will be given in detail as well as certain important general conclusions.[2]

The first evidence of the formation of the lymphatic system is the development of symmetrical sacs in the neck, which have been called the jugular sacs. These are found first in a human embryo 10.5 mm. long (*S.l.j.*, Fig. 488) as endothelial-lined sacs just lateral to the internal jugular veins (Sabin, 1909). In the same year Lewis (1909) described the jugular lymph-sacs in four human embryos, finding the beginning of the sac in an embryo 10 mm. long, in which it consisted of a single sac against the vein. In an embryo of 11.5 mm. he found four or five of such small sacs. His four stages are shown in excellent figures. He called attention to the fact (which is, I think, quite clear) that Ingalls (1908), in tracing the origin of the sac in an embryo 4.9 mm. long, was confusing veins and lymphatics. This jugular sac remains as the only sac until the embryo is 20 mm. long. The sac is formed in the following manner. Along the course of the jugular vein in early stages there is a series of branches which form a capillary plexus. Much of this capillary plexus disappears entirely, not being used to form the permanent branches. This destruction of capillaries is one of the fundamental factors in the evolution of

[2] The fact that until very recently the weight of evidence rested on the side of the theory that the lymphatic system arose from tissue spaces will be shown in the following quotation from the last—that is, the 6th—edition of Kolliker's Geweblehre, 1902, page 681, "Ranvier glaubt daher, dass die Lymphgefässe vom Venensystem nach der Peripherie in ähnlicher Weise durch Sprossung fortwachen, wie eine Drüse mit verzweigtem Gangssysteme von einer Schleimhautröhre aus . . . Die Aufstellungen Ranvier's sind keineswegs sicher erwiesen und stehen im Gegentheile in Widerspruch mit den anderen gefundenen Tatsachen; sie wurden jedoch hier angefuhrt, weil durch dieselben der Vorstellung von der gänzlichen Vershiedenheit von Bindegewebespalten und echten Lymphgefässen der schärfste Ausdruch gegeben wirt." Ranvier's comparison of the growth of the lymphatic system to the growth of a gland seems an unfortunate one, since the truer and more obvious comparison of the growth of lymphatic capillaries to blood capillaries, both invading by the same method, is thereby lost sight of. The second point brought out by Von Ebner, that, should the new theory prevail, it would lead to the sharpest possible separation of the lymphatics and the tissue spaces from the anatomical stand-point, is exactly what has happened.

the vascular system. In certain places, and first along the jugular vein, at the level of the primitive ulnar and cephalic veins, in embryos between 8 and 10 mm. long, some of the capillary plexus becomes cut off from the parent vein, and remains for a short time as a group of isolated endothelial-lined spaces close to the vein. The extent of this zone, which probably varies considerably in different specimens, can be seen in Fig. 489, which is from a reconstruction of the jugular sac of the same embryo shown in Fig. 488. These isolated capillaries, the anlage of the lymphatic system, gradually dilate and coalesce to form symmetrical endothelial-lined

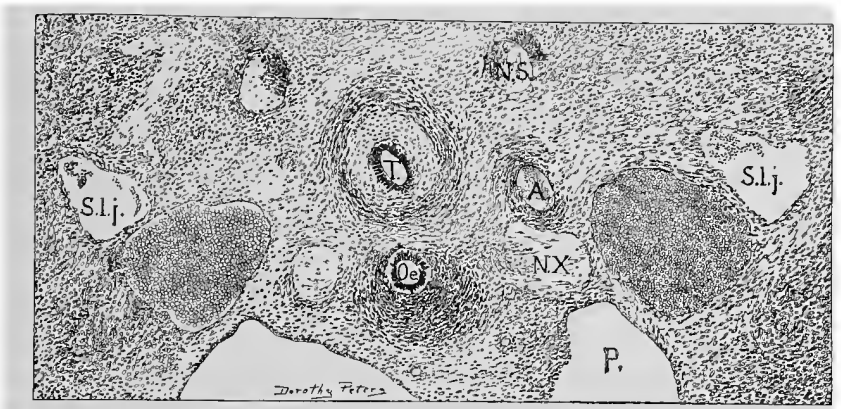


Fig. 488.—Transverse section through the neck of a human embryo 10.5 mm. long, showing the symmetrical jugular lymph-sacs. (Mall's collection, No. 109.) × about 36. *A.*, artery; *N.S.*, nervus sympathicus; *N.X.*, nervus vagus; *Oe.*, œsophagus; *P.*, pericardial cavity; *S.l.j.*, saccus lymphaticus jugularis; *T.*, trachea. The jugular veins are filled with blood and lie just medial to the lymph-sacs.

sacs, which subsequently rejoin the vein in such a way as to form a valve at the opening (Fig. 492). The time of the formation of the valve is in embryos between 10.5 and 12.5 mm. in length.

It is now necessary to prove that these jugular sacs are lymphatics, and, as this involves the use of the injection method on abundant material, it could not be done on human embryos. Conclusive proof that the jugular sacs are a part of the lymphatic system is readily obtained by injecting the lymphatics in the skin of the neck of other mammalian forms, as for example pig embryos, and proving that the lymphatic vessels empty into the sacs. This can be done in pig embryos from 18 to 20 mm. long. Below this stage the sacs could be identified in specimens in which the blood-vessels had been injected. After the position of the sacs had been determined, it was found that direct puncture of the sacs was the best method of obtaining extensive injections of the lymphatics which radiate out from them, thus indicating not only that the sacs are lymphatics but that they are important centres for the radiation of the lymphatic ducts.

That there are two large sacs in the neck of young sheep embryos, and that these sacs are lymphatics, was noted by Saxer (1896). Saxer, however, represents the theory, together with Gulland (1894), that the lymphatics come from tissue spaces, finding that the first lymph-vessels are in the subcutaneous tissue and are present in bovine embryos 25 mm. long. In 1900 Sala described the origin of the posterior lymph-sacs close to the veins in chick embryos. He

had, however, no conception of the significance of this discovery; if the earliest lymphatics are sacs close to the veins, the foundation is laid for the theory that the lymphatics grow from the veins to the periphery. Sala says that the

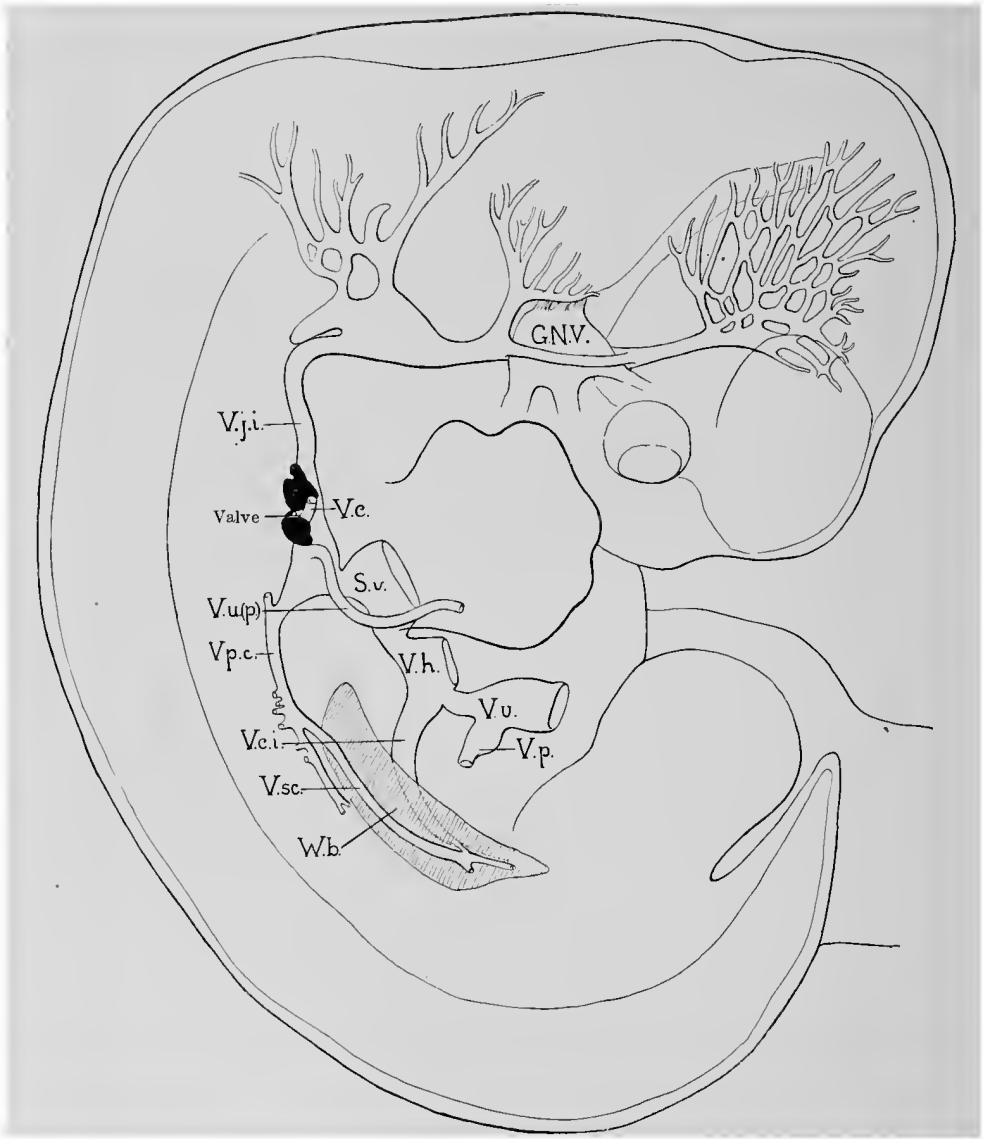


FIG. 489.—Reconstruction of the right jugular lymphatic sac, shown in solid black against the jugular vein, in a human embryo 10.5 mm. long. (Mall's collection, No. 109.) × about 14. *G.N.V.*, Gasserian ganglion; *S.v.*, sinus venosus; *V.c.*, vena cephalica; *V.c.i.*, vena cava inferior; *V.h.*, vena hepatica; *V.j.i.*, vena jugularis interna; *V.p.*, vena portæ; *V.p.c.*, vena cardinalis posterior; *V.sc.*, vena subcardinalis; *V.u.(p.)*, vena ulnaris (primitiva); *V.u.*, vena umbilicalis; *W.b.*, Wolffian body.

posterior sacs arise from the veins and again that they are tissue spaces, two statements which mutually exclude each other. In addition he finds that the thoracic duct arises as solid cords of cells which secondarily become hollowed out into tubes and join the veins. If this be true, it can not, as Von Ebner

says in Kolliker's Gewehlehre (Bd. 3. p. 682) in regard to these results of Sala's, "Wohl nicht bezweifelt werden, dass die Milchhrustgänge beim Hüchchen selbständige Bildungen sind und nicht aus den Blutgefässen hervorsprossen." But it is quite certain that in mammalian embryos the thoracic duct never arises as a solid column of cells. To return to the lymph-sacs, their significance as the first lymphatics, together with the fact that the lymphatics grow from centre to the periphery, lays the foundation for the new theory as was brought out hy myself in 1901 in the study of the system in pig emhryos.

F. T. Lewis then showed, in 1906, that in rabhit emhryos the jugular sacs are immediately preceded hy a plexus of blood capillaries, so that they themselves are transformed capillaries. During the same year (1908) this method was confirmed in pig emhryos hy the method of injection hy myself and in cat emhryos hy the method of wax plate reconstruction by Huntington and McClure together.[3] In pig embryos between 10 and 13 mm. long the entire plexus of capillaries external to the jugular vein can he injected from the vein, while in emhryos 13 to 14 mm. long the plexus injects less and less from the vein until the sacs are formed. In one specimen the sac itself on one side received some of the ink which had heen injected into the vein, showing conclusively that the sacs come from the capillary plexus. In pigs from 15.5 to 16 mm. long the sacs are never injected from the veins, and hence they are either entirely cut off, which condition lasts a short time, or the opening is guarded hy a valve. Huntington and McClure (1910) traced this process hy a complete series of wax models of the jugular region in cat embryos. The capillary plexus which is the anlage of the sacs, they called "veno-lymphatics." It may therefore be considered as proved that the jugular sacs are lymphatics and that they are transformed veins. The proof that they are the only lymphatics for a considerahle time, until the emhryo is 20 mm. long, that none of the tissue spaces, cœlom, or the arachnoid spaces are a part of the lymphatic system, will he taken up later, in connection with the general consideration of the relation of the lymphatic system to tissue spaces.

The extension of the sac along the jugular vein may be by the addition of more of the capillary plexus, as is suggested by Figs. 490 and 491. These two figures are coronal sections from an embryo 11 mm. long. If they are superimposed, which can readily be done by matching the curve of the arm bud and the cephalic vein, it will be seen that the capillary plexus, the anlage of the lymph-sac, extends from the root of the primitive ulnar vein along the internal jugular vein into the neck. The full series shows that the plexus also extends a short distance into the arm bud along the primitive ulnar vein. The linear extent of the plexus is about 1.2 mm., an increase over the length of the preceding stage, which was 0.7 mm. The plexus is filled with blood, as if the secondary opening had not yet formed, and indeed, though the place of the valve is indicated in Fig. 490 by the projection of the sac into the

[3] Huntington and McClure in 1907 had advanced the view that the lymphatics came from clefts between the intima of the veins and the connective tissue, calling these clefts "extra-intimal" anlages; but they retracted this theory, as far as the jugular sacs were concerned, during the following year (1908), and accepted the idea that the jugular sacs are venous in origin, though they think that the rest of the lymphatics are either "extra-intimal" or of tissue space origin.

angle between the internal jugular and cephalic veins, no break in the endothelium could be made out. This fact—that the endothelium shows no break in sections—is the only evidence on which rests the idea that the permanent opening is secondarily acquired. This contrasts sharply with the condition shown in Fig. 492 from an embryo 17 mm. long. The valve is first definitely open in an embryo 12.5 mm. long, as stated in the table on page 733, at which time the plexus has been transformed into a definite, long, empty sac of the type shown in Fig. 492. The valve is formed by a projection of the lymph-sac deep into the cleft between two veins, and it is so placed as only to be clearly evident in coronal sec-

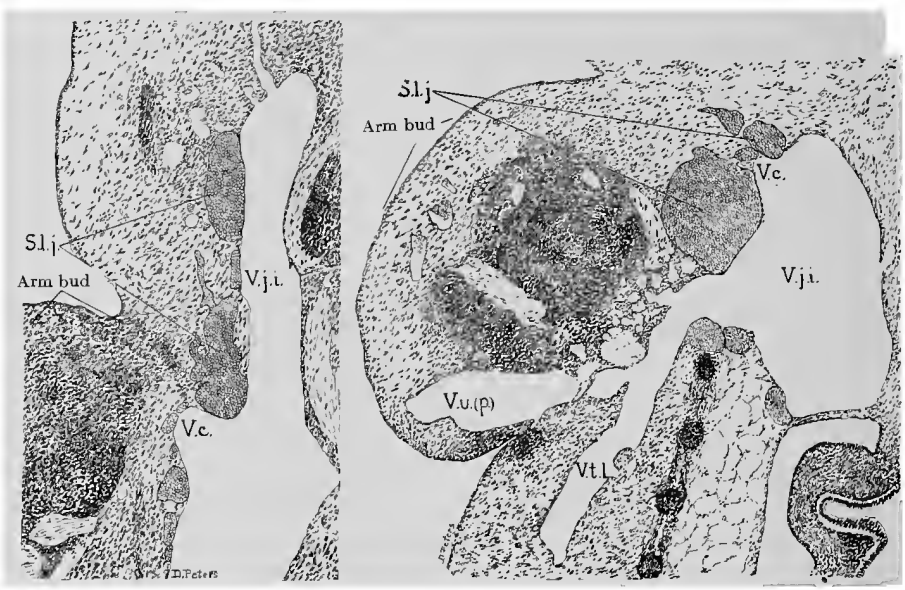


FIG. 490.—Frontal section through the arm bud of a human embryo 11 mm. long, to show the developing lymphatic sacs along the internal jugular vein. (Mall's collection, No. 353.) × about 37. *S.l.j.*, saccus lymphaticus jugularis; *V.c.*, vena cephalica; *V.j.i.*, vena jugularis interna.

FIG. 491.—Frontal section through the arm bud of the same embryo as Fig. 489, to show the relation of the lymphatic-sac anlage to the primitive ulnar vein. × about 37. *S.l.j.*, saccus lymphaticus jugularis; *V.c.*, vena cephalica; *V.j.i.*, vena jugularis interna; *V.t.l.*, vena thoracica lateralie; *V.u.(p.)*, vena ulnaris (primitiva).

tions. In transverse sections, as can be readily noted by comparison with Fig. 492, the valve is simply a tiny vessel between two larger veins; in sagittal sections it is even more difficult to locate.

There is no increase in the length of the sac in embryos between 12.5 and 17 mm. long, but from now on there is a rapid increase in size up to its maximum, which is reached in an embryo 30 mm. long, when the size is 5 mm. in length. This stage, which is an important landmark in several ways, is shown in a series of four figures,—493, 494, 495, and 501. Fig. 493 is a reconstruction

of the primitive lymphatic system in an embryo 30 mm. long and shows that the stage which marks the maximum development of the jugular sac shows also all the other sacs and that they have been united into a complete system through the thoracic duct. The peripheral system is also well under way, even much more than is shown in the figure, for the two stages of the lymphatic system—namely, the primitive central system of sacs and the peripheral system of ducts—overlap in their development. The position of the jugular sac can be seen by comparing Figs. 493 and 494. The level of the section shown in Fig. 494 corresponds with the line on Fig. 493. Both figures show the great size of the sac, it being by far

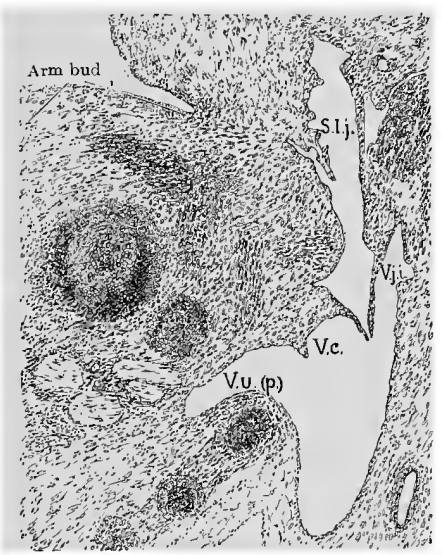


FIG. 492.—Frontal section through the arm bud of a human embryo 17 mm. long, to show the open valve of the jugular lymph-sac in relation to the veins. (Mall's collection, No. 296.) × about 26. *S.l.j.*, saccus lymphaticus jugularis; *V.c.*, vena cephalica; *V.j.i.*, vena jugularis interna; *V.u.(p.)*, vena ulnaris (primitiva).

the largest vascular structure in the neck. As shown in Fig. 493 it is now pierced by branches of three of the cervical nerves, namely the third, fourth, and fifth. These nerves help to orient the sac.

In the embryo 17 mm. long there was a slight extension of the jugular sac into the arm bud. This extension is now much larger, making a definite subclavian sac (*S.l.s.*) along the primitive ulnar vein (*V.u.p.*).[4]

The jugular sac in this stage shows two other important points,—namely, its relation to peripheral lymphatics, and an ex-

[4] This origin of the subclavian sac in human embryos as an extension of the jugular sac is interesting in connection with F. T. Lewis's (1906) discovery, that in rabbits the subclavian sac arises independently from the veins.

tensive bridging of its dorsal border, which is the process by which the sac is transformed into a chain of lymph-nodes. These two processes are closely related in function. In Fig. 493 one enormous superficial lymphatic vessel (*V.l.s.*), which arises from the lateral surface of the sac, extends out to the skin, and spreads out into a plexus of large capillaries in the subcutaneous layer. One of the smallest of these superficial lymphatics is shown on the left side of Fig. 494.

This group of vessels is the first set of lymphatics to reach the skin. This has been abundantly proved in pig embryos by many injections into the skin (Fig. 507). In pig embryos this set of vessels reaches the skin in the neck at about 18 mm.; in human embryos about 20 mm. long. At this stage no injection of any layers of the skin in any other place except the neck has ever entered lymphatics. The great size of these early lymphatic vessels to the skin is in some sense represented in the adult by the greater size of the vessels of the deep subcutaneous plexus in contrast with the superficial plexus, and calls to mind the size of the subcutaneous lymph-sacs of the amphibia.

In Fig. 493 are seen lymphatics extending over the skin of the head as a superficial plexus (*V.l.s.*) and deep lymphatics (*V.l.p.*) extending from the subclavian sac along the course of the primitive ulnar vein into the arm bud.

The bridging of the jugular sac along its dorsal border is shown in Fig. 495. The level of this section is also indicated on Fig. 493. This process of bridging or the cutting of the lumen of the sac by bands of connective tissue begins early, being first noted in an embryo 14 mm. long. It is a process by which the sac, originating from a plexus of blood-capillaries, is reconverted into a capillary plexus this time lymphatic in character. This lymphatic plexus is far more extensive than the preliminary blood-capillary plexus, as may be seen by comparing the early sac of Fig. 489 with the one in Fig. 493, from which the lymphatic plexus is formed, or by comparing the length of the blood-capillary plexus along the vein, 0.3 to 0.7 mm., with the length of the sac, 5 mm.

To complete the account of the jugular sacs as far as they have been studied—that is, up to the stage when the fetus measures 80 mm.—the sac becomes more and more encroached upon by the connective-tissue bridges, until it is transformed into a plexus of lymphatic capillaries, out of which chains of lymph-glands are evolved.

In Fig. 493, beside the jugular-subclavian sac, there are three other sacs, the retroperitoneal, the posterior, and the cisterna chyli. None of these sacs nor any anlage of them has been made out in embryos under 20 mm. in length. The retroperitoneal sac and cisterna chyli are present in a human embryo 23 mm. long, while all three are present in one 24 mm. long.

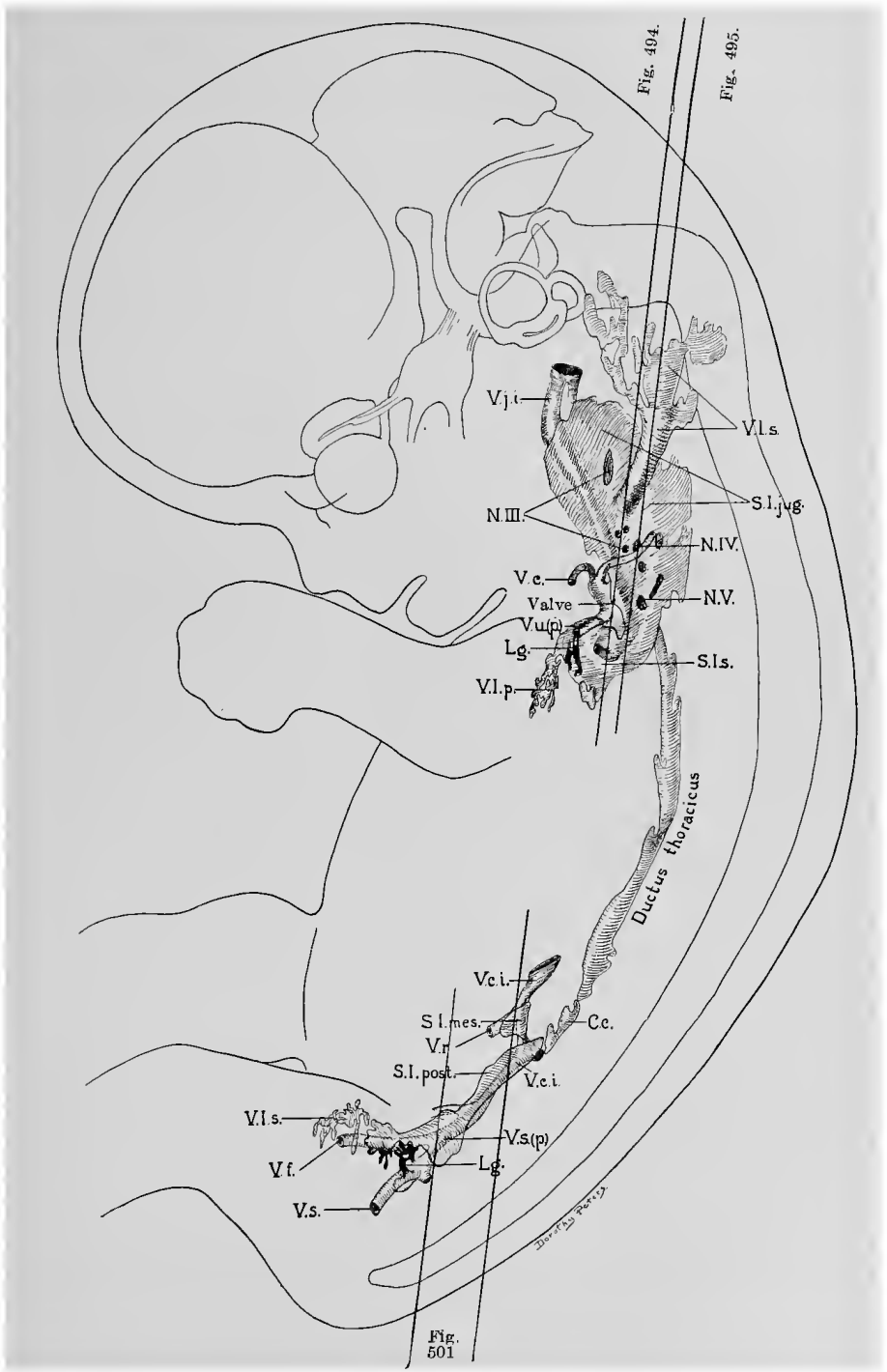


FIG. 493.—Profile reconstruction of the primitive lymphatic system in a human embryo 30 mm. long. (Mall's collection, No. 86.) × about 5.8. *C.c.*, cisterna chyli; *L.g.*, lymphoglandula; *N.III.*, *N.IV.*, and *N.V.*, nervi cervicalis; *S.l.jug.*, saccus lymphaticus jugularis; *S.l.mes.*, saccus lymphaticus retroperitonalis; *S.l.p.*, saccus lymphaticus posterior; *S.l.s.*, saccus lymphaticus subclavius; *V.c.*, vena cephalica; *V.c.i.*, vena cava inferior; *V.f.*, vena femoralis; *V.j.i.*, vena jugularis interna; *V.l.p.*, vasa lymphatica profunda; *V.l.s.*, vasa lymphatica superficialia; *V.r.*, vena renalis; *V.s.*, vena sciatica; *V.u.(p.)*, vena ulnaris (primitiva).

The retroperitoneal sac was discovered as a part of the lymphatic system by F. T. Lewis (1901–02 and 1906). Baetjer (1908) found in carefully tracing its history in embryonic and fetal pigs, that it is preceded in embryo pigs 17 to 18 mm. long by a plexus of capillaries in the root of the mesentery, which drained into the large anastomosing vein at the hilum of the two Wolffian bodies. These capillaries are readily injected from the vein, as is seen in Fig. 496. The same figure shows the large renal anastomosing vein between the Wolffian bodies ventral to the aorta. It also shows well the mass of connective tissue between the vein and the mesentery in which the retroperitoneal sac develops. The plexus retains its connection with the veins until the embryo is 20 mm. long, as is shown in Fig. 497. Other sections of the same series showed more of the ink within the plexus, but this section was chosen to show the connection with

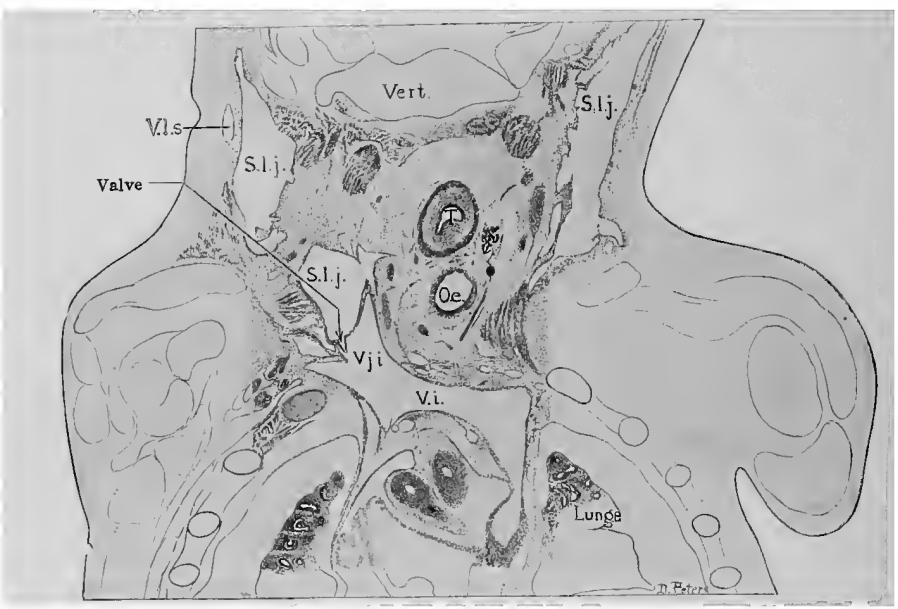
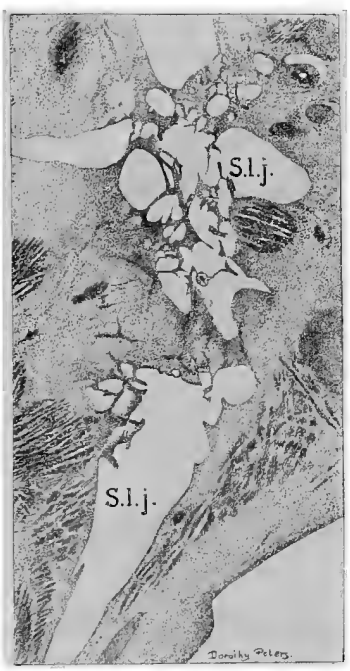


FIG. 494.—Frontal section through the jugular lymph-sacs in a human embryo of 30 mm. (Mall's collection, No. 86.) × about 9. The level of the section is shown on the reconstruction of Fig. 493. The section shows the complete lymph-sac on the right side and the valve on the left. *S.l.j.*, saccus lymphaticus jugularis; *V.i.*, v. innominata; *V.j.i.*, v. jugularis interna; *V.l.s.*, vasa lymphatica superficialis; *Oe.*, œsophagus; *T.*, trachea.

the vein. From this time on, the plexus is readily transformed into a sac, as shown in Fig. 498 in an embryo 23 mm. long, in which the sac is entirely separate from the vein. The sac joins the cisterna chyli, through which it can drain into the thoracic duct and the veins, in embryos 27 mm. long (Fig. 499). These four figures are the best representation that we have of the proof of the transformation of a venous plexus into a lymphatic sac.

In human embryos the stage corresponding to Fig. 496, in which there is a plexus of veins ventral to the renal anastomosis, has been identified in an embryo 20 mm. long, while at 23 mm. there is a definite retroperitoneal sac and a cisterna chyli. The retroperitoneal sac lies in the root of the mesentery adjacent to the great masses of the suprarenal bodies and the sympathetic nervous system (*S* and *G.s.*, Fig 500). It extends from a point

opposite the fourth lumbar vertebra anteriorly, to the point where the superior mesenteric artery enters the mesentery. The position of the retroperitoneal sac is also shown in Fig. 493 and its relation to the renal vein in Fig. 501, which corresponds with the line so marked on Fig. 493. The sac has never been found as large in human embryos as it is in the pig. In a fetus 80 mm. long it is represented by a long chain of lymph-glands or a plexus of lymph-vessels which form the anlage of the glands ventral to the aorta. It has recently been shown by Heuer (1909) that injections of the retroperitoneal sac enable one to follow the progression of vessels from this sac out into the mesentery along



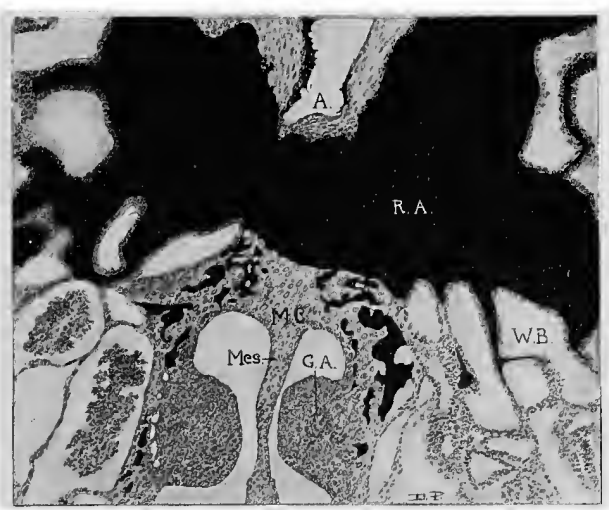


Fig. 495.—Frontal section through the jugular lymph-sac of the same embryo, at the level shown in Fig. 493, to show the bridging of the sac which is the anlage of the first lymph-gland. × about 19. *S.l.j.*, saccus lymphaticus jugularis.

Fig. 496.—Transverse section through the renal anastomosis of the subcardinal veins of an embryo pig 18 mm. long. (After Baetjer.) × about 43. *A.*, aorta; *G.A.*, genital anlage; *M.C.*, retroperitoneal capillaries; *Mes.*, mesentery; *R.A.*, renal anastomosis; *W.B.*, Wolffian body.

the superior mesenteric artery. Within the mesentery is formed a secondary great lymphatic plexus, the anlage of the lymphoglandulæ mesentericæ (*Lg.m.*), as shown in Fig. 502. From the mesenteric vessels lymphatics gradually invade the intestinal wall.

The posterior lymph-sac has as yet been identified only in pig and in human embryos among mammals. It has, however, been worked out in chick embryos by Sala (1900), where it is a true lymph-heart with muscle in its wall, as in the amphibia. Sala's work has already been referred to; it is the most recent work based on the theory, also brought out by Gulland (1894) and Saxer (1896),

that the lymphatics arise from tissue spaces, unless one includes the work of Huntington and McClure who hold a modified form of this theory (1910). Sala found that the posterior lymph-hearts begin at the middle of the seventh day in connection with the lateral branches of the first five coccygeal veins. He says that corresponding to these veins there are excavations in the mesenchyme which soon enter into communication with the lateral branches ("E sono rappresentati da spazi scavati nel mesenchima che sta lateralmenti ai miotomi caudali, a livello delle prime cinque vene coccygee," p. 292); and in fact one would say that these fissures are simply dilatations of the veins themselves ("Si direbbe anzi che esse non sono che semplici dilatazioni, ramificazioni delle stesse vene," p. 269). These two statements, of course, contradict each other, for spaces can not be both fissures in the mesenchyme and dilatations of the veins. Then he

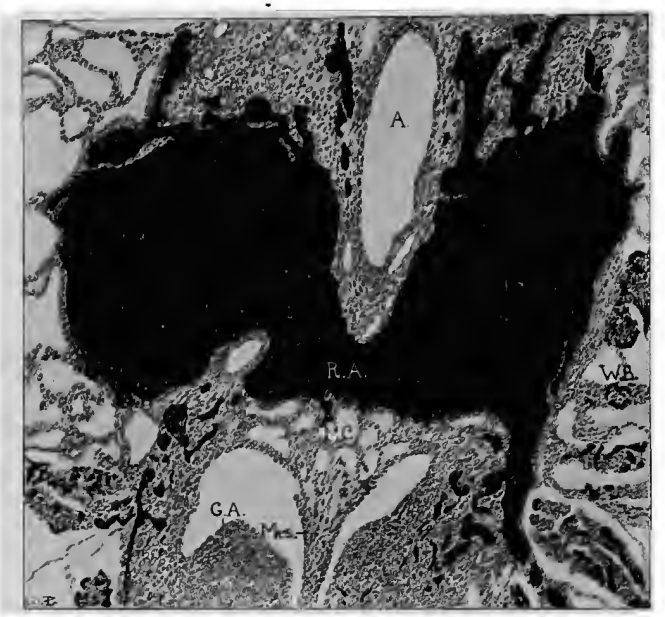


FIG. 497.—Transverse section through the renal anastomosis of the subcardinal veins in an embryo pig, 20 mm. long. (After Baetjer.) × about 43. In this section the venous channels in the root of the mesentery are beginning to show definite evidences of fusion and sac formation, though they are still connected with the veins, as is shown in the figure. *A.*, aorta; *G.A.*, genital anlage; *M.C.*, retroperitoneal capillaries; *Mes.*, mesentery; *R.A.*, renal anastomosis; *W.B.*, Wolffian body.

describes these fissures as becoming more abundant and confluent. By opening up communications with each other they form a sac or lymph-heart in the mesenchyme. This sac, he says, is lined with flattened mesenchyme cells, which, if it were so, would, according to our stand-point, exclude it from being a vein. He found muscle in the wall of the hearts on the ninth day, and was able to inject the heart directly by the second half of the tenth day. Sala's description of the origin of the posterior lymph-hearts in the chick is, nevertheless, so clear and graphic, and corresponds so closely with the method of origin of the lymph-sacs in mammals, that one easily suspects that the two processes are the same,—that the sacs arise from the veins in both cases. The fact that Sala uses the description as evidence of the old conception, of the lymphatic system as coming from tissue spaces, does not necessarily confuse the picture. Mierzejewski (1909), working on the chick, has confirmed Sala's description, and evidently is of

the opinion that both Sala and he find the sac arising from the veins, for he states that "An den Enden der lateralen Aeste der ersten fünf Coccygealvenen bilden sich kleine, blasenartige Ausbuchtungen, die sich beständig vergrössern und am siebenten Bebrütungstage eine Reihe von segmental nacheinanderfolgenden, mit den Vene in Verbindung stehenden Spalten im embryonalen Bindegewebe bilden. Diese Anlagen des späteren Lymphherzens nehmen im Verlauf der Entwicklung an Grösse zu und nähern sich einander immer mehr und mehr, so das sie schliesslich miteinander an den Stellen, wo sie berühren verschmelzen." He also states that he agrees with Sala, except that the process begins a little earlier than Sala described,—namely, in the middle of the 6th rather than the beginning of the 7th day. Thus it seems a fair conclusion that the weight of evidence from the study of the posterior hearts in the chick is on the side of their venous origin.

In a human embryo 20 mm. long there is a plexus of capillaries along the v. ischiadica which forms the anlage of the posterior sac.

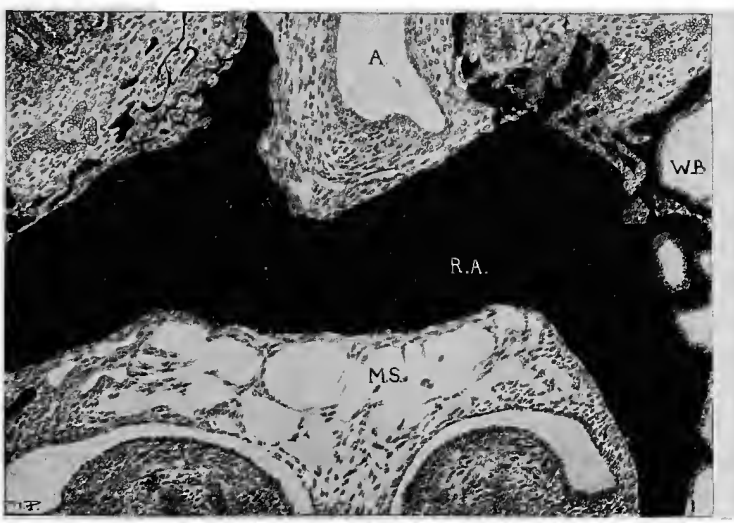


FIG. 498.—Transverse section through the rena anastomoses in an embryo pig 23 mm. long. (After Baetjer.) × about 53. This is the first appearance of a definite sac in the exact location of the venous plexus in the earlier stages. It will be noticed that the irregular margins suggest the fusion of many small vessels. At this stage no connection can be traced between the sac and either the lymphatic system or the veins. *A.*, aorta; *M.S.*, retroperitoneal sac; *R.A.*, renal anastomosis; *W.B.*, Wolffian body.

The saccus posterior or ischiadicus is first found in an embryo 24 mm. long, and is well shown in Fig. 493 in the embryo 30 mm. long. Here it is a long narrow sac—seen also on one side in Fig. 501—which extends along the external surface of the v. ischiadica primitiva (*S.l.p.*), from the posterior end of the cisterna chyli to the bifurcation of the v. femoralis and the v. ischiadica. The sac reaches an apparent maximum in fetuses 80 mm. long. It is shown to great advantage in sagittal section in a fetus 80 mm. long in Fig. 504. The posterior sac is now clearly a pelvic structure, being transformed into a chain of lymphoglandulæ iliacæ.

The question of the origin of the cisterna chyli and the thoracic duct has proved a difficult problem because the region is hard to eject.

Recent studies on pig embryos throw some light on the thoracic duct. In a pig embryo 23 mm. long (measured fresh along the mesencephalosacral line; compare Chap. VIII) the left jugular sac was filled with ink through the superficial lymphatics. The needle was then withdrawn and pressure applied to the head. By a fortunate chance most of the ink ran over into the thoracic duct while very little ran into the veins. Usually the ink passes readily through

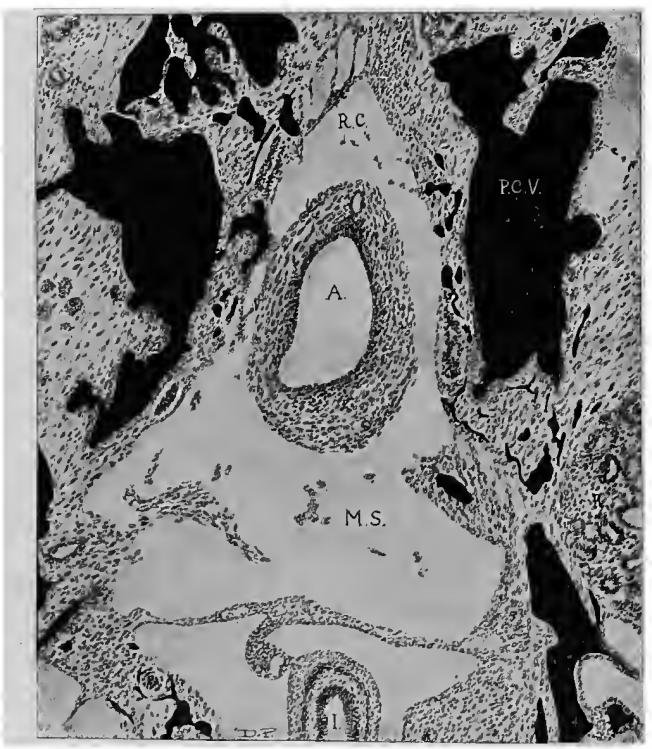


FIG. 499.—Transverse section through the early cisterna chyli and retroperitoneal sac in an embryo pig 3 cm. long. (After Baetjer.) × about 40. The section shows the connection of the cisterna chyli and the retroperitoneal sac, by large channels along the lateral margins of the aorta. *A.*, aorta; *K.*, kidney; *I.*, intestine; *M.S.*, retroperitoneal sac; *R.C.*, cisterna chyli; *P.C.V.*, postcardinal vein.

the valve into veins. In this specimen it can be shown that the jugular sac anlage of the thoracic duct has three connections with the jugular sac, and passes as a plexus of lymphatic vessels toward the median line between the sympathetic nerve and the common jugular vein (these relations can be made out in Fig. 488). The two ducts, the thoracic duct and the right lymphatic duct, extend in the loose connective tissue dorsal to the œsophagus about to the level of the arch of the aorta. At this stage there are no lymphatics corresponding to the cisterna chyli, but there are especially abundant median anastomoses of the posterior cardinal or azygos and hemiazygos veins dorsal to the aorta opposite the adrenal anlages.

In the next stage—namely, in an embryo 25 mm. long—the jugular sac anlages are more extensive and now symmetrical, for the right duct has turned ventralward toward the root of the lung while the left, or thoracic duct, remains near the aorta. A second change of importance has taken place,—namely, the separation of a new lymph-sac from the veins, the cisterna chyli, which exactly replaces the previous plexus of veins. An abundant plexus of lymphatic vessels encircles the aorta from this cisterna chyli, so that one can not in this region speak of a right and left duct, but rather of an aortic plexus. This fact is interesting in comparison with Pensa's (1908 to 1909) figures showing the comparative morphology of the duct in various forms, for he shows that in a number of forms the lower part of the thoracic duct is an abundant plexus of lymphatic vessels. By the time the pig is 27 mm. long the relations of the three prevertebral

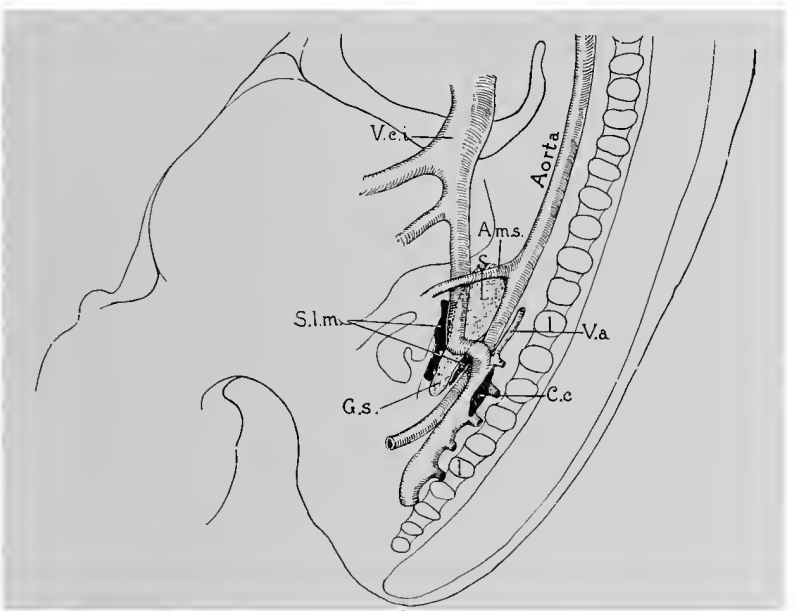


FIG. 500.—A composite diagram made by superimposing the sections showing the relations of the retroperitoneal sac and cisterna chyli to the veins, in a human embryo measuring 27 mm. (Mall's collection, No. 382.) × about 8. *A.m.s.*, a. mesenterica superior; *C.c.*, cisterna chyli; *G.s.*, ganglia sympathica; *S.l.m.*, saccus lymphaticus retroperitonealis; *S.*, suprarenal body; *V.a.*, v. azygos; *v.c.i.*, vena cava inferior.

lymphatic anlages are established, the right lymphatic jugular sac anlage, making the right duct, has reached the root of the lung, while the left jugular sac anlage has anastomosed with the cisterna chyli anlage along the aorta, making the thoracic duct. All the specimens studied show some isolated endothelial-lined spaces which cannot he traced to connect with the thoracic duct in serial sections. The existence of these isolated spaces was pointed out hy Lewis (1906), and, since he could trace a few of them to join veins, he suggested that there might be multiple venous anlages of the lymphatic vessels analogous to the lymph-sacs. Since these spaces or isolated islands are found along other veins as well as the azygos veins, they will be discussed under the general considerations (p. 737).

The other recent work on the thoracic duct is by McClure (1908), in which he agrees with Lewis that the thoracic duct arises by multiple anlages from the veins. This view he retracted in 1910 in favor of the extra-intimal theory; but, since he did not retract the evidence in his first paper but only the interpretation of the observations, it must be stated that he confused veins and lymph-

atics, calling certain veins lymphatic anlages, when it is easy to demonstrate that these same veins persist as veins after the thoracic duct is formed.

In human embryos the observations on the thoracic duct are still scanty. In the embryo shown in Fig. 488, which is 10.5 mm. long, there is on the left side a small vessel extending from the

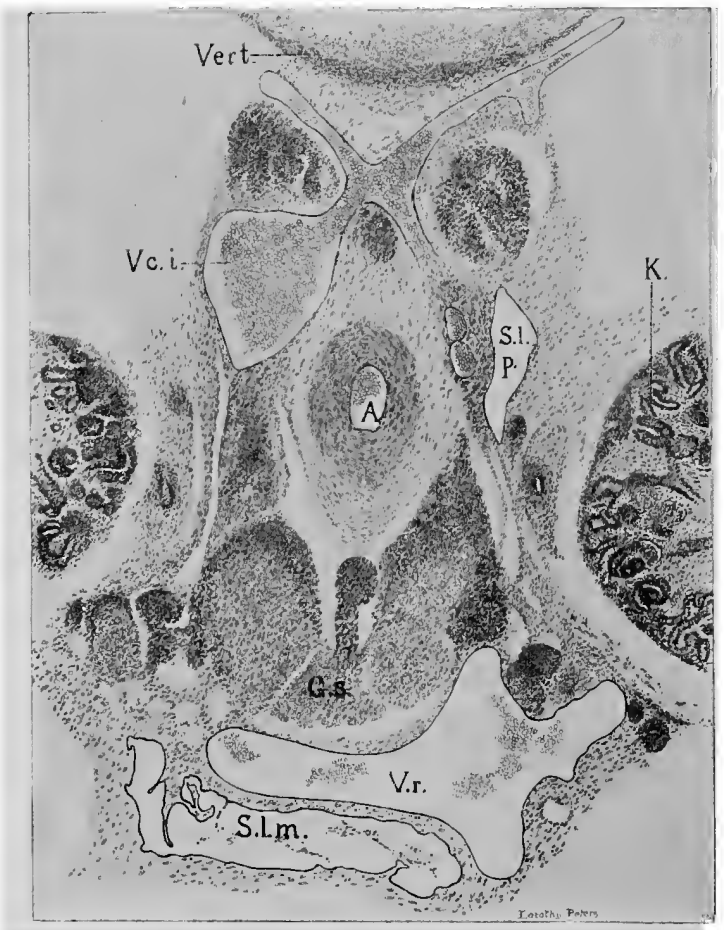


FIG. 501.—Frontal section through the retroperitoneal sac of the human embryo, at the level indicated on Fig. 493. × about 40. *A.*, aorta; *G.s.*, ganglia sympathica; *K.*, kidney; *S.l.m.*, saccus lymphaticus retroperitonealis; *S.l.p.*, saccus lymphaticus posterior; *V.c.i.*, vena cava inferior; *V.r.*, vena renalis.

sac toward the median line. In an embryo 16 mm. long there are symmetrical jugular sac anlages of the thoracic and right lymphatic ducts, which, however, do not reach the zone dorsal to the œsophagus. The first appearance of the cisterna chyli is in an embryo 23 mm. long, as shown in Fig. 500. Here it is a definite sac opposite the third and fourth lumbar vertebræ, at

the point where the vena cava curves ventralward and where it anastomoses with the azygos vein. By the time the embryo is 30 mm. long, as shown in Fig. 493, the thoracic duct is complete. The lower or cisterna chyli portion is much simpler than in the pig embryos, in fact there is a right and a left vessel, and the right duct crosses behind the aorta in the thorax to join the left. Thus the human embryos illustrate the double origin of the duct from the jugular sacs on the one hand and from the cisterna chyli, a true lymph-sac, on the other.

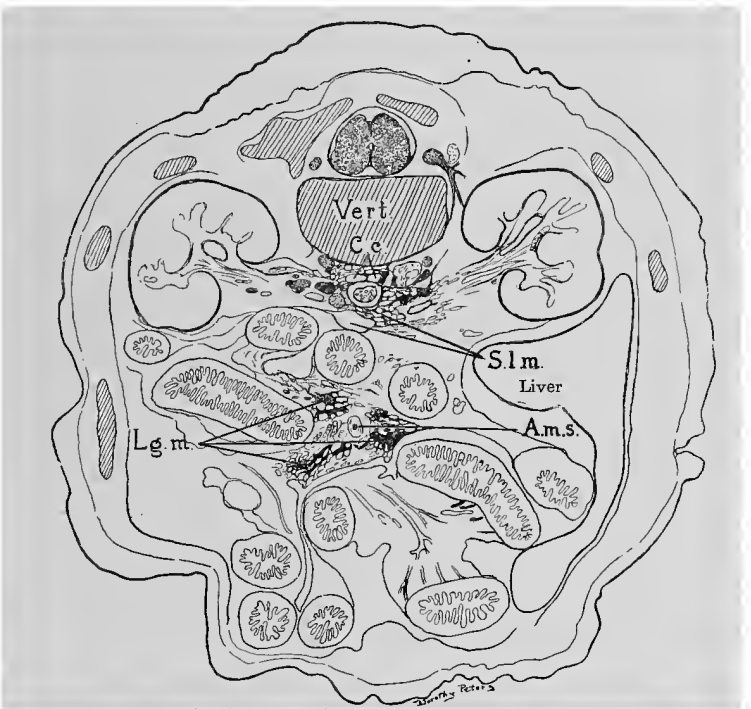


FIG. 502.—Transverse section through the abdominal cavity of a human embryo 80 mm. long. (Mall's collection, No. 172.) × about 8. *A.m.s.*, arteria mesenterica superior; *C.c.*, cisterna chyli at its lower border; *Lg.m.*, lymphoglandulæ mesentericæ; *S.l.m.*, saccus lymphaticus retroperitonealis.

The question of the peripheral growth of lymphatics is one which really lies at the root of the new conception of the origin of the lymphatic system from the veins. In studying the peripheral lymphatics it was found that they converged toward or radiated out from certain centres. These centres proved to be the lymphatic sacs. The lymphatic sacs become united into a system by means of the thoracic duct, and connected with the veins by the development of valved openings. The sacs and thoracic duct may be termed a primary system, which is shown on Fig. 493. The secondary or peripheral lymphatics, according to our view, grow out from the primary system. In tracing the peripheral

lymphatics we may refer again to Fig. 493, which shows not only the primary system of sacs complete but the beginning of the peripheral vessels. The earliest peripheral lymphatics that have been made out in a human embryo are those from the jugular sac to the skin of the neck in an embryo 20 mm. long. These vessels are shown (*V.l.s.*) in the embryo 30 mm. long in Fig. 493, and again as the large deep vessel behind the ear and pointing toward the shoulder in Fig. 505. At the stage of 30 mm., beside the superficial vessels for the back of the head, there are deep lymphatic vessels (*V.l.p.*) extending along the subclavian vein. The transformation of the jugular subclavian sac into a chain

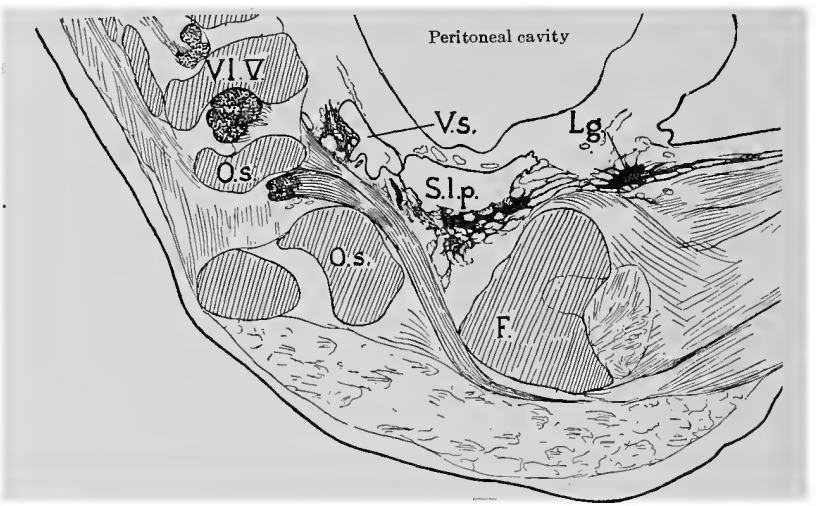


Fig. 503.—Sagittal section of a human embryo measuring 50 mm., showing the posterior lymph-sac within the pslvis and its extsnsion along the fcmoral vein. (Mall's collsction, No. 96.) × about 8. *F.*, fsmur; *Lg.*, lymphoglandula (femoralis); *O.s.*, os sacrum; *S.l.p.*, saccus lymphaticus postsrior with lymph-gland in ths bordsr; *V.s.*, vsna sciatica; *V.l.V.*, vstrsbra lumbalis V.

of lymph-glands makes the primary group of glands for these two sets of vessels. In Fig. 493 is shown a small gland (*Lg.*) on the course of the plexus of lymph-ducts at the edge of the subclavian sac. This marks the beginning of secondary glands, that is those that form on the course of lymph-ducts. From the posterior sac two sets of peripheral vessels are extending, one along the v. femoralis, shown as *V.l.s.*, while the second set, which follows the V. ischiadica to the hip, is not shown. The vessels along the v. ischiadica have, however, reached the skin and spread out over hip and back at this stage, as can be seen for the pig in Fig. 507.

Recently I have had the privilege of studying a remarkable specimen of a lymphatic distention in a human embryo. The embryo, which is 5.5 cm. long, was injected through the umbilical artery by Professor Max Broedel while the heart was still beat-

ing. It was then placed in formalin and left there for about a year. Dr. H. M. Evans then began to study the vascular injection in the skin vessels, and while working on it put the embryo into freshly made-up 50 per cent. alcohol. To his amazement, there appeared a wonderful injection of air in the skin, which proved to be a complete injection of the superficial lymphatic system. The irregular lymphatic plexus shown in silvery lines was of great beauty. Two tracings were made of the specimen under direct sunlight, with the aid of a camera lucida, one a side

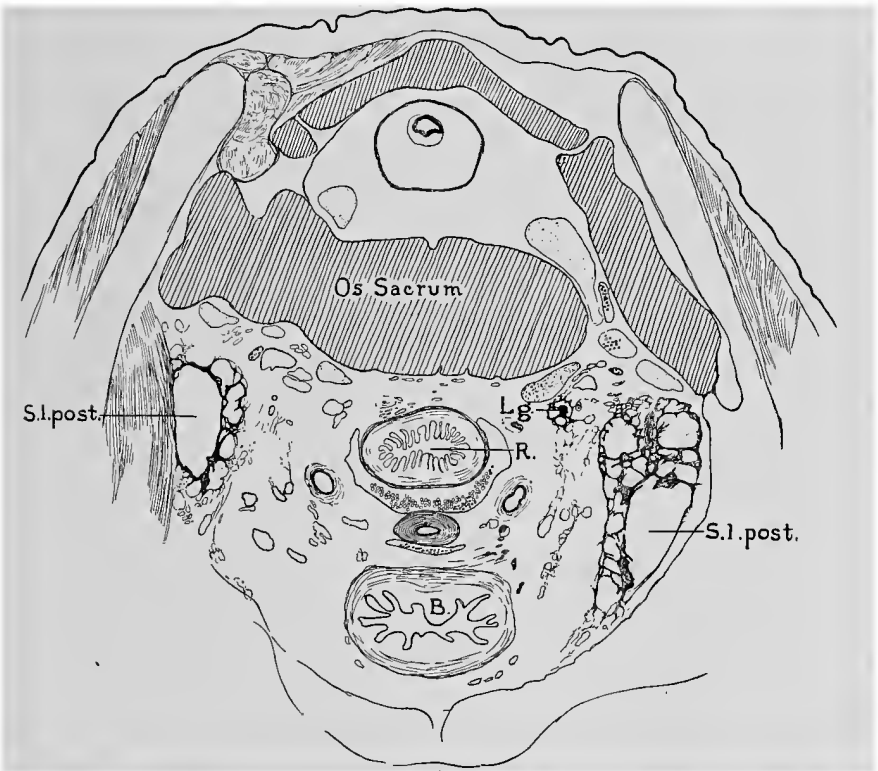


FIG. 504.—Transverse section through the pelvis of a human embryo 80 mm. long, to show the posterior lymph-sacs. (Mall's collection, No. 172.) × about 9. *B.*, bladder; *Lg.*, lymphoglandula; *R.*, rectum; *S.l.post.*, saccus lymphaticus posterior.

view shown in Fig. 505, the other a dorsal view, Fig. 506. The injection gradually disappeared, but for a few days could be restored by the use of fresh alcohol.

The specimen is of the same stage as the largest pig embryo figured in my article (1904) on the superficial lymphatics, and the two specimens make an interesting comparison. It is the stage of the single primary lymphatic plexus, and only in one area, namely in front of the ear, was there a double plexus, deep and superficial.

Notwithstanding the great irregularity of the plexus, a quite definite pattern is to be made out. The vessels all drain into two areas, as shown on the side view. First the vessels from the head, neck, arm, and thorax run toward the jugular-subclavian sac, and secondly those from the leg, hip, and abdominal wall run toward the groin to the posterior sac. These points of drainage

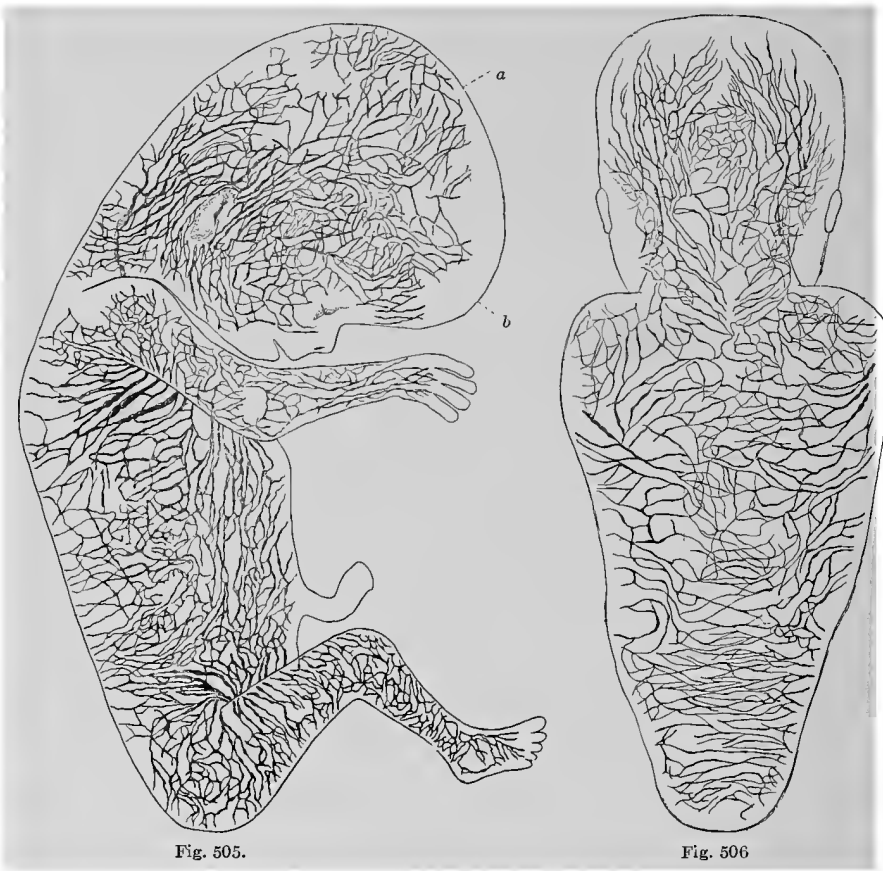


Fig. 505. Fig. 506

FIG. 505.—Distention of the lymphatic vessels with air of a human fetus 5.5 cm. long, drawn by means of a camera lucida. (Mall's collection, No. 448.) × about 2. The drawing had to be completed without the object. *a–b*, area without lymphatics.

FIG. 506.—Distention of the lymphatic vessels with air in the same fetus as in Fig. 505.

are marked on the surface by the few large definite trunks that radiate toward them. The vessels which drain toward the neck and axilla—namely, the trunk behind the ear and the pectoral trunks below the arm—have valves. The vessels on the abdominal wall pointing toward the groin are large and irregular, but are as yet without definite valves. Valves are wanting in all the rest of the vessels. It is striking how completely the entire lymphatic plexus anastomoses, so that theoretically one can inject the

entire lymphatic system through any one vessel whatever. The natural flow of lymph toward the sacs, however, is indicated by the size of the main trunks.

The extent of the injection is most interesting. There is a small area on the head in the mid-line (between the letters *a* and *b* in Fig. 505) which never showed any lymphatics. It is the same area, only less extensive, that could never be injected in the pigs of this stage, and thus is probably entirely free from lymphatics. The fingers, toes, the palms of the hands, and soles of the feet likewise had no injection whatever.

The pattern of the vessels over the head shows a number of interesting points. Over the face the mesh is much finer than over the scalp. The eyelids show a few vessels, the ear none. Behind the ear is shown a large deep trunk, seen in both figures, which drains the back of the head and neck and undoubtedly enters the jugular sac or gland. This trunk is to be compared with the vessel marked *V.l.s.* in Fig. 493 and in Fig. 494. There is probably also a deep, large channel in front of the ear, for the vessels of the face and chin converge there, but the double plexus of capillaries was so dense there that none could be made out. On the back of the head, long parallel vessels drain toward the jugular trunk on either side, while in the centre the plexus is fine-meshed toward the top of the head and coarse-meshed toward the neck. The vertebra prominens is marked by being rather free from lymphatics, and the same is true of the bony prominences at the elbow and ankle.

The arm shows a fine-meshed plexus; the vessels reach the cleft between the fingers in each case. The pattern of the forearm is made by long parallel vessels running lengthwise, while in the upper arm the vessels run around toward the axilla.

The plexus over the ventral surface of the body is fine-meshed, and there is a complete anastomosis across the mid-line; over the back the plexus is coarse-meshed. A few large vessels over the chest and back drain toward the axilla; a similar set converge to the groin. The latter do not yet show valves. The especial characteristic of the back region is that the mid-line is bridged by long, rather slender parallel vessels. This is more marked in the lower third.

On the foot the vessels reach the clefts between the toes just as on the hand they reach the clefts between the fingers. The malleoli are quite free from vessels. On the leg the vessels run obliquely rather than lengthwise on the lateral aspect, while on the thigh the plexus points toward the groin.

The double injection of blood-vessels with Prussian blue and of the lymphatic capillaries with air enabled one to see their relative positions with great clearness. The large main blood-vessels

of the skin were deeper than the lymphatics, while the entire system of smaller arteries and the blood-vascular capillary plexus lay superficial to the much larger lymphatic plexus.

The development of the peripheral lymphatics out from the sacs to the ultimate capillaries has been worked out in the skin of the pig, of the bird, (Mierzejewski, 1909), and of bovine embryos (Polinski, 1910). In the skin (Sabin, 1904) a great number of injections have brought out the fact that the vessels spread out from two great centres, the neck and the groin, so that the vessels gradually extend from lymphatic to non-lymphatic areas. Fig. 507 will

FIG. 507.—The lymphatic vessels of the skin of an embryo pig 4.3 cm. long. × about 2½. The injected vessels form the primary subcutaneous plexus and represent a complete injection except in the area dorsal to the ear,—that is to say, the uninjected areas have not yet received lymphatics.

serve to show the spreading out of the lymphatics in the primary subcutaneous plexus. The group in the neck is growing out from the jugular sac, the group over the hind leg is extending from the posterior sac. Both of these injections are complete or nearly so, showing that there is a large non-lymphatic area at this stage. Later a secondary, finer-meshed, and more superficial plexus develops.

From the retroperitoneal sac, the peripheral spread of the lymphatics to the ultimate lacteals of the intestine has been worked out by Heuer (1909) in the pig. Fig. 508, taken from this paper, shows the entrance of the groups of lymphatics from the mesentery into the intestinal wall, and the primary submucosal plexus not yet complete. Later a finer-meshed plexus forms in the mucosa, and from this plexus the lacteals grow into the villi.

This point of the gradual progression of the lymphatics within an organ out to the ultimate capilliaries, which is one of the strongest proofs of the growth of lymphatics from the veins to the periphery, rather than from the periphery to the veins, is also very convincingly shown by H. M. Evans. Fig.

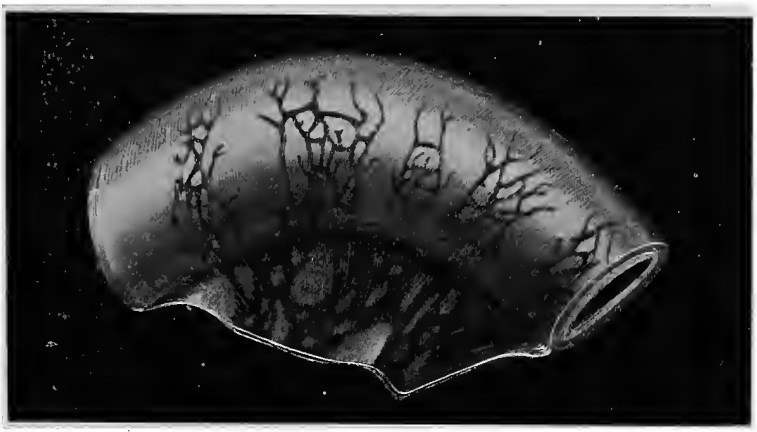


FIG. 508.—Loop of the small intestine of an embryo pig 100 mm. long, to show the growth of the lymphatics into the intestine, and the formation of a primary submucosal plexus out of a series of lymphatic loops. (After Heuer.)

509 is taken from this paper, which describes a case of sarcoma of the intestine in which there is a growth of new lymphatics out into the tumor mass. It will be noticed that the growth is from the mucosal or capillary plexus, that at the edge of the tumor the new vessels are like normal lacteals, while within the

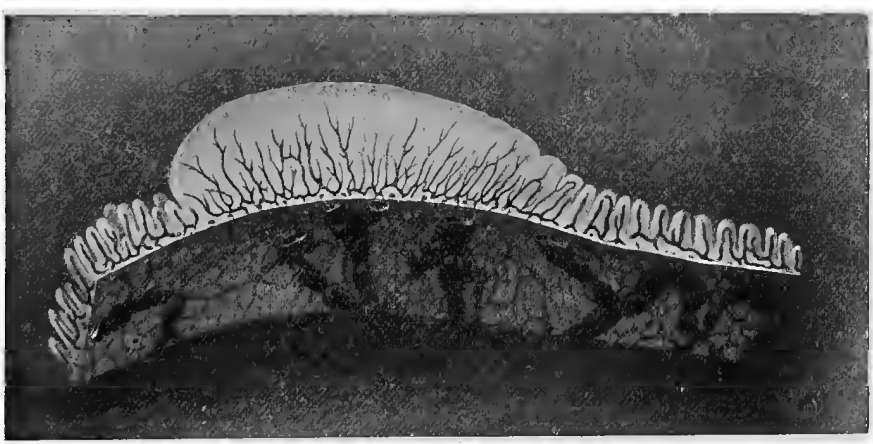


FIG. 509.—A piece of adult intestine showing a sarcomatous nodule which is being invaded by growing lymphatic capillaries from the mucosal plexus. The transition from the normal lacteals to the new vessels is to be noted in passing from right to left. The large submucosal ducts are seen in the shaded area. (After Evans.)

nodule there is an over-development of lymphatics in the form of an advancing plexus. It has also been pointed out to me by Dr. Evans that in the adult intestine the valves of the lymphatics occur at the base of the capillary bed, that is in the submucosal ducts, and that they mark the place of transition between the duct

and the capillary. Thus the mucosal plexus and the lacteals are the ultimate capillaries. This agrees with the general theory of Ranvier, that in the lymphatic system vessels without valves have the structure of capillaries. The discovery that the lymphatic vessels invade each organ, that the invasion can be demonstrated by injections of successive stages as soon as the line of growth or point of entrance is known, together with the fact that the valves develop at the base of the capillary bed, gives us the key by which the relations of the lymphatic system within each organ can be worked out from the primary distributing plexus of ducts to the ultimate capillaries. It may be well to note here that the lymphatics as they enter an organ are always capillaries, that is the growing zone is always the capillary bed.

To sum up, the peripheral spread of lymphatics thus far observed in human embryos, from the jugular-subclavian sac, two sets of vessels extend, one to the skin of the head, neck, and shoulder, the other as deep lymphatics to the arm. From the posterior sac two sets of vessels develop, one along the v. ischiadica to the skin of the hip and back, a second set along the v. femoralis to the leg (Fig. 493). The retroperitoneal sac sends vessels into the mesentery (shown as *Lg.m.* in Fig. 502). On the course of these vessels a mass of lymph-glands develops and vessels extend out from these glands to the intestine. The cisterna chyli drains both the retroperitoneal and the posterior sacs (Fig. 493). The progression of the lymphatics in the Mall collection is summed up in the following table.

In regard to the development of lymph-glands the series of human embryos serves to establish an interesting general relation and to illustrate certain phases in the development of an individual gland. In general, the first stage in the development of an embryonic lymph-gland is the formation of a plexus of lymph-ducts. This was one of the earliest points established and goes back to the time of Breschet (1836). The first lymph-gland to appear is through the transformation of the jugular lymph-sac into a plexus of lymph-vessels. This bridging of the sac is shown in Fig. 495, and is simply a reduction of the sac into a plexus of lymph-vessels lined with endothelium, with bridges of connective tissue between, in which the mesenchyme is slightly denser than in the surrounding tissue. All the primary lymph-sacs are thus transformed into a plexus of lymph-vessels. In the jugular sac the transformation extends over a series of embryos and fetuses from 14 to 80 mm. long. The bridging of the retroperitoneal sac is illustrated in Figs. 501 and 502, in the posterior sac in Figs. 503 and 504. The cisterna chyli becomes bridged only along its borders[5] (Fig. 502). Primary groups of glands may be

[5] In this connection it is interesting to note, that in the amphibia the pulsating lymph-hearts have exactly the same relation to the peripheral vessels as the sacs in mammals have to the corresponding vessels. Thus the sacs and primary lymph-glands represent the amphibian lymph-hearts.

TABLE SHOWING THE DEVELOPMENT OF THE LYMPHATICS IN THE EMBRYOS AND FETUSES OF THE MALL COLLECTION.

(Of the measurements, the first figure is the craniocaudal diameter, the second the transverse, and the third the dorsoventral.)

Length of the embryo in mm.	No. in the collection.	Direction of section.	Jugular lymph-sac.		Other lymph-sacs.		
			Size in mm.	Condition.	Cisterna chyli.	Saccus retroperitonealis.	Saccus posterior.
8	397	Transverse	0.3 x 0.19	Prelymphatic plexus of veins.			
9	163	Transverse	0.36 x .014	Prelymphatic plexus of veins.			
10.5	109	Transverse	0.7 x 0.28	Symmetrical sacs, empty, possible valves.			
11	353	Frontal	1.2	Sac full of blood. Capillary plexus along the v. jugularis. Valve not open. Extension of jugular sac along v. ulnaris.			
12.5	317	Frontal	1.5	Long sac has replaced previous plexus of veins. Valve.			
14	144	Sagittal	1.5	Empty sac, beginning of bridging.			
15	350	Frontal	....	Sac very small.			
15	423	Transverse	0.9	Sac very small.			
16	409	Transverse	.....	Large sac with the anlages of the ductus thoracicus and ductus lymphaticus dexter.			
17	106	Transverse	.....	Sac very small.			
17	296	Frontal	1.5	Large sac. Open valve. Small extension of the sac along the v. ulnaris primitiva.			
16	74	Transverse	1.8	Jugular sac with no extension along the v. ulnaris.			
20	22	Transverse	1.6	Sac wider, pierced by nerve. First vessels from the sac to the skin.	Plexus of capillaries along the anastomosis of the v. renalis.		
20	128	Frontal	0.75	Sac very small.	.....	.....	Capillaries along the v. ischiadica.
23	382	Sagittal	2 x 1	Large sac with valves.	Present.	Present.	
24	6	Transverse	.....	Large sac.	Present.	Present.	Present.
30	86	Frontal	5 x 3.6	Maximum size. Beginning formation of lymph-glands in the saccus jugulo-subclavius.	Present; thoracic duct complete.	Present.	4.6 x 1, with beginning lymph-node.
46	95	Sagittal	3.75 x 1.5	Sac with few lymph-nodes.	Not found.	Present, no lymph-nodes.	2.5 x 0.75.
50	96	Sagittal	4 x 1.5	Sac turning into lymph-nodes.	Not found.	Present, no lymph-nodes.	3 x 1.75.
50	84	Transverse	3 x 1.5	Many follicles.	1.2.	1.6 x 1.	1.7 x 2.5.
50	224	Sagittal	4 x 1.75	Five bridges throughout.	Damaged.	Damaged.	2 x 1.
80	172	Transverse	1.75 x 1 not complete	A chain of lymph-nodes.	Surrounded by lymph-nodes.	Mass of lymph-nodes.	Sac with lymph-nodes 2.8 x 2 x 3.5.

defined as those which develop from the lymph-sacs. They are the jugular-subclavian chain, the retroperitoneal or pre-aortic chain, and the chain of lymphoglandulæ iliacæ. All the lymph drains through these chains.[6] Secondary lymph-glands develop around plexuses of the peripheral vessels, and two of these are shown in Fig. 493, one in the arm, and the second in the leg. The secondary group from the retroperitoneal sac is shown in Fig. 502 as the mesenteric group of glands (*Lg.m.*). The ultimate lymph-glands which develop at the base of the final capillary bed as the lymph-follicles of the intestine were not found in the series; they are probably the last to develop. This is in harmony with the findings of Anton (1901) in connection with the lymph-glands of the Eus-

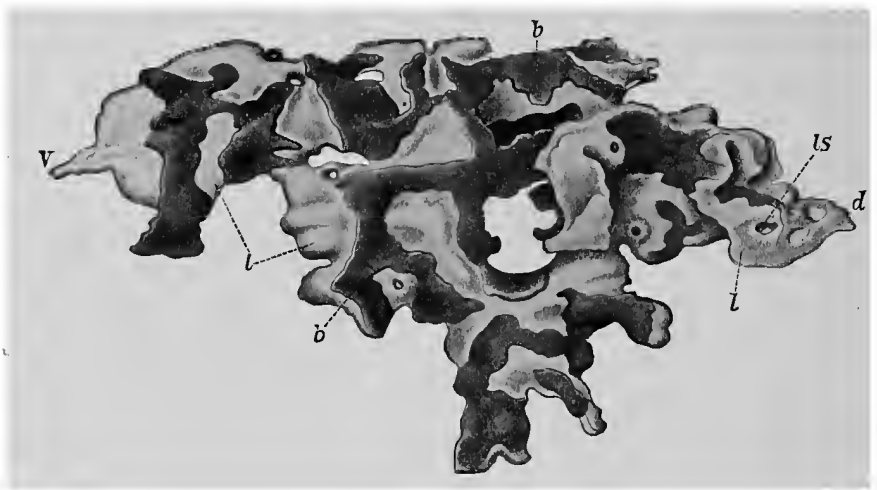


Fig. 510.—Reconstruction of an axillary ymph-node anlage from a human embryo 70 mm. crown-rump, showing the primary plexus of lymphatic capillaries. (After Kling.) × about 41.6. *b*, the bands of connective tissue between the lymphatics; these are shown as darker than the lymphatics; *d*, dorsal; *l*, lymphatic vessels; *ls*, blind end of a sprouting lymphatic capillary.

tachian tube and the middle ear. He found no glands there in the fetus, while during the first two years of life there was a gradual development of lymphocytes which subsequently formed definite follicles.

In regard to the development of an individual node, the important stages can be well illustrated in human embryos.[7] The

[6] This idea finds a very interesting confirmation in the work of Jolly (1910) on the lymph-glands of birds, for he finds that the first lymph-glands, the jugular and ischiatic groups, are centrally placed, and thus support Ranvier's theory of the growth of lymphatics from centre to periphery.

[7] The development of lymph-nodes has been followed in a number of recent papers by Saxer (1896), Gulland (1894), Kollmann (1900), Kling (1904), Sabin (1905 and 1909), and Jolly (1910), of which Kling and Sabin refer to human embryos.

first step in the formation of lymph-glands is a plexus of lymphatic capillaries, and this is true whether the gland forms out of one of the primary sacs or along the course of peripheral lymphatic vessels. This first stage of a lymph-gland is illustrated in section in Fig. 495 for the jugular lymph-gland in an embryo measuring 30 mm. long. The character of the lymphatic plexus is also well shown in Fig. 510, after Kling, from a reconstruction of the subclavian or axillary group of a fetus somewhat larger, measuring 70 mm. In the primary stage the lymph-node is wholly lymphatic in structure,—*i.e.*, it consists of a plexus of lymphatic capillaries with undifferentiated connective-tissue septa.

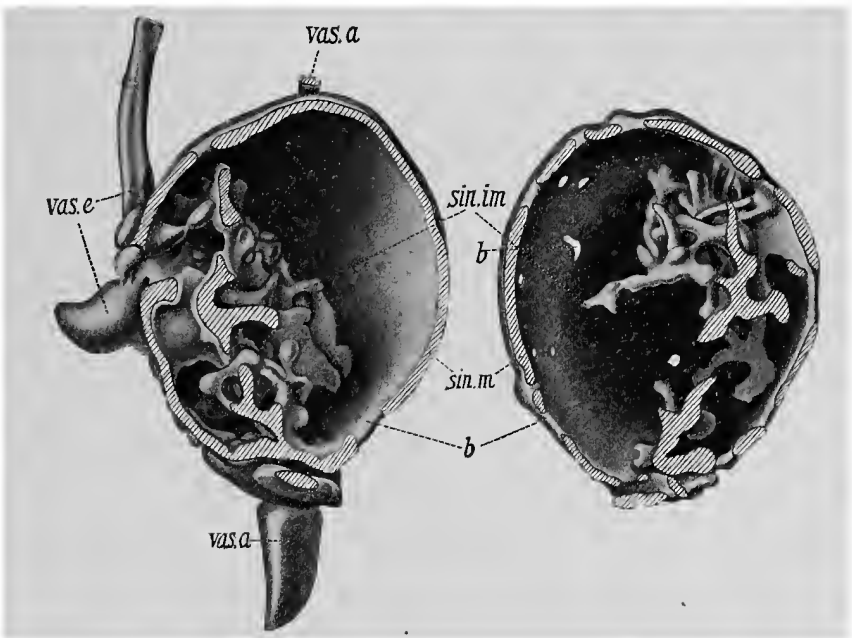


FIG. 511.—Reconstruction of a lymph-node from a human embryo 270 mm. long, showing the peripheral and central sinuses. (After Kling.) × about 41.6. *b*, connective-tissue bands; *sin.m.*, sinus marginalis; *sin.im.*, intermediär sinus; *vas. a.*, vas afferens; *vas. e.*, vas efferens.

The second step of the development of the node is the heaping up of lymphocytes or wandering cells in the connective-tissue septa, forming follicles. These masses of cells are shown in Kling's first model as the darker masses labelled *b*, some of which are oval, while more are irregular in shape. In our series the first definite follicles are found in a fetus 50 mm. long. The follicles are associated with a plexus of blood-capillaries. All the recent investigators note these blood-capillaries in the connective-tissue septa. Thus, in the second stage a lymph-gland contains two elements, a lymphatic element, or the plexus of lymphatic capillaries, and

a vascular element, consisting of blood-capillaries surrounded by lymphocytes in the meshes of the connective tissue, making the follicles. The follicles are well shown in Figs. 503 and 504. The first two stages, while they can be sharply separated in a series of early embryos, in later embryos develop side by side.

The third stage in the development of a gland is the formation of the sinus out of the plexus of lymphatic capillaries. That the sinus is a capillary plexus, as dense as the blood-vessels in cavernous tissue, is shown most beautifully for the adult in the injections of lymph-glands in Teichmann's Atlas. The reorganization of the node, the development of the peripheral and central sinuses, together with the great increase in the follicle, is well

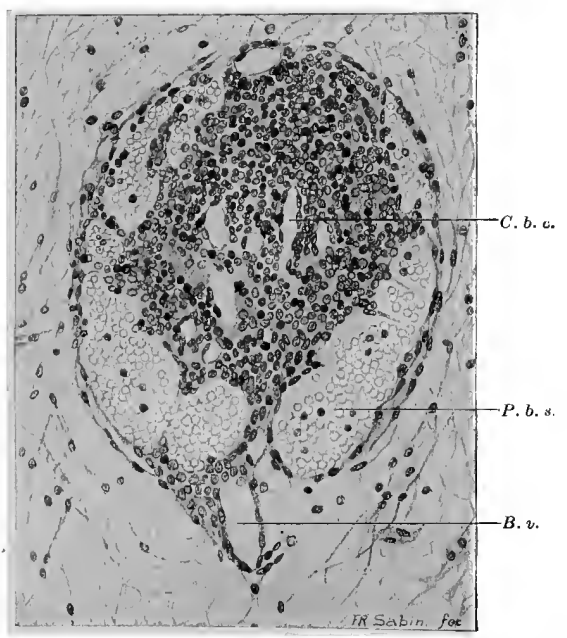


FIG. 512.—Hemal node from the neck of an embryo pig 245 mm. long. *B.v.*, blood-vessel at hilum; *C.b.c.*, central blood-capillary; *P.b.s.*, peripheral blood-sinus.

shown in Fig. 511, after Kling. It shows a model of the lymphatic part of a lymph-gland from a fetus 270 mm. long. The very great size of some of the vessels of the marginal sinus is to be noted. In the development of the various nodes the greatest possible variations occur in the proportion of the lymphatic element or follicle. The sinus formation is also shown in Fig. 504. The sinus differs from the primary lymphatic plexus in the extreme thinness of the connective-tissue septa. It remains to be shown whether it differs also in the nature of its endothelium,—that is, whether the sinus, which begins as a dense plexus of closed lymphatic capillaries in fetal stages, is a closed system in the adult or not.

In the alimentary canal there are certain special lymph-glands—namely the tonsils, solitary follicles, and Peyer's patches—that develop in the capillary bed close under the epithelium. In connection with these nodes there has been considerable confusion in regard to their development. This confusion was the more easy as long as it was thought that the thymus, derived as it is from epithelium, was lymphoid in character. Stöhr (1891 and 1898) and Köllmann (1900) have pointed out that the lymph-nodes in the mucosa of the alimentary canal are mesodermal in origin, as is all the rest of the lymphatic system, rather than ectodermal.

Hemal glands have not been found in human embryos. In pig embryos they appear only in late stages, the first and simplest type, shown in Fig. 512, being found in the neck of a pig 245 mm. long. Here the gland consists of a single follicle around a plexus of blood-capillaries and surrounded by a sinus of blood-vessels. It is thus possible to define the follicle as a collection of lymphocytes around a blood-capillary plexus. The follicle is surrounded by a sinus which may be made of a plexus of lymphatic capillaries forming a lymph-sinus, or by a plexus of blood-capillaries making a blood sinus. The lymphatic sinus is found in the lymph-glands, the blood-sinus is found in the hemal node and in the spleen. A group of lymph-follicles makes a lymph-gland; a group of blood follicles makes a hemal node. In shape the follicle is primarily round, but where the lymphocytes extend along the course of the artery the follicle becomes elongated into the ellipsoids of the spleen or the cords of the lymph and hemal glands. Meyer (1908) showed, by hundreds of injections of hæmolymph or better hemal nodes, that they are not connected with the lymphatic system nor are they intercallated in the course of the veins.

General Considerations.

It is now necessary to bring out certain general considerations which follow from the recent studies on the lymphatic system.

The relation of the lymphatic system to tissue spaces has been one of the greatest questions in connection with the system since it was first vaguely suggested by Aselli (1622) about three centuries ago, and clearly formulated by Lieberkühn (1760) in connection with the discovery of the central lacteals of the villi and the supposed opening of these lacteals into the connective tissue. The history and bearing of this great question were best brought out by His (1863). The general conception of the morphology of the lymphatic system has passed through a series of phases. The early experiments of Nuck (1691), of injecting air into the arteries and noting its return through the lymphatics, led to the theory of the connection of the finest arteries and lymphatics. These hypothetical connections may be grouped together under one general term by which they were known, namely vasa serosa. The vasa serosa are associated with a variety of names, notably Boerhaave, Haller, and Bichat (1818). It was the theory of Haller that the vasa serosa were so small that the red blood-corpuscles could not pass through them, and hence only the fluid of the blood ran over into the lymphatics. As the methods of injecting the fluids were perfected it was noted that only in exceptional cases did fluid forced into the arteries enter the lymphatics. But these observations did not have as much weight in overthrowing the theory of vasa serosa as the development of the ideas of Schwann (1839) and especially of Virchow (1863). From Schwann's observations on the capillaries in the tadpole's tail, he suggested, in connection with his discovery of cells in the animal body, that capillaries were a network of anastomosing cells making canals all over the body. Virchow overthrew the idea of the vasa serosa, as will be seen in the following quotation from the English translation of his Cellular Pathology (p. 76): "Amongst these different species of connective tissue, the most

important for our present pathological views are, generally speaking, those in which a reticular arrangement of cells exists, or, in other words, in which they anastomose with one another. Wherever, namely, such anastomoses take place, wherever one cell is connected with another, it may with some degree of certainty be demonstrated that these anastomoses constitute a peculiar system of tubes or canals which must be classed with the great canalicular system of the body, and which particularly, forming as they do a supplement to the blood and lymphatic vessels, must be regarded as a new acquisition to our knowledge, and as in some sort filling up a vacancy left by the old vasa serosa, which do not exist." Thus Virchow substituted the idea of hollow connective-tissue cells to connect arteries and lymphatics for the vasa serosa. The methods of injection, however, led to sharper and sharper conceptions of the lymphatic capillary, and made, as His (1863) says, the obscure lymphatic roots more and more of a myth. The beautiful injections of Teichmann, together with his own work, led His (1861) to formulate the opinion that "Die ersten wurzeln des Systems durchweg der eigenen, isolierbaren Wand entbehren, es sind Känale in das Bindegewebe der Cutis, der Schleimhäute usw. eingraben."

The next great step was the discovery that capillaries are lined with endothelium, one of the most important discoveries in histology. This dates back to the work of Hoyer in 1865. The names of Kölliker, Teichmann, His, Hoyer, Ludwig, and von Recklinghausen are to be associated with the development of the conception of a lymphatic capillary as an endothelial lined structure, either in the form of a network or as blind ends like the lacteals. The introduction of silver nitrate injections by Hoyer (1865), His (1863), and von Recklinghausen gave a method by which the limits of the endothelium of the lymphatics were more sharply determined; but the silver-nitrate pictures led von Recklinghausen astray, as we believe, to a conception of lymph radicles or tissue spaces as a part of the lymphatic system. The stomata and stigmata by which the lymphatic vessels were thought to connect with the lymph radicles have not been confirmed, and are more and more clearly seen to be mechanical defects of the silver-nitrate method. The question now presents itself in two phases, first the relation of the lymphatics to the tissue spaces in general, and secondly to certain special tissue spaces like the piarachnoid. To the first important question, the theory that the lymphatics come from the veins has a perfectly clear and satisfactory answer, and may be considered to have settled a difficulty which has faced anatomists for three hundred years. The lymphatic sacs and capillaries have exactly the same relation to the tissue spaces as have the blood-capillaries. Both are foreign structures that grow into or invade the mesenchyme. Tissue spaces are no more a part of the lymphatic system than they are of the blood-vascular system. Thus, fluid within the veins should be called blood-serum, the fluid in the tissue spaces might be termed plasma, while the term lymph should be reserved for fluid within the lymphatics. The use of three distinct expressions as indicating three distinct elements would be a decided advantage. Von Recklinghausen's silver pictures show two different systems, the lymphatic vessels and the tissue spaces or lymph radicles. Melzer (1896 and 1911) has brought out well the physiological meaning of these distinctions.

In embryos before the formation of lymphatics, the mesenchyme varies greatly in different places, that is, it is considerably differentiated. In certain special constant places the meshes of the mesenchyme are very large,—for example, around the central nervous system. These spaces around the nervous system have especial significance in connection with the lymphatics, for these mesenchyme spaces, the anlage of the piarachnoid spaces, extend along the peripheral nerves in young embryos and have been confused with lymphatics.

Sections of human and other mammalian embryos will show spaces along the growing nerves, contracted at the origin of the nerves but widely expanded at the growing tips. These spaces may be termed perineural spaces.

In studying a long series of pig embryos injected into the piarachnoid space, it is found that often the injection mass runs out into the perineural spaces, thus outlining the peripheral nerves. Such injections do not enter true lymphatics, thus showing the independence of these two systems. In a study of the arachnoid made by the injection method in the Anatomical Laboratory of the Johns Hopkins University by L. L. Reford, and as yet unpublished, it has been shown that the thinning out of the mesenchyme around the central nervous system is not haphazard, but that injections of the same stage give the same pattern, and that the form of the arachnoid space changes as the brain develops. That is to say, the arachnoid space has as definite a form as the cœlom and it never connects with the lymphatics. Moreover, no injections of lymphatics run over into the arachnoid or perineural spaces, showing that the great arachnoid and perineural space system is not a part of the lymphatic system.

Through the work of Budge (1880, 1887) there developed a theory that the cœlom had a genetic relation or developed in common with the lymphatic system. He injected the extra-embryonal cœlom in chick embryos, and found that the fluid passed out into the area vasculosa in forms simulating vessels and thought that this formed a primitive lymphatic system.

The finding that the lymphatic system arises from the veins, and that the tissue spaces and all the serous cavities of the body therefore stand in the same fundamental relation to the lymphatic system as they do to the blood-vascular system, marks a definite advance in our conception of the general morphology of the body, and is perhaps the most valuable result of the recent studies on the lymphatic system. This is as true for cavities like the various bursæ and chambers in the eye as for the piarachnoid, the cœlom, the pleural and pericardial cavities.

Closely associated with the question of the relation of the lymphatics to tissue spaces are two points—namely, the question of growth of the lymphatic capillaries and the time-honored question of open and closed lymphatics—which are the most interesting of all problems associated with the structure of the lymphatic system.

The question of the growth of lymphatics is the crucial point in connection with the new theory. That the lymphatic capillaries and blood-capillaries grow by the same method was suggested by Kölliker as early as 1846 in a study of the living tadpole's tail. The matter could not be on a firm basis until after the important discovery that blood-vessels were lined by endothelial cells. The idea of the growth of blood-capillaries by sprouting had its earliest beginnings in the work of Schwann (1839), and involves a long series of observations in which the most telling are those on the living amphibian larva. That the growth of the lymphatic capillary, like that of the blood-capillary, is from the sprouting of their endothelial lining cells was first discovered by Langer in 1868 in a study of the tadpole's tail.

These observations, long unnoticed, were rediscovered by Ranvier (1895–1897) in a series of studies on amphibian and mammalian embryos. Ranvier saw that with this method of growth it was impossible to think of lymphatics starting as dilated tissue spaces and growing toward the centre. MacCallum (1902) was the next to call attention to this method of growth, and he added the observation, that, in watching the injection of these growing capillaries under the microscope, there were no lymph radicles connecting the lymphatics with the tissue spaces as seen in silver-nitrate specimens, but that the lymphatics had a complete wall and ruptured explosively under too great pressure, and were hence anatomically closed vessels. The lymph radicles are tissue spaces. Bartels (1909) has repeated the injections of MacCallum, and obtains the same figures of the long sprouts of endothelium; he suggests, however, the theoretical objection to the theory growth of lymphatics by sprouting that this involves an idea of growth against the pressure of

the fluid contained (pp. 46–47). This theoretical difficulty is not a real one, since it is possible to watch the lymphatics grow in the living form. The final proof that lymphatics grow by sprouting of their endothelium has been given by E. R. Clark (1909 and 1911), who watched the growth of a given lymphatic vessel in the same tadpole's tail under the high powers of the microscope for long periods of time. He describes, that, from the sides and ends of the growing vessels, long processes of protoplasm push out into new territory; these processes now advance, now bend far out of their course to pick up some stray blood-corpuscles, and now retract entirely like long slender pseudopodia. Moreover, by subjecting the tadpole to lower temperatures, the activity of the endothelium can be checked, while under the stimulus of heat numerous tiny threads of protoplasm are pushed out, only a few of which grow into permanent lymphatics. Moreover, he has added an important discovery on the nature of the endothelium. He finds that the growing tip consists of a hyaline membrane, in which the nuclear areas, that is nuclei hidden by granular protoplasm, divide and move up and down the wall

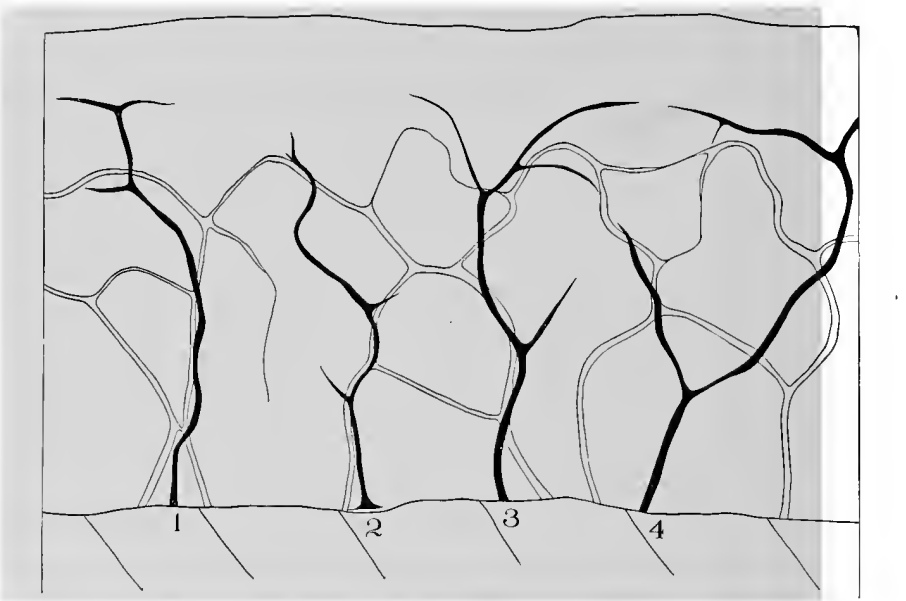


FIG. 513.—View of the blood-vessels and lymphatics (solid black) of a tadpole's tail (Hyla Pickeringii 10 mm. long). Fixation in Zenker's fluid. (After Clark, 1911.) The oblique lines represent the myotomes, and the numbers indicate the corresponding vessels of Fig. 514.

and out into the growing tips, even passing one another, so that the growing tip is unquestionably a synecytium. This clears up one difficulty long associated with the idea of growth by sprouting—namely, whether endothelial strands were individual cells which subsequently became hollowed out. The tiniest vessels are hollow tubes of protoplasm. This discovery enlarges our conceptions of endothelium, especially in connection with Mollier's (1911) beautiful specimens showing the endothelium of the splenic veins in the form of a reticular protoplasmic syncytium.

It cannot be said that there is agreement among the recent workers on lymphatics. This disagreement, we think, rests on a fact noted by His as far back as 1863, that "Eine nicht injizierte Lymphwurzelröhre zu erkennen, beinahe unmöglich ist." The lymphatic capillaries in early mammalian embryos seen in serial sections are conspicuously large in contrast with the blood-capillaries, but

they are at the same time extremely irregular and the largest vessels are often connected by the tiniest threads of endothelium. In 1906 F. T. Lewis showed in rabbit embryos certain small isolated spaces arranged in bead-like rows along the primitive veins extending out from the regions of the primitive sacs. These vessels are probably lymphatics; they are lined by true endothelium, are empty, and are larger than blood-capillaries. Their interpretation is given in Clark's figures 513 and 514. The study of these spaces, in their relation to the lymphatic system, resolves itself into an analysis of the limits of error of different methods. The three methods employed have been the study of the living by Clark, the study of serial sections of uninjected embryos by Lewis, Huntington, and McClure, and of injected embryos by myself. That the study of serial sections yields valuable results is unquestioned; the observations on the general distribution of the lymphatics in human embryos were made on such material. But in determining the essential point—namely, the method of growth of the lymphatic tip, whether by the addition of connective-tissue spaces, or by numerous venous anlages, or by

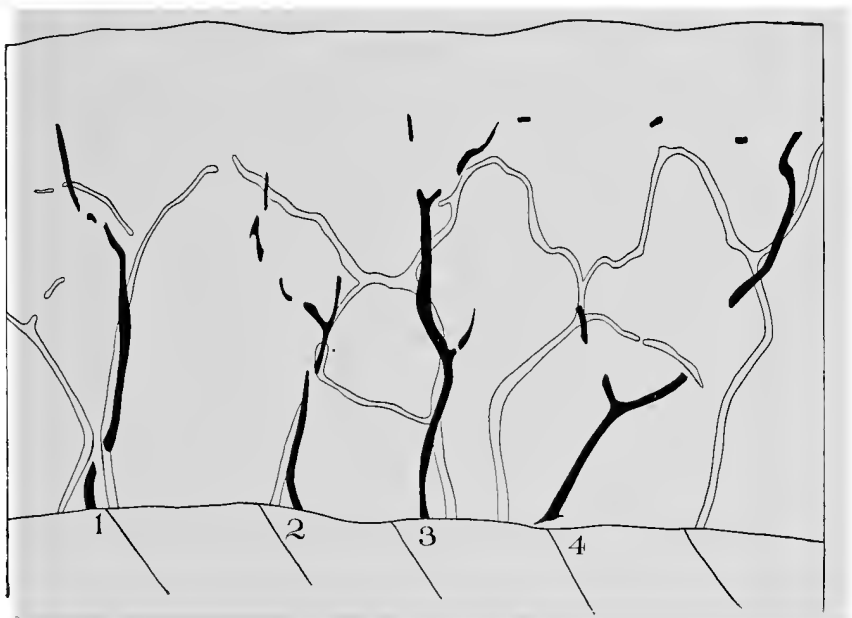


FIG. 514.—The same area as in Fig. 513. (After Clark, 1911.) Reconstruction from serial sections 10 μ thick, stained with hæmatoxylin and Van Gieson's mixture (acid fuchsin and picric acid), made by the use of an oil-immersion lens (Zeiss obj. 2 mm. and ocular 6).

the growth of its own endothelium—the method of the interpretation of sections fails, because the point at issue lies within the limits of error of the method.

The relative value of the method of uninjected and injected sections was in part tested in the skin of the embryo pig (Sabin, 1908), but the whole question has been much more conclusively tested by Clark (1911) in the tadpole's tail. His figures, two of which are copied, show the essential points. He first studied the entire lymphatic system as it can be seen in the living tadpole's tail. There is no question but that all of the lymphatics, to the last endothelial cell and protoplasmic sprout, can be seen. Moreover, the entire system so seen can be injected and nearly as much can be made out in a total specimen in alcohol. Such a specimen was drawn (Fig. 513). The tadpole was then sectioned and exactly the same area reconstructed. It was found, in the first place, that the amount which could be reconstructed varied greatly with the intensity of the stain.

With weak stains, like eosin or congo red, comparatively little could be seen, but an intense fuchsin stain gave the maximum advantage. By using a high dry lens (Zeiss 4 mm.) in specimens stained in fuchsin, both blood-capillaries and lymphatics split up into isolated islands or Lewis anlages. With the oil-immersion lens (Zeiss 2 mm.) more of the vascular and lymphatic systems could be reconstructed, but the isolated vessels were more distal, but still numerous, as seen in Fig. 514. This figure represents the maximum amount of blood-vessels and lymphatics that can be reconstructed in the tadpole's tail under the favorable conditions of knowing the extent of the lymphatics in the exact area and of intense protoplasmic stains. Clark regards this, and I think properly, as a crucial test of the relative value of methods.

The work of Huntington and McClure (1908–1910), presented for the most part in joint publications, advances a different idea in regard to the lymphatic system. Their position is a complicated one, for they hold that the lymphatic system arises by three different methods: first, that the jugular lymph-sacs are venous in origin; secondly, that some of the peripheral lymphatics are clefts between the endothelium of the veins and the surrounding mesenchyme, their so-called extra-intimal space theory; and thirdly, that some of the peripheral lymphatics arise as tissue spaces. In regard to the first point, they originally thought that the jugular lymph-sacs were extra-intimal (1906–08), but abandoned that idea in 1908. The extra-intimal theory is not a serious obstacle in connection with the lymphatic problem. Huntington and McClure find in specimens which have been fixed in Zenker's fluid, that the endothelium of the veins shrinks away from the surrounding tissue. This phenomenon they find more common in veins which are degenerating. In studying through a series of human embryos which show a great variation in the amount of maceration and in quality of fixation, we have found that such spaces vary according to the fixation. Moreover, in studying human embryos, it becomes clear that there are certain constant areas of unusually loose mesenchyme and these areas are the first to show the effects of maceration. In the living tadpole no extra-intimal spaces are to be seen, while in fixed specimens they are present. Thus the extra-intimal space is open to the charge of artefact, and, in order to be taken seriously, must at least first be shown to occur with all of the best fixatives. In connection with the lymphatics it can be shown that the growing lymphatic does not always follow the vein. Here it should be emphasized that the blood-capillaries lie in perfectly definite and constant areas, so that whether lymphatics actually replace them or not is readily tested. The lymphatic sacs do replace the veins; some at least of the peripheral lymphatics which McClure (1910) claims are extra-intimal do not replace veins, but exist beside them. Huntington and McClure show a tendency to abandon the extra-intimal theory in favor of the old theory of the connective-tissue origin of all the lymphatics save the jugular lymph-sacs. The theory that lymphatics grow by the addition of tissue spaces rests on the observations of sections. The appearances in sections remain open to a variety of interpretations, in contrast with the simplicity and sharpness of the appearances in the living form. Therefore for the theory that the lymph-vessels develop otherwise than by the sprouting of the endothelium of preceding vessels we have no sufficient proof.

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V. THE DEVELOPMENT OF THE SPLEEN.

By FLORENCE R. SABIN.

The fundamental problem in connection with the spleen is its general morphology,—that is, to which germ layer does it belong,—and to this question there is a clear, satisfactory answer in human embryology. The spleen is entirely mesodermal in origin. This was first suggested by Müller (1871) from a study of human embryos. He described the splenic anlage as a thickening of the peritoneum which took place early in the life of the embryo. The spleen arises from a thickening of the dorsal mesogastrium,[1] and is readily made out in embryos of the fifth week, 8 to 10 mm. long. Its relations to the stomach and omentum can be seen in Fig. 515 (after Kollmann, from an embryo 10.5 mm. long) and in Fig. 516 (after Tonkoff, from an embryo 20 mm. long).

In 1889 Toldt advanced the idea that an important part of the mesodermal anlage of the spleen came from the deeper layers of the cœlom epithelium. This has been confirmed and illustrated by Kollmann (1900) and by Tonkoff (1900). All three of them find that in human embryos about 10 mm. long the cœlomic epithelium over the splenic anlage is several layers thick, and that from the

[1] Kölliker (1854), Kollmann (1900), Phisalix (1888), Piper (1902), Toldt (1889), Tonkoff (1900).

deepest layers cells are being transformed into mesenchyme cells. Later the epithelium becomes again a single layer and then this transformation ceases.

The next problem in connection with the spleen is the development of its vascular system. Here it is impossible to give a satisfactory account, for our knowledge is but fragmentary. It will, however, be possible to indicate certain lines of investigation which promise to be fruitful. The study of the vascular system involves

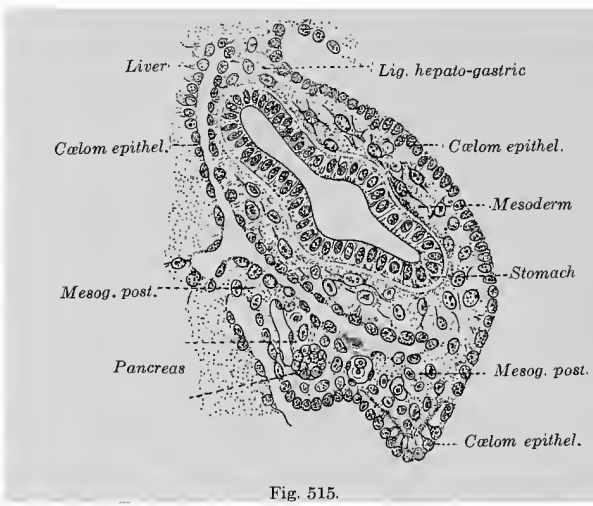

Fig. 515.

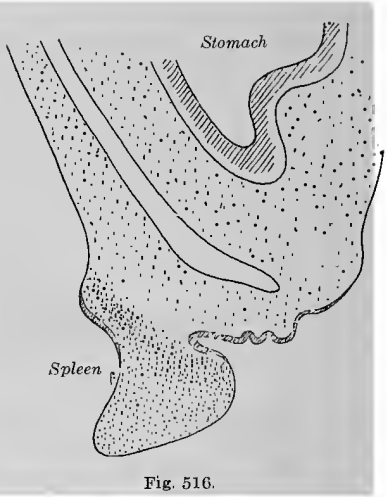

Fig. 516.

Fig. 515.—Anlage of the spleen in the posterior mesogastrium of a human embryo 10.5 mm. long. × 30. (After Kollmann.)

Fig. 516.—Diagram of the spleen showing its relations to the stomach and the omentum in a human embryo 20 mm. long. (After Tonkoff.)

the use of the injection method, and hence we shall turn to a study of injected pig embryos and fetuses.

In making injections of pig embryos through the umbilical artery, it is striking in how few cases any of the injection mass enters the splenic artery. For example, out of 22 specimens of apparently complete injections made into the umbilical artery, the spleen was injected in only four. Since the injections were all made on living embryos, this is probably due to the relative thickness and power of contraction of the muscle in the splenic artery. To get good injections it is best to open the embryo, tie off the aorta above and below the cœliac axis, and then inject the aorta with a hypodermic needle. When this small length of aorta is well filled, the fluid will run into the splenic artery. In a fetal pig 3 cm. long, the entire splenic circulation consists of a capillary network which extends throughout the organ. This condition is maintained until the fetus is 7.5 cm. long, as shown in Fig. 517. This represents the tip of the spleen and shows the central artery and vein which run along the hilum of the organ. As is shown in the figure, the branches of both artery and vein are soon lost in a diffuse capillary network. The branches of the artery can be distinguished for a short distance by being narrower than the veins. Thus the spleen confirms the principle that the primitive circulation of any organ is in the form of a capillary network out of which the arteries and veins are formed. The spleen is characterized by a long persistence of the primitive capillary network.

The embryo pig 10 cm. long marks the transition stage between this primitive condition and the type of circulation peculiar to the adult spleen. This point is shown in Fig. 518, where it will be seen that the branches of the central artery and vein extend much farther toward the border of the spleen, and the arterial branches lead into tufts of capillaries, making the anlage of the vascular unit. These capillaries have a wider calibre than those of the preceding stage.

When the fetus is 12 cm. long, as shown in Fig. 519, the transformation of the vascular system has been sufficiently marked to give the key to the adult circulation. By comparison with Fig. 518, which is at the same magnification, it will be seen that between the stages of 10 and 12 cm. there is a rapid increase in size, the spleen more than doubling in width. The position of the central artery and vein allows the comparison. As seen in Fig. 519, the central artery of the hilum gives off a series of branches of the first order which anastomose. These arteries bifurcate into branches of the second and third orders. The branches of the fourth or fifth orders lead into spherules of arterial capillaries which can be seen throughout the spleen, but best at the edge. Most of these spherules have only one artery, but a few receive two; most of them are isolated, but a few are connected by anastomosing loops. In the upper left-hand corner of the figure can be seen the relation of these spherules of arterial capillaries to the veins. The spherules lead by wide openings into a wide-meshed plexus of venous capillaries, which drain into the still wider venæ comites of the arteries of the third order. Thus is illustrated the separation of the artery and vein in the zone of the capillary bed.

At the edge of the organ, it can be seen in total mounts that each spherule of capillaries lies in the centre of a small compartment bounded by trabeculæ from the capsule. The spherules are the splenic capillaries, characterized by being wider than the usual capillaries. They are at the same time splenic pulp and represent the structural units of Mall (1900). It is the development of these spherules of capillaries that accounts for the rapid increase in the size of the spleen at this time. That they are not accidental is shown by several points,—1, their constant occurrence at the centre of the lobule at the end of the artery in injections; 2, their approximately uniform size; and 3, their definite connection with the veins.

It appears that the number of the structural units of Mall is fixed fairly early; for example, in three fetuses 17 cm. long the number of units along the edge was 150, 204, and 230 respectively, while in three adult spleens the numbers were approximately 190, 180, 260. The size and complexity of these units, however, change greatly; for example, at 17 cm. the average width of a unit is about 0.1 mm. while in the adult it is about 1 mm. Moreover, the embryonic unit consists of one central artery with a single bunch or spherule of capillaries leading to the vein, while the adult unit, as shown in Mall's Fig. 1 (Amer. Jour. of Anat., vol. 2, p. 321, 1902–1903), consists of a central artery with branches which end not in a single spherule of capillaries but in clusters of capillaries like a bunch of grapes. These clusters are the splenic capillaries or pulp. One of the spherules on the edge of the spleen in Fig. 519 shows the bifurcation of the central artery; how this complex unit of the adult is made out of the simple one of the embryo is yet to be determined, but the evidence of embryology is that the capillaries of the spleen are of a wider calibre than the usual capillaries, and that the wider capillary bed is compensated for in the development of the musculature of the spleen by which the capillary bed can be emptied with ease.

Mall (1902 to 1903) proved, by the method of subjecting the living adult spleen to a variety of injection methods, of which the most crucial test was the fixation of the spleen by the injection of formalin into the living animal, that

the splenic pulp is the capillary bed of the spleen; that the pulp intervenes between the artery and vein, and, in the normal, living animal, is engorged with blood when the spleen is hyperæmic. Hence the capillary circulation of the adult spleen is a cavernous one. The point at which the type of circulation of the early fetal stages—namely that of a primitive system of closed capillaries like the rest of the vascular system—changes over into the secondary type of circulation of the adult, namely a cavernous circulation, is shown in Fig. 519, for the fetal pig.

The work of Mollier (1911) carries us a step farther, by his beautiful specimens of the structure of the wall of the splenic veins. He also, as Mall had done, overthrows the idea of a homogeneous membrane around the endothelium of the adult splenic veins. He shows that the wall of the splenic veins consists of a reticular syncytium of endothelium with denser masses of protoplasm around the nuclei and wide-open meshes between.

It has thus become clear that there is a direct pathway from the terminal artery through the cavernous capillary system into the venous sinuses, and that

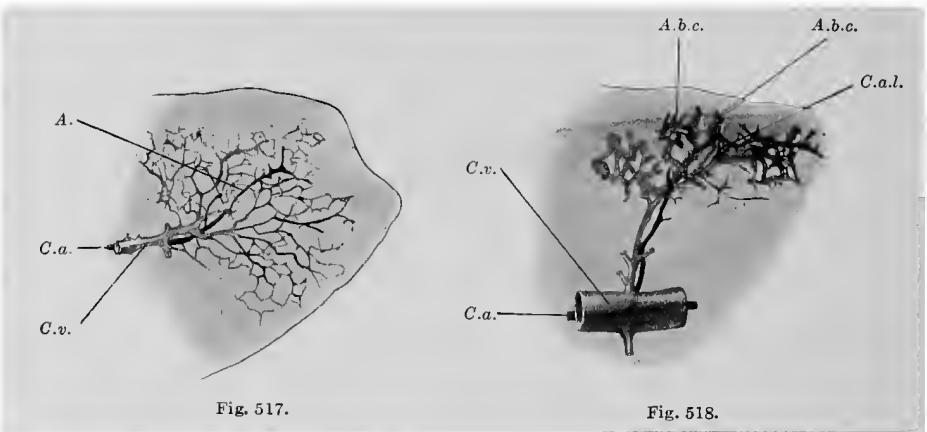

Fig. 517. Fig. 518.

FIG. 517.—Piece of a total mount of an injected spleen of an embryo pig 7.5 cm. long, showing the capillary plexus which is characteristic of the circulation at this stage. × 47. *A.*, artery; *C.a.*, central artery of hilum; *C.v.*, central vein of hilum.

FIG. 518.—Piece of a total mount of an injected spleen of an embryo pig 10 cm. long, showing that the anlage of the splenic unit is a tuft of widened capillaries. × 47. *A.b.c.*, anlage of capillary spherules or units; *C.a.*, central artery of hilum; *C.a.l.*, central artery of lobule or unit; *C.v.*, central vein of hilum.

to investigate the nature of the endothelium of the cavernous capillaries or splenic pulp is a problem which is becoming more and more hopeful. The transition stage between the two types of capillaries is the next point of attack.

The third problem in relation to the spleen is in connection with its function of the formation of red blood-cells. Kölliker (1854) was the first to suggest the idea of the spleen serving as a place for the formation of erythrocytes and leucocytes, and called attention to the relation of the giant cells to red-blood formation. Luzet (1901) pointed out in human embryos of from 3 to 5 months there were more nucleated red blood-cells than in the heart's blood. Sophie Lifschitz (1906) has shown, in a work which I regard as important, that the active formation of red blood-cells takes place in fetuses between 15 and 30 cm. long. She plotted the curve both of the number of red blood-cells and of the giant cells of the spleen, and found that both increase together to a maximum in fetuses 18 cm. long, while the curve

decreases at 24 cm. and is almost at the zero point at 30 cm. Moreover, she noted that the nucleated red blood-cells form clusters around the giant cells. It may be noted that this period of red blood-cell formation corresponds with the period of the formation of the capillary spherules or spleen pulp, which makes the spleen fall in line with the recent work on the bone-marrow by Bunting (1906), and on bone-marrow in the kidney of Maximow (1907), that red blood-cell formation

FIG. 519.—Piece of a total mount of an injected spleen of an embryo pig 12 cm. long, showing the vascular units. × 47. The arteries are shown darker than the veins. *A.b.*, anastomosis between two capillary balls; *c.a.*, central artery of hilum; *c.b.*, arterial capillary ball; *c.v.*, central artery of hilum; V_1, vein of first order; this vein up to the point marked × was taken from another area of the same slide where the injection was more complete; it is the rule that the veins accompany the arteries in this manner; *V.c*3., vena comites of the third order; *v.c.p.*, capillary plexus of veins.

goes on within the capillary bed, that it is intravascular. Lifschitz (1906) also called attention to the rapid increase in size of the spleen during the period of red blood-cell formation, which was also noted in connection with the period of spleen-pulp formation. The injection experiments show that its meaning lies in the rapid increase in the size of the capillaries. The fundamental point that the early spleen is only undifferentiated mesoderm, and that this condition remains until the embryo is 7 cm. long, was noted by Van der Stricht in 1892. He states that there is a

primitive stage in which the structure of the spleen is more or less uniform before there is any differentiation into splenic pulp and Malpighian corpuscles; then he finds a transitional stage characterized by an increase in white corpuscles in certain areas, an increase in erythroblasts and a retardation of the circulation, and finally a secondary stage in which the adult organization of the spleen with pulp and Malpighian corpuscles is established.

The fourth problem in the development of the spleen is in connection with the ellipsoids and Malpighian corpuscles. It is definitely known that these structures belong to the latter half of fetal life. In the spleen, as has been shown in the lymph-glands, the lymphocyte first appears in the adventitia of the artery, so that, though red blood-cell formation is within the capillary bed, the lymphocyte is extravascular. The ellipsoids, or capillarhülsen of Schweigger-Seidel, which are on the course of the smallest arteries, appear, as Bannwarth (1891) has shown, before the Malpighian corpuscles, which are the round follicles along the larger arteries. He found the ellipsoids in a four-months human fetus, while later—that is, in a seven-months fetus—the ellipsoids had disappeared and follicles were present. The follicle is found only in mammals and some birds, while the ellipsoids occur in fishes as well, as has been shown by Whiting (1895). Thus the ellipsoid is the primitive lymphoid structure of the spleen. In describing their development, Bannwarth shows that in the spleen, as in the lymph-gland, leucocytes appear in the loose adventitia of the artery, and at the same time there is a development of this adventitia, by which the connective-tissue fibrils are laid down in more or less concentric rings around the artery, forming the delicate reticulum characteristic of the lymph-follicle in general. Thus, the spleen, hemal glands, and lymph-glands are all vascular structures and are all built on the following simple plan: 1, along the arteries are clumps of lymphocytes in a reticulum called ellipsoids or Malpighian corpuscles or follicles; the ellipsoid is a special name used in the spleen for the oval masses of lymphocytes which lie nearest the capillary bed; 2, the capillaries, whether they be lymphatic capillaries in lymph-glands or blood-capillaries in the hemal nodes or the spleen, are all wider in calibre than other capillaries. They are densely packed together, and have been termed either sinuses in lymph-glands or pulp spaces in the spleen.

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XIX.

THE DEVELOPMENT OF THE URINOGENITAL ORGANS.

By W. FELIX, Zurich.[1]

The urinary and reproductive organs, notwithstanding their diverse functions, have been regarded in systematic anatomy and in embryology as constituting a single system, an arrangement which is undoubtedly correct for two reasons. In the first place both groups of organs open into the enlarged caudal portion of the digestive tract, the cloaca; by a subdivision of this cloaca into a ventral portion, which furnishes the anlage for the urinary bladder, the urethra and the urogenital sinus, and a dorsal portion, the rectum, the digestive tract becomes completely and permanently separated from the urinogenital organs, but, on the other hand, these remain connected by the urogenital sinus. In the second place one of the urinary organs, the mesonephros, unites with the reproductive gland and, giving up its provisional function of manufacturing and excreting urine, enters permanently into the service of the reproductive apparatus as the male efferent duct. The urinary and reproductive organs consequently form an inseparable whole in the adult organism.

The study of the development of the urinogenital apparatus divides itself into four portions. These are: (1) the development of the excretory glands and their ducts; (2) the development of the reproductive glands and their efferent ducts; (3) the development of the urogenital union, *i.e.*, the union between the urinary and reproductive glands; and (4) the development of the sinus urogenitalis and in connection with this the development of the external genitalia.

[1] That it has been possible to base this entire chapter on my own observations, I am indebted to the generous assistance of colleagues who have unselfishly placed at my disposal series of sections from their private collections and from institute collections. In this connection I desire to thank Professor Grosser, Geheimrath Professor R. Hertwig, the late Geheimrath Professor His, Professor Hochstetter, Professor Keibel, Professor R. Meyer, the late Geheimrath Professor Pfannenstiel, Professor Stoerk, and the late Hofrath Professor Zuckerkandl. My colleague, Rob. Meyer, in addition to placing at my disposal over sixty series of sections, has given me the benefit of his rich experience. To my colleagues Dr. Baltischwiler, the late Professor U. Krönlein, Professor Wyder and Professor O. Wyss I am indebted for fresh material and would also express to them my sincere thanks.

I. THE DEVELOPMENT OF THE EXCRETORY GLANDS AND THEIR DUCTS.

Introduction.

In most vertebrates the development of the excretory system from its first formation until its completion occupies an interval which is long in comparison with that shown by other organs. In this interval its activity becomes modified in accordance with the growth of the entire organism, and this modification of the organ, still in the process of development, impresses upon the development of the kidney its distinctive feature. We have to deal not with the *gradual* development of a *single* organ, which is laid down and brought step by step to its definitive completion, but with a *saltatory* development; three organs (pronephros, mesonephros, and metanephros) are developed in succession, and each of these organs is apportioned and adapted to a definite period of one entire development. Each new excretory organ supplants its predecessor and the last to develop, the third, the metanephros, becomes the *permanent kidney*. The pronephros and mesonephros are merely *provisional kidneys*, whose activities become superfluous and are supplanted on the formation of a new excretory organ. But when a structure in the animal body becomes functionless it undergoes degeneration; consequently the entire pronephros and the greater portion of the mesonephros disappear. The lesser portion of the mesonephros enters the service of the reproductive apparatus and is permanently retained in this new connection.

The development of the excretory system presents practically the same beginning and the same course throughout the entire series of vertebrates. Only the final results are different; the higher the grade of organization of the individual vertebrate classes, the higher the grade of development of the excretory organ; the number of provisional excretory organs stands in direct relationship to the grade of organization of the animal. In amphioxus and the myxinoids only a single excretory organ (the pronephros) is formed, in the teleosts and ganoids, the selachians, the petromyzonts, dipnoans and amphibia there is *one* provisional organ, the pronephros, and *one* permanent organ, the mesonephros. In the amniotes there are *two* provisional organs, the pronephros and mesonephros, and, as a permanent organ, the metanephros. The succession pronephros, mesonephros, metanephros, occurs not only in the ontogenetic development of the individual, but also has occurred in phylogenetic development of the kidney within the vertebrate group. The pronephros, which is a provisional organ in the classes mentioned above, corresponds in part to the persistent excretory organ of amphioxus and the myxinoids, just as the mesonephros of the amniotes corresponds to the permanent excretory organ of the teleosts, ganoids, selachians, etc.

A knowledge of the entire developmental history of the kidneys is very necessary in the consideration of human development, in which the pronephros and perhaps also the mesonephros no longer function as excretory organs, but represent only inherited stages of development.

Each excretory organ, whether it be provisional or permanent, represents a gland with its gland substance and duct. The gland substance is formed of individual urinary tubules, which in the primitive condition run transversely to the long axis of the body and may, therefore, in contrast with the longitudinal duct, be termed the transverse tubules. The duct, which is lacking only in amphioxus, opens into the cloaca. The transverse tubules open either directly or indirectly by means of a collecting canal into the duct. This opening into a common duct unites the separate urinary tubules to a single structure, the gland substance; when the duct is lacking each tubule stands by itself and represents an independent unit. The individual tubules are named according to the nature of the entire

gland, pronephric, mesonephric, or metanephric tubules. The pronephric and mesonephric tubules are recognized by their openings being into the original or primary duct, the metanephric tubules by their opening into a secondary duct (the ureter) specially developed for them.

Differentiation of the Mesoderm.

GENERAL.

The excretory system is of mesodermal origin. The story of the development of its parent tissue may begin with the fully formed but as yet undifferentiated mesoderm.

The account that I shall give will not be based on any definite example, but will rather represent a schema based upon the study of the development in the craniotes in general. The mesoderm forms a wedge-shaped plate on either side of the medullary tube (Fig. 520*a*), the base of the wedge being its medial surface directed toward the medullary tube and the notochord, its edge being the lateral border. Each mesoderm plate differentiates in two rapidly succeeding intervals into three portions: 1, the primitive segment in its narrower sense, 2, the primitive segment stalk, and 3, the lateral plate. In the first interval only the dorsal portions of the wedge and a narrow strip in its immediate proximity are divided into a series of successive and approximately equal portions, the primary primitive segments; the lateral, broader part of the mesoderm plate remains undivided and forms the lateral plate (Fig. 520 *b*). In the second interval the primary primitive segments become more sharply marked off from the lateral plates by their lateral portions being folded in from all sides and so converted into a stalk, which bears at its extremity the medial, unaltered portion of the primitive segment (Fig. 520 *c*); this medial, larger portion is termed the secondary primitive segment, the lateral, smaller one the primitive segment stalk (connecting cord, intermediate cell-mass, nephrotome, gononephrotome).

The primitive segment stalks furnish the material from which the tubules of all three excretory organs are developed, and it follows from this that the anlage of the excretory system cannot be a unit, but must be composed of as many parts as there are primitive segment stalks entering into its formation. Furthermore it follows that the tubules are formed outside the body cavity enclosed by the lateral plates, *i.e.*, they are from the beginning retroperitoneal.

With the progress of development the secondary primitive segments and the stalks become separated, the opening in the wall of each at the point of separation closing at the same time.

The stalk presents quite different arrangements in the representatives of the various vertebrate classes. It may: 1, preserve the form of an epithelial canal and its connection with the lateral plate, and be directly transformed into a

uriniferous tuhule; 2, it may hecome separated from the lateral plate and form either an isolated vesicle or an isolated solid mass of cells, and in this form it may be directly transformed into a tuhule; 3, it may he gradually taken up into the lateral plate hy an extension of the cœlomic cavity of the plate, and is then only distinguishable from the lateral plate hy its further development; 4, it may he transformed into a solid mass of cells and fuse with the neighboring stalks, similarly transformed, to form a single cord, known as the *nephrogenic cord,* which may or may not retain its connection with the lateral plates; or it may finally be transformed into mesenchyme tissue hy the separation of its cells, this tissue

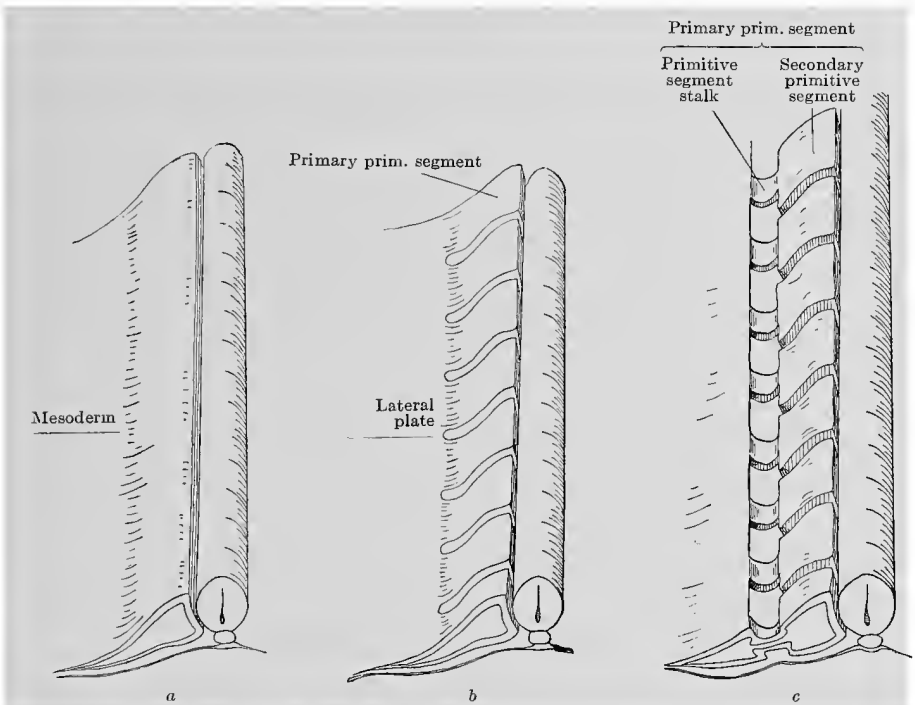


FIG. 520 *a*, *b*, and *c*.—Diagram illustrating the segmentation of the mesoderm. *a* shows the unsegmented mesoderm; *b* shows the first stage of segmentation, the separation of the primary primitive segment from the dorsal part of the mesoderm wedge; *c* shows the second stage of segmentation, the formation of the primitive segment stalk and the division of the primary primitive segment into the secondary primitive segment and the primitive segment stalk.

then fusing with the mesenchyme of the sclerotome to form a single mass in which the source of the constituent parts can no longer he determined. Several of these five modes of development may occur in the same emhryo, and, since neighhoring segment stalks develop similarly, groups of segment stalks may be distinguished.

Each primitive segment stalk may develop several tubules in succession. Since it itself passes along a definite path of development, during which its form changes, an opportunity is afforded for differences between the earlier and later formed uriniferous tuhules. Pronephric and mesonephric tuhules of the same animal need not therefore show a similar development, if, between their formations there occurs a distinct interval, during which their common source has acquired a new form. Similarly the pronephric tuhules of different animals show profound differences in their development, differences which find an explanation in the time relations of the formation of the tubules. The change of form which accompanies the progressive development of the common source of the organ

suffices to explain the difference in the development of a pronephric, mesonephric, and metanephric tubule.

Each primitive segment stalk has theoretically the potentiality of producing all three kinds of tubules; a very complicated organ would be produced in this manner. Actually the arrangement is simpler, since the primitive segment stalks of the cranial zone produce only pronephric tubules, those of the middle zone only mesonephric tubules, and those of the caudal zone only metanephric tubules, stalks, however, which produce two kinds of tubules, occurring in the intervals between the different zones.

THE SEGMENTATION OF THE MESODERM IN MAN.

In the human embryo the cœlom first appears as the exocœlom and at an early period separates the mesoderm into intra- and extra-embryonic portions, the boundary between the two being indicated by the adjacent vena umbilicalis (Fig. 521). The intra-embryonic mesoderm is at first absolutely solid, and while it is still in this condition its first segmentation takes place; the relations are accordingly as yet somewhat obscure. The formation of the primary primitive segments precedes the formation of a primitive segment plate, that is to say, the primary segments are separated from the lateral plates before they become separated from each other, and in an embryo with 5 or 6 pairs of primitive segments the primitive segment plate therefore extends almost to the caudal extremity of the embryo. The grooves which delimit from the primitive segment plate the 5 or 6 cranial segments do not separate the primary primitive segments throughout their entire width, but penetrate only to the lateral border of the future secondary segment, the segment stalk therefore remaining at first unseparated. Fig. 521 is taken from an embryo with 5 or 6 primitive segments; on the right side (the left in the figure) the section passes through the sixth primitive segment, which is not yet separated caudally, and on the left side it passes through the primitive segment plate at a level corresponding to about the middle of the future seventh segment. The intra-embryonic mesoderm of either side is not yet cleft. While on the right the primary primitive segment is not delimited from the lateral plate, and there is no indication whatever by which to distinguish the segment stalk from the secondary segment, on the left the arrangement of the nuclei indicates the future triple division of the intra-embryonic mesoderm into the secondary primitive segment, the segment stalk and the lateral plate; two crosses in the figure indicate the limits of the three portions. During the segmentation the formation of the cavity in the intra-embryonic mesoderm occurs. The cœlom may form discontinuously both in the cranio-caudal and frontal directions; the clefts which succeed one another in the cranio-caudal direction do not show a segmental arrangement, but, on the other hand, those following in the frontal direction may

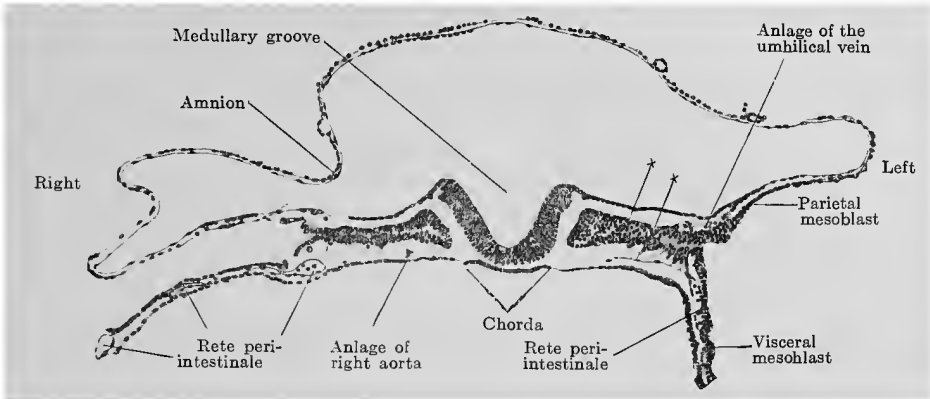


FIG. 521.—Transverse section of a human embryo of 1.38 mm. greatest length (as determined from the series) and with 5–6 pairs of primitive segments. (Embryo Pfannenstiel–Krömer, from the collection of Professor Pfannenstiel; slide 6, row 3, section 7.) × 120. The section passes on the right through the 6th segment and on the left through the primitive segment plate at the level of the future 7th segment. The section shows the cœlom relations. Only the exocœlom is present. On the right there is no apparent differentiation of the intra-emhryonic mesoderm; on the left a beginning differentiation of the secondary segment, the segment stalk and the lateral plate is visihle and is indicated hy two crosses (x). The peri-intestinal rete and the anlagen of the aorta can he seen. An injury to the emhryo accounts for the peculiar hending downward of the endoderm and visceral mesohlast in the left side.

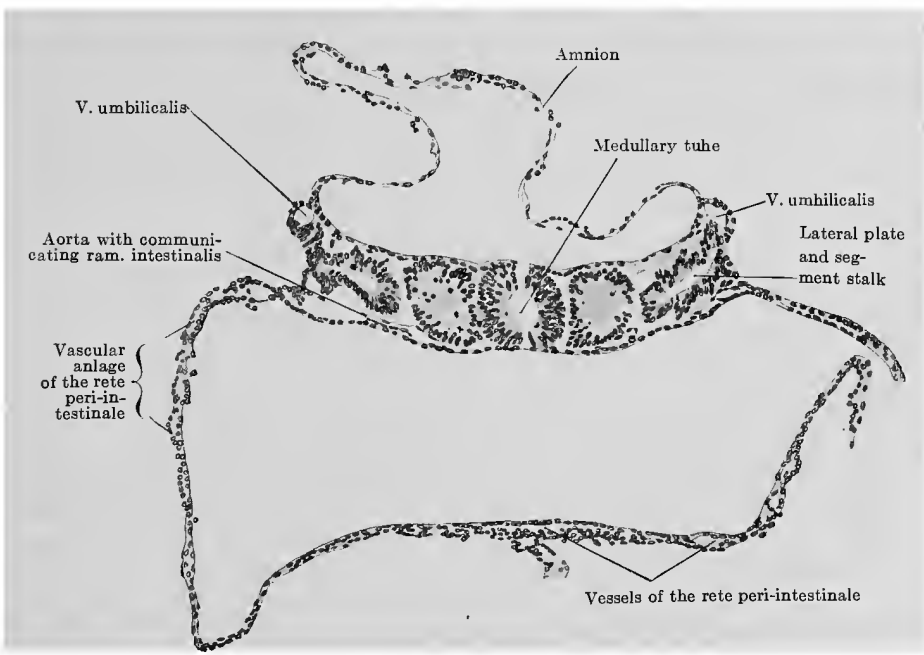


FIG. 522.—Transverse section of a human embryo with 9–10 pairs of primitive segments and 1.73 mm. in length (determined from the series). (Emhryo R. Meyer No. 335, from the collection of Professor R. Meyer, Berlin; slide 7, row 2, section 2.) × 135. The embryo is torn in the region of the medullary tube; there is a medullary tube and not a medullary groove. The yolk-sack is greatly folded, so that it appears as if divided into two portions; hence the peculiar appendage on the right side of the figure, which is the connection with the second portion of the yolk-sack, not represented. The section passes through ahout the middle of the 7th primitive segment. The lateral plate contains a single wide cœlomic cavity, which is not, however, in communication with the exocœlom. The segment stalk is not distinguishable from the lateral plate. The visceral mesoblast of the yolk-sack is giving rise to the rete peri-intestinale.

correspond to the region of the lateral plates and that of the primitive segment stalks; the lumen of the lateral plate is not at first continuous with that of the exocœlom (Fig. 522). In an embryo with from 8 to 10 pairs of primitive segments the secondary segments are completely delimited and enclose a distinct lumen (the myocœl), but their stalks are not yet separated from the lateral plates (Fig. 522). The first distinctly separated segment plates are shown by the anterior 8 or 9 segments of an embryo

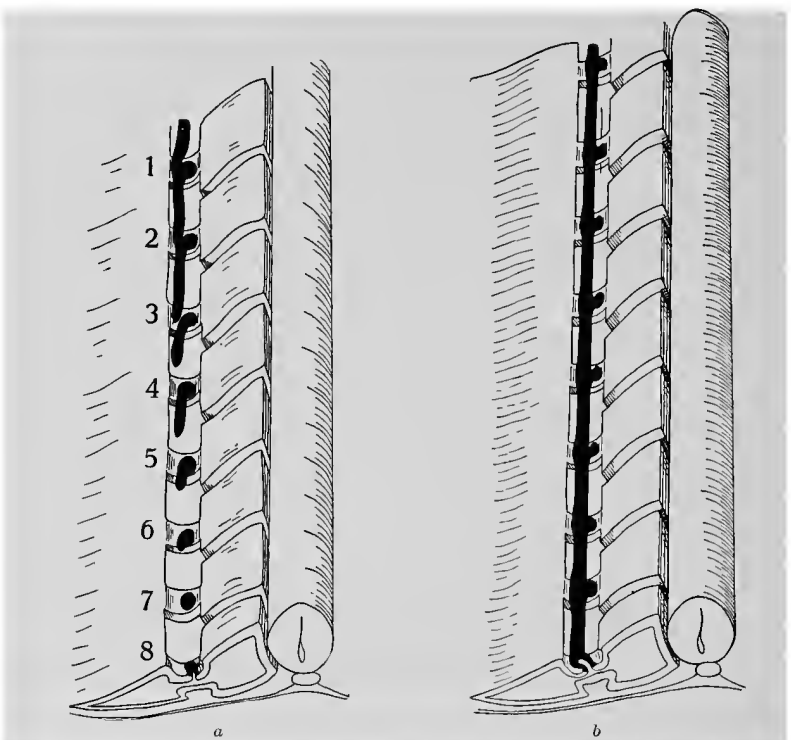


FIG. 523 *a* and *b*.—Diagram of the development of the pronephros. *a*. The principal tubules 5, 6, 7, and 8 develop by evagination from the parietal mesohlast of the primitive segment stalk. They grow caudally (3 and 4) and reach and overlap the succeeding tubules passing laterally to them (2). The principal tubules, which are thus brought into apposition, fuse, and a collecting duct (1) is formed. *b*. The collecting duct remains in connection with the various segment stalks by means of the principal tubules.

with from 12 to 14 pairs of primitive segments; from the tenth segment onward all the stalks are united with the nephrogenic cord. In the same embryo the degeneration of the more anterior segment stalks has begun; they are becoming mesenchyme tissue. In an embryo with 23 pairs of segments isolated segment stalks are to be distinguished only indistinctly, but, on the other hand, a nephrogenic cord extends from the 13th segment to the unsegmented mesoderm.

The human embryo forms, therefore, both secondary primitive segments and segment stalks. The latter retain their individual-

ity only in the anterior 8–9 segments, and from the tenth segment outwards they fuse to form a nephrogenic cord or are separated from the unsegmented mesoderm as such a cord. The connection between the nephrogenic cord and the lateral plate is sometimes retained and sometimes lost; but the connecting bridges, when present, show no segmental arrangement.

The Development of the Pronephros.

GENERAL.

The pronephros in man no longer functions as an excretory organ and its development has therefore become abbreviated, incomplete, and in consequence obscure. And a further difficulty is introduced by the fact that its appearance and formation occur in very early stages of development, for the study of which good material is only sparingly available; consequently the account of the development of the human pronephros must be incomplete. I shall therefore present a review of the development of the pronephros within the vertebrate stem and what is known as to its development in man may be readily included in this review.

The first anlage of the pronephros consists in the development of the pronephric tubules. The parietal layer of each primitive segment stalk forms an evagination directed toward the ectoderm, the *principal tubule* (Fig. 523 *a,* tubules 7 and 8). Each principal tubules extends caudally beneath the ectoderm, without, however, uniting with it (Fig. 523 *a,* tubules 6, 5, 4, and 3). The tubule reaches the next succeeding one, grows backward along its lateral surface (Fig. 523 *a,* tubule 2), and fuses with it (Fig. 523 *a,* tubule 1); by the fusion of all the principal tubules a longitudinal canal, the *collecting duct,* is formed and this is connected with each primitive segment stalk by a principal tubule (Fig. 523 *b*). The principal tubules of the various segments do not appear simultaneously, but are formed in successive groups, cranial ones first and then caudal ones. Once the collecting duct and the principal tubules are formed a differentiation of the primitive segment stalk begins (Fig. 524 *a, b,* and *c*). In Fig. 524 *a* a transverse section through the segment stalk and the pronephric tubule is represented, the segment stalk being hatched and the tubule black. In Fig. 524 *b* the secondary primitive segment has separated from the segment stalk, the stalk which has thus become free separates the elements of its medial portion to form mesenchyme tissue, indicated in the figure by the three dots, and the lateral portion of the stalk closes the opening thus formed and now appears as a connecting canal between the principal tubule and the lateral plate; we shall term it the *supplemental tubule.* In Fig. 524 *c* the principal tubule (black) and the supplemental tubule (hatched) have elongated; the supplemental tubule, by the broadening of the portion immediately adjacent to the principal tubule, has become divided into two parts, a broad medial one, which is invaginated by a vascular glomerulus, and a narrow lateral one, which establishes the connection with the lateral plate. The broad part may be termed the *inner pronephric chamber,* the narrow one the *nephrostome canal.* A vascular glomerulus similar to that which invaginates the medial wall of the pronephric chamber, pouches out the visceral layer of the lateral plate close to the opening of the nephrostome canal into the body cavity (Fig. 524 *c*). Both glomeruli are supplied by branches from the aorta; they may be termed the *internal*

and *external glomeruli.* The internal one is a portion of the pronephric canal, the external one is an independent structure and is related to the pronephric tubule only by its neighboring position. The portion of the body cavity that contains the external glomerulus may separate from the rest of the cœlom and thus constitute an *outer pronephric chamber.* These are all the constituent parts of a pronephric tubule, and together they form a pronephric segment; this in its fully

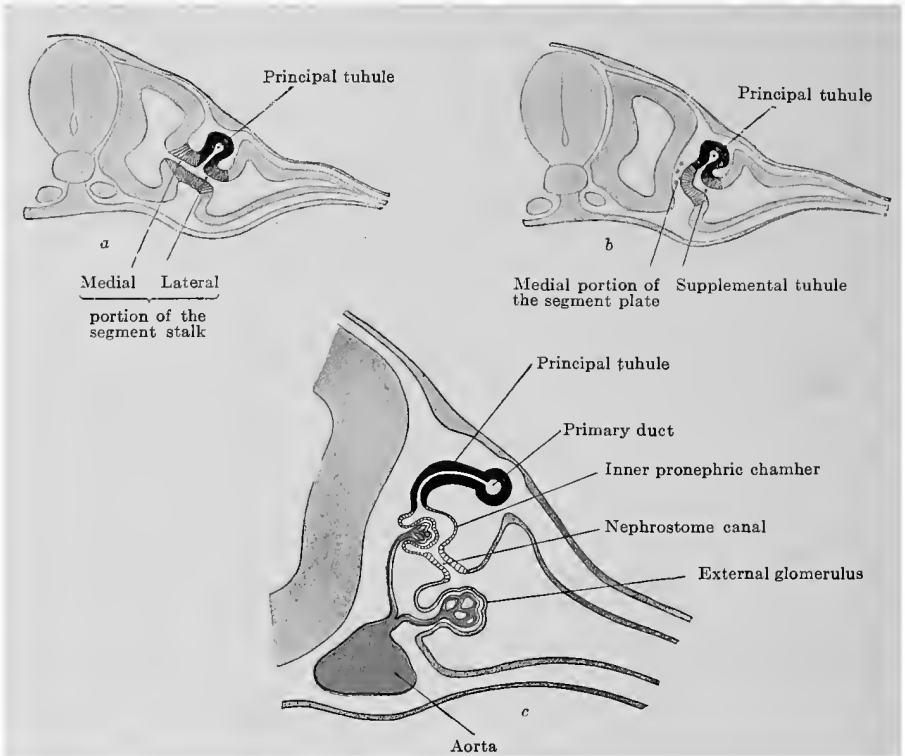


FIG. 524 *a*, *b* and *c*.—Diagram of the development of a pronephric segment. The segment stalk is hatched, the principal tuhule is hlack. *a*. The principal tuhule arises as an evagination of the parietal layer of the primitive segment stalk, its lumen heing continuous with that of the segment stalk and through this with that of the lateral plate. *b*. The segment stalk has lost its connection with the secondary primitive segment, its medial portion has become converted into mesenchyme tissue and its lateral part has united with the principal tuhule. The lateral part of the stalk thus becomes a tubule supplemental to the principal tubule. *c*. The supplemental tubule (hatched) becomes divided into the inner pronephric ohamher and the nephrostome canal. A glomerulus, forming the internal glomerulus and supplied by the aorta, invaginates into the inner pronephric chamber, the external glomerulus projects into the general body cavity (cœlom of the lateral plate). The pronephrio segment is now complete in all its parts; starting from the collecting duct we have the principal tuhule, the pronephric chamber with the internal glomerulus, the nephrostome canal and the external glomerulus.

developed condition consists of the principal tubule, the pronephric chamber, the nephrostome canal, the internal and external glomeruli and, in some cases, the outer pronephric chamber.

Originally each primitive segment stalk throughout the entire length of the body cavity produced a pronephric tubule. By the union of these tubules an excretory duct, the collecting duct, was formed, extending throughout the entire length of the body cavity, and this, or the last tubule, opened into the cloaca. This arrangement still persists in the myxinoids and the telosts, probably also in the ganoids, petromyzonts, amphibia and dipnoans. In the remaining classes, the selachians, gymnophiones and amniotes, there is an abbreviation of the pronephric

anlage, so that pronephric tubules are formed only in a varying number of the cranial segments. But since the excretion must still be conveyed to the cloaca, one of the most caudal tubules elongates on its own account and becomes the excretory duct. It grows caudally between the ectoderm and mesoderm and thus reaches the cloaca. During its elongation it lies in close apposition to the ectoderm, but probably is not in connection with it. In such a pronephric excretory duct, which we will term a primary excretory duct, two portions may be distinguished: one, the *collecting duct portion,* formed by the fusion of the principal tubules, and another, the *free terminal portion,* produced by the independent backward elongation of a pronephric tubule. If the pronephros of the selachians, gymnophiones and amniotes is an organ which has undergone retrogression, if its excretory duct has been formed under cœnogenetic conditions, the results of their ontogeny must be received with caution. At all events clear evidence as to the relation between pronephros and mesonephros *cannot* be obtained from these forms.

THE PRONEPHROS IN MAN.

The human pronephros is a quite rudimentary organ and its development is accordingly abbreviated and incomplete. The abbreviation reveals itself in the transitoriness of its occurrence, the incompleteness in the imperfection of the individual pronephric segments and in the small number of primitive segment stalks that form pronephric tubules. The abbreviation of the entire anlage necessitates—according to the general description (p. 753 and p. 759)—the division of its development into two portions: first, the development of the glandular portion—the pronephric tubules and the collecting duct—and, second, the development of the free terminal portion of the primary excretory canal.

The first anlage of the pronephric glandular portion occurs in an embryo with from 9 to 10 pairs of primitive segments and a greatest length (determined from the series) of 1.73 mm. A stage of greatest development cannot exist, since the cranial canals have already dissolved into mesenchyme tissue while the caudal ones are developing; the complete formation of these last is almost reached in an embryo of 2.5 mm. greatest length, with 23 pairs of primary segments. The degeneration of the pronephros is already well advanced in an embryo of 4.25 mm. vertex-breech length with from 27 to 28 pairs of primitive segments and, accordingly, takes place between the stages with 23 and 28 pairs of segments. The time of disappearance of the pronephros cannot be determined definitely, since it extends into the territory of the mesonephros, and the cranial tubules of this also degenerate immediately after their formation; it is consequently impossible to determine the significance of the remains of a tubule occurring in the pronephric region; it may represent a pronephric tubule, it may be a mesonephric tubule in process of degeneration, or, finally, it may be the remains of a primitive segment stalk or of the nephrogenic cord. As the approximate time for the complete disappearance of the pronephros a stage of 4.9 mm. vertex-breech

length may be named. But it is to be remembered that *one* constituent of the pronephros, the external glomerulus, may, on account of its independence, persist far beyond this stage.

The pronephric anlage extends from the 7th to the 14th primitive segment. It is very probable, however, that it may extend further forwards, since an embryo of 2.6 mm. greatest length and with 12–14 pairs of primitive segments showed on one side pronephric rudiments in the 2nd, 4th and 6th segments. The condi-

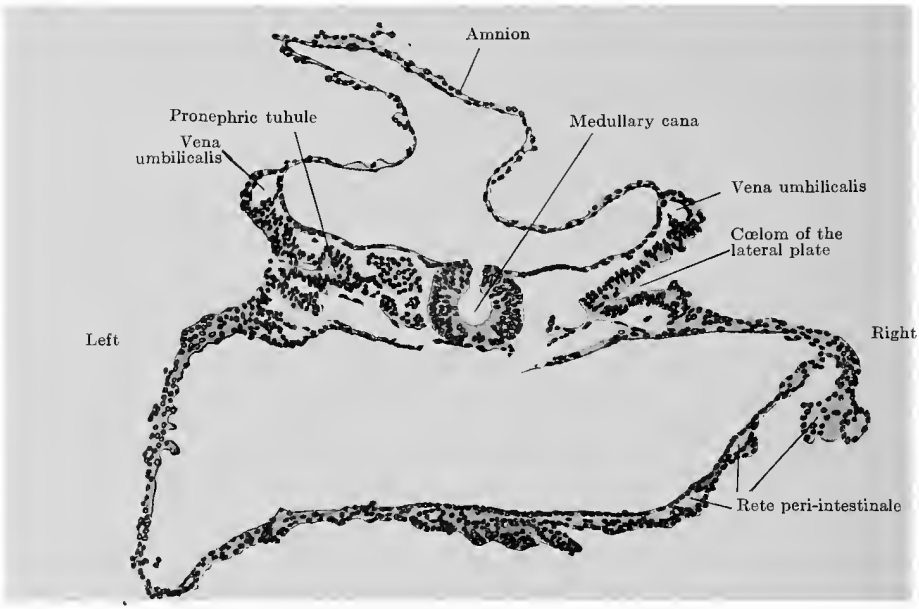


Fig. 525.—Human embryo with 9–10 pairs of primitive segments and a length of 1.73 mm. (determined from the series). (Embryo R. Meyer 335, in the collection of Professor R. Meyer, Berlin; slide 7, row 3, section 4.) × 135. The section passes on the right side through the cranial wall of the 8th primitive segment, on the left through the interstitium between the 7th and 8th segments (reversed in the figure). The cœlom is continuous with the exocœlom, the original boundary between them being marked by the vena umbilicalis. The cœlom is greatly enlarged, only the medial portion, corresponding to the primitive segment stalk, remaining narrow. On the left side of the figure the cœlom of the primitive segment stalk and that of the lateral plate are separate, and the parietal layer of the segment stalk is outpouched to form the first pronephric principal tubule.

tions in the other amniotes are also in favor of the possibility of this arrangement. The anlagen probably appear successively in groups. In an embryo with 9–10 pairs of primitive segments the pronephros extended from the 7th to the as yet unseparated 11th segment, and in one with 12–14 pairs of segments it reached from the 7th to the 14th segment.

The pronephric tubules appear as ridge-like thickenings of the parietal layer of the individual primitive segment stalks, and the lumen of the stalk may usually be followed into the thickening. Fig. 525 shows the pronephric tubule of the 7th segment (which is also the first pronephric segment) of an embryo of 1.73 mm. greatest length (determined from the sections) and with 9–10

pairs of primitive segments. The anlage begins in the posterior half of the 7th segment and extends to the anterior half of the 8th segment. The next anlage begins in the posterior half of the 8th segment, the third at the anterior edge of the 9th segment.

Only the most anterior anlagen are independent and completely separated from one another, showing a certain metamerism.

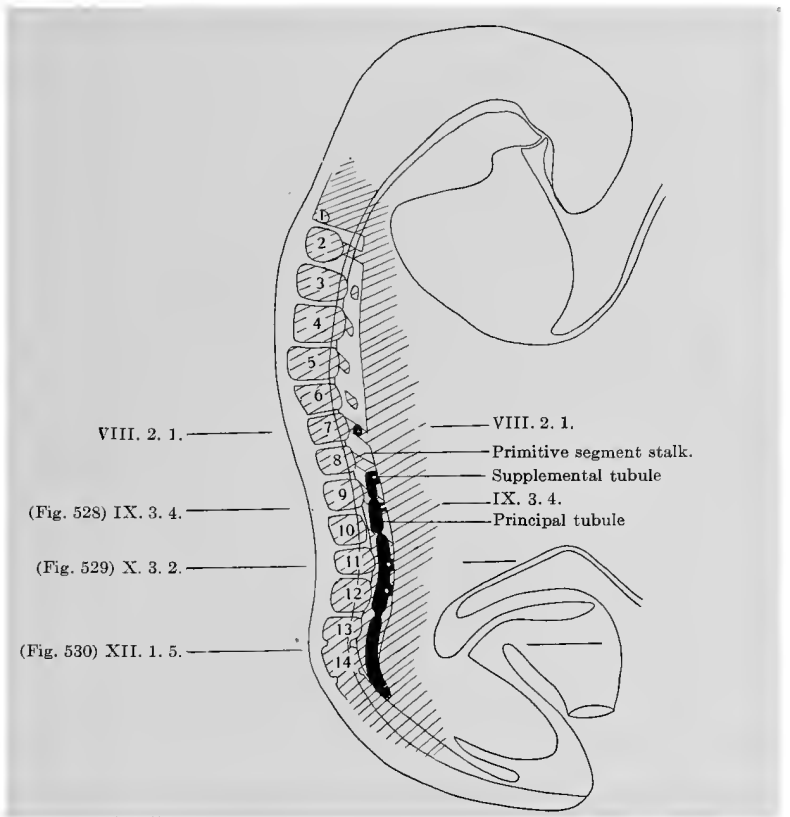


FIG. 526.—Reconstruction of the right pronephric anlage of an embryo of 2.6 mm. greatest length, with 13–14 pairs of primitive segments. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel.) The contours of the embryo, the medullary canal and the intestine are outlined, the mesoderm (secondary primitive segment, segment stalk and lateral plate) is shaded, the pronephric anlage is black. The anlage consists of five parts, a rudimentary tubule in the 7th segment, two well-developed tubules in the 8th and 9th segments, a pronephric ridge in the 10th, 11th and 12th segments and another ridge in the 13th and 14th segments. Lumina in the principal tubule and in the primitive segment stalks are left white.

For the posterior ones one or two continuous longitudinal ridges are formed, which lie in a direct line with the isolated tubules; I shall call these the pronephric ridges to contrast them with the pronephric tubules. The ridges are in some places separated from their parent tissue, in others they remain in connection with it and at each of these connection regions they possess a lumen. In Figs. 526 and 527 I give a reconstruction of the pronephric anlage of an embryo of 2.6 mm. greatest length and with 12–14 pairs of primitive segments; the pronephros here reaches its great-

est extent. The arrangement is somewhat clearer on the right side (Fig. 526) than on the left. The secondary primitive segments, the segment stalks and the lateral plate are shaded and the pronephros is black; the supplemental canals and the connections of the pronephric ridges with the segment stalks or the nephrogenic cord, have been in the figures displaced laterally to the boundary line of the lateral plate, although in reality they

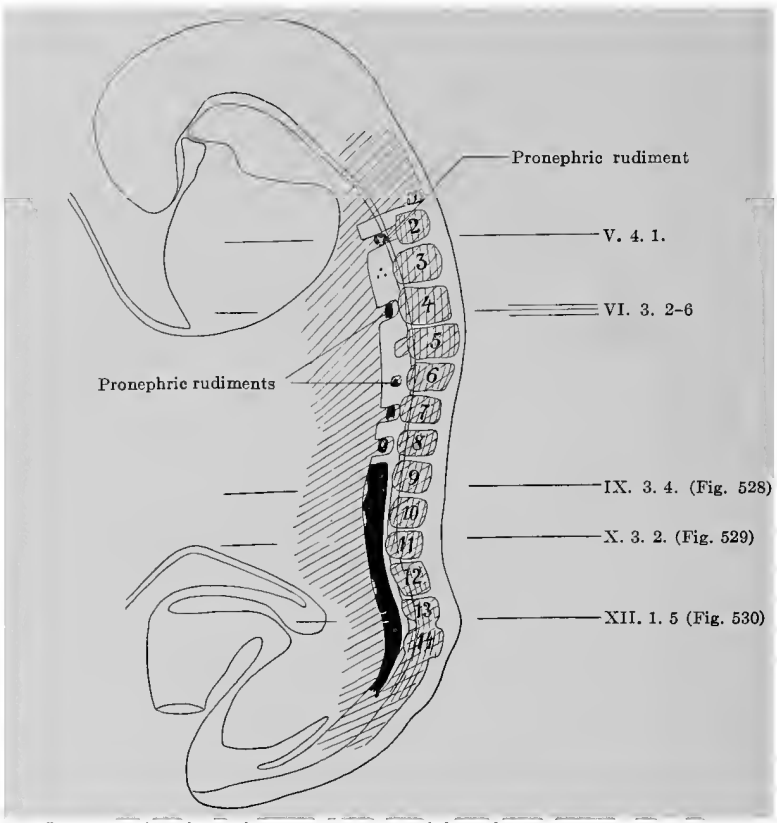


FIG. 527.—Reconstruction of the left pronephric anlage of the embryo shown in Fig. 526. The pronephros consists of rudiments in the 2nd, 4th, 6th, 7th and 8th primitive segments and of a long pronephric ridge extending from the 9th to the 14th segment. The horizontal lines in both figures indicate the locality of the transverse sections.

lie beneath the nephrogenic cord. Finally, where a lumen occurs, it is represented as white. In the 7th segment there is a rudimentary anlage and the 8th and 9th each contains a completely developed one. There are therefore three separate pronephric tubules. The second and third tubules are united together and with the following pronephric ridge. In the stretch from the 10th to the 12th segment and again in that from the 13th to the 14th there follow two pronephric ridges; the lumina in the anterior one show, though not strongly, a metameric arrangement. The left side

of this embryo shows the rudimentary anlagen in the 2nd, 4th and 6th segments that were previously mentioned.

This embryo with 12–14 pairs of primitive segments already shows progress in the development of the individual tubules. The anlagen of the 8th and 9th segments have separated from their parent tissue, have extended backwards to the next anlage and have fused with it to form the collecting duct. This further devel-

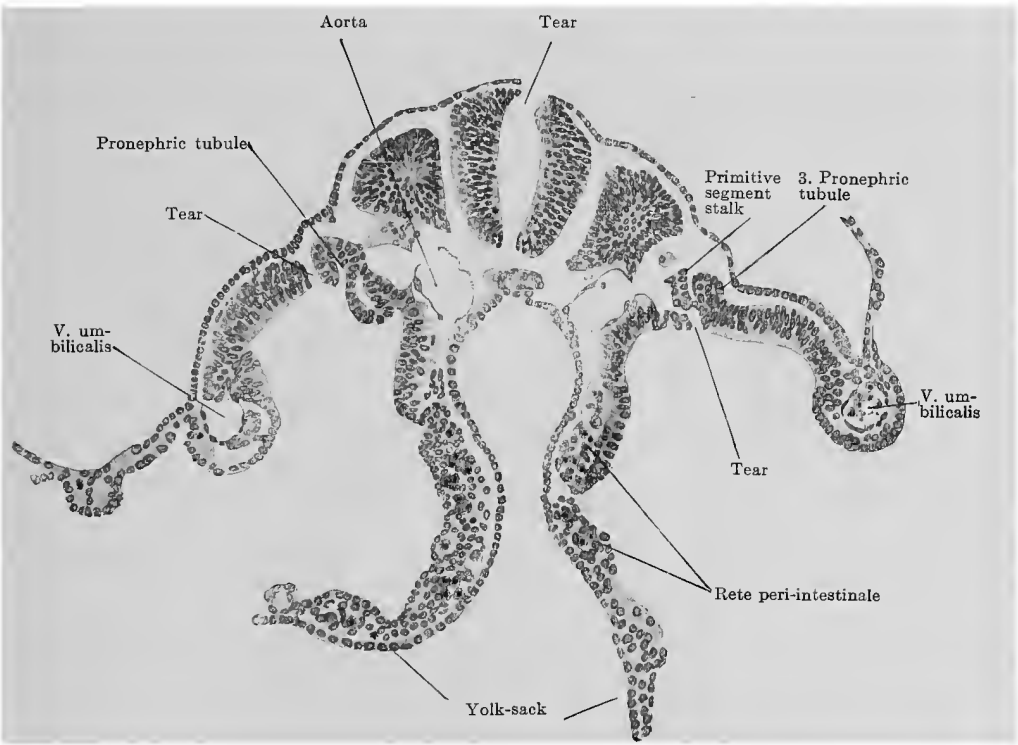


FIG. 528.—Embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel; slide 9, row 3, section 4.) × 182. The section passes on both sides through the caudal wall of the 9th primitive segment. On the left side the third, right pronephric segment, with the principal and supplemental canal, is cut. On the right side the section passes through the caudal end of the third, left pronephric principal canal and shows its relation to the primitive segment stalk. Between the ectoderm and the visceral mesoblast is the vascular layer, in which are young red blood-corpuscles, distinguished by the abundance of chromatin in their nuclei. The tears in the medullary canal and beside the pronepheric anlagen are artefacts.

opment corresponds in time with the establishment of continuity between the exo- and entocœlom and with the enlargement of the latter. In the entocœlom, however, only the cœlom of the lateral plate is enlarged, that of the segment stalk remains narrow so that the stalk looks like a tubule and gives the false impression of a direct origin of the pronephric anlage from the lateral plate. Fig. 528 passes on the right (left in the figure; the location of the section is shown in Fig. 527) through the cranial end of the third pronephric tubule, which here, notwithstanding its shortness, con-

sists of a principal tubule and the supplemental tubule formed from the primitive segment stalk. A comparison with the left side (right in the figure), where the section passes through the separated end of the third left pronephric tubule, shows that there the principal tubule and the segment stalk are distinctly separate. To show the arrangement in the pronephric ridge I give in Fig.

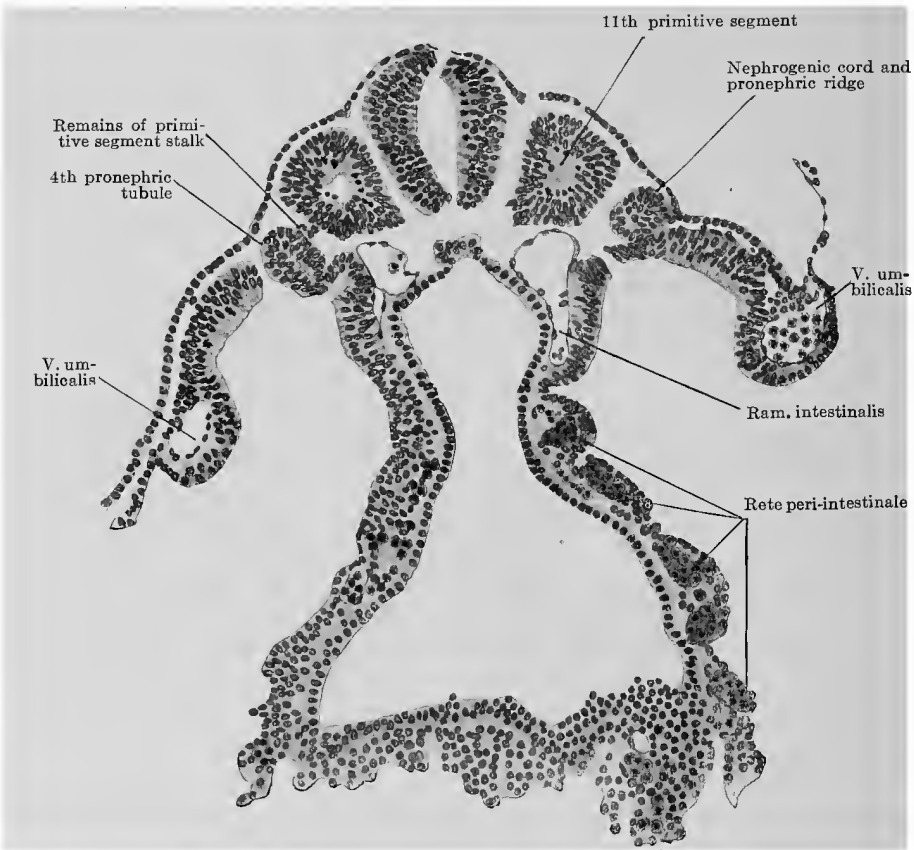


FIG. 529.—Human embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel; slide 10, row 3, section 2.) × 182. The section passes on both sides through the cranial half of the 11th primitive segment. On the right (left in the figure) the primitive segment stalk is cut and also the pronephric ridge and a lumen corresponding to the 11th pronephric tubule. The pronephric ridge and the segment stalk are not delimited from each other. On the right side the same arrangement. Between the visceral mesoblast and the digestive canal are the cells of the vascular layer. On the right side a ramus intestinalis passes to the vascular layer.

529 a second section through this embryo, which on the right (left in the figure) cuts the ridge just where it possesses a distinct lumen. Here the segment stalk together with its pronephric anlage is separated from the lateral plate, although it lies in close apposition to it. The existence of the two components is to be made out only by comparison with the anterior tubules and from the further development. Finally the question as to the caudal

end of the pronephric anlage is yet to be considered. In the embryo with 12–14 pairs of primitive segments, in which the pronephric anlage reaches its greatest caudal extension, it passes insensibly at its caudal end into the unsegmented mesoderm. The section shown in Fig. 530 passes through the 13th or 14th segment; its location is shown in Figs. 526 and 527. On the left side of the figure there is merely a thickened primitive segment stalk, sepa-

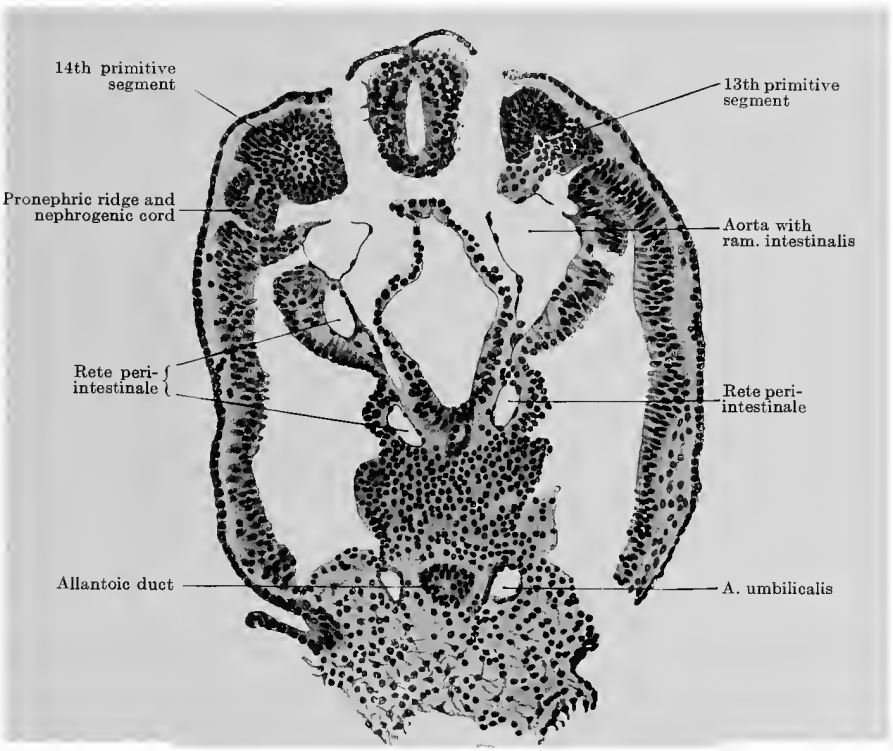


Fig. 530.—Human embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel; slide 12, row 1, section 5.) × 182. On the right side (left in the figure) the section passes through the forming cranial wall of the 14th primitive segment, on the left through the caudal wall of the 13th segment. On the right (left in the figure) it cuts the nephrogenic cord. A comparison with the right side of Fig. 528 shows at once that the primitive segment stalk is greatly enlarged, the enlargement heing due to the pronephric anlage. The anlage and the primitive segment stalk together form the nephrogenic cord. On the left side (right in the figure) the section passes through a point where the nephrogenic cord, delimited otherwise as on the right side, is fused with the lateral plate and receives a cleft of the cœlom. The rete peri-intestinale is well developed, since we are here in the region of the art. umhilicalis. Between the aorta and the rete there is on the right side of the figure another ramus intestinalis.

rated both from the primitive segment and the lateral plate; it is termed in the figure the nephrogenic cord and pronephric ridge: on the right side the segment stalk is in connection with the lateral plate and the lumen of the latter is continued directly into the stalk. In Fig. 527 the leader "Fig. 530" shows how far the lumen passes beyond the medial edge of the lateral plate. More caudally the right (left in the figure) thickened segment stalk also becomes

connected with the lateral plate and then the thickening fades out so gradually that a definite limit for its extremity cannot be established. The pronephric anlage is, accordingly, as far as the 14th primitive segment purely mesodermal, any participation of the ectoderm in it is excluded.

At this point there is a gap in the available material. The next oldest embryo is 2.5 mm. in length and possesses 23 pairs of primitive segments. The pronephros in this is almost completely

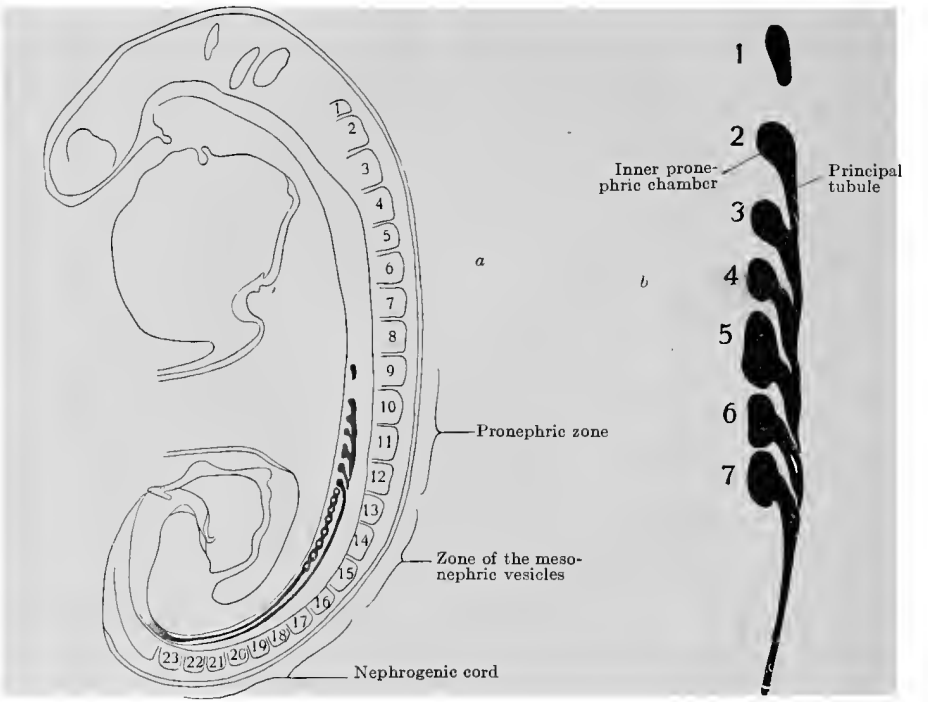


FIG. 531 *a* and *b*.—*a*. Reconstruction of the left pronephric and mesonephric anlagen of a human embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments. (Embryo R. Meyer 300, from the collection of Professor R. Meyer, Berlin.) The figures by Thompson were employed for the reconstruction. The pronephros consists of seven tubules; the most anterior in the 9th segment is in process of degeneration, the 2nd–5th have united to form the collecting duct, the 6th tubule is still free, but is about to unite with the 5th and 7th. The 7th is continued into the free terminal portion of the primary excretory duct and this extends to the unsegmented mesoderm. Beyond the 7th tubule is the beginning of the nephrogenic cord and in the region of the 13th–15th segments mesonephric vesicles are developed within this. *b* shows the pronephros under a higher magnification.

developed—so far at least as one may speak of its completion. It consists, as is shown in Fig. 531 *a* and *b*, of a number of tubules and the primary excretory duct. There are in all 7 tubules present, the most anterior of which is not united with the succeeding tubule, as was the case in the younger embryo. This fact, together with what was found in the embryo with 8–10 pairs of primitive segments, in which the most anterior anlage was in the 7th segment, and with what was found in the embryo with 12–14 pairs of segments, in which degenerating anlagen occurred in the 7th and

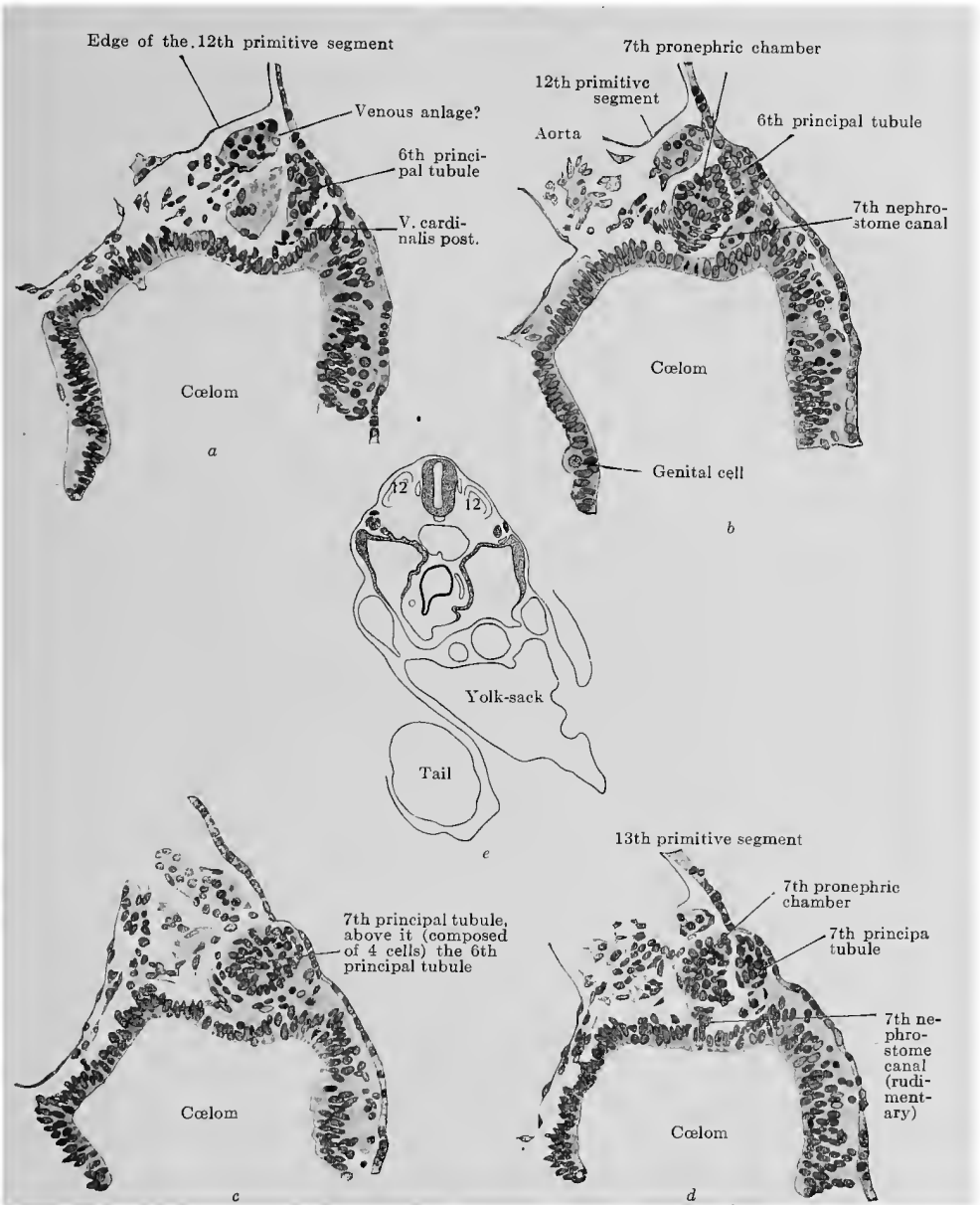


FIG. 532 *a*, *b*, *c*, and *d*.—Four sections from a human embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments. (Embryo R. Meyer 300, from the collection of Professor R. Meyer, Berlin; slide 11, row 5, sections 4 and 6; slide 12, row 1, sections 5 and 7.) × 238. *a*. Section through the 6th pronephric segment; the caudal wall of the pronephric chamber is just touched, the principal tubule is fully cut. Ventral from the pronephric segment is the anlage of the v. cardinalis post. *b*. Section through the 7th pronephric chamber and the 6th principal tubule; in the visceral mesoblast a genital cell. *c*. 7th pronephric chamber and 7th principal canal continuous. *d*. 7th pronephric segment separated into pronephric chamber and principal canal; rudimentary 7th nephrostome canal. The sections are 5μ thick; if *a* be taken as the first, then *b* is the third, *c* the eighth, and *d* the tenth section.

8th segments, confirms the conclusion that the cranial end of the pronephros degenerates and that only the tubules of the 10th and succeeding segments undergo a further development. The six pronephric segments that are developed, the 2nd to the 7th, lie in the 10th, 11th and 12th segments and in the interstitium between the 12th and 13th. Whether this concentration of six pronephric tubules within the limits of 3½ body segments indicates a primary dysmetamerism or has resulted from the approximation of originally more separated anlagen cannot be determined. Each pronephric segment (Fig. 531 *b*) shows distinctly a thickened beginning portion, the inner pronephric chamber, and a smaller canal-like portion, the principal tubule. The cells in the inner pronephric chamber are arranged in such a way as to be concentric to a latent lumen (Fig. 532). The tubules 2–5 have fused and so form a collecting duct (Fig. 531 *b*). The tubules 5, 6 and 7 are not yet united but their union is imminent (Fig. 531 *b*); this finding is conclusive as to the pronephric character of the 6th and 7th and therefore of the preceding tubules. In Fig. 532 the detailed relations of the 6th and 7th tubules are shown: section *a* cuts the principal tubule of the 6th pronephric segment and the corresponding 6th pronephric chamber is visible as a marginal section; Fig. *b* shows below the principal tubule of the 6th segment the primitive segment stalk of the 7th segment; the arrangement of its cells divides it into two portions, a medial thickened portion with its cells arranged concentrically, the inner pronephric chamber of the 7th tubule, and a lateral smaller portion whose cells are not concentric; this can only be the portion that I have termed in the general description the nephrostome canal, and section *d* shows its connection with the lateral plate. Section *c* shows the 7th inner pronephric chamber with the 7th principal tubule arising from it. Between this and the ectoderm are four additional cells, which represent the pointed end of the 6th principal tubule. Finally section *d* shows the 7th principal tubule separated from its pronephric chamber; the 6th principal tubule has disappeared.

In the region of the inner pronephric chamber there is never, so far as the material furnishes a definite indication, a formation of an internal glomerulus; but, on the other hand, in several embryos there was a rudimentary external glomerulus in whose interior sections of vessels could be seen. The external glomerulus first becomes formed when the pronephros is in full degeneration.

The human pronephros is by far the best developed within the group of the mammals. It shows its relations more clearly than it does in the birds and is at least as distinct as in the reptiles. With the exception of the internal glomerulus it possesses all the constituent parts that have been given in the general description as characteristic of a fully formed pronephric segment; the prin-

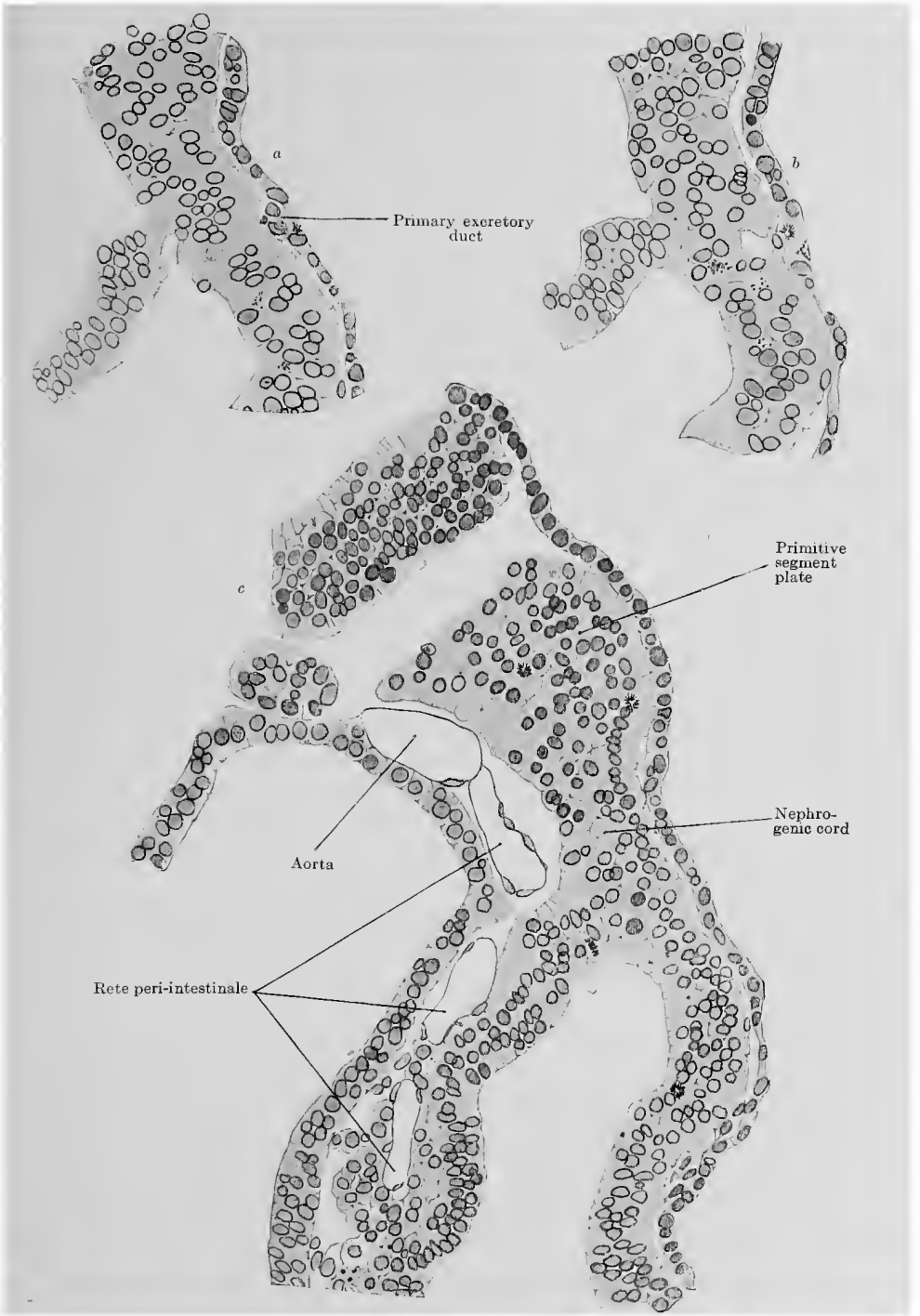


FIG. 533 *a*, *b* and *c*.—Three sections through the caudal end of the primary excretory duct. Human embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments. (Embryo R. Meyer 300, from the collection of Professor R. Meyer, Berlin; slide 13, row 4, sections 5, 6 and 7.) × 180. *a*. The end of the primary excretory duct is still to be distinguished from the ectoderm. *b*. Between the end of the primary excretory duct, consisting of a single cell, and the ectoderm there is interposed a cell in the act of division; whether it belongs to the ectoderm or the duct is uncertain. *c*. Section immediately behind the end of the duct; the ectoderm does not show the slightest alteration. The rete peri-intestinale between the visceral mesoblast and the intestine.

cipal canals and the collecting duct formed from them, the inner pronephric chamber, rudiments of nephrostome canals and one or several external glomeruli.

The development of the free terminal portion of the primary excretory duct cannot be clearly made out from the available material. While the embryo with 12–14 pairs of primitive segments did not possess such a structure, in the embryo with 23 pairs of segments it is developed throughout almost its entire length. It appears in this (Figs. 558 and 559) as a solid, semilunar mass of cells, which is in apposition by its concave surface with the nephrogenic cord or the mesonephric vesicles; it shows extensive variations in calibre and remarkably rare mitoses, while these are abundant in the neighboring tissues. Towards its caudal end it gradually diminishes in size, until, finally, it consists of only 1–3 cells and ends at the ectoderm. In Figs. 533 *a, b* and *c* the two last sections through the secretory duct and that immediately following are shown. One sees in section *a* the apposition of the duct to the ectoderm, but the two may yet be distinguished to a certain extent. In Fig. *b* the distinction is no longer possible; a mitosis is to be seen, but it is impossible to say whether it belongs to the excretory duct or to the ectoderm, its spindle being so placed, however, that the daughter cells must lie sagittally one behind the other. Finally, in *c* every trace of the duct has disappeared and there is not the slightest indication that preparations for its formation are to be met with in the ectoderm. The entire apposition has at most an extent of 50 micra and the sections that precede it sometimes show a sharp delimitation of the duct from the ectoderm and sometimes do not. It may furthermore be noted that the emigration of cells from the parietal mesoderm to form mesenchyme is already taking place and that these emigrated cells become interposed between the parietal mesoderm and the ectoderm, just as is the end of the primary excretory duct, and frequently their delimitation from the ectoderm cannot be made out. This is the only series which, perfectly preserved, shows the excretory duct on its way to the cloaca. I can make out from it neither a connection of the duct with the ectoderm nor a preparation for the formation of the duct on the part of the ectoderm. I cannot settle definitely the question as to the participation of the ectoderm in the formation of the excretory duct, but I am inclined to deny any such participation. As regards the formation of the duct from the 13th segment caudally, where in the embryo with 23 segments it lies free between the ectoderm and mesoderm, a definite conclusion is not possible. It may be recalled that in the embryo with 12–14 pairs of primitive segments the pronephric anlage was in connection with the mesoderm to beyond the 14th segment and that in its anterior and middle portions it was divided into pronephric

tubules and collecting duct. It is accordingly quite possible that the excretory duct had also been formed in the 13th and 14th segments by splitting from the pronephric anlage and the possibility that the same process is repeated in the more caudal segments must be given consideration. The variations in the caliber of the excretory duct and the lack of mitoses throughout its entire extent indicate a formation in loco.

The free terminal portion of the excretory duct has reached the cloaca in an embryo with 27–28 pairs of primitive segments and of 4.25 mm. vertex-breech length. It runs in a straight course, close to the ectoderm in the angle between the urogenital fold and the parietal mesoblast, to the level of the caudal surface of the 28th primitive segment, and there it bends ventrally and terminates in the angle between the cloaca and the ectoderm, close to the

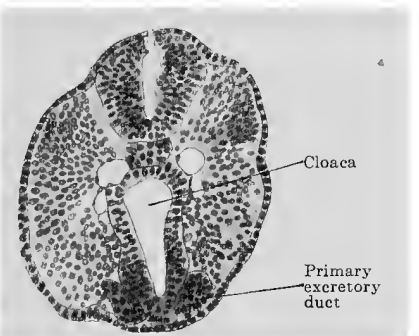


FIG. 534.—Human embryo of 4.25 mm. vertex-breech length and with 27–28 pairs of primitive segments. (Embryo H. M. I., from the collection of the Anatomical Institute, Zurich; slide 399, J. 13,2, row 15, section 5.) × 150. The ends of the primary excretory ducts are on either side of the cloacal membrane.

cloacal membrane (Fig. 534). The actual situation of its contact with the cloaca is caudal to the middle of the cloacal membrane and at the junction of the middle and lower thirds of the cloaca itself. The excretory duct is not evenly developed in this embryo; from the 9th or 10th to the 14th segment its diameter is small, but from the 14th segment on it increases rapidly in size and remains large to its termination, its blind end being enlarged to almost double the original size. The lumen appears first at two points, at the anterior end in the region of the 10th and 11th segments and in the enlarged posterior extremity. Its further development takes place discontinuously for the most part and the various cavities show no regularity in their arrangement. Frequently the lumen of the cloaca evaginates into the blind end of the excretory duct.

The perforation of the cloaca by the duct is said to occur in embryos of 4.2 mm. greatest length (Keibel, 1896), but I have first found it in an embryo of 7 mm. greatest length.

THE VESSELS OF THE PRONEPHROS.

In man the inner pronephric chamber, as it appears, is not invaginated by a vascular glomerulus and the external glomerulus is only a transitory formation; it contains a vessel it is true, but the relation of this to the rest of the vascular system has not been discovered. Where the actual pronephric vessels are to be looked for must first be learnt from comparative embryology.

In amphioxus the vessels pass in arches from a longitudinal vessel, situated ventral to the digestive tract, to a dorsal longitudinal vessel above the digestive

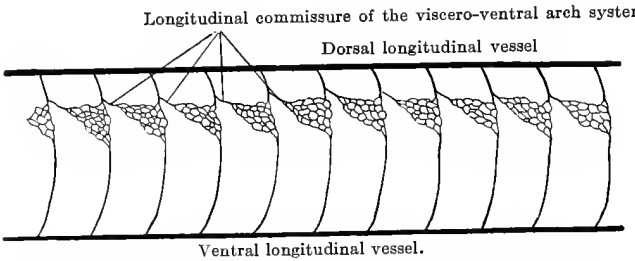


FIG. 535.—Diagram of the viscero-ventral arch system in amphioxus.

tract; these arches lie between the wall of the digestive tract and the visceral mesoblast (Fig. 535). To distinguish these arches from the dorsal arches which supply the dorsal musculature, the spinal ganglia and the spinal cord, I shall call them the ventral arches, and to further distinguish them from a second ventral arch system which supplies the ventral musculature and corresponds to the intercostal system of arteries, they may be called the viscero-ventral arches, the intercostal arteries being then termed the parieto-ventral arches.

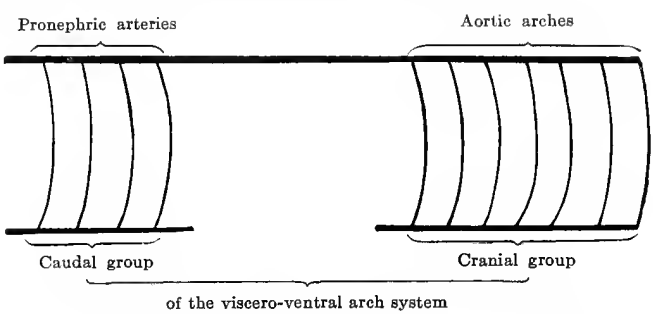


FIG. 536.—Diagram of the viscero-ventral vascular arches of a selachian.

In the viscero-ventral arch system of amphioxus there are retia mirabilia which surrounded the excretory ducts and their solenocyte areas, and these are so arranged that they unite successive arches (Fig. 535); thus the paired longitudinal commissure of the viscero-ventral arch system is formed.

In the selachians only a greatly reduced viscero-ventral system occurs. It is no longer a continuous system, but is divided into two groups of arches, a cranial one, formed by the aortic arches, and a caudal one, formed by the pronephric arteries (Fig. 536). The pronephric arteries, which, in consequence of the

rudimentary development of the selachian pronephros, do not form retia mirabilia, fuse later on the right side to form a simple and unpaired a. vitellina. The arteries on the left side, which from the beginning are merely rudiments, vanish completely. Later the a. vitellina gives off the a. mesenterica and becomes the a. omphalo-mesenterica. The supply of the digestive tract is, accordingly, from a part of the left viscero-ventral arch system.

In the ganoids (Fig. 537) we have the same division into groups and a still greater limitation of the viscero-ventral system. A cranial group is formed, as in the selachians, by the aortic arches, a caudal one—its relations in early stages of

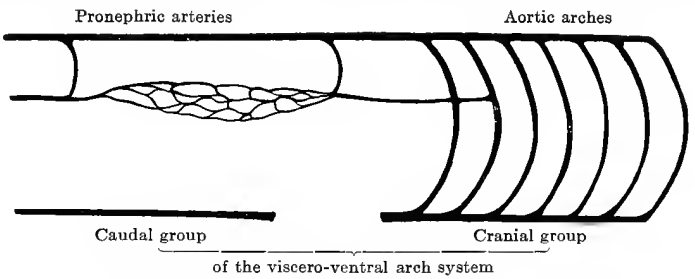


FIG. 537.—Diagram of the viscero-ventral vascular arches of amia calva.

development have not yet been studied—is formed by the roots of the pronephric vessels. This caudal group is, however, incomplete, since neither of the two arches present reaches the longitudinal vessel on the ventral side of the intestine (v. subintestinalis). The glomerulus itself forms a rete mirabile, which is spread out between the arches like a longitudinal commissure. The glomerulus is paired in its cranial portion and unpaired caudally, so that its rete mirabile has two poles cranially and one caudally. All three poles are in connection with longitudinal vessels; the two anterior ones run cranially along the dorsal surface of the intes-

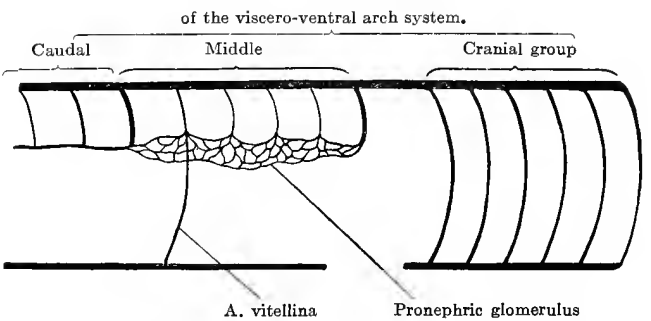


FIG. 538.—Diagram of the viscero-ventral vascular arches of a trout.

tine, reach the arches of the cranial group and unite with at least the sixth and fifth; the caudal longitudinal vessel passes backward as the a. mesenterica, supplying the entire intestine as far as its terminal portion.

There are accordingly in the ganoids two paired commissural vessels, which, like the paired longitudinal commissures of amphioxus, unite the arches of each group and also the groups themselves. In the region of the caudal group the paired commissures unite to form the unpaired a. mesenterica. Consequently in the ganoids also the vessel which supplies the digestive tract arises from the viscero-ventral arch system.

In the teleosts (Fig. 538) there is again the same grouping of the viscero-ventral arch system, the cranial group being formed by the aortic arches and the caudal group by the pronephric vessels. The caudal group is again incomplete, although not to the same extent as in the ganoids, for, in the first place, the number of its arches is greater and, secondly, one arch—and that on the right side—extends to the yolk-sack and so represents the a. vitellina. This fact justifies the assignment of the pronephric arteries of the ganoids and teleosts to the viscero-ventral arch system. Between the individual arches of the caudal group the glomerulus is again drawn out to form a longitudinal commissure. In its cranial half it is paired, in its caudal half it is unpaired, and therefore has three poles, as in the ganoids. It is prolonged, caudally only, into a longitudinal vessel that becomes the a. mesenterica. An important fact is still to be noted: the a. mesenterica in the embryo is connected with the aorta by arches not only in the region of the pronephric glomerulus, but also throughout its further course; the last arch occurs at the level of the cloaca. The caudal group of the viscero-ventral arch system accordingly extends in the teleosts throughout the entire posterior half of the body.

Among the amphibia the urodeles possess numerous intestinal arteries, the anura only one. The course of this single vessel is, however, such that we may derive the arrangement in the anura from that occurring in the urodeles by supposing the existence of a longitudinal commissural vessel, which united the individual intestinal arteries of the urodeles and thereby furnished a possibility for their intestinal arteries, with one exception, to relinquish their connection with the aorta. The actual development of the arteries in the anura has not yet been studied. But in any case it may be supposed that the urodeles possess both groups of the viscero-ventral arches; the unpaired condition of the posterior group offers, as we have seen, no obstacle to this homology.

In the reptiles the region of the a. omphalo-mesenterica is originally supplied by a large number of aortic branches, which arise for the most part in pairs, but are partly unpaired. With the formation of a mesentery the paired vessels unite together, and one of these unpaired vessels becomes the a. omphalo-mesenterica, while the others degenerate (Hochstetter, 1898). The original paired intestinal arteries may be identified as the caudal group of the viscero-ventral arch system.

In birds and mammals, finally, there are in early stages of development numerous intestinal or vitelline arteries, arising from the as yet ununited aortæ and passing over into a vascular network that surrounds the wall of the yolk-sack. There is not the slightest difficulty in the way of regarding these as the representatives of the caudal group of the viscero-ventral arch system.

From what has been said above we arrive at the following plan of development for the intestinal arteries. A viscero-ventral arch system unites a ventral and a dorsal longitudinal vessel; the individual arches of the system may originally have been arranged metamerically. In each of the various arches a rete mirabile is interposed, surrounding the region of a uriniferous tubule and uniting two successive arches. From the totality of these retia mirabilia a longitudinal commissure is formed. The gills and uriniferous tubules, originally lying in the same segments, migrate into different regions of the body, and both become reduced in number in the course of the phylogeny. There thus comes about the separation of the viscero-ventral arches into a cranial and a

caudal group. The anterior group enters the service of the branchial apparatus as the aortic arches, the posterior one is at first devoted to the supply of the pronephros and later, on the degeneration of this, enters the service of the digestive system. On the transformation of the caudal group of arches into the intestinal arteries they undergo such changes that their original arch

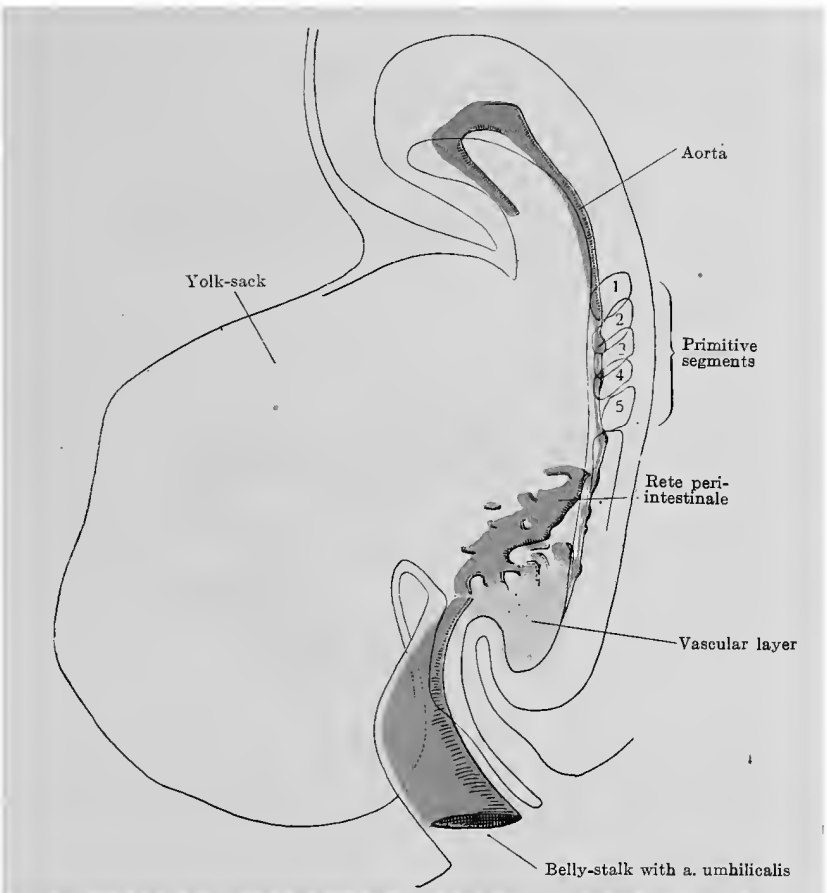


FIG. 539.—Reconstruction of the arterial system of an embryo of 1.38 mm. greatest length and with 5–6 pairs of primitive segments. (Embryo Pfannenstiel-Kromer, from the collection of Professor Pfannenstiel.) The aorta is a continuous vessel with completely closed walls from the level of the second primitive segment forward, from there backwards it is in anlage. On the posterior part of the yolk-sack and on the end-gut is the anlage of the rete peri-intestinale. The a. umbilicalis arises from this rete.

character is completely lost; both the longitudinal commissural vessels play an important part in the transformation.

Our task in connection with the investigation of the human pronephric vessels is now defined. We have to seek for the caudal group of the viscero-ventral arch system and its longitudinal commissure. The study of the development of the intestinal arteries and especially of the a. cœliaco-mesenterica must at some point lead to the viscero-ventral arch system.

The intestinal arteries in man develop from a vascular network which surrounds the intestine and yolk-sack. Fig. 539 shows the reconstruction of the vessels of an embryo with 5–6 pairs of primitive segments. The aorta as far as the second primitive segment is developed as a tube with completely closed walls; from there on it is still in anlage, appearing in section sometimes as a closed ring, sometimes as composed of individual cells. From the future 7th segment to the tip of the tail a vascular network, the rete peri-intestinale, is interposed between the yolk-sac or end-gut on the one hand and the visceral mesoblast on the other

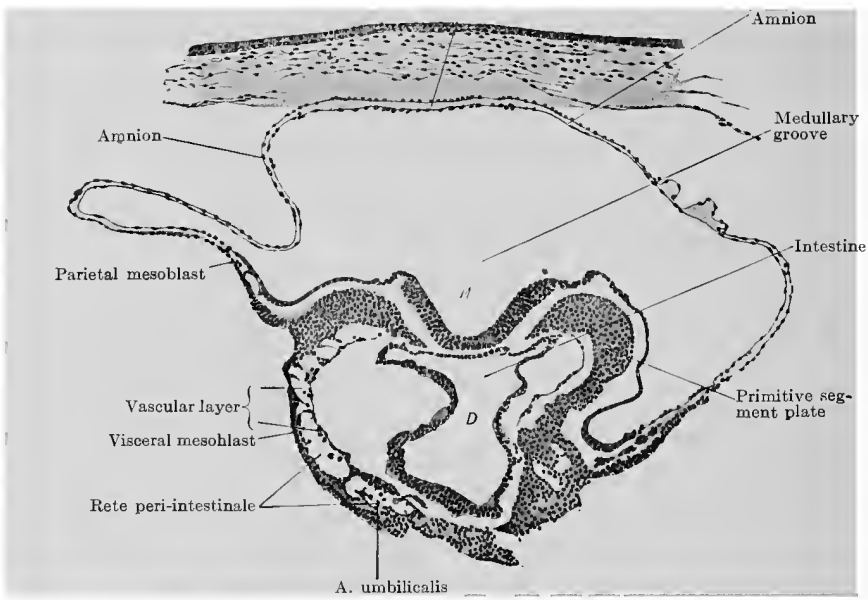


Fig. 540.—Transverse section of an embryo of 1.38 mm. greatest length and with 5–6 pairs of primitive segments, at the level of the cloaca. (Embryo Pfannenstiel-Krömer, from the collection of Professor Pfannenstiel; slide 7, row 3, section 3.) × 120. In consequence of a shrinkage the entoderm has separated from the mesoderm, and the formation of vessels, which takes place from the entire visceral mesohlast, is distinctly seen. It occurs hy the separation of an entire cell layer from the visceral mesoblast, with which it remains in connection by cell prolongations or cell groups. A distinction hetween rete peri-intestinale and aorta caunot he made; it is rather a question of the formation of an intestinal blood-sinus, such as we know from the invertebrates (Lang, 1903).

(Figs. 521 and 540). In the region of the mid-gut the meshes of this network are already provided with distinct walls (dark red in Fig. 539), but in the end-gut region there are no meshes whatever, but only a simple vascular layer (Fig. 540), which has separated by delamination from the visceral mesoblast and has not yet developed separate vessels (pale red in Fig. 539); the aorta becomes lost in this. From this vascular layer, accordingly, the rete peri-intestinale and the aorta develop. The umbilicalis stands in connection with this vascular network and determines its early formation; a connection between the a. umbilicalis and the aorta does not yet exist on the left side, but is present on the right.

Fig. 541 shows a reconstruction of the vessels of an embryo with 12–14 pairs of primitive segments. The aorta is fully formed up to the region of the end-gut; a vascular layer is spread out over the entire mid-gut (compare also Figs. 528 and 530) and is bounded

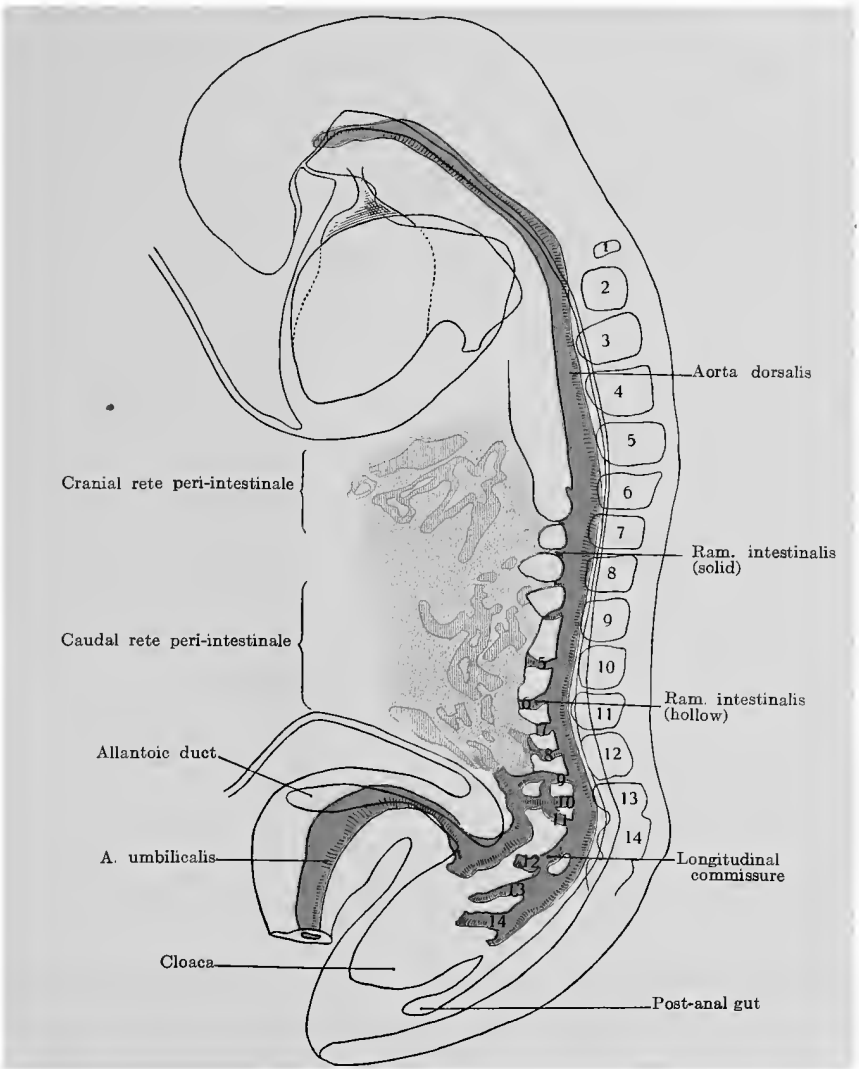


Fig. 541.—Reconstruction of the trunk arteries of a human embryo of 2.6 mm. greatest length and with 13–14 pairs of primary segments. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel.) The rete peri-intestinale is developed over the entire mid-gut and end-gut and is connected with the dorsal aorta by rami intestinales. The rete peri-intestinale and the rami intestinales are strongly developed at the point where the A. umbilicalis arises from them.

dorsally by a sharp line; it is represented in Fig. 541 by the pale pink tint. In this vascular layer two independent networks have developed, a cranial and a caudal one. The cranial network is in connection with the v. omphalo-mesenterica and need not here con-

cern us further. The caudal one shows an indistinct cranial and a well-developed caudal region. The cause of the different development of the two regions lies in the union with the a. umbilicalis, which, making use of this network wanders gradually caudalwards and only brings to complete development and preserves for a time

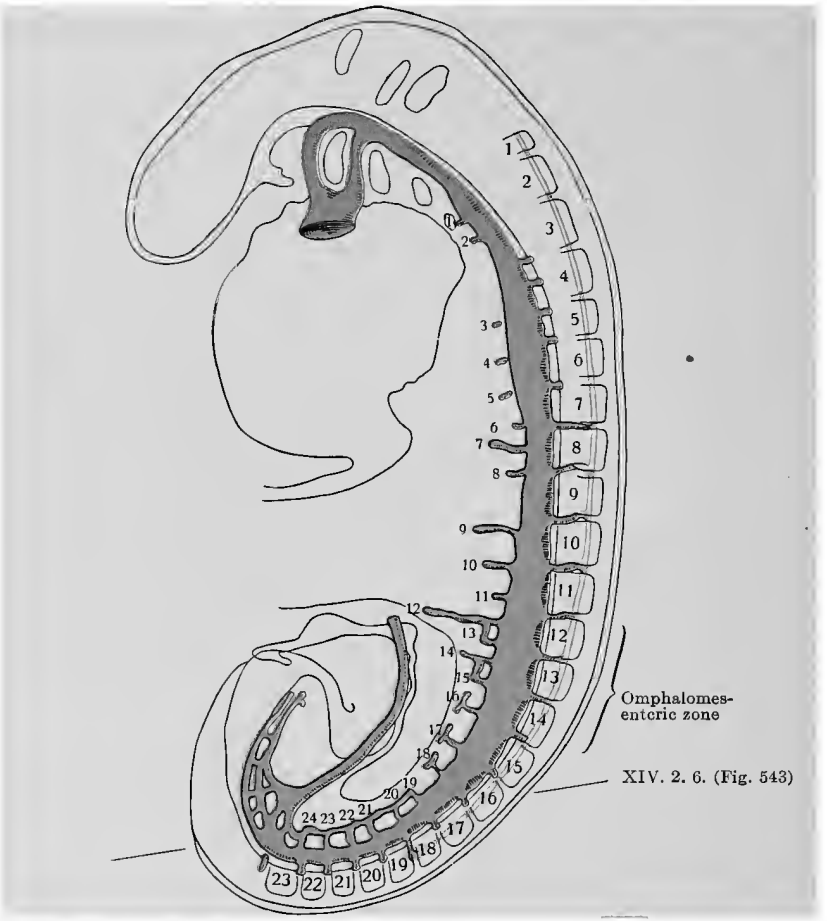


FIG. 542.—Reconstruction of the trunk arteries of a human embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments. (Embryo R. Meyer 300, from the collection of Professor R. Meyer, Berlin. The dorsal aorta is completely developed and from it there arise the viscero-ventral and the dorsal systems of arches. Between the arches of each of the two systems a longitudinal commissure is developed; the A. umbilicalis arises from the commissural vessel of the ventral arch system.

those portions of the network which directly place it in connection with the aorta. Between the vascular layer and the ventral periphery of the aorta there are stretched partly hollow (dark red in Fig. 541), partly solid (pale red) connecting vessels, the rami intestinales (Fig. 529, left side; Fig. 541). In the entire embryo there are developed 15 such arteries on the left side and 14 on the right side; on the left they lie in the regions of the 6th to the future

17th segment, that is to say in 12 segments, on the right in the regions of the 6th to the future 18th segment, that is to say in 13 segments; a comparison of these figures shows the non-metameric arrangement of the arteries. The rami intestinales are almost equally developed on both sides of the embryo, but they are not arranged in a perfectly paired manner; their difference in number depends on the variability shown by all organs in process of degeneration. The solid rami intestinales lie in the zone in front of the pronephros, in the 6th to the 9th primitive segments; the hollow ones lie in the pronephric zone, in the 9th to the 14th segments. Where the rami must effect the connection between the aorta and the a. umbilicalis they are especially large and at this point a longitudinal commissure between the rami begins to develop.

In Fig. 542 the development of the vessels shows a great progress. The aorta is developed as far as the tip of the tail and shows a commencing enlargement in the region of the pronephros (10th to 13th segments). In addition to the viscero-ventral arch system the dorsal one is also developed and from this the parieto-ventral one is beginning to form. With the formation of the yolk stalk the rete peri-intestinale is carried far from the embryo and is no longer shown in the figure. The number of rami intestinales present is 29, and they show no metamerism. The rami in the neighborhood of the 10th to the 12th segments are the best developed, and next those that connect the aorta and the umbilicalis, the latter having in the meantime wandered further caudally. In the 10th to the 12th segments is the pronephros (compare Figs. 531 and 542) and a relation between it and the development of the rami intestinales is therefore possible. Finally, it may be noted, that in this series a distinct longitudinal commissure is formed, extending as a continuous vessel from the tip of the tail to the 19th ramus intestinalis and as a discontinuous one to the 12th ramus. In Fig. 543 I have reproduced a section that has cut a portion of this longitudinal commissure lengthwise; the vessel is naturally developed on both sides. Just as in the reptiles, birds and other mammals, the paired rami intestinales become unpaired, as do also the paired commissural vessels. The development of the intestinal arteries from the unpaired rami intestinales and the unpaired commissural vessel does not fall within the scope of this chapter.

The description of the pronephric vessels may be summed up by stating that in the human embryo also a viscero-ventral arch system is developed, which separates into two groups, a cranial group of aortic arches and a caudal group of originally pronephric arteries. Just as in Amphioxus, the Ganoids and the Teleosts, a longitudinal commissural vessel develops between the arches of the caudal group, the relation of this vessel to the pronephros

no longer appearing in the development; it is possible, however, that the vessel of the external glomerulus may be derived from it.

Of the veins in the neighborhood of the pronephros, the v. cardinalis posterior, in the act of developing, is shown in Fig. 532 *a–d;* it arises in loco from elements which wander out from the middle plate of the mesoderm. A relation between the venous system and the pronephros cannot be made out in the limited material.

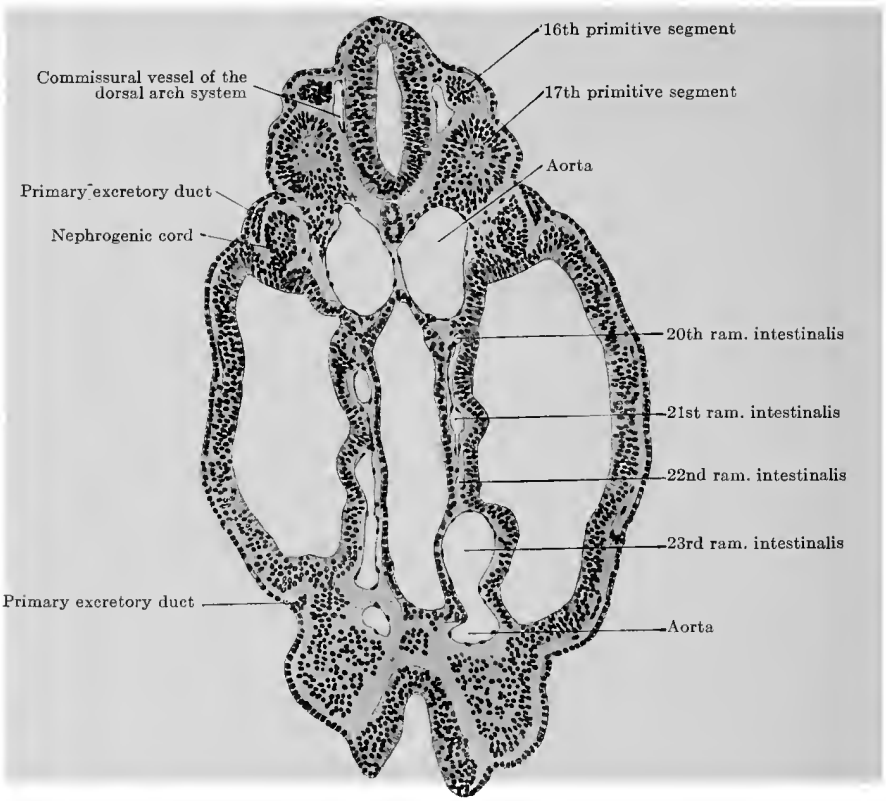


FIG. 543.—Transverse section of a human embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments. (Embryo R. Meyer 300, from the collection of Professor R. Meyer, Berlin; slide 14, row 2, section 6.) × 120. The section passes through the tail bend and cuts, above, the 16th and 17th primitive segments, below, the primitive segment plate. The aorta is cut twice and between the two aortæ are sections of four rami intestinales, which are united by the longitudinal commissural vessel. Above is the nephrogenic tissue and the free terminal portion of the primary excretory duct, below and on the left is the end of the primary excretory duct at the ectoderm.

DEGENERATION OF THE PRONEPHROS.

The pronephros undergoes complete degeneration, but for a time remains of the pronephric tubules and of the collecting duct may be preserved. They are to be found in the retro-peritoneum as completely closed vesicles of a spherical or cylindrical form. Their independence of the mesonephros and the cœlomic epithelium permits their displacement either dorsally behind the aorta and the v. cardinalis posterior or towards the cœlom; in the latter case

they may be situated in fungiform folds projecting into the cœlom. Similar displacements can also take place in the degenerating tubules of the cranial portion of the mesonephros, so that they constitute no specific characteristic of the pronephric remains.

The Urogenital Fold.

The mesonephros is formed along the posterior wall of the body cavity. Only at the very beginning of its development does it find sufficient space in the retroperitoneum; as soon as it begins to expand it needs more room and this it finds in the direction of the body cavity, invaginating the cœlom wall as a fold into the cavity. This fold later contains also the Müllerian duct and the

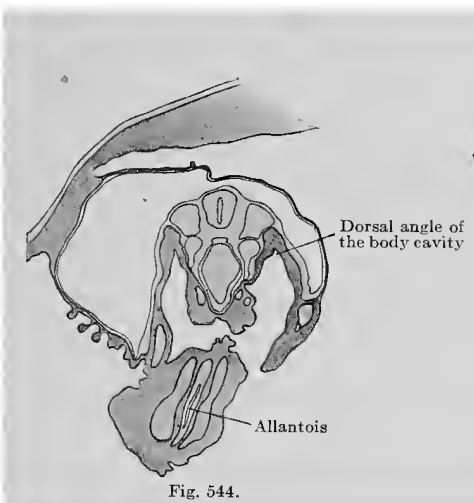


Fig. 544.

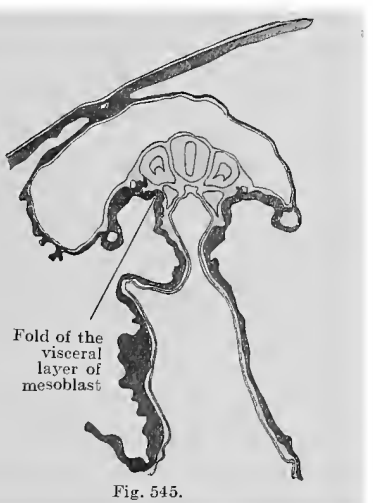


Fig. 545.

Fig. 544.—Transverse section of a human embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments, at the level of the 13th segment. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel; slide 11, row 3, section 5.) × 50. The parietal and visceral mesoblasts of the lateral plate meet to form an acute angle; there is only a dorsal body *angle* and no body *wall*. The aorta on either side with a ramus intestinalis.

Fig. 545.—Transverse section of a human embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments, at the level of the 9th segment. (Embryo Pfannenstiel III, from the collection of Professor Pfannenstiel; slide 9, row 2, section 5.) × 50. Near the dorsal body cavity angle the visceral mesoblast is forming a fold towards the dorsal surface of the intestine. The situation of the dorsal body cavity angle is marked by the attachment of the primitive segment stalk. The aorta on either side with a ramus intestinalis.

reproductive gland, in addition to the mesonephros, and is therefore termed the urogenital fold. It constitutes a region within which a series of very important processes occur, and its origin and fate may, therefore, properly receive attention at this point.

At first a posterior body wall does not really exist. The parietal and visceral mesoblast of an embryo of 2.6 mm. greatest length do not meet to form a *surface* but come together in an *angle* (Fig. 544); to this angle the primitive stalk is attached. Then the two layers of the lateral plate form folds one after the other, first the visceral mesoblast along the dorsal boundary of the entoderm,

towards the chorda, and then the parietal mesoblast towards the ectoderm; at the same time the body cavity, hitherto quite narrow, enlarges. The result of these two processes, a posterior body wall, is shown by an embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments (Fig. 546); the point of origin of the primitive segment stalk marks as before the original angle of the body cavity. This posterior body wall throughout its entire breadth and almost throughout its entire length is invaginated into the body cavity by the developing mesonephros and thus forms a portion of the urogenital fold (Fig. 547); of the contents of the fold the figure shows only the primary excretory duct (black) and the Malpighian corpuscles (white circles). Both are landmarks which afford the possibility for a detailed description of the further processes. The summit of the urogenital fold lies immediately

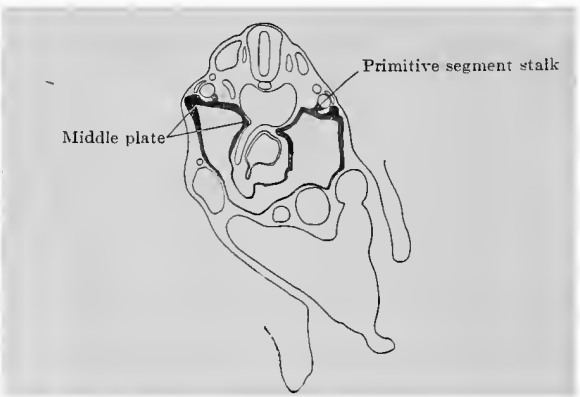


FIG. 546.—Transverse section of a human embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments, at the level of the 12th segment. (Embryo R. Meyer 300, from the collection of Professor R. Meyer, Berlin; slide 12, row 1, section 4.) × 50. A fold similar to that of the visceral mesoblast (Fig. 545) has also been formed by the parietal mesoblast. The dorsal body wall, middle plate, is formed by the two folds. The former angle is again marked by the attachment of the primitive segment stalk. A strong ramus intestinalis from the aorta on the left side of the figure (right side of the embryo).

below the Malpighian corpuscle and the excretory duct is not far from its lateral surface. The first changes in the form of the fold are brought about, first, by the entrance into it of the v. cardinalis posterior and, secondly, by the extension of the body cavity between the lateral body wall and the base of the fold. By the entrance of the vein, which at this time is still very large, the fold increases in size and appears almost quadrangular in section (Fig. 548). Two of the angles are formed by its base, a third represents the original summit, just beneath the Malpighian corpuscles, and the fourth is a newly-formed summit lateral to the primary excretory duct. A comparison of Figs. 547 and 548 shows clearly the extension of the cœlom on the lateral surface of the fold, an extension that leads to the narrowing and modification of its base. The fold, accordingly, is partly invaginated into the body

cavity and partly carved out of the dorsal body wall. The position of the primary excretory duct and that of the Malpighian corpuscles with reference to each other and to the surface have not undergone any important modifications.

The formation of the urogenital fold begins in the fourth cervical segment; it is limited at first to the cranial portion of the body cavity and later extends gradually and continuously towards the caudal end of the body cavity to about the 4th lumbar segment. A stage of maximum extent from the 4th cervical to the 4th lumbar segment does not occur, since a degeneration at the cranial end accompanies the caudally directed growth; actual figures showing the caudal growth and the cranial degeneration are given in the following table:

Size of embryo.	Number of trunk segments.	Extent of the urogenital fold.
2.6 mm. greatest length	10–11 (13–14)[1]	4th cervical to 1st thoracic segment
2.5 " " "	20 (23)	5th " " 8th " "
4.25 " vertex-breech ..	25 (28)	6th " " 2nd lumbar "
4.9 " nape-breech ...	30–32 (33–35)	6th " " 3rd " "
5.3 " greatest length	33 (36)	4th " " 2nd " "
7 " " "	36 (39)	8th " " 3rd " "
9.5 " " "	.....	2nd thoracic " 4th " "
10 " " "	.....	3rd " " 4th " "
11 " " "	.....	3rd " " 4th " "
13 " " "	.....	8th " " 4th " "
14.75 " " "	.....	9th " " 4th " "
17 " " "	.....	10th " " 4th " "
18 " " "	.....	9th " " 4th " "
19.4 " " "	.....	11th " " 4th " "
21 " " "	.....	1st lumbar " 4th " "
22.5 " " "	.....	12th thoracic " 4th " "
26 " " "	.....	1st lumbar " 4th " "
28 " " "	.....	1st " " 5th " "
29 " " "	.....	1st " " 5th " "
30 " " "	.....	3rd " " 5th " "
35 " " "	.....	3rd " " 5th " "
50 " head-foot length	.....	4th " " 5th " "

[1] The numbers in parentheses are the numbers for the primitive segments.

From this table it may be seen: 1. That even in an embryo of 9.5 mm. the caudal growth of the urogenital fold is completed; 2. that the degeneration of its cranial portion is complete in embryos of 2.6 mm. greatest length; in these the fold is limited to the lumbar region. In older embryos the descent of the cranial limit shows a still greater progress, but this is no longer a result of the abbreviation of the fold, but is due to its rate of growth lagging behind that of the vertebræ.

In the course of its development the urogenital fold undergoes a series of important changes. In the first place, it becomes divided throughout its whole length, with the exception of the cranial and caudal ends, into a genital and a mesonephric fold (Figs. 550 and 552). The anlage of the reproductive gland naturally precedes this division, and although the gland is not repre-

sented in Fig. 550, its presence is nevertheless indicated by the displacement of the Malpighian corpuscle (compare Figs. 548–550); the space that is formed between this and the surface of the fold is occupied by the genital anlage. The reproductive gland does not, consequently, grow out into the body cavity, but into the urogenital fold. Its growth is made possible only by the displacement of the mesonephric tubules and this displacement again only by the diminishment of the v. cardinalis posterior. Once the reproductive gland is formed it becomes surrounded by a fosse, deep grooves cutting into it laterally and medially. Fig. 549 shows the lateral groove at its first formation; in Fig. 550 both the lateral and the medial grooves are already considerably devel-

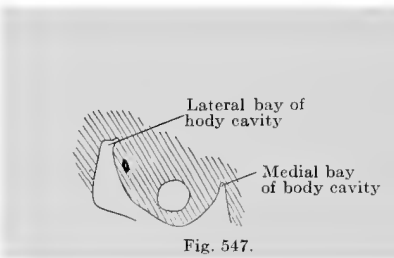


Fig. 547.

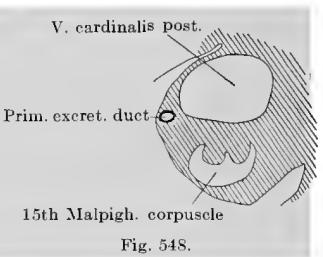


Fig. 548.

FIG. 547.—Transverse section of the middle plate of a human embryo of 4.9 mm. nape length, at the level of the 17th primitive segment. (Embryo 139, G. 31, from the collection of the 2nd Anatominal Institute, Berlin [Professor O. Hertwig].) × 50. The middle plate is evaginated into the body cavity by the development of the mesonephros; it forms the urogenital fold. The fold separates a medial and a lateral bay of the body cavity. In this and the succeeding figures the excretory ducts are black and the Malpighian corpuscles white. These latter lie just below the summit of the urogenital fold, the excretory duct at the lateral surface of its base.

FIG. 548.—Transverse section of the urogenital fold of a human embryo of 7 mm. greatest length at a level between the 13th and 14th trunk segments. (Embryo Chr. 1, from the collection of Professor Hochstetter, Vienna; slide 8, row 6, section 7.) · 50. By the ingrowth of the v. cardinalis posterior the urogenital fold is enlarged at the expense of the retroperitoneum, the lateral bay of the body cavity (Fig. 547) penetrates deeply into the latter, and the modification of the base of the fold is thus begun. Compare the depths of the lateral bay of the body cavity in Figs. 547 and 548. The Malpighian corpuscle determines, as in the preceding figure, the position of the summit of the fold. A new summit has formed near the excretory duct.

oped. During the division of the urogenital fold it becomes still more cut off from the dorsal body wall on its lateral and, as Fig. 550 shows, also on its medial side. Thus the urogenital fold, which at its first formation has a broad base, becomes stalked (Fig. 548) and, at the same time, the stalk becomes twisted; the fold, therefore, no longer lies sagittally (Figs. 547 and 548), but frontally. The formation of a fosse around the genital fold begins somewhat below the cranial pole of the reproductive gland and thence proceeds in a caudal direction. Fig. 552 shows the model of a dividing urogenital fold; the division is here completed to both the cranial and caudal poles.

The two grooves that form the fossæ around the reproductive gland anlage never meet, a portion of the urogenital fold persisting between them and giving rise to the stalk of the genital gland and to the mesogenitale (mesovarium, mesorchium) (Fig. 551).

The breadth of the stalk varies; at the cranial pole it is considerable, immediately below this it diminishes so much that the mesogenitale becomes thread-like, and it remains in this condition as far as the caudal pole of the reproductive gland, where it again increases in size so long as the gland is not completely developed in this region. Fig. 553 may serve to show the size of the urogenital fold as compared with the transverse section of the entire embryo and also to make clear its topographic relations; the fold is here divided into the mesonephric and genital folds, both of which seem very small as compared with the anlagen of the suprarenal body, the enormously developed liver and the large stomach.

In the second place the mesonephric fold, separated from the urogenital fold, becomes further subdivided in correspondence with

Fig. 549.—Transverse section of a human embryo of 12.5 mm. greatest length, at a level between the 18th and 19th trunk segments. (Embryo Ma. 1, from the collection of Professor Hochstetter, Vienna; slide 8, row 4, section 5.) × 50. The urogenital fold has completely altered its position; its base is sagittal and the tip in the neighborhood of the excretory duct has become the summit of the fold, so that a dorsal and ventral slope must be recognized. The lateral bay of the body cavity has penetrated to the medial surface of the the V. cardinalis post. Throughout almost the whole region of the ventral slope the reproductive gland has developed and, by its growth dorsally, the Malpighian corpuscle has been forced in that direction. A groove between the excretory duct and the lateral border of the reproductive gland begins to separate the reproductive gland area from the urogenital fold; consequently the summit of the fold containing the excretory duct projects in a tongue-like manner.

Fig. 550.—Transverse section of the urogenital fold of an embryo of 19.4 mm. vertex-breech length, at a level between the 21st and 22nd spinal ganglia. (Embryo Ma. 2, from the collection of Professor Hochstetter, Vienna; slide 59, row 1, section 3.) × 50. The medial bay of the body cavity now also penetrates into the retroperitoneum and narrows the base of the urogenital fold to a stalk. Two fossæ separate the area of the reproductive gland from the urogenital fold and bring about a division of the latter into the mesonephric and genital folds. The point where these are still connected is the first anlage of the mesogenitale. (Stiel = stalk.)

its contents. Proceeding medially from the lateral surface one meets in it (Fig. 551): the Müllerian duct, the excretory duct and the convolutions of the mesonephric tubules. The fold forms first a portion for the Müllerian duct, the tubar portion, then a common portion for the excretory duct and the mesonephric tubules, the gland portion, and, finally, the thread-like connection with the posterior abdominal wall, the mesentery portion. The tubar and gland portions regularly become separated by a slight furrow that projects in from the lateral surface; the gland portion passes over gradually into the mesentery portion. In the contents of these three portions a sexual difference becomes evident to the extent that while in female embryos the tubar portion contains only the Müllerian duct, in males it contains both the Müllerian and the

excretory ducts; in the male, however, there is frequently formed a secondary fold, the tubar portion becoming divided into a portion for the Müllerian duct and another for the excretory duct. The gland portion in male embryos contains only the mesonephric tubules, in females these tubules and the excretory duct. In older female embryos also the lateral portion, which contains the excretory duct, becomes separated from the medial portion containing the mesonephric tubules.

The formation of the various portions begins at the cranial pole and proceeds caudally, and the lateral portions are formed earlier than the medial ones. Consequently one sees at first only

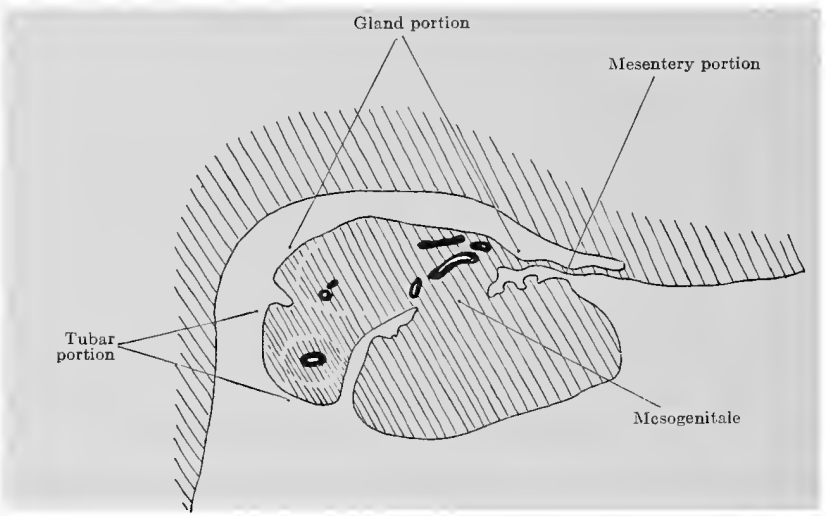


FIG. 551.—Transverse section of the right urogenital fold of a human embryo of 5 cm. head-foot length. (Embryo R. Meyer 272, from the collection of Professor R. Meyer, Berlin; slide 2, row 1, section 2.) The mesonephric fold is incompletely divided into three portions by a groove in its dorso-lateral surface and by the narrowing of its base; the tube portion with the transverse section of the Müllerian duct, the gland portion with the transverse section of the excretory duct and the mesonephric tubules, and the mesentery portion. The mesonephric fold is beginning to grow around the reproductive gland portion.

the tubar portion and this only in the cranial region of the fold. The separation of the tubar portion begins in embryos of 13 mm. greatest length. It is the most freely movable portion of the mesonephric fold and this mobility serves to explain the peculiar wandering of the ostium abdominale which occurs later on.

A third change is in the course of the urogenital folds. Originally both folds lie parallel to the vertebral column, as may be seen from the parallel course of both mesonephroi in an embryo of 9 mm. greatest length (Fig. 565); but as soon as new organs appear between them in the middle line, they become displaced. Already the influence of the suprarenal bodies may be seen in an embryo of 9.5 mm. greatest length, the two folds, which originally lay close together, becoming forced apart. What is begun by the

suprarenal bodies is continued by the metanephroi; they displace the two mesonephric folds still more laterally. We have seen above that at first the whole posterior body wall was invaginated into the body cavity as the urogenital folds. The folds can only be displaced laterally by a broadening of the posterior body wall and an increase in the frontal diameter of the body cavity. The increase occurs apparently in the middle line, since the topographic relations between the urogenital fold and the lateral body wall

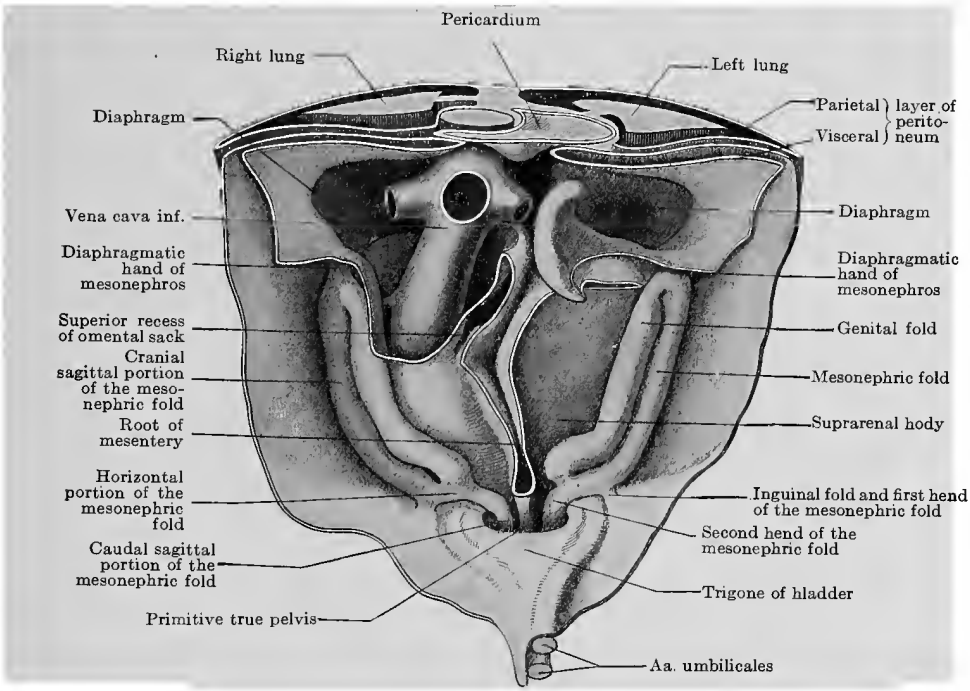


FIG. 552.—Model of the posterior abdominal wall of a human embryo of 19.4 mm. greatest length. (Embryo Ma. 2, from the collection of Professor Hochstetter, Berlin. The model was prepared by my students Massard and Chomé.) The visceral layer of peritoneum is shown cut and one sees the superior recess of the omental sack. The urogenital fold is divided as far as its upper and lower ends into the mesonephric and genital folds. The mesonephric fold is bayonet-shaped and an upper sagittal, a horizontal and a lower sagittal portion, and a first and second bend may be distinguished. At the first bend the mesonephric fold is connected with the anterior abdominal wall by the inguinal fold. Between the aa. umbilicales, which still run horizontally, is the bladder plate.

do not alter, as is shown in Figs. 547–551. Caudal to the metanephros the enlarging force ceases, and in this region the frontal diameter does enlarge and the urogenital fold is not displaced. The occurrence of a displacement above and its absence below necessarily produces a bend of the fold. This is a double bend, and the fold acquires by it a bayonet form; there may be distinguished an upper sagittal, a middle transverse and a lower sagittal portion (Fig. 552). The more the suprarenal bodies and the metanephroi grow later on, the more they cause the upper sagittal portion of the fold to assume an oblique position. The mesentery

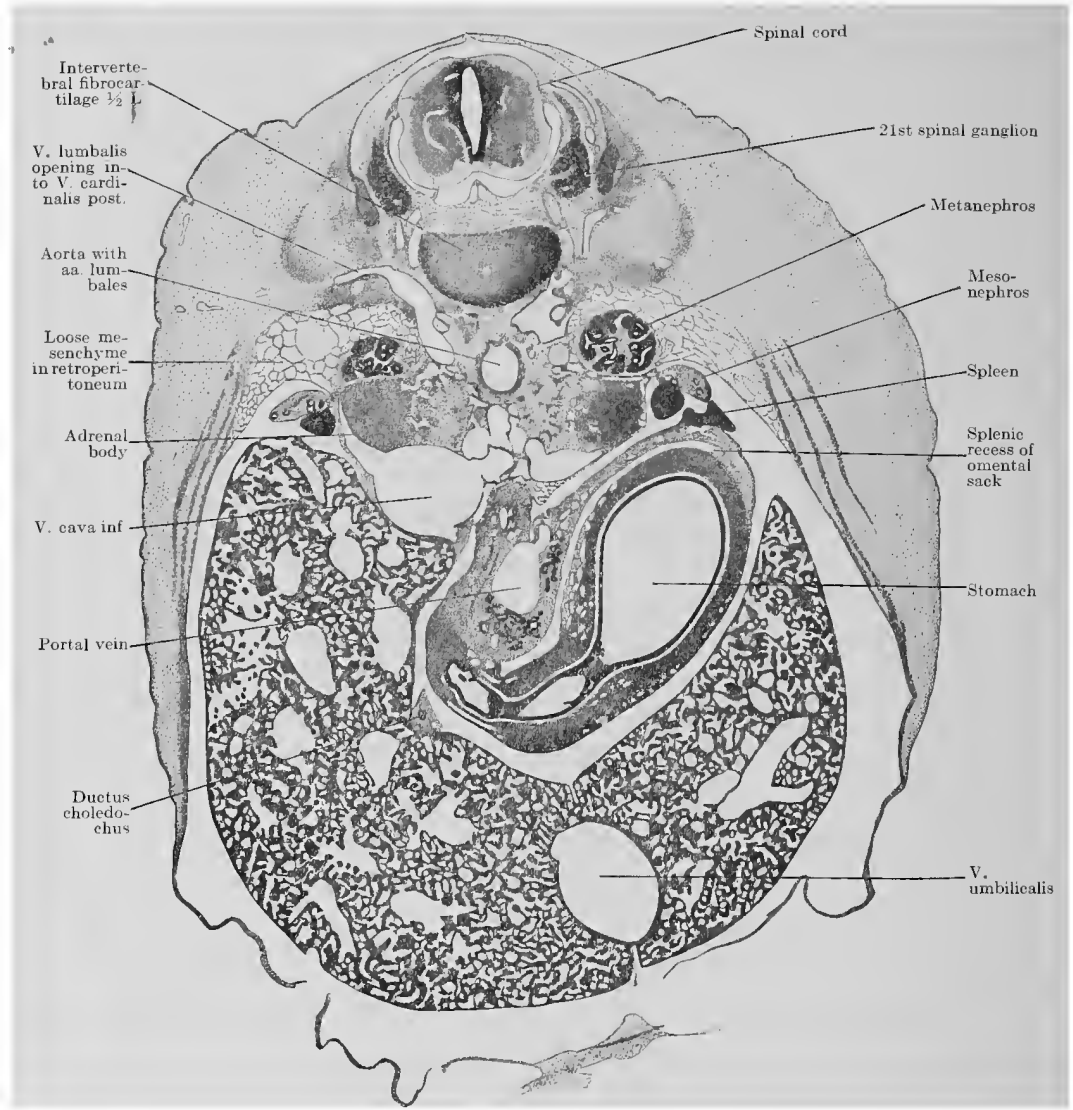


FIG. 553.—Transverse section of a human embryo of 19.4 mm. greatest length, at the level of the 21st spinal ganglion. (Embryo Ma. 2; slide 58, row 2, section 1. From the collection of Professor Hochstetter, Vienna.) The section is intended to show the topographic relations of the abdominal viscera. The stomach has begun to twist to the left and, with the spleen, is in contact with the left urogenital fold. The two urogenital folds are still symmetrically placed; they are divided into the mesonephric and the genital folds. Between the two urogenital folds are the adrenal bodies; behind these lie the metanephroi, surrounded by a very loose tissue.

of the genital fold is fully formed only in the region of the upper sagittal portion and this alone obtains from it a great mobility and consequently alone can yield to the pressure of the neighboring organs. The liver, which grows but does not undergo displacement, does not exert the slightest influence on the urogenital fold, but, on the other hand, both the stomach and intestine alter their

position and both must therefore influence the position of the urogenital fold. The stomach, and with it the spleen, becomes displaced to the left side and is rotated; the large coil which becomes the large intestine tends for the most part to the left, and, consequently, both it and the stomach will affect the left urogenital fold, the descending colon coming to lie on its medial side, while the ascending colon runs from the beginning on the lateral side of the right fold. The left urogenital fold yields to the pressure of the stomach and intestine and is displaced by it further in the same direction as it was forced by the suprarenal body and metanephros. This displacement may be carried to such an extent that the upper sagittal portion of the left fold comes to lie horizontally and, therefore, can no longer be distinguished from the horizontal portion. This displacement I observed first in an embryo of 29 mm. greatest length; from that stage onward it was usually to be made out in embryos of both sexes.

The influence of the intestinal tract in displacement may, of course, be stronger and may therefore produce anomalies of development. It will be seen in the following paragraph that the lower sagittal portions of the two urogenital folds unite throughout their whole length in the median line; the extent of the union may be lessened or quite prevented by an abnormal influence on the part of the intestine. This gives a possibility for the explanation of double formations of the uterus. In the same way the pressure of the stomach and intestine may give the reproductive gland a position in which it cannot effect the connections made in normal development; I refer, principally, to the connection of the testis with the inguinal fold, whose failure results in a failure of the testis to enter the inguinal canal.

A fourth change affects the caudal sagittal portion of the urogenital fold. In this region the two folds come together and fuse, and by this fusion a frontal partition is formed, which divides the primitive pelvis into a ventral and a dorsal half; this frontal partition is termed the genital cord (tractus genitalis); it fuses with the floor of the body cavity and the partition is thus a complete one. In Fig. 554 *a*, *b* and *c* three sections through the lower portions of both urogenital folds are shown; the mesonephric and reproductive folds are separated, merely a thread-like mesogenitale uniting them; the tubar portion and the lateral part of the gland portion are thrown into an angle directed towards the medial part of the gland portion and bend around the ventral surface of the reproductive gland; they are, however, still far from the median line. In section *b* the mesonephric folds are nearer together and in *c* their union has occurred. The formation of the genital cord takes place in embryos between 19.4 and 21 mm. greatest length; the upper edge of the genital cord lies at the level

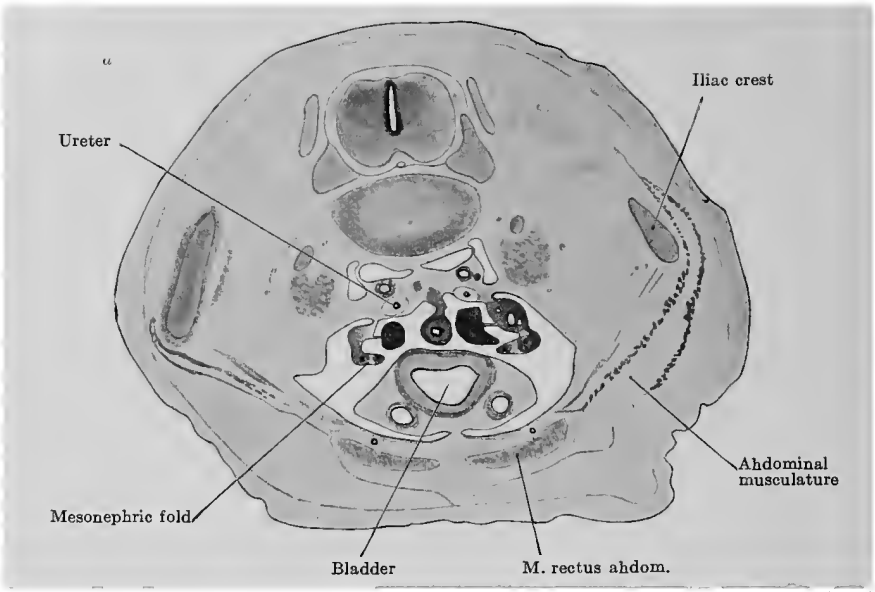
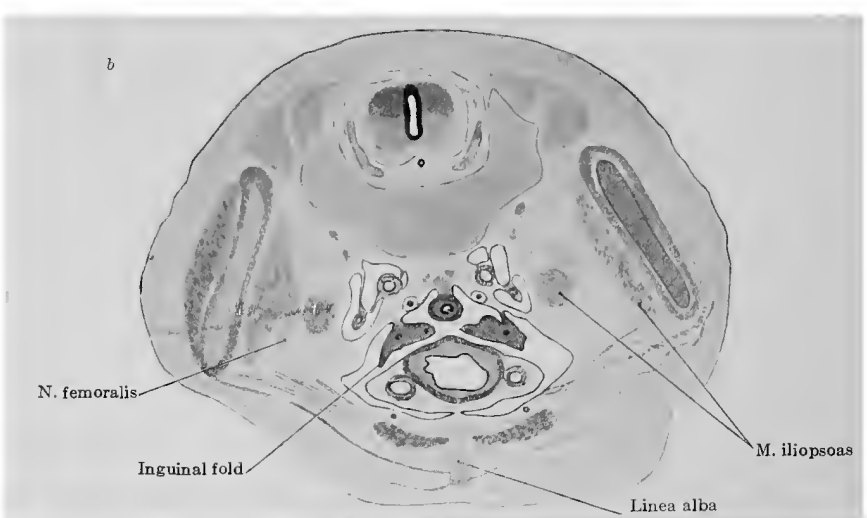


FIG. 554 *a*, *b*, and *c*.—Three transverse sections through a human embryo of 30 mm. trunk length. (Embryo R. Meyer 273, from the collection of Professor Meyer, Berlin; slide 11, row 4, section 2; slide 13, row 5, section 2; slide 14, row 5, section 2.) The three sections show the formation of the genital cord. The legends have been arranged so that different structures are indicated in each section and the reader should first study the legends in all three figures. *a*. The mesonephric fold bends between the tubar and gland portions at a right angle and is growing around the reproductive gland, so that the left and right mesonephros come to lie in the same frontal plane. The excretory duct and the tube are shown in the mesonephric fold. The originally lateral tube comes to lie medially, as a result of the bending of the fold.



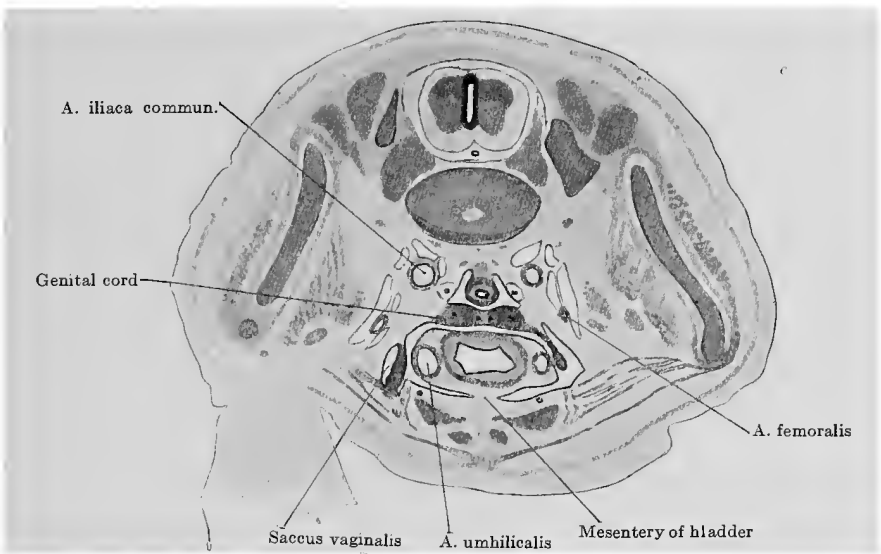
b. An evagination (the inguinal fold) extends from the mesonephric fold between the bladder and the lateral wall of the body to unite with the posterior surface of the anterior abdominal wall (in Fig. *c* it is cut throughout its entire length). The right and left mesonephric folds have come nearer together.

of the lower border of the third lumbar vertebra (embryos of 36 mm. greatest length), but later a passive displacement to the lower border of the fourth or even the fifth lumbar vertebra may occur.

The genital cord seems to be formed at once throughout its entire length, since the upper boundary is found at the same place in all embryos of this period.

Sexual differences appear with the formation of the genital cord. Fig. 554 *c* is taken from a female embryo and in it one sees a distinct excavatio vesico-uterina between the genital cord and the bladder; in male embryos the mesonephric folds, approaching one another in the median line, at once unite with the wall of the bladder and they, therefore, do not possess a vesico-uterine pouch (Fig. 555).

A fifth and last change in the urogenital fold is brought about by its connection with the lateral, later the anterior, abdominal



c. The two mesonephric folds have united in the middle line to form the genital cord. By this and the two inguinal folds the body cavity is divided into four parts,—the excavatio recto-uterina between the posterior body wall and the genital cord; a space between the genital cord, the posterior wall of the bladder and the inguinal folds, from which the excavatio vesico-uterina and the medial part of the saccus vaginalis (see section on descensus) are formed; and two lateral spaces between the plica inguinalis and the lateral abdominal wall, which become the lateral part of the saccus vaginalis.

wall. Already in an embryo of 13 mm. greatest length a knob-shaped growth, the inguinal fold, forms at the first bend (Fig. 552). In sections it resembles the anlage of the reproductive gland, which lies on the medial side of the urogenital fold, except that it is a true growth and is not, like the reproductive gland, grooved out of the fold. The growing inguinal fold very soon reaches the lateral abdominal wall in its dorsal half and then unites with a ridge of the wall which I shall call the inguinal crest (Fig. 556 *a* and *b*). By this union the horizontal portion of the urogenital fold becomes dependent from the lateral abdominal wall; as a result changes in the position of the urogenital folds must ensue.

The anterior abdominal wall is now almost horizontal; immediately at the oral slope of the genital tubercle the ectoderm of the surface of the body passes directly over into the wall of the umbilical cord. In Fig. 557 a median section of an embryo of 24 mm. vertex-breech length is shown; the outer contour of the body extends from the tip of the tail over the anal and urogenital orifices to the phallus, and at the cranial surface of this it bends around and passes over into the caudal surface of the umbilical cord. Later, on the closure of the wide umbilicus, the anterior abdominal wall is bent upward and becomes horizontal. That is one of the changes. The other

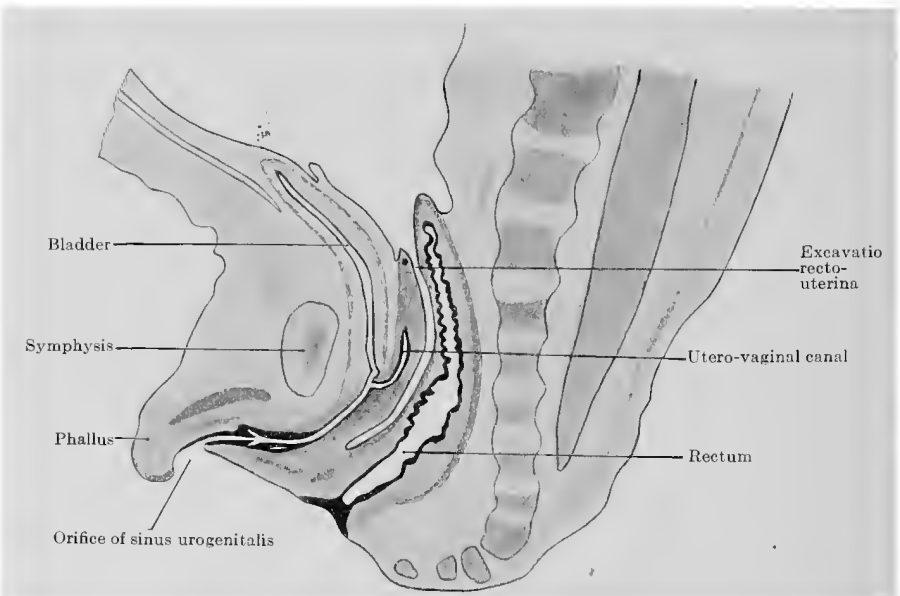


FIG. 555.—Median section of a human embryo of 50 mm. head-foot length. (Embryo R. Meyer 257, from the collection of Professor R. Meyer, Berlin; slide 16, row 3, section 1.) × 8. On the development of the genital cord the first indication of a sexual difference appears. In the male the two mesonephric folds fuse with the posterior wall of the bladder before they unite to form the genital cord, and this fusion persists also after the union. The urogenital sinus is cut lengthwise; the anterior border of its external orifice reaches already the coronary sulcus of the glans. Between the external orifice of the sinus and the anus the aboral periphery of the phallus and the perineum are beginning to form.

is best seen by comparing the position of the m. rectus abdominis in embryos of different ages; as soon as muscle fibres are to be made out, the muscle lies in the middle of the lateral wall of the body, so that to acquire its definitive position it must be pushed along the abdominal wall to the median plane. It may, in brief, be said that the anterior abdominal wall is pushed in two directions, on the one hand cranially and on the other medially. The pushing takes place during the division of the urogenital fold into the reproductive and mesonephric folds and during the development of the different parts of the latter. The inguinal fold thereby arises finally from the tubar portion of the mesonephric

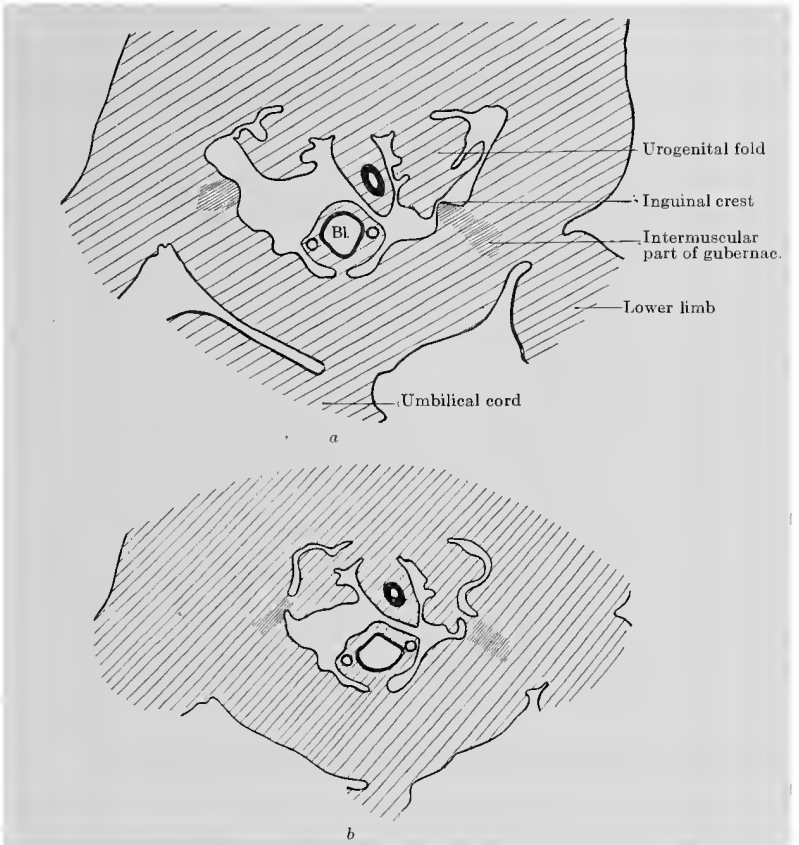


FIG. 556 *a* and *b*.—Transverse section through the urogenital fold at the level of the inguinal fold in a human embryo of 22.5 mm. greatest length. (Embryo R. Meyer 303, from the collection of Professor R. Meyer, Berlin; slide 34, row 2, slide 1 and row 4, section 1.) *a*. Passes through the inguinal crest and the intermuscular part of the chorda gubernaculi. *Bl.*, bladder. *b*. Shows the union of the inguinal fold with the inguinal crest, by which the urogenital fold becomes united with the lateral abdominal wall.

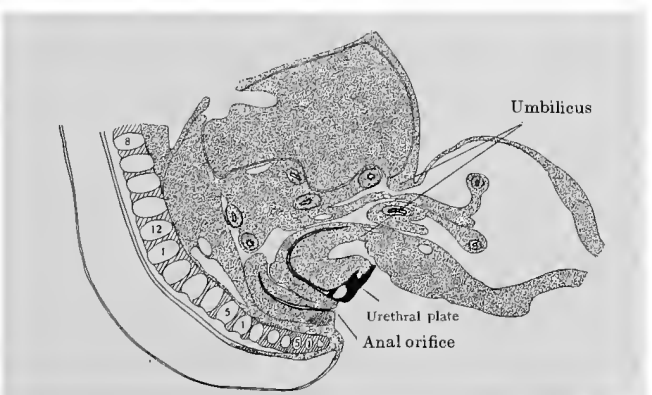


FIG. 557.—Median section of the lower half of the body of an embryo of 24 mm. vertex-breech length. (Embryo Hal. I, from the collection of the I Anatomical Institute, Vienna [Professor Zuckerkandl]; slide 44, row 1, section 2.) The urethral plate is reconstructed from four sections. An anterior body wall does not yet exist; the umbilicus begins immediately at the oral slope of the phallus.

fold (Fig. 554 *b* and *c*). The wanderings of the anterior abdominal wall will affect the tubar portion and the adjacent part of the gland portion, and we may theoretically assume a wandering of the tubar portion, such as actually takes place in the formation of the genital cord. If the formation of the anterior abdominal wall is disturbed or delayed an effect upon the formation of the genital cord is possible, and herein is a second possibility for double formations of the uterus.

The Mesonephros.

GENERAL.

The mesonephric tubules develop after the pronephric. They are formed from the same parent tissue, the stalks of the primitive segments, in almost the same segments, and they make use of the same efferent canal, the primary excretory duct. Comparative embryology teaches that the mesonephric tubule, like the pronephric one, is a composite structure. A mesonephric segment consists of a principal and a supplemental tubule, the former being an evagination of the parietal layer of the primitive segment stalk, while the latter is the lateral portion of the segment stalk itself. From the supplemental tubule there are formed the mesonephric chamber, in this case fermed Bowman's capsule, and the nephrostome canal, the distinction between the two resulting from the enlargement of the medial portion of the supplemental canal to form Bowman's capsule. This is invaginated by a vascular glomerulus, whose efferent stem arises directly from the aorta. A comparison of this account of the development of the mesonephric tubule with that given on p. 759 for the pronephric tubule will show a complete correspondence. The development of the mesonephric tubule might have been illustrated by printing for a second time the plan of the pronephric segment, modification being necessary only in two particulars, the formation of the collecting duct and the external glomerulus. If then the correspondence between the two sets of tubules is so close, how are they distinguished? In three ways: 1, by their appearance before or after the excretory duct; 2, by the presence or absence of an external glomerulus, and 3, by the point of origin of the principal tubule from the stalk of the primitive segment.

Let us first consider the last point. The principal tubules of the mesonephros arise more medially than do those of the pronephros. This difference does not, however, suffice in all cases for a differential diagnosis of the two kinds of tubules. If a pronephric and a mesonephric tubule are formed in the same segment and if, furthermore, the anlage of the mesonephric tubule appears while the pronephric tubule is still present, then it is possible to

distinguish the two by their position, the pronephric tubule lying lateral, nearer to the lateral plate, the mesonephric one medial, nearer to the primitive segment. But whoever has studied the development of the two provisional excretory organs in the vertebrate series must admit that these two conditions are very rarely fulfilled. If in a given segment only one excretory tubule is formed, or if the pronephric tubule is completely degenerated before the mesonephric one appears, then the position of the principal tubule under consideration, with reference to the primitive segment stalk can give no conclusive evidence as to its character, and this for the following reasons: The supplemental tubule, which, according to the account given above, is the same structure in both the pronephric and mesonephric tubules, may with advancing development be partly taken up into the lateral plate or into the body cavity derived from it. If this shortening of the supplemental tubule occurs before the mesonephric tubule is formed, the origin of the principal tubule of the latter may apparently lie at the very spot where that of the pronephric tubule should occur, namely quite laterally and close to the wall of the body cavity, in some cases, indeed, at the wall. As to the second distinction between the two tubules the following may be said: The occurrence of external glomeruli is distinctive for the pronephros; their absence, however, is no evidence that a tubule must be a mesonephric one, since the glomerulus may also be wanting to a pronephric tubule. I have expressly stated above that the external glomerulus is characteristic of the pronephros and not of a pronephric tubule; it is quite independent of its tubule and is merely invaginated into the body cavity beside it. This independence of the external glomerulus is shown by the fact that it degenerates independently of the other constituents of the pronephric segment; it always degenerates, but frequently only when the pronephric tubule has already vanished and the mesonephric tubule has developed. An external glomerulus may therefore occur beside a mesonephric tubule as well as beside a pronephric one, and its presence is no decisive evidence as to the character of the tubule occurring in the same segment with it. It tells that in a given animal a *pronephros* was present, but it does not say that the tubule occurring beside it is a *pronephric tubule.*

There thus remains as a distinctive indication of whether a tubule is mesonephric or pronephric only the first point, its relation to the excretory duct. Whatever tubules are developed before or simultaneously with the excretory duct are pronephric, those formed after it are mesonephric. This difference can only be determined embryologically, it is of no avail in the case of developed tubules. It is not possible, therefore, on the *first* study of a fully formed organ to determine whether it is pronephric or

mesonephric; but if by earlier studies the limits of the two organs have been determined and we know how far caudally the pronephros and how far cranially the mesonephros extends, then, without any further evidence, we may speak of pronephric or mesonephric tubules in the case of segments in which only one kind occurs; in all other segments the determination must rest upon a study of the development.

In those vertebrates in which the pronephros extends the entire length of the body cavity, it is at once evident that the pronephric tubules form a *first* and the mesonephric a *second* generation of excretory tubules. The mesonephric tubules are, accordingly, something new, distinguishable from the pronephric tubules; it will occur to no one to regard the fruit of one year as of the same generation as that of a preceding year. In the vertebrates in which the pronephros is shortened, the matter is not so clear; indeed, it may be so obscure that one is led so far astray as to regard the pronephric and mesonephric tubules as equivalent parts of a single system. All investigations that have led to this estimate of the mesonephric tubules have been made on vertebrates with a shortened pronephros. Whoever examines the development of the pronephros and mesonephros throughout the whole series of vertebrates cannot for a moment doubt that the pronephric and mesonephric tubules are members of two different systems.

So far as man, in particular, is concerned, the conditions are more favorable for a distinction between the pronephric and mesonephric tubules. Man has such a high grade of organization that the excretory organ has a long developmental path to traverse before it reaches its completion. This path is shortened by the pronephros developing only rudimentarily. So far as is yet known, no human pronephric tubule develops an internal glomerulus, and, so far as known, every mesonephric tubule, even the most cranial ones that at once undergo degeneration, develops one. In the presence or absence of an internal glomerulus in the Malpighian corpuscles of the human mesonephros we have, then, a means, important because it is so readily made out, of determining the mesonephric character of a tubule.

THE PARENT TISSUE OF THE MESONEPHRIC TUBULES.

The parent tissue of the mesonephric tubules is furnished by the primitive segment stalks. In describing the development of the pronephros the process of segmentation of the mesoderm has been considered. It presents two phases. The first phase, that of transverse division of the mesoderm, brings about the formation of the primary primitive segments, the second, that of the sagittal division, divides the primary segments into the secondary segments and the segment stalks (Fig. 520 *a*, *b* and *c*). In man the process of segmentation does not take place quite according to rule. In an embryo with 13–14 primitive segments all three mesodermal

structures, the secondary segment, the segment stalk and the lateral plate, are developed in the first ten segments, but from the eleventh on, while the longitudinal divisions occur in the old direction, the transverse ones no longer occur lateral to the region of the secondary primitive segment, so that while there are well-defined secondary segments, there are no distinct primitive segment stalks. The segment stalks, cut out as a whole from the mesoderm, form what is termed the nephrogenic cord. In an embryo with 23 pairs of primitive segments (Fig. 531 *a*) this cord not only extends throughout the entire segmental region, but also through a portion of the unsegmental one to the region of the cloaca; in other words, the segmentation process in the posterior portion of the embryo passes through two phases, but they are in inverted order. The sagittal divisions, which originally formed the second phase, occur first and separate, at first incompletely, the lateral plate, nephrogenic cord and primitive segment plate; the transverse divisions, originally the first, now succeed as the second phase, but they only divide the primitive segment plate into the individual secondary segments, the nephrogenic cord remaining undivided. In an embryo of 4.25 mm. vertex-breech length and with 28 pairs of primitive segments the nephrogenic cord extends to the 28th segment, in any case as far as the point where the primary excretory duct applies itself to the wall of the cloaca; here the cord appears somewhat thickened, its caudal end being lost in the as yet undivided mesoderm of the tail. In no embryo is the nephrogenic cord present in its full extent, for while it is growing caudally it is dividing at its cranial end into the anlagen for the individual mesonephric tubules.

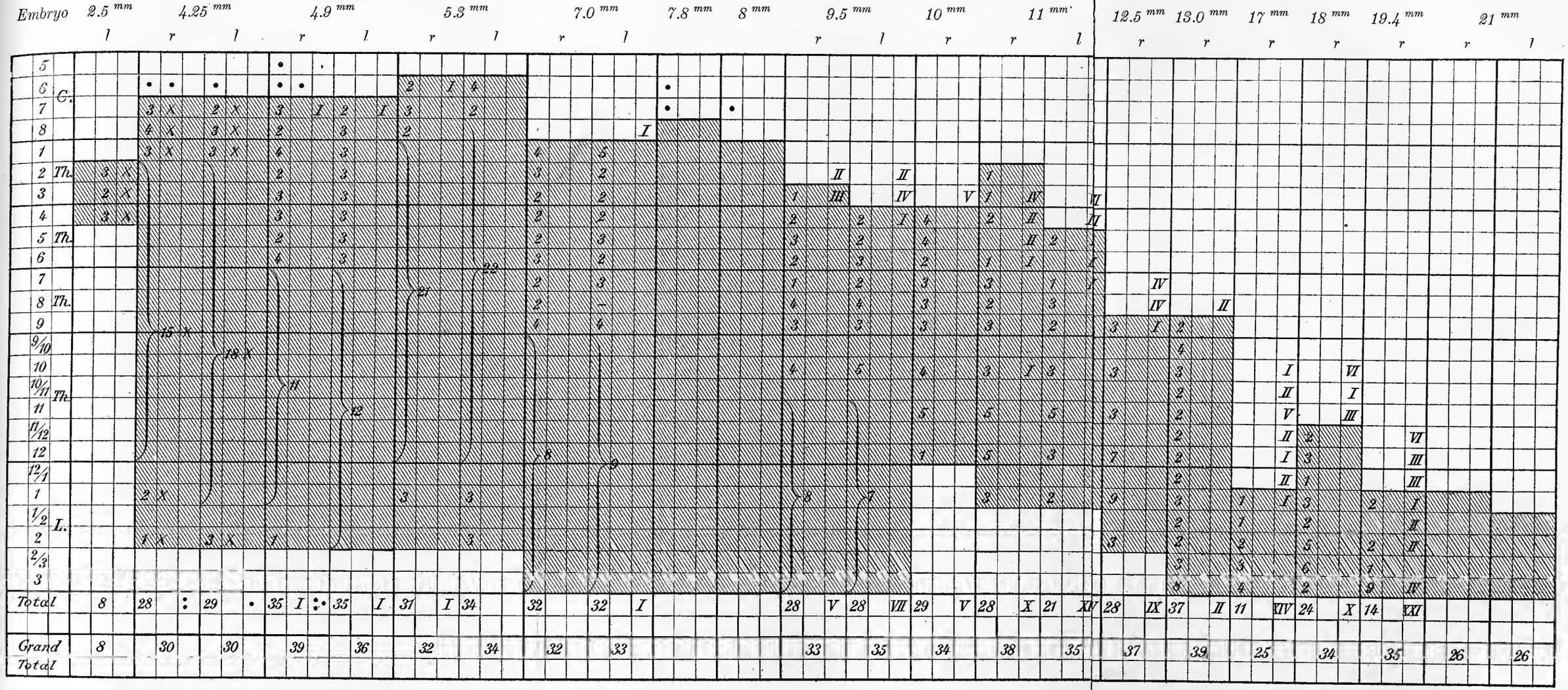
The primary excretory duct in the pronephric territory lay lateral to the primitive segment stalk. It retains this position in its growth caudally and accordingly lies lateral to the nephrogenic cord (Figs. 558 *a*, 559 and 562).

The nephrogenic cord in an embryo of 5.3 mm. greatest length and 4.6 mm. nape length is interrupted in the 26th or 27th segment (3rd or 4th lumbar segment). The compact cord, which is rather sharply marked off from the surrounding mesenchyme, becomes looser in this region, its cells separate from one another and, finally, are no longer to be distinguished from those surrounding it. Thus the cord becomes divided into two unequal portions, a long cranial one, from which the mesonephric tubules develop, and a short caudal one, from which the metanephric tubules arise. Following Schreiner (1902) the two portions may be termed the *mesonephrogenic* and the *metanephrogenic cords*. Nothing is to be seen of the division of the nephrogenic cord in an embryo of 4.9 mm. nape-length; in one of 5.3 mm. greatest length it is completed.

FORMATION OF THE MESONEPHRIC TUBULES FROM THE MESONEPHROGENIC CORD.

Immediately after its formation the nephrogenic cord becomes divided, at first only at its cranial end, into a series of spherical masses of cells. In an embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments, anlagen of mesonephric tubules are present in the 13th, 14th and 15th segments, *i.e.*, in the 2nd, 3rd and 4th thoracic segments (Fig. 531 *a*). In this embryo neither has the nephrogenic cord completed its growth caudally, nor has the excretory duct reached the cloaca. In an embryo of 4.25 mm. vertex-breech length and with 28 pairs of primitive segments, mesonephric anlagen occur as far back as the 26th segment, *i.e.*, as far as the third lumbar segment, and this caudal limit is not exceeded at first. In this embryo the growth of the nephrogenic cord is completed and the excretory duct has reached the cloaca. The formation of the mesonephric tubules is, accordingly, completed in a rather short space of time; they are formed almost at a stroke. The mesonephros, however, grows not only caudally, but also at first cranially. In an embryo of 2.5 mm. greatest length the first mesonephric tubule lay in the 2nd thoracic segment, in one of 4.25 mm. vertex-breech length and in one of 4.9 mm. nape length the first tubule was in the 7th cervical segment, and, finally, in one of 5.3 mm. greatest length in the 6th cervical segment; cranial to the 6th cervical segment I have found neither anlagen of mesonephric tubules nor tubules in process of degeneration. Details of the development of the mesonephros may be obtained from the appended table. Its anlage extends over 18 segments, from the 6th cervical to the 3rd lumbar, and in these eighteen segments there are developed in maximo 83 tubules; this number I have obtained by estimating from the table and adding together the maximal number of tubules occurring in each segment. The distribution of the tubules among the various segments is unequal, as will be seen from the table, but 28 occur in the last 4 segments. Since the pronephros extends from the 5th cervical to the 3rd thoracic segment, mesonephric tubules occur throughout almost its whole territory. Why cannot these later cranial mesonephric tubules be pronephric? At first they are not connected with the primary excretory duct and might therefore represent degenerating pronephric tubules, similar to those which actually occur in the 6th segment of the embryo of 4.25 mm. nape length and in the 5th and 6th segments of the embryo of 4.9 mm. nape length. The tubules, however, that I have regarded as mesonephric, are all in statu nascendi, they do not differ in any respect from what are undoubtedly mesonephric tubules in the more posterior segments and they also later acquire a connection with the primary excretory duct.

Table Showing the Length (Expressed in Segments) of the Mesonephros, and the Number and Position of the Mesonephric Tubules



EXPLANATION OF PLATE.

The mesonephros may be situated in the region between the fifth cervical and the third lumbar segment. These segments are given in the first vertical column. In the lower thoracic and the lumbar segments the tubules are placed more closely, and consequently the intervertebral regions are indicated by the fractions $\frac{9}{10}$, $\frac{10}{11}$, etc. The completely developed tubules are indicated by Arabic numbers and a cross (X) denotes a developing tubule. The Roman numerals denote tubules that are in process of degeneration, and dots indicate tubules of which it is uncertain whether they belong to the pronephros or mesonephros.

The extent of the various mesonephroi is shown in terms of the segments, and there is, accordingly, no comparison of absolute lengths. The table shows that the mesonephros, followed through embryos of different ages, grows both cranially and caudally. The cranial growth is completed in an embryo of 5.3 mm. and the caudal in one of 7 mm. Immediately on the completion of the cranial growth, degeneration sets in at the cranial end. From embryos of 5.3 mm. to those of 21 mm. one sees the cranial outline of the mesonephros gradually sinking. At first the organ extends throughout the lower cervical, the thoracic, and the first three lumbar segments; eventually it is limited to the lumbar segments.

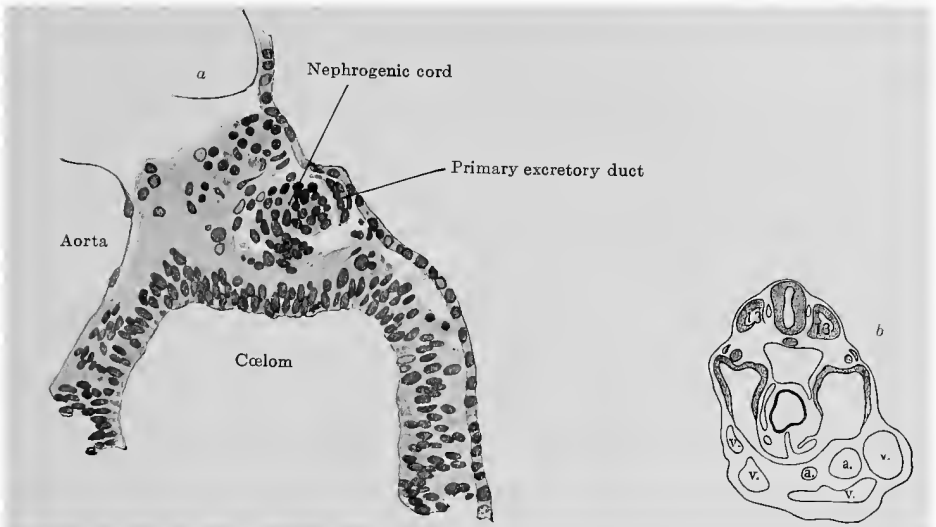


FIG. 558 *a* and *b*.—Transverse section of a human embryo of 2.5 mm. greatest length and with 23 paire of primitive segments, at the level of the 13th eegment. (Embryo R. Meyer 300, from the collection of Professor R. Meyer; elide 12, row 4, eection 5.) × 317. The section passes through the nephrogenic cord in the interstitium between two anlagen of mesonephric tubules. The primary excretory duct lies on the outer surface of the cord as a semilunar etructure.

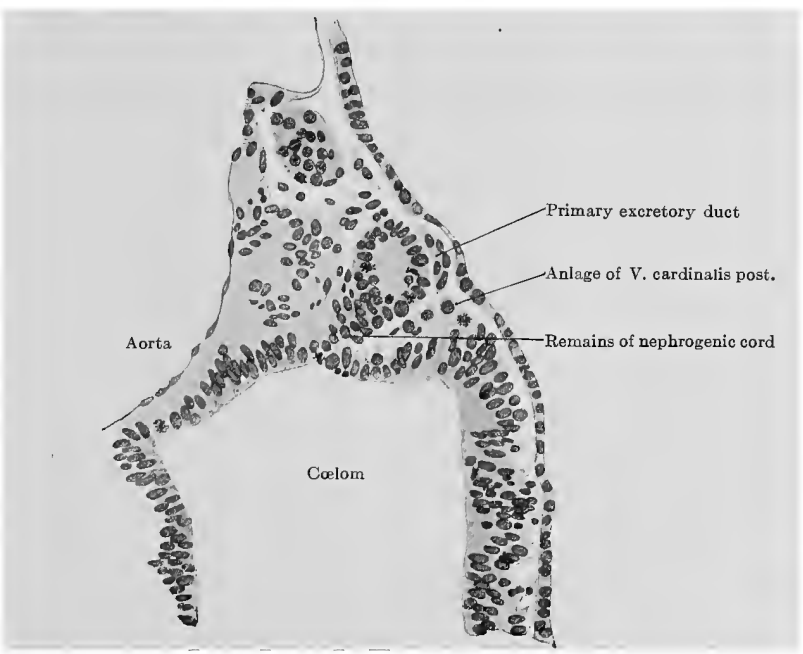


FIG. 559.—Transverse eection of a human embryo of 2.5 mm. greatest length and with 23 paire of primitive segments, at the level of the 13th segment. (Embryo R. Meyer 300, from ths collection of Profeeeor R. Meyer, Berlin; slide 12, row 4, eection 6.) × 317. The eection paeses through the middle of a mesonephric vesicle; the entire nephrogenic cord ie not used in the formation of a mesonephric tubule, but a portion of it, eituated laterally or ventrally, persists for a time as a rudimentary nephrostoms canal. Lateral from the tubule is the semilunar primary excretory duct and ths anlage of the V. cardinalis posterior.

The anlagen of the mesonephric tubules are from the first dysmetameric, as many as four occurring in a segment; details as to the numbers are given in the table facing p. 816. This is not remarkable since the parent tissue has already lost all traces of segmentation.

In the anterior segments, which are somewhat larger than the posterior ones, the anlagen appear as spherical vesicles in which no distinct lumen is yet visible; in the posterior segments

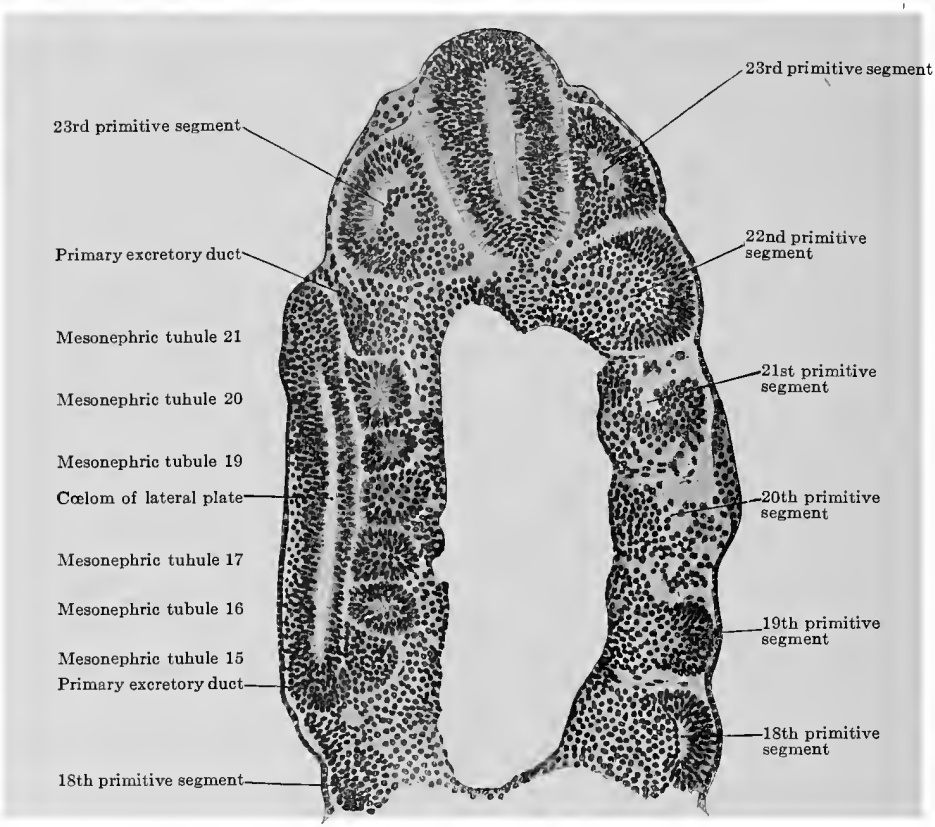


FIG. 560.—Frontal longitudinal section of a human embryo of 4.25 mm. vertex-hreech length and with 28 pairs of primitive segments. (Embryo H. M. 1, from the collection of the Anatomical Institute, Zurich; 399, J. 13, row 4, section 5.) × 150. The section shows the positions of the mesonephric tuhules relative to one another and to the hody segments. On thc left side only mesonephric vesicles are represented and on thc right side only primitive segments. No cells occur hetween the various mesonephric vesicles.

they are more cubical on account of mutual pressure. Figs. 558 and 559 represent sections through the mesonephric region of an embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments. Fig. 558 passes through the anterior wall and Fig. 559 through the middle of the third mesonephric vesicle. One sees from both sections that the mesonephric anlage does not exhaust the entire mesonephrogenic cord; a lateral portion remains to form a solid union with the lateral plate and it corresponds to a

nephrostome canal. In both figures the primary excretory duct lies lateral to the mesonephrogenic cord. The contour of the vesicle projects beyond that of the mesonephrogenic cord, compresses the excretory duct to a semilunar structure, presses it outwards, thins out the adjacent ectoderm and bulges it out. This prominence of the mesonephric vesicle is the commencing development of the principal tubule.

The section shown in Fig. 560 passes through the 15th to the 21st mesonephric anlagen of an embryo of 4.25 mm. vertex-breech length and with 28 pairs of primitive segments. On the right side of the figure only primitive segments have been cut, and on the left side only mesonephric vesicles. One sees the mutually flattening, almost quadrangular mesonephric anlagen so closely apposed that there is scarcely room between them for a single cell. A comparison of the right and left sides of the figure shows the dysmetamerism of the anlagen.

The mesonephric vesicles now undergo a series of modifications, which succeed one another in a cranio-caudal direction. I give a diagramatic representation of them in Fig. 561. The sphere or cube (Fig. 561 *a*) first becomes an olive-shaped vesicle by becoming hollow and by the lateral growth of the principal tubule (Fig. 561 *b*), the free end of this latter unites with the primary excretory duct (Fig. 561 *c*), and the original mesonephric vesicle enlarges, its wall at the same time becoming thin, to form a structure resting upon the principal canal just as the transverse bar of the letter T rests upon the upright. The transverse bar has a cranio-caudal direction, which is not shown in Fig. 561 *c*. In the angle between the upright and transverse bars the glomerulus appears, sometimes lying on the cranial and sometimes on the caudal side of the upright; the part of the transverse bar with which the glomerulus is associated later becomes much more strongly developed than the other part. Once the connection with the primary excretory duct is accomplished and the anlage of the Malpighian corpuscle is laid down, the tubule begins to bend (Fig. 561 *d*). The result is two loops with a limb in common (Fig. 561 *e*). The lumen of the tubule appears first at its medial end and thence extends through the entire tubule to its opening into the primary excretory duct. Of the three limbs the most ventral one situated toward the summit of the mesonephric fold (Fig. 562) becomes the Malpighian corpuscle, from the common limb there is formed a portion of the tubule which we shall term the secretory tubule, and from the third, dorsal limb another portion of the tubule, the collecting tubule (Fig. 561 *e*). Fig. 562 shows the general topography of a mesonephric tubule; the section passes through the 16th right (on the left in the figure) and the 18th left mesonephric tubules of an embryo of 4.9 mm. nape length. The mesonephric fold is

almost completely filled by the tubule, which shows its S-shaped bends and the commencing transformation of the ventral limb into the Malpighian corpuscle. The primary excretory duct lies quite laterally in the fold and beneath it is the forming v. cardinalis posterior.

As to the details of development the following may be noted. In an embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments there were 8 anlagen of mesonephric tubules, all in the vesicle stage.

In an embryo of 4.25 mm. vertex-breech length and with 28 pairs of primitive segments, of the 28 right and 29 left mesonephric anlagen the two first were in the olive-shaped stage (Fig. 561 *b*), all the rest were round or flattened vesicles. None of the anlagen are connected with the primary excretory duct.

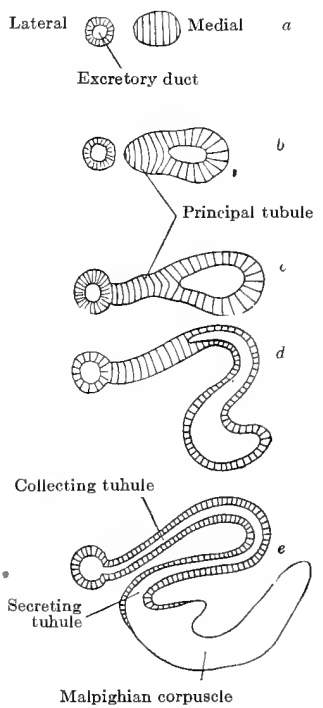


FIG. 561 *a*, *b*, *c*, *d* and *e*.—Diagrams showing the development of the individual mesonephric vesicles. *a*. Solid vesicle. *b*. Appearance of the lumen and growth of the principal tuhule towards the primary excretory duct. *c*. The principal tuhule reaches the excretory duct. *d*. Beginning of formation of the Malpighian corpuscle and the secreting and collecting tuhules. *e*. Development completed.

In an embryo of 4.9 mm. nape length and with 33–35 pairs of primitive segments there were 36 tubules, and of these the 1st to the 18th have an S-shape (Fig. 561 *e*), the 19th–20th the form shown in Fig. 561 *d*, the 21st–33rd are olive-shaped, and the 34th–36th have a round vesicular form; the 35th and the 36th are connected by remains of the nephrogenic tissue and the 36th is not yet separated on its caudal side from the nephrogenic cord. The 1st to the 25th tubules are connected with the primary excretory duct, the 26th–34th have grown toward the duct and are in apposition with it, the 35th and 36th are still free. In the 2nd–12th tubules there is a developed Malpighian corpuscle, in the 13th–18th tubules the corpuscle is forming.

In an embryo of 5.3 mm. greatest length and with 36 pairs of primitive segments there were 32 tubules, and of these the first 25 are S-shaped, the 26th–28th olive-shaped, the 29th–31st are round vesicles and the 32nd is not yet fully differentiated. The 1st–20th tubules open into the excretory duct, the 21st–24th are in contact with it, the 25th–32nd are still free. Tubules 1–4 are provided with Malpighian corpuscles.

In an embryo of 7 mm. greatest length of the 31 tubules the 1st–25th were S-shaped, the 26th–31st olive-shaped. All 31 tubules were connected with the primary excretory duct. Tubules 1–28 showed Malpighian corpuscles (Fig. 565).

In an embryo of 9.5 mm. greatest length all the tubules were S-shaped, all opened into the primary excretory duct and all possessed Malpighian corpuscles.

With the appearance of the typical S-shape the mesonephric tubule has essentially completed its development; what follows is an elongation of the individual limbs and their histological differentiation. Fig. 563 shows all parts of a mesonephric tubule in the same section. The Malpighian corpuscle has become a large

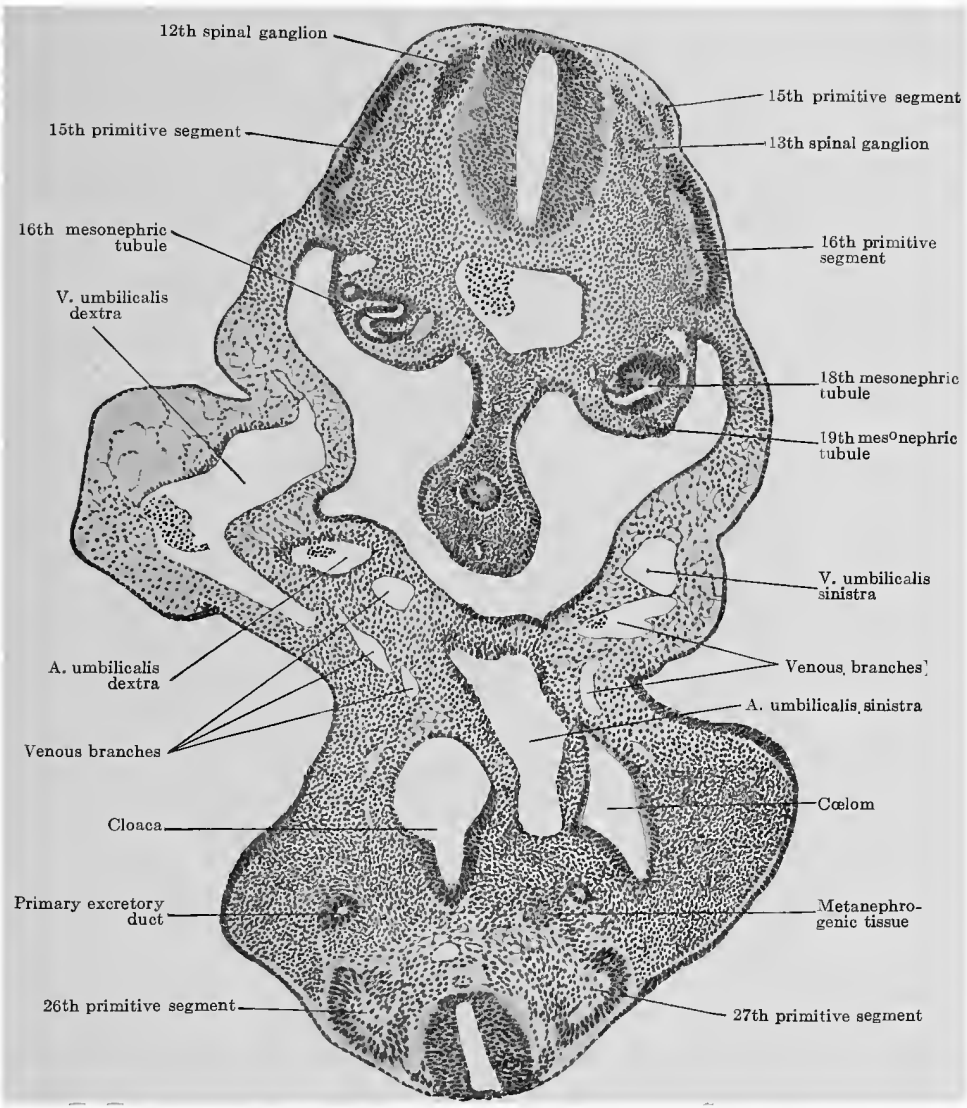


FIG. 562.—Transverse section of a human embryo of 4.7 mm. vertex-breech length, 4.9 mm. nape length, and with 33–35 pairs of primitive segments. (Embryo 137, G. 31, from the collection of the II Anatomical Institute, Berlin, Professor O. Hertwig; slide 12, row 2, section 1.) The section shows in its upper part the position of the completely developed mesonephric canal in the urogenital fold and the size of both relative to the entire embryo. In its lower part it still shows the nephrogenic cord plainly, on the left it is in process of breaking up. In the cloaca the rectal portion is beginning to differentiate from the urogenital sinus portion.

vesicle that is invaginated by the vascular glomerulus only at a limited region. The Bowman's capsule would enclose the glomerulus twice over; the smallness of the glomerulus in contrast with the size of the capsule must be taken as a characteristic of the human mesonephros. In the 22nd tubule only the edge of the vascular glomerulus is cut; in the 23rd tubule it is more distinct. The section through the corpuscle of the 24th tubule goes through a point where there is no invagination. All the vesicles are lined

on their parietal wall by a flattened epithelium; the visceral epithelium, which covers the glomerulus, is of a low cubical form. At the transition of the capsule into the secretory tubule the lumen of the Malpighian corpuscle diminishes and the flattened epithelium becomes cubical and finally cylindrical. The most characteristic feature of the secretory tubule, in addition to the cylin-

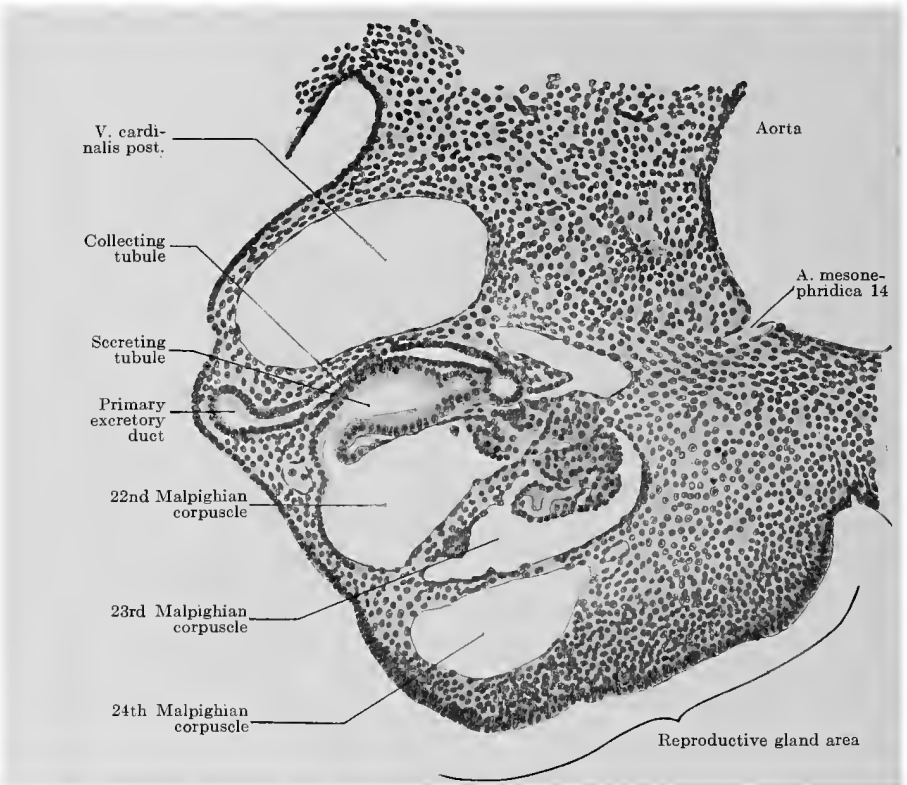


Fig. 563.—Transverse section of the urogenital fold of a human embryo of 9.5 mm. greatest length and with 38–39 pairs of primitive segments. (Embryo Ma. 3, from the collection of Professor Hochstetter, Vienna; slide 12, row 1, section 1.) × 175. The section passes through the 10th thoracic segment. In the fold there succeed each other in the dorso-ventral direction the v. cardinalis post., the complete 22nd tubule, a section of the Malpighian corpuscle of the 23rd tubule and a section through a portion of the Bowman's capsule of the 24th tubule, without any vascular glomerulus. From the Bowman's capsule of the tubule the secretory tubule gradually develops, it ascends upwards for a short distance and then bends medianly almost at a right angle, enlarges, and again bends around and runs as the collecting tubule to the primary excretory duct. At the point where it bends around to become the collecting tubule it makes a small loop and here the tubule appears to be interrupted, the ends of the secretory and collecting tubules appearing in section. The 14th mesonephric artery arises from the aorta, but it cannot be followed further. The reproductive gland anlage is of great extent, but has not yet begun to proliferate.

drical form of its cells, is their clear appearance. The cell boundaries become distinct, the oval nucleus passes into the basal half of the cell and the other half becomes eosinophilic. Very frequently the secreting tubule enlarges in a spindle-shaped manner, as is shown in Fig. 563; on the other hand, the transitional region into the Malpighian corpuscle and the collecting tubule always remain narrow. The epithelial differentiation is already indi-

cated in an embryo of 5.3 mm. greatest length in the anterior tubules, the spindle-shaped enlargement was first seen in an embryo of 8 mm. nape length. The transition of the secreting tubule into the collecting one does not fall within the section. At this point the tubule of older embryos forms a loop directed either cranially or caudally. This is the only change that occurs after the tubule has acquired its S-shape. I have studied 200 models

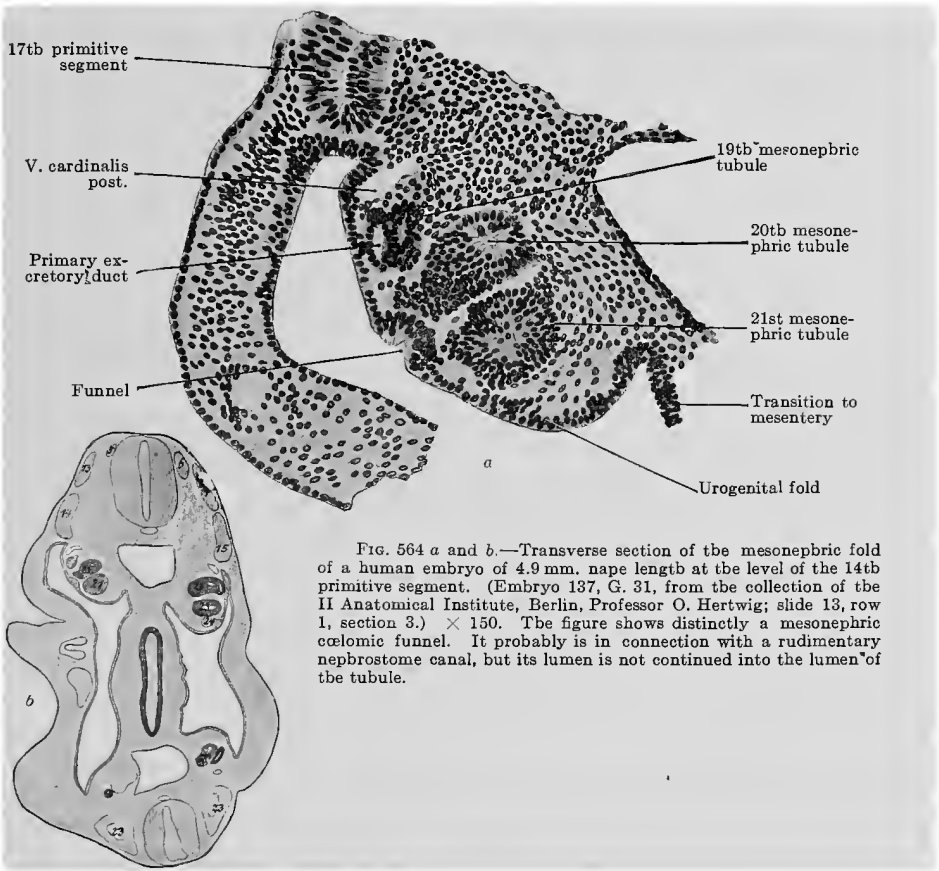


FIG. 564 *a* and *b*.—Transverse section of tbe mesonepbric fold of a human embryo of 4.9 mm. nape lengtb at tbe level of the 14tb primitive segment. (Embryo 137, G. 31, from tbe collection of tbe II Anatomical Institute, Berlin, Professor O. Hertwig; slide 13, row 1, section 3.) × 150. Tbe figure shows distinctly a mesonephric cœlomic funnel. It probably is in connection with a rudimentary nepbrostome canal, but its lumen is not continued into the lumen of tbe tubule.

of mesonephric tubules from the most different stages of development, and in none of them have I found any coiling of the tubule. Consequently the reconstruction of a tubule which I show in Fig. 192 of my contribution to Hertwig's Handbuch der vergleichenden und experimentellen Entwicklungsgeschichte (1905), taken from Kollmann, must represent a very exceptional rarity. The collecting tubule runs almost straight to the primary excretory duct and is lined by a dark, cubical epithelium.

Later, when the various parts of the tubules increase in thickness they no longer find sufficient room to lie beside each other in the transverse plane and they become displaced either caudally

or cranially, the collecting tubule sometimes and sometimes the secretory one coming to lie more cranially.

The connection of the various mesonephric vesicles with the lateral plate, which is shown in Figs. 558 and 559, disappears completely in the anterior tubules, but in the posterior ones it may persist for a time and may be invaginated in a funnel-like manner; the lumen of the body cavity, however, never reaches that of the mesonephric tubule. Fig. 564 shows one of these cœlomic funnels, that is situated at the point where the primitive segment stalk originally was. A large number of such funnels occur in an embryo of 4.9 mm. nape length, one corresponding to each 21st, 23rd and 28th–32nd tubule on the right and on the left to the 22nd and the 24th–34th.

The union of the tubules to form the mesonephros and the position of the various tubules in this can only be followed in a model. Fig. 565 shows a model of both mesonephroi of a human embryo of 7 mm. greatest length. The mesonephroi are still in the process of development; of the 30–31 tubules present on either side only the 25 cranial ones are fully formed. Both mesonephroi form almost a straight line and are parallel, the Malpighian corpuscles being so placed one above the other that they form a column; in reality, however, the mesonephroi are not straight but are curved in correspondence with the contour of the body. The Malpighian corpuscle passes over into the secretory tubule always at its lateral side, and the secretory tubule passes over into the collecting one on the medial side of the corpuscle. The corpuscle and the two tubules still lie in the same plane; the coil that they form is almost in contact with the primary excretory duct. The space at the disposal of the various tubules within the mesonephros is still quite sufficient for the degree of development they present, and consequently while the Malpighian corpuscles are to some extent in contact, they do not press upon one another. If one compares the corpuscles of the mesonephros with those of the metanephros, the size of the former is striking, and this size brings it about that the vascular glomerulus never fills the entire cavity of the Bowman's capsule, both its cranial and caudal ends remaining free from vascular loops. Figs. 566 and 567 represent the model of both mesonephroi of an embryo of 9.5 mm. greatest length. The organs are fully developed, each of the 32–34 tubules consisting of a Malpighian corpuscle, a secreting and a collecting tubule. A comparison with Fig. 565 shows that the separation of the two organs transversely has begun. The excretory duct in the model represented in Fig. 565 runs in a straight course to the point where the ureter is given off; the right-angled bend caudal to the 31st right tubule is an illusion of perspective, the excretory duct, which is seen partly from the right side, making a strong bend ventrally.

The duct of the model shown in Fig. 566 is curved and the curvature is especially marked in the lower portion caudal to the 24th right tubule. This curvature of the duct corresponds to the bayonet-shaped bending of the urogenital fold (Fig. 552). The Malpighian corpuscles also form a column. They press upon or overlap one another, however, as a result of their increased size. As the lateral view (Fig. 567) shows, individual corpuscles have already been forced dorsally or ventrally. The collecting and secreting tubules have increased in size and their connecting loops now frequently pass beyond the medial borders of the Malpighian corpuscles, a fact which is of importance for the understanding of the urogenital union. The parts of the various tubules no longer lie in the same transverse plane; the Malpighian corpuscle has dropped down and frequently lies at the same level as the collecting tubule of the

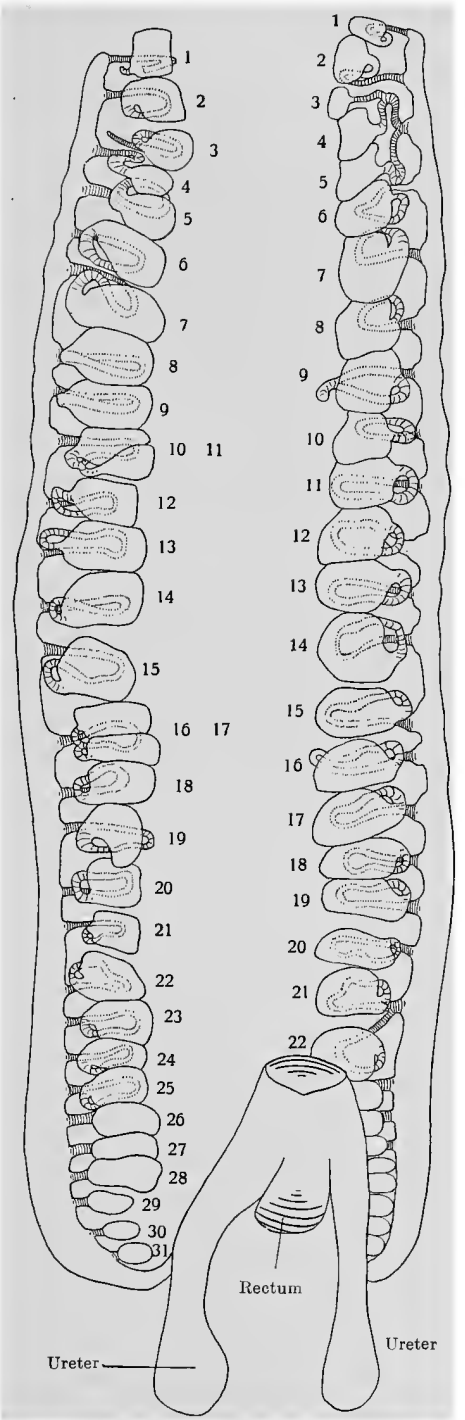


FIG. 565.—Model of the mesonephroi, the metanephroi and the bladder of a human embryo of 7 mm. greatest length. (Embryo Chr. 1, from the collection of Professor Hochstetter, Vienna. The model has been prepared by my students A. Wächter and E. von Wyss.) View from in front. × 75. The mesonephroi have a perpendicular position and the individual tubules are at sufficient distances, so that the Malpighian corpuscles lie in a single row. The lowest tubules are still developing, but have already united with the excretory duct (Fig. 561 *c*). The fully developed canals are S-shaped. Most ventrally are the Malpighian corpuscles, then in the middle is the secreting tubule and most dorsally the collecting tubule. The loop formed by the secreting and collecting tubules usually has not yet reached the medial border of Bowman's capsule. The whole coil of a mesonephric segment (Malpighian corpuscle and the two tubules) lies still in one horizontal plane. The primary excretory duct is narrow in its upper part and only widened in a spindle-shaped manner corresponding to the entrance into it of a collecting tubule; in its lower portion it is remarkably wide and the spindle-like enlargements have disappeared. Towards the bladder the duct narrows again. The ureters are short and almost straight canals terminating in club-shaped enlargements.

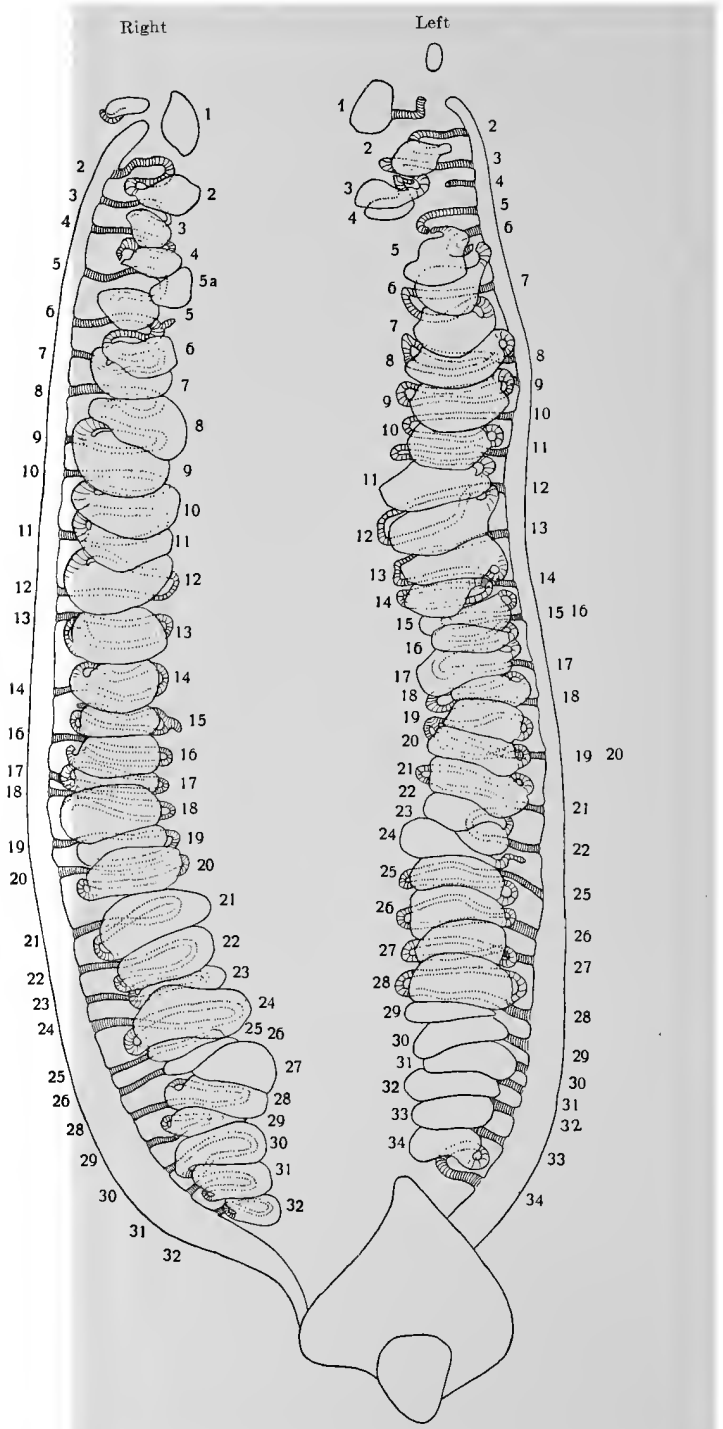


Fig. 566.

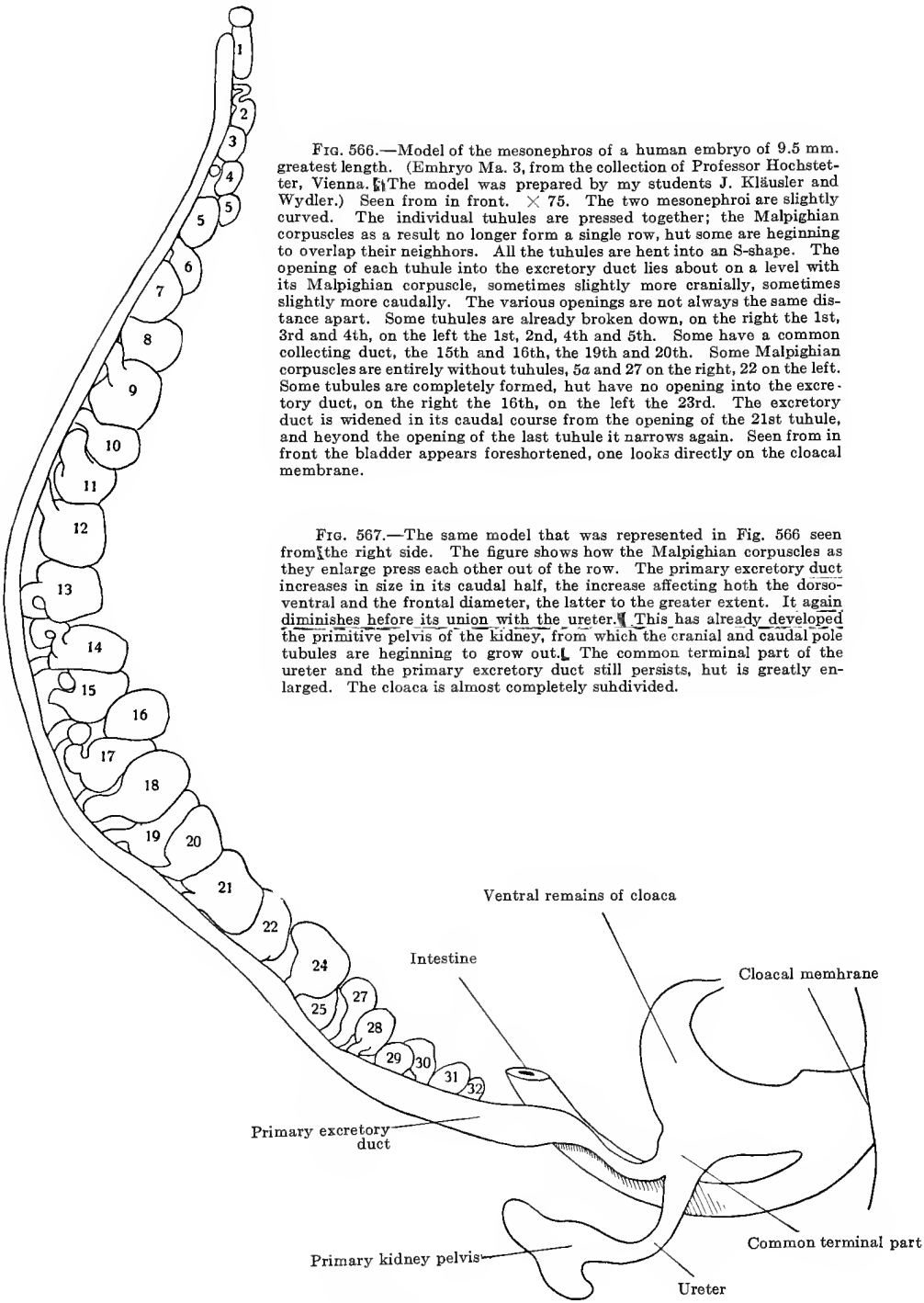


Fig. 567.

FIG. 566.—Model of the mesonephros of a human embryo of 9.5 mm. greatest length. (Embryo Ma. 3, from the collection of Professor Hochstetter, Vienna. The model was prepared by my students J. Kläusler and Wydler.) Seen from in front. × 75. The two mesonephroi are slightly curved. The individual tuhules are pressed together; the Malpighian corpuscles as a result no longer form a single row, hut some are heginning to overlap their neighhors. All the tuhules are hent into an S-shape. The opening of each tuhule into the excretory duct lies about on a level with its Malpighian corpuscle, sometimes slightly more cranially, sometimes slightly more caudally. The various openings are not always the same distance apart. Some tuhules are already broken down, on the right the 1st, 3rd and 4th, on the left the 1st, 2nd, 4th and 5th. Some have a common collecting duct, the 15th and 16th, the 19th and 20th. Some Malpighian corpuscles are entirely without tuhules, 5*a* and 27 on the right, 22 on the left. Some tubules are completely formed, hut have no opening into the excretory duct, on the right the 16th, on the left the 23rd. The excretory duct is widened in its caudal course from the opening of the 21st tuhule, and heyond the opening of the last tuhule it narrows again. Seen from in front the bladder appears foreshortened, one looks directly on the cloacal membrane.

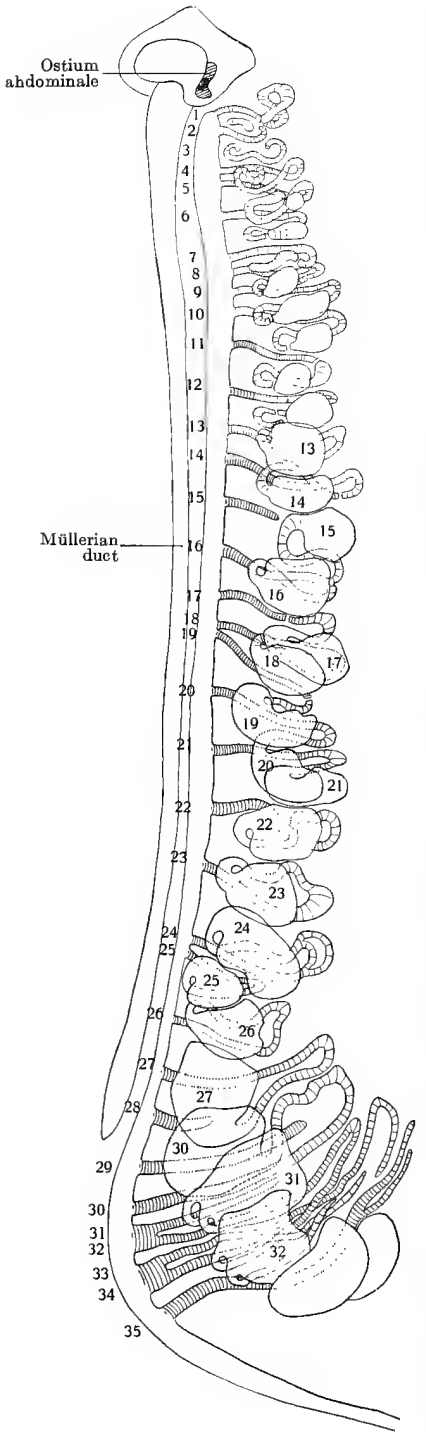
FIG. 567.—The same model that was represented in Fig. 566 seen from the right side. The figure shows how the Malpighian corpuscles as they enlarge press each other out of the row. The primary excretory duct increases in size in its caudal half, the increase affecting hoth the dorsoventral and the frontal diameter, the latter to the greater extent. It again diminishes before its union with the ureter. This has already developed the primitive pelvis of the kidney, from which the cranial and caudal pole tubules are heginning to grow out. The common terminal part of the ureter and the primary excretory duct still persists, hut is greatly enlarged. The cloaca is almost completely suhdivided.

next mesonephric segment. Finally, in Fig. 568 the model of the right mesonephros of an embryo of 19.4 mm. vertex-breech length is shown. The mesonephroi have separated still more (Fig. 552 is taken from the same embryo); that the cause of this separation is the suprarenal bodies and the metanephroi has already been shown in the section on the urogenital fold. As a result of it the curvature of the primary excretory duct becomes continually stronger, since it must reach the medially placed bladder, and now it appears to be bent around almost at a right angle. This strong curvature cannot be without influence on the tubules of the region in which it occurs. Even from the 24th tubule downwards the Malpighian corpuscles are pressed together and form in their totality an arch convex caudo-laterally. The corresponding tubules are greatly elongated, the collecting tubules form long passages which converge towards the concave side of the arch of Malpighian corpuscles and then bend around into the secreting tubules; they are thereby greatly pressed together, lying close beside each other through long stretches and may connect with one another. By this new union the collecting duct of one tubule may serve as the efferent for several. A further result of the bending of the excretory duct is the union of the orifices of several of the collecting tubules to form a single one. In this way the number of collecting tubules opening into the excretory duct is diminished and no longer corresponds with that of the Malpighian corpuscles. I shall discuss later in a special section the degeneration phenomena which are clearly shown in Fig. 568. As the result of a strong growth of the collecting tubules the entire coil of a mesonephric segment is further away from the excretory duct, and with further development the interval becomes continually greater until, finally, there occurs the already described subdivision of the mesonephros into two portions, a lateral one with the excretory duct and the lateral portions of the collecting tubules, and a medial one with the Malpighian corpuscles, the secreting tubules, and the medial portions of the collecting ones.

The special relations of the caudal tubules make possible a division of the mesonephros into a cranial and a caudal portion; a similar subdivision occurs in the mesonephros of all vertebrates. The upper portion later unites with the reproductive gland and becomes the sexual portion of the mesonephros, the epigenitalis (epididymis in the male, epoöphoron in the female). The lower portion in animals without a metanephros becomes the actual functioning kidney and is consequently termed the glandular portion, but in animals in which the metanephros separates from the mesonephros this lower portion also undergoes degeneration and becomes the paragenitalis (paradidymis in the male, paroöphoron in the female).

The primary excretory duct is also modified during the development of the mesonephros. It is at first (in embryos up to 4.25 mm. vertex-breech length) solid. Its lumen appears discontinuously, at first at both ends; at the caudal end the lumen appears to extend into it from the cloaca. In an embryo of 7 mm. greatest length the lumen is fully formed and the excretory duct is in open communication with the cloaca. The course of the duct to its opening is not straight. Attention has already been called to the frontal bend which gives the first impetus to the concentration of the paragenitalis. A second bend in the sagittal direction appears quite early. In an embryo of 4.25 mm. vertex-breech length, the duct extends to the 28th primitive segment, parallel to the vertebral column. Having arrived at this point it bends almost at a right angle and reaches the bladder by a short horizontal piece. This bend is important; I shall term it the sagittal bend of the excretory duct.

At the openings of the collecting tubules the excretory duct is widened. In the upper portion these widened places are separated by narrow ones, but in the lower part they flow together (Figs. 565, 566). The wide portion of the duct thus formed has at least twice the diameter of the unwidened cranial portion. This widening persists for an extraordinarily long time, and one might be inclined to correlate it with the ampulla of the ductus deferens which is formed later on. That is not possible, however, for the widening completely disappears, as will be seen from what follows. It has already been pointed out that the widened places receive the collecting tubules of those mesonephric tubules which later concentrate to form the paragenitalis. I shall anticipate by stating that the union of several collecting tubules of the paragenitalis to form a common terminal part, already referred to in the description of Fig. 568, continually progresses in the later stages of development, until, finally, only a single efferent duct remains, which, in the adult individual, is the ductulus aberrans Halleri. With the formation of this ductulus it becomes possible to determine the position of the embryonic widening; it corresponds to the lower part of the epididymis. It extends down to the sagittal bend of the excretory duct and at this point the duct becomes smaller; its horizontal piece is narrow. In Fig. 568 a narrowed portion of the excretory duct occurs in the region of the openings of the 24th–29th collecting tubules. The duct does not, however, actually narrow; the appearance is produced by a spiral twisting of the duct through 90°. It is very possible that this twisting is due to the union of the mesonephric fold with the anterior abdominal wall by means of the inguinal fold. In the section on the urogenital fold the displacement of the anterior abdominal wall and the influence this exerts on the entire meso-



nephric fold have been described. This influence will, naturally, also be felt by the contents of the fold and thus the spiral twisting of the primary excretory duct may be the result of a displacement of the anterior abdominal wall which is carried to the mesonephric fold by the inguinal fold.

Finally the relation of the excretory duct to the a. umbilicalis must be considered. The artery has two root areas, a visceral one from the rami intestinales and a parietal one from the parieto-ventral vascular arches of the aorta. The visceral root area begins in the third cervical segment and extends into the lumbar region. It is present throughout its entire length in no embryo; the individual roots are developed in succession; at first only the cervical ones are present; then

Fig. 568.—Model of the right mesonephros and Müllerian duct of a human embryo of 19.4 mm., greatest length. (Embryo Ma. 2, from the collection of Professor Hochstetter, Vienna. The model was prepared by my students Massard and E. Chomé.) The mesonephros has undergone extensive degeneration. All the tubules in the thoracic segments and some of those in the lumbar show degeneration. Either the Malpighian corpuscle is wanting or it is rudimentary and separated from its secreting tubule; this is the case in tubules 1–12, that is to say in a full third of those present. All these tubules are also broken, either in the secreting tubule or between this and the collecting one. These latter are rarely hollow, and if so, their lumina are filled with degenerating epithelium. Finally the tubules 33, 34 and 35 consist only of collecting tubules; 33 has still a portion of the secreting tubule and near it are two large Malpighian corpuscles without any connection. Similarly tubule 31 consists only of a collecting tubule; a Malpighian corpuscle with two secreting tubules seems to correspond with it; some of the remaining tubules are broken, 14, 17, 18, 19; some have solid collecting tubules, 13, 14, 15, 16, 17, 19, 21, 23, 25 and 26, and some solid secreting tubules, 22 and 24; the collecting tubules of 28, 29 and 31 form ureter-like structures. Only the remaining tubules 20, 27, 30 and 32 are fully formed. The appearances of degeneration seen in the most caudal tubules are not to be regarded as persistent without further evidence. From older series it is seen that the lower collecting tubules which have separated from the excretory duct may acquire a new opening into a neighboring collecting tubule, just as separated Malpighian corpuscles and secreting tubules may communicate anew with neighboring tubules. By the bending of the primary excretory duct at the end of the mesonephros, the Malpighian corpuscles of the 26th to the 34th tubules are pressed together so as to form a special group, from which, later, the paragenitalis is formed. The Müllerian duct is quite independent of the cœlomic epithelium and the excretory duct; it is still straight, since its down-growing tip has just reached the head of the excretory duct.

the origin of the artery wanders more caudally into the upper thoracic region, and the cervical roots degenerate; after the thoracic roots have functioned for a time the artery wanders into the lower thoracic and the upper thoracic roots become fused, and so on. The parietal root area first appears when the artery has reached the lumbar region. From its mode of origin the visceral root area must lie to the medial side of the excretory duct and the parietal area on its lateral side. Since both root areas exist for a time together, the excretory duct runs in an island surrounded directly by the arteries; in Fig. 569 a section is shown passing through a region where both roots of the a. umbilicalis are present at the same time.

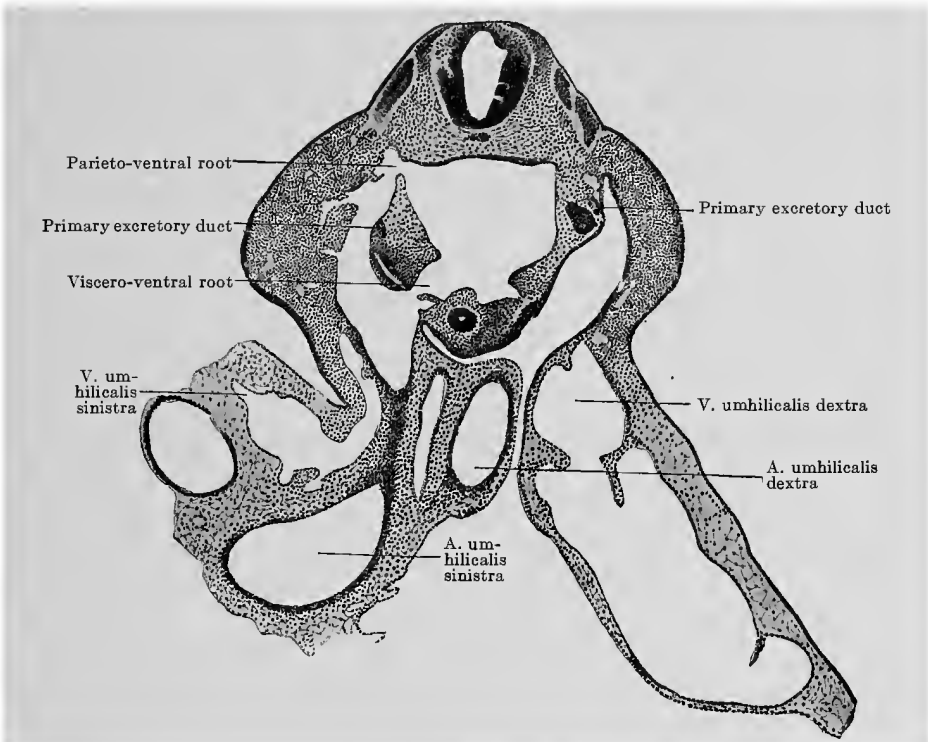


FIG. 569.—Transverse section of an embryo of 5.3 mm. greatest length and 4.6 mm. nape length, at the level of the 24th segment. (Embryo 1420, H. s. 112, from the collection of Professor Keibel, Freiburg i. Br.; slide 12, row 2, slide 1.) ×75. The section passes through the root area of the a. umhilicalis; between the parietal and visceral roots there is an island of tissue in which the primary excretory duct occurs.

THE FIRST DEGENERATION PERIOD OF THE MESONEPHROS.

The degeneration of the mesonephros occurs in two periods. The first begins even before the organ has reached its full extent and is finished in embryos of 21 mm. greatest length. During its progress the greater part of the mesonephros beginning at the cranial end, is degenerated. The second period comes on so gradually that definite time limits are not possible for it. In it there occurs a new suppression of tubules and the selection of those that will enter the service of the reproductive system and of those that will persist even in the adult as the paragenitalis.

The three models of the mesonephros (Figs. 565, 566 and 568) do not reveal the important part played by the degeneration, that is beginning in the cranial portion; its influence becomes clear only by a study of the table opposite. In the lowest horizontal column of this table the entire number of mesonephric tubules is given for each embryo in which they were counted. The numbers, as they stand there, vary so little that they do not suggest a necessity for further controls; we shall further learn from the description of the development of the Müllerian duct that its ostium abdominale lies apparently always at the upper end of the mesonephros in embryos of both sexes throughout the entire development. Both these facts distract the attention of the observer from the really enormous degeneration that the mesonephros undergoes.

The degeneration shows itself as soon as the growth cranially of the mesonephros is completed, that is to say in an embryo of 5.3 mm. greatest length, at a time therefore at which the organ is still growing caudally. It always begins at the most cranial tubule and makes a continuous and regular progress up to the time men tioned above. In the table the number of the tubules occurring in each segment is given, those that are degenerating being given in roman numerals and those that are fully formed in arabic. An asterisk with an arabic number indicates that the tubule is still developing. If we follow the cranial limits of the various mesonephroi through the table from left to right we see a marked and, what is important for the regularity of the process, a continuous recession of these limits. Beginning with an embryo of 5.3 mm. greatest length and ending with one of 21 mm. greatest length the line that unites the cranial limits recedes from the 6th cervical to the 1st lumbar segment, that is to say, there is a recession through 15 segments. The relative constancy of the total number of tubules throughout this period justifies the question whether the recession of the cranial limit may not find its explanation in the crowding together of the tubules within a smaller space; the question is all the more justified, because we actually know of the occurrence of this process in the development of other craniota, both in the case of the pronephros and in that of the mesonephros. That there is a crowding together of the tubules during the first period of degeneration is very probable, at all events the table opposite shows an increase in the number of tubules in the segments of the degenerating zone. The process plays, however, only an unimportant part, as is shown by the course of the mesonephric arteries, to be described later on. A crowding together of the tubules of 18 segments into 3 would cause the arteries to assume almost a vertical course, but they remain horizontal throughout the first degeneration period. The principal cause of the caudal recession is the progressive degeneration of the meso-

nephric tubules. Throughout this period I have not seen a single mesonephros that did not show degenerating tubules in at least one, usually in two or three of the cranial segments; the regularity of its occurrence speaks for the normality of the process. Reckoned by the segments the upper five-sixths of the mesonephros, the 6th cervical to the 12th thoracic, 15 segments in all, degenerate, and only the caudal sixth, the 1st to the 3rd lumbar segments, three segments in all, persist. Estimated by the tubules 57 are degenerated out of a maximum of 83 that develop, that is to say, two-thirds of all the tubules degenerate and 26, or one-third, persist. The number 57 is estimated, not observed; the number 26 was the maximal number found in the enumeration of the tubules of different embryos. Naturally the corresponding portion of the primary excretory duct disappears along with the tubules. Once all the tubules of the cervical and thoracic segments have disappeared,[1] a period of rest supervenes; from the stage of 21 mm. greatest length onwards, all embryos show a rather constant number of mesonephric tubules in the lumbar segments, but these tubules are almost all broken in one or several places.

The degeneration appears under very different forms: 1, the Malpighian corpuscle may separate from the secreting tubule; 2, the transition of the secreting into the collecting tubule may be broken; 3, the collecting tubule may be solid or its epithelium desquamated; 4, the secreting tubule may be broken into several portions; 5, the collecting tubule may not be connected with the primary excretory duct. The variations are arranged according to their frequency of occurrence. The separation of the Malpighian corpuscle from the secreting tubule is almost always to be found in all degenerating tubules and all show a tendency to lose to a greater or less extent their S-shape.

Notwithstanding the degeneration, which occurs in the cranial canals before the beginning of the histological differentiation of their epithelium, an epithelial differentiation between the collecting and secreting tubules occurs very frequently even in the remains of the cranial canals.

LATER FORMED TUBULES.

In a 7 mm. embryo the mesonephros has reached its caudal limit and no new anlagen are added in older embryos at the caudal end of the organ, and, furthermore, within the mesonephric area at least two-thirds of the tubules degenerate and yet the number of tubules between the stages of 5.3 mm. and 19.4 mm. greatest lengths increases rather than diminishes. This is only possible if a new formation of tubules occurs. From the table facing p. 816 one may determine this fact, at least for the lower thoracic and lumbar segments, by a comparison of the numbers for the individual embryos.

[1] Remains of cranial tubules may persist a long time; my colleague, Professor Zuckerkandl, called my attention to such remains in the 3rd thoracic segment.

The question as to the origin of these later formed tubules is difficult of solution and an absolutely certain statement cannot be made. In the first place, the sources from which they can not come may be excluded. In most vertebrates the later formed tubules arise from unused remnants of the parent tissue. At the first appearance of the mesonephric tubules (embryo of 2.6 mm.) such remnants of the nephrogenic cord may be seen, but in an embryo of 7 mm. they have completely disappeared; there is no trace of compact remnants of the nephrogenic cord and the only remaining possibility is that scattered cells, indistinguishable from the surrounding mesoderm, later become aggregated to form cell masses from which the later formed tubules arise just as the primary ones did. This process occurs in Teleosts and Amphibia, but the most thorough search fails to reveal any structures that might serve for such a method of new formation in human embryos. New formation from remnants of the nephrogenic cord I regard as excluded; there remains only the hypothesis that the new formation takes place from the tubules already present by division or budding. For both these methods incomplete evidence occurs. Malpighian corpuscles occur which are twice as large as the rest, others occur that are in process of division, others that are completely isolated and without a tubule, others with tubules which communicate after a short course with fully developed tubules, and, finally, completely developed tubules occur that are not yet in connection with the primary excretory duct. These facts taken by themselves might be interpreted by supposing that a Malpighian corpuscle divides, the one portion remaining in connection with the original tubule, while the other develops a new tubule, which opens either into a neighboring tubule or into the primary excretory duct. This process of development receives plausibility from the fact that the Malpighian corpuscle represents the original parent tissue, that is, the lateral part of the primitive segment stalk.

Further divisions occur in the canals, usually in the secreting tubules, and also diverticula occur, given off either from the transition of the secreting into the collecting tubule or, less frequently, from the transition of the Malpighian corpuscle into the secreting tubule; corresponding with this, collecting tubules occur with two or three secreting tubules communicating with them. This allows us to assume that a mesonephric tubule in some part of its course, almost always in the secreting tubule, forms a diverticulum which, elongating, gives rise to a new tubule with a Malpighian corpuscle. All the various conditions mentioned above are shown in Figs. 565–568 and are described in the explanations of these figures.

In the Gymnophiones and birds special efferent ducts are developed for the later formed tubules by the primary excretory duct sending out towards them small canals, which may serve as

collecting tubules for several of the later formed tubules. These new formed ducts are termed mesonephric ureters, in contrast to the metanephric ureter. Such ducts also occur in the human embryo. In an embryo of 12.5 mm. greatest length I found in the 12th thoracic and 1st lumbar segment six of them certainly and perhaps two others, and in an embryo of 19.4 mm. three of them.

All these pieces of evidence are, however, not final, since in addition to the new formation degeneration is also taking place and the degeneration, whose varieties have been mentioned above (p. 817), may present almost the same appearance as the new formation. Only those cases of division and diverticulum formation are of consequence which occur in segments lying far away from the degeneration zone. Since such cases may be found, I assume that later formed tubules arise by the division and budding of those already present.

RUDIMENTS OF PRONEPHRIC AND MESONEPHRIC TUBULES.

Now that the development and degeneration of the mesonephros has been considered, we are in a position to discuss the tubule remnants that have been described in the literature as pronephric rudiments. We have established

1. That pronephric tubules occur only in the region of the first 12 primitive segments; the pronephros, accordingly, never extends caudally beyond the 1st thoracic segment.

2. That mesonephric tubules are developed in the region from the 5th cervical to the 3rd lumbar segments; consequently the mesonephros does not extend cranially beyond the 5th cervical segment.

We may say then at once that all remnants of tubules from the 2nd thoracic segment caudally are to be referred to mesonephric tubules and all those in front of the 5th cervical segment are certainly derived from the pronephros. Those that occur between the 5th cervical and the 1st thoracic segment may be either pronephric or mesonephric, a certain diagnosis is impossible. According to the results of the table facing p. 816, however, it is probable that all these uncertain remains come from the mesonephros; the pronephros, therefore, has already completely degenerated. The statements that occur in the literature to the effect that the occurrence of the remains of a tubule dorsal to the v. cardinalis posterior is a certain indication of its pronephric origin (Tandler 1905, Veit 1909) have no weight.

It is clear that no pronephric remnants can persist in the neighborhood of the epigenitalis, which arises from the caudal sixth of the mesonephros; all accounts of the occurrence of pronephric tubules on the epoophoron are therefore incorrect.

MESONEPHRIC ARTERIES (AA. MESONEPHRIDICÆ).

There are developed on each side in maximo 30 mesonephric arteries, which are distributed throughout the entire mesonephric area. At first they are entirely distributed to the mesonephros, but later they also supply the reproductive glands, the suprarenal bodies, the metanephroi and the diaphragm. These new regions of distribution prevent their complete degeneration when the mesonephros disappears. A variable number of them persist as the phrenic, suprarenal, renal, accessory renal, internal spermatic, and accessory spermatic arteries and as the rami ad lymphoglandulas lumbales and ad sympathicum.

The first mesonephric arteries are found in embryos of about 5.3 mm. greatest length. They arise from the lateral surface

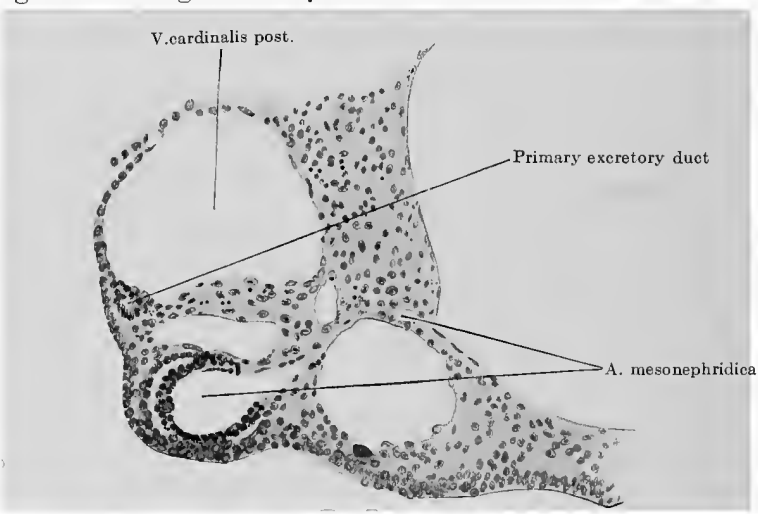


FIG. 570.—Transverse section of the right mesonephros of a human embryo of 5.3 mm. greatest length and 4.6 mm. nape length. (Embryo 1420, H.s. 112, from the collection of Professor Keibel, Freiburg i. Br.; slide 11, row 4, section 1.) A mesonephric artery is cut almost throughout its entire length; the middle portion on account of a curve does not fall within the plane of the section. The artery ends in a spherical enlargement within a Malpighian corpuscle.

of the aorta and pass almost horizontally laterally to the urogenital fold, reaching the Malpighian corpuscles and terminating in them with an enlargement which usually assumes a spherical shape (Fig. 570). Later a network of vessels (Fig. 571) occupies the place of the enlargement, and this also is connected with the v. cardinalis posterior. The number of the mesonephric arteries cannot be determined with perfect certainty, because in their case as in that of the mesonephric tubules degeneration follows upon the steps of the progressive development from the cranial end. The degeneration process is, however, less readily followed in the arteries, since many series are not satisfactory on account of the emptiness of the vessels; this may be shown by the following statements.

In an embryo of 7 mm. greatest length there were 10 mesonephric arteries in the region of the 1st–6th thoracic segments; an embryo of 9.5 mm. greatest length possessed 18 arteries in the 2nd–12th thoracic segments; in an embryo of 10 mm. greatest length 9 arteries were limited to the 7th thoracic–1st lumbar segments; one had 11 arteries distributed to the 6th–11th thoracic segments. In an embryo of 13 mm. the degeneration was completed, it still possessed 11 arteries in the region of the 10th thoracic to the 3rd lumbar segment, and, similarly, in an embryo of 18 mm., 9 arteries were counted from the 10th thoracic to the 3rd lumbar segment.

From this statement it appears that with increasing age the arteries continually recede into the lumbar segments, disappearing from the thoracic ones. Consequently the direction of the arteries

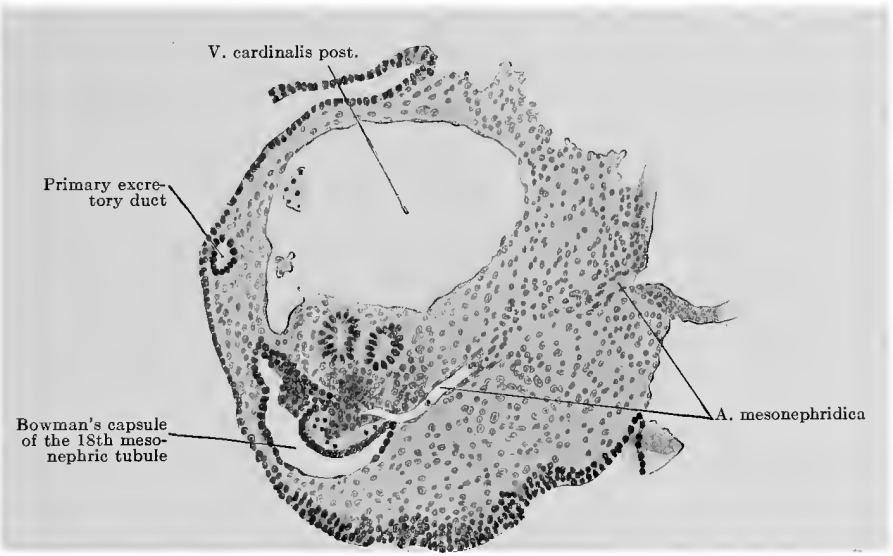


FIG. 571.—Transverse section of a human embryo of 7.0 mm. greatest length. (Embryo Chr. 1, from the collection of Professor Hochstetter, Vienna; slide 8, row 10, section 6.) The a. mesonephridica (the 8th) is cut almost throughout its entire length. It forms two distinct branches inside the glomerulus. The anlage of the reproductive gland, indicated by the thickening of the cœlomic epithelium, is of a fair extent; its growth has not yet begun.

is always horizontal (Fig. 572), so that an extensive compression of the mesonephros, which has already been excluded in considering the degeneration of the mesonephric tubules, cannot be assumed. If the mesonephros were compressed from a condition in which it extended from the 6th cervical to the 3rd lumbar segment to one in which it extended only from the 1st to the 3rd lumbar, the vessels remaining the same, as they naturally would if all the tubules persisted, then the arteries situated more cranially would run almost parallel to the aorta.

The arteries are not paired, nor are they arranged segmentally. In the cranial segments one artery may lie in each segment or two in three segments, but in the caudal region the arteries become more numerous, just as the mesonephric tubules are more

numerous in the lumbar segments than in the thoracic ones; in the lumbar region as many as 4 arteries may lie in a single segment. There are always fewer arteries than tubules, so that one artery must always supply several tubules; this may easily be seen in the lumbar segments. If, for the purpose of determining the maximal number of mesonephric arteries the highest numbers found in each segment be added together, one obtains 30 arteries for 83 possible tubules.

From the 16th thoracic to the 3rd lumbar segment all the mesonephric arteries may persist; from them are formed the

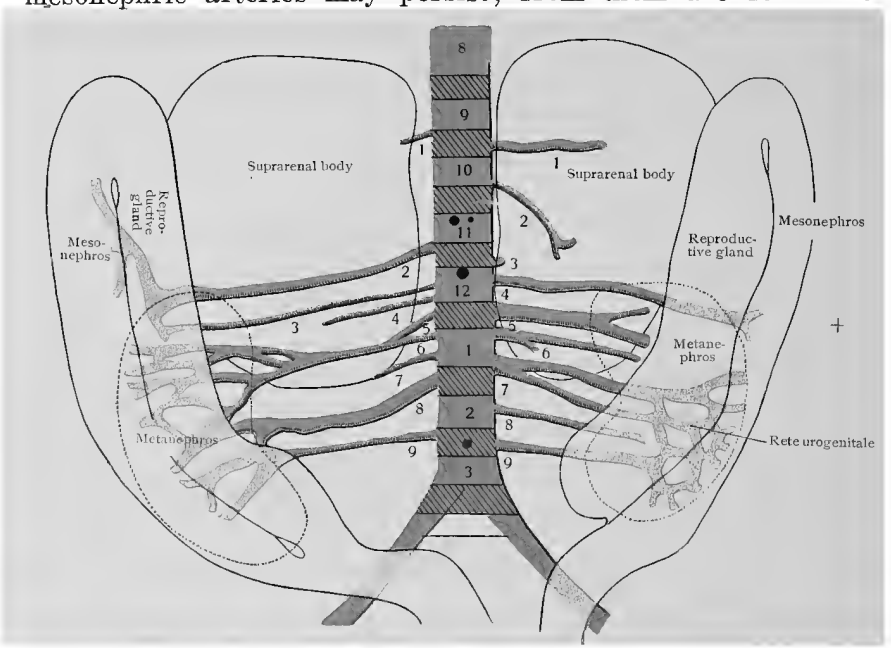


FIG. 572.—Reconstruction of the mesonephric arteries of a human embryo, made from an embryo of 18 mm. greatest length and superposed on the model of an embryo of 19.4 mm. greatest length. Mesonephroi, reproductive glands, and suprarenal bodies are represented with solid, the metanephroi with dotted contours. The circles on the anterior surface of the aorta indicate the origin of the cœliac (which in this embryo is still paired), the superior and inferior mesenteric arteries. The mesonephric arteries are indicated by numbers placed below them. The right 5th, 6th, 8th, and 9th and the left 7th, 8th, and 9th arteries form a network between the reproductive gland and the metanephros, the rete arteriosum urogenitale.

phrenic, suprarenal, renal, accessory renal, internal spermatic and accessory spermatic arteries and also the branches to the lymph nodes and the sympathetic ganglia in the region between the superior and inferior mesenteric arteries. These persistent mesonephric arteries we must consider more in detail. In order to reach the mesonephros they must traverse a rather broad area, in which the suprarenal body lies, this organ in consequence of its rapidly increasing size, coming to lie with its ventral surface in the same frontal plane with the mesonephric fold (Fig. 553). By the suprarenal body the arteries—I am describing them from

the reconstruction of the vessels of an embryo of 18 mm. greatest length shown in Fig. 572—are divided into three groups; a cranial group, running dorsal to the suprarenal body (1st and 2nd arteries on either side), a middle group, whose vessels pass through the suprarenal body (on the right 3rd and 4th, on the left 3rd–5th arteries), and, finally, a caudal group, whose vessels pass over the ventral side of the suprarenal body (on the right 5th and 6th, on the left 6th and 9th arteries). The 7th and 8th arteries on the right and the 9th and 10th on the left pass caudal to the suprarenal body and therefore are not necessarily influenced by it, so that they are compressed by the development of the metanephros in the same ventral position.

The mesonephric arteries 5–9 or 7–9, and probably more, in the angle between the reproductive gland ventrally, the mesonephros laterally, and the metanephros dorsally, form a network, the rete arteriosum urogenitale (Fig. 572). From this network, which is remarkably coarse-meshed and composed of large vessels, the mesonephros, reproductive gland and metanephros are supplied with arterial branches, these organs being thus independent of single branches for their blood supply; should one or several roots degenerate, neighboring ones can take their places. In Fig. 572, for instance, the second mesonephric artery on the right side has become divided into an ascending and a descending branch; the ascending one supplies the entire upper half of the mesonephros and the reproductive gland, a region that in younger embryos receives its blood from several mesonephric arteries belonging to more cranial segments. The occurrence of this network at once explains why all persisting arteries that arise from the roots of this network show, within certain limits, a variability in the point of their origin from the aorta.

Each of the 9–11 remaining mesonephric arteries may become an a. spermatica interna, since all supply the reproductive gland; this explains the frequently observed multiplicity of these arteries and the not infrequent difference in the place of origin of the right and left ones. Usually the artery is formed from one of the arteries of the third group and will therefore lie ventral to the kidney and to the ureter. Rarely an artery of the first group becomes a spermatic artery, the accessory spermatic; in this case the vessel will pass dorsal to the a. renalis, which is formed from an artery of the second or third group, and dorsal to the pelvis of the kidney.

The suprarenal arteries arise from the second, rarely from the first group. Since the inferior phrenics may also form from the first group it is clear that a suprarenal artery may arise from the inferior phrenic or vice versa. The renal arteries are not new formations, as has hitherto been supposed, but each is formed from

a mesonephric artery. The kidney climbs upwards to the mesonephric arteries, as if on a ladder: as soon as a sufficient blood supply is assured cranially, the caudal branches separate from it. When the kidney has acquired its definitive position it possesses several renal arteries, and of these one becomes greatly enlarged to form the definitive artery, while the others either degenerate or persist as accessory renals. The definitive renal artery is either the last vessel of the second group or the first of the third group. The relations of both groups, of the second to the suprarenal artery and of the third to the internal spermatic, explain the variation in which the renal artery arises from a suprarenal or from an internal spermatic; in the first case it may be the principal stem, in the latter only an accessory renal. The relations between the urogenital rete and the metanephros show how the accessory renal arteries may develop, and explain their very varied relations to the kidney. Accessory renals from the first group will be branches of the superior suprarenal and must pass over the dorsal surface of the kidney and consequently they first reach the kidney on its dorsal surface and there penetrate its cortex. Those from the second group will be branches of either the middle or inferior suprarenal and will reach either the hilus of the kidney or the medial edge above this. Those from the third group may enter at the hilus, at the medial edge below it or on the ventral surface of the caudal half of the organ.

Should, exceptionally, a caudal branch be retained, it will be drawn upwards by the migration of the kidney, a condition that explains why such an artery may cross the principal stem or another accessory.

Since the mesonephric arteries of the third group also give branches to the lymphatic nodes and to the sympathetic ganglia of this region, even if they do not become renal or internal spermatic arteries, they will be retained at least as far as the point of origin of the small branches. In consequence of the medial position of these structures these mesonephric arteries will run directly ventrally and there will be a displacement of their points of origin from the aorta, so that they seem to be purely ventral branches and might therefore readily be mistaken for persistent rami intestinales. One must, accordingly, be very careful in identifying as a ramus intestinalis any ventral branch occurring between the origins of the superior and inferior mesenterics or at the level of the latter. Only when they arise some distance below the inferior mesenteric may one without hesitation identify ventral branches as rami intestinales.

A displacement of their origins from the surface of the aorta appears very early in the arteries of the various groups. The vessels of the dorsal group shift their origins to the dorsal surface

of the aorta, those of the third group to the ventral surface, and only those of the second group preserve their original lateral position.

In embryos of 26 mm. greatest length the definitive arrangement of the arterial apparatus is acquired.

VEINS OF THE MESONEPHROS.

The veins form within the mesonephros a special circulatory system, the mesonephric portal circulation. A schematic description based upon the venous arrangement of all craniotes that possess mesonephroi, will explain what is meant by the above term.

The mesonephric portal circulation is formed by two veins, the v. cardinalis posterior and the v. subcardinalis. The former courses along the dorsal surface of the mesonephros, somewhat nearer its lateral border; and the latter along the ventral surface and somewhat nearer the medial border (Fig. 573 *a*). At the caudal border of the organ both veins are connected with the veins of the caudal half of the body, the v. caudalis and the v. ischiadica, and are thereby connected with one another (Fig. 573 *a*). Very soon numerous branches develop between them, these branches traversing the mesonephros (Fig. 573 *b*). From the beginning the v. cardinalis posterior opens into the ductus Cuvieri and through this into the sinus venosus of the heart (Fig. 573 *a* and *b*); the v. subcardinalis has to acquire a connection with the heart and it does so by means of the hepatic vein. This unpaired hepatic vein, v. hepatica revehens communis (Fig. 573 *a* and *b*), arises by three branches, the v. revehens dextra and sinistra and the ductus venosus Arantii; it grows caudally and, dividing, comes into connection with both v. subcardinales; these latter thus become connected with the heart, since the v. hepatica revehens communis opens into the sinus venosus. Accordingly the blood from the posterior half of the body flows toward the heart by the two paths: 1, by the v. cardinalis posterior and the ductus Cuvieri; 2, by the v. subcardinalis and the v. hepatica revehens communis. This changes, however, very soon; for, in the first place, the v. cardinalis posterior becomes interrupted at the upper pole of the mesonephros and the return of its blood to the heart is thus prevented, and, secondly, the connection between the v. subcardinalis and the vv. caudalis and ischiadica breaks, so that the blood from the posterior half of the body is received only by the v. cardinalis posterior (Fig. 573 *c*). If now the blood is to return from the latter to the heart it must make use of the transverse anastomoses between the v. cardinalis posterior and the v. subcardinalis, and reach its destination through this last vein. The transverse anastomoses, however, are broken up into capillaries between the coils of the mesonephric tubules (Fig. 573 *c*), so that the venous blood carried by the v. cardinalis posterior must, on its way to the heart, pass through a second set of capillaries, just as does the blood that passes by the vena portarum through the liver to the v. hepatica; hence the employment of the term mesonephric portal circulation. When this circulation is established we no longer speak of vv. cardinalis and subcardinalis, but of vv. mesonephridica advehens and revehens.

In the human embryo there also develops, in addition to the v. cardinalis posterior, a subcardinal vein, and the possibility is therefore present for the formation of a mesonephric portal circulation; that it really becomes functional is not proven, but all

observations made up to the present indicate that we have to do only with a rudimentary anlage, that exists only for a short time. The posterior cardinal vein is formed in a caudal direction from its opening into the ductus Cuvieri, and always lies in the angle between the primitive segment stalk and the parietal mesoblast. The discontinuity of the anlage and, in addition, the fact that it sometimes appears as a tube, sometimes as a groove, sometimes as composed of only one or two cells, makes probable its develop-

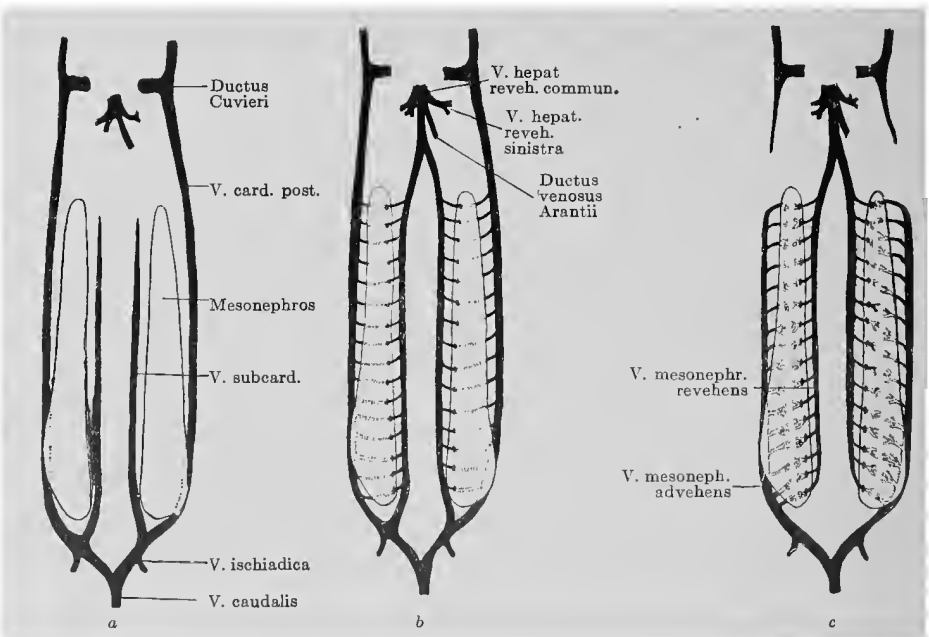


FIG. 573 *a*, *b* and *c*.—Plan of the development of the mesonephric portal circulation. *a*. A vein runs on both sides of the mesonephros, the posterior cardinal laterally and dorsally and the subcardinal medially and ventrally. The posterior cardinal opens cranially into the ductus Cuvieri, while the subcardinal ends blindly. Caudally both veins are connected with the paired v. ischiadica and the unpaired v. caudalis. *b*. Transverse anastomoses have formed between the posterior cardinal and the subcardinal, traversing the mesonephros. The subcardinal opene into the v. hepatica revehens communie. *c*. The cardinal has lost its connection with the ductue Cuvieri, but retains that with the vv. iechiadica and caudalis. The eubcardinal has retained its opening into the v. hepatica revehens communie, but has lost its connection with the vv. iechiadica and caudalis. Capillary networks have developed in the transveree anastomoses. The blood of thc vv. caudalis and ischiadica must now takc the following course: 1, v. cardinalis, 2, the traneverse anastomoses with capillary networks inside the mesonephros, 3, v. subcardinalis, 4, v. hepatica revehens communis, 5, sinus venosus.

ment in loco. The cell material used in its formation wanders from the parietal mesoblast and, eventually, from the primitive segment stalk; I observed cells that were still connected with this germ layer, but whose bases projected beyond the other cells and formed part of the wall of the vein.

In an embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments no posterior cardinal vein was present. In one of 2.5 mm. greatest length and with 23 pairs of primitive segments they were developed from the ductus Cuvieri to the posterior border of the pronephros, that is to say, from

the 5th to the 13th primitive segment. In an embryo of 4.9 mm. nape length they had already reached the caudal pole of the mesonephros—*i. e.*, the 3rd lumbar segment. Their connections with the mesonephric glomeruli were first seen in an embryo of 5.3 mm. greatest length and 4.6 mm. nape length. A duplication of the cardinal vein may occur in the anterior part of its course.

The subcardinal vein is at first double, a median and a lateral vein may be recognized. Both arise—so far as can be determined from individual embryos—from medial and lateral outgrowths from the posterior cardinal. The lateral outgrowths pass through the intervals that are left between the primary excretory duct and the coils of the mesonephric tubules, the medial ones run past the medial side of the Malpighian corpuscles (Fig. 574). Both sets of branches then develop ascending and descending twigs, which unite together to form a medial and a lateral longitudinal vessel, the subcardinal veins. Fig. 574 represents the arrangement of the mesonephric veins of a human embryo of 9.5 mm. greatest length. The posterior cardinal veins are fully developed and are connected with the v. caudalis and the v. ischiadica (these veins are not shown in the figure). The two subcardinals are in process of development; one sees in the cranial half of the mesonephros simple lateral and medial branches given off from the posterior cardinal, at the middle of the organ the formation of T-shaped branches and, finally, in the lower half the union of the T-shaped branches to large longitudinal pieces. A single complete subcardinal vein does not exist anywhere and it is questionable if such a vessel is ever formed. The two lateral subcardinals still terminate freely posteriorly and so also the left medial vein, but the right medial one is connected with a short but large vessel, which is developed on both sides and opens into the posterior cardinal after it has crossed the primary excretory duct; I term this the unpaired terminal part of the subcardinal vein.

I see in the arrangement of these veins the homologue of a portal circulation; but since in an embryo of 12.5 mm. greatest length the subcardinal veins, and with them the transverse branches which connect them with the posterior cardinal, are in the act of degeneration, I do not believe that a portal circulation is actually established. The anlage is accordingly probably only a rudimentary one.

The first outgrowths from the posterior cardinal vein occur in an embryo of 7 mm. greatest length. Corresponding to the cranio-caudal direction of the growth of the mesonephros these transverse veins develop in batches in the same direction, and similarly in correspondence with the early degeneration of the mesonephros the transverse veins in its cranial half degenerate very early, usually before they have reached the T-shaped stage. The unpaired terminal portion of the subcardinal appears in an embryo of 7 mm. greatest length, but at first only on the left side.

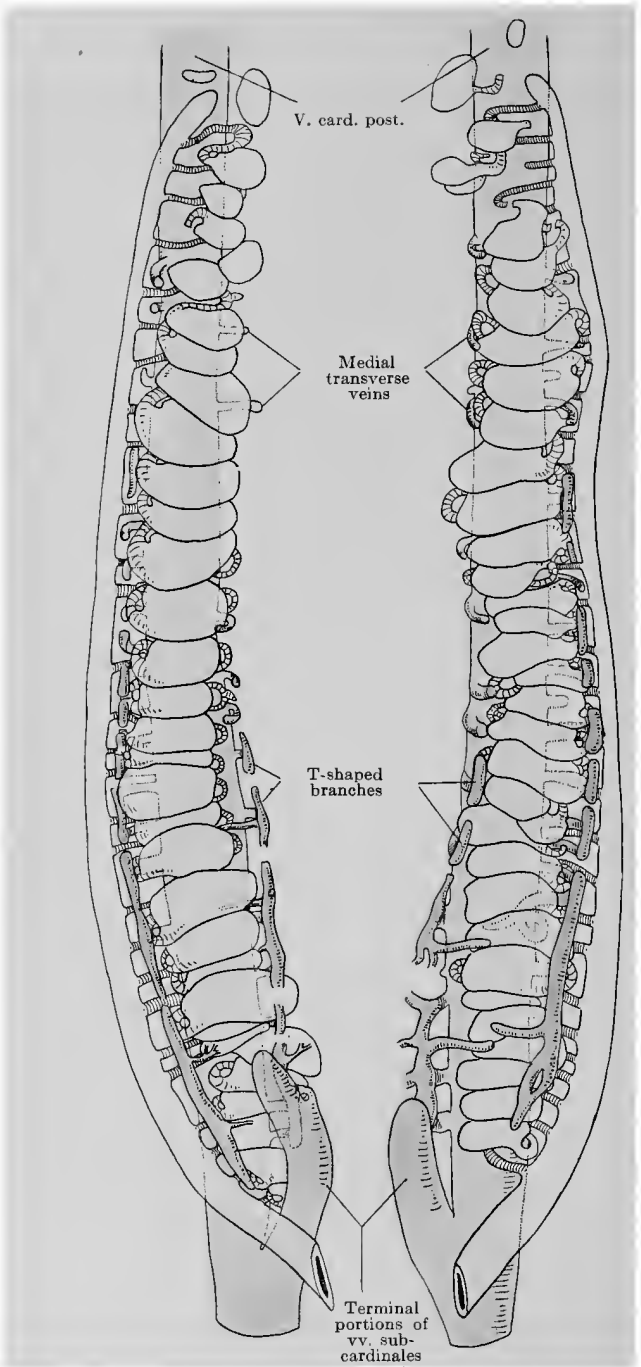


FIG. 574.—Mesonephric veins of a human embryo of 9.5 mm. greatest length. (Embryo Ma. 3, from the collection of Professor Hochstetter, Vienna.) The veins have been reconstructed and drawn upon the model of the mesonephros. The posterior cardinal vein develops horizontal branches arranged in two longitudinal rows, a medial and a lateral one. The branches of the medial row pass medially to the Malpighian corpuscles, those of the lateral row between the primary excretory duct and the coils of the tubules. At their ends most of the branches of both rows, especially in the caudal half of the mesonephros, develop ascending and descending branches, and portions of two longitudinal vessels are thus formed on either side, these vessels being the medial and lateral v. subcardinalis. The posterior cardinal, the transverse branches, and the two subcardinals represent a very rudimentary mesonephric portal circulation.

THE SECOND PERIOD OF DEGENERATION OF THE MESONEPHROS.

It has been shown above that the degeneration of the mesonephros is completed in two periods and the first of these has been described. We have now only to consider the second period. At its commencement, which occurs after a stage of 21 mm. greatest length, the mesonephros consists of only 26 tubules in maximo, all situated in the lumbar region and all broken, that is to say in process of degeneration, in some portion of their course, usually at the angle between the secreting and collecting tubules. This remnant of the mesonephros is divided into two portions by the establishment of the urogenital union, an upper genital and a lower so-called gland portion. I shall term the former the epigenitalis and the latter the paragenitalis. The number of tubules belonging to the epigenitalis varies between 5 and 12, and it is a striking fact that in the male embryo the lower number is more nearly approached and in the female the higher one. The number of tubules in the paragenitalis varies, since it is in process of complete degeneration. The epigenital tubules correspond approximately to the 58th–69th mesonephric tubules and the paragenital to the 70th–83rd.

The epigenital tubules in both sexes are all broken at the same point, namely, at the bend of the secreting into the collecting tubule. The secreting tubule and the Malpighian corpuscle of each tubule have either disappeared in the first period of degeneration or else disappear at the beginning of the second period. The blind ends of the persisting collecting tubules enlarge, their walls at the same time thickening; they may also become somewhat convoluted. Their further fate in both sexes will be described in the section on the urogenital union.

The tubules of the paragenitalis suffer at first only interruptions in their course. These breaks allow of a separation of the individual parts of the tubules and thus the formation of two groups of tubules; the one group includes the Malpighian corpuscles and portions of the secretory tubules, the other the primary excretory duct and portions of the collecting tubules. Both tubule groups lie at first rather close together, but with the formation of the anterior abdominal wall they become widely separated. Simultaneously with the formation of the anterior abdominal wall the coiling of the intestines, and with this the enlargement of the abdominal cavity, begins. The urogenital fold, however, is attached to the anterior abdominal wall by the inguinal fold, and since it must, consequently, follow that wall, it becomes drawn out ventrally in the horizontal direction. Where the urogenital fold unites with the anterior abdominal wall, the primary excre-

tory duct makes a double bend (Fig. 552), bending first around the caudal pole of the mesonephros and again as it enters the primitive true pelvis, and between the two bends there is a horizontal portion of the excretory duct; it is this horizontal portion that receives the collecting tubules of the paragenitalis. Along with the urogenital fold, this portion of the primary excretory duct is drawn out lengthwise and forms a loop directed towards the anterior abdominal wall. The formation of the loop, which the collecting tubules must follow, separates these latter from the secreting tubules and the Malpighian corpuscles. Both these structures retain their position immediately caudal to the epigenitalis and not infrequently are divided into two groups, a cranial one, that lies so closely upon the epigenitalis that it seems to consist of epigenital Malpighian corpuscles and secreting tubules, and a somewhat more caudal one. The corpuscles and tubules forming the first group usually vanish completely, but may sometimes persist. In the former case there is but a *single* paragenitalis, in the latter case *two*. The collecting tubules that are drawn out longitudinally by the looping of the excretory duct may unite with each other, so that one may become the efferent for several. The number of openings into the excretory duct may thus be reduced, and the reduction may be carried still further by the portions of the wall of the duct between the openings being employed in the elongation of the collecting tubules; thus it may happen that eventually only one opening remains, and this may persist in the adult condition as the canaliculus aberrans Halleri; a preferable name would be the ductus collectivus paradidymidis.

In the male the organ of Giraldés (paradidymis) develops from the paragenitalis; it may persist throughout life and will then be found between the epididymis and the testis, slightly below the head of the epididymis. In the female the paradidymis becomes the paroophoron; the tubules of this occupy a remarkable position in older fetuses and children, caudal to the lateral half of the ovary (Rieländer 1904), somewhat medial to the free edge of the broad ligament. How they acquire this position has not yet been explained. In exceptional cases the primary excretory duct persists in the female and it then runs from the epoophoron medially between the tube and the ovary to the uterus; the paroophoron, if it retained its original position, should be found medial to the epoophoron and therefore cranial to the medial pole of the ovary. Waldeyer, indeed, believes that he has found remains of tubules in this position, but his observation has not been confirmed by any other author. Apparently the branches of the internal spermatic artery play a part in the displacement of the paroophoron, at least one finds the remains of it always internal to the

first branch of this artery. The paroophoron quickly degenerates in extra-uterine life; Rieländer (1904) was able to detect remains of it with certainty only up to the 5th year.

The further history of the primary excretory duct in both sexes will be described in the section on the urogenital union.

Development of the Metanephros.

INTRODUCTION.

The metanephros may be divided embryologically, and to a certain extent physiologically also, into two portions, the secretory or actual glandular portion and the efferent apparatus. We find therefore in the metanephros the same two parts as in the mesonephros, where there were on the one hand the mesonephric tubules and on the other the primary excretory duct; in the metanephros, however, the two parts enter into much more intimate relations. The efferent apparatus in the last analysis develops from the primary excretory duct, which, by an outgrowth, forms on either side a ureter. This again gives rise to a series of tubules, the primary collecting tubules and each of these to secondary ones, these again to tertiary ones and so on, until finally there is formed an efferent apparatus consisting of thousands on thousands of collecting tubules. We therefore speak of a collecting tubule system, of collecting tubules of the 1st to the 12th order and of terminal collecting tubules.

The excretory apparatus develops from the nephrogenic cord; just as this gave rise to mesonephric tubules in its anterior three-fourths, so in its posterior portion it gives rise to metanephric tubules. The mesonephric tubules open into the primary excretory ducts, the metanephric tubules unite with the terminal collecting tubules. In order to determine accurately the limits of the two portions of the metanephros formed from different sources, we may briefly trace the course of a fully formed metanephric tubule from the Malpighian corpuscle to the renal pelvis (Fig. 575), and in so doing we shall set forth the nomenclature to be employed in the following description. To the Malpighian corpuscle there succeeds the tubulus contortus (represented by stippling), which may be divided into two parts, a part that is actually convoluted and a pars recta; this latter passes over into the narrow descending limb of Henle's loop and this again into the ascending limb. The broader limb may be divided into a darker and a lighter part, the darker part is cross-hatched and the lighter is left white. The lighter part of the ascending limb bends over the upper (peripheral) surface of the Malpighian corpuscle (collecting piece) and passes over into the intermediate tubule. Between this and the

terminal collecting tubule there is no definite boundary. From the terminal collecting tubule we pass by the collecting tubules of the 1st to the 12th orders to the renal pelvis and the ureter. From the Bowman's capsule of the Malpighian corpuscle to the intermediate tubule the tubule system develops from the metanephrogenic tissue; the development of the collecting tubule system up to the terminal collecting tubule has already been stated to be from the primary excretory duct. We must therefore look for the point of

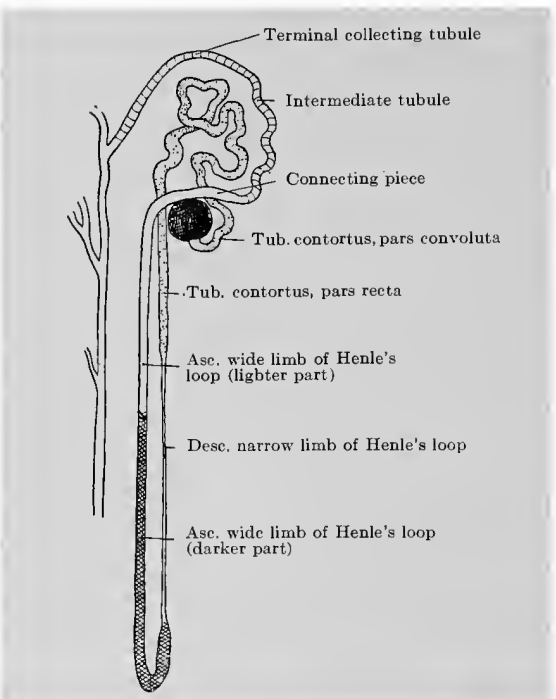


FIG. 575.—Diagram of a uriniferous tubule from the adult kidney, showing the relative positions of the various parts to one another and to the collecting tubule. The tubulus contortus consists of two portions, a pars convoluta, in which the Malpighian corpuscle lies excentrically, toward the renal pelvis, and a pars recta, which participates in the formation of the descending limb of Henle's loop. The summit of Henle's loop (in short loops), is formed by the wider ascending limb, which consists of a darker and a lighter portion; the lighter portion passes over into the connecting piece, which, crossing the vascular pole of the Malpigbian corpuscle, passes over into the intermediate tubule and this opens into the terminal collecting tubule.

union of the two systems at the junction of the terminal collecting and intermediate tubules. The two systems therefore grow towards each other from a considerable distance, and the length of the path which they must traverse before meeting forms a complication of the developmental process, and the more complicated such a process is, the greater is the possibility for disturbances of it. The cystic kidney, so familiar to the pathologist, is in many cases due to a failure to find one another on the part of the uriniferous tubules and the terminal collecting tubules.

Development of the Ureter, the Primitive Renal Pelvis, and the Collecting Tubule System.

It has been stated in the section on the pronephros (p. 772) that the primary excretory duct on its way to the cloaca runs beneath the ectoderm as far as the 28th primitive segment (5th lumbar), and that there it bends to a horizontal direction and reaches the lateral wall of the cloaca. At this sagittal bend the dorsal wall of the duct forms a hemispherical outgrowth, the anlage of the ureter (Fig. 576). Even before the appearance of the ureter bud the duct is enlarged at the bend and slightly thickened throughout its entire circumference. This enlargement affects only the limited region of the bend, the portion of the duct between it and the cloaca remaining narrow during the earlier

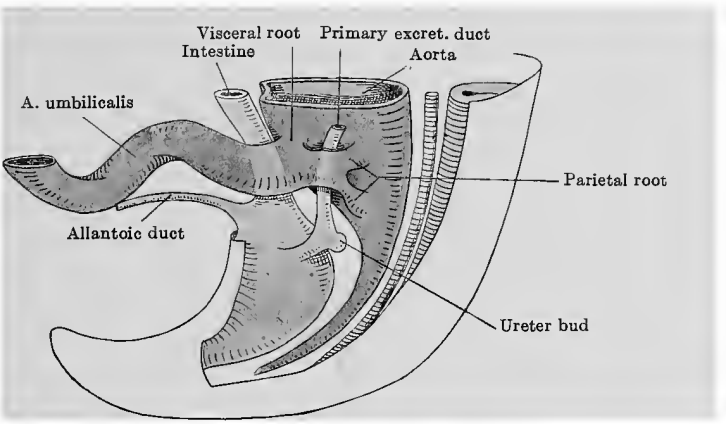


FIG. 576.—Reconstruction of the lower end of the body of a human embryo of 5.3 mm. greatest length, 4.6 mm. nape length, and with 36 pairs of primitive segments. (Embryo 1420, from the collection of Professor Keibel, Freiburg i. Br.) The primary excretory duct has come to lie between the visceral and the parietal roots of the a. umbilicalis. At the level of its opening into the bladder it bends at a right angle and at the bend it pushes out the ureter bud

stages of the development of the ureter. The hemispherical ureteric anlage is not exactly in the middle of the dorsal wall of the primary duct, but inclines more and more towards its medial surface, the degree of inclination varying in different embryos. When the anlage later elongates to form a canal it always lies at the middle of the dorsal surface of primary duct and, later on, even on its lateral surface, yet in an embryo of 7.8 mm. greatest length it still opened distinctly on the medial surface.

This original medial position of the ureteric bud is of importance from the comparative standpoint, since it persists throughout life in the marsupials, and in these forms is an obstacle to the union of the two Müllerian ducts (Keibel, 1896).

The time at which the ureteric anlage appears cannot be definitely determined, various observations giving different re-

sults, but it may with some assurance be placed between the stages of 4.5 mm. and 5.3 mm. total length.

An embryo of 4.25 mm. and with 28 pairs of primitive segments, another of 4.9 mm. vertex-breech length and with 33–35 pairs of segments and, finally, one of 5 mm. greatest length, showed no trace of an ureteric anlage, but, on the other hand, an embryo of 5.3 mm. greatest length, 4.6 mm. nape length, and with 36 pairs of segments, showed distinct ureter buds, that on the right having a length of 20 μ and that on the left, 30 μ. An embryo of 4.75 mm. greatest length already had a right ureteric anlage 80 μ in length, and a left one of 50 μ. The enlargement at the hend of the primary excretory duct had already appeared in an embryo of 4.25 mm. greatest length and with 28 pairs of primitive segments; in this embryo the primary excretory ducts had reached, but had not yet united with, the walls of the cloaca.

The short ureter bud grows at first almost altogether dorsally toward the vertebral column and the blood-vessels lying in front of it, but later (in embryos of 8.5–9.5 mm. greatest length) it forms a curve, which becomes gradually flatter with advancing age, and the ureter grows cranially. This ascent is due to actual growth of the ureter, since its tip presses against the surrounding structures. Thus the ureter gains the dorsal surface of the mesonephros lying in the retroperitoneum; although only loose mesenchyme is present in this situation, nevertheless it presents an obstacle to the forward growth of the ureter that can be overcome only so long as the anlage has but a single tip. As soon as the radial outgrowths of the collecting tubules begin, an obstacle will be presented sufficient to prevent any further forward growth of the anlage; consequently the definitive position of the renal pelvis in the fetus (2nd lumbar vertebra) has already been reached in embryos of 9.5 mm.–13 mm. greatest length . An examination of an embryo of 9.5 mm. greatest length (Fig. 578) will give an idea of how slight the forward growth of the ureter really is.

The two ureters do not grow with equal rapidity, but it is sometimes the right and sometimes the left that is in advance, and it cannot be said that either side is the more favorable.

The attainment of its definitive position by the tip of the ureter completes its forward growth, but not its increase in length, for in order to maintain this position during the growth of the body, it must elongate enormously, since it is in the region of the lumbar vertebræ that the body growth principally takes place. The growth in length is the result of growth along the entire length of the ureter, at least mitoses can be found from the opening into the primary excretory duct to the renal pelvis.

At the time when the renal pelvis has acquired its definitive position, neither that of the cranial nor that of the caudal pole of the kidney has been established; both are yet to be pushed cranially or caudally, as the case may be, by the outgrowing collecting

tubules. In this way the cranial pole of the kidney has reached the suprarenal body in an embryo of 18 mm. greatest length and is growing forward dorsal to that organ (Fig. 553). The space behind the suprarenal body and behind the urogenital fold affords ample room for it, and is occupied by a mesenchyme containing numerous large cavities (Fig. 553) and so loose that there can hardly be any question of a hindrance to the ascent of the kidney from the suprarenal bodies, nor can the liver have any effect in this respect; Fig. 553 shows that the latter does not come into contact with the metanephros. That it influences the postfetal development of the right kidney is not denied.

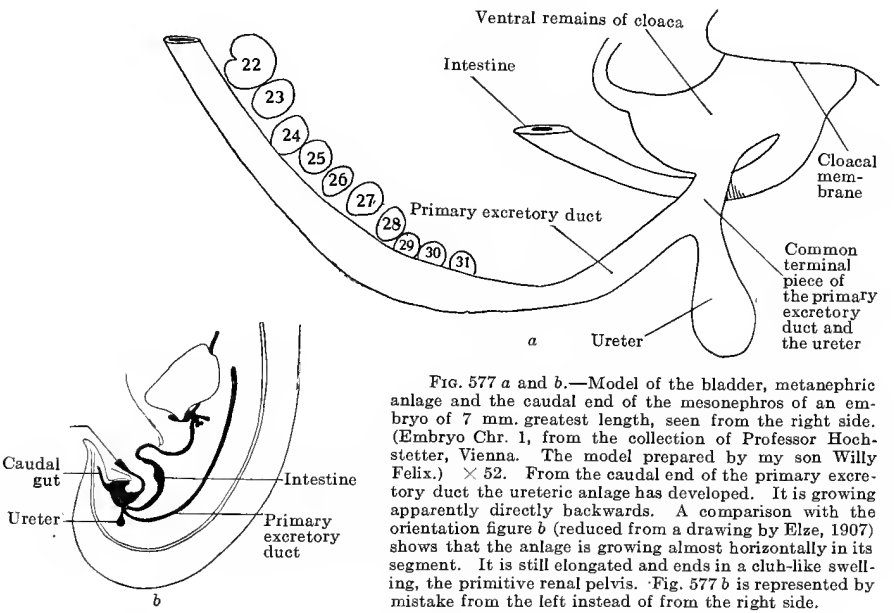


Fig. 577 *a* and *b*.—Model of the bladder, metanephric anlage and the caudal end of the mesonephros of an embryo of 7 mm. greatest length, seen from the right side. (Embryo Chr. 1, from the collection of Professor Hochstetter, Vienna. The model prepared by my son Willy Felix.) × 52. From the caudal end of the primary excretory duct the ureteric anlage has developed. It is growing apparently directly backwards. A comparison with the orientation figure *b* (reduced from a drawing by Elze, 1907) shows that the anlage is growing almost horizontally in its segment. It is still elongated and ends in a club-like swelling, the primitive renal pelvis. Fig. 577 *b* is represented by mistake from the left instead of from the right side.

The completely developed expansion of the ureter extends through the length of three or four vertebræ; from the upper border of the 12th thoracic to the lower border of the 4th lumbar is its maximal extent. The left kidney is already the higher as a rule in embryos of 22 mm. and onwards.

Even during the first stages of its growth the ureter changes its form; at first a simple hemisphere, it quickly develops a stalk and assumes the shape of a wedge, flattened from right to left (Fig. 577); later, the swollen end becomes marked off from the stalk, so that there is a differentiation of the primitive renal pelvis from the ureter in the narrower sense, the latter remaining narrow and having an almost circular transverse section. The primitive renal pelvis is broad in the cranio-caudal direction, narrow in the frontal one, and as seen in the model it has the form of a com-

pletely compressed funnel. It lies ventral to the v. cardinalis posterior. While the ureter is still in the period of outgrowth the primitive pelvis elongates in the cranio-caudal direction and thus acquires its poles, both of which begin on their own accounts to grow out in opposite directions and so begin the formation of the collecting tubules of the first order.

There are formed in all four collecting tubules of the first order, but their number may be increased to six or fall to three. The first two are formed by the elongation of the cranial and caudal poles of the primitive pelvis and I shall therefore name them the cranial and caudal pole tubules. Somewhat later hori-

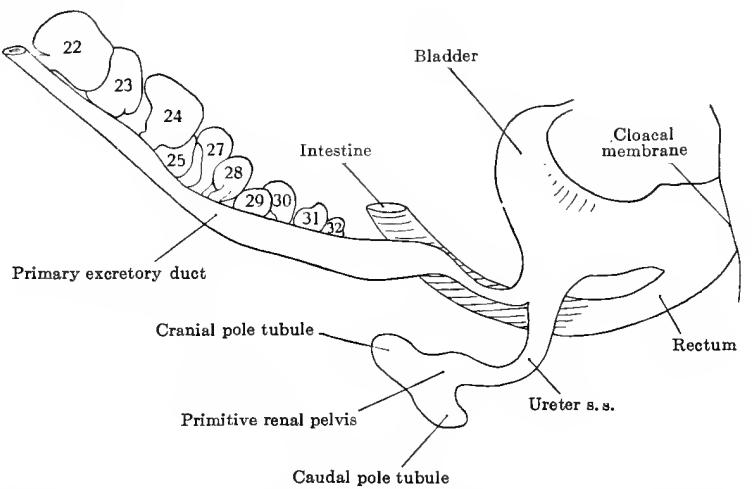


FIG. 578.—Model of the bladder, primary excretory duct, and ureter of an embryo of 9.5 mm. greatest length. (Embryo Ma. 3, from the collection of Professor Hochstetter, Vienna. Model prepared by my students J. Kläusler and Wydler.) The common portion by which the primary excretory duct and the ureter open into the bladder is enlarged and is more sharply differentiated from the wall of the bladder. The ureter has differentiated into the primitive renal pelvis and the ureter s. s. The two pole tubules are beginning to grow out from the primitive pelvis.

zontal tubules develop, corresponding to the middle of the renal pelvis, and since of these one is directed more ventrally and the other more dorsally, I shall term them the ventral and dorsal central tubules. These also appear as simple blind sacks and form with one another an angle of 45°. Rarely a doubling of the central tubules occurs and very rarely the formation of only a single one. The two pole tubules may show different relations to the v. cardinalis posterior; in an embryo of 12.5 mm. greatest length the pelvis and the caudal pole tubule were ventral to this vein, while the cranial pole tubule ran at first along its medial side and eventually reached its dorsal surface.

The four tubules of the first order never appear simultaneously; the pole tubules are always the first to form.

As soon as the primary collecting tubules have reached a certain length they become enlarged at their blind ends to the so-called ampullæ (Figs. 579–581); the primitive renal pelvis is after all merely a primary ampulla of the ureter. Each ampulla has from the beginning the shape of a sphere flattened towards the future surface of the kidney, and in its further growth it elongates parallel to that surface and forms, according to the number of collecting tubules of a lower order to which it gives rise, either a simple transverse tubule, or a three-sided or a four-sided prism (Fig. 579). From the two to four angles of the ampulla the secondary collecting tubules grow out parallel to the future surface of the kidney, and they also are at first simple blind sacks. When they have reached a certain length, they also develop ampullæ, from two to four sides of which tertiary collecting tubules are formed. And so the process goes on up to the formation of the terminal collecting tubules, and the ampullæ always persist, so that one can determine in young kidneys from their number, count-

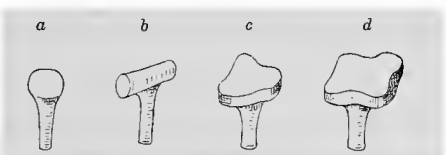


FIG. 579 *a*, *b*, *c*, and *d*.—Diagrams representing the form of the ampullæ of collecting tubules giving rise to 2, 3, or 4 tubules of a new generation.

ing from the pelvis to the surface of the kidney, the number of the budding centres, even although one may not see the branches that are given off. All the tubules, from those of the second and third order onwards, are so arranged that they run as well in the dorsal as in the ventral direction, two usually running ventrally and one dorsally. The formation of new collecting tubules ceases in the fifth fetal month, and the terminal collecting tubules are of the 11th to the 13th order; I may state, however, that these numbers are estimated, not observed. The primary collecting tubules are formed in two stages and in the formation of the secondaries still more occur. In Fig. 580 the caudal pole tubule has already developed three secondary tubules; the most medial of these is provided with three buds, representing tertiary tubules, the most lateral has developed an ampulla which shows preparations for the formation of the new generation, and only the middle one still preserves the form of a simple blind sack. Of the four central tubules only one is in the ampulla stage, and the cranial tubule does not yet show further development. Fig. 581 shows already a distinct ureteric tree; here there is only one central tubule, which is just forming an ampulla; the cranial and caudal pole tubules, on the other hand, are already far advanced in their

development. The individual tubules are labelled P or Z according as they arise from a pole or a central tubule and the figure gives the number of their generation. The cranial pole tubule (P_1) possesses three secondary tubules (P_2), the medial of which is the furthest developed, then the lateral one and least of all the middle one. If the medial secondary tubule be followed further, it will be seen to have developed tertiary tubules (P_3), and of these also

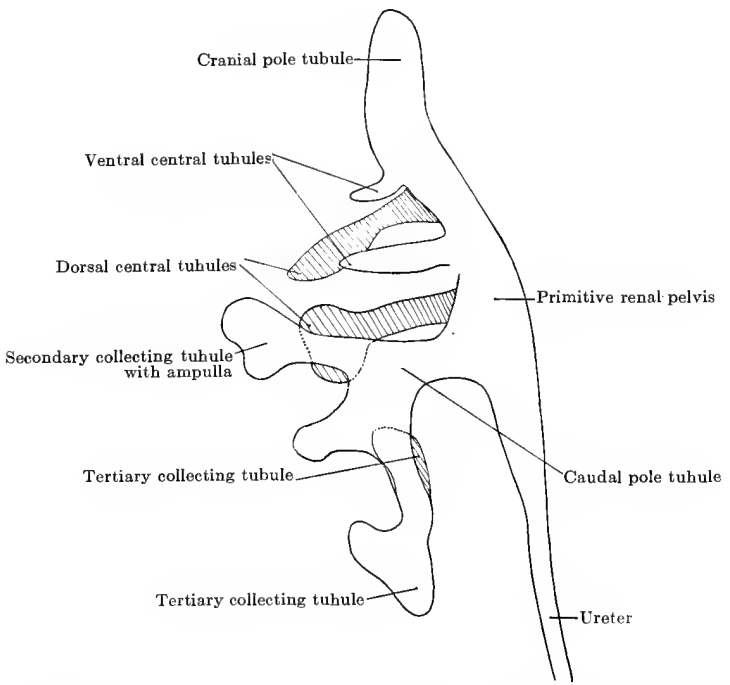


FIG. 580.—Ureteric tree of a human embryo of 12.5 mm. greatest length. Reconstruction of transverse sections. (Embryo Ma. 1, from the collection of Professor Hochstetter, Vienna.) ×100. From the primitive renal pelvis six primary collecting tubules have budded out, a cranial and a caudal pole tubule and four central tubules, two ventral and two dorsal. The development of the tubules proceeds in the caudo-cranial direction, the caudal pole tubule has already three secondary tubules, the caudal dorsal central tubule is just dividing, the cranial dorsal one is still pointed, the caudal ventral one is further developed than the cranial ventral one; the cranial pole tubule is still undivided. Of the three secondary tubules from the caudal pole tubule the caudal one has already developed three tertiaries, the cranial is just about to give rise to others, and the middle one has not yet formed an ampulla. Of the primary tubules the cranial pole tubule is a continuation of the ureter or renal pelvis, and the central and caudal pole tubules arise at right angles to the renal pelvis. The cranial secondary tubule is the prolongation of the primary caudal one, the caudal secondary has budded off at right angles. By these different relations of the primary and secondary tubules there is produced the first group-like expansion of the ureteric tree. The dorsal and ventral central tubules form an angle of 45° with one another.

the medial one is the furthest developed, for it has pushed out two quaternary buds and these have already their ampullæ so far developed that one may determine from their shape the number of tubules of the fifth order (P_5) that are to be formed; the lateral tertiary tubule has formed two quaternaries, only one of which is seen in the figure; the middle one (shaded in the figure) is still a simple blind sack. The lateral secondary collecting tubule has

only produced two tertiaries (P_3), and the most medial of these is again further developed. The same conditions obtain in the caudal tubules; in all cases the two outer of three tubules of the same generation are more developed than the middle one, and of the two outer ones the medial is more developed than the lateral. The only difference between the caudal and cranial pole tubules is that the former has already formed six generations, while the cranial one is just beginning to form a fifth. The constancy of these results, which are always obtained, leads to the following laws of development for the collecting tubules: 1. The two pole

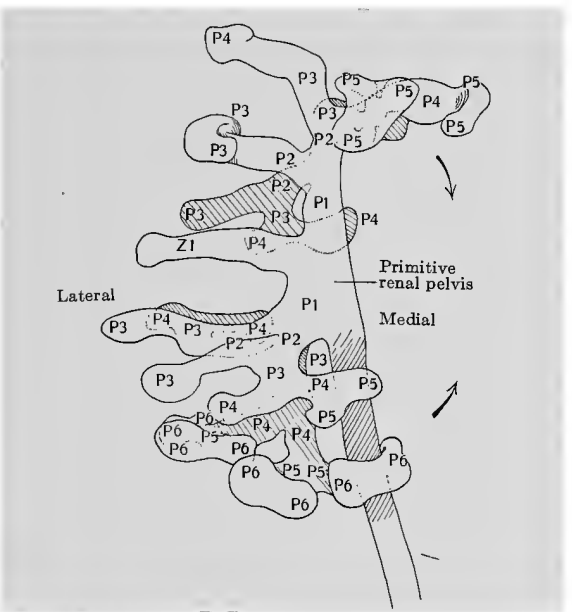


FIG. 581.—Model of the right ureteric tree of an embryo of 19.4 mm. vertex-breech length, seen from in front. (Embryo Ma. 2, from the collection of Professor Hochstetter, Vienna.) In this ureter there are two pole tubules and only one central tubule. The latter is greatly retarded in its development. The letters P and Z denote the pole and central tubules, the numbers accompanying the letters indicate the order of the tubules concerned. The caudal pole tubule is further developed than the cranial one, having produced tubules of the sixth order, while the cranial one is just producing those of the fifth order. If one traces out the various pole tubules one finds that the advancement of the formation of new tubules varies on the individual branches. If we regard the whole kidney as a half-moon, those branches of the pole tubules are most developed that are nearest the horns. This agrees with the general development; the ureteric tree curves medially around the renal pelvis in the direction of the two arrows. From the position of the tubules of the third and fourth orders one sees that already the growth in thickness in the dorso-ventral direction has begun.

tubules precede the central ones in development. 2. Each of the two pole tubules usually develops three secondary tubules and of these the most medial always precedes the other two in its development and only in its successive branchings is there a formation of four tubules in a generation, the maximum number; after it comes the lateral branch, which also shows a rich development of branches, and the middle branch, finally, remains behind the others. This process is repeated in the formation of each new generation

and must, therefore, lead to a differentiation between the various branches and twigs of the ureteric tree. Strong branches will be found to produce a rich crop of branches, moderate ones a less rich crop and, finally, weak ones only a poorer crop. The reason for this difference of development lies in the adaptation to abundant or scanty space. Since the tubules of the second order are at first developed horizontally, they must grow out from the various primary tubules toward each other. So long as there are only 4 primary tubules with in all 10–12 secondary ones, space is not yet limited, but as soon as the 30–36 tertiary tubules bud out and require room, the space becomes insufficient and this insufficiency will increase with the addition of each generation. Some relief from the insufficiency is afforded by the fact that the entire ureteric tree spreads in a fan-like manner, that is to say, it curves round the renal pelvis as a centre. (In Fig. 581 the direction of the curvature is shown by the arrows.) At first it surrounds only about two-fifths of an oval, but later more, until, finally, the form of the adult kidney is acquired. And now the various stem branches with their branch areas become arranged like the branches of an actual tree, those branches which lie to the outside having room for growth and those at the centre being prevented from growing, so that one finds the branching abundant at the periphery and scanty at the centre. Exactly so is it with the ureteric tree. Those collecting tubules which lie at the sides are favorably situated for development, these are the pole tubules; those situated in the centre are prevented from growing, these are the central tubules. Furthermore the tubules which occur in the centre of a branch area will not only form fewer branches of a younger order, owing to lack of room, but must also wait, before they can develop them, until by growth in length they have reached a region where there is sufficient room; these regions naturally can only occur towards the periphery. These tubules will, therefore, become longer than their favored fellows, but will develop much fewer budding centres, *i.e.*, ampullæ, in the same distance.

Since there are four primary collecting tubules, a special ureteric tree (primary tree, collecting tubule area of the 1st order) will be formed over each one; from what has been said the trees over the pole tubules will be large and those over the central tubules small; moreover the primary trees must influence each other and adapt themselves to the space available for the kidney, so that each tree in its entirety will have a conical shape, its tip being towards the kidney pelvis and its base towards the kidney surface. Within the limits of each of the primary trees the principal branches must adapt themselves to this conical shape, and, consequently, the tubules of the 5th, 6th, etc., orders, that were budded off at right

angles to the parent tubule, become more and more drawn out and thereby so crowded together that finally they run one close alongside the other as medullary rays radiating to the surface of the kidney. The tubules of the 2nd–4th order are not affected in this way, since they become enlarged and are later taken up into the kidney pelvis (see p. 859, the definitive renal pelvis and the reduction of the collecting tubules). The tubules of the 8th, and later those of the higher orders, retain partly their right-angled origin from the parent tubules, especially those that lie at the periphery of the branching of a tubule of the 3rd or 4th order (collecting tubule area of the 3rd or 4th order). By this right-angled origin the peripheral tubules of the 8th, etc., orders are pressed upon by the neighboring tubule areas of the 3rd or 4th order, so that they grow towards each other and force one another back; thereby the tubules of the 5th order (those of the third and fourth orders do not come into consideration on account of the reduction process mentioned above) hitherto lying massed together, are separated into groups, and each group with its branches forms a secondary tree. The stem of each secondary tree later becomes a secondary Malpighian pyramid. Within the individual secondary trees, at least within the pole pyramids, the formation of tertiary trees may occur.

The tubules of the first or second order, whose growth is prevented and which must grow far towards the surface before they can develop to a tree, must produce cones which, so far as their size is concerned, cannot be distinguished from secondary cones formed by tubules whose growth was not prevented. The branching of the central tubules presents enormous variability, for kidneys occur in which they almost keep pace with the pole tubules in the development of younger generations, naturally always remaining somewhat behind them, and, on the other hand, others occur, as for example that shown in Fig. 581, in which the central tubules have produced no second generation, while the pole tubules are always engaged in the formation of the fifth and sixth.

Detailed statements as to the branching of the individual primary collecting tubules will be possible only when numerous models have been prepared, since these alone allow of a certain count. Since such models are not yet available in sufficient numbers, I shall limit myself to a statement as to the highest number of orders of completed tubules that occurs in the branching of one of the primary tubules, without, however, wishing to imply that all the branches of this tubule give rise to as many orders. An embryo of 10 mm. greatest length had the two pole tubules in the process of formation, one of 11.5 mm. greatest length showed anlagen of the central tubules in addition to rather long pole tubules. One of 12.5 mm. greatest length possessed two pole tubules and four central tubules, the caudal pole tubule with tubules of the third order, the cranial one without branches, and the central ones in the act of forming ampullæ. An embryo of 13 mm. had two pole tubules and one central tubule, the caudal pole tubule had

quaternary and the cranial tertiary branches, while the central one had developed secondaries. An embryo of 17 mm. had two pole and two central tubules; both pole tubules had developed tubules of the 4th order and the central ones those of the third order. In an embryo of 18 mm. the pole tubules had tubules of the 4th order and the central tubules those of the 3rd order. In an embryo of 19.4 mm. greatest length the cranial pole tubule had tubules of the 5th order, the caudal pole tubule those of the sixth order, while the central tubules were branchless. In an embryo of 21 mm. the pole tubules possessed tubules of the 5th–6th order, the central tubules those of the 3rd order. In an embryo of 30 mm. greatest length (Hauch, 1903), collecting tubules of the 6th order were developed, in an embryo of 60 mm. head-foot length those of the 8th order, and in embryos of 65–70 mm. trunk length (Hauch, 1903), tubules of the 8th–11th orders.

The Metanephrogenic Tissue during the Development of the Collecting Tubules.

In the section on the parent tissue of the mesonephric tubules it was shown that during the segmentation a cord was cut off from the mesoderm between the primitive segments and the lateral plates, this cord representing the combined primitive segment stalks. This cord of nephrogenic tissue extends—this can be determined in all clearness in human embryos—only to the point where the primary excretory duct bends in to the cloaca, that is to say, to the 28th primitive segment (5th lumbar segment); throughout its entire length it lies on the medial side of the primary excretory duct. In an embryo of 5.3 mm. greatest length, 4.6 mm. nape length, and with 36 primitive segments it was interrupted in the region of the 26th and 27th primitive segments and thus separated into the long mesonephrogenic and the short metanephrogenic cord. It is only for didactic reasons that one speaks of a metanephrogenic cord in man, it is really only a small roundish heap of cells. The division of the nephrogenic cord coincides with the formation of the ureter bud; after the division the metanephrogenic mass of cells lies at first on the medial side of the ureter anlage—as is natural from its genesis,—but in an embryo of 7 mm. greatest length it has grown around it and covers it like a closely fitting cap (Fig. 582). On account of this intimate relation with the ureter the further development of the metanephrogenic tissue is closely associated with the fate of the ureter and its branchings. At first the metanephrogenic cap is forced dorsally by the growing ureter bud and thereby is carried out of the line of the mesonephrogenic cord, and it appears from now on as a special structure that has no longer any relation to the mesonephrogenic cord; nevertheless an embryo of 7 mm. greatest length still shows a denser strip of mesenchyme tissue extending from the cap toward the mesonephros, *i.e.*, cranially and ventrally, and ending at a distance from the last mesonephric tubule equal to about the diameter of two of these tubules. Then the metanephrogenic tissue accom-

panies the ureter in its ascent, always covering only the primitive renal pelvis. The cap, which it forms, is at first rather thin (Fig. 582), and it becomes still more so on the enlargement of the ureter bud to form the primitive renal pelvis; when now the budding out of the primary and secondary collecting tubules occurs the cap becomes so stretched that in an embryo of 9.5 mm. greatest length it becomes torn into as many pieces as there are collecting tubules of the first order present. Each of these four to six pieces

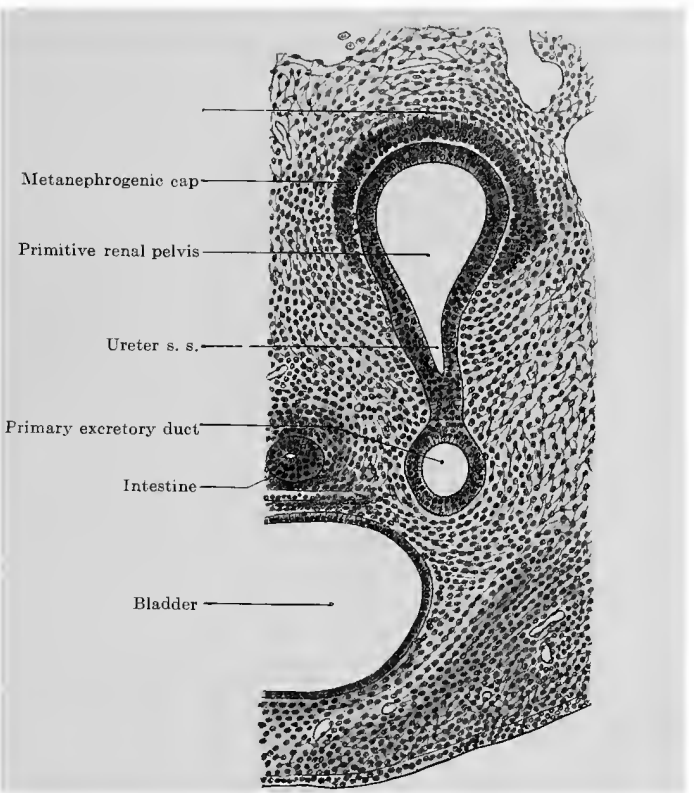


FIG. 582.—From a transverse section through a human embryo of the fifth week, after Schreiner (1902). ×120. The section cuts the primary excretory duct transversely; the ureter, which has already separated into the primary renal pelvis and the ureter s. s., is cut lengthwise. The metanephrogenic tissue lies like a cap around the primitive renal pelvis.

of the cap shows, however, rapid cell multiplication and again grows completely over the ureteric tree to which it belongs. The various ureteric trees are accordingly covered by metanephrogenic tissue not only on their surfaces but also on the sides turned towards neighboring trees; each ureteric tree and its metanephrogenic cap may be regarded as a unit and I shall term it a *primary Malpighian pyramid.* The various pyramids are closely pressed together and so their metanephrogenic caps are apparently united again to form a single investment over the entire kidney. The

various pyramids will naturally reproduce the form of the corresponding ureteric trees, and consequently possess a base directed towards the surface of the kidney and correspondingly curved, and an apex directed towards the renal pelvis. The more the ureteric trees develop and curve medially around the renal pelvis (Fig. 581), the more pronounced the lateral convex and the median concave surfaces of the kidney become, and, finally, the bases of all the pyramids (Fig. 583) form a shell with an opening directed medially for the entrance of the ureter; the renal pelvis and the ureteric tree accordingly lie in the space within the shell. The

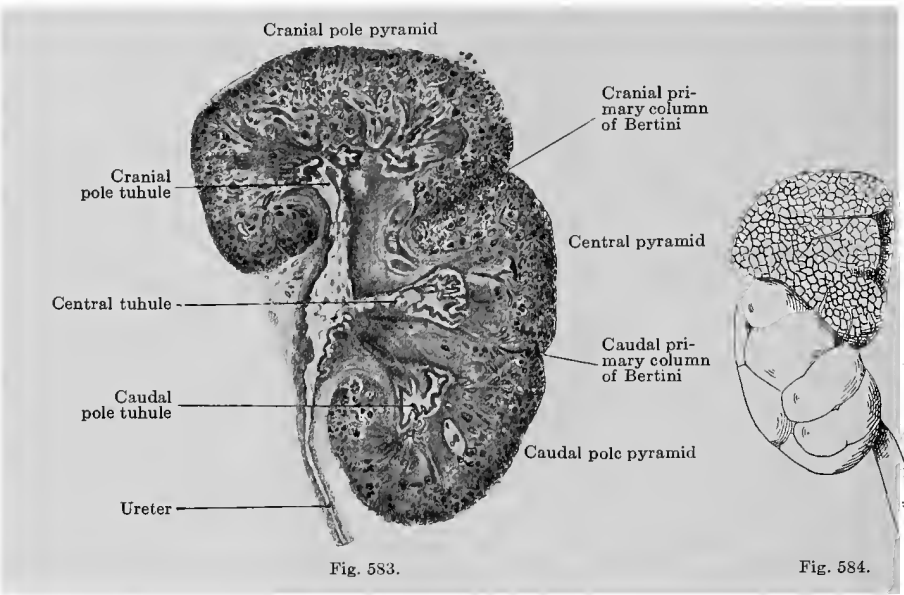


Fig. 583.—Frontal section of the kidney of a human fetus of 160 mm., 3¾ months old, after Hauch (1903). ×8. Three primary collecting tuhule systems are to be seen in the figure, those of the two pole tuhules and those of the central one. Around each of these systems is situated a cap of metanephrogenic tissue, each system with its cap forming a renal pyramid. Where the two pole pyramids abut upon the central one the neogenic zones of the two metanephrogenic caps come together to form a column of Bertini. This extends to the renal pelvis.

Fig. 584.—Right kidney of a five months' human fetus seen from the ventral surface. × about 3½. The relatively large suprarenal body is seated upon the kidney, whose surface is distinctly lohed.

space within the metanephrogenic shell unoccupied by the various ureteric trees may be termed the primitive renal sinus. The lines along which the metanephrogenic tissue passes down from the surface between the various pyramids are marked by grooves, which limit the area occupied by each pyramid, so that one may speak of a lobation of the kidney surface (Figs. 583 and 584). Beneath each groove and extending as far as the renal sinus small quantities of connective tissue lie between the metanephrogenic investments of adjacent pyramids, and these strips of connective tissue, together with the two accompanying layers of metanephrogenic tissue, form what are termed the columns of Bertini (Fig.

583). There will accordingly be at first four (three to six) pyramids—the two pole pyramids corresponding to the two pole tubules, and two (one to four) central pyramids, corresponding to the two (one to four) central tubules—and three columns of Bertini, a cranial one between the cranial pole pyramid and a central pyramid, one between the two central pyramids, and a caudal one between a central and the caudal pole pyramid (Fig. 583).

The columns of Bertini appear one after the other in the 9th to the 10th week, and are distinctly formed in the 12th week.

It has already been pointed out that each ureteric tree eventually divides into several parts and the various metanephrogenic

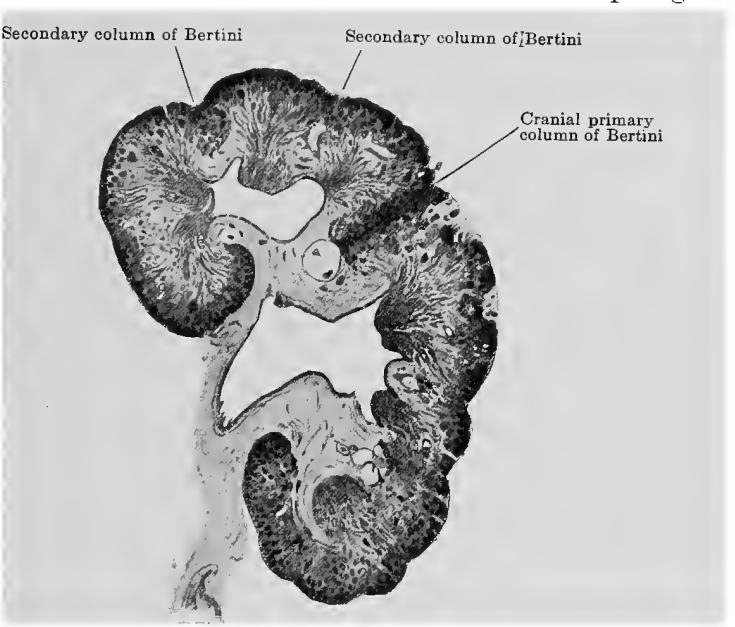


Fig. 585.—Frontal section through the kidney of a human fetus of the nineteenth week, 175 mm. in length, after Hauch (1903). The primary pyramids have been divided into secondary pyramids by the appearance of secondary columns of Bertini.

caps take part in these divisions. They divide into smaller portions and each of these tertiary pieces covers and encloses a minor ureteric tree just as completely as the secondary caps enclosed the undivided trees; thus secondary pyramids are formed within the primary ones (Fig. 585). Exactly as the metanephrogenic tissue sinks in between the primary pyramids to form a septum, so it also separates the secondary pyramids, and one may, therefore, speak of secondary columns of Bertini (Fig. 585). A finer lobation of the surface corresponds to these secondary pyramids, since each principal lobe is divided into subordinate lobes. Fig. 584 shows the extensive lobation of the surface of the kidney of a five months' fetus. The lobation of the kidney persists until

birth and disappears in the early years, although under some circumstances it continues to persist throughout life.

According to the number of collecting tubules of the second order that bud from those of the first order, from two to four secondary pyramids occur in the interior of each primary one. Within the secondary pyramids, at least within the pole pyramids, other tertiary pyramids, three in number, develop and with them of course the columns of Bertini that separate them. All the tertiary pyramids reach the surface, but the columns separating them penetrate inwards only a short distance. The tertiary pyramids therefore produce a distinct, finer lobation of the surface, but an incomplete separation of the pyramids. The variability that is to be seen in the lobation of the kidney surface—rich or scanty lobation—depends on the variable development of the secondary and tertiary pyramids.

The Development of the Uriniferous Tubules from the Metanephrogenic Tissue.

The metanephrogenic tissue is divided by the progressive outgrowth of the collecting tubule systems into separate portions, corresponding not only to the primary, secondary and tertiary Malpighian pyramids, but also, within all these pyramids, into as many separate masses as there are peripheral collecting tubules. The primary collecting tubules raise the metanephrogenic tissue as a whole away from the renal pelvis. As soon as the tubules of the second order grow out the mantle is split into four pieces, and again the tubules of the second order raise their quarters of the mantle as a whole and push it towards the periphery; when the tubules of the third order form, each mantle quarter is again divided and the portions are again raised up and again separated by the new generation. As a result around the end of each collecting tubule, which, in the stage under consideration, represents the temporary terminal tube, there is a cap of metanephrogenic tissue. When the new collecting tubules grow out the caps are again torn into from two to four parts according to the number of the tubules. This stage is shown in Fig. 586, in which we see a tubule that has grown to the periphery of the kidney and is there forming two new tubules, both of which carry in front of their pointed blind ends the metanephrogenic tissue. This surrounds only a small portion of the young tubule on the side nearest the surface of the kidney, but on the side towards the pelvis it surrounds it throughout its entire length, as far as its origin from the older tubule. In the angle between the old and the young tube the metanephrogenic tissue condenses to form a compressed, spherical cell-mass, whose constituent cells are arranged around a point situated somewhat

excentrically in the interior of the mass. A *single* cell mass is formed for each young tubule, so that around the older tubules usually three cell-masses are arranged. The concentric arrangement of the cells very soon renders the cell-mass independent of the rest of the metanephrogenic tissue and a sphere of cells, a metanephric sphere (Fig. 587, on the right side above), is formed. This is now completely isolated and has no connection whatever with any of the neighboring structures; its position in the angle between the older and younger tubule is typical and is repeated with absolute regularity in all anlagen, whether they are the first or last to form. A lumen situated excentrically appears (Fig. 586) and converts the sphere into a metanephric vesicle, whose walls vary in thickness at different parts owing to the

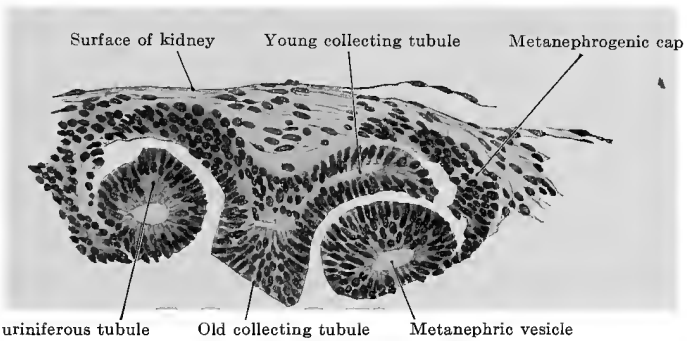


FIG. 586.—Portion of a section through the kidney of a human embryo of 30 mm. vertex-breech length. (From the collection of Professor Stoerck, Vienna; II, 3, 4.) ×300. An older collecting tubule with two young ones budding out from it is shown. Each young tubule carries in front of it a cap of metanephrogenic tissue, which surrounded the end of the older tubule, and tears it. In the angles between the older and each younger tubule there develops a metanephric vesicle from the metanephrogenic tissue. The left vesicle shows a slight growth directed towards the periphery, the anlage of a uriniferous tubule.

excentricity of the lumen. The wall towards the surface of the kidney—for brevity I shall term it the peripheral wall—is the thickest and from it the entire uriniferous tubule, with the exception of Bowman's capsule, is formed; the wall towards the renal pelvis—I shall term it the central wall—is thinner and it forms Bowman's capsule; the side towards the older collecting tubule I shall call medial and that directed away from the tubule will be spoken of as lateral. The two metanephric vesicles of Fig. 586 are unequally developed. In the left one the upper wall is drawn out to a knob, which is the anlage of the actual uriniferous tubule, and rising perpendicularly upwards it unites with the younger collecting tubule (Fig. 587, upper tubule). By this the uriniferous tubule becomes connected with the collecting tubule system, its lumen is continuous with that of the collecting tubule. The upper tubule of Fig. 587 shows a further progress in development; on its lateral side a slight groove has formed, which is so placed that it separates the former vesicle from the newly-formed uriniferous

tubule; it separates, in fact, the anlage of Bowman's capsule from the uriniferous tubule, and its central wall represents the anlage of the parietal layer of the capsule. In order that an idea of the actual appearance of the anlage of the uriniferous tubule may be obtained the left side of Fig. 588 should be studied; the anlage appears as a sack attached to the young collecting tubule. At the moment when the union of the uriniferous and collecting tubules is established, the former begins to bend, and the various new changes may be followed in Fig. 589 *a* and *b*. First it will be observed that the groove that separates the uriniferous tubule

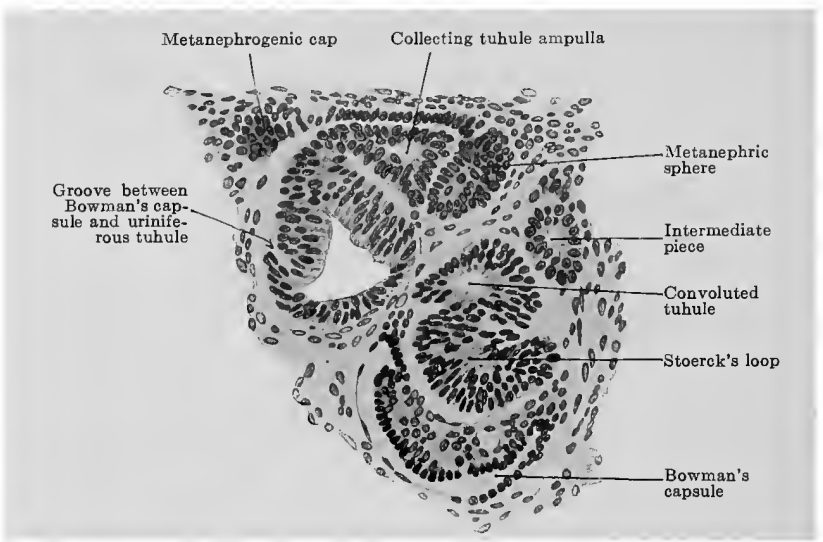


FIG. 587.—Portion of a section through the kidney of a human emhryo of 30 mm. vertex-hreech length. (From the collection of Profeesor Stoerck, Vienna; II. 1, 7.) × 300. The anlagen of two uriniferous tuhules are cut by the section. They are in different stages of development, belong to different generations, and therefore lie at different levels. The left upper anlage has developed a uriniferous tuhule that has connected with the collecting tuhule. It has a cluh-shaped form, the handle of the club being repreeented by the uriniferous tuhule and its head hy the anlage of Bowman's capsule. A slight groove begins to grow in on the left side, marking the limits hetween the tuhule and the capsule. The lower right tubule is just ahout to form Stoerck's loop. Its parts are not continuous in the section. Below is Bowman's capsule, etill shell-shaped; then comes a portion curved like the letter S, and from the upper limb of the S a convoluted tuhule arises; the middle limb is the parent tissue for Stoerck's loop and the lower one becomes the connecting piece. Ahove the S is the intermediate piece cut transversely.

and Bowman's capsule and was only indicated in Fig. 587, has now extended to the medial side of the vesicle, and the delimitation of Bowman's capsule is thus completed; its parietal and visceral epithelia are formed, the parietal being simple and already completely flattened, the visceral being two-layered and cubical; the shape of the capsule is that of a bowl with a doubled wall (Fig. 588, right tubule; Fig. 590). Since the groove penetrates to the medial side of the capsule, the passage of the lumen of the latter into that of the tubule is forced entirely to the medial side, whereas formerly it lay at the middle. From this point the tubule makes a triple bend into the shape of an S, the lower limb of the S extend-

ing from Bowman's capsule to the single asterisk (Fig. 589 *b*), the middle piece from this to the double asterisk, and the upper limb from this to the ampulla of the collecting tubule. In these three limbs all parts of the future uriniferous tubules are laid down and we are now in position to determine the portion of the

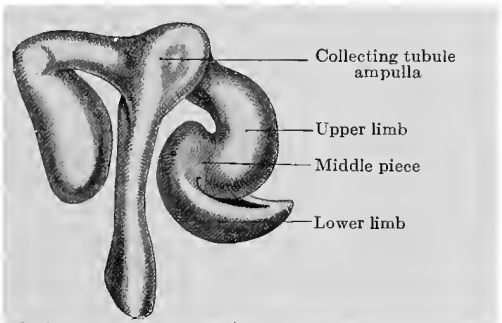


FIG. 588.—Model of two developing uriniferous tubules of a human kidney, after Stoerck (1904). ×400. The left tubule hangs from its collecting tubule as a plump sack; the right has differentiated somewhat further; the S-shaped uriniferous tubule is followed by the shell-shaped Bowman's capsule.

tubule from which, for example, the tubulus contortus or Henle's loop arises. This we are able to do because *one* topographic relation persists unchanged throughout all the future modifications, namely, the situation of the apex of the middle limb in the con-

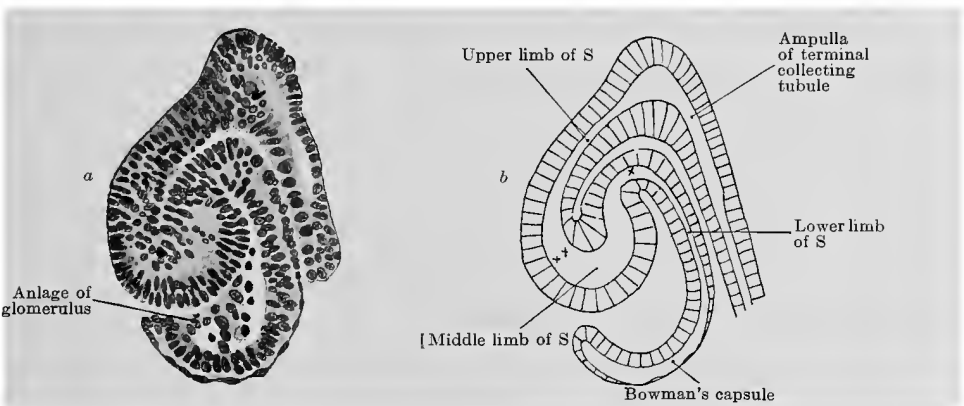


FIG. 589 *a* and *b*.—Anlage of a uriniferous tubule of a human embryo of 130 mm. (Embryo 217, from the collection of Professor Stoerck, Vienna; I, 6, 7.) The anlage of the tubule has bent to an S-shape, the limbs of the S being shown in the diagrammatic complementary figure 589 *b*. It is important that the tip of the middle limb comes to lie exactly in the concavity of the shell-shaped Bowman's capsule. It is held in this position later on by the capillaries developed from the vas efferens. The glomerulus is in the very earliest stages of development, but already contains blood-corpuscles.

cavity of Bowman's capsule; it is retained in this position by the capillary network arising from the vas efferens. In Fig. 591 the future parts are indicated by different kinds of shading; the apex of the middle limb is left unshaded and it becomes the connecting piece of the adult uriniferous tubule (compare Fig. 575

in which the connecting piece is also unshaded). The left part of the middle limb and the upper limb become the intermediate piece and both are simply shaded in Figs. 591 and 575. The right part of the middle limb (cross-hatched) becomes Stoerck's or Henle's loop, and the lower limb (stippled) becomes the tubulus contortus.

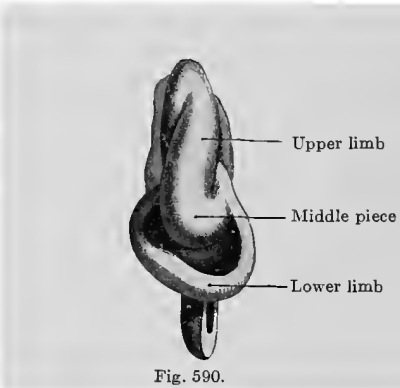


Fig. 590.

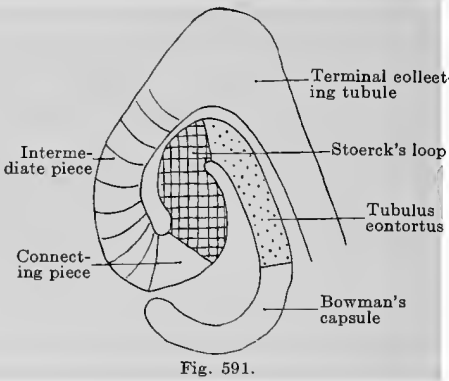


Fig. 591.

FIG. 590.—Model of a developing uriniferous tubule, after Stoerck (1904). ×400. One sees very well in this view the shell-like form of Bowman's capsule and the tip of the middle limb of the S-shaped tubule situated in its concavity.

FIG. 591.—Diagram of a young uriniferous tubule in which the various portions are distinguished according to their fate. The mode of distinguishing them (stippling, hatching, etc.) is the same as in Fig. 575 *a*. One sees that from the apex of the middle limb of the S-shaped tubule, which is retained in position by the vessels passing from the vas efferens, the future connecting piece is formed.

The formation of the S-shaped bends and the transformation of the various limbs into definite portions of the adult tubule are almost perfectly regular and are repeated with wearying regularity in thousands of tubules.

The formation of the S immediately succeeds the coiling of the

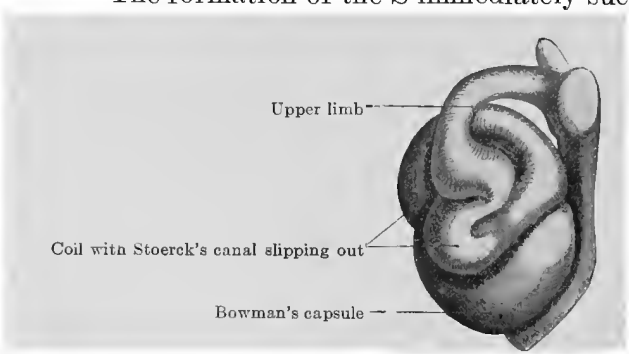


FIG. 592.—Model of a developing uriniferous tubule from a human kidney, after Stoerck (1904). ×400. One sees Stoerck's loop slipping out of the coil. Only the horizontal limb of the leader points to this.

tubule and the lower limb and the medial part of the middle limb of the S take part in the coiling, that is to say, those parts from which the tubulus contortus and Henle's loop are formed.

As soon as the coil is formed the loop slips out of it; since this is formed immediately above the Malpighian capsule (Fig.

591), it must grow out in an arch around this (Fig. 593, left tubule); then having a free path towards the renal pelvis it grows to a notable length (Fig. 593, right tubule, Fig. 594 *a*). During the formation of this loop, which is *not* Henle's loop—I must insist on this here to avoid errors—a histological differentiation of the epithelium occurs in the tubule, affecting only all parts of the tubulus contortus. The size of its lumen increases, its cells become large and the cell boundaries vanish completely in some

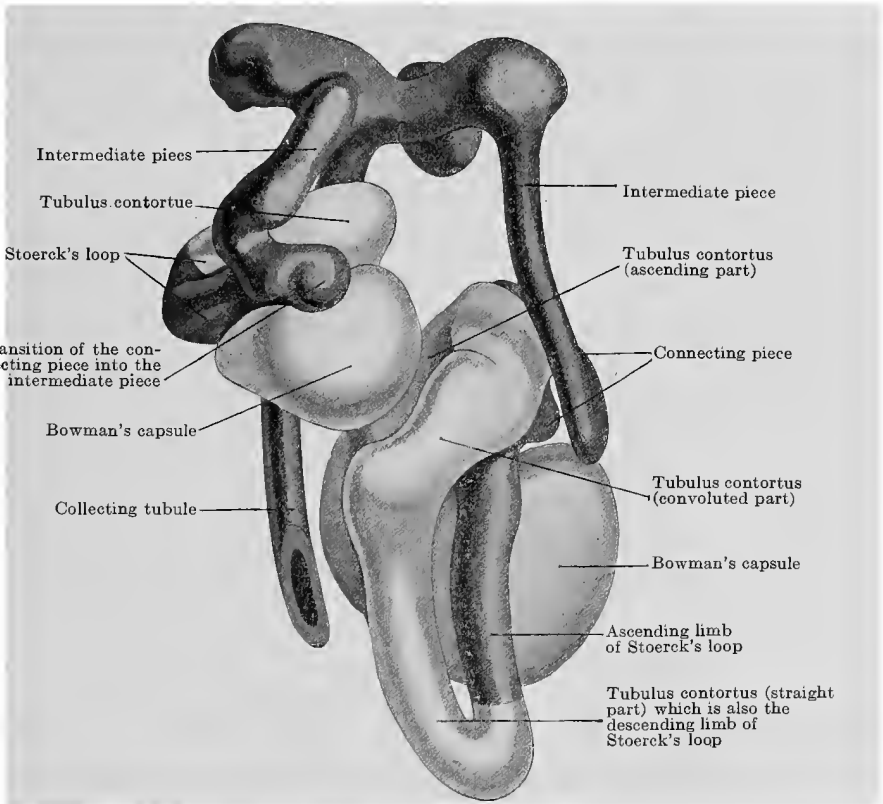


FIG. 593.—Model of two developing uriniferous tubules from a human kidney, after Stoerck (1904). ×400. The left tubule is just forming Stoerck's loop. One sees its long intermediate piece, that is beginning to coil somewhat. The right tubule already possesses a rather long Stoerck's loop.

places, while in others they become at least indistinct. The nuclei are round and pale and have retreated to the basal portions of the cells, the protoplasm is distinctly granular. All this leads to a very great thickening of the tubulus contortus, while the remaining portions remain thin as before. The tubulus contortus, stippled in Fig. 594 *b*, now forms an ascending, a horizontal and a descending portion. The ascending and horizontal portions later become the convoluted portion (compare Fig. 594 *b* and Fig. 595), the descending one forms the straight part and, at this stage of devel-

opment, almost the whole descending limb of the loop. The histological differentiation and the twisting of the tubulus contortus occur simultaneously in all the tubules of the same generation. Fig. 595 shows two adjacent tubules belonging to different collecting tubule systems and yet showing an almost ridiculous likeness even in the finest details. They do not lie in the same plane, so that in one the Malpighian capsule does not appear in the section.

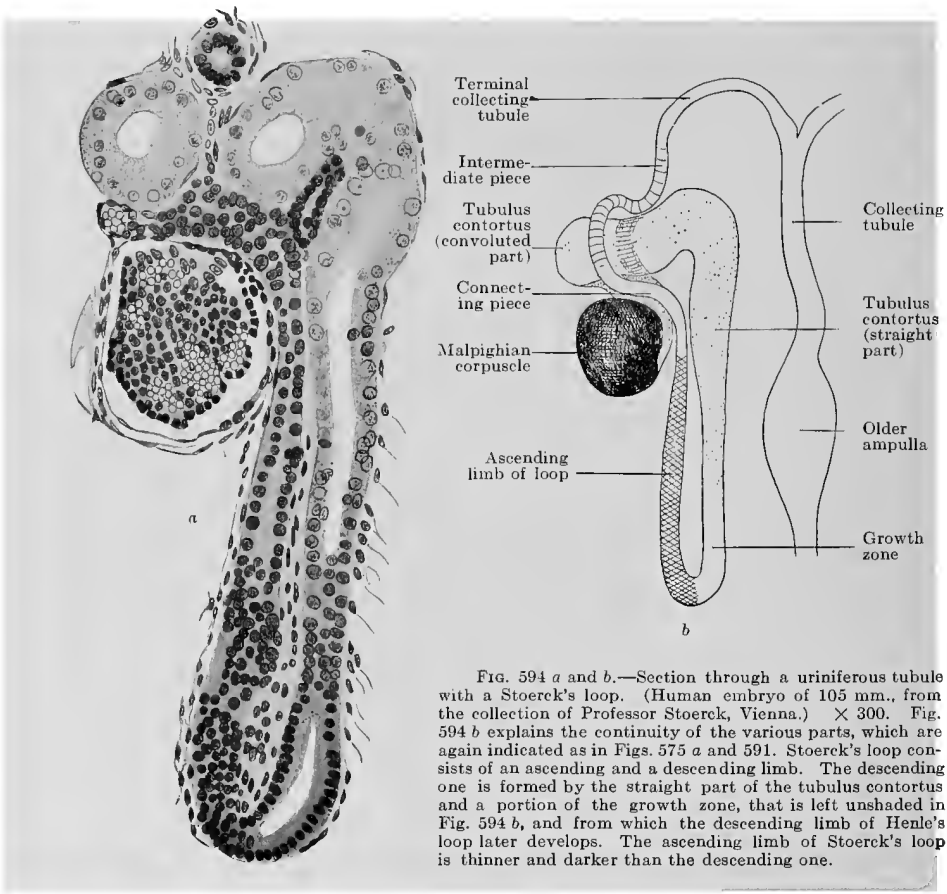


FIG. 594 *a* and *b*.—Section through a uriniferous tubule with a Stoerck's loop. (Human embryo of 105 mm., from the collection of Professor Stoerck, Vienna.) × 300. Fig. 594 *b* explains the continuity of the various parts, which are again indicated as in Figs. 575 *a* and 591. Stoerck's loop consists of an ascending and a descending limb. The descending one is formed by the straight part of the tubulus contortus and a portion of the growth zone, that is left unshaded in Fig. 594 *b*, and from which the descending limb of Henle's loop later develops. The ascending limb of Stoerck's loop is thinner and darker than the descending one.

After birth a considerable increase in length and thickness occurs in the tubulus contortus, and the increase in length leads to an enlargement of the coil. The enlargement may best be shown by determining the number of Malpighian corpuscles in equal areas taken from kidneys of different ages; the more the coils increase in mass the more must the corpuscles be separated from one another. According to the observations of Külz (1899) the cortical region of the kidney of a new-born child contains five times as many glomeruli as a corresponding area of the cortex of an adult kidney. As regards the increase in thickness Külz (1899) deter-

mined that the tubuli contorti of the adult were twice as great in diameter as those of embryos. The increase in length and thickness of the tubuli contorti is also shown by the formation of the so-called cortex corticis; the young corpuscles during the growth of the kidney lie close beneath the kidney capsule. This position they retain even after birth up to about the tenth day. At that time the tubuli contorti of the last generation are beginning to

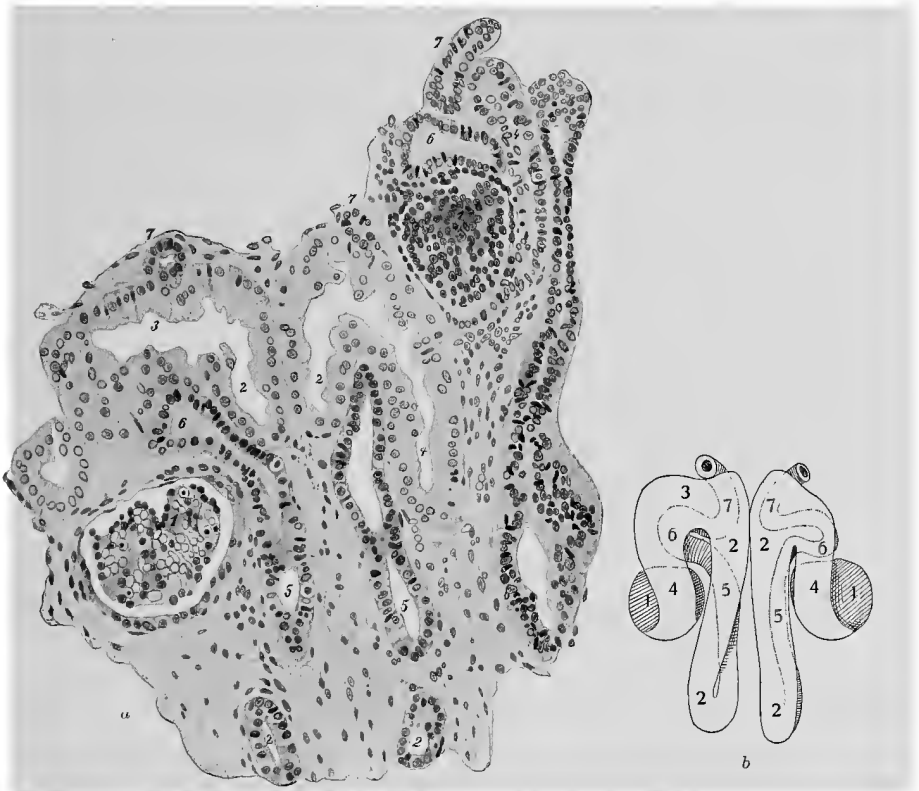


FIG. 595 *a* and *b*.—Section through three developing uriniferous tubules of a human embryo of 45 mm. nape length, from the collection of Professor Stoerck, Vienna; 4. 8. On the left side the section cuts two tubules of the same stage of development, but belonging to different collecting tubules; on the right side is a younger stage of development. The section shows the markedly intimate arrangement of the various portions of the tubules that all the tubules of this kidney present. 1, Bowman's capsule; 2, descending limb of Stoerck's loop; 3, horizontal part of the tubulus contortus; 4, ascending part of the tubulus contortus; 5, ascending limb of Stoerck's loop; 6, connecting piece; 7, intermediate piece.

grow out and thus form the outermost layer of the renal cortex, which no longer contains Malpighian corpuscles.

As a result of the extensive thickening of the tubulus contortus part and the formation of at least the proximal half of the descending limb of the loop by the straight part of the tubulus contortus, and further as a result of the absence of change in all the remaining portions of the tubule, that is to say, their retention of their original slenderness, the form of the loop seems to be almost the reverse of what it is in the adult (Fig. 594 *a*, *b* and Fig. 575); the

descending limb is the thick one and the ascending limb the thin one. We have therefore to do with a specific embryonic form of the loop and in order that we may have a definite term for it, I shall name it *Stoerck's loop* after its illustrious discoverer (Stoerck 1904). This loop is accordingly formed of the disproportionately long pars recta of the tubulus contortus and the actual Henle's loop, which, however, is not yet histologically differentiated in its two limbs. It is difficult to determine exactly how Stoerck's loop becomes converted into Henle's loop. I shall first call attention to the distal portion of the descending limb of Stoerck's loop shown in Fig. 594 *a*. It possesses a peculiar epithelium that corresponds

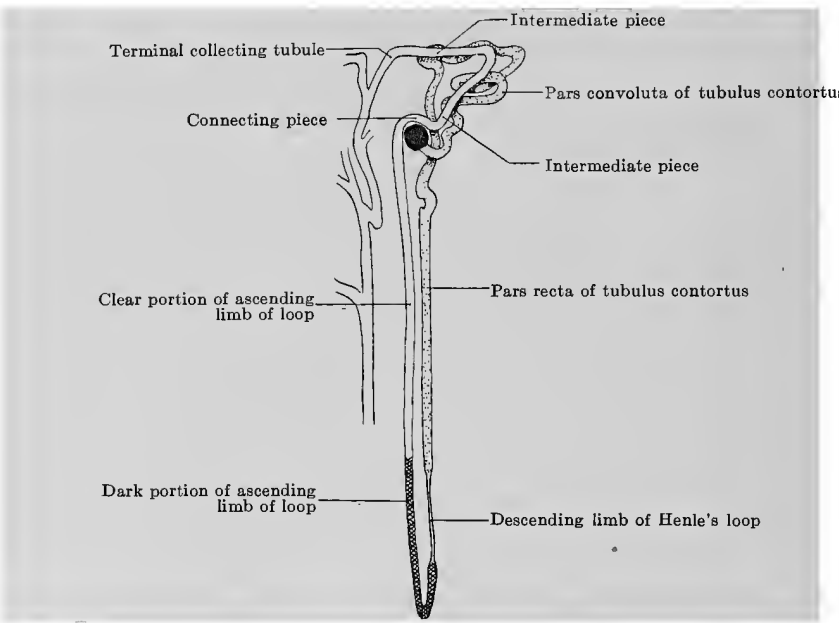


FIG. 596.—Short loop of Henle from an adult kidney, resembling exactly a Stoerck's loop as far as the broad ascending limb. Somewhat simplified from Peter (1909.)

neither with that of the pars recta of the tubulus contortus nor with that of the ascending limb of the loop; in older stages of development it is frequently in active division and in such cases resembles a proliferation zone. I am, accordingly, inclined, although I cannot make a positive assertion, to regard this region as the embryonic homologue of the descending limb of Henle's loop. I am strengthened in this view by the results obtained from the study of adult Henle's loops of different lengths. Peter (1909) has shown that the length of a Henle loop is chiefly dependent upon the development in length of the descending limb; in the formation of a long loop both limbs of course take part, the descending one, however, in the proportion of 1:15 and the ascending one only in the proportion of 1:2; in the short loops the apex is formed by the

ascending limb, in the long ones by the descending. Accordingly it is the greater or less growth of the thin descending limb that determines the length of the entire loop. In the short loops of the adult kidney that scarcely reach the outer zone of the medulla we have actual embryonic, that is to say Stoerck's, loops (Fig. 596), the descending limb remaining unaltered and the straight portion of the tubulus contortus forming the main portion of the loop; the actual descending limb corresponds to the proliferation zone of Stoerck's loop, while the ascending limb has become thicker and has differentiated into its dark and clear portions.

The differentiation of Henle's loops into a thin descending and a thick ascending limb takes place, according to Toldt (1874), in the fourth fetal month; in the 5th month the long loops reach the papillæ in embryos of 140–175 mm. (Hauch, 1903).

At its first development Stoerck's loop is always so placed that the descending limb is the farther away from the collecting tubule and therefore has a medial course, while the ascending limb is nearer to the collecting tubule and therefore runs laterally. In the stage shown in Fig. 595 *b* one limb becomes twisted around the other in a half spiral, so that each of the limbs in its course is sometimes lateral and sometimes medial. The loop may remain in this position throughout life, but in most cases there is a complete twisting and Peter (1909) is correct in naming the descending limb of the adult kidney the lateral one and the ascending the medial.

The intermediate piece also suffers a change in position. From its mode of development (see Fig. 591) it must be the most lateral of all the portions of the tubule. Originally all portions lie in one plane, but as soon as the tubulus contortus begins to coil and the loop slips out from it, a twisting of the tubule occurs, in such a way that a plane perpendicular to the surface of the kidney and passing through the intermediate piece is perpendicular to a similar plane passing through the tubulus contortus and Stoerck's loop; I have endeavored to show this in Fig. 594 *b*. As a result of this twisting the intermediate piece obtains room for further development and, when it begins to coil, some of its turns may come to lie medial to the Malpighian corpuscle. The growth in length of the tubulus contortus naturally determines also a corresponding growth of the intermediate piece. I shall consider further on the peculiar growth of the intermediate piece produced by the transference of the opening of a collecting tubule belonging to a lower order to one of a higher order.

The further development of the Malpighian corpuscle consists in its original shell-like form (Fig. 590 and 589 *a*) becoming gradually spherical. Three stages of the development are represented in Fig. 597. In *a* the corpuscle has its simple shell-like form, in

b there appears at the point where the tubulus contortus becomes continuous with Bowman's capsule—at the point marked by a cross in the figure—an evagination which tends to diminish the wide opening into the capsule, and in *c* this evagination has increased in size and at the same time the lateral wall of the shell has grown toward it, so that the wide entrance into the shell-like concavity has become converted into a narrow opening, the vascular pole; through it the vas afferens and the vas efferens find ingress or egress. These modifications of Bowman's capsule cause also a

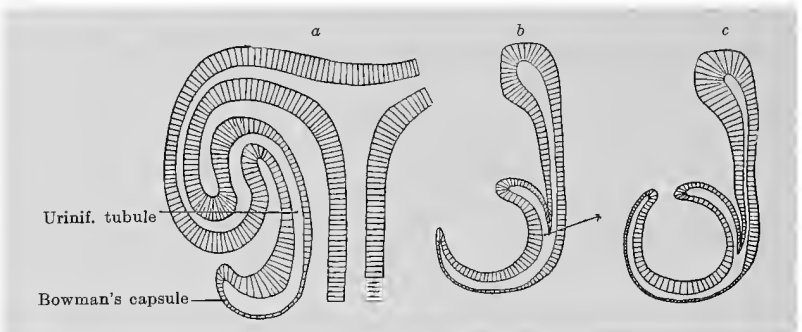


FIG. 597 *a*, *b*, and *c*.—Three diagrams showing the development of a Malpighian corpuscle.

displacement of its connection with the tubulus contortus, its urinary pole, and always in such a way that it comes to lie at the lower surface of the capsule; thus the vascular and urinary poles of the Malpighian corpuscles come to lie opposite each other. It must be possible under certain conditions, that the two poles wander in the opposite direction, at least Peter (1909) has seen, though only rarely, the urinary pole at the peripheral surface of the capsule; the curving of the renculi may well bring it about that individual tubules acquire unusual relations and so form departures from the usual plan. The table by Külz will best show

Table showing the Mid-size of the Peripheral and Central Glomeruli in Mikra.
(After Külz, 1899.)

	0 days.	9 days.	2.5 months.	5 months.	7 months.	9.5 months.	1¼ year.	2¼ years.	12 years.	16 years.	18 years.	23 years.
Mid-size of the peripheral glomeruli	99	97	107	110	121	129	132	157	192	231	213	237
Mid-size of the central glomeruli	138	135	139	138	140	139	143	158	192	229	219	237

the growth of the Malpighian corpuscles; since the various uriniferous tubules are arranged in layers one over the other, the more central ones are the younger and the more peripheral the older, and

therefore in the table representatives from an older are combined with those from a younger group.

From this table it will be seen that at birth the central Malpighian corpuscles are almost 1½ times as large as the peripheral ones, and that in the course of the second year of life this inequality disappears by the peripheral corpuscles growing while the central ones remain unchanged. When, at the close of the second year, all the corpuscles have attained the same size, the central ones begin to grow as rapidly as the peripheral and all the corpuscles double their diameter. Finally, it will be seen that the growth of the corpuscles lasts until the period of puberty.

The first metanephric spheres were found in embryos between 13 and 19.4 mm. greatest length. The first S-shaped tubules were shown by an embryo of 19 mm. greatest length, the first anlage of a Malpighian corpuscle—*i. e.,* of Bowman's capsule and a glomerulus—was seen in an embryo of 19.4 mm. greatest length, while in an embryo of 28 mm. greatest length the first completely developed Malpighian corpuscles were found. The first histological differentiation—*i. e.,* the appearance of secretory epithelium in the tubulus contortus—was shown by an embryo of 24 mm. greatest length, the first Stoerck's loops grow out in embryos of from 24–30 mm. greatest length. In connection with these data it is to be stated that each advance in the further development of the urinary tubules first occurs in the pole pyramids.

The metanephrogenic tissue, the parent tissue of the uriniferous tubules, lies, as has been stated above, as a cortical layer around the collecting tubules that have grown farthest towards the surface of the kidney. Around the ampullæ of each collecting tubule the anlagen of the first uriniferous tubules group themselves in correspondence with the outgrowing collecting tubules of a new order, which are usually in threes; all the uriniferous tubule anlagen, therefore, lie close together and the tubules connect with neighboring terminal collecting tubules. In this way there is formed around the entire kidneys a first investment of uriniferous tubules, which is always only one anlage deep. As soon as the tubules have separated from their parent tissue, the metanephrogenic tissue regenerates from what remains and is now raised up from the layer of uriniferous tubules and carried towards the periphery by the outgrowing collecting tubules of the new generation. Here the various pieces of metanephrogenic tissue again unite to form a continuous sheet, which may be called the *neogenic zone.* It invests the new terminal collecting tubules and the layer of uriniferous tubules. Now the same process is repeated, the neogenic zone again forms over the whole surface of the ureteric tree a second layer of uriniferous tubules—we may speak of them as a second generation—and it itself again regenerates to a new neogenic layer, which is again displaced peripherally by the outgrowing collecting tubules of a new order. Since the process

always repeats itself in the same way there is formed by apposition to the outer surface a new cortical layer, and the oldest generation of uriniferous tubules is that nearest the renal pelvis, while the youngest lies immediately below the neogenic zone. As soon as the various Malpighian pyramids of the first and second orders are formed, each pyramid becomes invested by its own cortex of uriniferous tubules and its own neogenic layer. The various layers of tubules are, naturally, in different degrees of development; in a stage with three generations of them, those of the first generation are in the stage with the loops of Stoerck, those of the second generation are in the S-shaped stage with the anlagen of Bowman's capsules, and the third generation is in the cell-sphere or cell-vesicle stage.

The formation of the uriniferous tubules is not completed at the close of the fetal period, but extends into the first days of extra-uterine life. It is only after the tenth day that the formation of new tubules ceases, the neogenic zone exhausts itself in the formation of the last generation and vanishes. From its remains a portion of the connective tissue of the surface of the cortex is formed.

The first generation of uriniferous tubules is to be found in embryos of from 13–20 mm., the second follows in embryos of 20–30 mm., the third in those of from 30 mm. trunk length to 75 mm. head-foot length; the fourth generation appears in embryos of from 60–150 mm., the 5th–8th generations in embryos of 120–150 mm. head-foot length; seven months' embryos possess 8–10 layers of uriniferous tubules (Toldt, 1874; Hauch, 1903); new-born children 10–14 generations, and, finally, children up to the third month 14–18 generations. The formation of the various generations takes place rather evenly within any one pyramid.

If one investigates the stage of development of the ureteric tree at the time when the first uriniferous tubules unite with the collecting tubules one finds that the union takes place in the 5th or 6th generation of collecting tubules. When one remembers that all the tubules of the adult kidney open into the collecting tubules of the medullary rays and that these belong to the ultimate or periultimate generation, the question at once arises: Do the openings of the uriniferous tubules become displaced or is there a degeneration of uriniferous tubules that have formed a fully developed union with the collecting tubule system. I may first answer the second question, since the reply is very simply "No"! I have seen degenerating uriniferous tubules in none of the embryos studied. There remains then only the question as to the displacement of the openings. For the first three generations I can admit the method of displacement, for one finds that in these the newly outgrowing collecting tubules carry with them not only the metanephrogenic tissue but also the openings of earlier uriniferous

tubules. In this way the uriniferous tubules of at least the three first generations all come to open into collecting tubules of the same order. This carrying outward of the opening of a uriniferous tubule can only, of course, occur along with a corresponding elongation of the intermediate piece. That the same processes occur in younger generations is possible, but it can only be determined in spite of unusual technical difficulties. One must therefore consider other possibilities, since one finds older uriniferous tubules that are not connected with any collecting tubule. Whoever has prepared models of metanephric tubules knows how difficult it is to prepare satisfactory ones, and on this account I am not yet quite certain that these blindly ending tubules really occur, and I would not mention them had I not made two other observations, namely, in the first place, an interruption of the lumen of a uriniferous tubule that, judging from its form in other respects, must have been functional some time previously, and, secondly, the occurrence of blindly ending diverticula at the transition of the tubulus contortus into the descending limb of Stoerck's loop. Both these observations suggest the possibility of a uriniferous tubule separating from its collecting tubule and opening into one of a higher order.

The Definitive Renal Pelvis and the Reduction of the Collecting Tubules.

We have termed the wedge-shaped enlargement of the ureteric anlage the primitive renal pelvis and from it the four collecting tubules of the first order arise. If we compare this primitive pelvis with the pelvis of the adult kidney we perceive, first, an enormous difference in size and, second, a difference in the number of collecting tubules opening into it; the pelvis of the adult kidney may receive over one hundred collecting tubules. This difference might be produced by a belated—but in that case enormous—new formation of collecting tubules of the first order, just as a belated appearance of them occurs in the two central tubules, but all investigations along this line have yielded negative results. We must therefore seek for another source of the increase and this is found in the so-called reduction of the oldest or older collecting tubules. These first of all become enlarged and are then taken up into the wall of the growing renal pelvis so completely that no traces of them remain. The reduction begins regularly at the centre and proceeds towards the periphery; if it begins in such a manner that the collecting tubules of the first order are taken up into the pelvis, then the so-called undivided form of kidney is produced, one with a single papilla and a single large calyx, represented by the entire pelvis, a form which is possessed by the rabbit, for example; if the reduction takes place in such a way that the collecting tubules of the first and second order are retained, and the

tertiaries and quaternaries are taken up into the enlarged secondaries, then the so-called divided form of kidney results, that is to say, the kidney possesses several papillæ, each surrounded by a special calyx. The tubules of the second order then form the calices minores, those of the third order the calices majores. The human kidney develops according to the divided type, the reduction begins in embryos of 22 mm. greatest length by an enlargement of the primitive pelvis and of all the collecting tubules of the first four orders. Their epithelium becomes at the same time very clear and, in spite of the enlargement, high cylindrical. Then in embryos of 60 mm. head length the tubules of the third and fourth order are taken up into those of the second order, whereby the tubules of the fifth order open directly into those of the second.

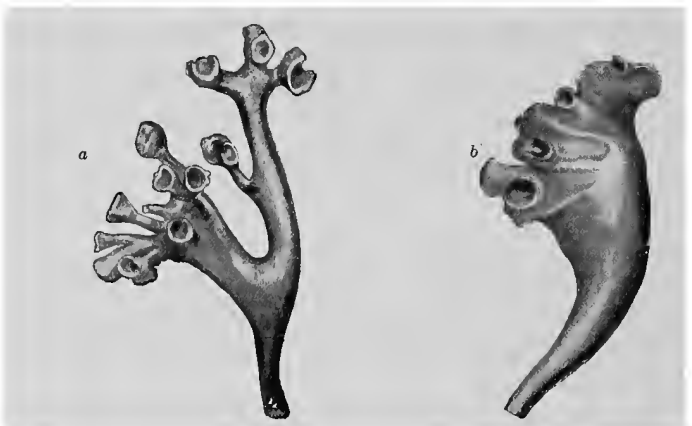


FIG. 598 *a* and *b*.—Casts of the renal pelves of two adult men to show the two types resulting from the simple and the double reduction. *a*, Ramified pelvis (simple reduction). *b*, Ampullary pelvis (double reduction). After Hauch (1903). Reduced to ⅔.

Into a tubule of the second order there open three tubules of the third order, nine of the fourth order and twenty-seven of the fifth order, and since 20–30 ductus papillares open upon a pyramid of the adult kidney, the complete reduction of the tubules of the third and fourth orders suffices to bring about the condition found in the adult organ.

The human kidney presents an additional point of interest in that in many kidneys a second process of reduction follows the first. The second reduction again starts from the renal pelvis and leads to the absorption into the pelvis of the tubules of the first order completely and those of the second order almost completely. The remains of those of the second order are then seated upon a plump pelvis as short stumpy calices. The simple and the double reduction produce, of course, quite different pelvic forms, the extremes of which I shall term, following Legueu (1891), the ramified and the ampullary renal pelvis (Fig. 598 *a* and *b*). The

form of the ramified pelvis will evidently depend upon the different amounts of growth in length of the tubules of the first and second orders.

It has been mentioned above that secondary and even tertiary columns of Bertini may develop. The secondary columns may be followed to the angle of division of the collecting tubules of the third order, the tertiary ones to the angle of division of the tubules of the correspondingly higher order. If now the tubules of the third and fourth orders are taken up into the renal pelvis, the secondary and tertiary columns will reach the sinus of the kidney and thus secondarily acquire the character that the primary columns possess from the beginning. In this way an increased number of pyramids will occur, their tips, the papillæ, projecting into the renal pelvis. An increase in the number of renal papillæ is, accordingly, closely associated with the reduction process. From one primary pyramid as many as nine secondary and tertiary ones may be formed. The definitive number of papillæ is probably already acquired by embryos of the third and fourth months (Toldt 1874); but it must not be assumed from this statement that the reduction process comes to an end at this time; it becomes retarded, but may be in action even at birth and still draw many a ductus papillaris into the pelvis.

The Formation of Cortex and Medulla—Medullary Rays—Papillæ.

The development of the cortex begins with the formation of the first generation of uriniferous tubules, and its increase in thickness depends in the first place upon the new formation of additional tubules and, in the second place, on the growth of those already present. The first generation of tubules produces at once a sharp delimitation of cortex and medulla. The latter is whatever lies in the primitive sinus and this space at first contains only a small number of collecting tubules but an abundance of mesenchyme tissue, whose meshes early arrange themselves transversely to the collecting tubules. One may, however, properly speak of a beginning of the medulla formation only after the formation of the definitive renal pelvis. The collecting tubules of the fifth order become grouped together into bundles and with this the actual development of the medulla begins, the collecting tubules of the fifth to the ninth or eleventh orders taking part in its structure. The medulla increases both in length and thickness, in thickness by an increase in the diameter of the individual collecting tubules and by the down-growth of the loops of Henle, in length by the growth in length of the individual collecting tubules.

A series of measurements has shown that a great difference in the relation of cortex to medulla may exist in different individuals

and in the right and left sides of the same individual. Furthermore in the period between the fifth fetal month and the adult condition a series of growth periods may be detected. During fetal development it is principally the medulla that grows; its transverse diameter enlarges on an average by 100 per cent., and at the same time the thickness of the cortex increases only by 20–25 per cent. The stronger growth of the medulla depends on the one hand on a change in the direction of the collecting tubules; with the growth of the ureteric tree the collecting tubules, which pass off at an angle of 90°, parallel to the surface, gradually become straightened out, only the terminal tubules for the time being retaining the original angle. In the second place the growth is associated with the development of the tips of the pyramids, the papillæ. After birth a cessation of growth of the medulla occurs and this lasts until the seventh year; its development remains as it was or progresses but slightly, but in the same period the diameter of the cortex increases regularly. After the seventh year both portions again grow equally and double their diameter by the time of puberty.

Medullary rays properly exist from the time when at least three generations of uriniferous tubules are arranged in layers one above the other. At least the cortex at this time becomes quite regularly divided into separate portions by collecting tubules. These embryonic medullary rays are, however, produced by the collecting tubules of the sixth or seventh order, while those of the adult kidney are formed by those of the tenth to the twelfth orders, the tubules of the sixth or seventh order coming to lie in the medulla proper. Embryonically, therefore, we must distinguish between the temporary and the persistent medullary rays. The first indications of the persistent rays are found in embryos of the 14th–16th week and with a length of 9–13 cm. (Hauch 1903). Each medullary ray contains at this time 3–4 tubules, which are collecting tubules of the 10th (or 11th or 12th) order that have budded out in threes or fours from the collecting tubules of the 9th (or 10th or 11th) order. To these medullary ray collecting tubules 9–16 terminal collecting tubules belong. The medullary ray tubules must behave differently than the tubules of older orders in respect to their mode of outgrowth. I draw this conclusion from the accurate results of Peter (1909). The collecting tubules of the 5th–9th or 11th order (1) give rise to new collecting tubules only at their blind ends, (2) they carry up with them the uriniferous tubules that open into them or (3) their uriniferous tubules break their connection with them and make a new union with a collecting tubule of a higher order, so that, finally, all the uriniferous tubules open into the collecting tubules of the medullary rays. If the medullary ray tubules behaved like those of

the medulla they would show openings of uriniferous tubules only at their ends, but according to Peter this is not the case; they receive terminal collecting tubules in groups along their entire length. How this arrangement is developed is at present unknown; since, theoretically, different ways of reaching this end may be imagined, it would be idle to discuss them so long as we possess nothing that points in favor of one rather than another of the possible ways.

The papillæ arise by the growth in length of collecting tubules belonging principally to the middle orders (Schweigger-Seidel 1865, Riedel 1874). If one compares a longitudinal section of a pyramid of a seven months' embryo with a similar section from the adult kidney one sees that in the embryo the branchings of the collecting tubules occur uniformly throughout the entire length of the pyramid, even into the medullary rays, while in the adult kidneys they take place in two groups; one group lies near the tip of the papilla, the other near the medullary ray. Both groups are connected by a longer undivided stretch of the collecting tubules. This grouping has correctly led Schweigger-Seidel to the conclusion that the growth in length occurs principally in the tubules of the middle order. It produces at all events a pushing of the tips of the pyramids towards the calyx. The first papillæ occur in the human embryo in the third month; at first they are small, and consequently appear to be very long, but the more the loops of Henle grow downwards, the thicker and more distinct they become. That primary papillæ may become divided, during the reduction, into secondary papillæ by secondary columns of Bertini is evident from what was said above concerning the reduction.

The Relation between the Right and Left Kidney.

According to the observations of Hauch (1903), there is a great correspondence of form in the kidneys of either side during development. The right and the left kidney are always at the same stage of development, the number of lobes is approximately the same and the form of the renal pelvis is very similar. Later on, however, the pressure of the liver causes a lesser development of the right kidney.

Change of Position of the Kidney.

The migration of the kidney cranialwards has already been described in connection with the development of the ureter (p. 834), and it was there shown how slight the actual migration really is. A second change of position of parts of the kidney occurs with the development of the collecting tubule system; the cranial and caudal poles are displaced in different directions around the renal

pelvis as a fixed point. In the first half of fetal life the craniocaudal diameter of the kidney corresponds approximately to the first three lumbar vertebræ, while in the second half of the same period the cranial pole rises to the level of the eleventh rib and the caudal one descends to the upper border of the fifth lumbar vertebra. In this growth in length, which depends on the broadening of the collecting tubule system, the left kidney is almost always in advance of the right, the difference in favor of the left kidney being the greater, the older the embryo examined. After birth a change in the position of the kidney also occurs. In children less than one year old Alglave (1910) in half the cases examined (16 out of 32) found the caudal pole of the kidney in the iliac fossa, in children between 1 and 2 years it was at the iliac crest in a minority of the cases (3 out of 9), and in those of more than 2 years it was always above the iliac crest. This change is a passive one, depending neither upon a more extensive growth in length of the kidney nor upon a displacement of it, but upon a stronger growth of the posterior abdominal wall and especially of the lumbar region. By this growth the space between the 12th rib and the iliac crest is greatly increased and room is thus made for the reception of the kidney. The growth in length and thickness of the kidney also takes place in periods; both diameters increase greatly during intra-uterine life, from 18–50 mm. in length and from 13–25 mm. in thickness; during the first year of life only a slight increase takes place, from 56–70 mm. in length and from 25–37 mm. in thickness. From the second year until the final completion of growth, especially during the period of puberty, there is again a rapid increase, from 73 to 120 mm. in length and from 36 to 60 mm. in thickness (Külz 1899).

During the growth of the kidney it also undergoes a rotation around its long axis. The renal pelvis and its first collecting tubules are at first almost dorsal to the ureter (embryo of 12.5 mm. greatest length), but in embryos of 19.5 mm. greatest length the ureteric tree is practically lateral to the ureter. In older embryos there is again a rotation in the opposite direction, probably a result of the development of the vertebral centra, so that the lateral border assumes the position it possesses in the adult, about midway between a frontal and a sagittal position.

The Vessels of the Kidney.

In the chapter on the mesonephric arteries it was stated that one or several mesonephric arteries may become the persistent metanephric arteries. The mesonephric arteries are transverse branches that arise from the aorta and run to the mesonephric

fold, and their terminal branches form a network, the rete arteriosum urogenitale, lying in the angle between the reproductive gland, the mesonephros and the metanephros. In 18 mm. embryos this network comes into connection with vessels which actually enter the renal sinus. In this way the vessels of the metanephros become connected with the mesonephric arteries and through them with the aorta. The network makes it possible for any of the mesonephric arteries, all of which participate in its formation, to become a metanephric artery; hence the variability in the origin of the latter, their frequent dissimilarity on the right and left sides and, finally, their frequent multiplicity. The mesonephric artery that is destined to become the metanephric artery is distinguished from its fellows by its greater diameter, and this difference can usually be made out in embryos of 21 mm. greatest length. The branches of the a. renalis in the renal pelvis are so arranged that they come to lie both on the dorsal and the ventral side of the pelvis. The first a. arciformis was shown by an embryo of 30 mm. greatest length.

The development of the v. renalis is so intimately connected with that of the v. cava inferior, that it is preferably considered with it.

The Capsule of the Kidney.

The actual capsule of the metanephros is first distinctly seen in embryos of 70 mm. head-foot length. Embryonic connective tissue, indeed, surrounds from the beginning the growing ureter and the outgrowing collecting tubules together with the metanephrogenic tissue, and is, moreover, arranged concentrically; it cannot, however, be separated from the surrounding connective tissue, and until this can be done one cannot speak of a kidney capsule as an independent tissue.

The Later Development of the Ureter.

The course of the ureter is always retroperitoneal and always close to the mesentery of the mesonephros. Within the abdominal cavity it is almost straight, but on entering the true pelvis it curves so as to be convex caudally and, again ascending to the dorsal side of the bladder, it passes to its opening. Since the ureter is developed from the primary excretory duct, it will at first open into this; how it acquires its opening into the bladder may preferably be considered along with the development of that organ. Up to embryos of 125 mm. the ureter is almost straight and has a uniform calibre from beginning to end. Later three narrowed and two fusiformly dilated parts appear (Seitz 1908). The first narrow part is at the origin of the ureter from the renal pelvis, the second is where the ureter crosses the linea innominata

between the false and the true pelvis, and the third is immediately above its entrance into the bladder. The first enlarged part, the lumbar one, is between the first and second stenosis and therefore in the abdominal portion of the ureter; the second, the pelvic one, is between the second and third stenosis and is therefore in the pelvic portion. The lumbar enlargement appears in embryos of 125 mm. and simultaneously with it the upper and middle narrow parts; the pelvic enlargement develops only later (in embryos of 320 mm.); it is inconstant, and may be completely wanting after birth (Gérard 1908). The lumbar enlargement is never lacking in embryos more than 125 mm. in length and in children may taper off very gradually above and below, in which case the upper and middle narrow parts are only indistinctly present, and the middle one may even be wanting; if the enlargement is sharply defined the upper and middle narrow parts are distinct, the cranial one being the more sharply pronounced (Gérard 1908). The lower narrowing is produced by the formation of the bladder wall and is, therefore, always present.

In the region of the lumbar enlargement the ureter is spirally twisted and this twisting may be the ultimate cause of the formation of the narrowed and enlarged parts.

The epithelium of the ureter is at first single-layered, sometimes more cubical, sometimes more cylindrical; the narrower the lumen, the higher the epithelium. In embryos of from 40–50 mm. greatest length the epithelium is two-layered at various places, especially in the region of the genital cord. In those places where a single-layered epithelium obtains in these embryos, isolated cubical cells occur among the cylindrical ones and so produce the appearance of gland-like depressions. In embryos of 55 mm. head-foot length the epithelium is three-layered in the upper half of the ureter and five-layered in the lower half, and in embryos of 70 mm. head-foot length, the transitional epithelium begins to form, although in an embryo of 90 mm. head-foot length no syncytium is yet to be discovered at its surface. It is remarkable that a sort of cuticular membrane extends from the bladder over the free surface of the ureteric epithelium; in embryos of 50 mm. head-foot length it is present only in the lower portion of the ureter, but later it extends further and further upwards, reaches the renal pelvis and finally also the collecting tubules, with the exception of those that are at the time terminal.

The mesenchyme forms delicate concentric rings, about twenty in number, around the ureter. Inside these rings fine strands of circular musculature appear in embryos of 70 mm. head-foot length. The musculature appears first at the lower end of the ureter and then gradually extends towards the kidney; in embryos of 150 mm. it is developed throughout the entire length of the ureter.

Malformations of the Kidney.

1. The union of the uriniferous tubules with the collecting tubule system is, as has been seen above, a complicated process, and it is conceivable that slight disturbances may prevent the union of a uriniferous with its collecting tubule. Nevertheless, such uriniferous tubules continue their development and secrete; but since there is no exit for the secretion, a cystic degeneration of the tubule eventually results. A certain proportion of cystic kidneys may, accordingly, be assigned with certainty to such disturbances of development.

2. A second malformation is produced by the union of the kidney blastema of the right side with that of the left. This union occurs very early. I found it in an embryo of 30 mm. greatest length. The united parts form a transverse bar caught by the inferior mesenteric artery and are retained by this in their caudal position. Nevertheless, the right and left kidneys may develop further in a wing-like manner and eventually almost reach the normal position of ununited kidneys. What the cause of the union of the two blastemata may be is unknown, but even in the transverse bar the constituents of the two kidneys are sharply separated.

3. A third malformation consists of a precocious splitting of the ureter, ureter fissus. The cause of a cleft ureter is to be referred to a non-development of the primitive renal pelvis, the pole tubules developing precociously and then ascending parallel to one another. The cleavage may later extend downwards into the undivided portion of the ureter, so that finally the latter is cleft right to its entrance into the bladder. All so-called double ureters which have a single opening into the bladder should be termed cleft ureters, and not double ureters. In this connection most autopsy protocols are defective; the ureter fissus is regularly termed a double ureter, although it is single.

4. The double or triple ureter (ureter duplex and triplex) represents a regressive variation. I shall have occasion to speak of them in the next chapter, and shall only point out here that they arise as two or three ureteric buds from the primitive excretory ducts, and that these multiple ureteric buds do not develop equally, the most caudal one showing the strongest development, not only as regards the expansion of its ureteric tree, but also as regards the height that it reaches in its development. It represents the normal ureteric bud and always reaches a more cranial level than the other two buds.

The Phylogenetic Development of the Metanephros.

We must define again in all clearness what we mean by the metanephros. It is an excretory organ whose tubules open into special collecting tubules, developed from the primary excretory duct. Whether these special collecting tubules are represented by a simple tube or develop to such an expanded ureteric tree as we see in man, the opening of the metanephric tubules into a special efferent duct developed from the primary excretory duct is the characteristic feature.

Starting with this point if we consider, first of all, the development of the mesonephros of the Gymnophiones, we will find that we have to distinguish in it between ventral mesonephric tubules, all of which are in a longitudinal row at the summit of the mesonephric fold, and dorsal mesonephric tubules which lie at the root of the fold and, in order to open into the primary excretory duct, must traverse a much longer path than the ventral ones. These dorsal tubules are developed for the most part later than the others, and may occur in varying number and in different series. The later formed series are always the more dorsal ones, and, finally, their tubules can no longer reach the primary excretory duct by their own efforts. Accordingly the primary duct sends out special collecting tubules for the reception of these canals; according to our definition we would have to regard these dorsal mesonephric tubules with their special collecting

tubules as metanephric structures. In the mesonephros of young Gymnophiones, then, there is scattered throughout its entire length a series of metanephroi; only the caudal ones persist, however, in the adult. In birds a similar observation is to be recorded. It must be pointed out, in the first place, that the length of the mesonephros in birds is markedly less than that of the mesonephros of the Gymnophiones, and, consequently, the mesonephric tubules are compressed into a smaller space. What the mesonephros loses in length, it gains in thickness, and since a great amount of development is possible only in the caudal portion of the body cavity, the mesonephros increases in man—*i. e.*, develops dorsal tubules, principally in this region. These dorsal tubules are too far away to open directly into the primary excretory duct, and, therefore, special collecting tubules are formed for them by the duct. According to our definition these dorsal mesonephric tubules, together with their collecting tubules, are also metanephroi. Their number, however, for the reason stated, is small; we have only a few metanephroi and a few special collecting tubules.

Finally, we have shown that in the development of the human mesonephros a heaping up of tubules occurs at the caudal end; furthermore, that these mesonephric tubules no longer lie in one series, and, finally, that special collecting tubules are formed for them from the primary excretory duct, but these are few in number in comparison with the condition in the chick.

In brief, then: At first numerous metanephroi are interposed between the mesonephric tubules; the more the space in the body cavity becomes limited as development proceeds, the more also the number of these metanephroi becomes diminished, until, finally, in adult mammals only one is developed. We must, therefore, distinguish between different ureters. *Those* ureters that are developed for the small metanephroi imbedded in the mesonephroi of the Gymnophiones and birds, and also for those in the caudal pole of the human mesnephros I term mesonephric ureters. *The* ureter which supplies the persistent metanephros I term a metanephric ureter, and logically we must distinguish in man between provisional metanephroi and definitive metanephros. When in man two or three ureters occur as an anomaly, it is, as I have said above, a reversion, since in such cases one or two of the mesonephric ureters and their tubules persist.

I have finally to consider why the last ureter becomes the metanephric ureter. I would associate this with the preference which the last ureter acquires in reptiles and birds. In these the mass of the mesonephric tubules extends caudally beyond the primary excretory duct and forms the so-called caudal kidney. For the tubules of this the primary excretory duct forms a special strong ureter, which must be the last of all the ureters. By the development of the caudal kidney the last ureter acquires a special importance and therefore a preference, which finally allows it to dominate over the others as the metanephric ureter.

The Function of the Mesonephros.

In most anamnia the mesonephros begins its activity while the pronephros is still at its functional height. For a time both organs function together; then the pronephros undergoes degeneration and the mesonephros becomes the only functional excretory organ. This entire complex of processes has without further consideration been transferred to the relation between the mesonephros and the metanephros, and the question whether the mesonephros is actually functional in the amniota has never been seriously considered. Weber (1897) was the first to take it up and he endeavored to answer it in the following manner. He compared the time of degeneration of the mesonephros with that of the development of the metanephros; when he found that the mesonephros degenerated before the metanephros could exercise an excretory function, he has assumed that the mesonephros did not function, for if it had been active and had then degenerated

before the metanephros had hegun its activity, there must have heen a certain period of development during which there was no excretion. Let us adopt this same method in considering the special case of the function of the human mesonephros. Already in an embryo of 19.4 mm. greatest length the majority of the mesonephric tubules are so far in process of degeneration that they cannot be regarded as having an excretory function. Of the 35 tuhules of this embryo only four are actually still intact. In an embryo of 22 mm. greatest length none of the mesonephric tubules were capahle of functioning; in all the tubulus secretorius had separated from the tubulus collectivus. If one inquires how far the development of the metanephros has progressed at this time, one finds that emhryos of 22 mm. have just reached the anlage of the second generation of uriniferous tubules. The first generation, however, has as yet no fully formed Malpighian corpuscles. If, then, the mesonephros had functioned as an excretory organ, there must necessarily have been an interruption of this function on its degeneration. Consequently, I regard the question as to the functioning of the mesonephros as settled; it does not function as an excretory organ. This does not, of course, imply that it may not have been active in another manner unknown to us.

Cloaca, Bladder, Urethra, and Urogenital Sinus.

The rectum, bladder, urethra and urogenital sinus are formed by a triple division of the cloaca. The first division completely separates the dorsal third of the cloaca or the rectum, and the remains of the cloaca are divided by a second incomplete division into the bladder, urethra and urogenital sinus.

From the physiologico-morphological stand-point these are grouped together under the term "bladder" organs, which show an entirely different development, and are not to be derived from one another phylogenetically. In the first place, it is necessary to distinguish between entodermal and mesodermal bladders; a mesodermal bladder arises in some manner from the primary excretory duct; an entodermal bladder may be formed from the cloaca or from its derivative, the allantois, and we may speak, therefore, of cloacogenic and allantoidogenic bladders. Finally, it must be pointed out that the bladder derived from the cloaca may be formed either from its dorsal or its ventral wall, and we must, therefore, distinguish between dorso-cloacogenic and ventro-cloacogenic bladders. The Amphibia possess a purely ventro-cloacogenic bladder, a purely allantoidogenic bladder occurs temporarily in some birds, a purely mesodermal hladder is developed in the selachians. All other bladders are of mixed origin. The Teleosts, Ganoids, Petromyzonts, snakes, crocodiles, and mammals have bladders of cloacogenic and mesodermal origin; the lizards derive their bladder from three sources: dorso-cloacogenic, allantoidogenic, and mesodermal; and, finally, in the turtles the bladder is formed from dorso-cloacogenic, ventro-cloacogenic, allantoidogenic and mesodermal anlagen.

In man a ventro-cloacogenic and mesodermal bladder develops; an allantoidogenic origin, such as was formerly supposed to occur, does not exist.

By cloaca is understood the part of the posterior intestinal bay that lies caudal to the point where the allantois is given off. Into it there open from above the end-gut and the allantois (Fig. 599). It is a blind sack, oval in transverse section, its longest axis standing dorso-ventrally and its ventral surface being compressed

almost to an angle (Figs. 530 and 534). By this ventral angle the cloaca comes into contact and fuses with the ectoderm of the surface of the body, the mesoderm being pressed aside. The area of fusion is termed the cloacal membrane (Tourneux 1888, Born 1894, Fig. 534). This consists, accordingly, of two layers of epithelium, a stronger ectodermal and a weaker entodermal one (Fig. 600); later the difference in thickness becomes more equalized and in the region of the urethral plate it becomes reversed. Seen from without the membrane lies at the bottom of a shallow rhomboid groove (Fig. 601, Keibel 1896). At first the cloaca is short in the

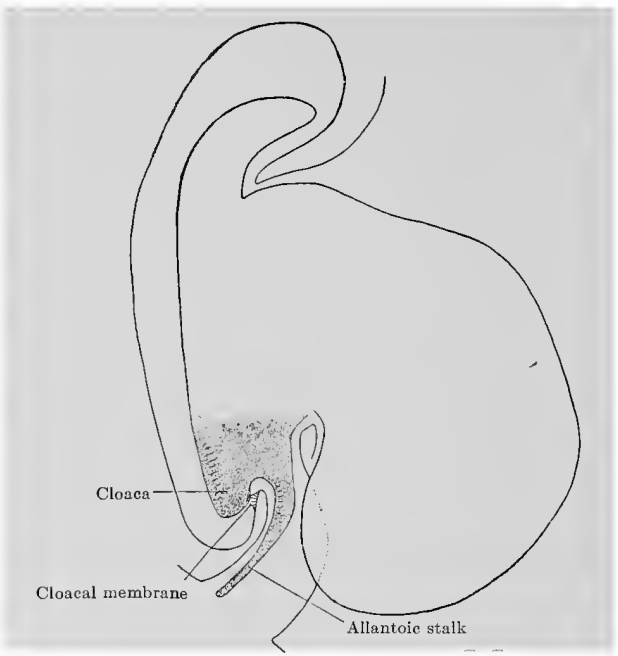


FIG. 599.—Reconstruction of the embryo Pfannenstiel-Krömer, 1.38 mm. long and with 5–6 pairs of primitive segments, seen from the right side. × 50. The figure is intended to show the relation of the cloaca and cloacal membrane to the allantoic stalk. The latter arises from the cloaca at a right angle, immediately above the cloacal membrane.

cranio-caudal direction; the more the tail grows, the more the cloaca becomes enlarged and the cloacal membrane keeps pace with it. A comparison of Figs. 599 and 600 shows the increase of both. In both figures the membrane begins immediately caudal to the point where the allantois is given off and extends in an embryo of 2.6 mm. greatest length (Fig. 600) to the caudal end of the cloaca; in this embryo, accordingly, the membrane forms the entire ventral wall of the cloaca.

The growth of the cloaca is shown by the following data. Embryo of 1.38 mm. greatest length: The length of the cloaca is 90 μ, that of the cloacal membrane 20 μ. Embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments: length of the cloaca 160 μ, that of the cloacal membrane 130 μ;

the cranial end of the cloaca is in the 14th primitive segment. Embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments: length of the cloaca and cloacal membrane 110 μ, the cranial end of the cloaca lies at the level of the future 26th primitive segment. Embryo of 4.25 mm. vertex-breech length: the length of the cloaca 250 μ, that of the cloacal membrane 240 μ; the cloaca lies in the 28th primitive segment. Embryo of 4.9 mm. nape length: length of cloaca 540 μ, that of the cloacal membrane 360 μ. Embryo of 11 mm. greatest length: length of the cloacal membrane 470 μ.

The first division of the cloaca begins in embryos between 4.9 mm. nape length and 5.3 mm. greatest length; it separates a dorsal third or quarter, the rectum, from the rest of the cloaca, the ventral remains of the cloaca. It takes place by the saddle between the cloacal opening of the intestine and that of the allantois growing as a partition downwards from above into the lumen of the cloaca, parallel to its dorsal wall (Fig. 602); this partition

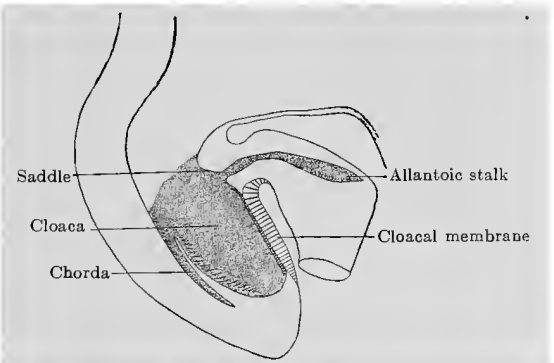


FIG. 600.—Reconstruction of the caudal end of the body of Embryo Pfannenstiel III, 2.6 mm. greatest length and with 13–14 pairs of primitive segments. ×50. Cloaca and cloacal membrane have grown greatly in comparison with the conditions in the embryo shown in Fig. 599; the allantoic stalk is given off at a right angle from the cloaca, immediately above the cloacal membrane. The ventral wall of the cloaca is formed only by the cloacal membrane.

is termed the *septum urorectale*. The lower border of the septum is not straight, but forms a curve, since it grows downward faster at the lateral walls of the cloaca than it does in the middle. One thus gets the impression that there are at the lower end of the septum two lateral folds, the plicæ urorectales, which unite in the median line and so form the unpaired septum. The middle line of the septum, however, never shows a raphe, such as would be formed by the union of folds, and therefore the description of the septum urorectale as unpaired is more correct. The line, along which the septum grows downwards in the interior, is marked on the outer surface of the cloaca by a groove or a slight ridge (Keibel 1896). The rectum and the ventral remains of the cloaca are differentiated even before the division by differences in the structure of the epithelium of the cloacal wall. That of the dorsal wall, so far as it forms the future rectum, remains high cylindrical and the portion of the lumen corresponding to it becomes narrow;

the epithelium of the ventral wall, so far as it forms the ventral remains of the cloaca, flattens out, and the portion of the lumen corresponding to it remains wide or even widens. At the line of transition of one portion of the lumen into the other there is a ridge (Fig. 562), which corresponds to the position of the future urorectal fold. Growing further down the urorectal septum reaches the neighborhood of the cloacal membrane and thus divides the cloaca almost completely into the rectum and the remains of the cloaca, a small connecting passage only remaining between the two immediately above the cloacal membrane (Fig. 603 *b*). At this stage the development may be inhibited and the communication between the rectum and urethra thus is made permanent. On this

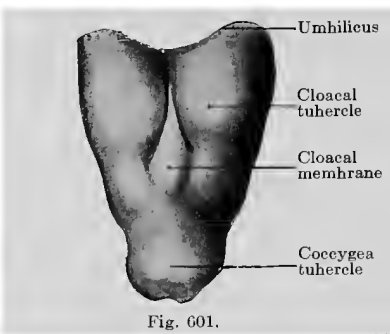


Fig. 601.

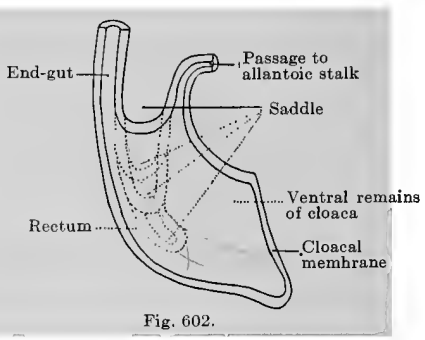


Fig. 602.

Fig. 601.—Model of the cloacal membrane of a human embryo of 3 mm. greatest length. (Embryo E. B., from the collection of Professor His, Leipzig; from Keibel, 1896.) The cloacal membrane forms a rhomhoidal groove slightly depressed helow the surface of the embryo, hetween the umhilicus and the coccygeal tuhercle. At either side is one of the paired cloacal swellings.

Fig. 602.—Model of the cloaca of a human embryo of 7 mm. greatest length (emhryo Chr. I, from the collection of Professor Hochstetter, Vienna), in which the gradual separation of the rectum from the ventral remains of the cloaca is shown diagrammatically hy the series of dotted lines.

account this communication is termed the *cloacal duct* (Reichel 1893). Normally, however, the urorectal septum grows through this last stretch also, reaches the cloacal membrane and fuses with it (Fig. 604 *b*). By the fusion the cloacal membrane is divided, and we now speak of an *anal membrane* that closes the rectum, and a *urogenital membrane,* that closes the ventral remains of the cloaca. In the later development both membranes are broken through independently, and so the urogenital and the anal openings are formed. The breaking through takes place in embryos of between 13 and 18 mm. greatest length; the anal opening generally is formed somewhat later than the urogenital.

As a mark by which the progressive division of the cloaca may be measured, only the point of opening of the primary excretory duct is available, and this is by no means satisfactory, since it also alters its position. As is shown in Fig. 534, when the point of contact of the primary excretory duct with the cloacal wall is first established, it lies close to the ventral ridge of the cloaca, and therefore close beside the cloacal membrane. At the beginning of the division of the cloaca this point moves dorsally, so that seen from the side, it comes to lie at the middle

of the lateral cloacal wall (Fig. 605). Whether a displacement in the cranial direction accompanies this evident horizontal one cannot be determined with certainty. With this limitation the following data may be accepted. In young embryos up to those of 4.9 mm. greatest length the opening of the excretory duct almost divides equally the cranio-caudal diameter of the cloacal wall. In an embryo of 7.8 mm. the saddle lies between the opening of the intestine and the allantois, somewhat above the opening of the excretory duct. In an embryo of 8.5 mm. greatest length the saddle already lies 50 μ beneath this opening—*i. e.*, the opening is already into the divided cloaca. In a 7 mm. embryo the saddle is 190 μ below the opening of the duct, in one of 9.5 mm. greatest length it is 260 μ below the opening and in one of 11 mm. greatest length the division of the cloaca is complete.

While the division that separates the rectum from the ventral remains of the cloaca is still progressing, the second division, which divides the ventral remains of the cloaca into the bladder, the urethra and the urogenital sinus, is beginning; the possibility

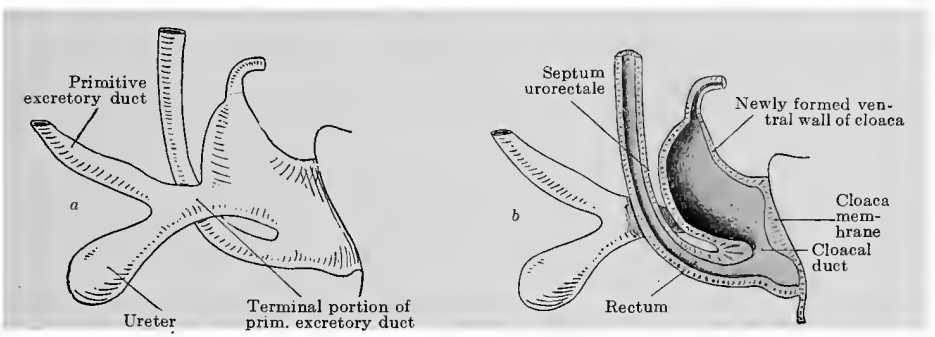


FIG. 603 *a* and *b*.—Model of the bladder of a human embryo of 7 mm. greatest length. (Embryo Chr. I, from the collection of Professor Hochstetter, Vienna.) Model prepared by my son, Willy Felix. *a*. From the right side; *b*, a median sagittal section. The cloaca has grown somewhat; by the gradual formation of the lower half of the ventral abdominal wall the umbilicus, and with it the allantoic stalk, is carried away from the cloacal membrane, and, as a result, there is formed, above the latter, a newly formed portion of the ventral wall of the cloaca, from which the allantoic stalk arises at a right angle as before. The division of the cloaca into the rectum and the ventral remains of the cloaca is almost complete, the saddle between the two being immediately over the cloacal membrane. Between the two there is still a tubular communication, the cloacal duct of Reichel.

of such a division depends on the curving of the caudal end of the body (see Vol. I, Fig. 272). The cloaca is fastened to the outer wall of the body at three points, to the umbilicus by the allantoic stalk or urachus, along the entire cloacal membrane to the anterior abdominal wall, and loosely by the primary excretory duct and ureter to the posterior wall of the abdomen. The positions of these three fixation points, relative to one another, determine the form and position of the cloaca. As has been pointed out the length of the cloacal membrane represents at first the length of the ventral wall of the cloaca; the membrane begins immediately below the origin of the umbilical cord or belly stalk and extends to the caudal end of the cloaca (Figs. 600, 605 and 606); the dorsal wall of the cloaca in young embryos lies on the ventral surface of the aorta or chorda (Fig. 600). This position changes with the

elongation of the embryo; the umbilicus and cloacal membrane become pushed apart, a piece of the anterior abdominal wall is formed between them and, corresponding to this, a new portion of the ventral wall of the cloaca is formed, situated cranial to the cloacal membrane; compare Figs. 600 and 603 *b*. A little later the anterior abdominal wall from the umbilicus to the caudal end of the cloacal membrane becomes pushed out to form an elevation (Figs. 607 and 608). On this elevation, the cloacal tubercle, the

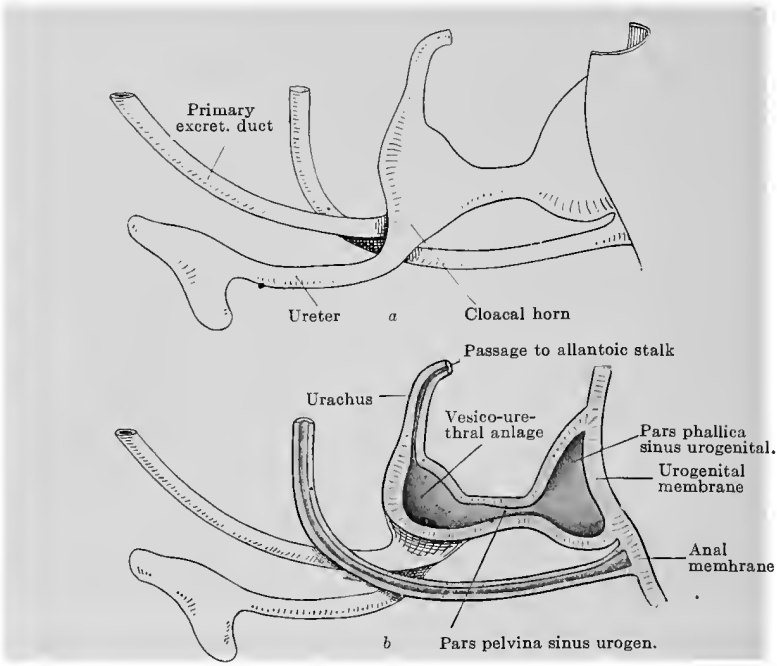


FIG. 604 *a* and *b*.—Model of the cloacal region of a human embryo of 11 mm. greatest length. (Embryo P. I., from the collection of Professor Hochstetter, Vienna.) Model prepared by my pupil Frau Gervai. *a*, From the right side; *b*, median sagittal section. The rectum is completely separated from the ventral remains of the cloaca, and the cloacal membrane has been divided into the canal and urogenital membranes. The ventral remains of the cloaca has changed its position in that it has been drawn dorsally by the ureters and primary excretory ducts as a result of the enlargement of the dorso-ventral diameter of the body cavity. Thereby its former dorsal wall—compare Fig. 603—is divided into a ventral and a cranial portion, the former being formed by the urogenital membrane and the latter by what was termed in Fig. 603 the newly formed ventral cloacal wall. The cranial wall is depressed caudally in its middle part. Thus the ventral remains of the cloaca is divided into three portions: into, 1, the vesico-urethral anlage, the dorsal portion, 2, the pars pelvina of the urogenital sinus, the middle narrow portion, and, 3, the pars phallica of the urogenital sinus, the ventral broad portion; the latter is closed externally by the urogenital membrane.

ventral wall of the cloaca is so placed that the cloacal membrane lies on the anal slope of the tubercle, extending from its summit to the caudal periphery of its base, *i.e.*, to the anus, while the newly-formed portion of the cloacal wall extends from the summit of the tubercle to the umbilicus (Fig. 608); the newly-formed wall and the membrane therefore form an angle open dorsally. The dorso-ventral diameter of the abdominal cavity increases with the curvature of the tail and thereby the primary excretory duct be-

comes at first elongated; compare its course in Fig. 606 and in Figs. 603 and 604. As the enlargement of the abdominal cavity increases still more, the primary excretory duct and the ureter, which are fastened to the posterior abdominal wall, draw out dorsally the posterior wall of the ventral remains of the cloaca (Figs. 603 and

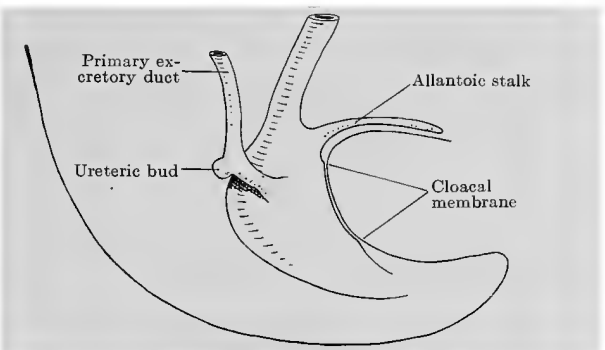


Fig. 605.—Model of the caudal portion of the body of a human embryo of 5.3 mm. greatest length. (Embryo 1420, from the collection of Professor Keibel, Freiburg i. Br.) Position and course of the primary excretory duct, position of its opening with reference to the cloaca and the cloacal membrane, anlage of the ureteric bud.

604). The form and position of the ventral remains of the cloaca become altered by these modifications, the cavity becoming almost quadrangular in median section; while in Fig. 603 *b* we can distinguish only a ventral and a dorsal wall in the remains, in Fig. 604 there is a ventral wall, formed by the urogenital membrane, a

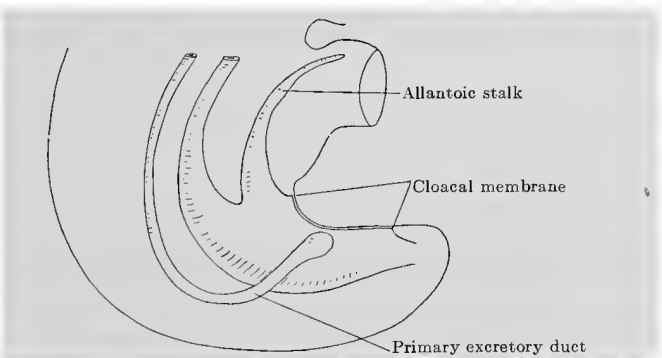


Fig. 606.—Reconstruction of the caudal end of the body of a human embryo of 4.25 mm. vertex-breech length and with 28 pairs of primitive segments. (Embryo H. M. 1, from the collection of the Anatomical Institute, Zurich.) Course of the primary excretory duct and the position of its orifice relatively to the cloaca and the cloacal membrane.

cranial one formed by the newly-formed piece of the ventral cloacal wall (in Fig. 604 *b*, this wall is already depressed caudally), a posterior one and a caudal one formed by a bending of the actual dorsal wall at the level of the primary excretory duct. The cranial wall now becomes curved downwards and the lumen, originally rectangular in median section, becomes divided into three portions

(Fig. 604 *b*). The depression of the cranial wall has taken place in an embryo of 11 mm. greatest length, a model of which is shown in Fig. 604, and the originally simple lumen of the cloacal remains is incompletely divided into a dorsal and a ventral wide portion and a median narrow portion. From the posterior broad lumen the vesico-urethral anlage is formed, the narrow middle portion becomes the *pars pelvina* and the broad ventral portion the *pars phallica* of the *sinus urogenitalis*. Since the urogenital membrane runs along the anal slope of the cloacal tubercle and later of the phallus, by the outgrowth of the phallus the pars phallica of the urogenital membrane becomes enclosed in that organ and hence its name.

The first traces of the division of the ventral remains of the cloaca into the vesico-urethral anlage and the sinus urogenitalis are already indicated in an

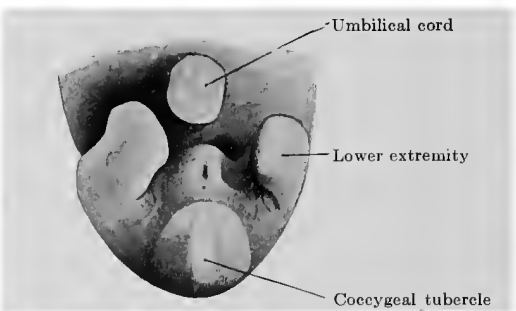


Fig. 607.—Caudal extremity of the body of an 18 mm. embryo. (From a photograph by Professor R. Meyer, Berlin.) Between the umbilicus and the coccygeal tubercle cranio-caudally and the two lower extremities laterally, the cloacal tubercle has appeared. On it there may be distinguished an oral slope towards the umbilicus and an anal one towards the coccygeal tubercle. On the anal slope the ostium urogenitale and the groove which later becomes the ostium anale are visible.

embryo of 7 mm. greatest length (Fig. 603 *b*). The division is more distinct in an embryo of 9.5 mm. greatest length (Fig. 567) and is complete in one of 11 mm. (Fig. 604).

With further development the vesico-urethral anlage and the pars pelvina of the urogenital sinus become broadened in the frontal direction and compressed in the sagittal one, so that the dorsal and ventral walls are almost brought into contact. The pars phallica of the urogenital sinus remains broad in the sagittal direction, but is very much narrowed in the frontal one, so that finally its left and right walls are in contact in the median line. Between the two walls there always remain one or several clefts; only the portion that corresponds to the future glans becomes completely solid, and this and this only can be termed the urethral plate.

The irregular form of the wall of the sinus urogenitalis, both in its pelvic and phallic portions, shown by the occurrence of several completely separated lumina, gives opportunity for the formation of diverticula and for duplication of the sinus (Grubenmann, 1911).

The broadening of the vesico-urethral anlage in the frontal direction is principally caused by that portion of the primary excretory duct that intervenes between the opening of the ureter and the bladder being taken up into it. We shall call this portion the *terminal piece of the primary excretory duct.* It is at first narrow, but during further development it becomes more and more enlarged in a funnel-shaped manner from the opening into the bladder upward, the enlargement forming the so-called cloacal

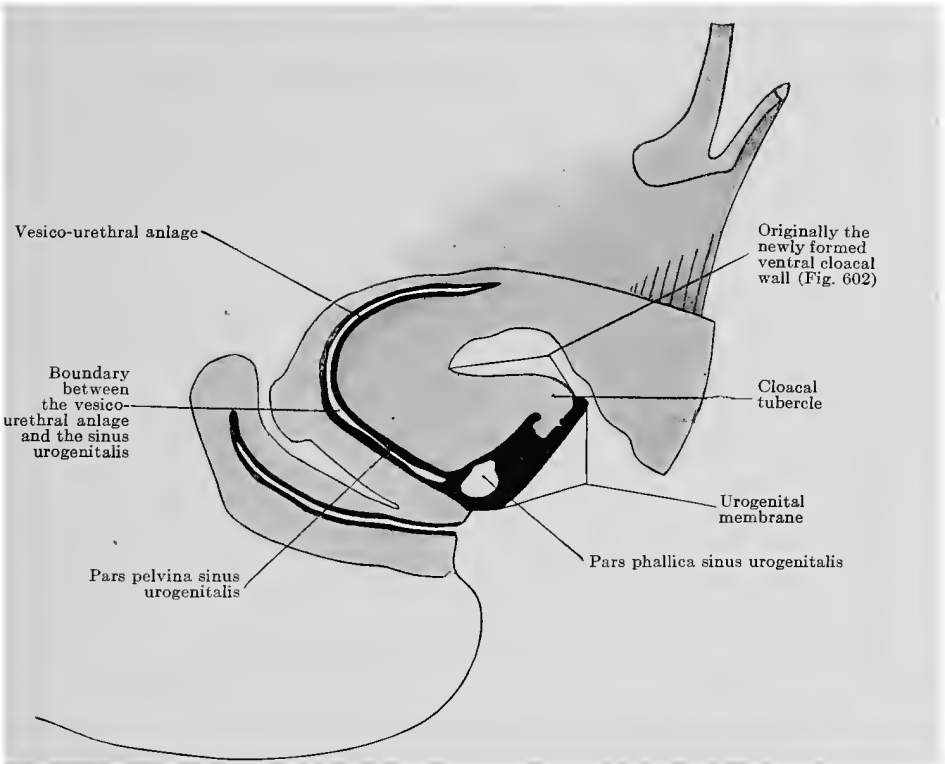


FIG. 608.—Sagittal section of the lower end of the body of an embryo of 24 mm. vertex-breech length. (Embryo Hal. 1, from the collection of the First Anatomical Institute, Vienna.) The division of the ventral remains of the cloaca is completed. The cloacal tubercle lies between the caudal periphery of the umbilicus and the base of the coccygeal tubercle. The urogenital membrane extends from its tip along its anal slope and forms the ventral boundary of the pars phallica of the sinus urogenitalis.

horn (Fig. 604 *a*). The neighboring portions of the wall of the vesico-urethral anlage also take part, however, in the formation of the cloacal horn, but, finally, the funnel is so completely taken up into the wall of the vesico-urethral anlage that it can no longer be recognized as a special structure. With the absorption of this terminal piece of the primary excretory duct into the wall of the bladder the ureter acquires a direct opening into the latter. At the beginning of its development the ureter lies on the dorsal wall of the primary excretory duct, but during the formation of the cloacal horn it passes to the lateral side of the duct, so that when

the direct opening into the bladder develops it lies immediately lateral to the opening of the primary excretory duct. The portion of the wall between the two openings then begins to grow extensively, so that while the opening of the primary excretory duct remains where it was, that of the ureter gradually migrates upwards. This migration takes place not only cranially, but also in a lateral direction. The two excretory duct openings remain close together, and the region in which they open becomes raised up into a hillock and projects into the lumen of the urethra (Fig. 655); this hillock we shall term *Müller's hillock*. The triangle that is marked out by the three points, Müller's hillock and the openings of the right and left ureters, and bears the name trigonum vesicæ in systematic anatomy, is, therefore, developed from the wall of the primary excretory duct, so that with it we have described the development and extent of the mesodermal portion of the bladder.

The absorption of the terminal piece of the primary excretory duct into the wall of the bladder begins in embryos between 5.3 and 7 mm. greatest length; in embryos of 9.5 mm. greatest length the formation of the funnel is completed and thereby the boundary between it and the wall of the bladder disappears. In embryos of from 10 to 14.5 mm. greatest length the ureters and primary excretory ducts open close together into the bladder. In those of 13 mm. greatest length the cranio-lateral migration of the ureters begins, and in embryos of 22.7 mm. greatest length it may be so far completed that the interval between the apex of the bladder and the openings of the ureters and that between the latter and the orifice of the urethra may have the same relative proportions as in the adult. The ureteric openings always lie at the tips of the half-moon which a transeverse section of the bladder presents. As to their lateral displacement I have obtained the following data: Embryo of 11 mm. greatest length, distance between the two ureteric openings 340 μ; embryo of 12.5 mm. greatest length, distance 460 μ; embryo 19.4 mm. greatest length, distance 500 μ.

SEPARATION OF BLADDER AND URETHRA.

The separation of the bladder from the urethra takes place quite gradually and consists, firstly, of an enlargement of the bladder portion while the urethral portion remains narrow, and, secondly, of changes in the epithelium of the urethral wall. At first the entire vesico-urethral anlage is lined by a single layer of cylindrical epithelium with a vesicular character, almost all the nuclei lying in the outer portion of the cells. The first changes take place in such a way that the boundary between the two kinds of epithelium is formed at about the openings of the ureters, ventrally at a somewhat more caudal point. Above the openings the epithelium remains one-layered at first, and later becomes at most two- or three-layered, while below it at once becomes two- or three-layered and later four- to five-layered. But in this also the superficial cells always show the vesicular character and have

their nuclei in their outer portions. As a result of the rapid cell-division which precedes the formation of new layers, the cells of the urethra become smaller and their nuclei come to lie closer together, so that they give the epithelium a darker appearance than that of the bladder; finally the superficial layer of the bladder loses its vesicular character and becomes cubical. Only one portion of the epithelium, that of Müller's hillock, remains exempt from this change; it remains for a long time one-layered and high cylindrical, and its nuclei lie close beneath the free surface.

The first difference in the epithelium—*i. e.*, the formation of a two- or three-layered epithelium in the vesico-urethral anlage—occurs in embryos of 13 mm. greatest length; a four- to five-layered epithelium occurs in the urethra of embryos of 45 mm. greatest length; and a transitional epithelium, similar to that found in the adult urethra, is shown by embryos of 55 mm. head-foot length. The enlargement of the lumen of the bladder is shown in embryos of from 25 to 30 mm. greatest length.

LATER DEVELOPMENT OF THE BLADDER.

The bladder, together with the aa. umbilicales that accompany it, lies at first (embryos of from 10 to 24 mm. greatest length) completely within the anterior body wall. Only on the enlargement of the bladder and the two arteries is the former crowded out of the abdominal wall and, developing a ventral mesentery, projects into the body cavity (Fig. 554 *a*). A view of the anterior abdominal wall from behind shows that the two umbilical arteries bound a triangular area, the vesical plate, whose apex is of course formed by the umbilicus (Fig. 552). Within this area the bladder lies in such a way that its cranial apex reaches the umbilicus, where it is connected with the remains of the allantoic stalk; the internal orifice of the urethra lies at about the level of the symphysis. This position the bladder retains at birth, except that its apex diminishes more and more and finally becomes the urachus, this structure being, accordingly, a product of the bladder, *i.e.*, of the cloaca and not of the allantoic stalk. Usually the urachus degenerates at an early period to such an extent that its lumen disappears, and later the epithelial cord thus formed becomes divided into separate portions which may completely vanish before birth, but persistent remains of the urachus may for unknown reasons enlarge in a vesicular manner and give opportunities for the formation of urachal cysts. While the epithelium of the urachus completely disappears the surrounding, concentrically arranged connective tissue persists as a cord, which forms the lig. vesico-umbilicale medium. So long as the bladder lies in the triangular area between the two umbilical arteries its mesentery persists, but when it gradually sinks down after birth and comes to lie in the

true pelvis, the vesical plate applies itself to the anterior abdominal wall and fuses with it; its margins, which contain the obliterated umbilical arteries, may, however, especially in fat individuals, remain free throughout life. In postfetal life the bladder gradually descends along the anterior abdominal wall into the true pelvis, this descent taking place differently in the two sexes. In females the process of descent is a continuous one; one may recognize in it two periods differing in the rate of the descent, it being rapid in the first and second years and quite slow from the 2nd to the 20th year. In males there are also two periods in the descent, but they are separated by a resting period; in the first two years the descent is rapid as in females of like age, then comes a resting period that lasts from the 2nd to the 8th year, and finally then succeeds the slow descent from the 8th to the 20th year. I have taken these data from a table by Disse (1891); Disse himself adopts a somewhat different grouping.

The Bladder Epithelium.—As has been pointed out (p. 878), the bladder epithelium remains unaltered for a long time. It is two-layered and thicker on the concave dorsal than on the concave ventral surface. The one-layered epithelium occurs at the apex and the many-layered at the fundus. The cells vary in height in different embryos, being sometimes high cylindical, sometimes low cubical. The epithelium first begins to be several-layered in embryos of 50 mm. head-foot length, first of all in the caudal portion. The first traces of the transitional epithelium are shown by an embryo of 60 mm. head-foot length.

The Bladder Musculature.—A condensation of the loose mesenchyme tissue surrounding the bladder precedes the formation of the musculature, the direction of the young cells indicating their later character as circular or longitudinal fibres. The condensation of the mesenchyme, as well as its later transformation into musculature, proceeds from the apex of the bladder towards the orifice of the urethra. The musculature varies in its development and a portion above and another below the openings of the ureters may be distinguished. We may consider, first, the upper portion. The first muscle layer appears in an embryo of 22.5 mm. as a longitudinal musculature, that extends from the apex almost to the openings of the ureters. This layer is always stronger on the dorsal than on the ventral surface, and, indeed, may be completely wanting ventrally. It surrounds the epithelium in wide curves, so that a broad sheet of loose mesenchyme persists between the two, and in this sheet a layer of circular musculature develops in embryos of 26 mm. greatest length, again appearing first in the upper portion of the bladder. In embryos of 55 mm. head-foot length a third and last layer—an inner longitudinal musculature—is formed, and both longitudinal layers give off oblique bundles to the intervening circular layer; in embryos of 80 mm. head-foot length, the distinctness of the various layers becomes obscured by the bundles of one curving into the others, so that a felted condition results.

The musculature below the openings of the ureters is always only in a single layer, and this is of circular fibres. It is to be seen first in embryos of 30 mm. and may extend as a longitudinal musculature upon the terminal portion of the ureter. The sphincter vesicæ is plainly developed in a male embryo of 90 mm.

The ureter traverses the wall of the bladder in a straight course, and this condition still persists in an embryo of 70 mm. head-foot length. When the oblique course, which is already present in the new-born child, is acquired, is unknown.

II. THE DEVELOPMENT OF THE REPRODUCTIVE GLANDS AND THEIR DUCTS.

Introduction.

The ovary and testis are up to a certain period of development exactly alike. Every vertebrate embryo forms at first an indifferent reproductive gland from which, by the emphasis of certain characters, the sexually differentiated organ is formed. The sexual differentiation of the reproductive gland is associated with a second differentiation which earlier, simultaneously, or later effects other organs. To the sexual differentiations of the reproductive glands belong:

1. The transformation of special *genital cells,* differing from all other cells of the body, into ova or spermatozoa.
2. The formation of ovarian follicles or seminal tubules.
3. A series of small differences:
   - (*a*) The caudal pole of the female reproductive gland reaches the posterior wall of the genital cord, while that of the testis ends just above it.
   - (*b*) The cranial half or two-thirds of the ovary is rotated during development through 90° and so comes to lie at right angles to the rest.
   - (*c*) The tunica albuginea of the testis appears very early, that of the ovary very late.
   - (*d*) The a. spermatica interna has a quite different course in the two sexes.
   - (*e*) The caudal pole of the testis is united by the ligamentum testis to the chorda gubernaculi, the caudal pole of the ovary by the ligamentum ovarii proprium to the wall of the uterus.

To the sexual differentiations of other organs belong:

1. The formation of different efferent ducts for the products of the two reproductive glands. It may be noted here that every embryo, whether it later manifests the male or the female type, develops efferent ducts as well for the ova as the spermatozoa; the duct which remains functionless degenerates.
2. The different formation of the external genital organs. Here also there is an indifferent shape through which both sexes pass before they acquire the special sex characters.
3. A series of small differences:
   - (*a*) Accessory tubes are only to be found in female embryos.
   - (*b*) The anlagen of the fimbriæ or accessory ostia are present at an early period in the female embryo, but are wanting in the male.

(*c*) The excavatio vesico-uterina is present in the female embryo, but not in the male.

(*d*) At the beginning of the third month the clitoris hangs decidedly downwards, while the penis stands out horizontally (Herzog, 1904).

(*e*) The developing penis rises directly from the cloacal tubercle, while the clitoris is separated from it by a groove.

(*f*) The præputium penis is formed by the ingrowth of *one* glandar lamella, which has the form of a cylindrical mantle. The præputium clitoridis develops by the ingrowth of three glandar lamellæ, an unpaired, middle, cylindrical one and two paired, straight ones, to the right and left of the unpaired one.

The Genital Cells.

The most important cells of the reproductive glands are the *genital cells.* They are distinguished from all other cells of the body, the soma cells, by the size of their cell-bodies and nuclei; the content of the cell-body is about 27 times as great as that of the nucleus. This latter has usually the form of a round vesicle, frequently of a double vesicle (twin form), and contains a wide-meshed delicate chromatin network (noyau leptotène [ταινία thread, λεπτός slender], von Winiwarter, 1900) with several nucleoli; the cell-body is feebly granular, stains only with difficulty and contains in the young condition yolk granules and granules (mitochondria) of a special form.

Hitherto it has been supposed that the genital cells were specially differentiated cœlom cells, derived from that portion of the cœlom wall that forms the reproductive glands. But the more our knowledge of the origin of the genital cells in the vertebrates increases, the more probable does it become that we must modify this original belief. It has now been shown for all the classes of vertebrates with the exception of the mammalia (Rubaschkin, 1909), that the first (?) genital cells have a special origin, probably being derived directly from the segmentation cells. I, therefore, term these cells *primary genital cells* in contradistinction to those that are differentiated from the epithelial covering of the reproductive glands; these may be termed *secondary genital cells.*

The proof of the origin of the primary genital cells from the segmentation cells is based on the special form in which the mitrochondria occur in their protoplasm (Lams and Doorme [1907], Meves and Duesberg [1907, 1908], van der Stricht [1900, 1909], Rubaschkin [1910], Tschaschin [1910]). The mitochondria of all the cells of the segmented germ have the form of granules, and the various granules are completely separate from one another. With the formation of the germinal layers a differentiation takes place among the cells in such a way that in the cells of the entoderm of the caudal portion of the body the mitochondria retain their granular form, while in those of the entoderm of the anterior part of the body, and in those of the ectoderm and mesoderm the isolated granules are transformed first of all into chains of granules and finally into rods or filaments.

Subsequently also the majority of the cells of the posterior half of the body show the filament form, so that at the stage of the first segmentation of the mesoderm only a few cells still show the original granular form of the mitochondria; these few cells are the primary genital cells. It is possible that with the aid of mitochondrial staining it will be shown that the secondary genital cells are derived from the primary ones and then all grounds will be removed for contrasting them as special cells with the primary genital cells.

In holoblastic ova the primary genital cells are formed in the posterior wall of the gut, in meroblastic ova in the floor of the segmentation cavity and in the germinal wall. Since the reproductive glands develop in all vertebrate embryos beside the root of the mesentery, we must suppose that a wandering of the primary germinal cells occurs. By noting all the localities in which primary genital cells are found we may reconstruct the path which is followed by the individual cells

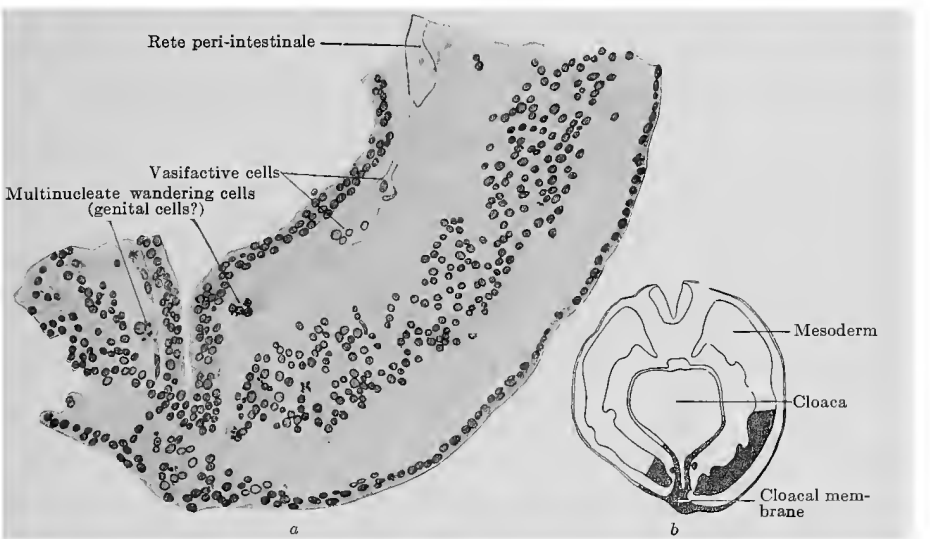


FIG. 609 *a* and *b*.—Part of a transverse section through the embryo Pfannenstiel III, 2.5 mm. greatest length and with 13–14 pairs of primitive segments. (From the collection of the late Professor Pfannenstiel, Kiel.) The section passes through the cloacal membrane and its exact position may be seen from the adjacent figure *b*. The mesoderm is still quite loosely aggregated. Between it and the entoderm there is at the upper edge of the figure a fully-formed portion of the rete peri-intestinale, and further down there are cell chains and masses (to the left of the cloaca) from which new networks of the rete are forming. The section shows at two places, to the right and left of the cloacal membrane, large cells partly multinucleate, partly filled with yolk granules and partly free from them, and lying free between the mesoderm and endoderm. These cells may be termed wandering cells and hypothetically may be interpreted as primary genital cells.

from their place of origin to the genital fold. It leads from the mesenchyme between the wall of the intestine and the parietal mesoblast into the root of the mesentery, and from there into the urogenital fold, at first into its connective tissue and finally into its epithelial covering. We may distinguish, therefore, between *regional* and *extraregional genital cells,* understanding by regional cells those that lie among the epithelial cells of the genital folds; all those that have not reached that position we group together as *wandering* or extraregional cells. All the primary genital cells do not migrate at the same time; whether all reach their goal is uncertain, but in any case the possibility of *strayed genital cells* must be admitted. The secondary genital cells occur only in the genital folds and they are, accordingly, regional from the beginning.

A series of transitional forms may be found between the secondary genital cells and the ordinary cœlom cells (cells with noyaux protobroques a and b, von

Winiwarter, 1900). I denote these transitional forms as *genitaloid cells* (cells with noyaux deutobroques, von Winiwarter, 1900). They agree with the genital cells in the structure of their nuclei, which are vesicular with a wide-meshed, delicate chromatin network, with the cœlom cells in the smallness of their cell bodies, which closely surround the nuclei. So soon as genital cells—whether they be primary or secondary—occur in the epithelium of the genital fold we speak of a *germinal epithelium* (Waldeyer, 1870); this, then, denotes a mingling of ordinary cœlomic and genital cells. Just as a region of cœlom epithelium may become germinal epithelium, so also it may lose its character of germinal epithelium should its genital cells migrate out of it or otherwise disappear. The ordinary cœlom cells react to the immigration of genital cells by increasing in volume, passing from a flattened into a cubical form. But such a modification of flattened cœlom cells must not, without the presence of genital cells, be taken as evidence of the formation of a germinal epithelium. For wherever, as the result of a folding process, two cœlomic epithelial surfaces come into contact, an increase in the height of the flattened epithelium occurs, apparently as the result of a mutual formative stimulus.

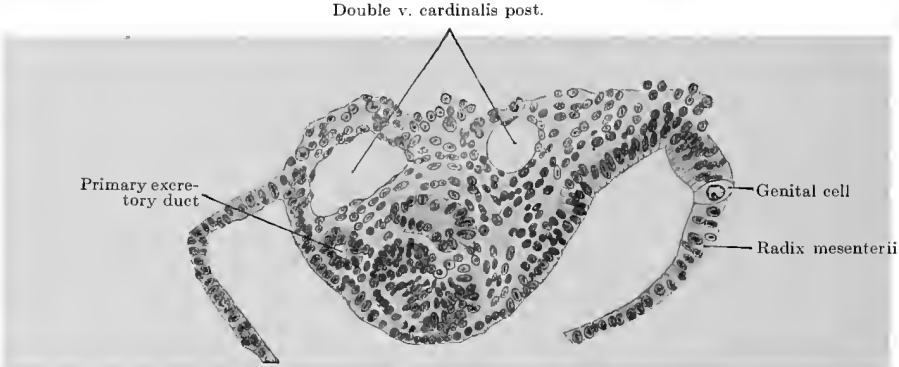


FIG. 610.—Transverse section through an embryo of 4.7 mm. vertex-breech length and 4.9 mm. nape length and with 33–35 pairs of primitive segments. (Embryo 137, G. 31, from the collection of the II Anatomical Institute, Berlin, Professor O. Hertwig; slide 9, row 3, section 1.) The section passes through the 11th primitive segment and the 5th mesonephric tubule. The urogenital fold is shown passing on the right into the root of the mesentery, on the left into the lateral wall of the body. A primary genital cell is to be seen in the root of the mesentery.

All the primary genital cells disappear in amniotes; whether they pass through a latent period to become manifest later as secondary genital cells, though possible, has not been proved.

And now, as regards man it is probable that he also possesses genital cells. The following facts are in favor of such a supposition: in an embryo of 2.6 mm. greatest length and with 13–14 pairs of primitive segments there were in the neighborhood of the cloaca, that is to say, in the region of what was originally the primitive streak, between it and the visceral mesoblast, large, free cells similar to the genital cells of other vertebrates and distinguished from the surrounding cells by the size of their cell-bodies and by possessing yolk granules. In the entire embryo seven such cells were recognizable, all in the immediate vicinity of the cloaca and all between it and the visceral mesoblast, *i.e.*, extraregional. In Fig. 609 *a* two of the primary genital cells of this embryo

are shown, one to the right and the other to the left of the cloaca. An embryo of 2.5 mm. greatest length and with 23 pairs of primitive segments had twelve primary genital cells, all extraregional, situated in the vicinity of the cloaca and the adjoining regions of the body; one of these cells is shown in Fig. 532 *b*. Finally an embryo of 4.9 mm. nape length and with 33–35 pairs of primitive segments showed typical genital cells in the first to the fifth and in the eleventh to the twelfth body segments, the cells lying partly in and partly below the cœlomic epithelium near the root of the mesentery or in the medial slope of the urogenital fold. I show in Fig. 610 one of these cells in the root of the mesentery.

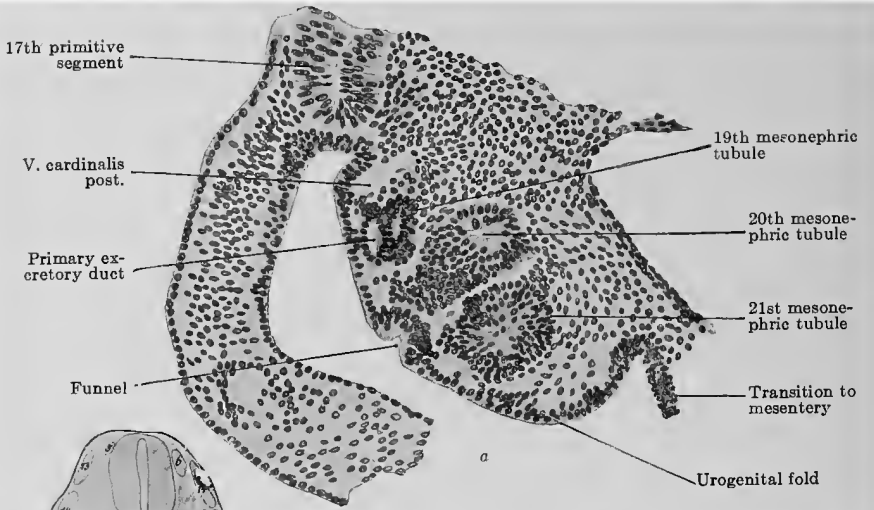
The smallness of the number of these observations allows of no final conclusion, but they speak in favor of the view that man also possesses primary genital cells.

But even if wandering genital cells are to be recognized in human embryos, there is still the possibility that they may be "strays." Such strayed genital cells do not, perhaps, degenerate, but may develop further, and, above all, divide, forming, perhaps, parent cells for tumors, and especially for teratomata.

What has been said above for the amniotes in general, namely, that all the primary genital cells disappear, holds also for man. In any case, at the time at which the indifferent reproductive glands are formed there are neither extraregional nor regional genital cells.

Development of the Indifferent Reproductive Glands.

The anlagen of the reproductive glands appear within the urogenital folds, whose development and fate have been described above (p. 783–787). A small strip of the epithelium of the genital fold and this alone, forms the parent tissue of the reproductive gland. The epithelium of the urogenital fold usually consists of two layers of cells (Figs. 558, 559, 611) and is spread out uniformly over the entire surface of the fold in embryos up to 4.7 mm. vertex-breech length. In embryos of 5.3 mm. greatest length the epithelium over the summit and the medial slope of the fold, as far as the root of the mesentery, commences to become many layered, that on the lateral slope remaining two-layered or even becoming single-layered (Figs. 563, 612). The region of the many-layered epithelium represents the reproductive gland area, which, as a broad strip, extends throughout the entire length of the medial half of the urogenital fold. Since the thickened epithelium passes over quite gradually into the non-thickened portion, the reproductive gland has no sharp boundaries either medially, laterally, cranially or caudally. To the stage of the thickening there follows the stage of the ingrowth of the epithelium into the interior of



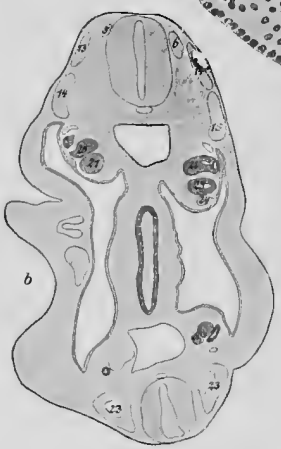


FIG. 611 *a* and *b*.—Transverse section of the urogenital fold of a human embryo of 4.9 mm. nape length, at the level of the 14th primitive segment. (Embryo 137, G. 31, from the collection of the II Anatomical Institute, Berlin, Professor O. Hertwig; slide 13, row 1, section 3.) × 150. The urogenital fold is uniformly covered over its entire surface by a one- to two-layered epithelium.

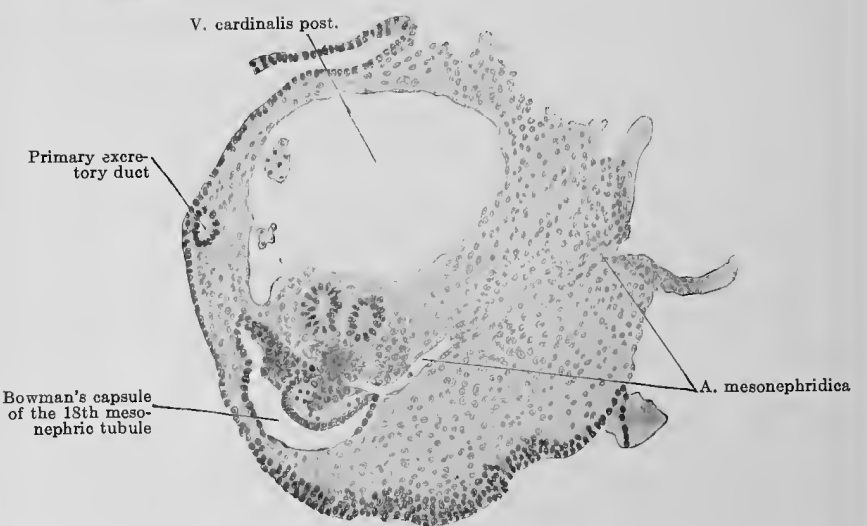


FIG. 612.—Transverse section of the urogenital fold of a human embryo of 7 mm. greatest length. (Embryo Chr. I, from the collection of Professor Hochstetter, Vienna; slide 8, row 10, section 6.) The epithelium on the medial side of the urogenital fold has thickened and forms the anlage of the reproductive gland.

the urogenital fold, and as the epithelium grows in it compresses the loose mesenchyme tissue of the fold and there is thus formed in the zone of ingrowth a strip of denser mesenchyme tissue, that is everywhere sharply defined from the ingrowing epithelium; in the epithelium itself there are numerous mitoses (Figs. 563, 612). That the epithelium actually grows inwards and not outwards towards the body cavity is shown, in the first place, by the permanent dorsoventral diameter of the urogenital fold and, in the second place, by the displacement of the Malpighian corpuscles of the mesonephros; the ingrowing epithelium pushes the various corpuscles before it; while the corpuscle in Fig. 548 is still at the surface of the fold, in Fig. 549 it is displaced quite dorsally. The growth of the epithelium of the reproductive gland area forms a solid mass, which has, however, a wavy boundary towards the mesenchyme (Fig. 613). As soon as the growth has reached about one-third of the dorsoventral diameter of the urogenital fold, the formation of the genital fold, described above (p. 785), begins. The lateral and medial grooves, which produce it, press inwards just at the boundary between the mesenchyme and the epithelial growth, and thus the whole genital fold is filled by a perfectly homogeneous mass, composed entirely of derivatives of the cœlomic epithelium. We must, consequently, note at this point that *everything* that is later developed within the genital fold has a common origin from the cœlomic epithelium.

Since the ingrowing epithelial mass displaces the mesonephric tubules, it is from the beginning in intimate relations with these, in the first place, with the medial surfaces of the Bowman's capsules and, in the second place, with the points where the tubuli collectivi bend into the tubuli secretorii; there is always, however, a sharp boundary between the mesonephric structures and the germinal epithelial mass.

The reproductive gland anlage accompanies the urogenital fold in its gradual growth caudally, but its definitive extent is reached only after sexual differentiation. In its maximal extent it reaches from the sixth thoracic to the second sacral segment. This extent, however, occurs in no one embryo, since degeneration begins at the cranial end before the addition of new reproductive gland elements at the caudal pole is completed. Since an epithelial thickening is present cranial to the sixth thoracic segment in the line of the anlage of the reproductive gland, the anlage may be regarded as reaching almost to the cranial end of the definitive body cavity. But no matter how far cranially we place the cranial end of the reproductive gland area, its cranial pole never reaches the cranial end of the urogenital fold. The caudal pole comports itself differently in the two sexes; while it reaches the dorsal surface of the

genital cord in the female and so comes to lie within the excavatio recto-uterina, in the male it remains above the horizontal portion of the urogenital fold.

In the following table I give determinations of the position of the upper and lower reproductive gland poles in a series of embryos and, when possible, the length of the entire anlage.

Table showing the Growth in Length and the Degeneration of the Reproductive Gland.

Embryo.	Direction of section.	Right gland.		Left gland.		Length of gland in micra	
		Cranial.	Caudal.	Cranial.	Caudal.	Right.	Left.
10 mm.	Transverse	6 Th	12 Th	7 Th	12 Th	.....	.....
11 "	"	7 "	1 L	7 "	1 L	.....	.....
12.5 "	"	8 "	1 "	8 "	1 "	.....	.....
13 "	Sagittal	**9** "	**2** "	**9** "	**2** "	.....	.....
13 " ♀?	Transverse	9 "	3/4 "	10 "	3/4 "	2805	2325
14.75 " ♂	Sagittal	....	**4** "	**9** "	.....	.....	.....
17 " ♀	Transverse	10 "	3 "	10/11 Th	3 "	.....	.....
18 " ♀	"	10 "	3 "	10/11 "	3 "	1720	1550
19.4 " ♀	"	11 "	3/4 "	10/11 "	3 "	2100	2010
21 " ♂	"	1 L	4/5 "	12/1 Th/L	5 "	1270	1550
22 " ♀	Sagittal	....	.....	**2** L	**5** "	.....	.....
22 " ♀	"	...	.....	**12/1** Th/L	**5** "	.....	.....
22.5 " ♂	Transverse	12 Th	3/4 "	12 Th	3/4 "	.....	.....
26 " ♂	"	1 L	3/4 "	12/1 Th/L	3/4 "	1290	1575
28 " ♂	"	12/1 Th/L	4 "	.....	4 "	1540	.....
28 " ♀	"	3 L	5 "	2 L	5 "	.....	.....
28.5 " ♀	"	1 "	3 "	1 "	3/4 "	.....	.....
29 " ♀	Sagittal	**1** "	**5** "	.....	.....	.....	.....
30 " ♀	Transverse	3 "	5 "	.....	.....	1500	1800
30 " ♀	"	2/3 "	5 "	3 L	5 "	2490	1980
35 " ♀	"	3 "	5 "	4/5 "	.....	1740	.....
50 " ♀	"	4 "	2 Sa	4/5 "	.....	.....	.....
60 " ♀	"	3/4 "	5/1 L/Sa	5 "	5/1 L/Sa	.....	.....
60 " ♂	"	5 "	1/2 Sa	5 "	1/2 Sa	.....	.....
70 " ♂	"	4 "	1/2 "	5 "	1/2 "	.....	.....

Explanation of Table: The table represents measurements from transverse and sagittal sections. The determinations of the position from sagittal sections are certain and their figures are printed in heavy type; the direction of the transverse sections varied in the various series and according as they were craniodorsal –caudoventral or caudodorsal–cranioventral they might yield quite different results.

The table shows the gradual extension of the anlage of the reproductive gland; it reaches in maximo from the sixth thoracic to the second sacral segment, that is to say, over fourteen segments, and, eventually, it extends over only three or four, so that it degenerates in ten to eleven segments.

The table also shows the caudally directed growth of the anlage. The caudal pole gradually descends from the 12th thoracic to the 2nd sacral segment (at least in female embryos). The caudal pole—whether the embryo be male or female—lies from the beginning as low as or very frequently lower than in the

adult and, accordingly, the so-called internal descent of the testis and ovary vanishes, neither really exists. The cranial pole of the gland does, indeed, change its position, but it changes not because it descends, but because the upper three-fourths of the gland degenerates. What seems to be a descent reveals itself to be a shortening, and we may see from the table that the absolute length

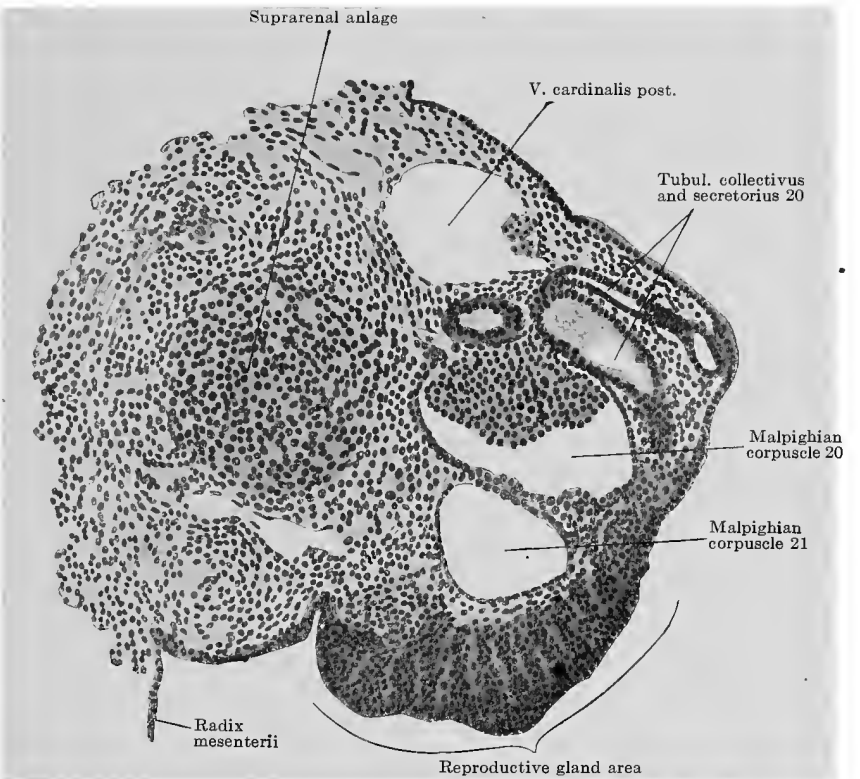


FIG. 613.—Transverse section of the urogenital fold of a human embryo of 11.0 mm. greatest length, 9.0 mm. head-foot length. (Embryo P. 1, from the collection of Professor Hochstetter, Vienna.) × 150. Almost all the parts of a mesonephric tubule are cut. Medial to the tubule is the suprarenal anlage; the mesonephric fold lies in the frontal plane, its summit is marked by the primary excretory duct and a dorso-lateral and a ventral surface may be distinguished. At about the middle of the ventral surface is the thickening of the peritoneal epithelium which forms the reproductive gland area. This consists solely of cœlomic epithelial cells, which are becoming somewhat loosely arranged. No differentiation whatever of the epithelial mass is to be seen.

of the gland diminishes in spite of its progressive growth in length along with the growth of the entire body. That the ovary eventually becomes rotated so that the cranial pole becomes the lateral and the caudal the medial, this has nothing to do with a descent, for during the rotation the caudal pole does not come to lie at a lower level. As regards the conus inguinalis (see p. 793), the mark for the later abdominal opening of the inguinal canal, the caudal pole of the reproductive gland lies lower than it does in both sexes.

The indifferent stage of the reproductive gland lasts only a short time. During it the uniform epithelial mass of the genital fold separates into a superficial epithelium and an epithelial nucleus, a sharp boundary existing between the two. The surface epithelium retains its closed epithelial structure and may consist of from one to at most two layers. The nucleus becomes looser in texture, so that at the end of the indifferent stage its epithelial origin is no longer evident.

The Differentiation of the Reproductive Glands.

In the differentiation of sex we must distinguish between the differentiation of the genital cells into spermatogonia or öogonia and the differentiation of the genital cell mass, the actual reproductive gland, into testis or ovary. This distinction finds its justification, in the first place, in the fact that a reproducive gland may assume the characters of a testis without forming spermatogonia, as is the case with cryptorchid testes, and, in the second place, in the occurrence of malformations, scattered ova in testicular tissue or testicular ampullæ in the ovary.

Whether or not a differentiation of genital cells into spermatogonia or öogonia really occurs is yet an open question. It is possible that the future sex of all the genital cells is already determined at fertilization. Every sex-cell, no matter whether it is male or female, possesses a definite force of heredity, which, during the course of development, becomes increased, or perhaps is only made more active, and reaches an optimum stage, after which it perhaps diminishes or become less active. In the optimum stage each sex-cell may possess the power of reproducing the other sex, the ovum males and the spermatozoa females (crossed inheritance). If now the ovum and spermatozoon unite during fertilization, differences in the immaturity, maturity or over-maturity of the two bring about numerous combinations, the stronger partner, that is to say the one which is nearest the stage of maturity, whether it be on the side of immaturity or over-maturity, will dominate in the determination of the sex. And the further possibility is not to be dismissed off hand, namely, that there are sex-cells of different types, male and female ova, etc. All these questions are not as yet ready for settlement, but will play an important part in the immediate future and therefore must at least be mentioned here.

The differentiation of the reproductive gland into testis or ovary is actually to be observed. The opponents of the theory that the sex of the ovum is already determined, overstep the mark when they deny a differentiation of the reproductive gland.

This differentiation consists in the characters of the male gland being developed in embryos of 13 mm. greatest length, at the

earliest, while the female reproductive gland of the same age still lingers in the indifferent stage. The two characters of the male gland are:

1. The occurrence of branched, anastomosing epithelial cords, the testis cords. 2. The occurrence of a broad tunica albuginea between the superficial epithelium and the testis cords. It is therefore possible in young stages to identify the male individuals positively, and the females per exclusionem. One may say that the embryo has reached the age when testis cords should be present; they are not present and therefore the embryo must be a female. Such a determination has always chances of error and the doubts of the observer increase the more the embryo reaches the limits of the indifferent stage. Probably no observer will venture to label an embryo of from 13 to 15 mm. greatest length as a female, if he finds in it no testis cords; the possibility that it is a case of retarded differentiation of a male, can never be excluded. Under these circumstances the small sexual differences in other organs acquire increased importance, because they are positive for the female sex. The formation of accessory funnels on the Müllerian duct seems to occur only in the female sex. Since the principal funnel occurs in embryos of 11 mm. and accessory funnels certainly in those of 13 mm., these latter will supply a valuable means for sex diagnosis, provided that further observations on a larger amount of material show that accessory ostia actually occur only in female embryos and that all female embryos develop them. Accessory tubes are too rare to be of use for sex diagnosis, but, on the other hand again, the presence or absence of the excavatio vesico-uterina is an important sign. The genital cord, by whose fusion with the dorsal wall of the bladder the excavatio is formed, is, indeed, first seen only in embryos of 20 mm., but the fusion of the urogenital folds (by whose union the genital cord is formed) with the posterior wall of the bladder takes place in male embryos before their union. The formation of the excavation in female embryos and its absence in males is a regularly occurring phenomenon.

By employing all these means the beginning of the sexual differentiation may be determined in female embryos at a stage of 18 to 20 mm. in length.

Transformation of the Indifferent Reproductive Gland into the Testis.

The differentiation of the sexless reproductive gland into the testis will be considered first, because in this case the relations are much simpler than in the differentiation into the ovary.

We left the indifferent reproductive gland at the stage of development in which the epithelial mass had separated into a superficial epithelium and the epithelial nucleus. This separation

is preserved throughout the entire development of the testis. Consequently the epithelial nucleus alone is the active layer, it forms the tunica albuginea, the testis tubules and the rete testis; the superficial epithelium remains passive and grows only in proportion with the enlargement of the entire organ, it is for the most part one-layered, several cell layers being present only on the surface opposite the attachment of the mesorchium; the greater portion of its cells are indifferent epithelial cells, among which genitaloid cells are scattered here and there. The superficial epithelium has, therefore, the character of a germinal epithelium formally but never functionally, and since it very early loses the genitaloid cells it is better not to speak of a germinal epithelium, but to adhere to the indefinite name "superficial epithelium."

The epithelial nucleus becomes very loose and develops quite suddenly the *testis cords,* the loosely arranged cells concentrating at certain places, separating incompletely from their surroundings and arranging themselves to form anastomosing cords. It seems as if all the testis cords are formed at once, and the subsequent enlargement of the organ depends entirely on the elongation of the tubules, on their coiling, which is associated with their elongation, and on their increase in diameter. The cords are arranged transversely to the long axis of the testis, their inner ends, being arranged around the point of insertion of the mesorchium—indicating at once, therefore, the future hilus—while the outer ones radiate towards the surface of the testis (Fig. 614). The outer end of each cord is thickened, the inner one is pointed, and all the inner ends unite to form a closely aggregated epithelial mass (Fig. 614), which extends along the insertion of the mesorchium throughout the entire length of the embryonic testis; this epithelial mass contains the cells that will form the anlage of the rete testis and may therefore be termed the *rete blastema.* This blastema stands in no relation to the parts of the mesonephros, except for its association with the epididymis tubules. The outer ends of the cords never reach the superficial epithelium, but a layer of at least two or three or usually more cells intervenes, from which the tunica albuginea develops. At first the testis cords have an irregular form on cross section, but later they become distinctly round. Since they all converge to the narrow line of insertion of the mesorchium, they cannot all reach the rete blastema, and therefore they unite by twos or threes in order to attain this connection in common. They are united together by anastomoses which are distinctly arranged in two groups; the one group lies about midway between the periphery and the hilus, the other unites their peripheral ends. These peripheral anastomoses are so constantly arranged in the same direction that they appear like large arches into which the testis tubules open (Fig. 614). The testis

cords are so arranged that they leave intervals or intermediate cords between them, of the same width as themselves (Figs. 614 and 615). At the boundaries between the two there is even in an embryo of 21 mm. a distinct formation of connective tissue, consisting of spindle-shaped cells arranged one behind the other and alongside each other, all with their long axes parallel to the long axes of the testis cords (Figs. 614 and 615). Thus there are formed around the individual testis cords and their anastomoses

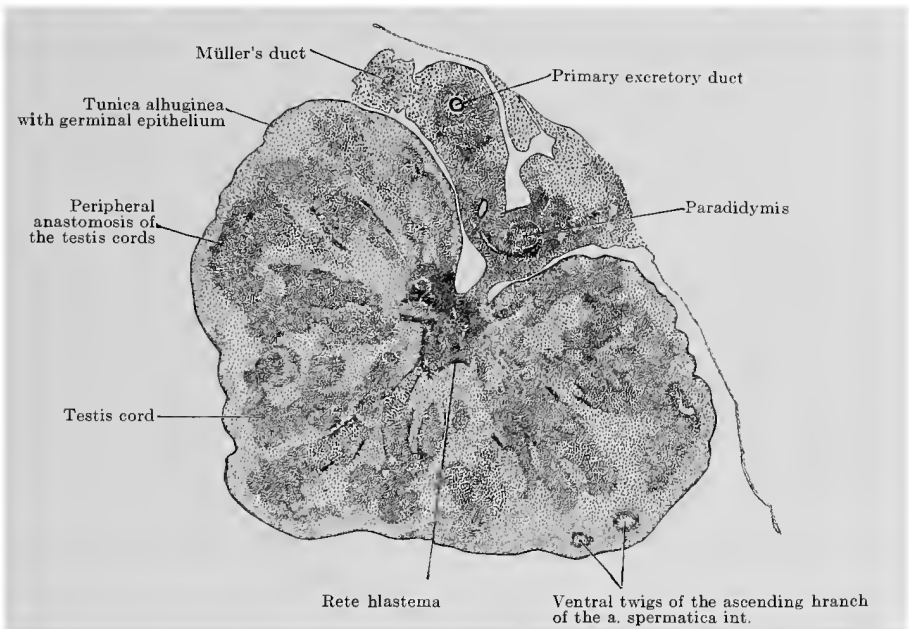


Fig. 614.—Transverse section of the testis of a human embryo of 70 mm. head-foot length. (Embryo R. Meyer 267; slide 35, row 3, section 3, from the collection of Professor R. Meyer, Berlin.) ×50. Solid testis cords have appeared in the testis and are connected by anastomoses at their middle and at their outer ends. The majority of them have already acquired an investment of young connective tissue. Their inner ends unite at the mesorchium to form the rete blastema and their connective-tissue sheaths form a connective-tissue boundary around the blastema, the first indication of the mediastinum testis. Two distinct layers may be recognized in the tunica albuginea, an outer one of connective tissue and an inner one composed of what are still indifferent epithelial cells. At the boundary between the two are twigs of the ascending branch of the a. spermatica int.

actual connective tissue sheaths; at the hilus all the sheaths unite to form a boundary around the rete blastema, surrounding it in a zig-zag line (Fig. 614); this is the anlage of the mediastinum testis.

The testis cords consist at first of numerous indifferent epithelial cells with dark, homogeneous nuclei. Between these lie scattered genitaloid cells, which very soon develop to genital cells (Fig. 615). These are usually present in embryos of 70 mm. head-foot length, while the genitaloid cells appear simultaneously with the testis cords. The narrow inner ends of the cords contain only indifferent cells; the tubuli recti are formed from them. The testis

cords once formed alter little during the fetal period. The indifferent cells, that at first are altogether without arrangement, gradually acquire one, their nuclei become oval and place themselves radially to the future lumen. Thus there is formed a many-layered epithelium, into which the genital cells enter as spermatogonia (Fig. 616 *a*). The first lumina appear quite irregularly at the outer ends of the solid testis cords in the seventh fetal month. They arise partly by the migration of the cells from the centre to the periphery, partly by the resorption of the inner cells. From the outer ends the lumen gradually extends towards the hilus, and a second lumen extends from the rete testis along the tubuli recti

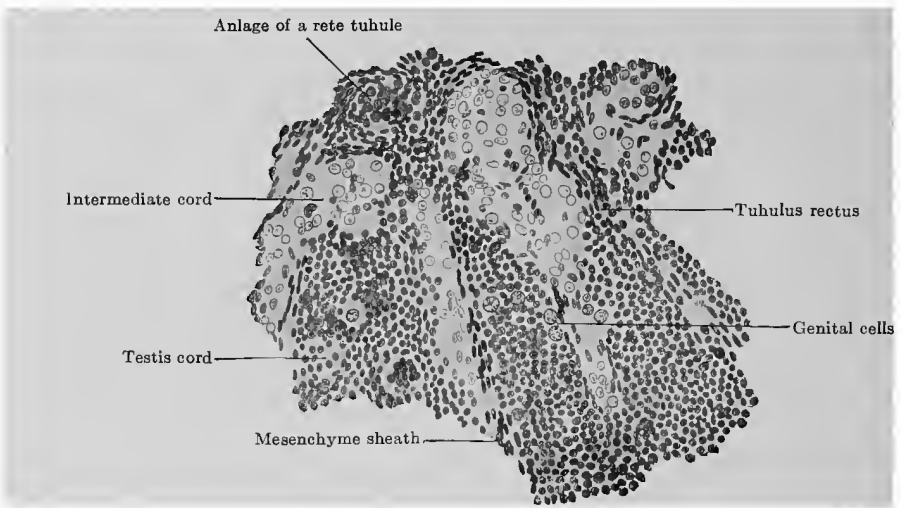


FIG. 615.—Part of a transverse section through the right testis of a human emhryo of 70 mm. head-foot length. (Emhryo R. Meyer 267; slide 35, row 1, section 2, from the collection of Professor R. Meyer, Berlin.) The testis cords are shown as they pass into the rete hlastema. One sees the structure of the testis cords from indifferent epithelial cells and genital cells, and, further, their passage into tubuli recti. Between the testis cords are the intermediate cords, filled with cells whose nuclei are vesicular and remarkably poor in chromatin.

towards the first one, the two meet and thus the testis tubules, the tubuli recti and the rete tubules become hollow. All the testis cords are not transformed into tubules at birth. According to the observations of Branca and Basseta (1907) the number of genital cells increases progressively from the fifth month up to birth; after birth all the genital cells disappear and the testis tubules are lined by indifferent cells alone. With the onset of puberty a new generation of genital cells is formed, which then enter upon the formation of spermatozoa. The results of these two authors have been confirmed by Popoff (1909). I have no personal experience on this question and can only point out that in a human embryo of the seventh month obtained by laparotomy the number of genital cells had not diminished and that a well-preserved testis from a newborn child showed a remarkable number of genital cells.

The intermediate cords are at first composed of indifferent and genitaloid cells, but later the indifferent cells disappear almost completely; I assume that they are employed in the formation of the connective tissue sheaths. In embryos of 45 mm. greatest length the genitaloid cells are transformed into large pale cells (interstitial cells), which resemble genital cells in shape and size,

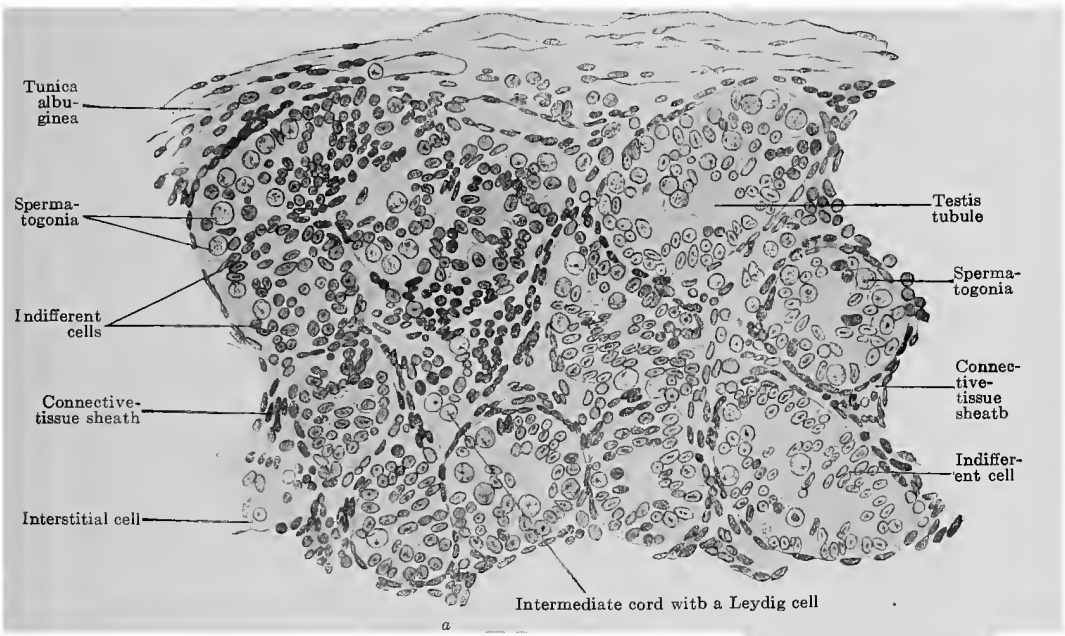


FIG. 616 *a* and *b*.—Transverse section through the testis of a human embryo of the 7th month. (Embryo obtained by operation. From the collection of the Anatomical Institute, Zuricb.) Tbe testis cords have a rounded form; their cells are partly indifferent epithelial cells that are beginning to arrange themselves like an epithelium, and partly genital cells, scattered as spermatogonia among the indifferent cells; in the centre is the remains of an intermediate cord witb Leydig cells. The tunica albuginea is already formed of a distinctly fibrous connective tissue.

but their nuclei contain only little or even no chromatin (Fig. 615). These cells gradually disappear after the fifth month, and in fetuses of the seventh month (Fig. 616) they are still present only here and there beside the vessels in the spaces between the testis tubules. After birth an abundant connective tissue develops between the tubules, and, as a result, the number of interstitial cells diminishes still further; after puberty (in the 33rd, 37th and 40th year) they again appear to occur in increased numbers (Popoff 1909).

The septula testis are formed by the thickening of the connective tissue sheaths of the testis cords. After the resorption of the

intermediate cords the sheaths of adjacent testis cords come into apposition and then appear as a single structure, which extends radially from the hilus to the periphery. True septula testis are present from the sixth fetal month onwards.

It has been stated that the rete blastema is derived from a cell mass formed by the union of the thin inner ends of the testis cords. It extends throughout the entire length of the testis, leaving only the cranial and caudal poles free. It is certainly a derivative of the epithelial nucleus and is always, in young stages, sharply defined from the mesonephros and its mesenchyme. One sees, indeed, sharply defined mesonephric tubules passing in the region of the epididymis as far as the rete blastema and even producing depressions in it, but one never sees a proliferation arising at their blind ends, from which the rete blastema might be derived. A union between them and the rete occurs later as the urogenital union and will be discussed under this title in a special section. The rete blastema is surrounded by a mantle of young connective tissue on the surface towards the testis (Fig. 614). In the blastema there now occurs at definite points a concentration of the cells and there are formed irregular solid spheres of cells, imperfectly bounded externally. The individual spheres are connected by straight cords and there is thus formed a solid network (rete testis) which gradually becomes more distinct by the remaining cells of the blastema assuming a spindle shape and becoming connective tissue cells (Fig. 615). From these spindle-shaped cells of the rete and from the connective tissue boundary that separates them from the testis tubules the mediastinum testis is developed. Since it is derived from the rete blastema, like this it must extend throughout the entire length of the testis, as it actually does in the testes of older fetuses and in those of new-born children. When, at puberty, an unequal growth of the testis occurs, the mediastinum comes to lie more in the cranial two-thirds of the organ.

The tunica albuginea appears simultaneously with the formation of the testis cords and represents simply the cortical portion of the epithelial nucleus that is not traversed by the cords; it is accordingly formed at first only of scattered, loosely arranged, round cells. Then the cells lying immediately below the superficial epithelium begin to be transformed into connective tissue, whose spindle-shaped nuclei are all parallel to the surface (Fig. 614). The remains of the epithelial bounding layer that is not converted into connective tissue increases very greatly; thus there is gradually formed an exceedingly thick bounding layer, which step by step from the periphery is transformed into connective tissue. In fetuses of the fifth month there is already a broad connective tissue tunica albuginea.

Malformations of the Testis.

Only those malformations that are due to inhibitions of development will be considered, and no mention will be made of those resulting from pathological processes.

A testis may be lacking, in which case the entire urogenital fold has usually failed to form, and therefore the kidney, ureter, ductus deferens, and suprarenal body of the same side will also be lacking.

The testis may be doubled. Ahlfeld (1880) records only one autopsy in which the duplication was observed; all other cases were determined during life and are therefore not certain. One must guard against errors in diagnosing a duplication; Romanovsky and von Winiwarter (1905) have described a case in which the right and left testes were both situated in the left scrotal sack.

Both testes may come into contact in the median line and may be united together; in such a case they will lie between the bladder and the anterior abdominal wall. In one embryo (R. Meyer, 270) of 60 mm. head-foot length the two testes had their hilus sides turned towards each other, the retia testis being well developed and fused.

The form of the testis may be completely normal macroscopically, while the microscopic examination shows that spermatogonia are completely lacking; the testis was accordingly sterile. This sterility is usually associated with cryptorchism.

The Transformation of the Reproductive Gland into the Ovary.

The indifferent reproductive gland consists of an epithelial nucleus and a superficial epithelium, both sharply separated from one another. But while in the testis this first separation is a permanent one and the superficial epithelium is reduced to an insignificant investment, this is not the case in the ovary. Between embryos of 70 mm. head-foot length (this limit may perhaps be placed somewhat earlier) and those of 180 mm. head-foot length there is a development period in which the superficial epithelium is sometimes only indistinctly and sometimes not at all marked off from the subjacent epithelial nucleus. Whether this undeniable new union between the two parts is to be regarded as a new impulse by which a second epithelial nucleus is formed from the superficial epithelium, cannot be determined with certainty. The arguments pro and con will be considered later on and it will suffice at this point to indicate the possibility of such an impulse; for by it the superficial epithelium of the female reproductive gland acquires the significance of a germinal epithelium, and even although it contains no genital cells, yet it has cells which are able to transform themselves into these and into young ova. The superficial epithelium possesses the significance of a germinal epithelium, however, only during the period mentioned above. In embryos of 180 mm. trunk-length, a connective tissue layer, the tunica albuginea, develops between it and the epithelial nucleus, and with this a sharp delimitation of the epithelial nucleus occurs, the tunica forming a partition which excludes any further participation of the germinal epithelium in the formation of young ova;

the germinal epithelium thus again becomes a simple superficial epithelium.

In older fetuses and in new-born children foldings of the surface epithelium occur, but they have nothing to do with the formation of ova, indicating only the completion of the lobed form of the ovary. Solid, hair follicle-like, downwardly growing epithelial cords are formed from the superficial epithelium, but they never extend beyond the limits of the albuginea and again degenerate without effect.

The actual reproductive gland producer is the epithelial nucleus. In embryos of 22 mm. greatest length it is composed of

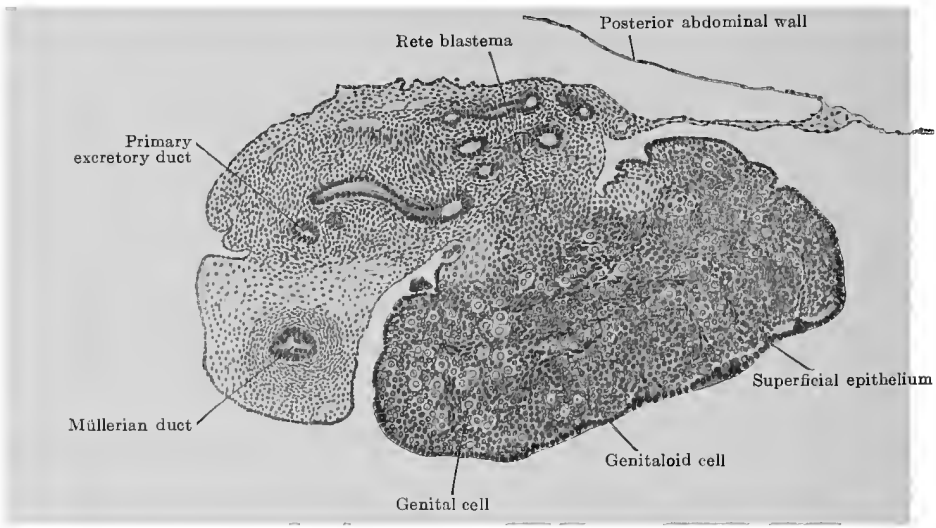


FIG. 617.—Transverse section of the ovary of a human embryo of 50 mm. head-foot length. (Embryo R. Meyer 272; slide 2, row I, section 2, from the collection of Professor R. Meyer, Berlin.) × ca. 75. The section shows the triple division of the mesonephric fold into a tubal portion with the Müllerian duct, a gland portion with the primary excretory duct and mesonephric tubules and, finally, a very thin mesentery portion. In the ovary the superficial epithelium is distinctly separated from the epithelial nucleus. The nucleus is indistinctly dividing into a medullary layer, with numerous genital cells, and a cortical layer, poor in genital cells. Numerous trabeculæ of young connective tissue occur in the epithelial nucleus. The rete blastema is partly in the mesovarium and contains genitaloid cells.

indifferent cells with sparingly scattered genitaloid and genital cells and it shows this composition up to embryos of 50 mm. head-foot length (Fig. 617). The nucleus fills the entire space enclosed by the superficial epithelium and also projects like a knob into the mesovarium. This knob consists of indifferent cells and very few genitaloid cells; it forms the rete ovarii and therefore deserves the name of rete blastema. Between the stages of 50 mm. and 80 mm. head-foot length the epithelial nucleus begins to become looser, starting from the rete blastema which remains unaltered, and one can distinguish a clear medullary zone from a denser cortical zone (Fig. 618). The loosening may occur under most varied forms; the special example represented in Fig. 618 shows a struc-

tureless medullary zone and a cortical zone that is incompletely broken up into anastomosing cords.

In the epithelial nucleus three concomitant but independent processes occur: (1) the ingrowth of connective tissue and vessels from the hilus towards the periphery; (2) the conversion of most

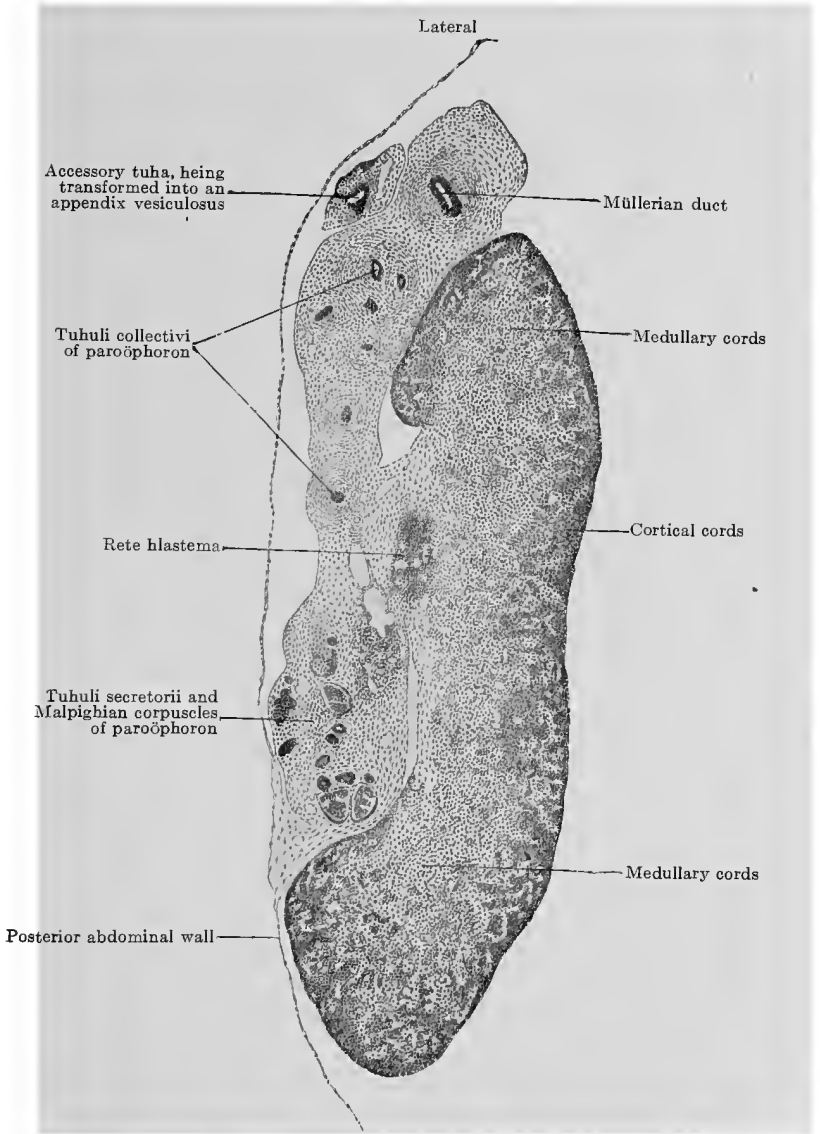


FIG. 618.—Transverse section of the left ovary of a human emhryo of 80 mm. hcad-foot length. (Emhryo 266; slide 31, row 1, section 2; from thc collection of Professor R. Meyer, Berlin.) ×40. The section passes longitudinally through the upper horizontally hent part of the ovary and hence its apparent breadth. The epithelial nucleus has divided into medullary and cortical zones and the retc hlastema is distinctly at the attachment of the mesovarium. Besides the Müllerian duct there is an acccssory tuha, the portion of the mesonephric fold that contains it has already separated and we have before us the anlage of the appendix vesiculosus. The mesonephros is in complete degeneration; the section cuts it in the region of the paroöphoron, and one may see how far the tubuli collectivi have already separated from their tubuli secretorii and Malpighian corpuscles.

of the genitaloid and indifferent cells into young ova, and (3) the new formation of the epithelial nucleus at the periphery, that has already been mentioned. While in the epithelial nucleus of the testis active testis cords appear, this is never the case in the ovary, its epithelial nucleus forming no cords, but becoming split up into portions of the most varied forms by ingrowing connective tissue. The first traces of the connective tissue are seen in embryos of 28 mm. and are at first without regularity (Fig. 617). Then they gradually arrange themselves so that one can recognize a central investment around the rete blastema, a sort of *mediastinum ovarii,* and bands radiating out from this, the *septa ovarii* (Fig. 619). The septa traverse the central two-thirds of the transverse section and then begin to develop lateral branches and send out several apical shoots. These branches and shoots unite with those of neighboring septa so that a network is formed, which has wide and coarse meshes in the so-called medullary zone and narrow and fine ones in the so-called cortical zone; the fine cortical network eventually extends to the under surface of the superficial epithelium. The form of the meshes is exceedingly variable, the one extreme—very rare and only observed in one case—shows long rectangular meshes containing long, slender epithelial cords, such as are seen in the ovaries of other mammals, which unite to form a trabecular network like that occurring in the medullary cords of lymph-nodes; the other extreme—very frequent —shows polygonal meshes containing plump masses of the epithelial nucleus of most varied forms and all, of course, in connection. Between the two extremes are all sorts of intermediate forms, one of which is shown in Fig. 620.

Almost simultaneously with the connective tissue the first vessels appear at the hilus—probably in situ—and they grow towards the periphery more slowly than the septa. Since the vessels have a definite diameter and since, also, they produce a stronger development of the surrounding connective tissue, there is for a time a rather sharp distinction in the mesh-work of the connective tissue between a medullary zone with vessels and a cortical zone without them. The boundary between the two may coincide with that between the medulla and cortex, as this is drawn out by the loosening up of the medullary cells (Fig. 618) or, what is most frequently the case, there is no coincidence. It follows that a precocious differentiation into medullary and cortical zones is somewhat doubtful, since different processes—we shall hear of others—cause a separation into different cortical and medullary zones.

The tunica albuginea is also a formation of the septa ovarii. One sees (Fig. 620 *a*) how prolongations of the septa reach the superficial epithelium and then begin to creep under it. The more

prolongations reach the surface the more compact becomes the layer formed by them beneath the superficial epithelium and the more distinct does the tunica become. It is difficult to assign a definite time for the beginning of its development. I have chosen the stage of embryos of 180 mm. trunk length, because in these the connective tissue prolongations first reach the superficial epithe-

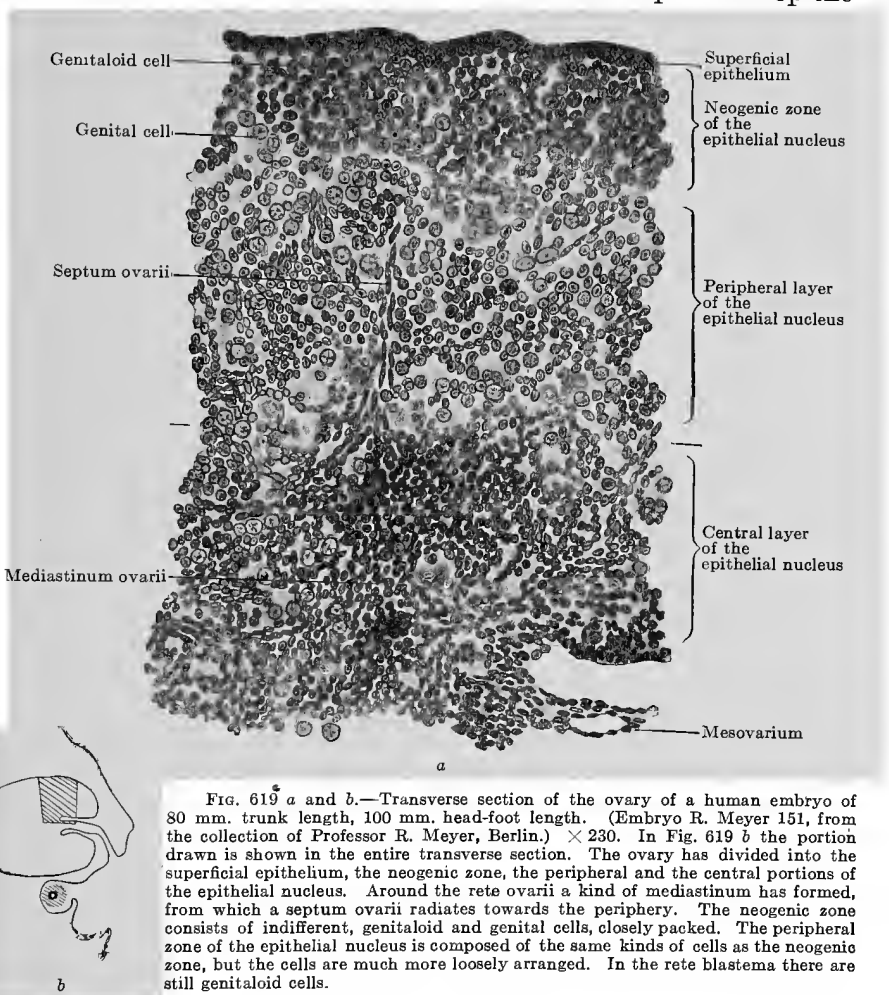


FIG. 619 *a* and *b*.—Transverse section of the ovary of a human embryo of 80 mm. trunk length, 100 mm. head-foot length. (Embryo R. Meyer 151, from the collection of Professor R. Meyer, Berlin.) × 230. In Fig. 619 *b* the portion drawn is shown in the entire transverse section. The ovary has divided into the superficial epithelium, the neogenic zone, the peripheral and the central portions of the epithelial nucleus. Around the rete ovarii a kind of mediastinum has formed, from which a septum ovarii radiates towards the periphery. The neogenic zone consists of indifferent, genitaloid and genital cells, closely packed. The peripheral zone of the epithelial nucleus is composed of the same kinds of cells as the neogenic zone, but the cells are much more loosely arranged. In the rete blastema there are still genitaloid cells.

lium. An actually closed layer is formed only later. Fig. 621 shows the tunica of an embryo of eight months; one sees the connective tissue septa entering it perpendicularly and then bending in arches to a horizontal direction. It is noteworthy that the folds of the ovarial surface, mentioned above, occur at the places where a perpendicular connective tissue strand enters the tunica.

The transformation of the indifferent and genitaloid cells into genital cells and young ova begins in the immediate vicinity of the

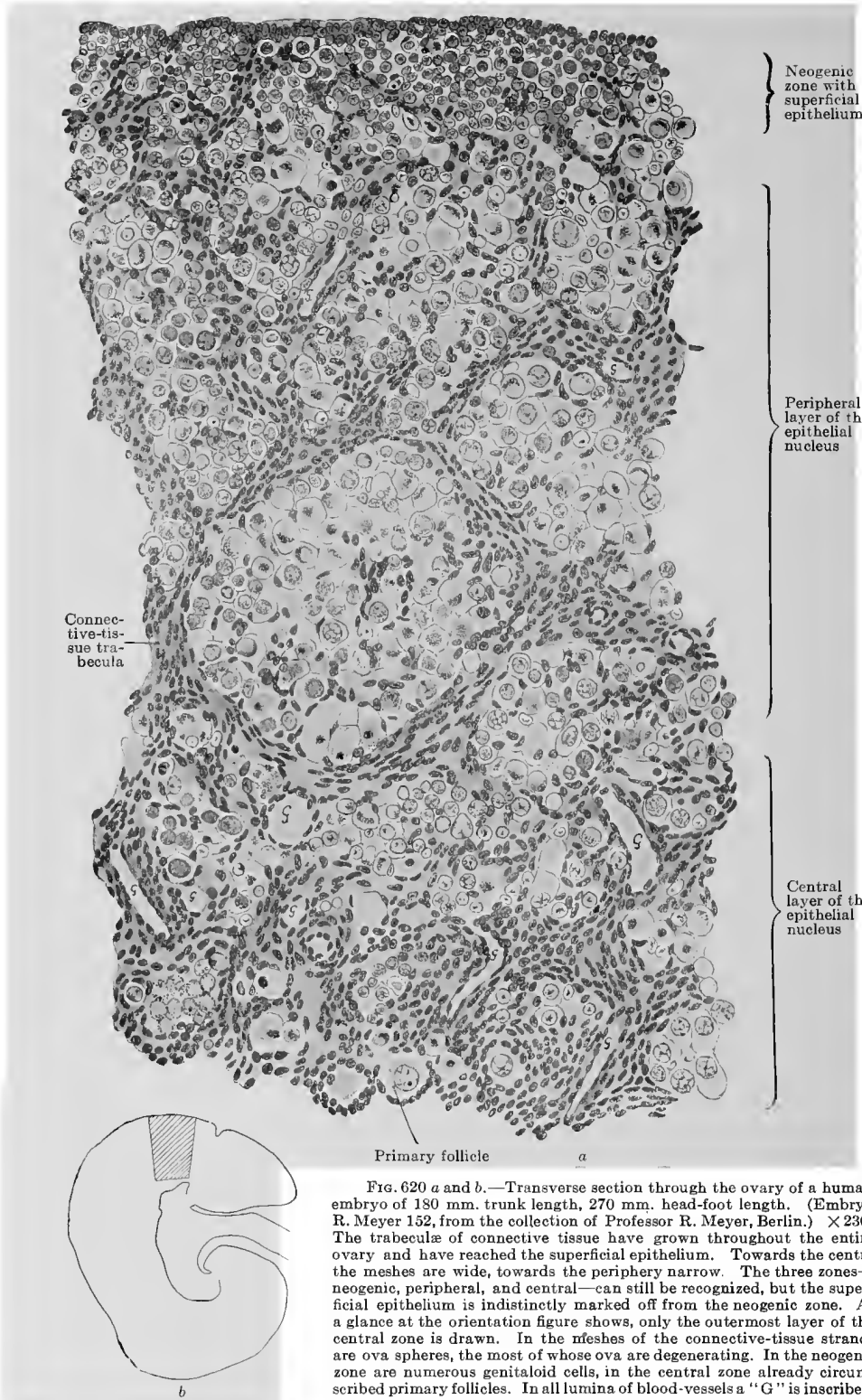


FIG. 620 *a* and *b*.—Transverse section through the ovary of a human embryo of 180 mm. trunk length, 270 mm. head-foot length. (Embryo R. Meyer 152, from the collection of Professor R. Meyer, Berlin.) × 230. The trabeculæ of connective tissue have grown throughout the entire ovary and have reached the superficial epithelium. Towards the centre the meshes are wide, towards the periphery narrow. The three zones—neogenic, peripheral, and central—can still be recognized, but the superficial epithelium is indistinctly marked off from the neogenic zone. As a glance at the orientation figure shows, only the outermost layer of the central zone is drawn. In the meshes of the connective-tissue strands are ova spheres, the most of whose ova are degenerating. In the neogenic zone are numerous genitaloid cells, in the central zone already circumscribed primary follicles. In all lumina of blood-vessels a "G" is inscribed.

rete blastema and proceeds thence towards the periphery. This transformation process enlarges the poorly staining cell bodies and makes the nuclei paler, so that the central portion of the medulla appears very pale in comparison with the peripheral portions and with the cortex. If the transformation of the indifferent cells begins with the development of the connective tissue and vessels and progresses synchronously with these towards the surface, a marked distinction is established between medulla and cortex: the "medulla" is traversed by a broad, vascular connective tissue network, in whose coarse meshes are pale, young ova; the "cortex" is traversed by fine connective tissue trabeculæ, whose narrow meshes contain dark indifferent cells. This synchronous progress is, however, of rare occurrence. The two processes are usually not only unequally advanced, but one of the processes may show very different degrees of progress at different parts of the same ovary; there is thus brought about so much confusion that the determination of a boundary between the medulla and the cortex becomes impossible.

At first the ovary grows rapidly. A comparison of the transverse sections 619 and 620, both drawn under the same magnification, shows this at once; so much of Fig. 619 as extends from the surface to the transverse line corresponds to the entire Fig. 620. While the length of the body has increased in the proportion of 4:9, the ovary has grown in the proportion of 7:22. The growth of the testis is quite regular, the tubules elongating and enlarging and also the intermediate cords and the tunica albuginea. The ovary grows irregularly, the cortical portion of the epithelial nucleus alone undertakes the new formation of indifferent and genitaloid cells, the medullary portion remaining unaltered; a young cortical zone is thus developed over the old epithelial nucleus. Whence this young cortical zone comes I cannot say with certainty; there are, however, two possibilities which may act singly or together. On the one hand, the indifferent and genitaloid cells of the cortical zone of the epithelial nucleus divide and thus, notwithstanding the progressive transformation of the cells of the nucleus into young ova, a new neogenic cortical zone may be continually reformed, just as the neogenic zone of the growing metanephros continually regenerates, notwithstanding its transformation into uriniferous tubules. In favor of this mode of development are the mitotic figures and the gradual transition of the cortical zone of the epithelial nucleus into the neogenic zone. The second possibility has been referred to above; just as the cœlom epithelium grows in to form the epithelial nucleus at the beginning of the development of the reproductive gland, so the process may repeat itself, the superficial epithelium alone forming the neogenic zone. In favor of this mode is the temporary impossibility of distinguish-

ing the epithelium from the neogenic zone; against it is the striking absence of mitoses in the epithelium. I assume, therefore, that the principal growth takes place in the cortical layer of the epithelial nucleus and that only a very slight addition, if any, takes place from the superficial epithelium. But no matter how the development of the neogenic zone occurs, cords are never formed, the zone always forms a single mass. I come to the conclusion, therefore, that *Pflüger's cords* do *not* occur in man.

As soon as the neogenic zone has appeared it becomes modified by the two processes described above; the connective tissue divides it into irregular masses of cells connected with each other and the cells for the most part become transformed into ova. According as the two processes develop quickly or slowly and according as they proceed continuously or are interrupted by pauses, we find a broad or a narrow neogenic zone.

While epithelial material is being newly formed at the periphery, a degeneration of genital cells and young ova takes place at the centre from the third month onwards. In the destruction of both kinds of cells the nucleus is first broken down, its chromatin becomes massed and the nuclear membrane disappears (Fig. 620). The first sight of such a picture as is shown in Fig. 620, when whole meshes are filled only with degenerating cells, suggests that the process is not a normal one; it is only when one finds such pictures over and over again and finds no ovary of the last fetal months without degenerating cells that one becomes convinced that the destruction is a normal process. It progresses from within outwards and produces decided differences between the medulla and cortex, since with the destruction of the ova in the medulla there is a formation of the stroma ovarii. When, that is to say, all the epithelial cells in a mesh have been destroyed, the connective tissue grows strongly and fills the entire space, and when adjacent meshes have become transformed into connective tissue there is formed a closed connective tissue nucleus, the stroma ovarii. Gradually the connective tissue consumes in this manner so much of the epithelial nucleus that the old one (medulla *and* cortex) completely vanishes, as is shown in Figs. 617 and 618; layers of the neogenic zone probably undergo the same fate; the cortex of the mature ovary is, accordingly, a product of the neogenic zone alone. In different embryos cortex should not be compared with cortex or medulla with medulla off hand. When statements occur in the literature to the effect that "the medulla degenerates," "the medulla persists in certain cords," "the medulla forms Graafian follicles," they can be confirmed, with an addition, however, to the effect that quite different generations of medulla are under consideration and that in the "medullary portions" cortical portions of younger embryos are included.

All the cell masses and cords in the region of the stroma ovarii are not destroyed by this tissue: some always persist and deserve the name of "cords," since they are completely closed, elongated, sometimes straight and sometimes curved structures. They are always situated close below the rete and therefore are derived from the central portions of the epithelial nucleus; accordingly they are correctly termed "medullary cords." These eventually degenerate, the last disappearing usually towards the close of fetal life, although scattered cords are frequently still to be found in the first year of life and very rarely in the adult ovary.

The extension of the destruction process to young ova varies, so that one finds ovaries that are rich in ova and others that are poor, the number of ova showing very decided differences.

When the formation of cortical substance ceases and the process of destruction, whose final result is the formation of the stroma ovarii, comes to a standstill, the remaining cortical layer becomes broken up by outgrowing connective tissue. In this process also a great variability occurs. The connective tissue may divide the cortex into individual ova (Fig. 621) or into larger masses of ova. Each ovum surrounds itself with an investment of cells, the follicle cells, which are in no way to be distinguished from the surrounding connective tissue cells. The ovum together with its follicle cells form what is termed a primary follicle.

In the first year a part of the primary follicles begin to grow and to be converted into Graafian follicles; scattered Graafian follicles are to be found even in the ninth month. In the second year some of the follicles are fully formed and contain apparently mature ova. In the third year all the characters of the adult ovary are present and from that time onwards there is no further histological differentiation but merely an increase in size (Runge 1906). The question arises as to the fate of these precociously mature follicles. Runge found in a new-born child (in one case only) a true corpus luteum; it is accordingly possible that a new-born child may extrude sexually mature ova in the normal manner, but the usual fate of these precociously formed Graafian follicles is that they become transformed into atretic follicles or undergo cystic degeneration.

The rete blastema, whose formation was described above, remains unaltered for a long time. It always lies partly in the ovary and partly in the mesovarium. Genital and genitaloid cells gradually disappear from it completely and it then consists only of closely packed indifferent cells; the last genital cells in the rete were seen in an embryo of 55 mm. head-foot length. While the rest of the epithelial nucleus is divided up by strands of connective tissue, this is not the case with the rete blastema. It is, indeed, traversed by some blood-vessels, but it always remains a remark-

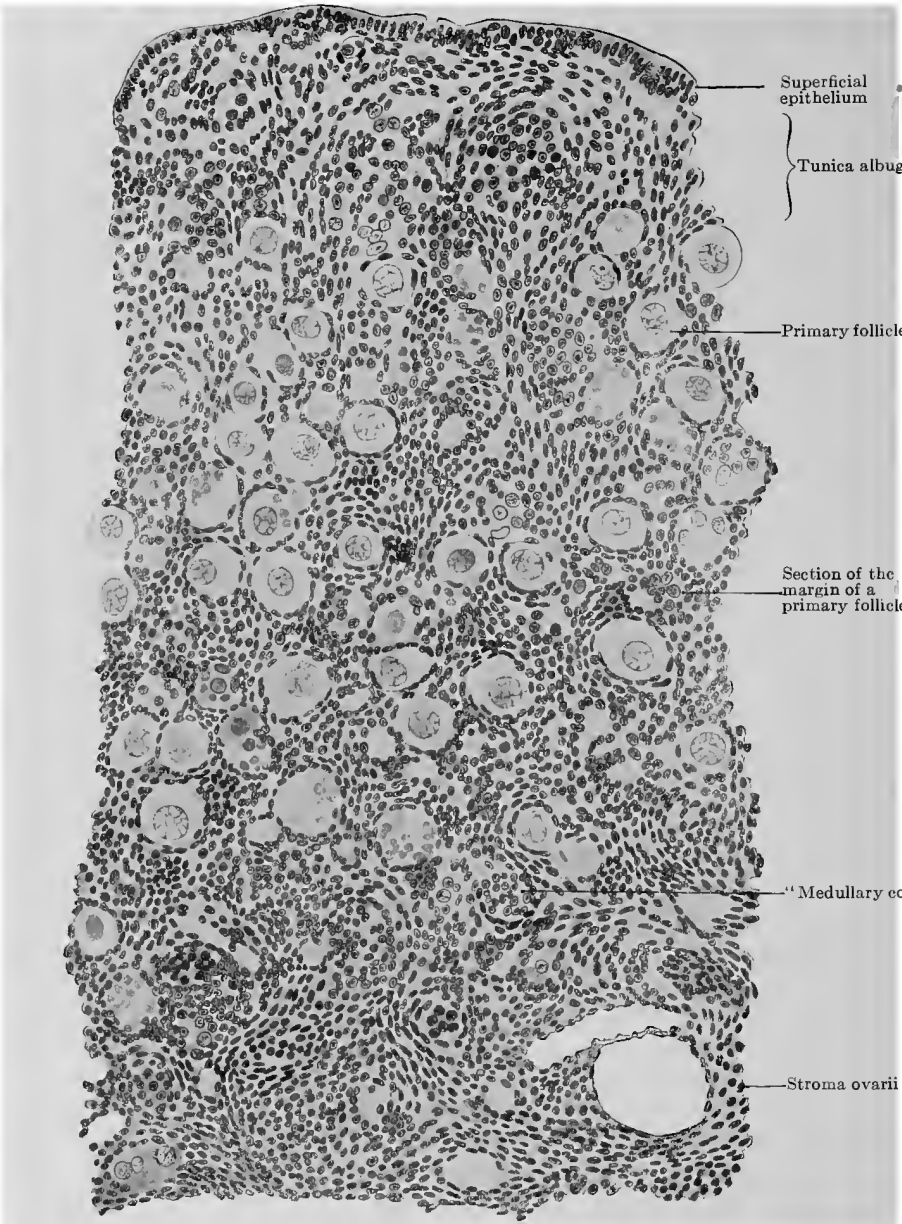


FIG. 621 *a* and *b*.—Transverse section of the ovary of a human embryo of the 8th month. (From the collection of Professor R. Meyer, Berlin.) × 230. The superficial epithelium, tunica albuginea, cortical layer, and medullary layer are all well marked; of the last only the outer third is shown, as may be seen from the orienting figure. In the cortical layer are isolated primary follicles, whose epithelium is formed by genitaloid and indifferent cells and, on account of the latter, cannot be separated from the adjacent connective tissue. The superficial epithelium is sharply defined from the tunica albuginea and prevents thickening where connective-tissue strands ascend vertically towards it. In the stroma there are still remains of "medullary cords" and masses of genital cells.

ably compact mass and is always delimited, though not sharply, from the surrounding tissue. Only towards the medulla of the ovary is it connected with the medullary cords (Fig. 618). In it there arise, in embryos of 60 mm. head-foot length at the earliest, net-like branched areas, in which the nuclei are even more closely packed than in the surrounding tissue; these are the *rete cords*, which are completely solid and are never sharply defined from the surrounding rete blastema. These cords are connected both with the medullary cords and with the tubules of the epoophoron (see under Urogenital Union). Towards the end of the fetal period distinct lumina appear in the solid rete and tubules lined with a single layered epithelium are formed. These tubules may persist throughout life (von Franqué, 1896), but they always show a tendency towards cystic enlargement.

The form of the fully developed ovary is very variable, since it must adapt itself to the space left free by the coils of the intestine. Even more than in the adult the position of the portions of the intestine with reference to each other and to the abdominal wall is very variable in older embryos, and this variability will produce a variability in the space available for the ovaries. The usual form of the ovary may best be compared with a three-sided prism, whose principal surfaces are pointed. The ovaries are sometimes short and thick, sometimes long and slender, sometimes straight, sometimes angled, sometimes twisted spirally. When the ovary has a sagittal direction one can distinguish a dorsal, a ventral, and a medial edge; when it is rotated into a horizontal position the dorsal edge becomes caudal, very rarely cranial, the ventral one cranial, very rarely caudal, the medial one dorsal, very rarely ventral. The three edges are generally sinuous and especially in the case of the medial, later the dorsal ones do not always extend throughout the whole length of the organ. Corresponding to the position of the edges one can recognize a lateral (later dorsal), a dorsal (later caudal) and a ventral (later cranial) surface. In the middle of the lateral surface the mesovarium is attached. Since the dorsal and ventral edges overhang slightly, the lateral surface is sometimes strongly, sometimes weakly concave (Figs. 619 *b*, 620 *b*, 621 *b*). The three edges are sometimes smooth, at other times they are sparingly or frequently notched. The notches are for the most part quite superficial, rarely deep, in which case they may extend for a considerable distance on the surfaces. They are either arranged parallel to one another or may radiate somewhat towards the hilus, but they are never so arranged as to permit of the derivation from them of that form of ovary which, on account of its likeness to the surface of the cerebral hemisphere, is termed an ovarium gyratum. This is not a persistent embryonic form, but one sui generis.

The position of the ovary in older embryos is, like its shape, very variable. The two organs may be quite symmetrical, but they may both be crowded to the same side and assume various positions. In the displacement of both ovaries to the same side portions of the intestine (rectum and sigmoid flexure), excessively filled with meconium, play an important part. The rotation of the ovaries into the horizontal position occurs at very different periods, frequently one still finds the sagittal position in new-born children, frequently the rotation is completed in the fourth fetal month. It is quite possible that each ovary again becomes upright after the rotation and is later again brought into the horizontal position, and these changes may be repeated several times. Until the first year of life both organs lie for the most part in the false pelvis or above the entrance into the

true pelvis; usually they are symmetrically placed, the most striking asymmetry being produced by one ovary having descended into the true pelvis, with its long axis placed sagittally; it is usually the left ovary that undergoes this displacement. According to the position of the coils of the small intestine one finds the ovaries at one extreme pressed against the posterior abdominal wall and at the other against the anterior wall. Between the two extremes all intermediate positions occur; usually they lie in the dorsal portion of the false pelvis, as is to be expected from their development.

The relative position of the ovary and tube also varies. If both are still sagittal, the ovary usually lies medial to the tube. As a result of the degeneration of the mesonephros, especially in its cranial portion, the tube, however, acquires a very broad mesentery, and may be pushed by other viscera over the ventral surface of the ovary to its medial side, in which case the ovary lies in a bay of the plica mesonephridica, completely surrounded by the mesosalpinx. If the rotation to the horizontal position is completed, the tube usually lies ventral and somewhat caudal to the ovary. If the tube and ovary are forced strongly ventrally, the ovary may be pushed over the upper edge of the ligamentum latum and come to lie in the excavatio vesico-uterina, instead of in the excavatio recto-uterina; the tube then lies dorsal to the ovary.

The following table shows data concerning the growth of the ovary. One may see from it that a slow and continuous growth is maintained throughout the entire embryonic period. After birth the rate of increase seems to be somewhat accelerated, but it diminishes again, to increase a second time at puberty. A difference in growth between the left and right ovaries can hardly be perceived.

Vertex-breech length.	Greatest diam. of head.	Right ovary.		Left ovary.		Comparison between			
						Length.		Breadth.	
		Breadth.	Length.	Breadth.	Length.	R.	L.	R.	L.
50.0	42.6	0.9	1.9	0.9	2.5	..	+	−	−
125.0	123.0	1.2	5.9	1.5	4.1	+	..	..	+
138.0	115.0	1.6	5.0	2.0	5.0	−	−	..	+
156.0	131.0	1.9	7.2	2.0	7.1	+	..	..	+
173.0	163.5	3.0	9.0	....	....	..	..	..	..
190.0	175.0	2.9	7.7	2.1	7.8	..	+	+	..
223.0	162.0	2.9	10.5	3.0	9.1	+	..	..	+
235.0	190.0	4.2	10.0	3.8	12.0	..	+	+	..
260.0	213.0	3.6	11.1	4.0	11.4	..	+	..	+
272.0	213.0	3.0	10.0	3.5	9.2	+	..	..	+
305.0	238.0	3.0	9.9	3.9	10.9	..	+	..	+
347.0	.....	3.5	10.8	4.9	8.5	+	..	..	+
355.0	273.0	4.0	14.0	5.2	9.9	+	..	..	+
386.0	324.0	5.1	11.5	3.0	9.9	+	..	+	..
402.0	301.0	5.05	10.5	3.0	12.0	..	+	+	..
3 weeks	.....	5.0	17.0	5.0	14.0	+	..	−	−
6 "	.....	7.5	15.0	7.0	14.7	+	..	+	..
6 "	.....	7.0	18.0	8.0	17.0	+	..	..	+
10 "	.....	....	14.0	....	16.0	..	+	−	−
2 months	.....	6.0	14.5	4.0	13.0	+	..	+	..
3 "	.....	6.0	15.5	5.0	14.7	+	..	+	..
7 "	.....	5.9	15.5	4.5	18.1	..	+	+	..
15 "	.....	9.0	18.0	9.0	19.5	..	+	−	−
1¾ years	.....	7.0	20.0	8.5	15.0	+	..	..	+
4 "	.....	10.0	27.0	12.7	23.2	+	..	..	+
5½ "	.....	11.1	29.0	9.1	26.1	+	..	+	..
14 "	.....	11.9	26.5	12.0	29.5	..	+	..	+

EXPLANATION OF TABLE.—The measurements are all given in millimeters. The vertex-breech length is measured along the nape and the back.

Malformations of the Ovary.

A complete absence of both ovaries is very rare, and, according to Nagel (1897) and Gebhard (1899), occurs only in monsters incapable of maintaining life. Menge reports a case during life in which it was readily seen that in an otherwise normal person both ovaries, the uterus and the vagina were wanting. Such cases must, however, be accepted only with caution, since observations made upon the living body can never give assurance that the case is not one of secondary atrophy. Even an autopsy is not always sufficient to demonstrate this process; I may recall the case recorded by Braun (1896) in which several years after ovarial atrophy not even the slightest trace of scar tissue was to be found at the point of constriction (Menge, 1910).

The absence of one of the ovaries is also very rare, yet it has certainly been observed, usually, but not always, with a concomitant absence of the Müllerian duct of the same side (Kossmann, 1899). Hypoplasias are more frequent and are associated with a hypoplastic condition of other portions of the genital apparatus (Menge, 1910). Supernumerary ovaries occur; von Winckel has described a third ovary in the vesico-uterine fold, together with a third tube.

Divided ovaries—ovaria partita, usually bipartita—are usually secondary formations; they may be derived from the lobed condition.

The Development of the Blood-Vessels of Both Reproductive Glands.

The aorta develops on either side about 30 mesonephric arteries, and of these 9–11 persist on each side (see p. 820). The majority of these persisting arteries form the rete arteriosum urogenitale in the angle between the metanephros, mesonephros and reproductive gland, and this rete unites with vascular lumina which are formed independently inside the three organs. The first vascular lumina in the reproductive gland occur in an embryo of 18 mm. greatest length. Of the 9–11 persisting mesonephric arteries one, and that the lowest, is destined to become the a. spermatica interna, the rest become obliterated or else one or two persist as aa. spermaticæ accessoriæ. Up to this point the development is exactly alike in the two sexes (see p. 822), but now it begins to differ. In the male (embryo of 60 mm. head-foot length) the artery passes from its origin from the aorta downwards in the retroperitoneum, meets the mesonephric fold a little below the cranial pole of the testis, traverses it obliquely cranio-dorsally to caudo-ventrally, and, finally, reaches the surface of the testis at the level of its lower pole. Here it lies in the tunica albuginea, runs as a rule on the dorsal surface around the caudal pole, reaches the lateral surface and again ascends cranially, lying always in the albuginea. Thus the artery forms an actual loop, between the limbs of which the testis is situated. A medial descending and a lateral ascending limb may be recognized; with the exception of a small lateral twig to the caudal extremity of the testis, the descending limb is without branches, and it is important to note that it also passes the hilus without branching. The ascending limb divides into several branches, in the present case into two ventral

and one dorsal, which ascend respectively on the ventral and dorsal surfaces of the testis. From these three branches the actual nutritive vessels of the testis arise, penetrating between the testis tubules and branching among them as far as the mediastinum. In this they are collected into venous stems, pass out as veins from the hilus into the mesorchium and there open into the v. spermatica interna. The branch given off by the descending limb at the lower pole of the testis behaves differently on the two sides, but it eventually ascends to the middle of the testis and participates in the supply of the testis cords. The three or four ascending arteries run upwards in the tunica albuginea, and mark out a tunica vasculosa (Fig. 614).

The a. spermatica of female embryos has at first the same path as in males, but very early it meets the mesovarium and there gives off branches to the hilus of the ovary until it is exhausted. It never reaches the caudal pole of the ovary.

The very different relations of the aa. spermaticæ in the two sexes furnish a means for determining at once the sexual character of a reproductive gland. If the artery consists of merely a descending limb and this runs only along the hilus of the gland, this is an ovary; if the artery consists of a descending and an ascending limb and the latter lies on the surface of the gland, this is a testis.

The development of the vv. spermaticæ is so intimately associated with the development of the veins in general that it may better be considered in that chapter.

Comparison of Testis and Ovary.

The testis and ovary agree in that the superficial epithelium, the so-called germinal epithelium, either plays no part or, as in the ovary, only a small, diminishing one. The epithelial nucleus has the principal rôle in the development of both glands. But while in the male the nucleus is developed quickly and at a single stroke and then enlarges by the growth of all its parts, in the female its formation is slow and by steps; special germinal zones may be recognized in it and their growth is independent. The testis forms from the epithelial nucleus active testis cords, which only secondarily become surrounded by a connective tissue investment; no cords are formed in the ovary, but its epithelium is passively divided by inwandering connective tissue into a plump network of masses and cords of cells, whose individual constituents show very varied forms. The division goes so far that eventually each genital cell, or the young ovum developing from it, forms a unit by itself. In the testis the epithelium, in the ovary the connective tissue determines the form of the epithelial constituents. The testis tubules are formed mainly from indifferent cells, the form of the

cord and later of the tubule is determined by these alone, the genital cells or spermatogonia are intrusions which have no influence on the form. The primary follicles of the ovary have their form determined by the ova, the indifferent cells play, as follicle epithelium, a rôle which is unimportant so far as the form of the follicle is concerned. In Graafian follicles, it is true, the follicle epithelium has a dominant influence, but we cannot take these structures for comparison, since they are secondary formations, without homologues in the testis. We arrive, then, at this conclusion: testis cord and primary follicle, the foundation stones of the two sexes, arise from the same parent tissue, but follow very different developmental paths. The testis cords have no homologues in the female reproductive gland.

The tunicæ albugineæ may be regarded as homologous, in spite of the difference in their mode of formation, both are formed ultimately from the outermost layer of the epithelial nucleus. The rete testis and the rete ovarii are completely homologous, both as regards their anlage and their further development.

The Development of the Female Ducts.

THE EARLY DEVELOPMENT OF THE MÜLLERIAN DUCT.

As an efferent path for the products of the female reproductive gland a round duct, the *Müllerian duct,* is formed in *both* sexes on either side of the body; it attains complete development only in the female and undergoes degeneration in males while they are still in the fetal period. According to its development the duct is divisible into a very short cranial portion (ostium abdominale tubæ) and a very long caudal portion (the tube proper). The ostium abdominale is formed by an invagination of the cœlomic epithelium into the summit of the urogenital fold, the tube proper by an independent outgrowth of the blind end of this invagination. From the beginning the Müllerian duct lies in the secondary summit of the urogenital fold (p. 784), lateral to the primary excretory duct. This summit portion of the fold prepares itself for the reception of the Müllerian duct by beginning to separate from the rest of the fold as the tubar portion, and its epithelial covering becomes higher, at least in the region of the thoracic segments. The first anlage of the ostium abdominale is noticeable in embryos of 10 mm. greatest length as a circumscribed thickening of the epithelium at the summit of the urogenital fold on a level with the third thoracic segment; this place is termed the *funnel area;* in an embryo of 11 mm. greatest length the area has extended into the region of the fourth thoracic segment. The funnel area is situated immediately below the dorsal limb of the pleuro-peritoneal membrane at the opening of the pleuro-peritoneal duct into the

abdominal cavity. In an embryo of 11 mm. greatest length a deep groove (Fig. 622) appears in the region of the posterior part of the third and in the whole of the fourth thoracic segment, in the middle of the transverse section of the funnel area, projecting into the subjacent mesenchyme of the urogenital fold; the groove presents, therefore, a dorsal and a ventral lip. The deeper posterior part of the groove closes to form a tube by the ventral lip growing toward and fusing with the dorsal lip. The tube thus formed separates from the epithelium of the urogenital fold; and the anlage

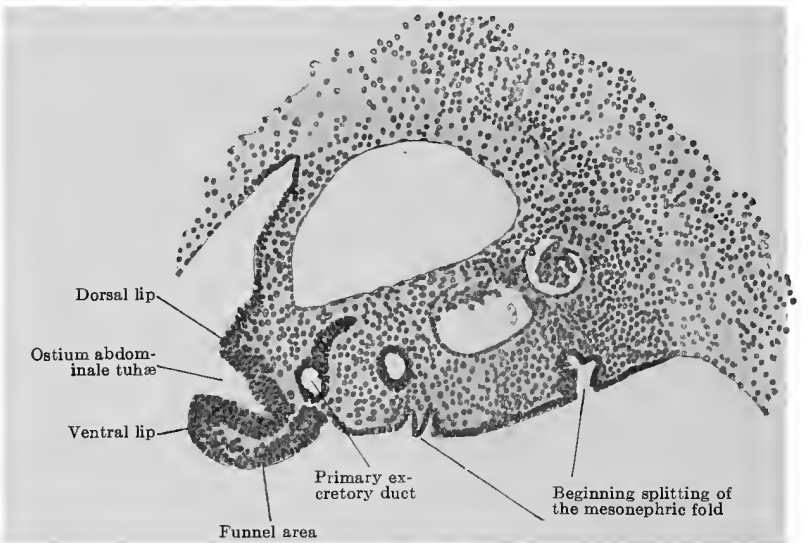


FIG. 622.—Transverse section of the urogenital fold of a human embryo of 11 mm. greatest length and 9 mm. head-foot length. (Embryo P. 1; slide 13, row 3, section 5; from the collection of Professor Hochstetter, Vienna.) The section passes through the middle of the third thoracic foramen intervertebrale. The mesonephros is undergoing degeneration in its cranial portion, and the urogenital fold has therefore diminished in size and appears to he triangular; its covering of cœlomic epithelium is greatly split on the ventral surface. At the apex of the triangle the cœlomic epithelium of the urogenital fold is greatly thickened (funnel area) and invaginated. This funnel-like invagination is the anlage of the ostium abdominale of the Müllerian duct. The funnel is placed frontally, and one can therefore distinguish a dorsal and a ventral lip. The latter has grown out and is curved into a hook to close the opening of the funnel. Into the primary excretory duct the degenerating tubulus collectivus of the second mesonephric tubule opens, beside it and medially is the tubulus secretorius of the third tubule, then the third Malpighian corpuscle, and, finally, the second Malpighian corpuscle.

of the cranial portion of the Müllerian duct is thus completed. When fully formed it is cornet-shaped, the opening of the cornet corresponding to the cranial portion of the groove which remains open, while its tip corresponds to the closed portion, separated from the cœlomic epithelium; the opening of the cornet into the abdominal cavity is termed the ostium abdominale tubæ. The separated apex of the cornet lies in the immediate neighborhood of the primary excretory duct, between it and the cœlomic epithelium; it has, however, no connections with either.

In addition to the principal funnel, whose development has just been described, two to four accessory funnels are also formed as solid growths of the funnel area

in the neighborhood of the principal funnel. These growths also separate partly from the parent tissue and their ends, which have thus become free, unite with the principal funnel; when this union is completed they become hollow. The accessory funnels are situated both on the dorsal and on the ventral side of the principal funnel; the scattered dentations of the margin form the anlage of the fimbriæ. The first distinct fimbriæ occur in embryos of from 28 to 30 mm.; in those of 60 mm. head-foot length the fimbria ovarica appears as a grooved projection directly caudally towards the cranial pole of the ovary. These accessory funnels I have so far found only in female embryos, but in these they occur regularly; in the males they are wanting and the male tubes develop no fimbriæ. From accessory funnels the accessory tubes are to be distinguished; these occur in female embryos, but not regularly. They are usually situated somewhat more caudally than the accessory funnels and—what is characteristic—they never unite during development with the principal funnel or principal tube; they end blindly after a short course. The portion of the urogenital fold that contains such an accessory tube may be grooved out from the rest of the fold so that it remains in connection with it only by a narrow stalk (Fig. 618); in this way the appendix vesiculosus, the hydatid of Morgagni, is formed. The number of accessory tubes in the best example was four; they also appear to occur only in female embryos. All accessory tubes, with the exception of that one which forms the appendix, appear to vanish in the course of development. Concerning the origin of a double tube and concerning the tubar appendages such as have been described in the adult (Kossmann, 1895) I have no personal knowledge.

At the very time when the posterior end of the groove is separating from the epithelium it begins to grow out caudally, and in this process we come to the development of the distal portion of the Müllerian duct; it is formed by the gradual outgrowth of the tip of the cornet. The path that it will follow is already laid out; it must pass, caudally between the cœlomic epithelium laterally and the primary excretory duct medially, as if between two bars. Its growth results entirely from its own forces, the outgrowing tip being always free and connected neither with the cœlomic epithelium nor the primary excretory duct; only poorly preserved or poorly fixed preparations could deceive one on this point. The growth depends on the increase of cells partly along the entire extent of the duct, as is shown by the mitoses, partly at the outgrowing end, which is frequently swollen and presents all the peculiarities of a so-called cone of growth. The reader will find the various stages of growth in the following table.

The lumen extends continuously from the funnel into the caudal portion of the duct, and follows the growth of the duct so closely that all that is ever solid is a small terminal portion. In this way the larger proximal portion of the duct becomes hollow; in its distal portion the lumen arises in loco, and is, accordingly, frequently discontinuous.

When one considers that the duct rapidly grows from the third or fourth thoracic segment to the sacral region it is clear that one has to deal with a decided increase in length; from the third row of the table one sees in fact the rapid increase. In an

embryo of 12.5 mm. greatest length the length of the duct is 330 μ, in one of 17 mm. it is already 1440 or 1220 μ. In this latter embryo the duct has just reached the level of the second lumbar vertebra. Notwithstanding that the duct has still to grow over four or five vertebræ and these the highest in the entire vertebral column, there is from this time onwards a remarkably slight increase in length. This fact finds an explanation when one compares in the two first columns of the table the position of the ostium in successive stages. It lies at the beginning of its development

Table showing the Growth of the Müllerian Duct.

Length of the embryo (mm.)	Right.		Left.		Right, absolute length in mikra.	Left, absolute length in mikra.
	Beginning.	End.	Beginning.	End.		
12.5	7 Th.	8 Th.	.....	.....	330	.....
13.	9 "	11/12 "	8/9 Th.	11 Th.	.....	.....
13.5	9 "	11/12 "	11 "	1 L.	990	1035
14.75	....	.....	10 "	1 "	.....	.....
17.	10/11 "	2 L.	10/11 "	2 "	1440	1220
18.	10 "	2 "	10/11 "	2 "	1420	1270
19.4	11/12 "	3 "	.....	.....	1785	.....
21.	1 L.	1 Sa.	1 L.	1 Sa.	1560	1740
22.	12 Th.	.....	.....	.....	.....	.....
28.5	2 L.	Müller's tubercle	.....	.....	.....	.....
30.	2/3 "	"	3 L.	Müller's tubercle	.....	.....
35.	2/3 "	"	4/5 "	"	.....	.....
50.	4 "	"	5 "	"	.....	.....
60.	4 "	"	5 "	"	.....	.....
70.	1 Sa.	"	.....	.....	.....	.....

in the third and fourth thoracic segment and at the close of development it is in the fourth lumbar segment, having wandered downwards through twelve segments. Since the ostium is always the same one, no traces of a new structure being shown, this wandering must be regarded as a true descensus. This is the more peculiar as the similar wandering seen in the cranial part of the mesonephros and of the reproductive gland is, in both these organs, due to the degeneration of the cranial portion. The wandering of the ostium abdominale is, of course, a passive process, and is probably due to three causes: First, the upper portion of the Müllerian duct no longer increases in length, it therefore lags behind in the total growth. Secondly, the ostium is attached to the crus of the diaphragm; since this descends, the ostium must follow it. Thirdly, the cranial part of the urogenital fold degenerates when its principal contents, the mesonephros and the reproductive organ, vanish; the upper portion of the Müllerian duct then hangs by a very loose fold and may therefore curve and bend and thus bring the ostium into a lower position. The end of the tube never quite reaches the cranial pole of the ovary, it always

projects beyond it even in the adult; in the new-born child the cranial or lateral pole of the ovary still lies frequently at about the middle of the tube.

The Müllerian duct grows along the primary excretory duct. This makes a double bend in its course (Fig. 552); we may distinguish (1) a cranial vertical portion, (2) a horizontal one, and (3) a lower vertical one. The bends of the excretory duct appear before the Müllerian duct in its caudal growth has reached the places where the bends occur; Fig. 558, for example, shows the tip of the tube not yet arrived at the first bend of the excretory duct. As the Müllerian duct now grows onwards it lies ventral to the horizontal portion of the excretory duct, sometimes more cranially, sometimes slightly caudally. As it grows along the horizontal portion of the excretory duct the union of the two urogenital folds to form the genital cord occurs, and the Müllerian ducts now transverse this, situated between the two primary excretory ducts, lying now medial to these and close together. The space between the two primary excretory ducts is, as is shown in Fig. 552, exceedingly small. The two Müllerian ducts, accordingly, grow downwards close together until they reach the Müllerian tubercle. When they have arrived at this level they suddenly bend almost at right angles and run horizontally on the wall of the urogenital sinus. This horizontal portion is usually thickened, and without a lumen; very frequently it is filled from the beginning with a vesicular epithelium. Müller's tubercle is at first merely the entire dorsal wall of the vesico-urethral anlage at the level of the orifice, and projects into the lumen of this. The vesico-urethral anlage then grows greatly in breadth by taking up into itself the two cloacal limbs (see p. 878), and thus Müller's tubercle becomes marked off as a special projection within the dorsal wall of the vesico-urethral anlage.

The left Müllerian duct reaches Müller's tubercle at the earliest in embryos of 21 mm. greatest length, the right in embryos of 28.5 mm. greatest length. The union of the duct with the sinus epithelium does not occur for some time; in embryos of 45 mm. the blind ends of the ducts first bore into the stratified epithelium of the sinus; they do not reach its surface, however, but end blindly under the superficial layer of cylindrical epithelium. The actual breaking through takes place first in embryos of 70 mm. head-foot length.

Formation of the Utero-vaginal Canal.

In both sexes there is a union of the right and left Müllerian ducts within the genital cord, and the unpaired canal so formed is termed the *utero-vaginal canal*. The union occurs at the earliest in embryos of 22 mm. and at the latest in those of 28.5 mm.; the sex seems to have no influence on the early or late union. The

union takes place first in the second fourth of the later utero-vaginal canal and advances thence in both the cranial and caudal direction; frequently, especially in the caudal portion, the union takes place discontinuously. It extends upwards nearly to the upper end of the genital cord, *i.e.*, to the level of the second bend of the urogenital fold (Fig. 552), between the horizontal and lower vertical portions. This bend later on lies almost at the same level as the first bend between the horizontal and upper vertical portions (Fig. 552) at which the inguinal fold arises; but on this account one cannot give this first bend as the cranial limit of the union of the ducts. While the union in male embryos proceeds at once in the horizontal terminal portions of the Müllerian ducts as far as their blind ends, in females these portions remain separate for a long time; their union first occurs in embryos of 50 mm. head-foot length.

The length of the utero-vaginal canal is 600 μ in embryos of 26 mm.; at 28 mm. it is 860 μ, at 30 mm. 1000 to 1550 μ, at 50 mm. 2000 μ, at 60 mm. 2040 μ.

When the union of the two Müllerian ducts is completed above we term the portions that remain separate the tubar anlagen. The primitive tube consists of two portions, a sagittal and a horizontal, the sagittal one lying in the upper vertical and the horizontal one in the horizontal portion of the urogenital fold (compare Figs. 552 and 623).

The union of the two ducts is at first only an external one. They are placed together so that they form a *single* external contour, but in the interior each has still its own medial wall. Later the two medial walls fuse to form a septum, and then this becomes resorbed in the caudo-cranial direction. Since frequently the two Müllerian ducts do not lie in the same frontal plane of the embryo, the utero-vaginal canal is frequently placed obliquely, and since, furthermore, the ducts change their position during their course, sometimes the right one and sometimes the left lying more ventrally, a spiral twisting of the canal may be brought about.

Formation of the Wall of the Utero-vaginal Canal.

GENERAL STATEMENT AND EXTERNAL FORM.

After the completion of the utero-vaginal canal the following relations obtain in the genital cord: In the mesonephric fold the primitive tubes run vertically downwards (vertical portion), reach the lateral edge of the genital cord, bend at right angles and run almost horizontally towards the middle line (horizontal portion) and there unite to form the utero-vaginal canal (Fig. 623 *a*). At the transition of the vertical into the horizontal portion of the tube the plica inguinalis (shown in Fig. 623 as the lig. rotundum) arises from the mesonephric fold.

The first anlage of the supportive tissue portion of the uterine or vaginal wall consists of a thickening of the surrounding mesenchyme; from the beginning a rather sharp and smooth line of demarcation exists between the connective tissue investment of the uterus or vagina and the loose mesenchyme of the broad ligament,

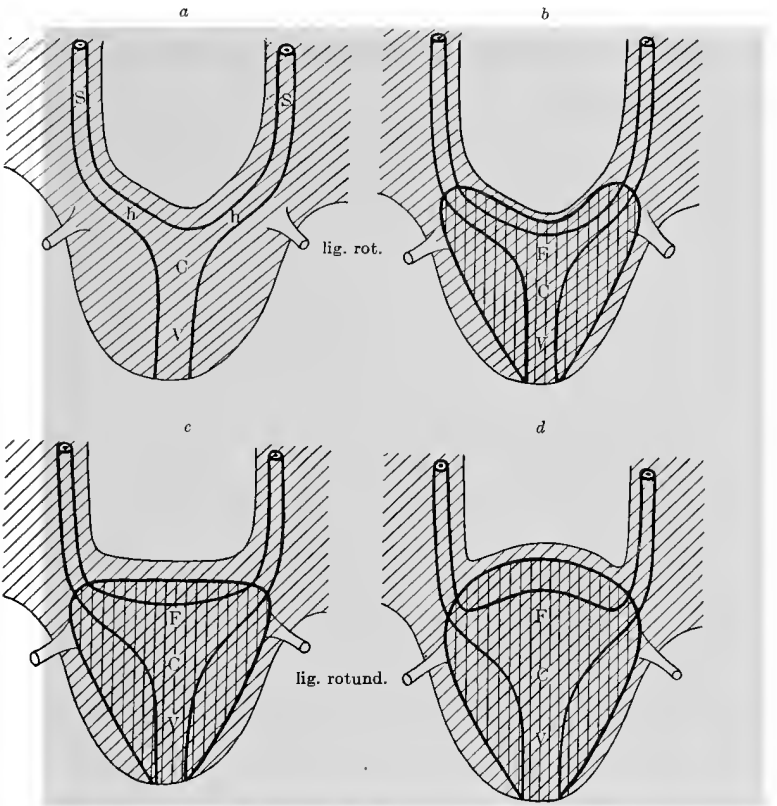


FIG. 623 *a*, *b*, *c*, and *d*.—Four diagrams of the development of the external form of the female uterus. The mesonephric folds and the genital cord are shaded obliquely, the mesenchymatous uterine wall vertically. The various parts of the primitive uterine wall and of the utero-vaginal canal are lettered. *S* vertical portion; *h*, horizontal portion of the wall of the primitive tube; *F*, fundus uteri; *C*, cervix uteri; *V*, vagina. Diagram *a* shows the position of the primitive tuhes and of the utero-vaginal canal after it is completed. Diagram *b* shows the relation of the mesenchymatous uterine wall to the primitive tuhes and to the utero-vaginal canal. It encloses the whole of the horizontal portion of both tuhes in the uterine region and as a result the lig. rotundum is hrought into relation with the uterine wall. The fundus uteri is hent in at an angle (*uterus introrsum arcuatus*). Diagram *c* shows the hroadening of the horizontal portion of hoth tuhes to form the fundus uteri, the broadening taking place in such a way as to straighten out the inward hend (*uterus planifundus*). Diagram *d*: The broadening of the fundus has increased and it is curved outward (*uterus foras arcuatus*).

so that the external contour of the uterus is clearly defined (Fig. 623 *b*). The mesenchymatous wall of the uterus appears in both sexes, but in quite different form. In the female embryo it surrounds the utero-vaginal canal and the horizontal portion of both tubes (Fig. 623 *b*); in the male embryo, where it develops after the degeneration of the horizontal portion of the tubes, it surrounds only the utero-vaginal canal (Fig. 624).

Development of the External Form of the Female Uterus.

In consequence of the horizontal portion of both tubes being taken up into the uterine wall, the primitive tubes may be divided into the definitive tubes and the tubar portion of the uterus. Since the two tubar portions of the uterus give the lumen of the uterus a triangular form from the beginning and produce in the fundus an angular bend towards the lumen (uterus introrsum arcuatus, Fig. 623 *b*), we may distinguish between the broader corpus (uterine portions of the tubes) and the narrow cervix portion (utero-vaginal canal). Then the corpus portion begins to broaden, its angled inward bend being thus straightened out (uterus planifundus, Fig. 623 *c*) and then curved out cranially (uterus foras arcuatus, Fig. 623 *d*). How much of the later uterine mucous membrane is formed from the uterine portions of the tubes and how much from the utero-vaginal canal can hardly be determined with certainty; probably the point of entrance of the primary excretory duct into the wall of the uterus forms the limit between the two. This much is certain, that the fundus is formed from the tubar portion, the cervix from the utero-vaginal canal; the boundary between the two must lie in the isthmus and may coincide with the boundary between the corpus epithelium and the cervix epithelium of the adult. By the extension of the mesenchymatous uterine wall outwards upon the tubes the inguinal fold, or the round ligament derived from it, first comes into relation with the uterine wall (Fig. 623 *b–d*); the ligament has nothing to do with the utero-vaginal canal.

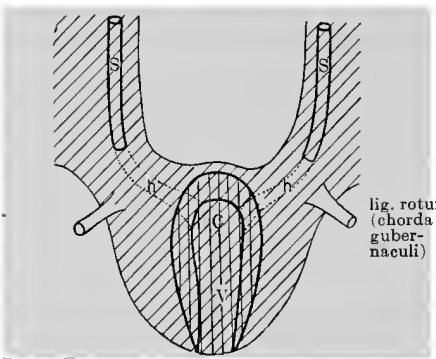


FIG. 624.—Diagram of the development of the male uterus. Only the utero-vaginal canal becomes enclosed by the mesenchymatous uterine wall, the horizontal portions of both primitive tubes had previously degenerated. Consequently the plica inguinalis, or the chorda gubernaculi which is derived from it, does not come into relation with the uterus.

Development of the External Form of the Male Uterus.

On account of the non-participation of the horizontal portions of the tubes in its formation the fundus, and perhaps also the entire corpus, must be wanting in the male uterus; it represents, accordingly, from the beginning only the cervix and perhaps a part of the isthmus (Fig. 624). We shall learn later that in it more than the half of the utero-vaginal canal is degenerated in the cranio-caudal direction, so that in the male there is no persistence of the uterine portions but only of the vaginal one; the term uterus masculinus is therefore certainly incorrect.

Formation of the Definite Wall of the Tubes.

In embryos of 50 mm. head-foot length the loose connective tissue of the tubar fold begins to arrange itself in concentric rings around the epithelium of the Müllerian duct, and so forms the anlage of the supportive tissue of the tube (Fig. 618). In fetuses of 80 mm. trunk length the mesenchyme of the tube wall separates into two layers, an inner one composed of round cells, no longer arranged regularly, and an outer one, three times as broad as the inner, formed of curved, spindle-shaped cells in regular layers; thus the mucosa and muscularis are separated. In embryos of 180 mm. trunk length the first muscle fibres appear. the circular musculature being the first to form and then an outer and an inner longitudinal layer.

The epithelium of the tube is from the beginning single-layered, but is in several rows. According to the degree of extension it is sometimes high cylindrical, sometimes cubical. In new-born children one finds between stretches with cylindrical epithelium groups of cubical cells which have the appearance of single alveolar glands. As to the time at which the ciliation begins I possess only negative results; according to Popoff (1893) the epithelium bears cilia in the ninth fetal month.

An embryo of 50 mm. head-foot length already shows folds projecting into the lumen, two ventral and two dorsal (Fig. 617), giving a cross section of the lumen the form of a four-rayed star. The formation of the folds begins in the ostium abdominale and proceeds slowly towards the uterus. At first the folds are produced almost altogether by the difference in the height of the epithelium, but later the connective tissue of the mucosa grows into them and forces the epithelial covering apart. In embryos between 80 and 250 mm. trunk length secondary folds form on the primary ones and in the eighth month in addition to folds (directed towards the lumen), depressions (directed towards the mucosa) occur. The tube of the new-born child already shows almost completely the form of that of the adult. As soon as the folds have reached a certain size the connective tissue in them forms a special scaffolding of parallel bundles of connective tissue fibrils, which are surrounded by looser connective tissue.

Transformation of the Tubar Portion of the Uterus and the Utero-vaginal Canal into the Uterus and Vagina.

The utero-vaginal canal is a long tube (Fig. 625). It runs vertically downwards parallel to the posterior surface of the bladder and urethra, bends almost at right angles at the level of Müller's tubercle, and accordingly at the boundary between the

urethra and the urogenital sinus, forming a horizontal portion, and opens into the sinus. The vertical portion is long, the horizontal quite short (Fig. 625). In transverse section the utero-vaginal canal forms a flattened oval, whose longest axis lies in the frontal plane. The epithelium is in general arranged so that it is high on the ventral and dorsal surfaces and low at the angles; at first it is everywhere one-layered and high cylindrical. The nuclei are in several rows. To this rule only the horizontal portion forms an exception from the beginning, it being completely filled with a vesicular polygonal epithelium. In embryos of 38 mm. greatest length differences between the epithelium of the tubar portion of the uterus and that of the utero-vaginal canal appear; in the tubar portion a cylindrical one-layered epithelium, varying in height, occurs; in the utero-vaginal canal it is several layered and the superficial layer is sometimes cylindrical, sometimes cubical. This many-layered epithelium appears first in the cranial part and gradually extends into the caudal part of the utero-vaginal canal, meeting (in embryos of 70 mm. greatest length) the vesicular epithelium that gradually ascends from the horizontal portion; wherever the vesicular epithelium extends it completely fills the lumen. Towards the middle of the fourth fetal month three regions may be distinguished in the uterine and vaginal canals by means of differences in their epithelium: first, about an upper fourth, hollow and lined with a simple cylindrical epithelium, the future corpus uteri (probably formed from the tubar portion of the uterus); second, a second fourth, hollow and lined by a many-layered, cylindrical epithelium, the future cervix uteri; and, finally, a distal half, filled with a vesicular, polymorphous epithelium, the future vagina; the cervix uteri and vagina are derived from the utero-vaginal canal. The boundary between the corpus and cervix epithelium corresponds almost with the internal os uteri, and it is also marked externally by a bend or at least a greater distinctness of the ventrally concave curvature. I shall consider the topography of the boundary between the cervix and vagina later on.

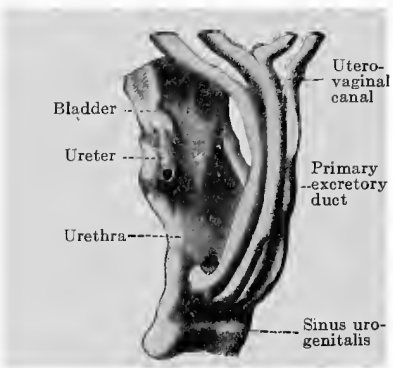


FIG. 625.—Primary excretory duct and utero-vaginal canal seen from behind and somewhat from the left. Human embryo of 29 mm. nape length. (After Keibel 1896, from Felix-Bühler, Entwicklung der Geschlechtsorgane in Hertwig's Handbuch der Entwicklungsgeschichte, Vol. 3.) The two Müllerian ducts have united to form the utero-vaginal canal. The latter shows a long vertical and a short horizontal portion. Also the two primary excretory ducts are bent and accordingly also possess a horizontal portion at their orifices.

Development of the Vagina.

In the third to the sixth fetal month (the statements of authors vary, apparently on account of a variability in the appearance of the structure) the portio vaginalis is formed by the following processes: first, the wall of the utero-vaginal canal thickens in all its dimensions—even in the third month, and, second, the epithelium forms at the boundary between the cervix and vagina, but always in the vaginal territory, a ventral and a dorsal solid projection (Fig. 626), and these grow out into the mesenchyme in a shovel-shaped form; they are the solid anlagen of the fornix anterior and posterior vaginæ and therefore bound the anterior and posterior lips of the external os uteri. The projection that represents

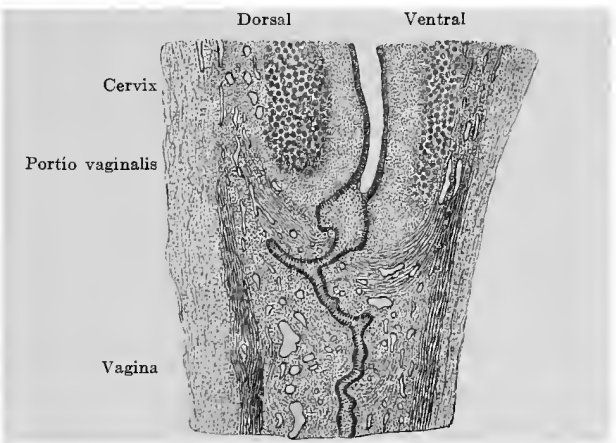


Fig. 626.—Median longitudinal section of the utero-vaginal canal at the level of the portio vaginalis uteri of a human embryo of 260 mm. (After Werth and Grusdew, from Felix-Bühler, Entwicklung der Geschlechtsorgane in Hertwig's Handbuch der Entwicklungsgeschichte, Vol. 3.) The portio vaginalis is beginning to be defined and the supravaginal circular muscle is developed in it. Its lumen extends to its lower end, which is closed by an epithelial plug. The vagina is still altogether solid, but its future lumen is indicated by the solid epithelial cord that traverses it. From this cord there grow into the surrounding mesenchyme, forward and backward at different levels, two solid projections of epithelium, the anlagen of the fornix anterior and posterior.

the anterior fornix is always considerably lower than that representing the posterior fornix and in consequence the anterior lip of the os is lower than the posterior, a relation that may be retained even in the adult. With the anlage of the portio vaginalis or of the two fornices the upper limits of the vagina become sharply determined.

Only after the formation of the fornices does the vagina become hollow. The lumen first appears in embryos of 150 to 200 mm. trunk length (Nagel 1891) in the distal portion of the vagina. It is formed by the breaking down of the central cells and the arrangement of the peripheral ones into a stratified cubical and later a stratified pavement epithelium; starting in the distal portion the breaking down of the central cells proceeds cranially. In this manner the vagina, together with the two fornices, becomes hollow and

the protuberant portio vaginalis is grooved out from its surroundings. Since the utero-vaginal canal is bent or strongly curved at the point where the portio vaginalis projects, the angle between the uterus and the vagina is present from the beginning.

In older embryos, new-born children and young girls until puberty, the outer surface of the portio vaginalis of the uterus is marked in the most delicate manner by fine grooves, which appear quite symmetrically. They occur always on the borders of both lips, almost always on the outer surface of the anterior lip and more rarely on the outer surface of the posterior lip. They appear as principal grooves that usually run radially towards the os and are connected by transverse grooves; more rarely transverse grooves are the principal ones and in this case they are connected by very few radial accessory grooves.

The epithelium of the vagina is henceforward a many-layered pavement epithelium, that of the cervix is a stratified cylindrical epithelium; the question arises where the boundary between the two occurs. According to R. Meyer (1910) it always lies at first in the cervical canal. Then "the cervical epithelium differentiating in the mucous epithelium destroys the pavement epithelium as far as the external os uteri and in about one-third of the cases even further." "There is thus formed Fischel's congenital histological ectropion." "Some islands of the basal cell rows of the pavement epithelium are spared and these always regenerate the pavement epithelium of the outer surface of the portio vaginalis uteri, raising up and compressing the mucous epithelium." "The definitive abolition of the congenital histological ectropion occurs, however, only in childhood." We see then that the cervical and vaginal epithelium are engaged in a mutual struggle. At its close the boundary between the cervical and vaginal epithelium coincides in general with the level of the external os. With a small portio vaginalis, a narrow cervical canal and a narrow external os the boundary lies above the os; with a large portio vaginalis and a broad os externum it lies below the os, that is on the vaginal surface of the portio vaginalis (R. Meyer, 1898 *c*). Since the boundary struggle does not progress equally over the whole periphery, the boundary line comes to be wavy and, indeed, islands of one kind of epithelium are included within the other; islands of cervical epithelium on the vaginal surface of the portio vaginalis have been termed physiological erosion.

With the formation of the portio vaginalis uteri and the anlage of the two fornices the cranial limits of the vagina are determined once and for all. The length relations between the vagina and uterus remain the same during the late fetal period and the first year of extra-uterine life, that is to say, the vagina is as long as or longer than the uterus.

The columnæ rugarum are formed by the ingrowth of numerous solid epithelial projections into the subjacent mesenchyme at a time when the lumen of the vagina is not quite filled by epithelium.

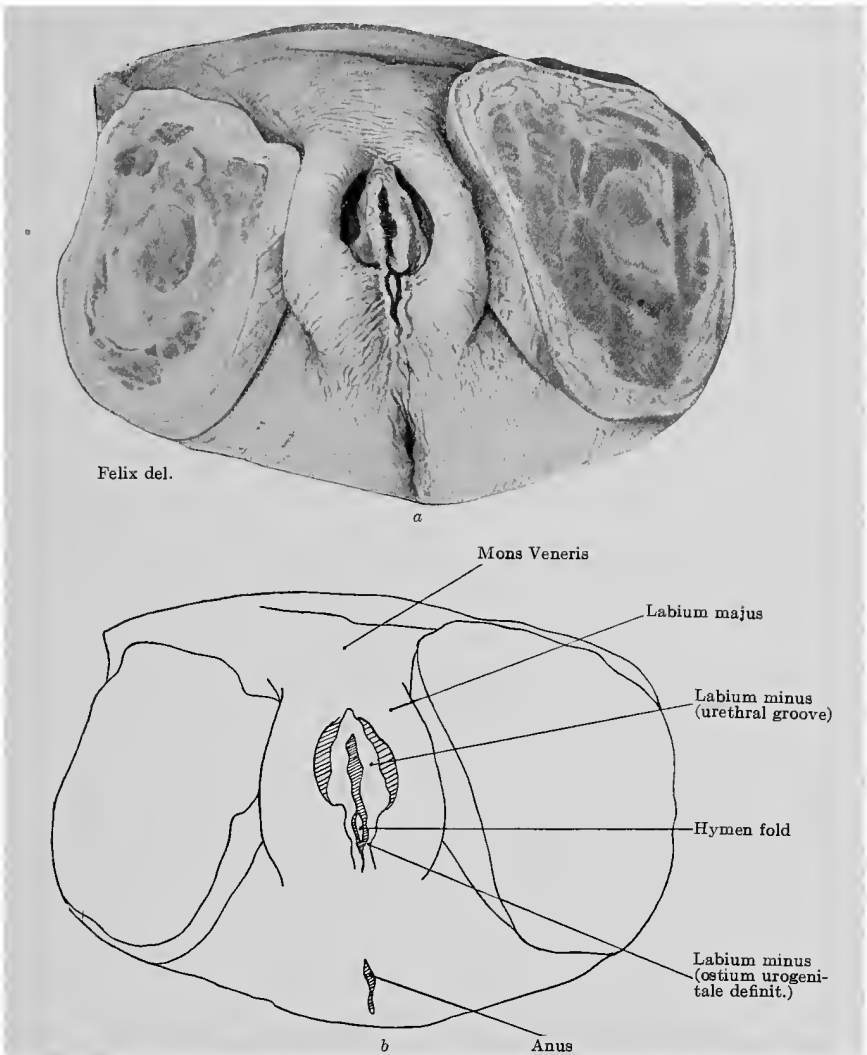


FIG. 627 *a* and *b*.—External genitalia of a female embryo of 40.2 cm. vertex-breech length (measured over nape and back) and 30.1 cm. greatest head circumference. × 1½. The labia minora surround a long slit-like opening, the urogenital orifice, and present two distinct portions, an oral high portion (6 mm.) and an anal low one (1–1.5 mm.). Between the oral portions is the shallow urethral groove, between the anal portions the urogenital sinus. The hymen appears between the anal portions of the labia minora.

The lower boundary of the vagina is formed from the hymen, which is formed from Müller's tubercle. It has been shown above that the distal end of the utero-vaginal canal fuses with the epithelium of the urogenital sinus, and that this point of fusion persists as a solid mass of epithelium even when the rest of the vagina

becomes hollow. Immediately above Müller's tubercle the vagina then forms an ampulla-like enlargement, by which Müller's tubercle is compressed to a disk. This is lined on one surface by vaginal epithelium and on the other by epithelium from the urogenital sinus; the two layers of epithelium and the intervening mesenchyme form the hymen. In its centre the hymen has for a long time a cavity closed by a solid knob of epithelium, the remains of the point of penetration of the utero-vaginal canal.

Later the disk-like hymen becomes funnel-shaped; the funnel is compressed from right to left so that the ostium vaginæ no longer is a circle, but a sagittal slit. In embryos of 272 mm. vertex-breech length (measured over nape and back) and 213 mm. in the greatest circumference of the head, there regularly develops between the hymen cleft and the anal periphery of the hymen, usually somewhat to the left of the middle line, a sagittal fold, the *hymen fold* (Figs. 627, 645 and 646). At first small and inconspicuous it may increase in height up to birth to such an extent that it projects out like a partition between the labia minora. Rarely the fold is double, that is to say, a right one may be present in addition to a left one, the two folds then uniting at their anal ends and thus enclosing a groove that extends orally as far as the ostium vaginæ (Fig. 646).

Recently it has been suggested that the vagina has a double origin, a pars Mülleriana and a pars adjuncta being distinguished. The pars Mülleriana is supposed to be derived from the utero-vaginal canal and the pars adjuncta from a frontal division of the urogenital sinus (Bolk, 1907). If this were true the hymen could not correspond with Müller's tubercle, but would be a new formation inside the urogenital sinus. Bolk's suggestion is, however, incorrect. In the first place direct embryological observation shows that the hymen arises from the tubercle, and, in the second place, cases in which the distal end of the primary excretory duct persists show this running to the hymen; the opening of the primary excretory duct is always at Müller's tubercle.

Development of the Uterine Wall.

The transformation of the tubar portions of the uterus and of the proximal portion of the utero-vaginal canal into the corpus and cervix uteri will first be considered together. In this connection I would refer to the work of R. Meyer (1898). The epithelium of both forms in transverse section an oval, whose longest axis is placed in the frontal plane (Fig. 628). In embryos of the fourth month the oval becomes a wavy slit, the number of waves depending on the width of the uterus and of the slit. In the lower part of the uterus one finds, therefore, only one entire wave, in the upper part 1½ or 2. The anterior and posterior uterine walls are so close together that the summit of a wave on one wall fits into the depression between two waves of the other and vice versa.

This wavy form of the uterine slit persists as the fundamental form until birth and is often found in children and, in rare cases, even in the adult. In embryos of about 150 mm. secondary folds arise from the depressions between the waves and, indeed, from their deepest parts, these folds appearing as longitudinal folds of the mucous membrane; in the upper part of the uterus, where there are two waves, there are two folds on each of the walls, in the lower part only one. From these folds other smaller accessory folds arise and produce throughout the entire cavity of the uterus a very complicated pattern. But as the accessory folds develop the entire lumen of the corpus uteri elongates and, consequently, the folds again become flattened out, until, finally, the surface of the mucous membrane in the adult corpus uteri appears quite smooth. The folds are retained most distinctly in the cervix.

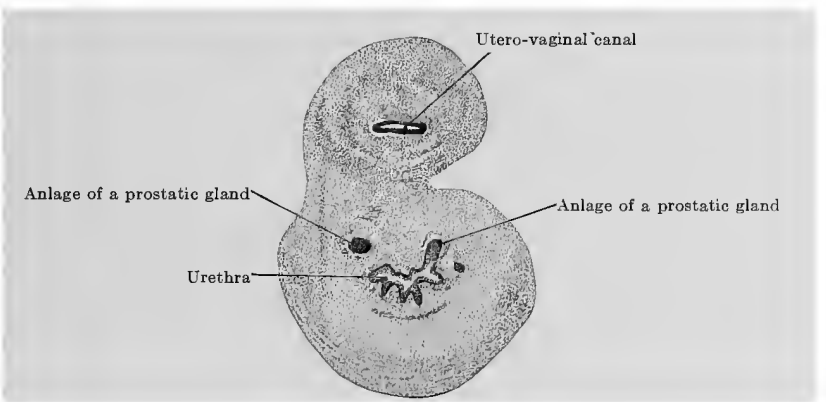


FIG. 628.—Transverse section of the utero-vaginal canal at the level of the upper anlage of the prostatic glands of a female embryo of 80 mm. head-foot length. (Embryo R. Meyer 266; slide 69, row 1, section 1, from the collection of R. Meyer, Berlin.) The epithelial cylinder of the utero-vaginal canal is surrounded by an extensive layer of thickened mesenchyme, the primitive utero-vaginal wall. In this a middle zone is beginning to be defined by a closer arrangement of the nuclei; this is the future muscularis. Inwards from this is the future mucosa and outwards the future subserosa and serosa. The urogenital sinus develops on its dorsal surface two solid epithelial projections, the anlagen of the prostatic glands.

Long transverse folds are added to the longitudinal ones in embryos of 125 mm. at the earliest, and these form broad swellings projecting into the lumen. When these folds become so long that there is no longer space for them in the cervix, they ascend obliquely and the uppermost may then separate the corpus from the cervix like a valve. In such cases, if the mucous membrane of the corpus secretes mucus there will necessarily be a retention of the secretion in the uterine cavity. The transverse folds—forerunners of the plicæ palmatæ—appear in the cervix in such a manner that in embryos of 160 mm., for example, an upper third and also a small marginal zone above the ostium externum remain free from them. Consequently the upper third of the cervix—frequently even more (see the following table showing the growth in length of the uterus)—belongs macroscopically to the cervix

but microscopically to the corpus uteri. On this account this portion of the cervix has been termed the isthmus and as a result two different internal ostia have been recognized, the ostium internum anatomicum, between the corpus and isthmus, and the ostium internum histologicum, between the isthmus and cervix.

The mucous glands of the cervix develop in embryos of from 110 mm. (Rösger 1894) to 175 mm. (Tourneux and Legay 1887), and always at the base of a fold. The cylindrical glands of the corpus uteri appear at very different times; one may find them abundant and well developed even in new-born children and fail to find them in young girls of 12 or 14 years. (Wyder 1878). Their appearance and growth in length is, therefore, until puberty, altogether independent of age. The cilia of the uterine epithelium first appear with the approach of puberty (Wyder 1878).

Development of the Musculature of the Vagina and Uterus.

Around the epithelial cylinder of the utero-vaginal canal the mesenchyme thickens to form a closed investment. This primitive utero-vaginal wall extends forward and backward to the surface of the genital cord and, accordingly, fills the cord completely in the sagittal direction, but in the frontal direction a strip occurs right and left along the lateral walls of the primitive true pelvis, which still contains the original loose mesenchyme. In this way the genital cord becomes divided into three parts; the uterus and the right and left ligamentum latum (Fig. 629). The boundary between the uterus and the ligamenta lata almost corresponds with the course of the primary excretory duct, which is enclosed in the uterine wall so far as this corresponds to the utero-vaginal canal. In the primitive uterine and vaginal walls strands of spindle-shaped cells arise in embryos of 60 mm. head-foot length, and are arranged concentrically around the lumen in such a manner that they mark off three zones; first and most internally, a zone of round cells, the future mucosa, then the layer of spindle-shaped cells, the future muscularis, and, finally and outermost, a second layer of round cells, the foundation for the future subserosa and serosa. The same arrangement of layers is also found in the wall of the tube and the tubar layers pass over praeter propter into those of the uterus. The blood-vessels, already present in considerable numbers, still lie in the subserosa and thereby define this from the serosa. In embryos of 80 mm. head-foot length the primitive muscularis becomes stronger and splits into a series of concentric rings, but it is only in embryos of from 120 to 140 mm. trunk-length that the first muscle cells are distinct.

The musculature of the uterus and vagina may be traced back to three primitive layers: inner and outer longitudinal and

middle circular musculature. In the uterus the circular musculature appears first, in the vagina the longitudinal. Since the anlage of the cervix musculature is entirely under the influence of the vaginal musculature, we must distinguish embryologically between the corpus musculature on the one hand and the cervix-vaginal musculature on the other.

In embryos of from 240 to 300 mm. (according to Werth and Grusdew 1898) two superposed muscle rings appear in the muscularis of the uterus, the one, strong and compact in the corpus,

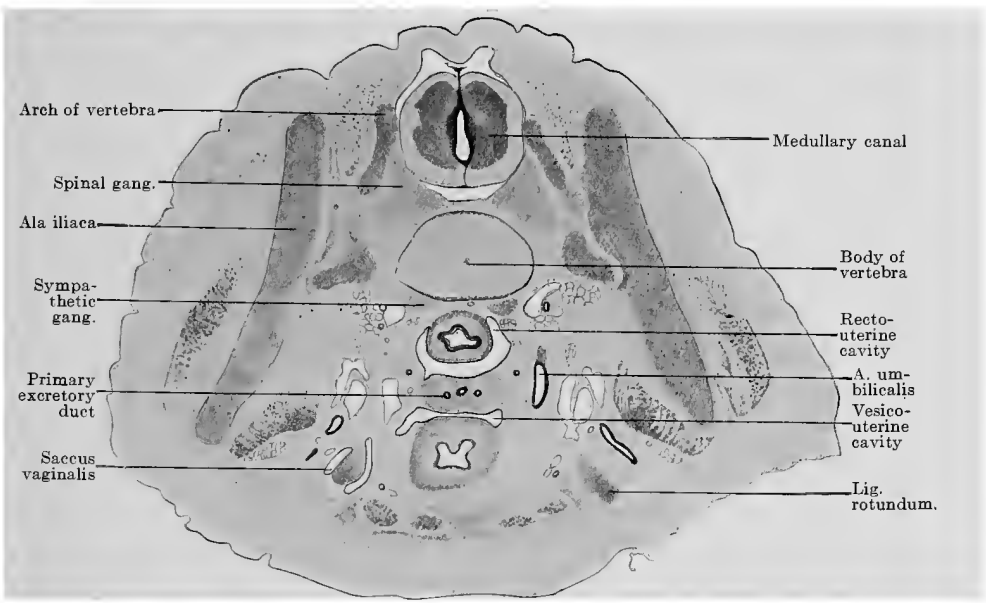


FIG. 629.—Transverse section of a human embryo of 32 mm. vertex-breech length at the level of the utero-vaginal canal. (Embryo 426, I, 18 in the collection of the Anatomical Institute, Zurich, IX. 1, 2.) ×15. The section shows the genital cord stretched transversely through the cavity of the true pelvis, and in it are the two primary excretory ducts and the utero-vaginal canal. The mesenchymatous uterine wall, which encloses the two primary excretory ducts, is so situated that it divides the genital cord into three portions, the uterus and the two lig. lata.

extends almost to the cervix, the other, weak and scattered, occurs in the neighborhood of the portio vaginalis. The vagina at the same time forms a longitudinal layer at the boundary between the subserosa and the primitive muscular wall, and this layer extends upwards over the vagina and into the cervix. In embryos of from 340 to 355 mm. the circular muscle layers of the corpus and those of the cervix fuse, and, in addition, the circular musculature of the corpus fuses with that of the tube. The two tubes meet the body of the uterus at an angle, and that produces a certain amount of confusion in the previously simple arrangement of the musculature. The inner strands of the musculature of the tubes pass directly over into the circular layer of the uterus, but the outer strands stream out as longitudinal bundles both on the ventral and on the

dorsal surface of the uterus, and thus form an outer longitudinal muscle layer on the body of the uterus. The circular musculature of the cervix, which has hitherto remained weak, now becomes very strong and forms the supravaginal muscle ring. This develops in the region of the longitudinal musculature streaming up from the vagina, and becomes intermingled with it. In the meantime a circular layer has appeared in the vagina itself, in the region of the longitudinal layer which has now become considerably thickened; it intermingles with the longitudinal layer and a pure longitudinal layer is left only on the outer and inner surface. With this the anlage of the vaginal musculature is completed; there is an outer and an inner longitudinal musculature and an intermediate circular one.

The inner longitudinal musculature of the uterus has a double origin; on the one hand longitudinal bundles stream from the orifices of the tubes on the inner surface of the circular musculature, and, secondly, fibres separate from the inner ring of the supravaginal circular muscle, and these also lie on the inner side of the circular musculature of the uterus, passing upwards towards the muscle bundles streaming down from the tubes and fusing with these to form the stratum longitudinale submucosum.

From the seventh fetal month to the end of pregnancy there is at first only an enlargement of the layers already present. In the body of the uterus the circular musculature always constitutes the principal mass. It grows in a three-fold manner: by increase in the thickness of its parts, by the development of new layers at the periphery and between the bundles of the circular muscle. These last, the interstitial bundles, are sometimes oblique and sometimes longitudinal, and produce the felted mass of the adult uterus, whose constituent parts can scarcely be made out. The outer longitudinal bundles that stream down from the tubes become included in this confused mass.

The vessels situated in the subserosa still lie on the outer surface of the musculature, but later they become enclosed by it, bundles of circular muscle fibres forming a coarse-meshed network, the stratum vasculare, around them. External to this network an outermost layer, the stratum supravasculare, is also formed, consisting principally of longitudinal bundles, which are in connection with the muscle bundles in the ligamentum rotundum, the ligamentum ovarii proprium and the plicæ recto-uterinæ.

Growth of the Uterus in the Postfetal Period.

The following table, compiled from data given by Hegar (1908), will furnish information as to the growth of the uterus. It gives the length of the corpus uteri, isthmus, and cervix and the entire length.

Age.	Length of corpus (mm.)	Length of isthmus (mm.)	Length of cervix (mm.)	Total length (mm.)
Fetus of 7 months	..	..	..	22
Child of 5 weeks	..	..	..	27
1 year	10	..	..	23
14 months	10	5	12	27
2½ years	8	6	12	26
3 years	9–10	5–6	10	25
3½ years	6	5	16	27
9 years	9	4.5	13	27
11 years	12	6	19	37
13 years	..	..	27	56
15 years	..	..	..	59
16 years	41	12	25	78
17 years	27	6	22	55
17 years	20	4	16	40
18 years	36	5	31	72
19 years	27	5	28	60
19 years	28	6	27	61
19 years	24	8	21	53
20 years	30	6	16	52
20 years	30	7	21	58
22 years	35	5	29	69
28 years	40	10	28	78
29 years (nulliparous wife)	34	10	34	78
30 years (virgin)	38	7	29	74

The table shows that the entire uterus passes through a resting stage in the early years of life, the uterus of a child of five weeks having the same length as that of a child of nine years. From this time onward an actual increase in length takes place, at first slowly, but more rapidly with the beginning of puberty. The increase is not, however, equally distributed among the various portions of the uterus. The body and neck elongate, but the isthmus practically not at all. Furthermore the body grows decidedly more than the neck.

Degeneration of the Tubes and of the Utero-vaginal Canal in Male Embryos.

We have seen that the Müllerian ducts are formed in both sexes and that in both sexes they unite with the lower portion of the utero-vaginal canal; it has also been stated that this union occurs in embryos between 22 mm. and 28.5 mm. greatest length. Almost immediately after the union, that is to say in embryos of 30 mm., the degeneration of the ducts and of the utero-vaginal canal begins in male embryos. It makes its appearance in the middle of the anlage, in the portion of the tube that lies between the lower pole of the testis and the utero-vaginal canal. Both tubes lose their lumina, their epithelial cells show signs of degeneration at the centre and of proliferation at the periphery. In embryos of 60 mm. the tubes have degenerated as far as the portion between the testes and epididymides, and the utero-vaginal canal as far as the lower horizontal portion; in the intervening

space only scattered remains occur, as a rule in the neighborhood of the point of crossing of the ureter and the primary excretory duct; these remains regularly show proliferation phenomena. In embryos of 90 mm. remains of the tubes always occur along the upper two-thirds of the testis and the ostia abdominalia are still open; data are wanting as to the time of their closure. Finally, of each entire tube only a very small portion remains, situated between the testis and the head of the epididymis; it is known in systematic anatomy as the hydatid of Morgagni. It contains a simple, rarely stalked, epithelial canal, frequently without pouchings. Of the utero-vaginal canal only the epithelium degenerates at first, the dense mesenchyme enclosing it persisting for a long time as a sort of primitive uterine wall. A collapse of the epithelial canal regularly precedes its degeneration, so that one frequently sees a small, solid, sagittal portion resting upon the persisting, broad horizontal terminal piece; evidences of nuclear degeneration are, however, distinctly visible, so that one has to do not with a new formation, but with a degeneration. Only the broad horizontal portion persists throughout life, forming the vagina masculina. The portion of its wall surrounding the slit-like opening will represent a male hymen. The vagina masculina frequently shows gland-like growths in older fetuses, but very rarely true open gland sacks (R. Meyer 1909). Müller's tubercle persists as the colliculus seminalis, the upper and lower cristæ urethrales are defined quite early in the embryo.

Inhibitions of the Development of the Uterus and Vagina.

It is almost self-evident that an organ with so complicated a development as that shown by the uterus and vagina would show disturbances of the development. The many forms under which these disturbances present themselves may be arranged in groups, each of which may be brought into relation with a definite stage of development. In the following schema I follow, with slight modifications, the subdivisions proposed by von Winckel (1899); more important departures for it will be considered later.

Normal Development.	*Inhibitions of Development.*
1. The mesonephric fold is completely developed, but as yet shows no trace of an anlage of the Müllerian duct.	1a. Complete absence of both Müllerian ducts, together with complete absence of the tubes, uterus and vagina (probably never occurs [von Winckel, 1899] or only in association with extensive bodily malformations [Nagel, 1897]). 1b. Complete absence of one Müllerian duct occurs only in association with a total absence of the urogenital fold, its organs, and the kidney of the same side (uterus unicornus verus [semiuterus]).

2. Formation of the funnel of the tube in the mesonephric fold, outgrowth of both blind ends as Müllerian ducts into the urogenital fold along the primary excretory duct.

2a. Complete failure of the fusion of the two Müllerian ducts (uterus didelphys [= uterus duplex separatus], vagina duplex separata.

2b. Combined with a failure of one vagina to communicate with the exterior.

2c. Combined with a failure to develop lumina (uterus didelphys solidus, vagina duplex solida).

2d. Combined with the formation of only a partial lumen in the uterovaginal canal (uterus didelphys partim excavatus, vagina duplex partim excavata).

2e. Combined with a varying amount of inhibition of one-half (uterus didelphys asymmetricus, uterus unicornis spurius [semiuterus spurius] cum rudimento uteri alterius).

3. The Müllerian ducts unite, at first in the middle of the later utero-vaginal canal, extending thence cranially and caudally. The union is at first only an adhesion, later the septum between the two ducts is resorbed. Around the epithelial utero-vaginal canal the mesenchymatous wall of the uterus is formed like a sheath, and in such a manner that portions of the walls of the primitive tubes enter into the formation of the uterus (see Fig. 623, p. 894), and for this reason the fundus of the uterus appears slightly depressed.

3a. The union of the Müllerian ducts fails completely or partially (uterus bicornis sæptus, subsæptus, simplex; vagina sæpta, subsæpta, simplex).

3b. Uterus introrsum arcuatus sæptus, subsæptus, simplex; vagina sæpta, subsæpta, simplex.

3c. Combined with a failure of one side to open to the exterior.

3d. Combined with incomplete development of lumen.

4. The flat fundus uteri gradually becomes convex outwards (uterus foras arcuatus). The form of the uterus fetalis is thus acquired.

4a. The fundus of the uterus remains flat (uterus planifundus).

4b. Combined with various degrees of inhibition of resorption of the septum.

4c. Combined with a partial failure of the lumen.

4d. Uterus foras arcuatus.

4e. Combined with various degrees of inhibition of the resorption of the septum, and with partial failure of the lumen.

5. The uterus infantilis is formed by a strong growth of the cervix and a weak growth of the corpus.

5. The growth of the uterus does not take place; it remains a uterus fetalis.

6. The uterus virgineus develops from the uterus infantilis by a stronger growth of the corpus.

6. The stronger development of the body fails, the uterus infantilis persists.

7. The sexually mature uterus develops from the uterus virgineus by equal growth.

7. The growth takes place unequally or insufficiently and there is formed a uterus virgineus inæqualis or hypoplasia of the uterus.

Various theories have been proposed to account for the origin of malformations of the uterus and vagina. To-day they all have the fault that they are based

on a plan of development that needs correction in important points. We have at present—basing our opinion on the facts described above (pp. 916–920)—to distinguish between

1. Disturbances of development in the formation of the mesenchymatous wall, and

2. Disturbances of development in the anlage and in the further development of the epithelial canal.

The epithelial canal is formed in the first place from the utero-vaginal canal, and, secondly, from the uterine portions of the two tubes. Since the tubar portion of the uterus practically forms the corpus uteri, and the utero-vaginal canal the cervix and the vagina, the development of these two portions of the uterus takes place under quite different conditions. The difference in their manner of development leads one to expect differences in the causes of their disturbances of development, and one may therefore subdivide the disturbances in the development of the epithelial canal into

2a. Disturbances in the development of the utero-vaginal canal; they affect the cervix uteri and the vagina.

2b. Disturbances in the further development of the tubar portions of the uterus; they affect the corpus uteri.

1. DISTURBANCES OF DEVELOPMENT IN THE FORMATION OF THE MESENCHYMATOUS WALL OF THE UTERUS.

It has been pointed out above that the mesenchymatous wall of the uterus is developed in such a manner that it encloses the utero-vaginal canal as well as

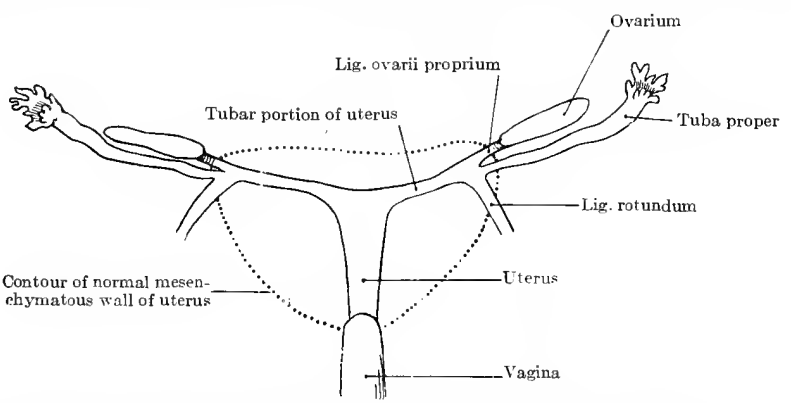


FIG. 630.—Copy of Fig. 17 by Kussmaul (1859). The normal extent of the mesenchymatous wall of the uterus is indicated by a dotted line on the figure of the uterus rudimentarius solidus.

the two uterine portions of the tubes (Fig. 623 b). By this inclusion of the horizontal portion of the tubes in the mesenchymatous wall the plica inguinalis, or the ligamentum rotundum that is developed in it, is brought into connection with the uterus. If now one finds in autopsies uteri in which the round ligament is attached to the wall of the tube, but not to the uterine wall, it must either be the result of an inhibition of the development of the mesenchymatous wall of the uterus or a hermaphroditic character. In the fundamental work of Kussmaul (1859) there are two figures, Figs. 17 and 18 (of which Fig. 17 is here reproduced as Fig. 630), which show conditions that are identical so far as our present purpose is concerned. The uterus is T-shaped, the transverse bar of the T being twice as long as the vertical one, and having attached to its ends the two round ligaments and the ligamenta ovarii propria. The point of insertion of both ligaments marks the boundary between the tube proper and the uterine portion.

The normal extent of the mesenchymatous wall of the uterus is shown in Fig. 630 by the dotted line. A comparison of the normal and inhibited uterus shows the remarkable lack of development of the latter. This anomaly was termed a uterus rudimentarius by Kussmaul (1859), but we now describe it more in detail as a uterus with its mesenchymatous wall developed. It can naturally, and it usually does, occur in association with inhibitions in the development of the epithelial canal, complete or partial degeneration of this, obliteration of the lumen, a failure of the union of the two ducts, etc.

In considering a uterus with imperfect mesenchymatous wall one should not fail to notice its great similarity with the male type. We have seen (p. 916) that the formation of the mesenchymatous wall differs in the two sexes. In the male the mesenchyme surrounds only the utero-vaginal canal, the uterine portions of the tubes remaining free from it; furthermore, in the male the epithelial canal of the utero-vaginal wall within the mesenchymatous investment degenerates, though the investment itself persists for a longer time. In all cases of uterus with imperfect development of the mesenchymatous wall, accordingly, one must take into account the possibility of its being a case of hermaphroditism, and eventually consider whether there may not have been an error in the determination of the sex.

2a. DEVELOPMENTAL DISTURBANCES IN THE REGION OF THE EPITHELIAL PORTION OF THE UTERO-VAGINAL CANAL (CERVIX UTERI AND VAGINA).

Here belong all cases of double vagina, double cervix, vagina septa and cervix septa. They arise by the non-union or incomplete union of the two Müllerian ducts or by the non-resorption or incomplete resorption of the septum after the union. What can hinder the union of the two Müllerian ducts to form the utero-vaginal canal? I have collected the following suggested causes from the literature:

1. Hydronephrosis.
2. Abnormal distention of the bladder and rectum.
3. Anomalies in the formation of the abdominal wall (hernia umbilicalis, cleft pelvis, abdominal clefts, abnormally short yolk stalk).
4. Fetal peritonitis.
5. Ligamentum recto-vesicale.
6. Shrinkage of the lig. rotunda.
7. Too great breadth of pelvis.
8. Long persistence and too great separation of the mesonephroi or the primary excretory ducts.
9. Congenital tumors.

The first four of these causes can hardly be effective. In the first place, the utero-vaginal canal is formed before the metanephroi become functional, and consequently hydronephrosis and an abnormal distention of the bladder are excluded. Secondly, the formation of meconium begins a considerable time after the completion of the utero-vaginal canal. Meconium was first found in an embryo of 223 mm. vertex-breech length (measured over the back) and 162 mm. greatest head circumference; filled with meconium, but not dilated, was the rectum of an embryo of 235 mm. vertex-breech length (measured over the back) and 190 mm. greatest head circumference; a strongly dilated rectum was first found in an embryo of 347 mm. vertex-breech length (measured over the back). An abnormally dilated rectum cannot, therefore, prevent the union, which has already been completed for a very long time (embryos of 22–28.5 mm.). Thirdly, the normal hernia umbilicalis occurs long after the completion of the utero-vaginal canal. If it could prevent the union, non-union would be the rule, union

the exception. I shall discuss the disturbance produced by an abdominal cleft later on; what influence a too short yolk-stalk can have upon the union I cannot understand. Finally, in the fourth place, a fetal peritonitis at the time of the development of the utero-vaginal canal is practically excluded and has never been observed. The ligamentum vesico-rectale—a short falciform fold of peritoneum that extends sagittally from the posterior wall of the bladder to the anterior wall of the rectum, through the true pelvis (Krieger, 1858)—is rather the result of a non-union of the two Müllerian ducts than its cause; it also is frequently lacking in cases of divided uterus (Kehrer, 1899).

According to Thiersch (1852) the non-union of the Müllerian ducts is to be attributed to a strong development and long persistence of the two mesonephroi; Frankl (1902) and Holzbach (1909) have endeavored to establish this theory on a broader basis. The ontogenetic foundations upon which it is built, however, I cannot—at least for man—admit as correct. Firstly, the mesonephros never descends into the region of the utero-vaginal canal and never lies in the true pelvis. Secondly, the union of the two Müllerian ducts is accomplished even although the caudal end of the mesonephros increases considerably in man at the time. If persistence and stronger growth of the mesonephros could prevent the formation of the utero-vaginal canal, its non-formation would be the rule, and its formation the exception. Thirdly, the caudal portion of the mesonephros is actually not degenerated but persists as the epigenitalis and paragenitalis. The results of autopsies also argue against this theory. If an excessively developed mesonephros prevented the union of the Müllerian duct it should, as Kussmaul pointed out, leave behind it a paragenitalis more strongly developed than usual, but this is not the case.

According to R. Meyer (1898) the cause of a non-union of the ducts is frequently an abnormal shortness and strength of the ligamentum rotundum, eventually strengthened by a disproportion between the breadth of the lig. latum and the transverse diameter of the true pelvis. I hold, on the contrary, the shortness of the round ligament to be a result of the non-union of the ducts, but I agree as far as the influence of an excessive breadth of the pelvis, associated with a short lig. latum, is concerned.

Pick (1896, 1898) endeavored to explain the non-union by intervening detached germinal tissue and by the tumors formed from them. Since he observed a simultaneous occurrence of tumors and deformed or double uteri in 30 cases, his theory cannot be dismissed off-hand. It fails, however, to explain cases of double formation unaccompanied by tumors—and these are the most frequent.

Pick's idea is strengthened by the observation of von Recklinghausen (1896), who, in his search for adenocysts in uterine tumors, structures which he showed to be pathologically altered remains of the mesonephros or paragenitalis, found his best material in deformed uteri of the smooth broad forms and in uteri bicornes.

Von Winckel (1899), who accepts the theories of both R. Meyer and Pick, has called attention to the relation between the Müllerian and the primary excretory ducts. The Müllerian ducts lie at first lateral to the excretory ducts, then they cross over their ventral surfaces and come to lie medial to them, so that a separation of the excretory ducts laterally must produce a lateral pull on the Müllerian ducts. The displacement laterally of the primary excretory ducts may be caused by the mesonephros and the metanephros. Whoever is familiar with the relations which the primary excretory duct holds to the lateral wall of the pelvis at the time when the utero-vaginal canal is formed, will admit that a lateral displacement of the primary excretory duct is possible only with an enlargement of the true pelvis; von Winckel's theory, therefore, agrees closely with that of R. Meyer.

An account of how the mesonephric fold is united to the lateral abdominal wall by the plica inguinalis has been given in the section treating of the uro-

genital fold (p. 793). At the same place it is furthermore pointed out that on the formation of the ventral abdominal wall all its parts are pushed cranially and medially. With the abdominal wall, the point where the urogenital fold is attached to it and, finally, also, the urogenital fold itself, must alter their positions in the directions named. The best evidence of the nature and extent of the displacement is the varying position of the m. rectus abdominis during the formation of the anterior abdominal wall; it lies at first at the middle of the lateral wall and later immediately beside the ventral median line. This passive displacement of the two urogenital folds towards the median line, however, favors their union. Perhaps it is also the cause of the spiral twisting of the mesonephric folds and thus of the spiral course of the Müllerian ducts around the primary excretory ducts. If the displacement of the anterior abdominal wall takes place early, that is to say, before the enlargement of the transverse diameter of the true pelvis—as actually happens—then a genital cord of normal extent will be formed and the mesonephric fold will be twisted spirally. If the displacement is retarded, that is, until after the enlargement of the true pelvis, then the formation of the genital cord at least becomes difficult, and the difficulty will increase in proportion as the amount of retardation increases, until finally the union is impossible.

If, however, the fusion of the two mesonephric folds fails partially or wholly, the pull falls on the plica inguinalis or on the round ligament developed in it, and thereby the ligament becomes shortened. This shortening of the round ligament is in this case, in my opinion, the result and not the cause of the non-union of the Müllerian ducts. In this connection I would call attention to an observation by Rudolph (1909), in which the ligamentum rotundum was stated to be completely wanting in a case of uterus didelphys.

I have already called attention to the influence of extensive displacements of various portions of the intestine on the position of the mesonephric fold. On the left side the influence is so strong that we must accept a right-angled bend of the mesonephric fold as a regular result of its action (p. 791). If we suppose that the pressure of the intestinal tract on the mesonephric fold becomes greater by some disturbance in its development, then we would have the abnormal pressure demanded by all the authors cited above, but produced by quite a different organ; it would be a second cause of the non-union of the Müllerian ducts.

Finally, I must mention the topographical relations of the ascending and descending colons on the one hand and the mesonephric fold on the other. It must be noted, in the first place, that the ascending colon lies from the beginning lateral to the right fold, and, further, that the descending colon usually runs along the medial surface of the left fold; it is this latter condition, principally, that produces its bend. If we suppose that the descending colon does not come to lie on the lateral side of the mesonephric fold at the end of the process of readjustment of position, as is normally the case, the outward pressure, already existing, would be active beyond the usual time and so offer an obstacle to the union of the folds.

The same result would occur if the ascending colon came to lie on the medial side of the mesonephric fold. The colon would then force the fold laterally and so again prevent its union with the fold of the opposite side. That such a thing is possible is shown by a case observed by Descomp (1909), in which the right ovary and tube were covered by the cæcum, that is to say, were lateral to it. The influence of abnormalities in the position of the large intestine forms a third cause for the non-union.

All these considerations lead to the conviction that the causes for the occurrence of double formations of the utero-vaginal canal are more manifold than had been supposed, and that in any case several causes may act.

2b. DISTURBANCES IN THE DEVELOPMENT OF THE EPITHELIAL CANAL IN THE REGION OF THE CORPUS UTERI.

Here belong the uterus bicornis in all its different degrees of development, the uterus introrsum arcuatus and the uterus planifundus.

The corpus uteri—it must be continually borne in mind—is *not* formed by a *union* of the two Müllerian ducts, but the two uterine portions of the tubes, just as they are and just as they lie, combined with the cranial blind end of the utero-vaginal canal, are transformed into the corpus uteri by simple enlargement (Fig. 623 *a* and *b*). The two uterine portions of the two tubes lie almost in the same line, and, consequently,—compare Fig. 623 *b*—there is sufficient room cranially for their former medial, now their cranial, walls to be raised up and so form the fundus uteri (Fig. 623 *c* and *d*). On the other hand, if the two portions meet at an acute angle, if they form with the utero-vaginal canal a Y instead of a T, room is lacking for the upgrowth of the fundus, that is to say, the developmental stage of the uterus planifundus cannot be formed and the epithelial canal of the corpus remains two-horned. The more acute the angle at which the tubar portions of the uterus meet, the more the two-hornedness of the corpus uteri will be emphasized, and if this form of the epithelial canal persists until the musculature develops, it remains persistent; thus the uterus bicornis is formed. From this mode of development it follows that the forces that produce the uterus bicornis act in exactly the opposite direction from those that prevent the union of the Müllerian ducts to form the utero-vaginal canal. If the urogenital folds are drawn too far laterally, the genital cord is not formed and there is therefore no development of the utero-vaginal canal; if, on the other hand, the urogenital folds are pressed too far medially, although the Müllerian ducts will unite to form a utero-vaginal canal, the formation of a single corpus uteri will be prevented.

The urogenital fold is influenced most strongly and for a very long time by changes in the position of the developing intestine. In different embryos one finds the fold in very different positions: 1, completely rotated outwards, so that its medial surface rests upon the posterior and lateral abdominal walls; 2, placed sagittally so that it projects into the abdominal cavity as a ridge; 3, completely bent over medially, so that its medial surface rests on the posterior abdominal wall and its apex, which contains the Müllerian duct, reaches the root of the mesentery. This third position especially is interesting in connection with the formation of a uterus bicornis; if both Müllerian ducts run downward close to the root of the mesentery a horizontal tubar portion of the uterus cannot be formed (compare Fig. 552). Thus the condition is produced from which we started in the explanation of the uterus bicornis. The size of the angle between the two limbs of the Y will determine the degree of the two-hornedness—if the word is allowable; the more acute the angle the longer the horns and vice versâ.

If the formation of the utero-vaginal canal is prevented there can, of course, be no formation of a single corpus uteri, and a totally divided cervix uteri must always be associated with a divided corpus. On the contrary, even after the completed union of the utero-vaginal canal, the formation of the corpus uteri may be prevented; the force which makes the formation of the fundus uteri impossible, must even increase the force that unites the utero-vaginal canal. Also in cases of uterus didelphys it is possible—at least in fetuses and young girls in the early years of life—to distinguish between the portion of the Müllerian duct intended for the formation of the utero-vaginal canal and the portion intended for the formation of the tubar portion of the uterus, and this by the relations of the primary excretory duct, which lies only within the mesenchymatous wall of the utero-vaginal canal or the portion homologous with it.

The formation of the utero-vaginal canal throughout its entire length is not necessary for the formation of a single corpus uteri, a union at the cranial end is sufficient and the rest of the canal need not be formed. That such a malformation is possible is shown by the occurrence of a uterus unicorporeus bicollis (that is, with doubled cervix).

The different septa that occur in the female genital canal have, naturally, a different genesis. The septa in the region of the vagina and cervix are the persistent medial walls of the two Müllerian ducts, those of the corpus uteri, on the contrary, are the remains of an inward bending of the fundus uteri.

III. THE UROGENITAL UNION.

The efferent apparatus for the male sexual products is produced in both sexes by a union between the mesonephros and the testis. In describing the second period of degeneration of the mesonephros (p. 829) we have spoken of a division of its remains into the epigenitalis and the paragenitalis. The tubules of the epigenitalis, 5–12 in number and corresponding to the 58th–62nd or 69th mesonephric tubules, degenerate completely as far as the tubuli collectivi. The angle at which the transition of the tubulus secretorius into the tubulus collectivus occurs, and at which the interruption between the two first takes place, of all parts of the mesonephros, projects furthest medially or, what is of especial importance here, furthest towards the reproductive gland area. The blind ends of the tubuli collectivi become surrounded by the epithelial nucleus of the indifferent reproductive gland, so that each comes to lie in a bay within the nucleus. This portion of the epithelial nucleus gives rise, as has been seen, to the rete blastema; from the beginning, accordingly, the tubuli collectivi and the rete tubules lie wall to wall. This proximity of the two has led some observers who studied poorly preserved embryos—and these form the majority—to the erroneous conclusion that the tubules of the male and female rete, and even the tubuli recti of the testis and the medullary cords of the ovary, arose by the ingrowth of mesonephric tubules. There can be no question of such an origin. The rete tubules are developed before their union with the mesonephric tubules occurs, the tubuli collectivi of the latter end with broadened and thickened ends, sharply defined and distinctly marked off from the rete cords. The union of the two, the urogenital union, takes place at very different periods; I saw it for the first time in embryos of 60 mm. head-foot length. Up to this time the development in the two sexes is alike; a further development now begins in the males, degeneration in the females.

The Further Differentiation in the Male Sex.

As soon as the tubuli collectivi have broken through into the rete tubules, we term them the ductuli efferentes testis. In the fourth to the fifth fetal month (Kölliker 1879) they begin to coil

at their ends that are towards the primary excretory ducts, while towards the testis they remain straight. As a result they appear as wedge-shaped structures, whose apices are towards the testis and the bases towards the excretory duct; when, later, they are surrounded with a firm connective tissue membrane, they are known as the coni vasculosi. All the 5–12 tubules of the epigenitalis do not necessarily take part in the urogenital union, nevertheless they frequently persist, appearing as mesonephric remains in the epididymis. They may make secondary connections with neighboring parts, and especially, may break through into the tunica vaginalis propria, that is to say, into a portion of the abdominal cavity. Several coni may unite to form a duct before opening into the rete, the union resulting from the coni being connected in the first place with the rete and, secondly, with each other by means of longitudinal anastomoses, so that the individual tubules become independent of their connections with the rete and may lose them. Those that behave thus are usually the most caudal efferentes. The primary excretory duct becomes the canalis epididymidis and the ductus deferens. At first it is lined by a one-layered cylindrical, non-ciliated epithelium; in its upper part it coils in the manner described in works on systematic anatomy (canalis epididymidis) and at its lower end it dilates almost to four times its original size and forms the ampulla; the dilatation ends just at the beginning of the horizontal portion (Fig. 625), so that even before the anlage of the vesicula seminalis, the ductus ejaculatorius, which is developed from the horizontal portion, is recognizable.

In fetuses of 50 mm. head-foot length there begins, first in the lower portion of the ductus deferens, a concentric layering of the mesenchyme around the epithelial cylinder, and thence this arrangement extends over the whole of the primary excretory duct. I believe that I was able to recognize the first cilia on the epithelium in embryos of 70 mm. head-foot length. The musculature of the duct must first appear very late, since no muscle fibres were present in a fetus of 240 mm. head-foot length.

The vesicula seminalis arises from the primary excretory duct, and from the lower portion of it which has dilated to form the ampulla. In this region a simple epithelial tube is gradually constricted off in the cranio-caudal direction. The constriction is first found in embryos of 60 mm. head-foot length; it ends at the beginning of the horizontal portion. This, therefore, from the beginning is the anlage of the later ductus ejaculatorius.

Degeneration of the Urogenital Union and of the Primary Excretory Duct in the Female.

The connection of the epigenitalis tubules with the rete is completed either at birth or even before it. Since the degeneration of the primary excretory duct has already begun some time before this, the epoophoron has become completely free. Notwithstanding its degeneration, it continues to grow and its tubules acquire a ciliated epithelium and subepithelial smooth muscle cells (Bühler 1894). The primary excretory duct is already degenerated in embryos of 30 mm., at the very time, it is interesting to note, at which the degeneration of the Müllerian duct begins in male embryos. The first degeneration is exactly the same as in the case of the Müllerian duct, it affects the portion between the caudal pole of the ovary and the beginning of the utero-vaginal canal. The cranial portion may remain connected with the epoophoron for a longer or shorter time, the distal portion is usually completely degenerated; all the remains of the primary excretory duct are known as Gartner's canal. This may run (R. Meyer 1909) "from the epoophoron through the ligamentum latum, at first parallel with the tube, then more obliquely as the base of a triangle whose opposite angle is formed by the uterine portion of the tube and the corpus uteri." "At about the level of the internal os uteri, the canal first sinks into the substance of the uterus, and running downwards through the muscle layers, it gradually approaches the mucous membrane medially, without reaching it, however, and then passes from the upper part of the portio vaginalis into the lateral fornix of the vagina to run caudally at about the middle of the lateral wall of the vagina." "In its lowest portion the canal lies usually rather far dorsally in the lateral wall and thence passes ventrally in the lateral part of the hymen to reach the free border of that structure." "Its opening to the exterior is immediately at or very close to the free border of the hymen, through the vestibular epithelium; rarely it is more lateral, in the nympho-hymenal sulcus of the vestibule." Gartner's canal is very seldom indeed present throughout its whole extent. Up to the end of the third fetal month one finds, without exception, remains of the canal in the uterus, in the vagina or in the hymen; from the fourth month onwards the number of cases increases in which remains are no longer present: in new-born infants and in children, one always finds smaller or larger remains of the canal in about one-quarter to one-third of all cases, and the proportion is not much less in adults (R. Meyer 1909).

If one compares the course of the primary excretory duct in the embryo with the course of Gartner's canal in the adult, the different relation of the two to the wall of the uterus at once reveals

itself. The primary excretory duct of the embryo is completely surrounded by the mesenchymatous wall of the uterus that encloses the utero-vaginal canal; Gartner's canal enters the uterine musculature only at the level of the internal os uteri. The difference between these two arrangements is, however, only apparent; the uterine wall is formed not only by the mesenchyme of the utero-vaginal canal, but also by the mesenchyme of the horizontal portion of the tubes (Fig. 623 *b*, p. 917). The entrance of Gartner's canal marks the point where, in the adult, the portion of the uterus formed from the tube passes over into that formed from the utero-vaginal canal. I was, therefore, correct when (p. 918) I placed the boundary between the two at the internal os.

The persisting Gartner's canal may also form in the fifth month an ampulla and a vesicula seminalis (for details, see R. Meyer 1899 and 1909), and the ampulla then lies at the level of the cervix uteri, of the upper part of the portio vaginalis, and extends to the fornix of the vagina and into the uppermost part of the lateral wall of the vagina.

The Ligaments of the Reproductive Glands.

The urogenital fold divides into a series of portions (pp. 785 and 787). First there is a division into the mesonephric and genital folds (Figs. 631 and 632), and the former is again divided into the tubar, gland and mesenterial portions (Figs. 632). Let us first consider the mesenterial portion. The most cranial portion of it fastens the mesonephros to the diaphragm for a limited period of the development and, therefore, bears the name of diaphragmatic ligament of the mesonephros (Fig. 631). During the development of the mesonephros this ligament is continually degenerating and continually being formed anew. This process depends on the degeneration of the mesonephros and of the mesonephric fold itself. Both undergo an extensive process of degeneration, as we have seen on p. 816, and, since the degeneration of the fold begins at the cranial end and proceeds caudally, it must at once affect the most cranial portion, the diaphragmatic ligament. This will disappear, only to be immediately formed again, since the succeeding portion of the mesonephric fold will now attach the new cranial pole of the mesonephros to the pillar of the diaphragm, which has in the meantime grown downwards, and will so become a new diaphragmatic ligament. This process will be repeated from segment to segment, until an obstacle occurs to end it, and this obstacle is supplied in the vasa spermatica interna. We may say, therefore, that the diaphragmatic ligament of the mesonephros continues to degenerate until it becomes the mesentery of the spermatic vessels; as such it persists throughout life, along with the rest of the mesonephric fold.

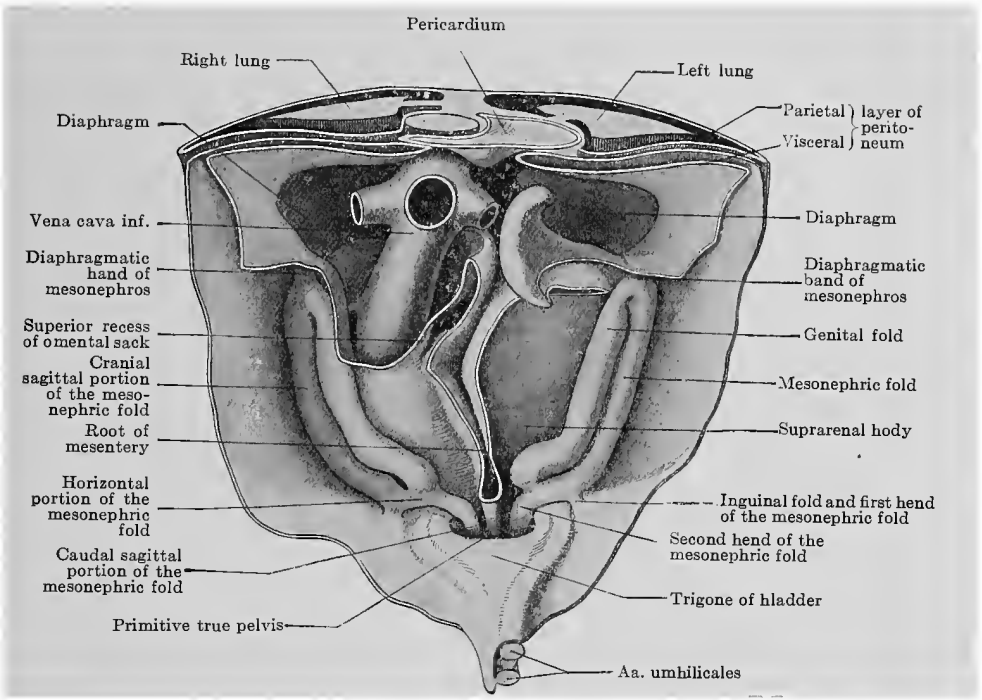


FIG. 631.—Model of the posterior abdominal wall of a human embryo of 19.4 mm. greatest length. (Embryo Ma. 2, from the collection of Professor Hochstetter, Vienna.) Model prepared by my pupils Massard and Chomé. The urogenital fold is separated by a deep groove into the mesonephric and genital folds. The upper pole of both these folds is attached to the diaphragm by the diaphragmatic ligament of the mesonephros. The mesonephric fold is bent at two places, and we may recognize an upper sagittal, a horizontal, and a lower sagittal portion. At the first bend, between the upper sagittal and horizontal portions, the mesonephric fold is connected with the lateral wall of the abdomen by the inguinal fold.

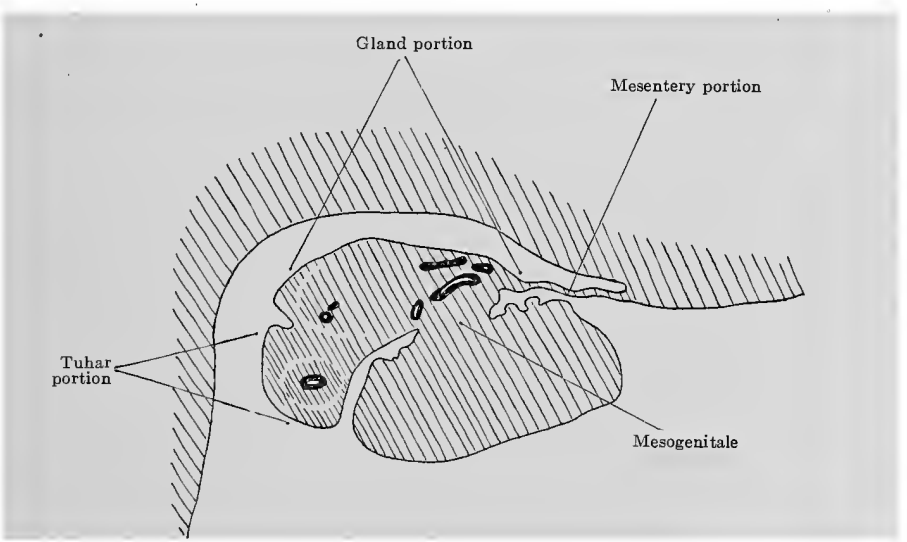


FIG. 632.—Transverse section of the urogenital fold of a human embryo of 50 mm. head-foot length. (Embryo R. Meyer 272, from the collection of Professor R. Meyer, Berlin; slide 2, row 1, section 1.) The urogenital fold is divided by two deep grooves into the mesonephric and genital folds; both are connected by the mesogenitale. The mesonephric fold is again divided into the tubar, the gland and the mesenterial portions.

The mesenterial portion of the mesonephric fold is connected with the tubar portion and the mesogenitale by means of the gland portion. In female embryos the tubes and ovary become greatly developed, but the mesonephros degenerates and, in consequence, the gland portion collapses and appears to be merely the continuation of the mesenterial portion, which seems to split into the tubar portion and the mesogenitale. We speak, therefore, of a *ligamentum ovarico-pelvicum* (the mesogenitale) and a *ligamentum infundibulo-pelvicum* (tubar portion). Both become greatly thickened by acquiring blood-vessels, but they always remain connected by the former gland portion.

Development of the Ligamentum Ovarii Proprium, the Ligamentum Uteri Rotundum, and the Chorda Gubernaculi.

The genital fold is also a structure that continually alters its form, growing caudally by apposition and shortening at the cranial end by degeneration. The indifferent reproductive gland does not occupy the entire length of the fold, but leaves a portion of it free at either end. One may therefore recognize three portions in the human fold: (1) the *progonal* portion, the upper end without the reproductive gland; (2) the *gonal* portion, the largest, middle portion with the reproductive gland, and (3) the *epigonal* portion, the lower end without the reproductive gland. The degeneration of the genital fold precedes that of the reproductive gland, and the growth of the reproductive gland that of the genital fold. As long, therefore, as growth in length and degeneration prevail in the reproductive gland, so long will gonal portions be transformed into progonal at the upper end and epigonal to gonal at the lower end. In female embryos the caudal pole finally reaches the true pelvis and lies on the posterior surface of the genital cord. The epigonal portion of the genital fold consequently unites the caudal pole of the ovary with the genital cord, but in the genital cord the formation of the primitive wall of the uterus (see p. 916) extends just so far that the point of insertion of the epigonal portion comes to lie on the surface of the uterine wall. Exactly opposite the insertion lies, as we will see shortly, the ligamentum rotundum. In the interior of the epigonal portion the mesenchyme tissue condenses to form a cord, the *ligamentum ovarii proprium,* the cells of which very quickly become connective tissue and smooth muscle fibres, all of which have a parallel course and stream out into the subserous musculature. From what has been said, it will be clear that the lig. ovarii proprium must arise from the caudal pole of the ovary and pass to the posterior surface of the uterus.

In male embryos the homologue of the lig. ovarii proprium, the lig. testis, is also found, but it has a different form and a dif-

ferent course. The difference in form depends in the first place on the greater length of the epigonal portion (the caudal pole of the testis lies higher than that of the ovary), and, in the second place, in its being constricted off from the rest of the mesonephric fold; the difference in the course depends, firstly, on the position of the caudal pole of the testis, which does not enter the true pelvis, and, secondly, on its non-union with the wall of the uterus; consequently the insertion of the epigonal portion, that is to say, the lig. testis, into the mesonephric fold must be at the boundary between the true and the false pelvis. That the points of insertion of the

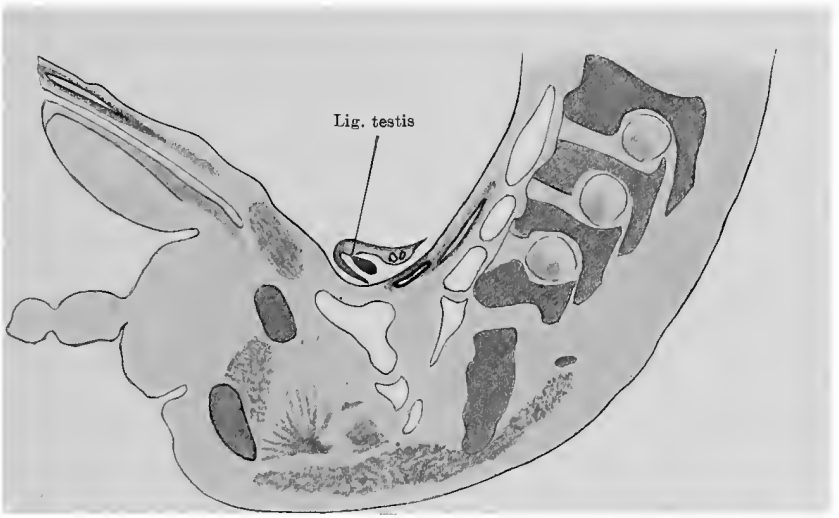


FIG. 633.—Sagittal section of the lower end of the body of a human embryo of 40 mm. trunk length. (Embryo R. Meyer 259, from the collection of Professor R. Meyer, Berlin; slide 4, row 2, section 2.) ×5.5. The section just cuts the right wall of the primitive true pelvis, and shows the foramen obturatum with the m. obturator internus and the levator ani. The testis lies just at the entrance into the true pelvis and is connected with the mesonephric fold, which is drawn out into a loop, by the lig. testis.

lig. testis and lig. ovarii proprium into the mesonephric fold or genital cord are homologous, is evident from the fact that both are opposite the insertion of the chorda gubernaculi or the round ligament (see below).

The urogenital fold in both sexes is united by the inguinal fold (p. 793) with the crista inguinalis, situated on the posterior surface of the anterior abdominal wall (Fig. 634 *a* and *b*). This connection constitutes a bridge between the urogenital fold and the entrance into the inguinal canal, for this is marked quite early by the base of the crista inguinalis. In the interior of the crista there is from the beginning a cord of compact mesenchyme, the *chorda gubernaculi* (Fig. 634 *a* and *b*), which is evident even before there is any indication of a differentiation of the abdominal musculature. It has a conical shape in transverse section, the apex being towards the crista inguinalis and the base almost at the

integument (Fig. 634). When, later, the abdominal musculature begins to develop, it must grow around the chorda gubernaculi, and thus there is necessarily formed a canal (the *inguinal canal,* Fig. 635), whose contents were there from the beginning. The developing muscles behave differently with reference to the chorda gubernaculi. The transversus and obliquus internus give off fibres

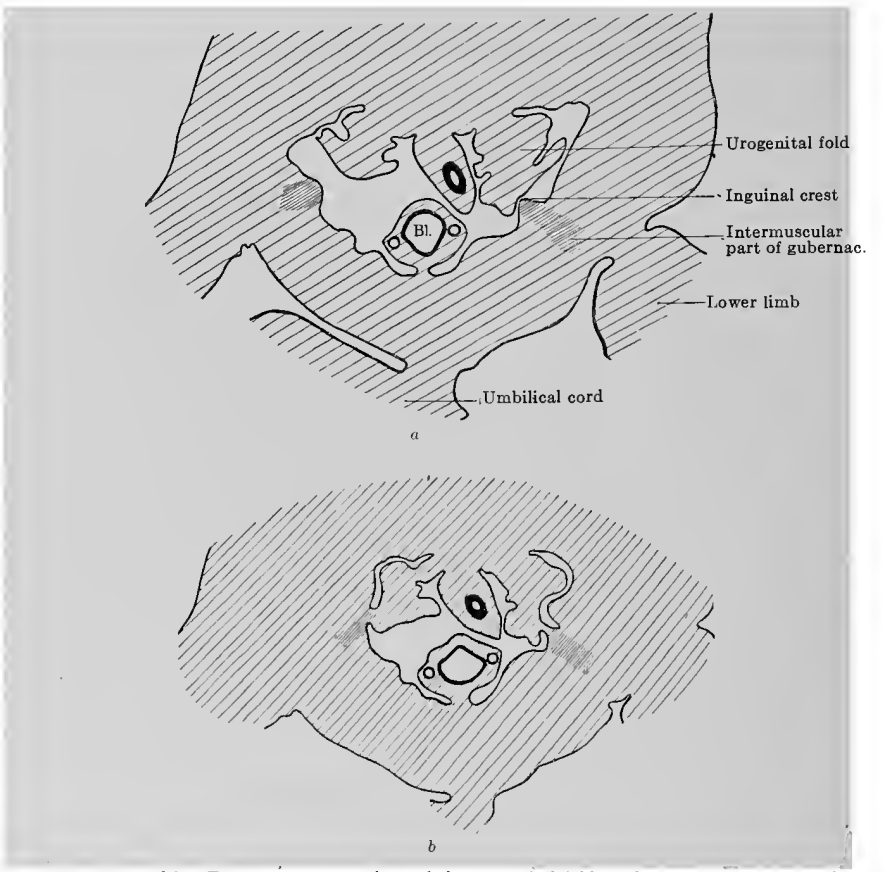


FIG. 634 *a* and *b*.—Two transverse sections of the urogenital fold at the level of the plica and crista inguinalis of a human embryo of 22.5 mm. greatest length. (Embryo R. Meyer 303, from the collection of Professor R. Meyer, Berlin; slide 34, row 2, section 1, and row 4, section 1.) The plica inguinalis arises from the lateral surface of the urogenital fold at the boundary between the false and the true pelvis; opposite the plica on the lateral abdominal wall is the crista inguinalis (a). The plica and crista grow together (b).

to its surface, which bend around and accompany it to the crista inguinalis; by these fibres a muscular mantle is formed around the chorda, and this is known in comparative anatomy as the conus musculosus inguinalis. The obliquus externus presents at first a distinct foramen corresponding to the base of the chorda (Fig. 635), and through this foramen the chorda stands in connection with a second mesenchymatous cord (Fig. 635), which has long been known as the *lig. scroti.* This extends from the outer open-

ing of the inguinal canal to the integument and to the base of the genital tubercle. Later the aponeurosis of the external oblique grows around the lig. scroti, which in the mean time has completely united with the chorda gubernaculi, and so the aponeurosis forms a sort of thin hernial sack, which becomes the *fascia cremasterica;* this fascia, accordingly, is not a true fascia, but an aponeurosis. Up to this point the development is the same in both the male and the female embryo. In the male the union of the gubernaculum with the mesonephric fold is exactly opposite the insertion of the lig. testis (Fig. 635). In

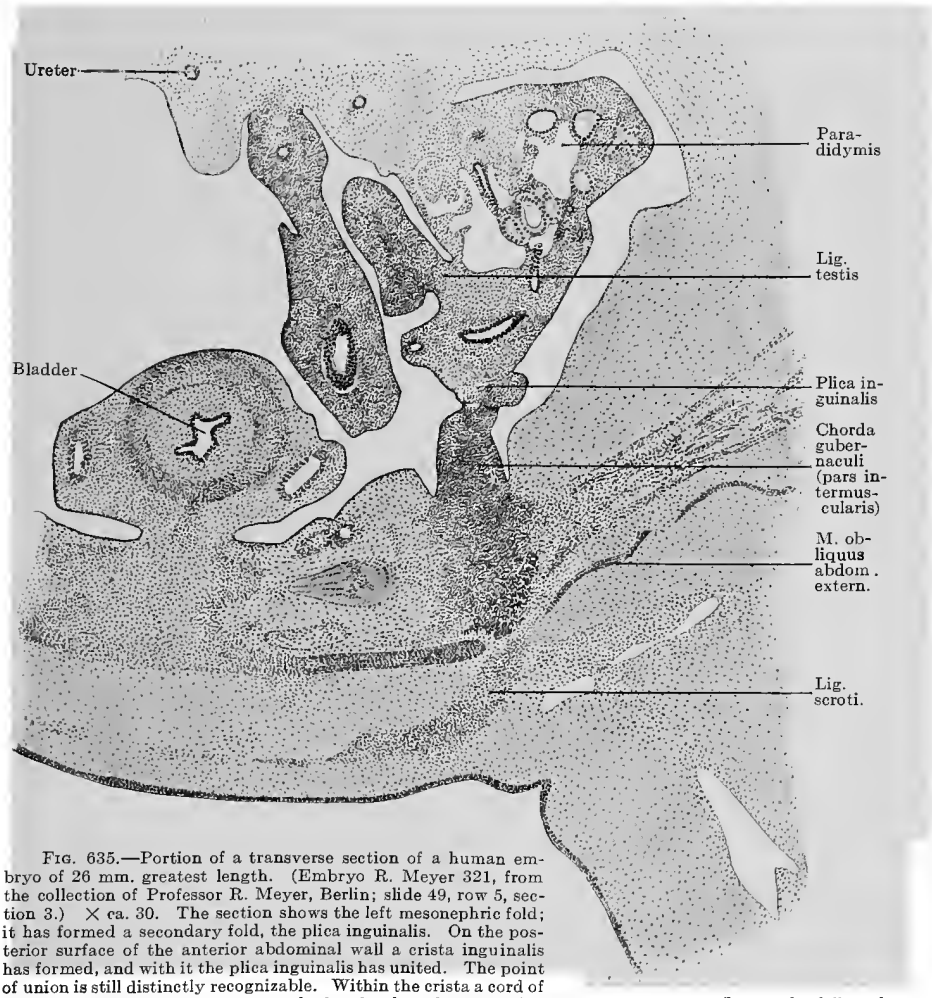


FIG. 635.—Portion of a transverse section of a human embryo of 26 mm. greatest length. (Embryo R. Meyer 321, from the collection of Professor R. Meyer, Berlin; slide 49, row 5, section 3.) × ca. 30. The section shows the left mesonephric fold; it has formed a secondary fold, the plica inguinalis. On the posterior surface of the anterior abdominal wall a crista inguinalis has formed, and with it the plica inguinalis has united. The point of union is still distinctly recognizable. Within the crista a cord of compact mesenchyme has appeared, the chorda gubernaculi in the narrower sense. It may be followed through the abdominal wall to an opening in the aponeurosis of the obliquus abdominis externus. From this opening a second cord of compact mesenchyme, the lig. scroti, extends to the integument. The anterior abdominal wall has thickened except at the point of insertion of the crista inguinalis; thus the crista comes to lie in a groove, the anlage of the saccus vaginalis.

the portion of the mesonephric fold between the two insertions there develops another mesenchymatous cord, which connects both with the lig. testis and with the chorda gubernaculi, and so unites the two. On the completion of this union there is a continuous cord extending from the lower pole of the testis through the inguinal canal and terminating in the integument at the base of the genital tubercle. I shall term this cord the chorda gubernaculi in a broader sense (Fig. 636). Its individual parts are (Fig. 636): the *pars mesorchica,* formed by the lig. testis, the *pars mesonephridica,* the mesenchymatous cord in the mesonephric fold

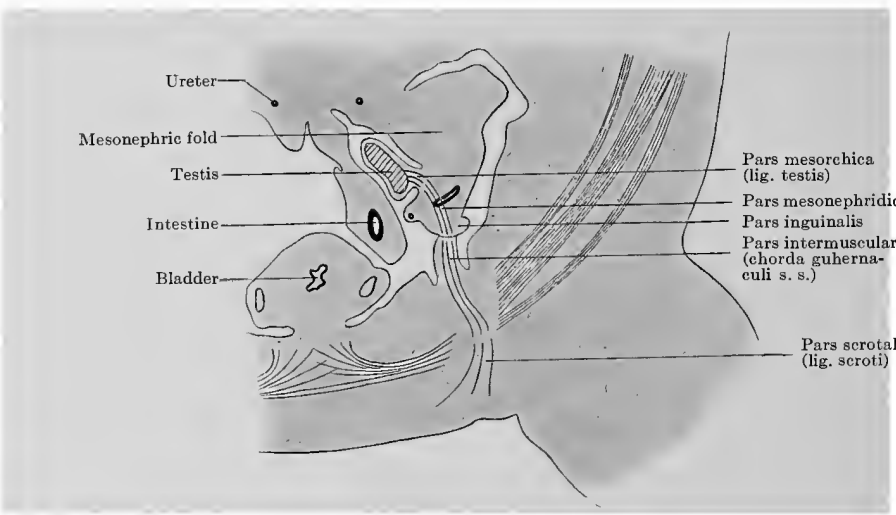


FIG. 636.—In a transverse section of the urogenital fold, of the inguinal fold, and of the body wall of a male embryo of 26 mm. greatest length, the various parts of the chorda gubernaculi are represented diagrammatically. The chorda guhernaculi in the broader sense consists of: 1, the lig. testis (pars mesorchica), 2, a mesenchymatous cord in the mesonephric fold and its plica inguinalis (pars mesonephridica), 3, a mesenchymatous cord in the crista inguinalis and between the abdominal muscles (pars intermuscularis), and 4, the lig. scroti (pars scrotalis).

and the inguinal fold, the *pars intermuscularis,* formerly the chorda gubernaculi in the narrower sense and, finally, the *pars scrotalis,* formerly the lig. scroti.

In the female embryo the affair is simpler. The lig. ovarii proprium, which corresponds to the lig. testis, and the chorda gubernaculi in the narrower sense, which in this case is termed the *lig. rotundum uteri,* are no longer separated by the mesonephric fold, but by the primitive uterine wall. Consequently a union of the two is imposible, but both have an insertion into the wall of the uterus, and it is evident from the development that these insertions must take place in the posterior or anterior wall of the uterus. Consequently there also results in the female embryo a union of the lig. rotundum with the lig. scroti, or if we would be precise, with the *lig. labiale.* The lig. rotundum extends,

acordingly, from the anterior wall of the uterus through the inguinal canal to the base of the genital tubercle; it consists of a *pars intermuscularis,* the former chorda gubernaculi in the narrower sense, and a *pars labialis,* the former lig. labiale.

If one would draw homologies, the male chorda gubernaculi in the wider sense corresponds to the following parts in the female: (1) the lig. ovarii proprium, (2) a part of the wall of the uterus, (3) the lig. uteri rotundum. The lig. ovarii corresponds to the former lig. testis or the pars mesorchica of the chorda gubernaculi in the wider sense. The lig. uteri rotundum corresponds by its pars intermuscularis to the similarly named portion of the chorda gubernaculi, by its pars labialis to the pars scrotalis. Finally, one might homologize a portion of the subserous uterine musculature, which is connected on the one hand with the lig. ovarii proprium and on the other with the lig. uteri rotundum, with the pars mesonephridica of the chorda gubernaculi.

IV. DEVELOPMENT OF THE EXTERNAL GENITALIA.

The parent tissue for the external genitalia is the cloacal tubercle. It has already been pointed out (p. 874) that this appears between the umbilicus, the coccygeal tubercle and the two lower limbs in an embryo of 13 mm. (Figs. 637, 638). We may

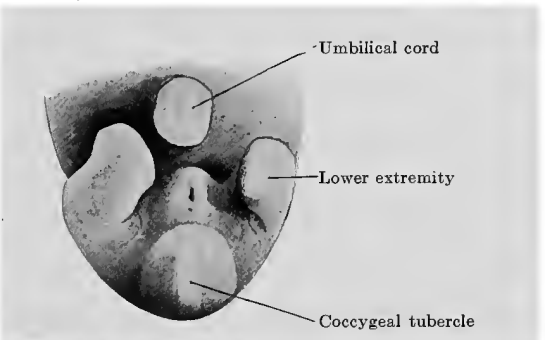


FIG. 637.—Caudal end of the body of an embryo of 18 mm. greatest length. (From a photograph kindly supplied by Professor R. Meyer, Berlin.) Between the umbilicus, the coccygeal tubercle, and the right and left lower limbs is the cloacal tubercle; on its anal slope are the ostium urogenitale and the anal groove.

distinguish on it an oral and an anal, a right and a left slope. Along the anal slope, from the summit to the base, there is, in the interior of the tubercle, the pars phallica of the urogenital sinus (Fig. 638), whose ventral wall, formed by the urogenital membrane, abuts upon the surface of the cloacal tubercle (Fig. 638). The tubercle is originally a paired structure, lying on either side of the cloacal membrane (Fig. 601), but the paired condition is converted into an unpaired one by the elevation of the entire anterior abdominal wall (Figs. 601, 637).

Upon this cloacal tubercle the sexual organ, the *phallus,* is seated like a tower on a hill. The base of the phallus thereby comes to lie excentrically on the cloacal tubercle, occupying the

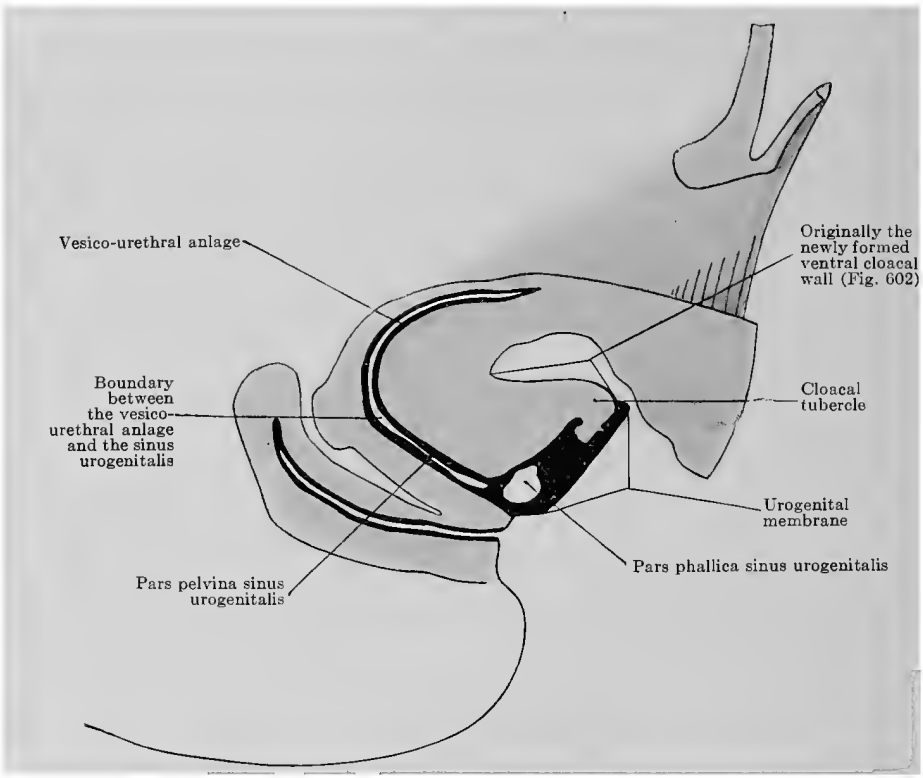


FIG. 638.—Sagittal section through the caudal end of the body of an embryo of 24 mm. vertex-breech length. (Embryo Hal. 1, from the collection of the I Anatomical Institute, Vienna.) The cloacal tubercle projects between the umbilicus and the coccygeal tubercle. The pars phallica of the sinus urogenitalis runs along its anal slope.

whole of its anal slope and a part of the right and left ones (Fig. 639). The tubercle is thus divided into the almost circular base of the phallus and the semilunar *genital tubercle* (Fig. 639). This

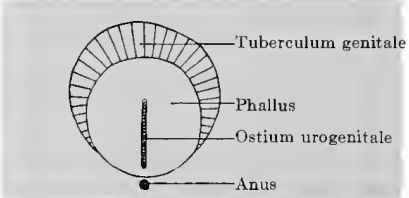


FIG. 639.—Diagrammatic representation of the division of the cloacal tubercle into the phallus and genital tubercle.

latter represents an originally unpaired structure, lying cranial to the phallus and surrounding it on two sides; from it there are formed later the two genital swellings. The genital tubercle is

separated from the phallus in female embryos by a deep groove which is the anlage of the later sulcus nympholabialis, the groove between the labia majora and minora. In male embryos this groove is absent from the beginning.

The Indifferent Phallus.

The quickly growing phallus assumes the penial form at an early stage in both sexes, and at the beginning of the third month a transitory sexual difference occurs in the direction of the phallus, which in female embryos bends downwards, while in male embryos it retains its direction more or less perpendicular to the long axis of the body (Herzog 1904).

The pars phallica of the urogenital sinus, which is contained within the phallus, behaves differently in different parts, that part which corresponds to the future glans becoming perfectly solid and forming the urethral plate, while the part corresponding to the rest of the penis remains hollow, and by destruction of the urogenital membrane breaks through to the exterior throughout its entire length; it forms the trough-like *orificium urogenitale primitivum*. As soon as the coronary sulcus of the glans is developed in embryos of 21 mm., it lies at about the boundary between the anterior circumference of the orificium urogenitale and the urethral plate.

The glans is marked off as a spherical protuberance in embryos of 26 mm.

The Sexual Differentiation.

The beginning of the sexual differentiation can hardly be assigned to a definite period, since it takes place quite gradually and even in advanced stages presents difficulties to diagnosis. We base our diagnosis on the position of the ostium urogenitale relative to the coronary sulcus on the one hand and the anal opening on the other. Male embryos are distinguished by the distal ("distal" has reference here to the base of the phallus) circumference of the ostium urogenitale always lying in the coronary sulcus, while the proximal circumference becomes more and more distant from the anal opening. Female embryos may be recognized by the urogenital opening retreating away from the coronary sulcus by the gradual closing of its distal part, while its proximal part always lies close to the anal opening; the differentiating moment is, accordingly, both positive and negative in each sex. In Fig. 640 are shown the external genitalia of an embryo in which a determination of the sex from the external genitalia is impossible. The urogenital opening is on the anal slope of the phallus, whose projecting summit already shows the anlage of the glans. The distal circumference of the opening reaches the sulcus, the proximal one still

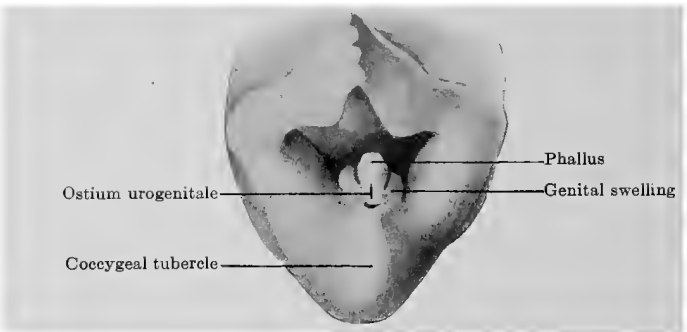


FIG. 640.—The indifferent external genitalia of an embryo of 28 mm. greatest length. (From a photograph kindly furnished by Professor R. Meyer, Berlin.) The cloacal tubercle is divided into the phallus and the genital tubercles or swellings. The ostium urogenitale and anus are still close together.

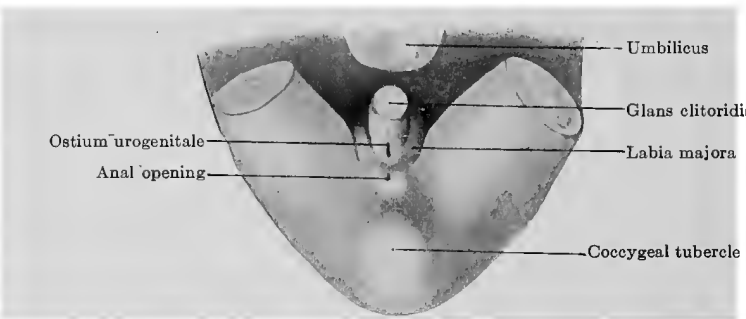


FIG. 641.—Female external genitalia of an embryo of 32.5 mm. greatest length. (From a photograph kindly furnished by Professor R. Meyer, Berlin.) The phallus has become the clitoris, the glans and coronary sulcus are recognizable. The ostium urogenitale has preserved its relation to the anal opening, but no longer reaches the sulcus coronarius glandis.

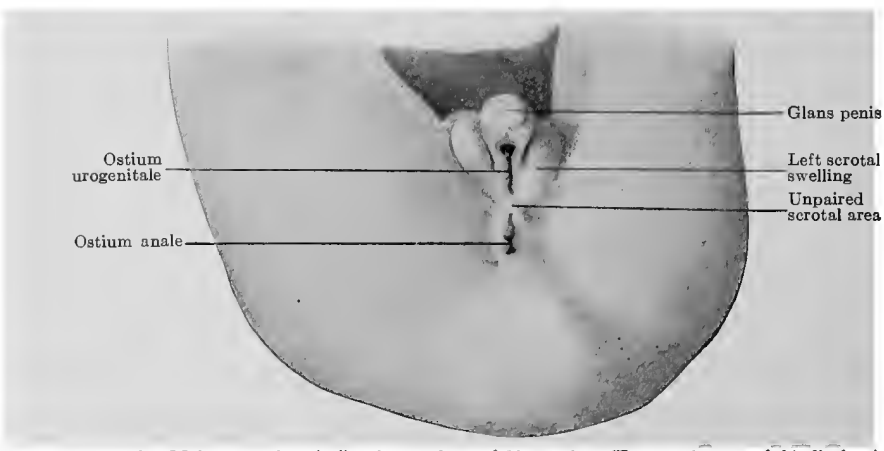


FIG. 642.—Male external genitalia of an embryo of 3½ months. (From a photograph kindly furnished by Professor R. Meyer, Berlin.) The phallus has become the glans penis, the scrotal swellings are fully developed and the unpaired scrotal area is indicated. The ostium urogenitale and ostium anale have separated, the ostium urogenitale extends to the sulcus coronarius glandis.

lies close in front of the anal opening; the first fact is positive for male embryos, the second positive for female ones, and consequently these genitalia are to be termed indifferent. Fig. 641 shows the female differentiation: the phallus has become the clitoris; the urogenital opening lies close in front of the anal opening, and from its distal circumference a shallow groove, the *urethral groove,* extends to the coronary sulcus. A wandering away from the sulcus coronarius and a persistence of the relations to the anal opening are both female characters. Fig. 642 shows the male type. The urogenital opening is preserved throughout its entire length, its distal circumference reaches the sulcus coronarius, the proximal one has separated from the anal opening: a wandering away from the anal opening and the preservation of the relation to the coronary sulcus are both male characters.

Development of the Penis and Scrotum.

The most striking characteristic of the transformation of the indifferent phallus into the penis is the great elongation of the male organ. The formation of the penis takes place in such a way that the glans and the distal portions of the shaft of the penis are first formed. It has been pointed out that the sulcus coronarius glandis appears in the indifferent stage in embryos of 21 mm. and that embryos of 26 mm. already possess a distinctly projecting glans. After the glans and distal portions of the shaft are formed, the formation of the rest of the shaft occurs, and these newly-formed portions gradually raise up the already formed glans and distal portions of the shaft. The glans is passive to the extent that it only enlarges in proportion to the entire growth. Along with the glans and the distal portions of the shaft the coronary sulcus and the ostium urogenitale are also raised up. The form, size and position of the latter remains the same from the beginning to the end of the growth of the penis and is in all stages of development a distally broadened slit (Fig. 642), which extends to the sulcus coronarius glandis.

The urogenital sinus, accordingly, appears at once in its whole length; it does not grow by the gradual closure of a groove along the anal wall of the penis until it reaches the glans, but its growth in length keeps pace with that of the penis. The ostium urogenitale, accordingly, already represents the primitive external orifice of the sinus urogenitalis.

Since in this growth the first-formed parts of the penis are pushed out passively, we must assume the existence of a basal zone of growth lying to the pelvic side of the urogenital opening, that is to say, in the neighborhood of the pars pelvina of the urogenital sinus. The pars pelvina is, accordingly, with reference to the growth, the active portion of the urogenital sinus, and the pars

phallica the passive portion. The basal growth in the pars pelvina must produce a new area, interposed between the base of the penis and the anal opening, and the best name for this is the *unpaired scrotal area* (Fig. 642). In embryos of 60 mm. head-foot length this becomes raised up in toto and forms the unpaired scrotal swelling, into which the two genital swellings, which we now must term the scrotal swellings, extend from above. Since the middle of the area is connected by dense connective tissue with the con-

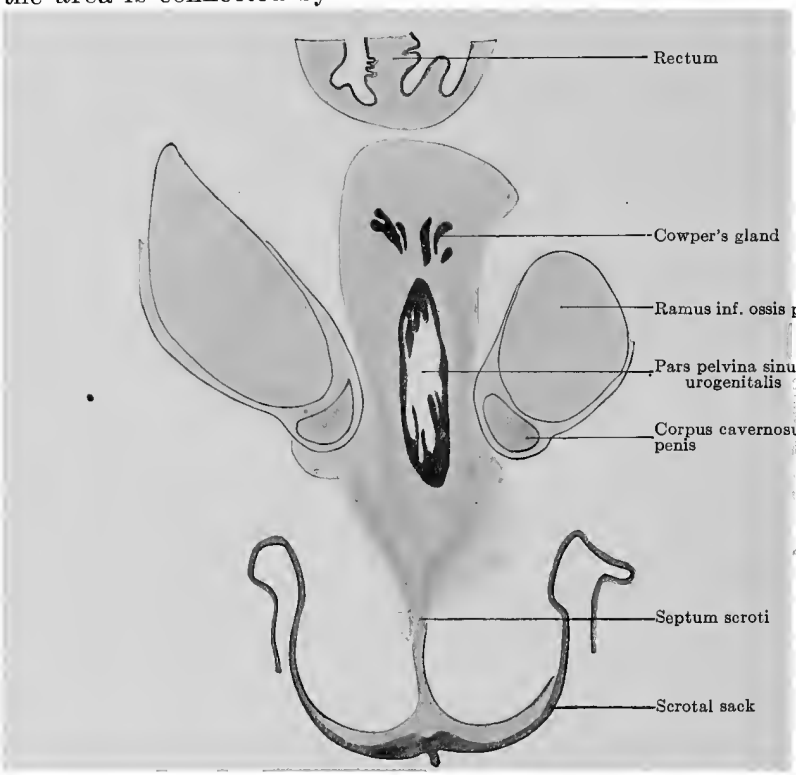


Fig. 643.—Transverse section of a male embryo of 70 mm. head-foot length (embryo R. Meyer 267, collection of Professor R. Meyer, Berlin; slide 67, row 1, section 3), below the symphysis pubis. × ca. 23. From behind forwards the following parts are cut: rectum, pars pelvina of the urogenital sinus and scrotum. From the pars pelvina Cowper's glands have developed and between the mesenchyme of the urogenital sinus and the epithelium of the scrotum there is stretched the septum scroti

nective tissue of the pars pelvina, the projecting scrotal swellings gradually draw out this connective tissue to a band and so the *septum scroti* is formed, it being at all times only a connective tissue structure. To its stretching it offers a certain amount of resistance, and consequently, there is formed at the surface of the scrotal area a median depression (Fig. 643), which, from the beginning, is the only external division of the unpaired scrotal swelling into a right and left half, while the septum scroti effects a complete internal division. As soon as the descensus is complete this unpaired scrotal area alone forms the scrotal sack, the paired

scrotal swellings to the right and left of the penis fading out into the surrounding areas.

The primitive glans becomes divided into two portions (Fig. 644 *a* and *b*) by an epithelial cylinder that grows in from the epithelium of the external surface; the two parts are an outer cylin-

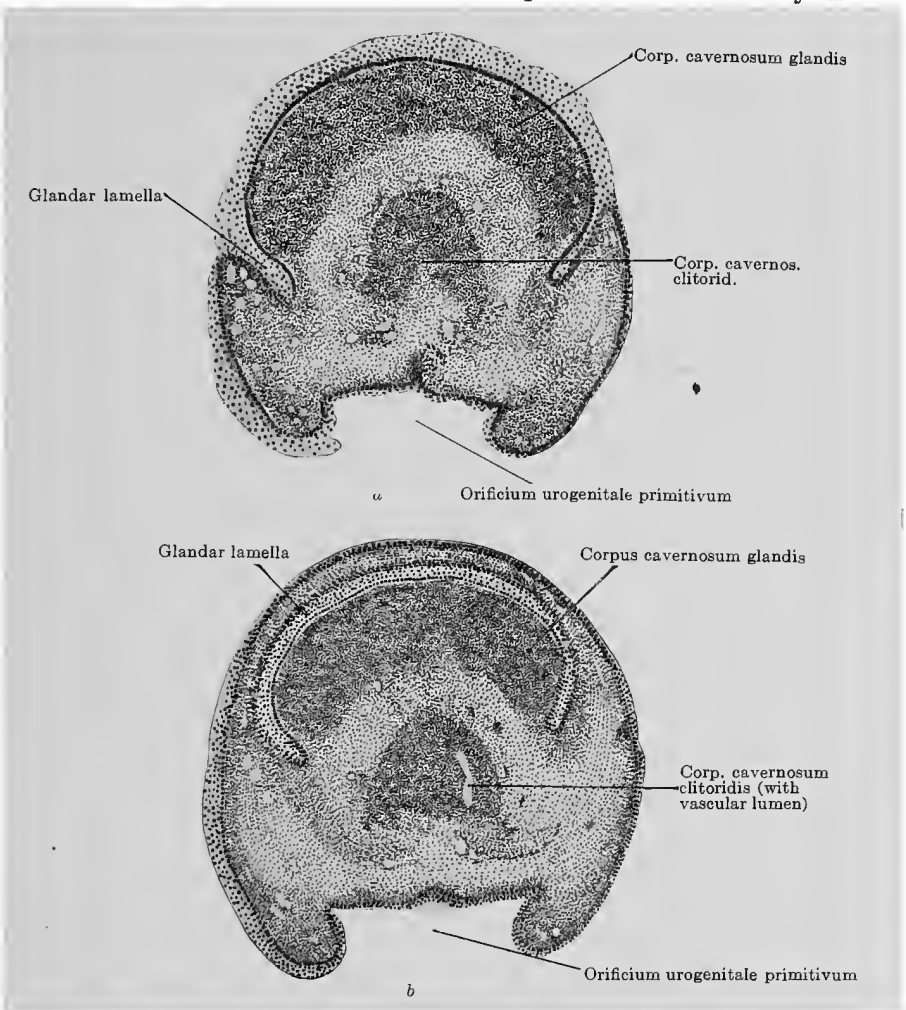


FIG. 644 *a* and *b*.—Two sections through the glans clitoridis of a human embryo of 80 mm. head-foot length. (Embryo R. Meyer 266, from the collection of Professor R. Meyer, Berlin; slide 88, row 2, section 5, and row 2, section 3.) From the surface epithelium a solid lamella, the glandar lamella, grows into the mesenchyme of the glans and separates the glans proper from the præputium.

drical mantle, the præputium, and an inner sphere, the glans in the narrower sense. The *glandar lamella* (Fleischmann 1907), as we shall term this epithelial cylinder, is not a closed tube, but is imperfect on the anal surface; by this opening the præputium and the glans in the narrower sense remain in connection, the *frenulum præputii* is a persistent portion of the mesenchyme of the primitive

glans. The solid glandar lamella becomes hollowed out by the degeneration of its central cells, the cavity breaks through to the exterior and so the space between the prepuce and the glans in the narrower sense is formed. The glandar lamella makes its appearance in embryos of 50 mm. head-foot length.

The corpora cavernosa appear as four portions, which, enumerated in the order of their appearance, are: the two corpora cavernosa penis, the corpus cavernosum glandis and the corpus cavernosum urethræ. They are formed from the young connective tissue by a dense aggregation of the mesenchyme cells, which are packed so closely together that the anlage has the appearance of being perfectly solid; only after some time greatly scattered vascular lumina occur and these later enlarge; between the first formed vessels new ones are formed and the characteristic structure of the spongy tissue is acquired.

The corpora cavernosa penis are united together at their apices and along their oral surfaces.

The first traces of a corpus cavernosum penis are to be found in embryos of 14.75 mm., the corpus cavernosum glandis occurs in embryos of 22 mm. greatest length. A compact layer of mesenchyme cells occurs around the epithelial lining of the sinus urogenitalis, at an early period, but a definite delimitation of a corpus cavernosum urethræ is first seen in embryos of 70 mm. head-foot length. The first vascular lumina occur in the glans in embryos of 28 mm. greatest length and in the corpora cavernosa penis in embryos of 70 mm. head-foot length.

Development of the Clitoris and of the Labia Majora and Minora.

In the female there is formed from the phallus the clitoris, the frenulum clitoridis and the labia minora. Since the penis develops from the entire phallus it cannot be considered exactly homologous with the clitoris. The clitoris corresponds to the entire glans penis and the oral slope of the penis shaft, the frenula clitoridis and the labia minora correspond to the anal slope of the penis shaft (Fig. 648).

The phallus of the female shows at first the same amount of growth as that of males of the same age, indeed, it may even be longer. The urogenital opening always remains at the base of the phallus and must, therefore, descend anally along the anal surface of the clitoris; a groove, the *urethral groove,* between it and the sulcus coronarius of the glans shows the former extent of the urogenital opening. We may therefore recognize in the female also an ostium urogenitale primitivum and definitivum. The principal growth in length, which in the male occurs in the neighborhood of the pars pelvina of the urogenital sinus, is entirely wanting in the female and consequently after a short period of growth there is cessation of the growth in length of the clitoris and the urogenital opening remains in the neighborhood of the anal opening; between the two there develops a short perineum, but never a scrotal area.

The two genital swellings on this account are not prolonged anally to form an unpaired scrotal tubercle and consequently they do not fade out as in the male, but persist as the labia majora. The middle part of the genital tubercle becomes the mons Veneris.

The labia minora or nymphæ arise in their oral parts from the margins of the urethral groove, in their anal parts from the margins of the ostium urogenitale definitivum, that is to say, they arise from the entire anal surface of the phallus with the exception of the short portion that forms the anal surface of the clitoris; they extend from the anal periphery of the ostium urogenitale definitivum to the sulcus coronarius glandis. The oral and anal portions do not arise simultaneously; the time of the first development of the oral portions cannot be given, for they are present as the swollen margins of the urethral groove so soon as the urogenital opening has broken through (Fig. 645); the swelling of the margins of the ostium urogenitale definitivum and consequently the anlage of the anal portions of the nymphæ begins in embryos of 223 mm. vertex-breech length (measured over the nape and back) and 162 mm. in greatest head circumference; it remains, however, quite insignificant for a long time and it is only in embryos of 347 mm. vertex-breech length (measured over the nape and back) that one can speak of labia minora in the neighborhood of the ostium urogenitale definitivum, but even in this embryo the oral portions of the nymphæ are still almost three times as high as the anal portions (Fig. 627). In embryos of 386 mm. vertex-breech length (measured over the nape and back) and 324 mm. in greatest head circumference the form of the adult nymphæ is acquired and no difference obtains between the oral and anal portions.

The formation of the glandar lamella proceeds somewhat more complicatedly in the female than in the male. Indeed, we must recognize in the female three glandar lamellæ, an unpaired, ring-shaped one that penetrates at the tip of the clitoris, and two paired lateral ones, that lie in the oral portions of the nymphæ (Fig. 646). All three lamellæ together form a narrow band, which encloses the glans clitoris and the later formed frenula clitoridis (Fig. 646). The middle ring-shaped lamella I found macroscopically for the first time in an embryo of 173 mm. vertex-breech length (measured over nape and back) and with a greatest head circumference of 163.5 mm.; it corresponds to the male glandar lamella, but is less complete than this, forming only somewhat more than the half of a cylindrical mantle (Fig. 644 *a* and *b*). The frenulum præputii is consequently broader than in the male. The formation of the cavity in the glandar lamella takes place practically as in the male and by it the glans clitoridis and the middle part of the præputium are separated. Whether the two lateral lamellæ, like the middle one, are actually formed as lamellæ and later form a

cavity, or whether they occur as grooves from the beginning I cannot state positively. Both the lateral grooves appear simultaneously in embryos of 347 mm. vertex-breech length (measured over nape and back); they begin at the left or right periphery of the middle groove and run obliquely over the outer surfaces of the nymphæ to the sulcus nympholabialis (Fig. 646). By them the oral portions of the nymphæ are divided lengthwise and from now on we may recognize an undivided portion, the definitive

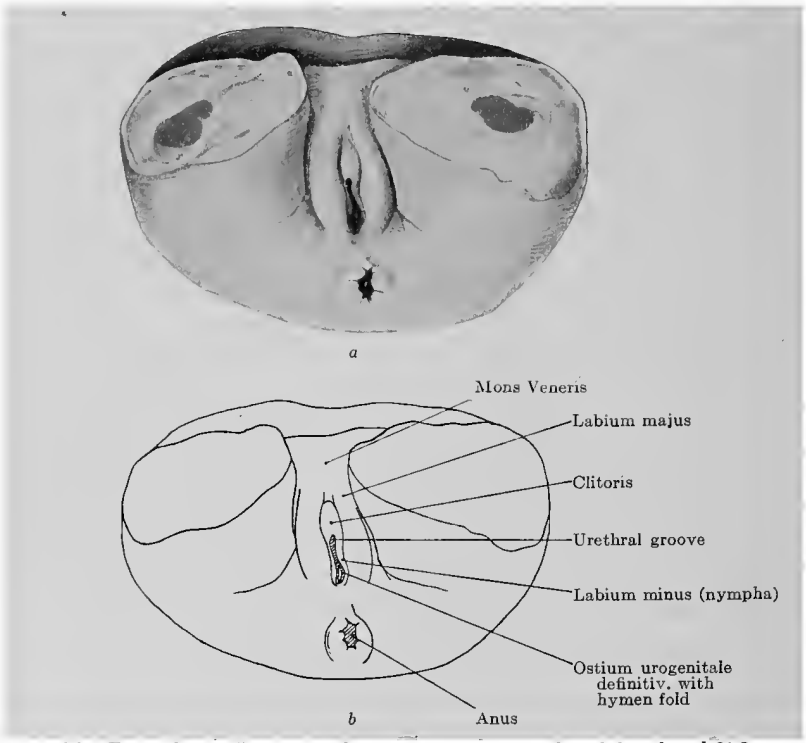


FIG. 645 *a* and *b*.—External genitalia of a female embryo of 27.2 vertex-breech length and 21.3 mm. in greatest head circumference. ×1½. The phallus is enclosed by two genital swellings (labia majora). Its shorter oral surface is lost in the mons Veneris, the longer anal surface fading out into the posterior commissure of the labia majora. The summit of the phallus is occupied by the slightly projecting glans; a sulcus coronarius glandis cannot be seen. Anal from the glans is the cleft-like ostium urogenitale, that leads in its oral two-thirds into a shallow groove, the urethral groove, and in its anal third into the sinus urogenitalis. Into this sinus the hymen fold projects, but it does not reach the margin of the ostium urogenitale.

nymphæ and a genital portion, whose lateral parts give rise to the lateral parts of the præputium, while its medial part becomes the frenulum clitoridis. Both frenula may be followed orally to the clitoris; they are incompletely separated from the frenulum præputii by the ends of the circular glandar lamella (Fig. 646). Although actually separated, the three glandar lamellæ give the impression of a single structure; between them and the sulcus præputio-labialis (Fig. 646) lies the præputial area (Fig. 646), which is composed of the greater part of the anal and the

right and left surfaces of the phallus. This præputial area becomes raised up like a wall along the boundary formed by the three glandar lamellæ, and so forms a rather deep groove (sulcus præputio-clitoridis) between itself and the glans and frenula clitoridis. When the wall has reached a certain height it advances over the

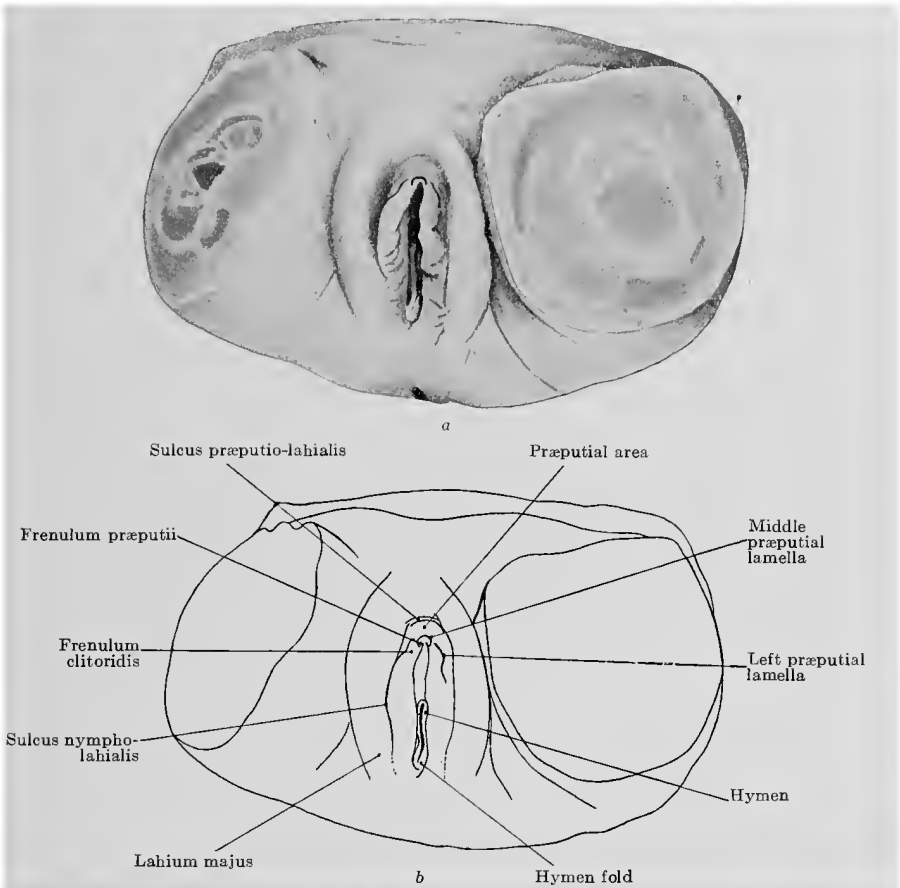


FIG. 646 *a* and *b*.—External genitalia of a female embryo of 34.7 cm. vertex-breech length (measured over nape and back). ×1½. On the oral surface of the phallus and in the oral portions of the two nymphæ three glandar lamellæ are developed, a middle unpaired one and two lateral paired ones. The three lamellæ bound an area oralwards, the præputial area, whose oral limit forms a groove (sulcus præputio-labialis) between itself and the labia majora; from the præputial area the clitoris sack develops. Between the two nymphæ the hymen fold projects; it has in this case the unusual spoon-like form.

sulcus præputio-clitoridis, the clitoris and its frenula. The extent of this advancement varies individually; when it is slight the clitoris remains free, when it is greater the clitoris may be completely covered. What is termed the præputium in systematic anatomy is formed from this fold of the præputial area and consequently the præputium of the adult is a single structure, if, however, it is drawn backwards one may see the sulcus præputio-clitoridis and at the bottom of this the three grooves formed by the splitting of

the glandar lamellæ. The adult præputium is therefore a pseudo-præputium, the true præputium lies at the bottom of the sulcus præputio-clitoridis; we may preferably speak of a clitoris sack. From what has been said it follows that the præputium penis cannot be directly homologized with the præputium clitoridis; the præputium penis is equivalent only to the small, middle, ring-shaped, true præputium clitoridis.

The formation of the corpora cavernosa takes place in the following order: corpus cavernosum clitoridis, corpus cavernosum glandis; a corpus cavernosum urethræ does not occur, since the growth in length of the pars pelvina of the urogenital sinus is omitted. The formation of the corpora takes place as in the male.

The corpus cavernosum clitoridis appears in embryos of 19.4 mm., the corpus cavernosum glandis in embryos of 28 mm. greatest length and probably earlier.

Homologies of the Male and Female External Genitalia.

I shall now give a résumé of the entire development of the external genitalia and shall endeavor to represent it in four diagrams. (1) The cloacal tubercle forms between the umbilicus and the oral periphery of the coccygeal tubercle (Fig. 647 *a*). (2) The phallus is placed excentrically on the cloacal tubercle, as one erects a tower on a hill. Thereby the cloacal tubercle is divided into the base of the phallus and the semilunar tuberculum genitale (Figs. 639 and 647 *b*). The indifferent condition lasts up to this period. (3) In the female the phallus becomes separated from the tuberculum genitale by a groove, sulcus præputio-labialis and nympholabialis. The latter surrounds the phallus and so forms a circular swelling from which are formed: (1) the mons veneris from the oral portion, (2) and (3) the right and left labia majora from the right and left portions, and (4) the posterior commissura labiorum, from the anal portion (Fig. 648 *a*). On the phallus the glans becomes separated from the shaft by a groove, the sulcus coronarius glandis. From this sulcus the urethral groove runs along the middle of the anal surface to the base of the phallus, where it is continued into the ostium urogenitale definitivum (Fig. 645). On both sides of the urethral groove and of the ostium urogenitale the anal surface of the phallus becomes enlarged and forms the labia minora (stippled in Fig. 648 *a*). The rest of the phallus becomes the clitoris and clitoris sack. (4) In the male the tuberculum genitale fades out in all its parts and in its place there is formed at the anal periphery of the phallus, from the unpaired scrotal area, a new swelling, the unpaired scrotal sack. The entire phallus becomes the penis, in which, as in the female, the glans becomes marked out by the sulcus coronarius glandis.

According to this account the clitoris corresponds only to the glans and the neighboring oral portions of the penis shaft (white

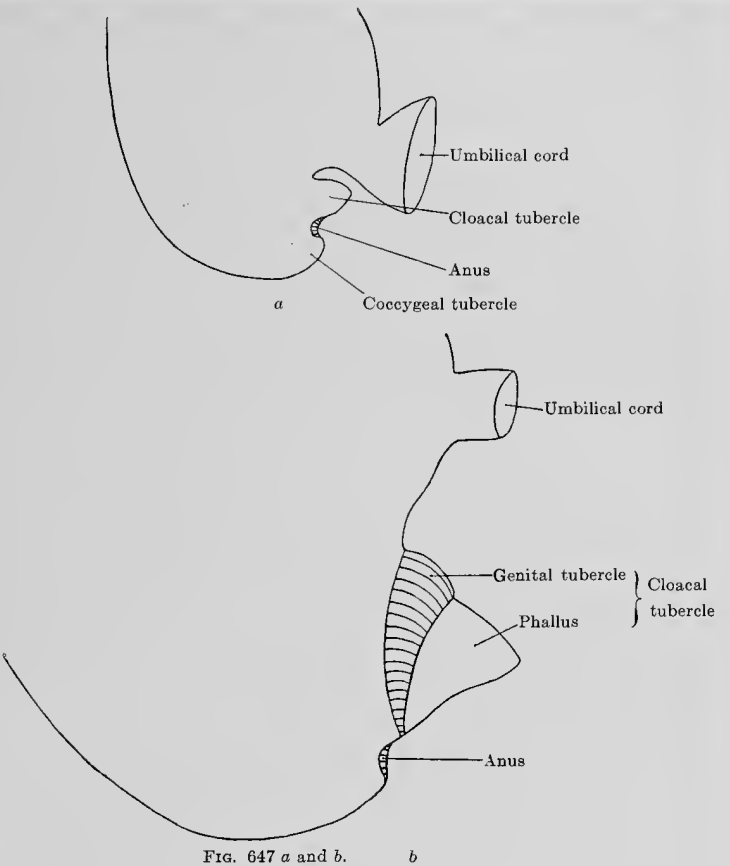


FIG. 647 *a* and *b*.

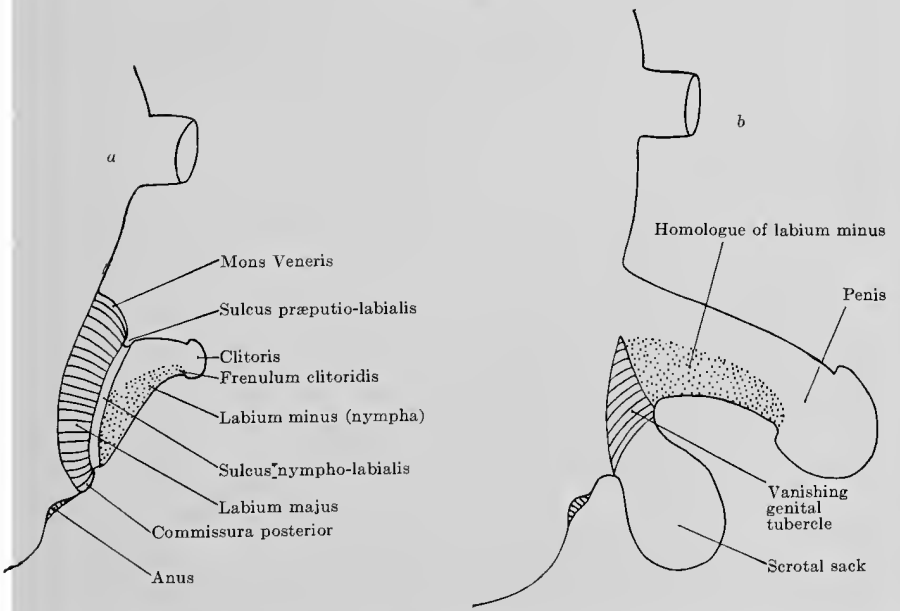


FIG. 648 *a* and *b*.

in Fig. 648 *b*); a portion that corresponds to about the basal three-quarters of the penis shaft is not formed in the case of the clitoris. The primitive ostium urogenitale of the male is not equivalent to that of the female, since in the male the ostium retains its place, while in the female it is displaced basally, or at least is shortened along the urethral groove. A homologue of the labia majora exists in the male only during development in the paired scrotal swellings. No structure corresponding to the unpaired scrotal swelling is formed in the female; we must take the commissura posterior to be its equivalent. The homologue of the labia minora of the female is not formed in the male, the anal surface of the penis between the sulcus coronarius glandis and the base is the corresponding region (stippled in Fig. 648 *b*).

Further Development of the Sinus Urogenitalis.

In the preceding sections of this chapter it has been impossible to avoid occasional allusions to the development of the urogenital sinus; I shall now give an account of the entire development. The sinus is formed by a division of the cloaca into three parts in the frontal direction. The first division separates off the rectum (Figs. 649 and 650), the second divides the remains of the cloaca

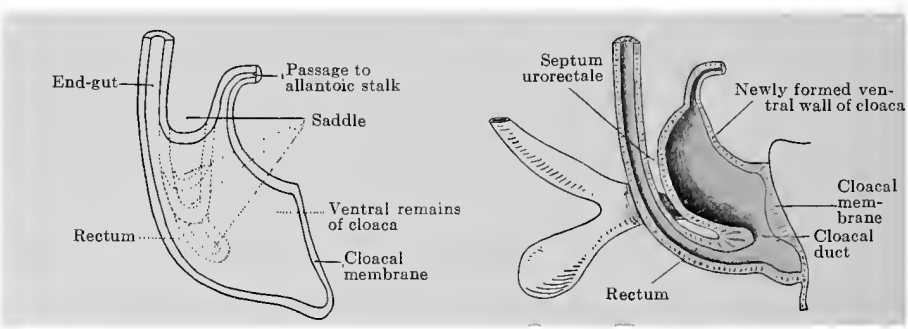


Fig. 649.—The cloaca is divided into the rectum and the ventral remains of the cloaca by the gutter-like saddle sinking down between the end-gut and the allantois stalk.

Fig. 650.—The division of the cloaca into the rectum and the ventral remains of the cloaca is almost completed, between the two there remains for a time a cloacal duct, as an undivided portion of the cloaca (see also the explanation to Fig. 603).

into the vesico-urethral anlage and the pars pelvina of the sinus urogenitalis on the one hand, and the pars phallica of the sinus urogenitalis on the other (Fig. 651). The sinus begins at Müller's tubercle and ends at the tip of the phallus (Fig. 652). It is laid down at the beginning throughout its entire length and from the beginning is divided into its two portions, the pars pelvina and the pars phallica. The lumen of the pars phallica, which was formerly the lumen of the cloaca, and is present from the beginning, persists only in the basal portion of the cloacal tubercle, vanishing in the distal portion by the right and left walls of the pars phallica

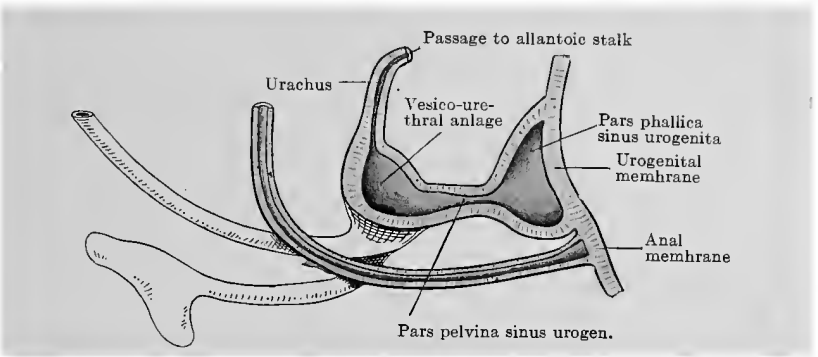


FIG. 651.—The ventral remains of the cloaca is drawn out in the ventro-dorsal direction and we may distinguish in it four walls,—cranial, ventral, caudal, and dorsal. The cranial wall is depressed so that it approaches the caudal one. Thereby the ventral remains of the cloaca is incompletely divided into three parts, a dorsal hroad part, the vesico-ure hral anlage, a middle narrow part, the pars pelvina, and a ventral broad part, the pars phallica.

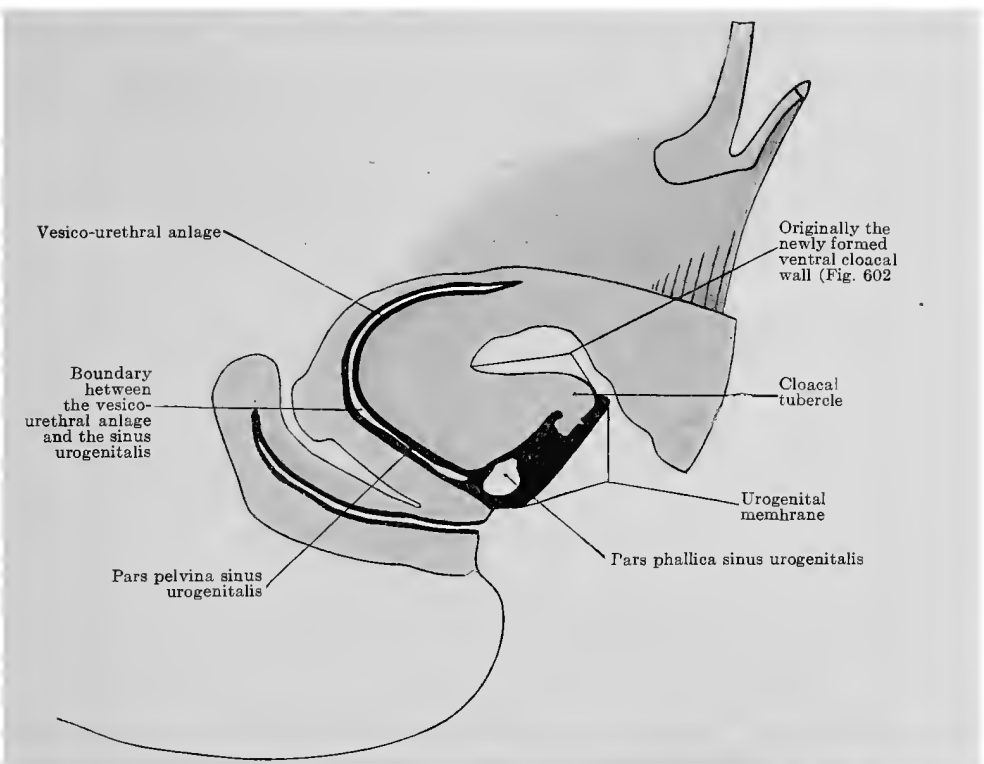


FIG. 652.—The division of the ventral remains of the cloaca is completed. The vesico-urethral anlage and the pars pelvina of the sinus urogenitalis are narrowed in their dorso-ventral diameters, hroadened in their frontal ones. The pars phallica remains broad in the sagittal diameter, hut is narrowed in the frontal one, so that the lumen is abolished in the region of what will later he the glans; from the two walls an epithelial plate, the urethral plate, is formed. The lumen is retained, corresponding to the extent of the ostium urogenitale (not cut in the section figured).

being pressed into contact and finally fusing (embryos of from 24 to 29 mm. greatest length). The hollow portion of the pars phallica breaks through to the outside by the resorption of its ventral wall throughout its entire extent and so the ostium urogenitale primitivum is formed. The solid part, which occurs only in the region of the glans, is termed the *urethral plate*. From its mode of origin the urethral plate must extend to the summit of the cloacal tubercle and must be fused with the anal slope of the tubercle throughout its entire extent; the region of fusion corresponds to the cranial portion of the former cloacal membrane. Seen in a transverse section of the phallus the urethral plate extends from the anal periphery only to about the centre and, accordingly, it divides into two parts only the anal portion of the phallus (Fig. 653 *a*); at the summit the division is incomplete (Fig. 653 *b*),

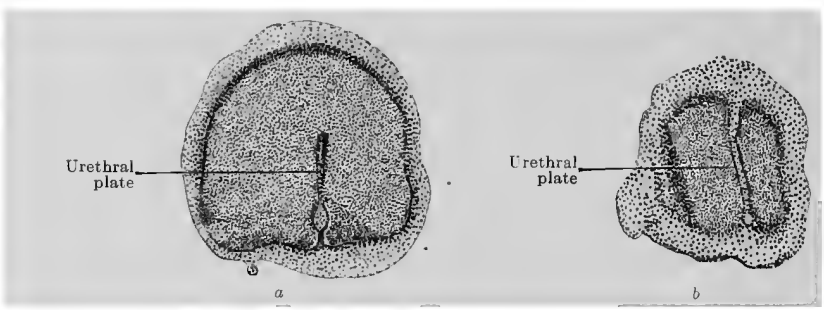


FIG. 653 *a* and *b*.—Two sections through the clitoris of an embryo of 60 mm. head-foot length. (Embryo R. Meyer 268, from the collection of Professor R. Meyer, Berlin; slide 66, row 2, section 1 and slide 67, row 1, section 2.) The urethral plate in section *a* extends from the anal surface of the clitoris only to the centre. In section *b*, which passes through the tip, the clitoris is completely divided by the urethral plate.

the urethral plate here standing in connection with the so-called epithelial horn, a meaningless epithelial growth (Fig. 652).

In both sexes the ostium urogenitale primitivum is broadened out in a trough-like manner at the tip of the phallus (Fig. 642 and 654), and at the point where it breaks through there is a sharp distinction between the endodermal epithelium of the sinus and the ectodermal epithelium of the surface.

With the growth of the phallus and penis described above there is also, of course, growth of the sinus urogenitalis. In Fig. 654 one sees almost the entire length, perhaps it would be better to say shortness, of the sinus urogenitalis. It begins above with the *crista urethralis*, which runs downwards from Müller's tubercle, and ends in the urethral plate. The pars pelvina and the pars phallica were originally of the same length, but during the growth in length of the entire region the pars phallica remains unchanged and the pars pelvina becomes enormously enlarged. The ostium urogenitale primitivum always extends to the sulcus coronarius glandis, its sagittal diameter remains always the same. The

entire length of the sinus depends solely on the enlargement of the pars pelvina, which carries before it the pars phallica or the ostium urogenitale primitivum and the urethral plate. It has thus been shown that the urogenital sinus extends from Müller's tubercle to the primary ostium urogenitale and is entirely of entodermal origin.

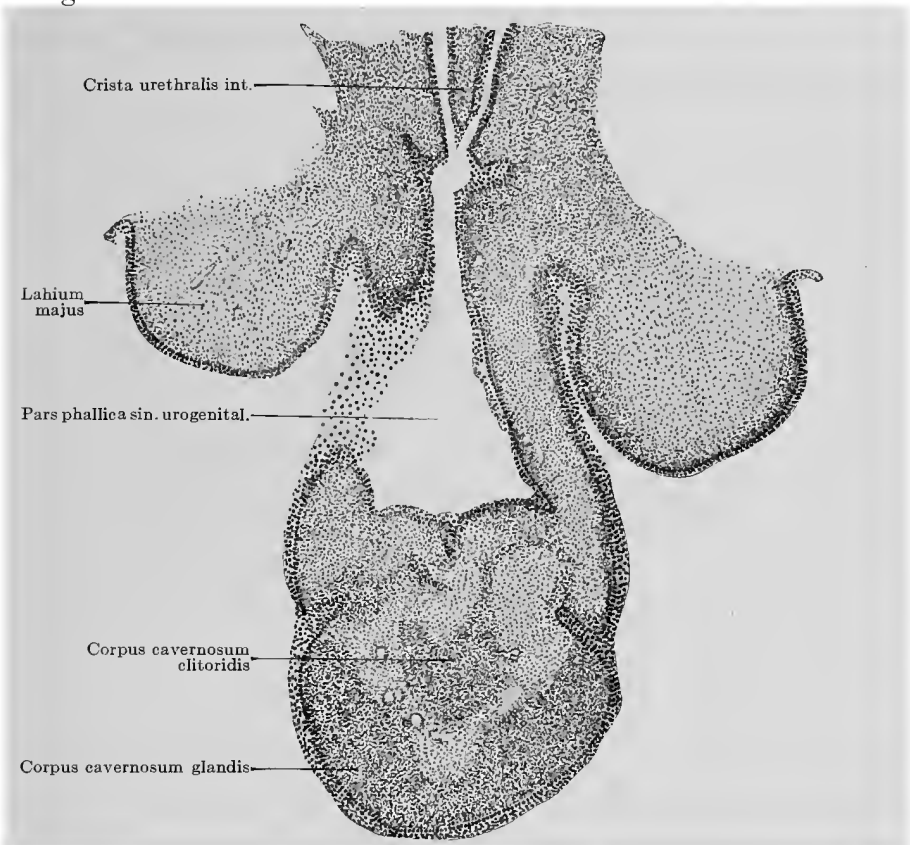


FIG. 654.—Longitudinal section of the clitoris of an embryo of 60 mm. head-foot length. (Embryo R. Meyer 268, from the collection of Professor R. Meyer, Berlin; slide 64, row 2, section 1.) ×50. The section cuts the sinus urogenitalis lengthwise from the crista urethralis int. to the ostium urogenitale. The lumen of the sinus is enlarged at its end to a triangular basin, on whose distal wall is the urethral plate. To the right and left are the genital swellings, the anlagen of the labia majora, which are becoming separated from the clitoris.

The ostium urogenitale primitivum is the definitive one in neither of the sexes; we know from macroscopic anatomy that the sinus of the male opens at the summit of the glans. This elongation is brought about by the closure of the ostium primitivum and the development of the glandar portion of the sinus from the urethral plate. I have not observed these processes myself and therefore follow the account given by Herzog (1904). In an embryo of 68 mm. greatest length the trough-like groove begins to close from the basal side, the closure taking place not at the margins of the

opening where the ectoderm and endoderm meet, but at the middle of the groove; the wide groove is thus divided into a closed tube, the prolongation of the pars phallica of the shaft, and a shallow groove. This mode of closure is important in that it shows that the formation of the pars glandaris of the sinus takes place entirely in the region of the endoderm. In embryos of 105 mm. a splitting of the urethral plate begins, whereby the plate is converted into the urethral groove. This is then gradually closed again from behind forwards and is so transformed into a tube. During this process the ostium primitivum is completely closed and the new ostium wanders forward with the closure of the urethral groove, along the anal surface of the glans to its tip. In embryos of 105 mm. the ostium is already on the surface of the glans and in those of 180–190 mm. the position at the summit of the glans has been reached.

The male sinus urogenitalis is accordingly formed in three stages: (1) The formation of the sinus from Müller's tubercle to the sulcus coronarius glandis, the opening of the ostium primitivum immediately behind the sulcus; (2) closure of the ostium primitivum; (3) formation of the glandar portion and of the ostium urogenitale definitivum.

In the female the wandering of the ostium urogenitale is probably partly active and partly passive. It is active in that the part that reaches the sulcus coronarius degenerates and persists only as a groove, it is passive in that the shaft of the clitoris enlarges between the distal periphery of the ostium and the sulcus coronarius glandis. Growth of the pars pelvina does not take place and hence the shortness of the female sinus.

The epithelium of the sinus urogenitalis is two-layered from the beginning. The more the sinus grows the more numerous do the layers become in the basal portion, where as many as five may be seen superposed. The epithelium is a stratified cubical one up to embryos of 90 mm. head-foot length; when the superficial layer becomes columnar is unknown.

Malformations of the Sinus Urogenitalis.

From the account of the sinus urogenitalis given above an entirely new view of hypospadias results. Under this name is understood the opening of the sinus urogenitalis at any point whatsoever of the anal surface of the penis. In hypospadias of the glans the sinus opens into the sulcus coronarius; this opening is nothing else than the persistent ostium urogenitale primitivum, and this form of hypospadias is a simple inhibition of development, the closure of the ostium primitivum and the formation of the glandar portion of the sinus and of the ostium definitivum are omitted. Hypospadias on the free shaft of the penis or in the region of the scrotal sack is not an inhibition, and, therefore, not true hypospadias, but an hermaphroditic phenomenon, a further development of the sinus urogenitalis in the female sense.

Epispadias, the opening of the urogenital sinus on the oral surface of the penis, can only be explained by assuming a displacement of the pars phallica towards the oral surface of the cloacal tubercle.

The Glands in the Sinus Urogenitalis.

DEVELOPMENT OF THE PROSTATE.

A prostate is developed in both sexes; at its first appearance it consists of several independent glands, which grow out into the surrounding denser mesenchyme. By the formation of smooth muscle fibres and strands of denser connective tissue this mesenchyme later becomes marked off from the surrounding tissue in the male and encloses the various glands to form the prostate; in

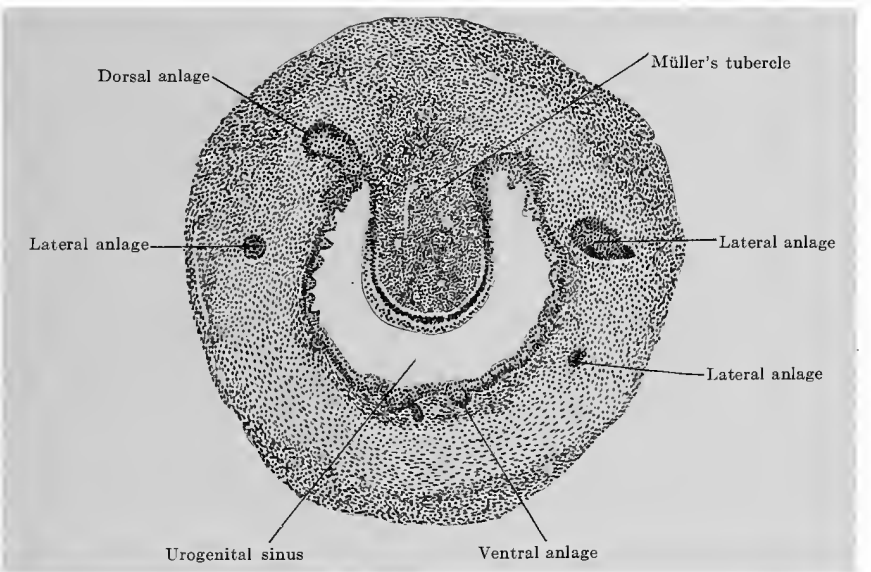


FIG. 655.—Transverse section of the urogenital sinus of a male embryo of 70 mm. head-foot length. (Embryo R. Meyer 267, from the collection of Professor R. Meyer, Berlin; slide 60, row 2, section 3.) ×47. The section shows Müller's tubercle projecting into the lumen of the sinus and around the sinus the anlagen of the prostatic glands.

the female the development of smooth muscle fibres and of a more compact connective tissue does not take place and the prostatic tubules remain isolated structures.

In its development the prostate belongs to the urethra as well as to the sinus urogenitalis, since the glands develop both above and below the opening of the primary excretory duct.

I have found the first anlage of the prostatic glands in a male embryo of 55 mm., and in a female embryo of 50 mm. It consists of solid epithelial buds that grow out into the surrounding thickened mesenchyme from the epithelium of the urogenital sinus (Figs. 628 and 655). These epithelial buds may arise around the whole periphery of the sinus, but they are most numerous on the dorsal surface, less so on the lateral surfaces and rare ventrally. Simultaneously with their appearance those of the dorsal and lateral surfaces branch, while those of the ventral surface remain unbranched and for the most part degenerate. The maximal number of glands

that appear is twenty-six; a bilateral symmetry is unmistakable in the anlage. The direction of growth of all the glands is cranial, only the lowermost anlagen of the lateral surfaces grow caudally; at least two-thirds of the glands arise caudal to the openings of the primary excretory ducts.

The first muscle cells make their appearance in male embryos of 60 mm. head-foot length; in the upper part of the prostate they are principally developed on the ventral surface, at the middle they form a closed ring and towards the lower border they are limited to the dorsal surface. Since the prostatic glands grow into this muscle mass, they force the muscle fibres apart and so produce the characteristic trabecular arrangement of the musculature. All the prostate glands are not united in the prostate, accessory glands occur in the interval between the prostate and Cowper's glands.

An embryo of 55 mm. head-foot length had four anlagen in the right side and none in the left; of those on the right 1 was above the primary excretory duct and 3 below it. An embryo of 60 mm. head-foot length had 7 anlagen on the right side, 4 of which were dorsal and 3 lateral; on the left there were 7 anlagen, of which 4 were dorsal, 2 lateral and 1 ventral. Of these anlagen 6 were above and 18 below the opening of the primary excretory duct. Another embryo of 60 mm. head-foot length had 11 anlagen on the right side, 7 of which were dorsal, 3 lateral and 1 ventral; on the left side there were 13 anlagen, 9 of which were dorsal, 3 lateral and 1 ventral. An embryo of 70 mm. head-foot length had 13 anlagen on the right side, 5 of which were dorsal, 5 lateral and 3 ventral; on the left there were 13 anlagen, 6 of which were dorsal, 4 lateral and 3 ventral; 8 were above and 18 below the primary excretory ducts.

In the female embryo few glands are formed, I have found as a maximal number only three; they may undergo development and are then known as the *paraurethral* or *Skene's ducts*.

Development of the Bulbo-Urethral (Cowper's) and the Vestibular (Bartholin's) Glands.

Cowper's glands are formed from the pars pelvina of the urogenital sinus and are therefore of endodermal origin. Their first appearance has not been established. Lichtenberg (1906) found them already advanced in development in embryos of 48 mm. They arise as paired solid epithelial buds from the pars pelvina of the urogenital sinus. Frequently there are two on each side, and frequently one on one side and two on the other. The solid epithelial buds grow upwards almost parallel to the urogenital sinus, and lie from the beginning (Fig. 643) in the compact mesenchyme which forms the corpus cavernosum urethræ. The glands grow through this mantle, and only when they have reached the looser mesenchyme between the rectum and the sinus are they able to enlarge. Each gland will therefore possess an intrabulbar portion with few, short and slightly developed lateral branches, and an extrabulbar portion with numerous longer and richly

branched lateral branches. The lateral branches appear immediately after the anlagen, the lumina develop in the main stem and in the primary branches in embryos of 65 mm., in the smaller later branches in those of 105 mm. (Lichtenberg 1906). In embryos of 120 mm. the transformation of the ordinary epithelium into a glandular epithelium takes place. The epithelium of the main stem also shows the character of glandular epithelium, and Lichtenberg (1906) is therefore right when he speaks, not of an efferent duct, but of a glandular stem tubule.

Bartholin's glands are the exact homologues of Cowper's glands, and, like them, arise as solid buds from the dorsal wall of the pars pelvina of the urogenital sinus. I first found them in an embryo of 36 mm. greatest length, their first division in one of 80 mm. head-foot length. The first appearance of a lumen in the efferent duct was observed by Spuler (1910) in an embryo of 82 mm. vertex-breech length, the first terminal vesicles in one of 120 mm., and the first formation of a secretion in embryos of from 150 to 160 mm. vertex-breech length. Up to and after birth there is a slow increase in the number of the terminal vesicles (Spuler 1910), and after puberty there is another more rapid growth (Huguier 1849). At the climacterium these glands undergo degeneration and may be entirely wanting in old age (Tiedemann 1840).

Development of the Small Sinus Glands.

These glands also are of endodermal origin; only in the case of those situated in the glans penis is it impossible to exclude a participation of the ectoderm. The glands appear in succession around the entire periphery of the sinus, first on the oral surface in embryos of 60 mm., on the right and left in embryos of 70 mm. and, finally, on the anal surface in embryos of 120 mm. (Lichtenberg 1906). These glands possess the same character as Cowper's glands, except that they do not attain to the same extensive development.

Descensus Testiculorum.

It has been accepted by all authors as an established fact that the mesonephros, ovary and testis undergo an active displacement in the abdominal cavity. All three organs are supposed to gradually glide downwards from their original positions into the true pelvis, or, in the case of the testes, as far as the true pelvis. After what I have said as to the development of the mesonephros (p. 815 *et seq.*) and of the indifferent reproductive glands (p. 885 *et seq.*), it is clear that I cannot agree with this view. The descent of the mesonephros or the ovary and the internal descent of the testis to the inguinal canal does not take place, but on the other hand the testis does wander from the abdominal cavity into the scrotal sack. The anlagen of the mesonephros and of the reproductive glands

extend from the diaphragm to or into the true pelvis. When the growth in length of the anlagen is completed their caudal ends become stationary, those of the mesonephros and testes at the boundary between the abdominal cavity and the primitive true pelvis, those of the ovaries in the true pelvis at the posterior surface of the genital cord. What seems to be a descent of the organs is caused, on the one hand, by their degeneration in their cranial portion, which produces a shortening of the entire organ and a downward displacement of its cranial end, and, in the second place, by the fact that the degeneration of the formed parts is proceeding while the anlagen themselves are still progressing caudally. We have to consider, then, only the external descent of the testis.

Between the testis, lying in the abdominal cavity, and the floor of the scrotal sack there is formed a band, the chorda gubernaculi,

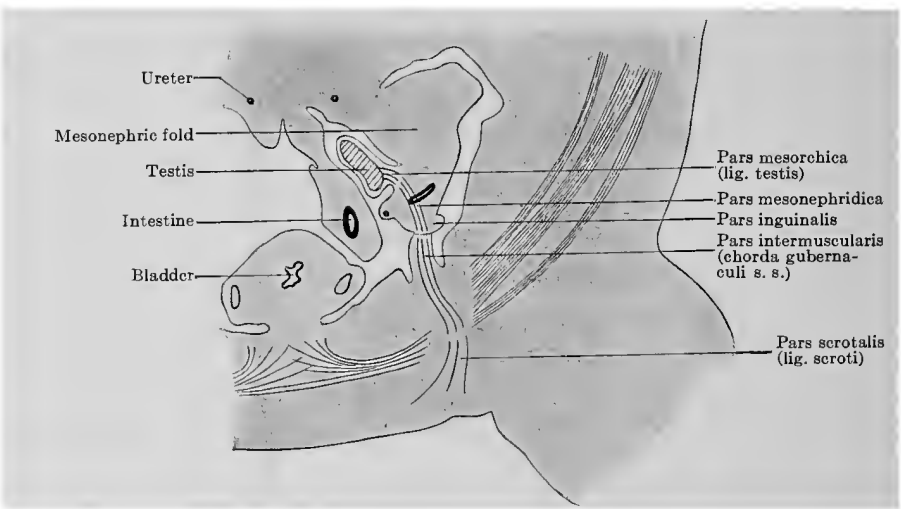


FIG. 656.—The various parts of the chorda gubernaculi are shown diagrammatically in a transverse section of the urogenital fold and body wall of a male embryo of 26 mm. greatest length. The chorda gubernaculi in the broader sense consists of 1, the lig. testis (pars mesorchica), 2, a mesenchymatous cord in the mesonephric fold and its plica inguinalis (pars mesonephridica), 3, a mesenchymatous cord in the crista inguinalis and between the abdominal muscles (pars intermuscularis), and 4, the lig. scroti (pars scrotalis).

whose development has already been discussed at two different places (p. 943), and may therefore be recapitulated here. Between the mesonephric fold and the lateral or anterior abdominal wall a connection is effected; the mesonephric fold sends out from its lateral surface a secondary projection, the *inguinal fold;* covered by a thickened epithelium and filled with a somewhat more compact mesenchyme; the lateral or anterior abdominal wall, on its part, forms an almost sagittal, ridge-like fold, the *inguinal crest.* The upper third of the crest lies opposite the fold, and in this upper third there develops in the crest a thickening of the mesenchyme, and spindle-shaped cells appear and form bundles that run in a

horizontal direction from the crest towards the integument (Fig. 634). The fold and the upper third of the crest fuse together (Fig. 635), and thereby the connection between the mesonephric fold and the anterior abdominal wall is accomplished. Since the testis is united to the mesonephric fold by its mesorchium and by the epigonal portion of the genital fold, it too, along with the mesonephric fold, is attached to the anterior abdominal wall. The epigonal portion of the genital fold lies on the medial or dorsal side of the mesonephric fold, just where the plica inguinalis is given off from the ventral or anterior surface of the mesonephric fold (Fig. 635). We may, accordingly, recapitulate thus: The testis is connected with the anterior abdominal wall (1) by its mesorchium or the epigonal portion of the genital fold; (2) by the plica mesonephridica; (3) by the plica inguinalis, and, finally, (4) by the crista inguinalis (Fig. 656). Within the fold so constituted there is formed, at first in separate parts, a cord of closely compact, spindle-shaped cells, the *chorda gubernaculi*. In Fig. 656 the chorda has been inserted and its various parts are indicated by interruptions of the lines representing it; in the mesorchium and the epigonal portion of the genital fold the pars mesorchica develops, in the mesonephric and inguinal folds the pars mesonephridica, in the inguinal crest and the abdominal wall, so far as this is formed of the abdominal muscles, the pars intermuscularis, and, finally, in the integument, the pars scrotalis. This last streams out into the subcutaneous connective tissue of the genital swellings at first, and into that of the unpaired scrotal area, when this is developed. In this way the caudal pole of the testis is connected with the testis sack and the chorda marks the path which the testis must traverse in its descensus.

The Formation of the Saccus Vaginalis.

The saccus vaginalis is a part of the general body cavity that becomes completely cut off from the rest of the cavity by the formation of the anterior abdominal wall.

We may start the account of its development from the conditions seen in the body cavity of an embryo of 19.4 mm. greatest length (Fig. 631). The cavity may be divided into an upper broad portion and a lower narrow one, the primitive true pelvis. In the latter lie the rectum, projecting from the posterior wall, the urogenital fold projecting from the right and left walls, and, finally, the vesico-urethral anlage with the two art. umbilicales projecting from the anterior wall. At the boundary of the true pelvis and still lying in the primitive false pelvis is the union between the urogenital fold and the anterior abdominal wall (Fig. 631). Two processes bring about a change in these simple relations: (1) The bringing into the upright position of the anterior abdominal wall

which in Fig. 631 is still horizontal, and (2) the taking into the body cavity of the loops of intestine that lie in the exocœlom. We may consider first the effect of this latter process. Space must be made in the body cavity for the loops of the intestines, which consist of almost the entire small intestine and a part of the large. This is accomplished by the enlargement of the sagittal diameter. The anterior abdominal wall thus becomes separated from the posterior one; but the mesonephric fold is attached to the anterior abdominal wall by the gubernaculum and the testis is attached to the mesonephric fold by the mesorchium and the epigonal portion of the genital fold. Both the mesonephric fold and the testis must therefore follow the anterior abdominal wall and become separated from the posterior one; the caudal pole of the testis thereby becomes directed ventrally and the long axis changes from a vertical to a more horizontal position. The mesonephric fold always lies in front of the pole of the testis; since it is attached not only to the posterior abdominal wall by its mesenterial portion, but also by its transition into the genital cord to the posterior wall of the vesicourethral anlage, it forms a loop around the testis, and the gubernaculum is attached at the summit of the loop. The formation of the loop naturally results in a stretching of the fold and its contents, and it is the medial limb of the fold that is most stretched, the lateral one, which forms the attachment to the posterior abdominal wall, being hardly stretched at all. The posterior abdominal wall follows the testis, an extensive layer of loose mesenchyme tissue becoming interposed between the cœlomic epithelium and the actual wall (Fig. 657). Thus the lower portion of the abdominal cavity, which in position corresponds to the fossa iliaca, is narrowed in its sagittal diameter to a third of its original size (Fig. 657), and appears to be a sack-like evagination of the undiminished portion of the abdominal cavity; this sack-like portion is the anlage of the *saccus vaginalis*. What affects the mesonephric fold affects also its contents, but the primary excretory duct alone concerns us here. It also is thrown into a loop, whose summit corresponds to the first bend of the mesonephric fold, where the upper sagittal portion (Fig. 631) passes into the horizontal portion, and at this summit the tubuli collectivi of the paradidymis and, later, the ductus aberrans Halleri open (Fig. 657). It thus becomes certain that the entire ductus deferens is formed only from the medial limb of the loop of the excretory duct.

The bending of the anterior abdominal wall into the upright position will, of course, affect all the organs attached to its posterior surface; these are the bladder and the umbilical arteries. The bladder is simply brought from its bent position into an upright one, but it is different with the arteries. Since they arise from the aorta they are attached to both the anterior and posterior

abdominal walls. From the aorta they run at first almost horizontally along the boundary between the false and true pelves (Fig. 631) to the anterior abdominal wall, and produce in this situation low peritoneal folds. Then they bend, and ascend towards the umbilicus along the bladder. When the arteries are drawn upwards by the pull exerted by the anterior abdominal wall, the horizontal portions are of course also raised, and by this elevation the peritoneal folds already present are materially increased in size.

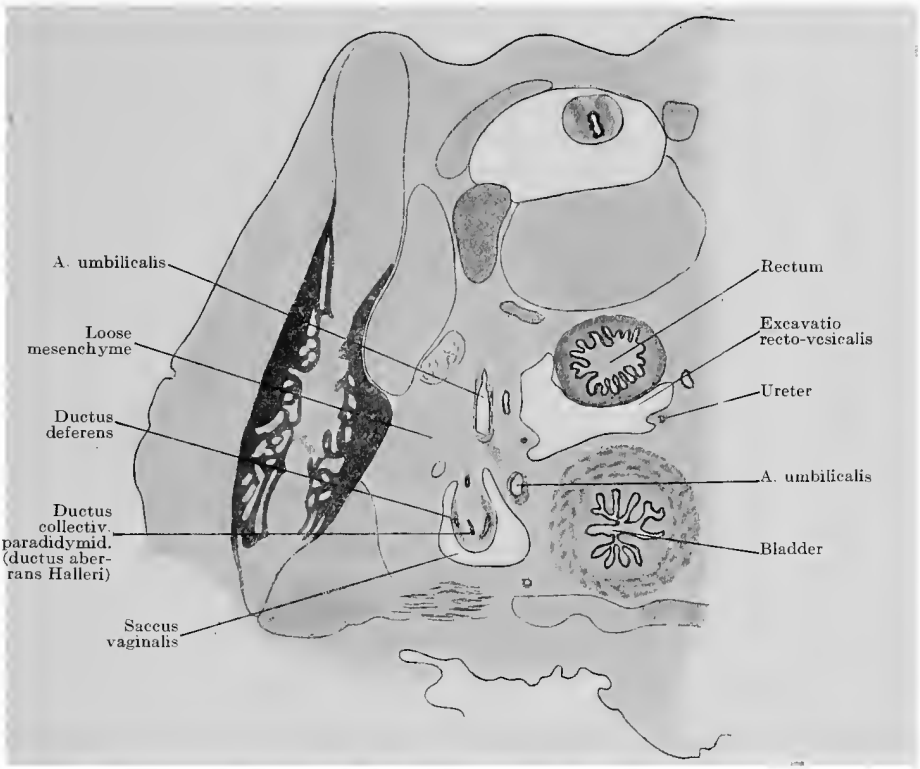


FIG. 657.—Part of a transverse section through a human embryo of 60 mm. bead-foot length. (Embryo R. Meyer 264, from the collection of Professor R. Meyer, Berlin; slide 44, row 2, section 2.) By the union of the mesonephric fold and testis to the anterior abdominal wall, formed by the chorda gubernaculi, both have been carried quite away from the posterior abdominal wall. Between the urogenital fold and the posterior wall a layer of loose mesenchyme has formed. Thereby the portion of the abdominal cavity which contains the urogenital fold is separated off from the rest of the cavity as the saccus vaginalis. The separation between the two is completed by a peritoneal fold formed by the a. umbilicalis.

Rising from below like a septum, they form a partition between the primitive true pelvis and the anlage of the saccus vaginalis (Fig. 657), and the latter becomes marked off from the true pelvis and now appears to be a sack-like evagination of the body cavity, well defined on all sides, although actually, as we have seen, it is not an evagination, but a portion cut off from the general body cavity by the encroachment of the neighboring parts. In the region of the saccus vaginalis lie the caudal pole of the testis, the loop of the mesonephric fold and the gubernaculum. All three

structures are at first so placed that they run through the centre of the saccus vaginalis, but later the lateral surfaces of the urogenital fold and gubernaculum fuse with the lateral wall of the saccus, and the lumen of the saccus thus disappears on the lateral side and persists only on the medial one. The saccus vaginalis is so large that it extends both over and under the point of insertion of the gubernaculum into the anterior abdominal wall, that is to say, above and below the opening of the inguinal canal.

The so-called invagination of the saccus vaginalis into the abdominal wall is certainly at first not an invagination. The anterior abdominal wall thickens greatly, but the thickening does not affect the point at which the gubernaculum passes through the wall. Consequently the abdominal wall grows around the saccus and a groove appears in the wall for its reception (Fig. 635).

After this point there is a considerable hiatus in the history of the descent. We know that the saccus vaginalis eventually penetrates through the musculature, and, passing on below the former genital swelling, enters the scrotal sack. How this outgrowth takes place has not yet been determined. In the seventh month the testis wanders down through the inguinal canal and retains its original relation to the saccus, *i.e.*, it is, as before, invaginated into it. The definitive position of the testis in the testis sack is acquired in the eighth month or at the latest before birth. The retention of a testis in the abdominal cavity or the inguinal canal is due to an inhibition of development, and constitutes what is known as *cryptorchism.*

After the completion of the descensus the saccus vaginalis remains connected with the abdominal cavity by a narrow canal. A short time after birth this becomes at first solid and is then resorbed. The saccus vaginalis, now completely cut off from the abdominal cavity, has become the *tunica vaginalis propria testis.* All possible variations in the extent of the degeneration of the narrow canal between the abdominal cavity and the tunica vaginalis propria may occur; parts of it may remain unclosed. If the opening of the canal into the abdominal cavity remains unclosed its persistence may predispose to an oblique inguinal hernia; a persistence of the entire vaginal canal may lead to the occurrence of a congenital inguinal hernia.

The tunica vaginalis communis develops from the fascia transversa. The spermatic fascia, as was pointed out above, is not a fascia but is formed from the hernia-like protrusion of the aponeurosis of the musc. obliquus abdominis externus.

In the female embryo there is an incomplete formation of a saccus vaginalis, which is frequently persistent as the diverticulum of Nuck, but otherwise it vanishes completely. The ovary cannot undergo a descensus similar to that of the testis because: (1) it descends lower than the testis; (2) it comes to lie in a different

portion of the body cavity (the testis lies in the saccus vaginalis, the ovary in the recto-uterine excavation); (3) the lig. ovarii proprium is attached to the wall of the uterus, *i.e.*, at the middle line.

Diagrammatic Representation of the Fate of the Mesonephros, Primary Excretory Duct, and Mullerian Duct in Both Sexes.

In conclusion I present in three diagrammatic figures (Fig. 658 *a*, *b* and *c*) a résumé of the changes in position undergone by the

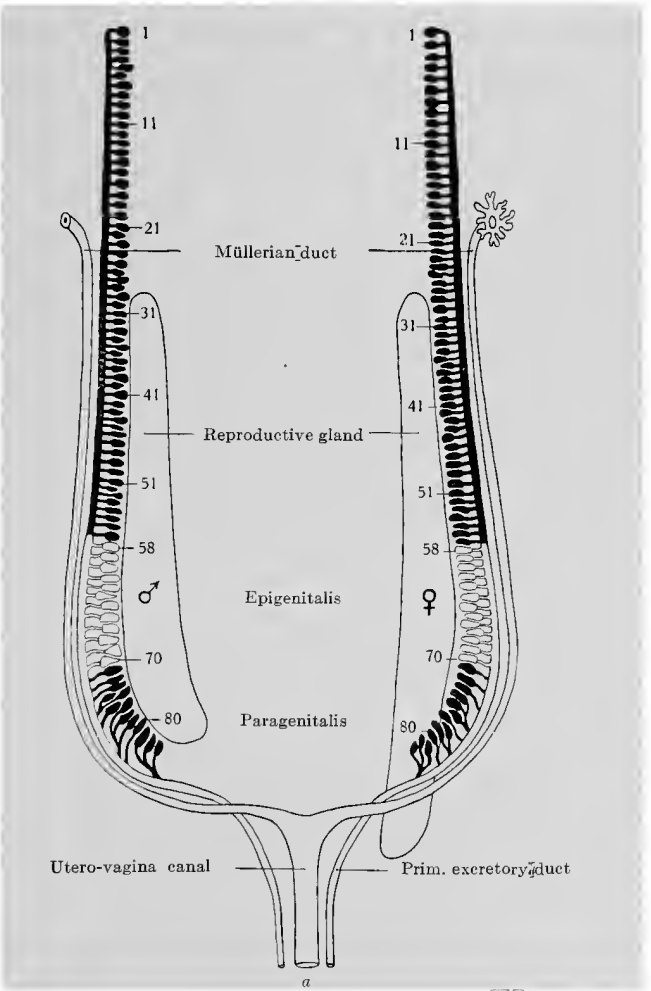


FIG. 658 *a*, *b*, and *c*.—Diagrammatic representation of the entire renal organ, reproductive gland, and the efferent ducts. What persists is represented by solid, and what degenerates by dotted lines; whatever changes its position is shown in grey, whatever has reached its final position is in black. *a*. On the left is the male and on the right the female reproductive gland. Before the migration. The numbers are the serial numbers of the tubules.

organs of the urogenital fold in the two sexes. Those structures that are retained are represented by solid lines, and those that degenerate are outlined by broken lines; the structures that change

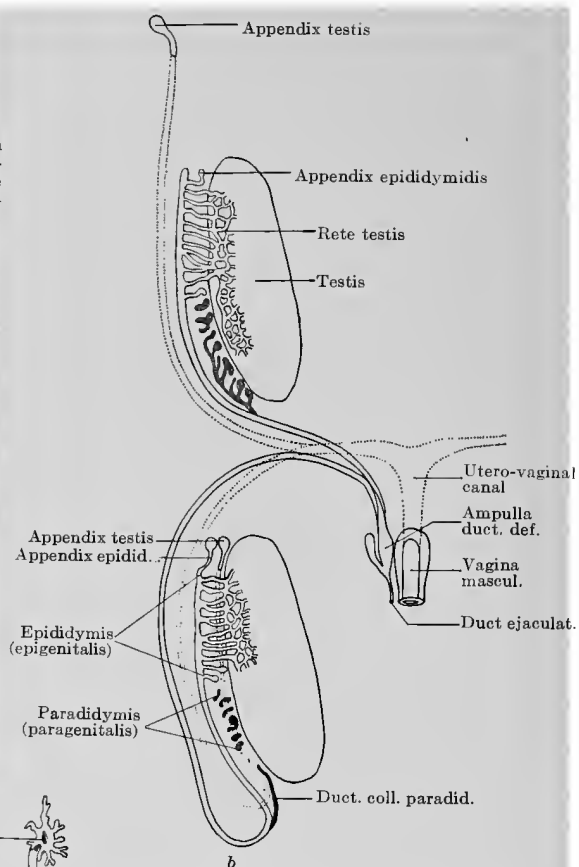


FIG. 658 *b*.—After the migration in the male embryo. The testis wanders out of the body cavity into the scrotal sack (descensus). The Müllerian duct degenerates throughout the greater part of its extent, the closed ostium abdominale persisting as the appendix testis (hydatid of the testis), and the lowest portion of the utero-vaginal canal as the vagina masculina. All the tubules of the epididymis are not employed in the urogenital union: the first tubule remains free and becomes the appendix epididymis (hydatid of the epididymis) and the other unemployed tubules persist as appendices retis. The paradidymis (paragenitalis) is separated into its individual parts, some of the ductuli collectivi persist as the organ of Giraldès and the terminal portions of the ductuli, united to form a canal, persist as the ductus collectivus paradidymidis (ductus aherrans Halleri).

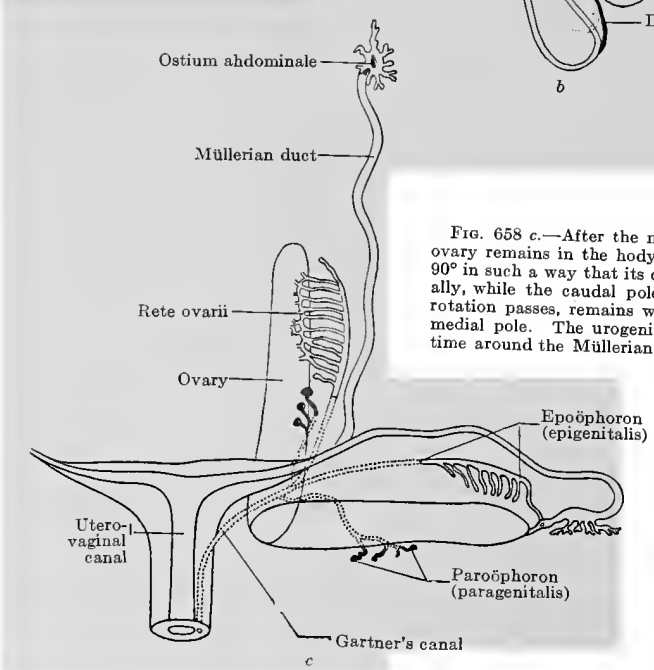


FIG. 658 *c*.—After the migration in the female. The ovary remains in the body cavity, but rotates through 90° in such a way that its cranial pole comes to lie laterally, while the caudal pole, through which the axis of rotation passes, remains where it was and becomes the medial pole. The urogenital fold is rotated at the same time around the Müllerian duct, and as a result the tube comes to lie cranial to the ovary. The mesonephros and primary excretory duct degenerate; of the mesonephros the epigenitalis persists as the epoöphoron and parts of the paragenitalis as the paroöphoron. Of the primary excretory duct only the portion that receives the tubules of the epoöphoron is retained, though portions of the rest may persist as Gartner's canal.

their position are shown in grey, and those that have attained their final position are in black. The diagrams show that no internal descent of the testis occurs, nor is there any downward migration of the ovary or mesonephros. The mesonephros and the reproductive gland are laid down throughout the entire length of the abdominal cavity, and their lower poles lie from the beginning at or in the true pelvis; on the other hand, in both organs a cranial portion, which may include more than half of the entire organ, degenerates, and this degeneration may simulate a descent of the organs.

The diagrams show furthermore that the tubules of the epigenitalis and paragenitalis—the persisting tubules of the mesonephros—are the most caudal tubules.

The testis undergoes an external descensus, during which no alteration of the relative position of the parts occurs. The ovary rotates through 90° and comes to lie with its long axis horizontal. Simultaneously with this rotation the genital fold rotates around its longitudinal axis, the Müllerian duct forming the axis. In consequence of this rotation, which is through almost 180°, the Müllerian duct comes to lie more cranially and the ovary more caudally.

The ostium abdominale of the Müllerian duct always lies in the neighborhood of the cranial pole of the ovary, notwithstanding that this wanders downwards as a result of the degeneration of the cranial portion of the ovary; this is due to the fact that its growth ceases for a considerable time, during which all the other organs increase materially in dimension.

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[1] Since my manuscript was sent to the publisher, more than a year has elapsed. The literature has been brought up to July, 1911, although, with a few exceptions, only that which had appeared up to the summer of 1910 could be used in the text.

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XX.

THE INTERDEPENDENCE OF THE VARIOUS DEVELOPMENTAL PROCESSES.

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Except in the chapters in which the earlier stages of development are considered and in that in which a review of the entire development and of the elaboration of the external form is given, the development of the various organs and systems of organs has been so far presented as if it took place for the most part individually and independently for each organ or system. We have now to consider how the development of the individual organs combines to produce the development of the whole. It is clear that the normal fully developed organism cannot be produced without a certain regular succession in the development of the organs and a regular interdependence of the individual developmental processes, but it is open to question whether this interdependence is the result of the individual and independent development of each organ taking place in such a way that it fits into that of the others or whether it is due to the individual anlagen of an organism mutually influencing one another during development so as to cause the formation of a normal organism. Both these views have their supporters. Roux (1893) advocates the theory that the various cell complexes of the ovum differentiate independently even from the segmentation stages (Mosaic theory). Mehnert (1895) says: "The study of the individual time differences in the differentiation of the same organ within the same species shows that a constant correlation of the organ development in the same embryo does not exist."

"The frequently striking lack of correlation in the development of organs shows that each developmental process in an organ is to a certain extent an independent process. The development of a vertebrate embryo consists of a series of successive individual processes, regulated only by phylogenetic relations. Only the form and position of any organ can be modified by the environment." Also, so worthy and thoughtful an observer as Born (1897), in his investigations in regeneration in Amphibian larvæ, comes to the conclusion that the development from its beginning (that is to say, from larvæ in which the medullary canal

had just closed and the tail-bud had begun to grow out) [1] depends essentially on the self-differentiation of the individual parts. "A correlation influence of the neighboring parts or of the whole can never be perceived—neither a negative nor a positive one." " The development corresponds throughout to the mosaic theory of Roux."

On the other hand, His has incorrectly been claimed as an advocate of this view. He says (1874) in the sixteenth letter of " Unsere Körperform ": " The orderly connection of all the processes underlying the development of the body is a principle which the theory of descent must take into consideration in the future to a greater extent than it has up to the present. So long as investigators of phylogenetic problems have been content to sketch out special histories of individual organs or parts of organs, so long have they perceived the task to be accomplished only in what is certainly a very limited portion of its actual extent; for the development of each individual organ is always merely a dependent partial phenomenon of a huge total process, which links itself up in all directions." He expresses himself similarly in his paper on " Die Entwicklung der menschlichen und tierischen Physiognomien " (1892), and in his treatise on "Der Prinzip der organbildenden Keimbezirke und die Verwandtschaften der Gewebe " (1901) he assumes the existence not only of spatial and temporal but also of chemical influences; consequently the principle of " organ forming germinal areas " that His has established is not to be interpreted in the sense of Roux's mosaic theory.

A standpoint similar to that of His is also taken by O. Hertwig. In various places in his writings he maintains that all the individual parts of the embryo always develop in relation to one another and the development of each part is dependent on the development of the whole (compare O. Hertwig, 1892 and 1906). This is the view that I also hold, and in what follows I shall endeavor to supply further reasons in support of it. I am of the opinion that the individual anlagen of an organism mutually influence one another in the development so as to contribute to the production of a normal organism. I do not in this dispute the fact that a relatively great individuality, varying in amount in different species of animals, occurs in the development of individual organs and organ complexes. That this is so is shown by the investigations of Born, already referred to, and also by

[1] For earlier stages there are similar investigations by W. H. Lewis, who transplanted pieces of the dorsal and lateral lip of the blastopore of Rana palustris and was able to show that even the different parts of the blastopore lip possessed in a high degree the power of self-differentiation.

numerous malformations, of man as well as of other animals; in these, individual organs or parts of organs may be developed relatively normally, while others may be abnormal to a high degree or may even be wanting. But neither by the experiments of Born and others, among which those of W. H. Lewis (1907) may be especially mentioned, nor yet by such malformations is it disproved that the individual developmental processes influence one another.

Fischel (1896) has been led to assume such an influence from the measurements he has made of duck embryos with from 1 to 20 primitive segments. He finds that the older the embryo the more regular is the relation of the individual portions of the body one to another, and assumes "that during the development regulating influences make themselves felt and bring it about that gradually a distinctly orderly structure of the body supervenes, whereby variations become slighter and rarer." He regards the correlation of the developing organs as such a regulating influence. It may be remarked that long ago Karl Ernst von Baer (1828) arrived at similar conclusions. Furthermore, one may appeal to experimental observations for evidence of the existence of a correlation between the individual parts of a developing ovum, as, for instance, the fundamental experiments in which several embryos are obtained from a single ovum, the experiments of Lewis (1904) and Spemann (1901, 1903) on the relation of the development of the lens to the optic cup and numerous experiments in regeneration.

In many of these experiments one may imagine a pure contact action, in others one must assume action at a distance. Undoubtedly action at a distance obtains when the development is influenced by the reproductive gland. I do not intend to enter into details here as to the effects of castration, but will merely recall the influence that it has unquestionably been shown to exert on the formation and growth of the bones. The epiphyses persist for a longer time and so the growth also lasts longer (compare Sellheim, 1899). Very interesting for their bearings on the doctrine of action at a distance in development are the investigations of Paton and Goodall (1904) and Paton (1904) on guinea-pigs, and especially those of Hammar (1909) and his pupils, Soederlund and Backman (1909), Jonson (1909) and Syk (1909) on the development of the thymus in the rabbit and man. The human thymus and also that of the mammalia grows until the onset of sexual maturity and then undergoes a rapid involution. Also the occurrence of an age-involution of the lymphoid tissue (Berry and Lack, 1906) may be mentioned. Furthermore, Hammar's pupil Lindberg has found that at about the time of puberty the number of the blood lymphocytes distinctly diminishes. To

what extent the suprarenal bodies, as well as the functioning reproductive glands, inhibit a development of the thymus, acting as thymus depressors, and to what extent the thyreoid, the hypophysis, and the parathyreoids favor it, acting as thymus excitators, will not be further considered here. These are investigations that have invaded new territories and still need much enlargement.

The investigation of the interdependence of the various developmental processes has been the purpose of the publication by Keibel (since 1897) of the Normentafel zur Entwicklungsgeschichte der Wirbeltiere. A Normentafel zur Entwicklungsgeschichte des Menschen has been published by Keibel and Elze (1908) and some of the tables given in this may find place here.

Desig.	Size	Age	Body form	Primitive streak	Primitive segments	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*3 Human embryo Klb. Kroemer-Pfannenstiel. Collection of Prof. Pfannenstiel, Giessen. N. T. Fig. IIIa and III d. Text-fig. 5a to 5n.	138 sections of 10 μ = 1.38 mm. Kroemer gives the following data: "The greatest length of the embryonic anlage from the anterior edge of the amnion of the head cap to the chorion end of the belly-stalk 1.95 mm., the length of the embryo without the belly-stalk from the head to the tail 1.8 mm., the greatest width of the yolk sack barely 1.2 mm., the width of the embryonic disk at the boundary between the amnion and yolk sack (measured in the head view) 0.9 mm. The measurements of the yolk sack were 1.1 mm. (height), 1.4 mm. (width), 1.5 mm. (length)."	The age is estimated by Born at from 10 to 14 days.	No dorsal bend. Head end bent down at right angles and cut by 24 sections of 10 μ.	Still indications of a neurenteric canal. Short primitive streak. Cloacal membrane.	5–6 pairs of primitive segments.	The chorda throughout is contained in the entoderm.	The medullary canal is everywhere wide open, but the brain portion is already marked off from the cord and shows beginning segmentation.	Optic anlage not yet evident.				Primary pharyngeal membrane. No oral sinus.

Digestive tract, liver and pancreas	Branchial pouches, thyreoid thymus, trachea and lungs	Uro-genital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
	The 1st branchial pouch is formed but does not reach the ectoderm.		Heart ventral, but still paired. Paired aortæ. 1st branchial arch artery. Aa. umbilicales. Vv. omphalo-mesentericæ. Vessels on the yolk sack full of blood-corpuscles.				No amniotic duct evident.	Allantoic duct.	Obtained by laparotomy. Fixation: Müller's fluid. Stain: alum carmine; paraffin. Sections: 10 μ trans. Literature: Pfannenstiel in Handbuch der Geburtshilfe, published by Winckel, Wiesbaden 1903.—Kroemer, Wachsmodell eines jungen menschl. Embryo. Verhandl. d. Ges. f. Gynäkologie, 1903. The wide pericardial cavity is not connected with the peripheral cœlom. The embryonic cœlom is being formed caudally. On the chorion the layer of Langhans cells and syncytium.

Desig.	Size	Age	Body form	Primitive streak	Primitive segments	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*6 Human embryo Pfannenstiel III. Collection of Prof. Pfannenstiel, Giessen. N. T. Fig. Vr and Vv. Textfig. 6a to 6w.	Gr. L. about 2.6 mm.		Embryo bent over the ventral surface and slightly bent spirally.	Tail bud, on its ventral side doubtful remains of primitive streak.	13–14 pairs of primitive segments.	Chorda emerging from entoderm. Cranially is still in entoderm, caudally it is probably primarily independent of the entoderm and in this region it is no longer included in the entoderm.	In brain region medullary canal is open to caudal to the region of the optic vesicle, similarly the caudal end. Anlagen of neuromeres already present.	Primary optic vesicles. They lie close to the ectoderm; in their region the medullary canal is wide open.	Anlage of the auditory vesicle recognizable as a thickened and at first but little depressed plate of ectoderm.		Hypophysis just indicated.	Primary pharyngeal membrane still closed. Oral sinus.
*7 Human embryo No. 300, from the collection of Dr. Robert Meyer, Berlin. N. T. Fig. VI l, VI r and VI v.	Gr. L. 2.5 mm.			Remains of primitive streak. Cloacal membrane.	23 pairs of prim. segments.	Chorda separated from entoderm.	Anterior neuropore closed, but its position still recognizable. Medullary canal still wide open for a stretch caudally. Roof of 4th vent. beginning to thin out. Neuromeres. Trigeminus and acustico-facialis ganglia distinct.	Optic vesicles. Mesoderm between ectoderm and optic vesicle.	Auditory vesicle almost closed (open through 4 or 5 sections of 5μ). Ductus endolymphaticus not yet visible.		Anlage doubtful.	Pharyngeal membrane just torn, still abundant remains of it.

Digestive tract, liver and pancreas	Branchial pouches, thyreoid, thymus, trachea and lungs.	Urogenital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
Wide hepatic bay just cranial to the intestinal umbilicus. No trace yet of hepatic trabeculæ.	The two first branchial pouches reach the ectoderm, the 3rd is formed.	Quite rudimentary "pronephric anlage" in 8th, 9th and 10th pairs of primitive segments. No trace yet of a Wolffian duct. Segmental vesicles in 11th, 12th and 13th pairs of primitive segments.	Heart S-shaped. Posterior mesocardium through a few sections. Aorta paired throughout.					Allantoic duct.	Extirpation of uterus for carcinoma. Fixation: Formalin-Müller's fluid. Stain: Paracarmine. Sections: 10 μ. Recent mitoses. Septum transversum. No ventral connection between pericardial and peritoneal cavities.
Intestine still communicates widely with the yolk sack. Liver a thick-walled sack from which the trabeculæ are beginning to bud.	The 3 anterior branchial pouches reach the ectoderm; the 4th, though formed, does not. Thyreoidea mediana formed. Pulmotracheal groove. The paired condition of the pulmonary anlage already indicated.	Rudimentary "pronephric anlage." Mesonephric anlage (segmental vesicles) with rudiments of nephrostomes. Mesonephric cord partly connected with the primitive segments, extends to the end of the defined primitive segments. Wolffian duct begins to acquire a lumen cranially; it ends enclosed in the ectoderm, still some distance from the cloaca.	Heart strongly S-shaped. Anlagen of the atria are beginning to differentiate. The first two branchial arch arteries distinct. The aortæ fused for a short distance.						The embryo was obtained by operation. Abundant mitoses in the embryo. Fixation:? Stain: Borax carmine. Sections: 5 μ. The embryo was modelled by Dr. Peter Thompson. Cf. Thompson, P., Description of a Human Embryo, etc., Journ. of Anat. and Phys., Vol. 41, 1907. Also Meyer, Rob., Ueber die Beziehung der Urnierenkanälchen zum Cölomepithel, etc., Anat. Anz., Vol. 25, 1904.

Desig.	Size	Age	Body form	Primitive streak	Primitive segment	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*10 Human embryo, 4 mm. (1 Feb. 1895). Collection of Prof. Strahl, Giessen. N. T. Text-fig. 9a–9s.	Gr. L. 4 mm.		Between Figs. 5 and 7 of His' Normentafel. (The embryo of Fig. 6 of His' Normentafel is probably pathological.) Vertex bend complete. Nape bend has begun.			Chorda separated from the entoderm, but in the cranial part, through 19 sections, it has as yet no mesoderm below it.	Roof of 4th ventricle thinned out. Neuromeres. In cord no dorsal column and no anlagen of the anterior horns. Branchial cleft organs of the facialis and glossopharyngeus recognizable as placodes.	The distal wall of the optic vesicle is somewhat thickened and is almost in contact with the ectoderm. A wide communication between the optic vesicle and the cavity of the ventricle. Anlage of the lens recognizable as a thickened epithelial plate.	The right auditory vesicle completely constricted off and showing the first indications of a ductus endolymphaticus. The left vesicle, which has no signs of a ductus endolymphaticus, is connected with the surface ectoderm by an epithelial cord.	Convex olfactory areas less distinct.	Early anlage of hypophysis.	Oral sinus, pharyngeal membrane vanished. No tuberculum impar as yet.

Digestive tract, liver and pancreas	Branchial pouches, thyreoid, thymus, trachea and lungs	Urogenital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
Sagittal stomach enlargement. Hepatic trabeculæ, but remains of the liver sack still visible. Anlage of dorsal pancreas, not yet very distinct, in region of 6th pair of somites. Very short tail gut. Early anlagen of so-called "glands" in yolk sack.	4 branchial pouches reach the ectoderm, all closed, ectoderm and entoderm partly fused. Early anlage of median thyreoid. Tracheal groove. Very early anlage of lung.	"Pronephric" rudiments on right side in region of 8th somite (5th cervical), on left in region of 7th (4th cervical). Mesonephros (anlagen of segmental vesicles and also rudimentary nephrostomes) begins on right in region of 10th, on left in region of 11th somite. Wolffian ducts end independently, thickened and with lumen, close to the ventral surface of the cloaca, near the cloacal membrane. Pronounced intestinal and bladder bay.	Heart differentiated into ventricular and atrial portions. Anlagen of trabeculæ in ventricle. Distinct atrial canal. Posterior mesocardium no longer complete. 1st branchial art, beginning to degenerate in its ventral part, 2nd and 3rd well developed, 4th formed (almost completely on right). Primary origin of aa. umbilicales, secondary one forming. Aortæ fused in region of 5th pair of somites (2nd cervical). A. subclavia formed.	Hirschland (1899) speaks of an early stage of the milk ridge in this embryo; we would hesitate to give the epithelial thickening in question this name.		Upper limbs unsegmented swellings (Hirschland, p. 235); lower limbs not recognizable in sections. (Hirschland speaks of the "anlage of the as yet very small lower extremities").	Amnion lying very close		Embryo obtained by operation and fixed while fresh. Somewhat compacted mitoses. Fixed in the chorionic vesicle with nitric acid. Stain: Borax carmine. Cut into 3 pieces. Literature: Hirschland, L., Beiträge zur ersten Entwicklung der Mammarorgane b. Menschen. Anat. Hefte, Heft 34–35, 1899, also Inaugural Dissert. Giessen, 1898. Jahrmärker, E., Ueber die Entwicklung des Speiseröhrenepithels beim Menschen. Inaug. Dissert. Marburg, 1906. Recessus and mesolaterale present on right, no recess and no mesolaterale on left.

Desig.	Size	Age	Body form	Primitive streak	Prim. segments	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*14 Human embryo G. 31. Collection of the Anat-hiol. Institute, Berlin (Prof. O. Hertwig.) N. T. Fig. VIII. Text-fig. 12a–12p.	Gr. L. = nape-hreech length, 4.9 mm. Ver-tex-hreech length 4.7 mm. Greatest diameter of yolk sack 0.58 mm.	Supposed to be 4 weeks	Between Figs. 6 and 7 of His' Nor-mentafel, nearer Fig. 7.	Vanish-ed up to the tail hud.	35 pairs of seg-ments, the most anterior quite ru-dimen-tary.	The an-terior end ter-minates close to the hy-pophy-sis. Very thin chorda sheath.	Infundibu-lum. Roof of the 4th ven-tricle thin. 7 distinct neuromeres in 4th ven-tricle region. No dorsal columns in spinal cord as yet. Neu-renteric cord.	Transition from optic vesicle to optic cup. Lens repre-sented by a thickened area of ectoderm. Scattered mesen-chyme cells between lens and optic vesicle.	Auditory vesicle just constricted off. The point of constric-tion still visible at the ecto-derm. Duc-tus endo-lymphati-cus just formed.	Distinct convex olfactory areas	Very broad hypophyseal pouch	No re-mains of the phar-yngeal mem-brane. Tuber-culum impar.

Digestive tract, liver and pancreas	Branchial pouches, thyreoid, thymus, trachea and lungs.	Urogenital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
Stomach anlage already slightly twisted. Tail gut. Abundant trabeculæ in liver anlage. Gallbladder formed. Distinct anlage of dorsal pancreas. Early anlage of ventral pancreas. (Jankelowitz [1895] describes 2 ventral pancreas anlagen. It is douhtful if there are really two; it seemed to us that there was only one.)	4 branchial pouches reach the ectoderm. The solid, twolohed anlage of the median thyreoid is connected with the floor of the mouth. Trachea constricted off. Undivided bronchial buds.	Wolffian duct interrupted cranially, free glomeruli right and left ("pronephric remains"). In mesonephros cranially anlage of glomeruli, caudally segmental vesicles, partly with rudimentary nephrostomes. Wolffian ducts have reached the cloaca, hut do not yet open into it. Very early anlagen of the metanephric buds as enlargements of the Wolffian ducts. Nephrogenic cord. Cloaca with bladder and intestinal hay. Primitive germ cells.	Atrial and ventricular septum formed, also the right valvula venosa. Primary origin of the aa. umbilicales. The aa. omphalomesentericæ form a ring around the intestine. Vv. omphalo-mesentericæ connected hy an anastomosis dorsal to the intestine.			Upper extremity plate-like, lower one like a swelling.			Numerous fresh mitoses. Fixation: (according to Herr, 1893) suhlimate-acetic acid; (according to Jankelowitz, 1895) picric-suhlimate-acetic acid. Stain: Borax carmine-aurantia. Sections: 10 μ, trans. The emhryo was modelled by Dr. Ingalls, compare Ingalls (1907). Literature: Herr, Beitrag zur Entwicklungsgeschichte des menschl. Auges. Dissert. Berlin, 1893.—Jankelowitz, Zur Entwicklung der Bauchspeicheldrüse. Dissert. Berlin, 1895. Also, Ein junger menschlichen Emhryo, etc. Arch. f mikr. Anat., Vol. 46, 1895.—O. Hertwig, Lehrhucb der Entwicklungsgeschichte. Also, Elemente der Entwicklungslehre, 3rd ed., 1907.—Ingalls, N. W., Beschreihung eines menschl. Emhryo, etc., Arch. f. mikr. Anat., Vol. 70. 1907. Bursa omentalis, with foramen of Winslow, is formed.

Desig.	Size	Age	Body form	Primitive streak	Primitive segments	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*21 Human embryo Walther. Collection of Prof. Strahl, Giessen. N. T. Text-fig. 16a-16s	Gr. L. 6.75 mm.		The embryo is figured by Hirschland (1899, Plate XIX to XX fig. 2). Somewhat more advanced than the embryo of Fig. 8 of His' Normentafel. Distinct nape and dorsal bends. Maxillary process distinct. Sinus cervicalis wide open. Tail to the right. Slight spiral twisting.		38 primitive segments, the last not delimited (3 cranial and 35 trunk segments).		Neuromeres in region of 4th ventricle not very distinct. Infundibulum. Cerebral hemispheres indicated. In spinal cord anlagen of the anterior horns distinct, those of the posterior columns are just beginning to form.	Optic cup. No retinal pigment as yet. Stalk of optic cup still very wide. Anlage of lens a flat groove, in which are cell proliferations.	Ductus endolymphaticus still short and wide.	Flat, and with still somewhat flat olfactory areas.	Wide open hypophyseal sack.	Tuberculum impar well developed.

Digestive tract, liver and pancreas	Branchial pouches, thyreoid, thymus, trachea and lungs.	Urogenital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
Stomach distinct, half rotated. Ductus vitello-intestinalis still connected with intestine, still shows no interruption, is partly enlarged, partly solid. Tail gut degenerating, but not yet interrupted. Gall bladder and ductus choledochus solid. Dorsal and one ventral pancreatic anlage.	Wide open sinus cervicalis. 4 branchial pouches reach the ectoderm, all closed. Rudimentary 5th pouch. Anlage of median thyreoid connected with the epithelium of the mouth cavity by a long slender stalk. Trachea already constricted off from the œsophagus for some distance. Undivided lung vesicles.	"Pronephric rudiment" only on the right (in 11th segment = 8th trunk segment). Large glomeruli in mesonephros, quite caudally there are still 3 segmental vesicles unconnected with the Wolffian duct. In about the last 6 tubules the anlage of the glomerulus is forming. Mesonephros begins on right in 11th, on left in 12th segment. Wolffian ducts open into cloaca. Metanephric buds. Metanephric mesenchyme in direct contact with mesonephros, that of right and left come together medially. Large cloaca. Intestinal and bladder bays.	Atrial septum not yet complete. Foramen ovale not yet formed. Left valv. venosa still but little developed, and so the ventricular septum. 1st branchial arch artery completely, 2nd partly obliterated, 3rd, 4th and 6th completely. Aa. subclaviæ arise at the point of union of the aortic roots. A. cœliaca at level of 10th, a. omphalo-mesenterica (with two roots) at that of the 13th and 15th segmental arteries. Primary origin of the aa. umbilicales obliterated. Left ductus Cuvieri quite small.	So-called "milk streak" (Hirschland, 1899, p. 234) present to a considerable extent.		Upper and lower extremities unsegmented stumps.		Allantoic duct in umbilical cord enlarged for some distance	Obtained by laparotomy. Mitoses. Fixation: Formol. Stain: Borax carmine. Sections: 15 μ, trans. Literature: Hirschland, L., Beiträge zur ersten Entwicklung der Mammarorgane b. Menschen, Anat. Hefte, Heft 34–35 1899, also Inaug. Dissert. Giessen, 1898.—Jahrmärker, E., Ueber die Entwicklung des Speiseröhrenepithels, etc. Inaug. Dissert., Marburg, 1906. Dorsal and ventral pillars of the diaphragm, but as yet no pleuroperitoneal membrane. Pericœsophageal space (recessus superior sacci omenti) in wide communication with saccus omentalis. No mesolaterale sinistrum. Spleen anlage.

Desig.	Size	Age	Body form	Primitive streak	Primitive segments	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth	Digestive tract, liver and pancreas
*28 Human embryo Chr. 1. Collection of Prof. Hochstetter, Innsbruck. N. T. Fig. XIII. Textfig. 20.	Gr. L. about 7 mm.	27–28 days (estimated)	Between Figs. 10 and 11 of His' Normentafel. Open cervical sinus. Opercular process on 2nd branchial arch.		3 cranial and 37 trunk segments.	Chorda homogeneous from the hypophysis to the tip of the tail, finally united with the tail gut.	7 neuromeres in region of the 4th vent. Cerebral hemispheres formed. Early anlage of epiphysis. In the spinal cord anterior horns, anterior and posterior columns. About 34 spinal ganglia and 27 spinal nerves. Well-developed branchial cleft organs on facialis, glossopharyngeus, and vagus.	Optic cup. Traces of pigment in retina. Lens vesicle just closed, point of closure still evident, proximal wall thickened. In interior of lens vesicle scattered degenerating cells, on proximal wall a heap of cells.	Auditory vesicle with rather long ductus endolymphaticus (about 300 μ long).	Slightly depressed olfactory areas. Anlage of Jacobson's organ not yet distinct.	Hypophysis sack deep, in wide communication with the mouth cavity.	Tuberculum impar, basal lingual and arytenoid swellings.	Rotation of stomach around its sagittal axis not yet completed. Duodenum almost blocked by epithelial proliferations. Simple intestinal loop. Cæcum a spindle-shaped enlargement. Point of attachment of the vitello-intestinal duct to the intestine recognizable as a small enlargement of the lumen. Tail gut recognizable as a solid cord from the cloaca to tip of tail, enlarged at end and with a lumen. Gall bladder solid. Ductus choledochus with lumen. Pancreatic anlagen still far apart.

Branchial pouches, thyreoid, thymus, trachea and lungs.	Urogenital system.	Heart and vessels.	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
4 branchial pouches reach the ectoderm. A 5th branchial pouch. Median thyreoid bilobed, a lumen in left lobe. Ductus thyreoglossus completely obliterated. Trachea constricted off. Bronchi giving off their first divisions.	Reproductive gland indifferent. "Pronephric rudiment" on left side (tubule and "free glomerulus"). Mesonephros at the caudal end with segmental vesicles that have already reached the Wolffian duct. Wolffian ducts open into urogenital sinus after giving off ureters. Renal pelvis roundish. Anlage of cortical portion of suprarenal body.	Septum I not yet complete. Very early anlage of the foramen ovale. Valv. venosa dextra and sinistra, septum spurium. Septum ventriculorum still but little developed. Beginning division of truncus arteriosus. 1st branchial arch art. completely obliterated, 2nd interrupted, 3rd, 4th and 6th complete, 5th incomplete. Aortic roots unite between 6th and 7th segmental artery (count by Hochstetter). Post-cardinal veins not yet united by anastomosis ventral to aorta. Anlage of V. cava inferior.	Milk streak.	Skeleton in mesenchyme stage. Base of skull, pars petrosa, vertebræ, humerus, femur and some ribs recognizable as mesenchyme thickenings.				Extirpation of uterus on account of carcinoma. Fresh mitoses. Fixation: Sublimate. Stain: Alum cochineal. Sections: 10 μ, trans. Literature: Hochstetter, Ueber die Bildung der primitiven Choanen beim Menschen. Verh. Anat. Ges., 1892; Entwicklungsgeschichte des Venensystems der Amnioten. III. Säuger. Morph. Jahrb., Vol. 20, 1893; Die Entwicklung d. Blutgefasssystems in O. Hertwig's Handb., 1901 and 1903.—Salzer, Entwicklung der Kopfvenen des Meerschweinchens. Morph. Jahrb., Vol. 23, 1895.—Tandler, Ueber die Entwicklung des menschlichen Duodenum in frühen Embryonalstadien. Morph. Jahrb., Vol. 29, 1900 (1902).—Narath, Der Bronchialbaum der Säugetiere und des Menschen. Bibliotheca med., Part A, Anatomy, Heft 3, 1901.—Keibel, Die Entwicklung der äusseren Körperform, etc., in O. Hertwig's Handb., 1902.—Fuchs, Lehrb. der Augenheilkunde, Leipzig and Vienna, 9th Ed. 1903.—Toldt, Anat. Atlas, 3d Ed., 1903.—Langer, Zur Entwicklungsgeschichte des bulbus cordis bei Vögeln und Säugetieren. Morph. Jahrb., Vol. 22, 1895.—Elze, Beschreibung eines menschlichen Embryo, etc., Anat. Hefte, Heft 106, 1907. Left mesolaterale in one section. Spleen tubercle.

Desig.	Size	Age	Body form	Primitive streak	Primitive segments	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*50 Human embryo No. 250. Collection of Dr. Robert Meyer, Berlin. N. T. Text-fig. 31a–31c.	Gr. L. 11 mm.		Caudal knob.			Chorda still homogeneous in pelvic region.	Still indications of neuromeres in region of 4th vent. Epiphysis. Posterior commissure. On the spinal side of post. commiss. still 2 epiphysis-like structures. Medullary canal still extends to the caudal knob.	Optic stalk still open. Abundant retinal pigment. Lens vesicle ¾ filled, not yet forced away from ectoderm. Early but distinct anlage of ductus nasolacrimalis.	Semicircular canals present as pouches.	Primitive choanæ closed by the membranæ buccopharyngeæ. Primary palate formed. Jacobson's organ.	Infundibulum and post. lobe of hypophysis. Anterior lobe not yet budded out, connected with the pharynx by a rather narrow duct.	Primary palate.
*78 Human embryo Krönig. Keibel's collection. Series No. 1446. N. T. Fig. XXIII v and XXIII i.	Gr. L. (measured in alcohol) 20.5 mm.		Between Figs. 24 and 25 of His' Normentafel. Locality of the nape bend still indicated. Eyelids beginning to grow over the eyes. Tail knob. Physiological umbilical hernia.			Chorda still homogeneous in region of coccyx.	Epiphysis with buds. Chiasma. The medullary canal extends to the tail knob into which it is continued as a solid cord.	No lachrymal glands yet. Nasolachrymal ducts and lachrymal canals do not yet reach the epithelium of the nasal cavity or conjunctiva.	Cochlea with ¾ coil. Cartilaginous auditory ossicles. Cartilage in external ear and in auditory meatus.	External nares in epithelial anlage. Upper, middle and lower conchæ.	Hypophysis richly budded. Remains of the hypophyseal duct persist.	Palatal processes beside the tongue. Epithelial papillæ on tongue. Intrinsic musculature of tongue differentiated. Early anlagen of teeth. Submaxillary gland has budded out, parotid not yet, sublingual?

Digestive tract, liver and pancreas.	Branchial pouches, thyreoid, thymus, trachea and lungs.	Urogenital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
Cæcum and vermiform process. Scanty remains of the tail gut. Anlagen of epithelial buds in small intestine. Pancreatic anlagen almost in their final position but still distinguishable from one another.	Remains of the sinus cervicalis unconnected with the surface epithelium. Median thyreoid has not yet reached the lateral thymus and lateral thyreoid still connected with pharynx by epithelial cords. Bronchi divided twice.	Reproductive gland indifferent. Müllerian duct still short. "Pronephric rudiment" on the left side. Mesonephros with large glomeruli. Renal pelvis budded out. Renal mesenchyme beginning to differentiate. Ureters open into the Wolffian ducts. Cloaca not yet completely divided up (cloacal duct). Suprarenal bodies.	Septum I complete. Foramen ovale. Ostium atrioventriculare commune divided. Septum ventriculorum not yet complete.	Anlage of mammary gland club-shaped.	Base of skull and vertebræ præcartilaginous, also ribs and scapula. Humerus, radius, and ulna cartilaginous. Femur præcartilaginous.				Abortion. Mitoses. Stain: Borax carmine. Sections: 10 μ trans. Pericardial cavity separated from pleural cavities, on the left ductus pleuro-pericardiacus is just closed. Communication between pleural and peritoneal cavities is still wide. Caudal limiting fold (Hochstetter) formed on both sides. Spleen.
Longitudinal and circular muscles in œsophagus. Musculature in stomach, duodenum and rectum. Anlagen of fundus glands in stomach? Beginning formation of villi in duodennm. Epithelial buds of small intestine in diverticulum stage. Anus closed.	No cartilage in epiglottis yet. Larynx cartilaginous. Tracheal rings formed of young cartilage. Cartilages of bronchi in præchondral stage. Bronchi divided up to eigbt times.	Reproductive gland distinctly an ovary. Lumina of Müllerian ducts not yet connected and ending some distance from the sinus urogenitalis in the genital cord. Well-developed glomeruli in the kidney. Urogenital sinus open.	Ventricular septum complete.	On each side a principal anlage of the mammary gland in the club-shaped stage, in addition hyperthelial structures. No hair anlage yet.	Terminal phalanges of great toes cartilaginous; in those of the other toes cartilage is not yet distinct. Bone in humerus, femur and tibia. Mandible, maxilla, præmaxilla and palatine ossifying, clavicle osseous and cartilaginous.	Toes separate, Distinct touch pads on foot.			Gift from Professor Krönig. Artificial abortion. Mitoses. Fixation: Zenker's fluid. Stain: Hæmatoxylin-orange, some sections water-blue-orcein-safranin after Schridde. Sections: 15 μ. Pericesophageal space.

Desig.	Size	Age	Body form	Primitive streak	Primitive segment	Chorda	Nervous system	Eye	Ear	Nose	Hypophysis	Mouth
*84 Human embryo No. 321.& Collection of Dr. Robert Meyer, Berlin.	Gr. L. 26 mm.		The eyelids have grown over the eyeball for a considerable distance. Very small tail-knob.			Chorda is still homogeneous at end of coccyx, shows lateral buds in that region.	Olfactory lobe with evagination of ventricle. Epiphysis with buds. Chorioid plexuses in the lateral and fourth ventricles enormously developed. Medullary canal extends to the coccygeal tubercle, its lumen enlarged towards the end.	Lachrymal gland formed. Naso-lachrymal ducts do not yet reach the epithelium of the nasal cavity, nor the lachrymal ducts that of the conjunctiva. Beginning differentiation of the retina. Prox. part of the vascular capsule of the lens formed. Endo-epithelium on the proximal surface of the cornea distinctly differentiated. Iris, anterior and posterior chambers of the eye.	Cochlea has 1¾ coils	External nares completely plugged with epithelial proliferation, epithelial knobs projecting from it. Jacobson's organ in connection with the epithelium of the nasal septum by a thin solid cord.	Anterior part of hypophyseal anlage richly budded out. Hypophyseal duct vanished except for doubtful remains.	Palatal ridges beside the tongue. Dental ridges with toothgerms. Parotid gland beginning to sprout out. Submaxillary branched. Sublingual beginning to sprout out. Papilla salivalis, sublingua, plicæ fimbriatæ.

Digestive tract, liver and pancreas	Branchial pouches, thyreoid, thymus, trachea and lungs	Urogenital system	Heart and vessels	Integument	Skeleton	Extremities	Amnion	Allantois	Remarks.
Anlagen of gland-like structures in fundus of stomach. Circular musculature throughout whole intestine. Villi in duodenum and a large part of small intestine. Epithelial buds or diverticula in small intestine. Anus still closed.	No cartilage as yet in epiglottis. Opening of larynx partly fused. Cartilage rings in trachea and main bronchi. Bronchi divided up to 8 times. Lungs at level of 2nd –9th thoracic vertebræ.	Reproductive gland a testis. The Müllerian ducts extend to the immediate neighborhood of the urogenital sinus, they are fused to form the genital cord, but their lumina are separate throughout. Doubtful "pronephric rudiment." Mesonephros greatly degenerated. Glomeruli and tubuli contorti distinct in metanephros. Smooth musculature of bladder formed. Urogenital sinus open. Sympathetic tissue in centre of suprarenal body. Suprarenals lie in region of the 10th thoracic–1st lumbar vertebra, the kidneys in that of the 12th thoracic –3rd lumbar. The mesonephros extends from 1st–end of 3rd lumbar, the reproductive gland from 1st–middle of 3rd lumbar.	Ventricular septum complete. All the valves formed.	In addition to the principal mammary gland a number of hyperthelial structures on either side, some of which have distinctly the appearance of early stages of mammary gland anlagen. Early hair anlagen in region of eyebrows.	34 vertebræ. Cartilaginous skeleton complete (even in the terminal phalanges of the toes). Mandible, maxilla, præmaxilla, palatine, frontal, zygomatic together with squama temporalis osseous. Bone and cartilage in clavicle. Osseous anlagen in humerus, radius, ulna, femur, tibia and fibula.				Mitoses. Stain: Borax carmine. Sections: 15 μ. Pericœsophageal space not found. Peculiar epithelial growths in the median line of the ventral body wall.

These tables will suffice to give a general idea of the time relations of the development of the various organs. The practical value of the tables is also plainly evident. The investigator who wishes to study some particular organ may quickly determine from the Normentafel what stages he requires for his investigation. And I would place especial importance on the fact that the Normentafel make it possible to estimate the proper value of isolated observations and to assign them readily to their proper place.

Furthermore, as may be readily seen when one examines the entire series of Normentafel, in which numerous closely succeeding forms are shown, the tables furnish a measure for the determination of individual variations in the embryonic development of man. Such variations undoubtedly occur, but, as in other amniotes that have been studied, they are not very important. However, the tables also furnish information on more general questions. Even in the preparation of the first Normentafel, that of the pig (published 1897), Keibel (1895) was able to demonstrate that the modification of the time relations, indeed, one may say that overlapping in the development of the various organs is so extensive, that a satisfactory division of the entire development into stages corresponding to a præpiscine form, a fish, a terrestrial animal and an amniote, such as Oppel (1891), for example, has assumed and which must be assumed if the biogenetic law is strictly applicable, such a division is impossible. This was then found to be true for other amniotes that were studied in this way, and especially for man. We see a regular succession of the individual ontogenetic stages only when the preceding stage is the necessary condition for the succeeding one. "The unicellular organism," says O. Hertwig (1906[2]), "from its nature, can be transformed into a multicellular one only by cell-division. Consequently in all animals the ontogenesis *must* begin with a division of the ovum. An organism with definitely arranged cell-layers and cell-groups can only be formed from a mass of cells when the cells, during their division, begin to arrange themselves into firm unions." In this sense one may speak, with Oppel (1891), of indispensable stages of development. Otherwise, however, we find in the time succession of the organs no indication whatever of the succession in which they were acquired phylogenetically. It is sufficient to point out that the embryonic organs, the amnion, chorion, and allantois, appear before other organ anlagen are recognizable. Keibel (1895) has shown that this precocious appearance of various organ anlagen is probably associated with the necessity for their earlier or later activity. That definite traces of the path taken by phylogeny are retained by heredity is, nevertheless, not to be denied, but for the time suc-

cession heredity has proved to be a force of little moment. That an actual recapitulation of the phylogeny in the ontogeny, and, therefore, the validity of the so-called biogenetic law, is impossible for purely logical reasons Keibel (1893) has already pointed out, when he states that "already in the first member of a developmental series the last one" is determined, and that, consequently, the first member of a series must appear modified, when compared with the first member of another series "which may have had the same phylogenetic beginning, but was completed at a lower stage of development."[1] O. Hertwig (1906[2]) has termed "this relative dependence between the ovum condition on the one hand and the course and final result of the ontogenesis on the other hand, the ontogenetic law of causation and the parallelism of anlage and anlage product." It follows from this law that all intermediate members will show modifications. These questions, however, need not be further discussed in this place, but I would refer the reader to Keibel (1903) and O. Hertwig (1906 [1] [2]). I would call the attention of those who may be interested in comparing the interdependence of the different developmental processes of the human embryo with those of ape embryos to the 9th part of Emil Selenka's Menschenaffen, in which F. Keibel (1906) discusses the external form and degree of development of the organs in ape embryos and has given tables showing the development of the apes in the same way that Keibel and Elze (1908) have shown that of man in the Normentafel zur Entwicklungsgeschichte des Menschen.

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