NATIONAL ACADEMY OF SCIENCES
OF THE UNITED STATES OF AMERICA
BIOGRAPHICAL MEMOIRS
VOLUME XVI—THIRD MEMOIR

BIOGRAPHICAL MEMOIR

OF

FRANKLIN PAINE MALL

1862-1917

BY

FLORENCE R. SABIN

PRESENTED TO THE ACADEMY AT THE ANNUAL MEETING, 1934

Franklin P. Mall.

Recent Portrait of Dr. Franklin Paine Mall
By
Thomas C. Corner
(From a Photograph Taken in 1913 by the Late Dr. Frederick L. Gates)

FRANKLIN PAINE MALL

1862-1917

BY FLORENCE R. SABIN

Seventeen years have elapsed since the death of Franklin Paine Mall, and the interval between his death and this belated report to the National Academy of Sciences but serves to make one the more aware of the power of the man and the enduring influence of his life.* Little known to the public then or now, never heralded as a brilliant discoverer, one has but to mention his name to his colleagues to hear that he was the leader of them all.

In Mall's files was a note from P. A. Levene, in which is condensed into one sentence what one must reveal to paint Mall's portrait: "The few times I have met you are a radiant memory", and such he remains to those who knew him. Mall must be described as a man of power, yet he was modest, unassuming, even shy. Physically he was unimpressive, thin, of average height and sallow complexion. His face, when not lighted by a smile, was apt to be sad. Always youthful in appearance, he was often mistaken for a student, yet this frail young man was one of the outstanding educators of his time. In the days when scientific research in medicine was taking root in this country, he was one who planted and nurtured it. He found that the ancient science of anatomy was only a handmaid to surgery in this country, with practically no independent status, and he left it in its rightful place with a school of disciples. To this day there is no dearth of well trained, scientific anatomists, the second and third generation from Mall. Moreover, his influence was felt throughout medical education, in the founding of journals and scientific societies, in that period of awakening which began in this country in the last decades of the nineteenth century.

The story of Mall is of a mind brilliant and original, with a strange enigmatic quality and a complex combination of opposites—wit and wisdom, humor and sadness. One might easily insist that raillery or a certain acid quality of his comment was his most striking characteristic, but another would combat this with surprise and substitute kindliness and judgment. But all

*A more extended life of Doctor Mall will be published by the Johns Hopkins Press.

were aware of his tendency to say the unexpected and of an extraordinarily cryptic quality of his mind, which acted like an enzyme or ferment on the minds of others, goading them to thought and action. In this lay his power as a teacher, combined with the example of an enduring enthusiasm for study. Endowed with exceptional ability for organization, in a country where this power receives the highest recognition and rewards, he continued to lead the simple life of the scholar, as active in research at the time of his death as in the early years of his training. It is interesting to note that he had no ability as a lecturer and left no popular writing whatever, yet no medical student escapes his influence.

He was a leader in the sense of one who foresees the trends of development of his times and sets the stage for their fulfillment. He can best be described as having the abilities of generalship. He knew exactly what he wanted; he could plan his campaign for years in advance and could wait with patience until the time was ripe for the next step in his program. He could bend the will of others to the interests of causes. Of William Welch he once said to me that no one had ever found him working for his own advancement, and the same was true of Mall. His interests were wholly objective; he was a fighter for freedom in education; an ardent democrat, he knew the elements of danger in democracy and knew how to combat its leveling tendencies. His vision was of the development in this country of a university of scholars in the European sense; and medical education is on a higher level because he lived and taught. In the medical school which developed in Baltimore, he and Osler represented two different phases of thought, a difference which Osler has expressed better than anyone else can do, for he said that he himself was of the type who would rather be wrong with Plato than right with Aristotle. As in ancient days, two types still make up the medical profession. It is clear enough to which Mall belonged for the motive of his life was a profound belief in the benefits of the growing science of medicine; he had unbounded faith in the ability of man's mind to solve the problems of disease.

Franklin Paine Mall was born in Belle Plaine, Iowa, September 28, 1862, and died in Baltimore, November 17, 1917, at the age of fifty-five, following an operation for gallstones. He was of German parentage on both sides of the family. His father, Franz Mall, was born in Söllingen, near Durlach, in the Province of Baden, Germany. Mall's branch of the family has lived there for three hundred years.[1]

There are two strains of the Mall family in Germany: one, descendants of Tobias Mall, who was born in 1570 and lived in Donnstetten, and the other, the line from which Mall came, descendants of Hans Wendel Mall, a linen weaver, born in 1625, who lived in Söllingen. Before this time the name of Mall, meaning "hammer", does not appear in the records of the town. It was the period of the thirty years' war, during the early years of which Hans Wendel Mall was born. The region of Durlach was invaded; at the beginning of the war, Söllingen had 750 inhabitants, and at the end only 250, which tells the tale of Hans Mall's youth. The records of births and deaths were kept by the church, and though all of the church books of the neighboring towns were destroyed during the war, there is a church record of baptisms in Söllingen which begins May 8, 1614. Further back than this it is difficult to trace the name of Mall, but it is probable that the family originally stemmed from the Tyrol. The record that Johann Erhard Mall married a Papist, which I found in a note left by Mall's father, indicates that the family was Protestant.

Mall's grandfather had seven sons, six of whom emigrated to America. Mall's father was a boy of nineteen at the time of the revolution of 1848. He belonged to a choral society of twenty-four young men and during the revolution some of their songs, referring to liberty, so displeased the authorities that all

[1] For the data in regard to Mall's family in Germany, I am indebted to Mr. Daniel Mall of Württemberg, Germany, a second cousin of Dr. Mall. In part the data are from letters from Mr. Mall and in part from his book, *Das Geschlecht der Mall,* published by Hugo Kretschmer, Kunstanstalt für Hoch- und Flachdruck, Görlitz. Volume I in 1925; Volume II in 1926.

twenty-four served a term in prison. The following years were a period of unrest in Germany, times were hard and there was a shortage of food. In 1852 Mall's father and one of his friends, Joseph Wenz, went to America in a sailing vessel, being thirty-six days on the water. They joined the trek westward, finally reaching St. Louis, whence they went on foot to Iowa where they had heard of a chance to buy land. Franz Mall bought a tract of land there which later became his farm. In two years, however, he had news that his father was ill with gastric cancer, and he returned to Söllingen. He seems to have been a leader among his companions for when he returned to America that same year, 1854, all of his choral society came with him. Moreover, through him five of his brothers came to America and settled on farms in Iowa and Kansas. In 1855, the year after his return to America, he married Louise Christine Miller of Oswego, Illinois. Little is known of her except that she was born in Germany. There were four children, only three of whom grew up—two daughters and one son. Mall's father must have been a well-to-do farmer, for he was able to give his son an education that took years, and he himself returned to Germany four times and finally died in Söllingen. To those who remained in Germany the brothers who went to America must have seemed rich for in the town of Söllingen the family were all small farmers. None of them had more than about twenty-five acres of land, divided as was the custom in Germany into small plots of from a half to one and a half acres. The value of these small plots of land depended not only on the nature of the soil but on the nearness to the village. Since these holdings of land were not enough for the support of a family, each man had some other occupation such as a grafter of trees, stone cutter, quarryman, mason, worker on the railroad and cultivator of vineyards. The records state that none of the Malls had wealth, but that as a family they stood out in the community for honesty and for idealism. In these two qualities it is clear enough that Mall was representative of his family, but there is little to indicate that Mall was interested in tracing his ancestry or in handing down the knowledge to his children. However, he did

tell his daughter Margaret that there had been a Margaret Mall in the family for several generations and that one of them, a cousin, was an able teacher. Up to the time of Franklin Mall, none of the family had ever had a university education; but since his time three of the Malls of Söllingen have studied medicine and in America, several of the family have had advanced education, including both of Mall's daughters.

Mall's mother died when he was ten; his father married a second time and, as the stepmother was unsympathetic toward the boy Frank, an elder sister took his mother's place in his affections. Mall was evidently a difficult child; he was clearly unhappy; neither at home nor in school did he find outlet for his active mind, and the whimsical humor of his later life was shown in endless teasing. It was a teacher in a local academy, a John McCarthy, who changed the whole tenor of his attitude, as is shown in a few words from one of Mall's letters to a nephew who is a teacher of history: "Your schedule of work looks very interesting and it must be very interesting to you to give it. My avocation has been a study of history, especially that of the Renaissance. If I had not gone into anatomy, I might have taken up history with equal enthusiasm. When I was a boy I detested history, but good old Mr. McCarthy showed me that I liked it. I only detested the detestable way of teaching it by rote." These words, which paint the picture of the boy, Frank Mall, make one certain that he made the teachers of the "detestable way" fairly unhappy in their turn. The intensity of his own reaction was shown years later in his determination to reform the methods of teaching science by rote. On this boy the influence of McCarthy was profound and in Mall's files is a treasured letter from him in his old age: "I keep up the study in a stumbling way, but when I am ready to perish from lack of knowledge my help comes from those wonderfully kind and modest managers of observatories. I am more contented when doing a little studying. I would love to teach, if I could only hear well enough, but that day is over." This letter reveals the secret of Mall's start in life and it tells as well the whole theory

of teaching. Mall met a teacher in an obscure academy in Iowa, who loved study and could awaken that spirit in others.

Our recent interest in the history of the settlement of the west in our country makes it possible to picture a small town in Iowa in the years following the Civil War—a farming community of English and German people, pioneers of English stock from New England, and forty-eighters directly from Germany. In Mall's home one can estimate that there was relatively little culture, for his early style in writing does not show any familiarity with good literature. It was a time when few homes had many books but when more than one of our public men had a style clearly formed from the Bible and Shakespeare. I well remember the keen interest with which Mall in his mature years read the Bible for the first time and his amazement at its beauty, for he read it as literature with an appreciation not dulled by any familiarity with the text. Likewise he read Shakespeare and the German classics for the first time in his student days in Germany. Nevertheless Mall's father had the traditional German respect for learning, for Mall wrote of him later: "I have been unusually fortunate in having a father who believed in education." Thus, after McCarthy had shown the boy Frank Mall that he loved study, Mall's father, though with slender means, helped him to get an education.

At the age of 18, Mall entered the Medical Department of the University of Michigan. There is no record whatever as to what turned his mind toward medicine, but it is said that the local physician had studied at Ann Arbor. It was a period when Michigan University was clearly making progress in education. The year Mall entered, 1880, the standards of admission were raised. The records show that no student was admitted to the Medical School under the age of 16, and that every candidate, who could not show a certificate of graduation from a respectable high school, academy or college, had to submit to an examination in the elementary branches of an English education. This now seems meager enough but it was a real advance in medical education in this country, for as President Eliot of Harvard University has said, "In the Sixties and Seventies there were no

requirements for admission to our medical schools. To secure admission a young man had nothing to do but to register his name and pay a fee." In 1880 the medical course at Ann Arbor was graded and for the first time in any institution in this country raised to three years. Many years later, from the standpoint of his mature judgment, Mall wrote of these changes in Michigan University as follows:

"Twenty years ago the medical department of the University was just beginning the transformation which has changed it from a school of low standard, as were all medical schools at that time, to one of high standard as it is at present. Requirements for admission had just been introduced, and a graded course of study extending through three college years was made compulsory for all students. During this transformation it was necessary to introduce much new work both in the laboratory and in the lecture hall to occupy the students during the increased time they now had to study medicine. Old instructors filled their share of the additional time by requiring the students to attend their lectures a second time in order that they might remember better the many facts presented to them. Yet there was considerable vacant time to be filled, which thus gave an opportunity to new instructors to come to the front with new ideals and methods to enrich the medical course. It was this second group of instructors, whose ideals and methods are now generally acceptable, that made the greatest impression upon me. Foremost among them were Professors Victor C. Vaughan and Henry Sewall. I can remember well the first lecture of each of these men. They entered upon their work by giving out matter first hand, and from the beginning made the impression that they mastered their respective subjects. They dealt little with the opinions of others, but instead produced trustworthy facts and demonstrations, as well as laboratory experiments for the students, upon which to build. The principle involved appeared to be the development of the student while presenting the subject matter, and now it is plain to me that no one but an investigator in his subject can do this.

"These high ideals were shared to a greater or less extent by other instructors, and were acceptable, it appeared to me, to only a minority of the students. The majority of students were seeking a certain quantity of knowledge, and preferred to have it drilled into them. Little did the solving of problems and the development of reason appeal to them, and it naturally followed that they mistook versatility for power. An educational

institution of highest order must carry on perpetual warfare against drilling trades into inferior students, in order to retain its high position. And above all the medical profession should be filled with learned men, and not tradesmen, in order to be of the greatest good to the community. It appears to me that the change beginning to take place in the medical department in 1880 was towards training thinking physicians with an underlying foundation composed of recent medical research. In other words its goal was toward the university stature. At this time, however, the department was yet only of high-school stature, and university ideals certainly seemed much out of place. But its rise has been very rapid, for it is now through its college stage and is about to enter its true university career.

"It is then the force which marked the beginning of the university ideal in the medical department at Ann Arbor which I remember best. This force which encouraged thinking and investigating has been carried from the University by many of its graduates, and has always proved to be a trustworthy friend. Fortunately for the medical department as well as for medicine of the entire land, this force has been carefully guarded and cultivated by our present distinguished dean."

After graduation from Michigan University, Mall went to Germany to study. The influences which sent him abroad must be surmised. While for a hundred years men from the eastern seaboard had been going abroad, first to Paris and later to Edinburgh to study medicine, it was probably a rare thing for any of the early settlers of the west to do so. Dr. Henry Sewall, just referred to, who went to Michigan in physiology in the spring of the year Mall graduated, had studied under Sir Michael Foster in Cambridge and under Kühne and Ludwig in Germany and had taught under Newell Martin in the Johns Hopkins University, before the Medical School was started in Baltimore. There is a story that Sewall, who had given the seniors a few lectures, asked the Dean of the School what he should do about an examination, with the result that the four best students of the class were sent to him for a test—Frank Mall, Will Mayo and two others. They all failed and Sewall is said to have predicted that none of them would succeed either in science or in medicine. It is clear enough that this episode did not delay graduation for any of them, nor did it dull Mall's appreciation

of Sewall, but its immediate effect on him is an interesting speculation. Did failure at Michigan send Mall to Europe and did it spell success at Leipzig? At any rate Michigan did not introduce Mall into scientific medicine, for he went to Europe for clinical work rather than for research, for Dr. William H. Welch, who first met Mall in Ludwig's laboratory in Leipzig, has written to me: "Mall went to Germany for clinical work, as so many young doctors were accustomed to do and without any particular interest in science. It was his contact with His and later with Ludwig which opened his eyes to the sciences of anatomy and physiology. Ludwig, with whom I had worked in 1876-77 at the time of my first two years in Germany and who greatly influenced me by turning me to Cohnheim instead of to Virchow, used to love to talk with me about Mall, whom he credited with remarkable gifts of observation, *'Raumsinn,'* he called it."

The first year in Germany Mall spent in Heidelberg working mainly on the nervous system and on the eye, both in the laboratory and in clinics, with the intention of going into ophthalmology. It was, however, the golden age of the German university and here Mall passed directly from what he had termed the medical high school into the freedom of university life. Here he found students who were mature men, better trained than he, and planning their own education. This he was keen to do, and his notebooks show that he planned his own course and worked with tremendous energy. He used to say that he enjoyed the chance to study pathology before he had taken a course in histology and it is clear that he found out for himself that he wanted to try research. Perhaps the same thing happened to him that history shows had happened to von Baer sixty years earlier, namely that a great dissatisfaction with medicine as it stood came over him and made him determine to find out what research was like. At any rate, in the fall of 1884, Mall went to Leipzig and started in research under His. Mall was interested in structure and His was the most outstanding anatomist of his day. Mall knocked several times at his door before he was finally admitted. His did not seek students to work with him; he was not interested in beginners. But something in the per-

sistence of that spare, young American of twenty-two years must have impressed the professor, for he finally gave Mall a place in his laboratory.

The history of Mall's first problem under His reveals at once Mall's ability. Inexperienced in research, a novice in embryology, he made acute observations, clarified an obscure field, and came to conclusions directly opposed to those of His. There thus arose between the two men, one, an experienced professor of years, the other a young student with his first problem, a scientific controversy rarely surpassed in its high plane of intellectual fairness. In retrospect one could not wish a word of it changed.

His suggested to Mall that he study the development of the gill arches in the chick and the results of his work focused attention on the question of the origin of the thymus. Shortly after Rathke [2] (1825) had discovered the occurrence of gill clefts in mammalian embryos, the subject of the origin of the thyroid and thymus became active problems. When one reflects on the crudeness of the early methods, without serial sections or any form of reconstruction, it is not difficult to understand why differences of opinion arose. It is interesting to note that it was in connection with the active discussions concerning the origin of these glands that Born [3] devised his method of reconstruction by wax plates, and that the first results of this method were to show that there are both median and lateral primordia of the thyroid, and that the thymus arises in the third branchial cleft. The most important of the earlier studies on the thymus were those of Remak [4] who formed the view that the thymus arose from the endoderm of the pharynx. But this view, now believed correct, was soon replaced even in Remak's mind by the theory that the thymus was mesodermal in origin, an opinion

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[2] Rathke, M. H., *Isis* von Oken, 1825, 747-749, 1100-1101.

[3] Born, G., Die Plattenmodelirmethode, *Archiv. für mikroscopische Anatomie,* 1883, *22,* 584.

[4] Remak, R., Untersuchungen über die Entwickelung der Wirbelthiere, Berlin, G. Reimer, 1851 [1855].

which obtained until Kölliker[5] and His[6] both held that it came from epithelium. In the study of human embryos with the methods of serial sections which he had perfected, His believed that the thymus arose from the ectoderm of the third gill cleft, along the wall of a deep groove which he called the sinus praecervicalis. Mall found evidence, on the other hand, that the thymus came from the endoderm of the pharynx. It is clear that the matter was not much discussed by the two men while Mall was at work, for it was the theory of the older man that a research worker should be wholly independent while his work was in progress. As Mall has related, when His took a student in research, he outlined a problem, explained and demonstrated the methods, and then was annoyed if he was consulted over the details. Thus at the end of the year, Mall told His of the results of the work and gave him his paper written in English. Under the advice of His, Mall had applied to work in Ludwig's laboratory and during the next winter Mall restudied the development of the thymus, coming, however, to the same conclusions as at first, and thus he returned the paper to His, now translated into German. This time it was accepted, and, to follow its fate, we pass over, for the moment, the momentous year which Mall spent with Ludwig.

Mall left Germany in the summer of 1886, to become Fellow in Pathology under Welch in Baltimore. During the year which followed, before his paper appeared in the *Archiv für Anatomie und Entwicklungsgeschichte,* of which His was editor, there was much interesting correspondence between the two men. His studied Mall's paper carefully, selected the best of the drawings, and had them copied on lithographic plates, concerning which Mall wrote to His, February 23, 1887: "A few days ago I received the plates and could hardly believe that they represented the rough work I gave you last autumn. I hardly know how to express my gratefulness to you." His then wrote that he was

[5] Kölliker, A., Entwicklungsgeschichte des Menschen und der höheren Thiere, Leipzig, W. Engelmann, 1861.

[6] His, W., Anatomie menschlicher Embryonen. 3 vols., Leipzig, F. C. W. Vogel, 1880-1885.

reworking the subject in new human embryos, to which Mall replied: "I am glad to hear that, in your reworking of the thymus, you find again that it arises from the ectoderm." In this statement Mall was entirely sincere, for his respect for the elder man was so great that emotionally he would have been content to have His correct, but he added at once: "From my material, I cannot see how it is possible. My embryo shows definitely whence the thymus comes. In the near future I hope to take up the subject in the dog. If I have been mistaken in the chick, it is my duty to find it out and acknowledge it."

It is interesting to note with what courtesy and deference he addressed the older man, using always the title of "Honored Professor" and concluding his letters with "Your grateful pupil", and yet how clearly and positively he expressed his own views. His wrote that in the correction of Mall's paper he had been exceedingly careful not to change Mall's meaning, but that he had omitted considerable of the data since the reader wishes only to get a clear picture of the chief points and not to follow through the entire material. The clear-cut statement of Mall's difference from his own views was not deleted and in the printed article is as follows (1, Page 18):

"This nodule is a round or oval body which His, in his study of the chick, has described as the beginning of the thyroid and Seessel as the parathyroid; but, as a matter of fact, as will be shown later, it is the thymus."

These were the words of the young man of twenty-two, working under the direction of a recognized master, to whom he gave in the same paper the following significant expression of his gratitude:

"This work was done under the direction of Herrn Prof. Dr. His, to whom I am extraordinarily indebted, not only for having been allowed to work with unlimited freedom in his laboratory, but also for instruction in methods, and for the expression of his views on various points during the progress of the work."

In the number of the journal preceding the one in which Mall's paper appeared, His published again on the thymus, strengthening his own opinion, and later Mall's paper was accompanied

by a footnote by His, explaining the delay in publication and adding: "The work gives evidence, moreover, as one can easily note, of its completely independent character."

When Mall first saw his paper in print, he wrote:

"A few days ago I saw the new number of the *Archiv für Anatomie und Entwicklungsgeschichte* and was gratified to see how much better my article appeared than when I handed it over to you. . . . You do not know how grateful I am to you for all the trouble you have put yourself to in going through my terrible article. I know that I shall profit by it. At least I shall try to follow the example you have set." Then immediately he dropped the rôle of the beginner and set forth his views as a mature and experienced worker. In a brief paragraph he analyzed the whole matter. He had now a new series of dog embryos and he had found the small epithelial structure which His had taken for the thymus was a transitory organ which joined the vagus and thus could not be the thymus, or, in Mall's own words: "But I am fully convinced that you have erred regarding the thymus and the body you have described as such is an organ of the vagus." This organ is now known as one of the placodes, or the homologue of the lateral line sense organs of fishes.

Mall then published three papers, two of them from material he had prepared in Leipzig. The first was on the development of the Eustachian tube in the chick (5), the second on the first branchial cleft in the chick (3), and the third on the branchial clefts in the dog (6). In these papers he described in detail the placodes, to which he had referred in the letter to His (3, 4, 5, 6). The union of the ganglion of the facial with the ectoderm was first seen by van Wijhe [7] in 1882, then by Froriep,[8] by Beard,[9] and then by Mall, in 1888 (6). In this paper Mall made it clear that the corresponding body (placode) which joined the vagus

[7] van Wijhe, J. W., Ueber die Mesodermsegmente und die Entwicklung der Nerven des Selachierkopfes, Amsterdam, 1882.

[8] Froriep, A., *Archiv für Anatomie und Entwickelungsgeschichte,* 1885, 1.

[9] Beard, J., Zoölogischer Anzeiger, 1884, 7, 123-126, 140-143.

had nothing to do with the formation of the thymus gland, for he said (6, page 211):

"Can it now be possible that the organ from the third pocket comes and disappears, and that the organ of the vagus leaves the vagus and forms the thymus? Prof. His' error no doubt lies in the fact that the sinus præcervicalis is long in developing. It forms a very conspicuous body in the region of the thymus. Just as this body from the sinus præcervicalis is disappearing, the thymus rapidly appears and takes its place."

Thus again one see the decisiveness with which Mall expressed his differences with his former teacher, both in letters to him and in print, so that there was no ambiguity either as regards Mall's views on the problem or concerning his profound respect for and gratitude to His. When he sent these reprints to Prof. His, he wrote: "Today I send you two reprints of some work, partly done with you and partly done by myself during last summer's vacation. I am really sorry that the work turned out as it did, for I should much rather have been able to retract my former statement regarding the thymus than to confirm it. I hope that you will not find these pages worthless."

The answer to this letter must have been exciting to Mall, for His had obtained some new human embryos and in reworking the subject he had found that Mall had been right—that is, he now saw that the thymus arises from the lining of the pharynx. He said, however, that there might be a small addition to the organ from ectoderm, and it is probable that His never appreciated the force of the evidence concerning the placodes, as Mall indicated later in his final reviews of the subject (17, 51). His[10] made the correction of this matter in the form of an open letter to Mall published in the same journal in which their articles had appeared.

This letter from His, as well as the correction in print, must have been a gratification to Mall, for it is but human to rejoice when one's work has been proved correct. But the reply again

[10] His, W., Schlundspalten und Thymusanlage. (Aus einem Briefe von W. His an F. Mall in Baltimore), *Archiv für Anatomie und Entwickelungsgeschichte,* 1889, 155.

shows an ideal relation between two scientific workers, and only in the greeting does one sense the difference in age.

"Honored Professor:

"In one sense of the term I am grateful that our controversy is over, for ever since my conclusion was so different from yours, I have not felt any too well over the subject. It would have been far more agreeable to me had I found that my view was incorrect.

"Regarding the possibility of the ectoderm aiding to form the thymus, I see no good reason why it should be so. The concentric corpuscles do represent the pathological changes that take place in the skin, but a new formation from the larynx or from the esophagus shows the same changes. If I do not mistake you, you compare the concentric corpuscles to the pearls of epitheliomata, and since pearls are formed in cancers of the alimentary canal above the stomach, endoderm may as well form concentric corpuscles as ectoderm. On the other hand, first, amphibian thymus glands have no concentric corpuscles, while in higher vertebrates (dog, cat) the thymus is frequently filled with cysts lined with ciliated epithelial cells. This fact would argue in favor of endoderm.

"The argument that makes it highly improbable to me that the ectoderm does participate in the formation of the thymus is that, as I believe, the sinus præcervicalis is the 'branchial sense organ' of the vagus. It does not seem possible that an involution of ectoderm should partly blend with a nerve and partly with a gland.

"In my work I am still engaged with connective tissue. Among a few new things, I find that the bone is quite full of elastic fibrils. Also, I find that striated muscle behaves quite differently at the tendon than has formerly been described. I send you a sketch of such a muscle ending which is obtained by boiling in dilute acetic acid. I also send you two poor photographs of a reconstruction of the stomach.

"Otherwise I am getting along nicely, only that I have to teach (?) somewhat, for I have been appointed assistant. Most of my time I have for myself. Last spring I worked through the development of the frog. This winter, with the aid of the Government, I hope to work the development of the codfish and to pay especial attention to the blood vessels.

"I am looking forward to going to Leipzig for a few months next summer. This has been my very strong desire for the last two years.

"With best wishes,

Very gratefully, (Signed) F. P. MALL."

The history of Mall's first problem revealed his ability. It is clear that he went to Leipzig without preliminary training in embryology, that in a brief year he acquired the technique of serial sections, and then, by the new methods of reconstruction, he mastered the complex forms of the gill arch region in the embryo chick and put his finger on the crux of the differences of opinion regarding the origin of the thymus. He saw that the transitory ectodermal placodes, then just beginning to be recognized by embryologists and now well-known as the homologues of the lateral line sense organs of fishes, were the cause of the confusion, for the one which joined the vagus was close to the position of the future primordium of the thymus. In two years Mall had established the endodermal origin of the thymus gland and his final summing up of the subject, published only a few years later, 1893, (17) in the chapters on the origin of thymus and thyroid for Buck's Reference Handbook of Medical Sciences, is a clear description of a complex region. Following an account of the same region in fish embryos, he said: "In mammals the condition is much simpler. The branchial grooves lie on the side of the body, are shallow on their dorsal side and deep on their ventral. As these arches fall over one another, the grooves, as well as the third and fourth arches, are buried in the side of the neck. While this is taking place, a pit is first formed, the sinus præcervicalis of His. From the dorsal side of the first groove an invagination unites with the ganglia of the fifth nerve; from the second, the invagination is to the ninth nerve; and from the third and fourth it is to the tenth nerve. A section through these organs in the region of the vagus and of the thymus is shown in Fig. 627." (This figure from 17 is reproduced here.) "The ectodermal invagination is absolutely blended with the vagus and is only in apposition with the thymus."

The simple woodcut of this figure gives such convincing evidence of the statement above as to explain fully the decisiveness of Mall's conclusions on the origin of the thymus. These articles in the Reference Handbook are still the best articles yet written on the embryology of the gill arch region. To the medical historian they might serve as models for a study of the growth of

medical thought, for they show how problems arise, how they depend on the development of methods, and how they are based

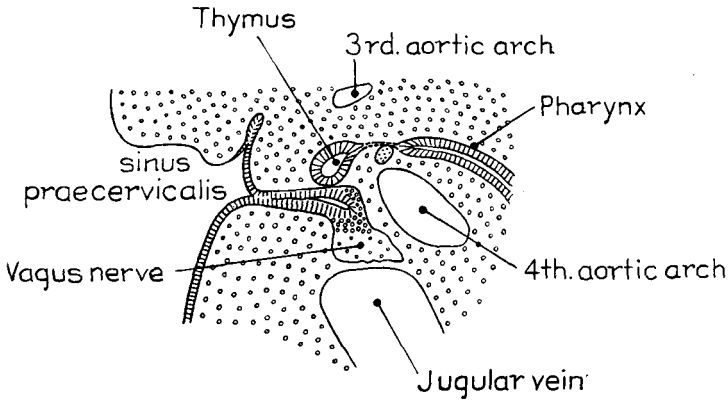

FIG. 1. (Fig. 627 in 17.) Section through the Thymus and Fundus Præcervicalis of a Dog's Embryo 10 mm. long: X 65. It is seen that the thymus is still in connection with the pharynx.

on previous work. To the student of Mall's development they reveal how profound a mastery of the work of the earlier embryologists he acquired in the laboratory of Professor His, and they show also his own originality and his independence of thought.

In October of 1885, Mall entered the laboratory of Professor Carl Ludwig. Just as had happened to him when he applied to work with His, he was not received at first, in this case because Ludwig's laboratory was always full of students and there was no room. By a fortunate chance, however, one of Ludwig's students left and, perhaps at the suggestion of His, Mall was offered this place; indeed, Mall's trunk was already on the way to the station when the invitation came. Thus began an influence which was the most dominating in Mall's life.

Ludwig suggested to Mall the study of the blood vessels and lymphatics of the small intestine, a problem in structure, but conducted without that artificial separation which certain techniques, such as the kymograph of Ludwig and the microtome of His, were soon to bring between physiology and anatomy. Under

the guidance of Ludwig, Mall learned the methods of injections of blood vessels and of lymphatics and made the specimens from which the well-known beautiful lithographic plates of his article were made. The brief introduction to this article, stating that while the study of the blood vessels of an organ could not give evidence of blood pressure or rate of blood flow, nevertheless, a complete picture of the pathways for the blood and lymph throughout an organ was essential for an understanding of the distribution of the force of the blood stream, shows plainly enough the guidance of the work along physiological lines, for which Mall was indebted to Ludwig.

In this study Mall not only got a concept of the entire vascular system of one organ, but he was able to make a reconstruction which enables one to visualize how all of the functioning tissues of that organ, the muscle coats and the mucosa, get their blood supply. I think that there is evidence that this was Mall's own contribution to the problem, for it was this which made Ludwig say of him that he had remarkable sense of structure in three dimensions—*"Raumsinn,"* as he call it. To gain this concept, Mall applied the methods of maceration and pulled the intestine apart into all of its various layers, so that he saw each layer of the organ in its relation to the rest; in other words, he took the intestine apart as a mechanic does an engine, so that from his own experience he knew the properties of each coat as a background for the study of its blood supply.

In the study of the complex vascular pattern he saw that the blood vessels of the intestine had developed in such a way as to give every segment of the organ an equal supply of blood and that the pattern of these vessels, complex as it might seem, could really be expressed as a simple branching of one artery into five different orders. Subsequently he was to show that this simple concept of five different orders of arteries for an organ had a general application to the vascular supply of all organs. His reconstruction made it easy to follow this pattern; the single superior mesenteric artery, with its rays of mesenteric branches, as vessels of the second order, and their anastomosing loops near the wall of the intestine, is easily seen and had, of course, long

been known. From these loops, long and short arteries, vessels of the third order entered the submucosa, giving rise there to the fourth order of distributing vessels, with a second series of anastomoses which completed the pattern for equalization of the blood flow. From the plexus of the fourth order, the mucosal vessels became broken up into the capillary bed around the crypts and under the epithelium of the villi. From this study, Mall got the concept of structural units of organs, using the villus of the intestine as the type. Thus the villus, with its single artery and capillary bed which it supplies, represents a final unit of function for which all of the various coats of the intestine are adapted.

In like manner Mall found that the lymphatics of the intestinal wall may be injected, if the needle enters the right level. The difficulty of lymphatic injections in the adult animal is due to the abundance of the valves. For the intestine, an injection of the central lacteals can be made only when the needle penetrates into the plexus at the base of the crypts, since there are no valves between these vessels and the central lacteals; while the two main plexuses, the one in the submucosa and the other between the two layers of the muscle, are demonstrated when the needle enters these two levels.

This study of the walls of the intestine, with the picture of vascular and lymphatic supply, has so completely entered into the body of our knowledge that one can say without exaggeration that no one studies the function of this organ without reference to Mall's work.

The years with His and Ludwig had been far more to Mall than just guidance in scientific problems, for the whole range of scientific thought and of general culture had been opened up to him. Especially in the year with His, he must have read a prodigious amount and it is clear that he had been led to follow the scientific work of the master minds. Also he attended many clinics, he followed cases to autopsy and studied the pathological sections. His letters home showed that art and literature, the drama and music had come into his ken for the first time; he wrote to his sister to read Shakespeare, not once but a dozen times and then its beauty would begin to appear. Likewise he

mastered Goethe as it can be done only in Germany with the aid of the theatre as well as by reading. Between him and Ludwig there developed a rare friendship, and in the companionship of these two men, both in the laboratory and in Ludwig's library at home, there was revealed to the younger man an idealism and a devotion to scientific research which was to mean so much to the development of American medicine. When Mall said good-bye to Ludwig, and tried to thank him for all he had done for him, Ludwig said to him, "If you feel this way about it, pass it on." This is the key to Mall's devotion to the cause of research and to the teachings of this master Mall was faithful unto death. None of Mall's letters to Ludwig has been kept, but the following one from Ludwig to Mall shows what the worship of Nature meant to Ludwig and gives a glimpse too of what the young American student meant to Ludwig.

"Dear Professor,

"So you are happy in your new position, provided with everything necessary to wring from Nature her all too long guarded secrets. The world hopes,—she demands imperiously from you great results, which can only be accomplished with the severest labor. But the world will not thank you for them, rather she will look upon all that you do as only a duty, as a small return for what you owe. So it is when we are thrown entirely upon our own resources; quietly and alone the work goes forward and the nearer we approach to the eternal works of magnificent Nature, so much the happier we become; and finally we lose sight of all the petty intrigues around us and become wholly absorbed in our work.

"The traditional isolation of the life of the research worker is broken, when a spirit akin to his comes near. Those are the days of the greatest happiness when in the rivalry and the strife to understand Nature, now the one, and then the other, opens up his heart. So was it when we two worked together, but not often comes such fortune into one's life.

"You had so much of interest to tell me of your work on the stomach; gladly would I hear more of it, but perhaps it has not yet been printed. Send me a reprint when it appears, I hope in the near future. I rejoice over every step in advance: prodigal Nature is so niggardly with us research workers.

Faithfully yours, (Signed) CARL LUDWIG."

Mall had gone to Europe a crude and uncultivated, but very gifted youth; and in three years he had jumped to his full stature and returned a mature man far more European in type than American, except in his ardent love of democracy. His mind had in that brief time grasped the culture of Europe and from then on he seemed singularly adult; he became a directing force rather than the directed. More than anyone I have ever known he seemed released from fear of criticism from his fellows, because he was sure of the principles which guided him and because he saw the issues involved clearer than they. In this release from fear lay Mall's great strength.

The period of his return to America was one of remarkable awakening here. Gilman had already established a university along German lines in Baltimore and he and Welch were then planning a new medical school. Clark University was soon to be started, and then Chicago University—both founded as universities and not on the basis of the American college.

After the year in the laboratory of Prof. Ludwig, Mall wanted to take a year in pathology under von Recklinghausen, but it was now impossible for his father to help him further and he had to seek a position in which he might make his living. Mall had now decided to go into scientific medicine. In 1885 he wrote to his sister, "I can see back a year of great improvement in myself, I have made the acquaintance of and worked with two of the greatest professors living. Whether that will do me any good only the future can tell," and again, "My aim is to make scientific medicine a life work. If opportunities present I will. This has been my plan ever since I left America and not until late, since having received encouragement, have I expressed myself. I shall, no doubt, meet many stumbling blocks, but they are anticipated." The encouragement which he referred to was undoubtedly the faith of Ludwig in his ability. In 1885, William H. Welch, whom Mall had met in Leipzig, had been appointed Professor of Pathology in the Johns Hopkins University at Baltimore, as the first step toward the founding of the Johns Hopkins Hospital and Medical School, and Mall now applied to him for a position in the spring of 1886. Welch answered Mall

that the chances for scientific work in America were very scanty, but that he would try to get him an appointment. The appointment was, however, slow in coming and it was a period of great anxiety to Mall; of the event Dr. Welch has written to me: "When I started work at the Johns Hopkins in the autumn of 1885, I managed to have one of the twenty fellowships granted by the University given to pathology, and when Mall was ready to start he applied for one of these and became, I think, the first Fellow of Pathology. He helped to some extent with the teaching, but the fellowships were intended for research and he followed mainly his own lines. Among these was his study of the fermentative or digestive powers of the various species of bacteria upon the different tissues—fibrous, reticular, elastic—and he obtained interesting results, only in part published. His especial interest was reticulum. Mall was one of the group—Councilman, Halsted, Herter, Booker, Bolton, and others—who worked in the Pathological Laboratory before the Hospital was opened in 1889, a really creative, formative period for the future hospital and medical school."

Thus for the years 1886 to 1889 Mall was a Fellow, then Assistant, in pathology under Welch in the Johns Hopkins University. In the fall of 1886, Mall wrote to His that he planned to go on with the study of the intestine, and that his work would probably be from the pathological standpoint. But the events proved that he was wholly free to follow his own bent, which was more physiological. Mall seemed to jump at once to his full stature. His work on the stomach—just referred to in Ludwig's letter—representing perhaps his first work done without guidance, has always seemed to me one of his most interesting. Here was an organ, built from the same simple tube as the intestine embryologically, and yet entirely lacking the simplicity and the symmetry of the intestine. From every aspect it was divided into three zones which he studied first from their marked differences in thickness. By stripping the coats apart he found that every coat differed in the three regions, though the most striking difference was the thickness of the circular muscle coat of the pyloric region, fully twice as thick as in the middle region.

He observed that under varying functional states the dilatation of the pyloric region was slight; then by artificial distention, he found that at first each part expanded equally, until the folds of the mucosa were flattened out, after which the cardiac zone would continue to expand until it ruptured, while the rest of the organ showed little or no change. During digestion it was clear that some mechanism caused a regional distribution of blood, because the middle zone was always hyperaemic and there was an active contraction of its muscle coats, while the pyloric region remained firm, hard, and pale. Indeed, several hours after ligation of the coeliac axis, the middle portion would still be hyperaemic and its mucosa would be found completely digested, showing that its glands produced the digestive ferment, while the mucosa of pyloric and cardiac regions would still be normal. He passed in review all of the evidence then available for the view of Heidenhain that the chief cells secrete pepsin and the border cells the acid, since so convincingly demonstrated by Harvey and Bensley,[11] because the region containing the glands with these two types of cells, that is the middle, or fundic region was so favored by the circulation.

Unlike the intestine, which is supplied from one artery, the stomach is supplied from the coeliac axis, whose three branches, hepatic, gastric, and splenic, supply three different organs. Mall was concerned with finding out why the fundic region received the greatest blood supply. The anastomosing loops between the first branch of the superior mesenteric artery, with the hepatic, and then in turn with the gastric, he viewed as a continuation of the intestinal anastomosing loops, and from these arches the pyloric region was supplied with smaller, but at the same time, more numerous branches. The splenic system, on the other hand, with the right and left gastro-epiploic veins, formed a system of arches entirely peculiar to the stomach. Thus, while the pyloric part of the stomach was supplied from small hepatic branches, the fundic region, from which the pepsin and the acid were obtained, was supplied from both gastric and splenic vessels. This

[11] Harvey, B. C. H., and Bensley, R. R., *Biological Bulletin*, 1912, *23*, 225.

he said might prove to be of great significance because this is the zone with the greatest blood supply and because the spleen contains the most blood just at the end of digestion. The middle zone of the stomach he found supplied by the largest branches, which entered the submucosa and there formed a double network of arteries, the wider meshed one with free anastomoses. This wider meshed network lay in the middle of the submucosa, in contrast to the position of the major arterial plexus of the intestine which was closer to the circular muscle. The meaning of this striking difference in the position of the main distributing vessels he found by making an injection of the vessels of the stomach with the muscle cells still alive, and then forcing their contraction. This showed that the outer zone of the submucosa then became smaller in area, while the inner layers became folded with the mucosa, and the vessels were suspended between these two different zones of connective tissue fibers. The blood supply of the intestine had been adapted to bringing the capillary plexus beneath the functioning epithelium of the villi, that is, into the area of absorption. The pattern of capillaries in the stomach was quite different, for the arteries which penetrated to the mucosa broke at once into a candelabra-like arterial plexus around the depths of the gastric glands, this being the main functioning zone of the gastric mucosa, and there was a double plexus of veins, one just beneath the epithelium of the gastric pits on the surface of the stomach, and the other at the base of the glands. Thus, as Mall put it, the intestinal mucosa had two arteries, one to the crypts and one to the villus and one plexus of veins, while the gastric pattern was the reverse, one artery and two venous plexuses. In both cases, the arterial capillary plexus surrounded the main functioning zone of the organ, in the one case the surface, absorbing epithelium, in the other case the glandular, secreting epithelium. The transition between these two types of circulation he showed at the pyloric valve.

During these years Mall was still studying the intestine (20) with methods which might well be applied again. He became interested in the type of contractions and the influence which they had on the circulation. Measuring the cross section of the

different orders of vessels throughout their course from the mesenteric artery to the portal vein, he plotted a curve of these areas and showed that there were two areas of extreme expansion of the vascular bed: first, there was a sudden and marked expansion in the capillaries of the mucosa, followed by a fall in the veins at the base of the mucosa, and still more as they passed through the muscularis mucosae, and then succeeded by a still greater rise in the plexus of veins in the submucosa, leading finally to an area of the main portal vein not much larger than the original artery. In the plexus of the submucosa, where this remarkable expansion of vascular area occurs, are numerous retia mirabilia, still inadequately understood.

Mall studied the power of distention of the intestine on the basis of its connective tissue coats and the nature of its contractions on the basis of its muscular coats. The submucosa, isolated and macerated, or dried and distended, could be seen to be made up largely of white fibrous tissue, in the form of two opposing spirals of fibers, which came to lie more at right angles to each other as the wall was distended. He believed that this arrangement of the inelastic fibers was adapted to aid the muscles in changing the lumen of the intestine.

The elastic tissue, instead of being uniformly distributed between the white fibers of the submucosa, as it is in the skin, he found in two layers; one of these was very finely meshed and could be stripped off from the submucosal surface of the muscularis mucosae. It was filled with holes which marked the position of the mucosal arteries. The second elastic coat was of coarser mesh and lay outside the muscularis mucosae, and its mesh made a pattern for the bases of the crypts of Lieberkühn.

It was these studies that made Mall realize that the surgery of the intestine depended on the properties of the submucosa. Halsted told me that it was Mall who made this suggestion. In Welch's department in those early years, one sees an example of joint research at its best, for Halsted[12] worked out his methods of intestinal anastomosis, while Mall both assisted with

[12] Halsted, W. S., *American Journal of Medical Sciences*, 1887, *94*, 436, and *Johns Hopkins Hospital Bulletin*, 1921, *32*, 98.

the operations and studied the results from the structural standpoint. The histological work was published later by Mall (21) and showed that when the sutures entered but did not penetrate the submucosa, the best results were obtained. The submucosa, with its predominance of white fibrous tissue, was the only coat strong enough to hold the sutures; the muscle coat, of course, allowed the sutures to pull out, while when the needle penetrated the muscularis mucosae there were two dangers, one of infection along the sutures and, failing that, when the muscularis mucosae was torn, of a marked new growth of the glands into the zone of the submucosa.

In his study on intestinal contraction, Mall made wide use of the work of previous observers, showing how much he had learned under Ludwig and from his later reading. He saw that intestinal contraction had to be studied in connection with the blood supply, for on contraction the intestine invariably became paler, harder, and longer. Under Ludwig, Mall had learned of the two kinds of intestinal contraction, first, the local rhythmical, regular contractions, and second, the peristaltic waves. From his own studies, he found that there were three types of contractions to be considered, first, the rapid peristaltic waves so frequently seen after the death of an animal, which pass rapidly over the intestine and may go in either direction. This type of wave cannot be demonstrated in the living animal except under conditions that may be considered as pathological; and Mall considered they were not present during normal digestion and were only aroused by strong irritants.

The second form is the normal peristalsis of digestion, with a rate about 1/90 as fast as the abnormal contractions. This wave is always in the one direction, which Mall proved by getting Halsted to make several operations involving a reversal of an intestinal loop (22). The animals recovered from the operation and for a short time were well and then became ill. When killed it was found that the reversed loop was dilated most markedly at the proximal end, where there was a piling up of intestinal contents and an ulceration of the mucosa. This demonstrated

that the mechanism of the normal peristalsis lies within the wall of the intestine itself and that this wave is irreversible. The third, local, rhythmic contractions, now known by the work of Cannon with the newer technique involving X-rays and the fluoroscope to be significant in the breaking up of the food and the mixing of it with the digestive fluids, Mall studied with reference to the circulation. He found that each contraction of the circular muscle expelled blood from the plexus of veins in the submucosa and raised the pressure in the portal vein. He found that each of the rhythmic contractions in the intestine was followed by a wave in the superior mesenteric vein. Thus he studied the rhythmic contractions as giving rise to a venous pulse to aid in the hepatic circulation. He added these words (20, page 72): "Whether our rhythmic wave is present in the living animal has not yet been shown. This is a subject which, when investigated, will probably yield valuable and interesting results." And his final summary was (20, page 74): "To conclude, we may state that with this arrangement, each contraction of the muscle-walls of the intestine not only propels the contents of the intestine downward; not only aids in mixing the chyle, but also expels blood from the intestine into the portal vein, makes room for new blood, and thus acts indirectly upon the liver."

From the preceding pages, it is clear that the studies on the wall of the intestine made in Ludwig's laboratory, as well as the studies just described, focused Mall's attention on the subject of the fibers of the connective tissues. To this interest the work of His also contributed, based as it was on Bichat's concept of the importance of the connective tissues, an idea which His had analyzed and developed.

In the study of the intestinal and gastric walls, it had been the white fibrous coat (submucosa) and the elastic membranes which had occupied Mall's attention. Now he realized that the reticulum must also be considered. Years before Billroth (quoted by His in 1861) had called attention to the reticular framework of lymph nodes and had described it as made of multi-polar cells, but

both Ranvier [13] and Bizzozero [14] had shown that this framework is actually made up of a network of fibers on which the cells described by Billroth rest. In 1861 His [15] had shown that the reticulum is best seen when frozen sections of lymph glands are shaken in a test tube of water, until most of the lymphocytes are removed, and undoubtedly these preparations of His stimulated Mall's mind. Mall then discovered that the reticular network of fibers not only makes the framework of the lymphoid tissues, but also forms the supporting tissues of all the organs, and his work is considered as having established the fact that the reticular framework of organs is independent of cells. Mall showed that reticulum is so labile a framework that it adapts itself to and supports all of the functioning cells of each organ. Thus, when the cells of each organ, for example, the liver cells, the gastric glands, or all of the secretory cells of the pancreas are removed, the reticular framework so faithfully outlines the patterns of these cells that each organ can be told by the framework alone. When it is realized that this framework also conforms to the pattern of new growths of cells, the significance of this tissue, both in normal structure and in pathological processes can be grasped.

Mall discriminated the fibers of the connective tissues by various chemical means; on the one hand, the yellow elastic tissue, and on the other hand, the two closely related types, the white fibrous bundles and the reticular fibers. The yellow elastic tissue, with its protean forms, fibers, fine and coarse, dense networks and membranes, he found to be made up of two different substances, an outer, continuous membrane, not taking any stain, and an inner, discontinuous, stainable material, giving the appearance of fenestrae to the membranes. The elastic tissue he found resistant to acids and alkalies, unless boiled in strong concentration. It, however, could be digested slowly in pepsin, rapidly in pancreatin and papain. In this process, it was the inner

[13] Ranvier, L., Traité technique d'histologie. Paris, F. Savy, 1875, 689.

[14] Bizzozero, G., *Rendiconti, Real Ist. Lombardo,* 1872, *5, 2.*

[15] His, W., Untersuchungen über den Bau der Lymphdrüsen, Leipzig, W. Engelmann, 1861.

stainable material that was attacked by the digestive enzyme. The converse was true of the white fibrous tissue and the reticulum, for they were destroyed by acids and resisted digestion. These observations led Mall to the study of putrefaction, that is to say, he made use of bacteria as ferments and in these studies made interesting discoveries concerning bacteria. Thus, in a letter to Stanley Hall, April 21, 1889, concerning the position which Hall had offered to Mall at Clark University, Mall wrote:

"It is my plan to sail for Europe on June 1. I hope to pass what remains of the summer semester in Ludwig's laboratory. My acquaintance with the master ripened into friendship and I long to see him. At the same time, I desire to obtain some advice on certain points in physiological chemistry. My work this year, I am sorry to say, drifted into the subject of symbiosis and into the subject of putrefaction. Some of the observations are extremely interesting. A marked example is as follows. Certain anaerobic microorganisms will not grow when they are exposed to air unless they are mixed with facultative anaerobic organisms. I think also that I have considerably improved the method of cultivating anaerobic organisms."

He found that certain aerobic bacteria, which did not digest elastic tissue, nevertheless enhanced the power of anaerobes to digest it. Thus he discovered that the aerobic organism, in using up the oxygen, made favorable conditions for the growth of the anaerobic germs. These observations demonstrate Mall's originality in making important new observations in the then new field of bacteriology. He found that an anaerobic organism, which he got from garden soil and termed the "knob bacillus," on account of its tendency to grow spores at one end, when combined with Brieger's bacillus, gave a characteristic color reaction with elastic tissue, so constant as to be diagnostic of the digestion of elastic tissue. The effect of the bacteria on the elastic tissue he found to be exactly like that of the digestive ferments, namely, a preliminary splitting of the central stainable material of the fiber. He said that it was probable that the bacteria acted through ferments, though he could not isolate them. In the caseous tubercles in the lungs of cattle and of man, he found that the elastic tissue showed the same sort of damage as with the

digestive ferments, the process starting always in the center of the caseating material.

The property of the reticulated tissue in resisting the action of ferments made it possible to digest out the cells of the organs and reveal the reticulated framework. Mall's beautiful preparations of reticulum are known to all histologists. Of the lithographic plates of these preparations Ludwig wrote to Mall, November 16, 1890: "Day before yesterday on November 14th, I spread your beautiful plates before the astonished sight of the Fellows of our society."

Indeed, several letters from Ludwig showed that Mall had interested him so much in the experiments with digestion of connective tissue fibers that he was also working with the method. The plates referred to demonstrate how completely each organ can be identified from its framework. Some of the most beautiful of Mall's preparations were made with the spleen; the method was as follows: the spleen was removed, care being taken not to injure the capsule except for two small cuts at each end, into which small glass cannulae were tied. The entire organ was then submitted to digestion with pancreatin or with putrefactive bacteria. When the splenic cells were digested out, the spleen was attached to the water tap and washed with a slow stream of water until clear of debris. Then the entire reticular framework was immersed in a solution of magenta, and then distended and dried with air. The entire framework of reticulum was then exposed by dissecting off the capsule. In these original studies Mall found slight chemical differences between the reticular fibers and the white fibrous tissue, but eventually he believed that the major difference was morphological, in that the white fibers ran in wavy bundles and never branched, while the reticular fibers were always in networks. In this early work Mall said that elastic tissue is present only in vertebrates that have a bony skeleton and that it appears when the bones begin to ossify. Also, at that time, he believed that the fibers formed outside of the cells, which is the view accepted at present, though later, in a study of the development of connective tissue fibers, Mall changed to the view that the first fibrils

are formed within the cytoplasm of the so-called fibroblast. This view, on what is still conceded to be one of the most difficult phases of histology, is one of the few observations of Mall which has not stood the test of time. It is clear enough that to tell whether the delicate fibrils of the connective tissues are actually within or on cells is not possible by observation alone and the matter must be subjected to the experimental test of seeing whether fibers, chemically identifiable, can be developed without cells, as in tissue culture (Baitsell).

The presence of vasomotor nerves for the portal vein is regarded as one of the most important of Mall's discoveries. The first observation which led to this discovery was in the work on the intestine done in Ludwig's laboratory, where Mall (2) noted that the intestinal and mesenteric veins, interpolated as they are between two systems of capillaries, those of the intestine and those of the liver, had an unusually marked circular musculature and that under certain conditions of injection these veins were irregularly constricted. In 1890, Mall (8) published the first demonstration of motor nerves for the portal vein. In this paper he stated the problem clearly, saying that while in Ludwig's laboratory he had already seen constrictions of the portal vein due to contractions of the ring muscles of the portal vein; that when one considered that the portal vein was in lieu of a second artery to the capillaries of the liver, it was easy to hypothesize vasomotor nerves to this vein. To prove their presence it would be necessary first to eliminate all blood flow from the hepatic artery in the living animal and then stimulate the splanchnic nerves. Again in 1896, in his studies on the circulation of the stomach, Mall referred to the matter, saying (19, page 23):

"Recently I have found that irritation of the splanchnic nerve causes contraction of the walls of the mesenteric vein. All these influences brought together in all probability have a marked effect on the circulation through the liver and finally upon the circulation in general."

The final publications on this important subject, the first in German (13) in 1892, and the second in English (23) in 1896,

contained the complete proof of the action of those nerves. After Ernst Heinrich Weber showed that stimulation of the splanchnic nerves or irritation of the spinal cord caused a constriction of the arteries, it was thought that this was sufficient to account for the rise in pressure in the vena cava and aorta following the stimulation of these nerves. But Mall said that since the capacity of the arteries is insignificant as compared with the veins, it was necessary also to take into consideration the possible effect of a contraction of the veins, especially when it was shown that dilatation of the abdominal veins had a marked effect in lowering blood pressure. Mall proved the presence of motor nerves to the mesenteric and portal veins and their effect in raising blood pressure in the following manner. He found that when the aorta was tied just below the origin of the subclavian artery, the blood flow was completely stopped. This was long before the days of thoracic surgery and the operation, first made from the front at the level for good exposure of the splanchnic nerve was difficult and did not completely eliminate the flow of blood from the aorta. Mall finally devised an operation which was feasible, going into the thoracic cavity from the side, beneath the pectoralis major between the second and third ribs; from this position it was easy to tie the aorta just below the origin of the subclavian. With this method, the arteries below the ligature became entirely empty while the portal vein and its branches remained distended with blood. When in such a preparation the splanchnic nerve was stimulated, these veins contracted and emptied themselves completely. Then he showed also that even with the aorta intact, one could see the mesenteric veins and the portal contract under the stimulation of the splanchnic nerves, while an effect on the vena cava could not be determined on account of the pulsation of that vessel. He also demonstrated the rise in blood pressure in the portal. These studies carried the following acknowledgment to Ludwig (23, page 112):

"Most of the work recorded in this paper was performed in the laboratory of Professor Ludwig, and a portion of it dates from Clark University. It has been interrupted at various intervals and the reader will excuse its incompleteness. The diffi-

culty in performing the various experiments and the extensive bearing of the question are my apology. To exhaust this work will require many more hours of patient labor of combined forces (See also Thompson, *Arch. f. Physiol.,* 1893, and Bayliss and Starling, *J. of Physiol.,* 1894. Vol. 17). The substance of this paper has ben published in German (13) but in a different form; it bears the stamp of Ludwig. To that master I owe much,—all."

During the years that Mall was Fellow in Pathology under Welch, he worked on the development of the thymus, he made the model of the circulation of the vessels of the dog's stomach, he made all of the studies on intestinal contraction, the studies of intestinal anastomosis, and of the reversal of the intestinal loops with Halsted as well as the studies in bacteriology as applied to the fibers of the connective tissues and he performed the experiments proving vasomotor nerves for the portal veins just described. Thus were passed four active and remarkably fruitful years.

In the spring of 1889, Mall accepted a position as Adjunct Professor of Anatomy at Clark University, in Worcester, Massachusetts, and thus after years of training in embryology, physiology, bacteriology and pathology, he finally decided to go into anatomy, basing his decision on his interest in structure and on his talents as Ludwig had seen them. Stanley Hall, who had been in psychology at the Johns Hopkins University while Mall was in Welch's laboratory, was organizing the new university and Mall joined his faculty, which was as brilliant a group as was ever assembled in America. There was Michelson in physics, Nef in chemistry, Donaldson in neurology, Whitney in zoölogy, Mall, Lilly, Mead, Jordan, McMurrich, William Snow Miller, and others. It was to be a university in the true sense, with adequate time and facilities for research, and Mall spent three active years there. It was here that he finished the work on the reticulum and made the final experiments on the nerves of the portal vein. Most of his time, however, was now spent in embryology. Already while in Baltimore, or more especially in the summers at Woods Hole, Mall had been studying embryology, stating in his letters to His that he was working on the development of frog and fish embryos. Moreover, he began at this time the study

of the early development of the liver, seeking to reconstruct the liver lobule.

When Mall had returned to America, Professor His had given to him several human embryos cut in serial sections for study. When he had studied them he returned them to His who, however, gave them back to form the nucleus of a new collection to be made by Mall. Mall began to write short articles to be distributed to doctors about the preservation of the valuable human material that came into their possession. While still in Baltimore he had received a well preserved specimen, entirely normal, which he estimated to be twenty-six days old. It measured 7 mm. and had thirty-eight muscle plates. Mall had learned the Born method of three dimensional reconstruction with wax plates in His' laboratory and he now made several models of this specimen. It was closely like the well-known His embryo, Br_3. This was the first embryo ever modeled in America and at the time it was the most complete study yet made of any human embryo. This work laid the foundation for Mall's knowledge of embryology. Especially interesting to him were the form of the central nervous system and the cranial nerves. At this time he began the investigation of the coelom, making a cast of it by cutting out the plates and filling the cavity with plaster. Here again he showed the well developed form sense which Ludwig had noted. January 17, 1890, Mall wrote to His, from Clark University:

"My work progressed better than I had anticipated. The human embryo of which I told you (7.5 mm. long) has already been modeled after Born's method. The model brought out most decidedly the so-called neuromeres and many other points which were new to me. I am busily engaged with the liver and find that at first the liver cells grow into the omphalomesenteric vein and soon break it into many small vessels. I have also succeeded in isolating in large quantities the fibrils around the liver capillaries, as described by you. In section they seem to be identical with the reticulum of lymph glands. I hope ultimately to be able to give a reconstruction of the liver lobule and also its development."

And then later, December 19, 1900. "I have been quite busily engaged all autumn on the development of the liver and the pleuro-peritoneal cavity by means of corrosion methods. The way is quite round about. I first make the plate drawings and cut out the portions I desire to reconstruct, and then cast them with metal (Wood's metal). This method proves to be very valuable with arteries and all small spaces."

This was the start of Mall's interest in the development of the coelom and he ultimately went back to early stages, restudying the work of Budge on the development of the coelom in chick embryos. Budge had made injections of the true coelom and the extraembryonic coelom in chick embryos, and in later stages had injected the thoracic duct and thought that some of the original spaces of the coelom became the lymphatic system. It was these studies of Budge which suggested to Mall the problem of the origin of the lymphatic system, which he subsequently offered to me as a problem in his laboratory, and thus it is interesting to read (17) that Mall had studied Budge's actual specimens in His' laboratory. It proved subsequently that the lymphatics form much later, after the body cavities are well established. Mall followed with reconstructions all of the complex forms of the development of the pleural-peritoneal cavities, including the separation of them by the development of the diaphragm, as well as the forms of the greater and the lesser peritoneal cavities.

Mall now began to study the nervous system, specifically with reference to the development of the eye in amphibian forms, Amblystoma and Necturus. This work was begun at Clark University (15) and of it he wrote to His, January 31, 1892: "I hope that my communication will not be considered by you as worthless as you know I am not too well posted on the literature." As a matter of fact this paper is far more than just the embryology of an amphibian eye; it shows a remarkable insight into the problem of the histogenesis of the central nervous system, a subject then in its infancy. Mall's first conception of the neurone doctrine was based on the early work of Remak and

Helmholtz, who, soon after the discovery of the cell by Schleiden and Schwann, had postulated that the nerve fiber is an outgrowth of a nerve cell. This concept was then made more likely through the discrimination of axone and dendrite by Deiters as well as by the now well-known methods for specific staining of neurones devised by Golgi and Ramon y Cajal. His had, however, brought the strongest evidence of the outgrowth theory by direct observation in embryos of a nerve fiber which was a continuation of a single nerve cell. This concept was subsequently conclusively established in Mall's department by Ross G. Harrison[16] many years later, in 1910, by watching the outgrowth of the fiber in tissue cultures, a method which he devised for the specific study of this problem. In 1893, Mall judging that the balance of evidence at that time was in favor of the neurone doctrine, developed the concept that there was a specific polarity of the developing neurone, in that the receiving pole of the cell always pointed to the surface of the ectoderm, or toward the central canal of the central nervous system. The lining of the central canal was, of course, originally surface epithelium on account of the involution of ectoderm to make the nervous system. Mall described the pattern of each of the sense organs, from the simplest one in the olfactory nerves to the most complex in the retina, on the basis of this polarity. He observed that not only in the retina but in the central nervous system as well the polarity of the nerve cell was foreshadowed by a constant position of the axis of cell division, the axis always being parallel to, or the plane of the spindle perpendicular to the original ectodermal surface. The concept involved specific growing zones in the nervous system, which in the developing retina he found to be always in the periphery of the optic cup and primarily at the surface of the central canal. W. Müller [17] had suggested in 1874 that the optic nerve arose in the retina and grew to the brain; this was demon-

[16] Harrison, R. G., *Journal Experimental Zoölogy,* 1910, *9,* 787.

[17] Müller, W., Festgabe an Carl Ludwig, *Beiträge zur Anatomie und Physiologie,* Leipzig, F. C. W. Vogel, 1874.

strated later by His [18] and by Martin in 1890 [19] for mammalian material, and in the next year by Froriep [20] who reported a shark embryo in which the optic nerve had started from the retina but had not yet reached the brain. Mall now reported the same observation in the amphibian material. This series of reports in quick succession on this important point shows that it was a timely subject. On January 31, 1892, Mall wrote to His about his observatons on the retina and the growth of the optic nerve in amphibia and enclosed a diagram in which he outlined his concept of the polarity of the neurone, as a general law of growth of the nervous system. To this letter His replied, February 27, 1892, "Your scheme for the growth of fibers of the neuroblasts has, however, exceptions. In the forebrain, most of the cells develop their fibers toward the ventricle." To this letter Mall replied, March 17, 1892:

"Your objection to the 'polarity of the nerve cells' I think can be met. Recently the beautiful paper of von Lenhossék, as well as my observation that various sense organs in Necturus develop fibers to the central nervous system, gives new evidence. The ear, according to Ayers, is formed the same way. As regards the cerebrum I think that the sketches I enclose will also overcome the difficulty. The case you mention to me is identical with the young retina where also the cells are directed in the wrong way. This may only indicate that cells are wandering.

"In order to form the grey substance in the brain or the commissures, the cells would have to develop their fibers on the wrong side. . . . But the more I think of it, the more I believe that there is a great law of growth at the bottom of it all and that the polarity of cells is present in all animals. I hope that you will

[18] His, W., Histogenese und Zusammenhang der Nervenelemente. *Archiv für Anatomie und Entwickelungsgeschichte,* 1890, Supp.-Bd., 95-117.

[19] Martin, P., Die Neuroblasten des Oculomotorius und Trochlearis. *Anatomische Anzeiger,* 1890, *5,* 530-532. Zur Entwickelung der Netzhaut bei der Katze. *Zeitschrift für vergleichende Augenheilkunde,* 1893, *7,* 25-41.

[20] Froriep, A., Ueber die Entwickelung der Seenerven. *Anatomischer Anzeiger,* 1891, *6,* 155-161.

forgive me for speaking of theories instead of facts, but I believe they will cover all the known facts with the exception of the spinal ganglia." In the paper on the retina, Mall explained that the difficulties in following the cells of the spinal ganglia were due both to the fact that in their division after separation from the neural crest all orientation to the original position was lost and also that the sensory cells, originally bipolar, soon became unipolar. Continuing the letter to His, he said, "At any rate, if you will be forgiving and feel that the question is worth criticizing, I shall be very thankful." Then on December 27, 1892, Mall wrote again to His, now from the University of Chicago: "I am at present occupied with the polarity of cells in the various portions of the brain, and find that it holds in many portions, as in the corpus dentatum and olivary body." Again, Oct. 9, 1893, he wrote to His, "I have sent you a small paper on the retina. Forgive it." These references to the patterns of growth of neurones in the letters to His are exceedingly interesting in the light of the theory of neurobiotaxis as developed by Ariëns Kappers. Realizing that he was dealing with an obscure field with somewhat vague hypotheses, Mall clearly foreshadowed Kappers' theory that throughout the central nervous system each group of developing neurones is oriented in the lines of the incoming sensory impulses. Thus again one sees the originality of Mall's mind, for, in taking up a new field, neurology, he made observations which have stood the test of time, sensed their meaning and judged the force which directs the path of the growth of neurones.

When Clark University was first founded, it had seemed to its faculty that it might develop into what we now know as the research institute; but two factors militated against this, first that Jonas G. Clark, who founded it, was not sympathetic toward this idea nor had he any realization of the endowment necessary, and secondly that Stanley Hall failed to take his faculty into his confidence over his difficulties and that he lacked the power to create for them the peace of mind essential for research. It is now known that when Mall once realized that the others felt as he did, he took the steps which solved the difficulty. Mall

was an intimate friend of R. F. Harper, the brother of President Harper, then organizing a faculty for Chicago University and in the spring of 1892, Whitman, Michelson, Nef, Bolza and Mall went to Chicago University.

The correspondence between Mall and Harper shows that it was Mall who persuaded Whitman to go to Chicago University, a decision so momentous for Chicago. This, however, was not his only service to the University, for though he remained there only one year, through his friendship with President Harper and through the wisdom of his counsels, Mall not only founded the Department of Anatomy in the University but he was a powerful factor in the organization of the whole biological department. Here he developed the plans by which each department of the University might develop into an Institute, with the encouragement of research as its major activity both for faculty and for students.

In the spring of the next year, 1893, Mall was offered the Professorship of Anatomy at the Johns Hopkins University, where the new medical school was to be opened in the fall. This was the third professorship which Mall was offered in four years' time—Clark University, Chicago University, and the Johns Hopkins University. It was, of course, Welch who had called him back to Baltimore and Mall made the decision on the score that he could more quickly organize a department there to his liking, one in which he could devote a greater proportion of his time to research. He was now thirty-one years old and with this decision the period of his training may be considered as complete. His work during the years between twenty and thirty had shown his originality and his power in mastering new fields. He had established the endodermal origin of the thymus and clarified its relation to the lateral line sense organs; he had worked out the vascular supply of intestine and stomach so completely that the work still remains the standard; he had studied the physiology of the movements of the intestine and had aided in working out the surgery of intestinal anastomoses; he had discovered the vasomotor nerves of the portal vein; he had improved the methods for cultivating anaerobic bacteria, showing that they would grow

in the presence of facultative anaerobes because they used up the oxygen; he had used bacterial ferments as well as digestive ferments to work out the nature of the reticular framework of organs and had made valuable contributions to an understanding of the laws underlying the growth of the neurones of the central nervous system.

Mall's mature years were spent in Baltimore; his profound influence on medical education, his share in the founding of anatomical journals, in the leadership of scientific societies, and finally in the establishing of a Research Institute for Embryology are part of the story of his life. His effect on medical teaching in this country was due not only to the originality of his ideas on education but also to the power of his example; gifted with powers of organization, he nevertheless continued to put his major efforts into research to the very end.

His research work in Baltimore may be classified under three heads: embryology, the structure of organs in the adult as adapted to their functions, and a beginning in anthropology.

Mall now made a series of embryological studies, all closely connected in thought; they included the development of the diaphragm in human embryos, the development of the ventral abdominal walls, the development of the body cavities and of the loops of the intestine. In the study of the diaphragm and of the body walls he was interested in the primary relation of the nerve to its myotome or muscle mass as a guide to the amount of wandering and differentiation of muscle groups. Subsequently he suggested the study of this principle to two of his students, Dr. Charles R. Bardeen and Dr. Warren H. Lewis, who followed the development of the muscles and nerves of the arm buds in human foetal stages. Concerning this work, His wrote to Mall that the pages of the *American Journal of Anatomy* gave brilliant evidence of Mall's activities and those of his students. The figures of the body wall and of the extremities he thought excellent and that they showed a rich material.

From the study of the early stages of the development of the liver, Mall was led to the consideration of the whole development of the body cavities and of the loops of the intestine. Both

of these he followed by means of three dimensional, wax models, carrying the subject through to the condition of the adult. In connection with the coelom, Mall started with the very early stages, when the extra-embryonal coelom is just being incorporated into the body to make the coelom and His wrote to him that he was especially glad that he had made clear the early forms of these cavities. For the earliest stages of the intestine he depended on the embryo of Graf Spee, in which the endoderm had not yet been incorporated into the body of the embryo. In Mall's youngest stage there was already a fore gut, a mid gut and a hind gut, and from then on the intestine showed the same shift in position in development as the muscles, in this case, however, determined by the position of the arteries to the umbilical vesicle which showed a shift of at least ten segments. Mall determined certain fixed points of reference. While this shift was taking place, the intestinal loop bent so that the oral end was bent toward the right and the aboral toward the left; the right loop then was the forerunner of the small intestine and the left the large gut. Thus was formed a primary loop of the intestine and already in this primary loop Mall could mark out the definitive loops of the small intestine, as indicated by the branches of the superior mesenteric artery. These loops he found more constant in their position in the adult than the convolutions of the brain. Of this work His wrote that it was the very first time that the development of any organ had been carried from its early stages through the transition forms to its condition in the adult and that he regarded this as a great advance.

There was a slaughter house near the anatomical department in Baltimore, from which an abundant supply of embryo pigs in every stage could be obtained in fresh state, with the heart still beating. With this material Mall started the study of the development of the blood vessels, a problem which he gave to a series of workers—J. B. MacCallum, H. M. Evans, G. L. Streeter, and myself. Likewise with the same material Mall suggested to me the problem of the origin of the lymphatic system while the growth of the lymphatics in amphibian forms was fol-

lowed by E. R. and E. L. Clark. These problems became thoroughly identified with Mall's laboratory. The study of the development of the blood vessels led to the fundamental concept that blood vessels come from cells, that is angioblasts, and that endothelium is the primary tissue of the vascular system; the progression of the development of the vascular system was shown by Dr. Streeter to be determined by the functional or developmental needs of each part at each stage in growth rather than as a foreshadowing of the pattern of the vessels in the adult. The work on the lymphatic system likewise led to a concept of the fundamental nature of the endothelial cell; the theory involved the idea that lymphatics are modified veins and have the same relation to the tissue spaces that the blood vessels have. In the development of these concepts Mall took the deepest interest.

There are a number of general problems in embryology of great practical significance to medicine and to human welfare which depend upon large collections of embryos and embryological institutes. These problems attracted Mall even when he first started his collection; and, with the full development of his powers, they became increasingly significant to him, until at the time of his death he was almost wholly occupied with them. The study of his publications on these subjects as they followed year after year enables one to trace both the growth of the subject and the development of Mall's power and critical judgment. His "Plea for the Foundation of an Institute of Embryology" had as its climax a clear statement of the nature and the significance of these problems.

Of first importance was the question of the age of embryos, both with relation to the time of conception and to the more general problems of growth. The history of the efforts to determine the duration of pregnancy and the age of embryos covers centuries and was outlined by Mall in 1910 in his chapter on the Age of Embryos and Foetuses in the Human Embryology, edited by Keibel and Mall. Mall's chapter was written seven years before the discovery of a method of following the oestrous cycle

in guinea pigs by Stockard and Papanicolaou [21] which opened up the comparative aspects of this subject for experimentation. It was likewise before the discoveries of the hormones which control the reproductive cycle and all of the resulting experimental work on this cycle, such as that of Leo Loeb, Edgar Allen, H. M. Evans, G. W. Corner, and C. G. Hartman. Lacking the data from the comparative side which indicate that the oestrus and ovulation in animals are synchronous but that menstruation probably occurs in the interval between ovulations, Mall concluded from the statistical analysis of human material that the relation between ovulation and menstruation was inconstant, coinciding in about two-thirds of the cases, and that fertilization tended to occur just before or just after menstruation. As soon as it was determined that fertilization of the ovum takes place in the tube or around the ovary and not in the uterus, it was clear that a certain variation in the relation of fertilization to menstruation occurred. Lacking reliable data as to time of occurrence of ovulation and its relation to the menstrual period, Mall was unable to harmonize the variations that occurred in his assembled records. He recognized this and pointed out that the real age of the embryo is the ovulation (or fertilization) age and not the menstrual age.

Mall analyzed all of the known data on measuring embryos. The difficulties are associated with the fact that the earliest embryos are straight and then curved, and finally straight again, so that the greatest length cannot be correlated with growth. On this account it was essential to determine certain fixed points for measurement and Mall judged that of all the measurements the crown-rump and neck-rump are the best. The curvature being at the anterior end of the embryo, making the rump point fixed, the two most constant anterior points are the center of the midbrain and the line between the skull and the cord, that is, the foramen magnum. He showed that the latter can always be determined by the extension of a line which connects the center of the

[21] Stockard, C. R., and Papanicolaou, G. N., The existence of a typical oestrous cycle in the guinea pig with a study of its histological and physiological changes. *American Journal of Anatomy*, 1917, *22*, 225.

eye with the center of the external auditory meatus. Added to the difficulties associated with the curvature of the embryo itself, is the fact that few of the embryologists making the measurements have been trained in methods of measurement developed by the anthropologists. Mall was fully aware of the latter difficulty, and making his measurements with proper instruments and with the care of an expert, he constructed a mathematic growth formula, represented as a curve, which makes him, according to Scammon, one of the pioneers in biometrics.

At the beginning of his study of the pathology of embryos, Mall had even less aid from preceding work than for the determination of the age of embryos, in spite of the extensive work on teratology. Three studies, a report of forty-five aborted ova in 1834 by Granville,[22] the work of Giacomini,[23] and of His[24] gave material which he used as freely as his own. Mall gave four reports of his material; the first (40) was published in 1900 in the volume of the Johns Hopkins Reports in honor of Dr. William H. Welch, in which he reported fifty-three pathological ova; three years later he described twenty more (48); in 1908, in his study of the causes of human monsters (71), he reported 163 specimens from the first 400 specimens of his collection, and in the final report, published after Mall's death, as a joint work of Mall and A. W. Meyer (104), all of the pathological ova, namely, 353, in the first 1,000 specimens of the Mall collection, are analyzed.

The most fundamental question in relation to pathological embryos is that of heredity versus environment. The whole subject of genetics has grown up since Mall started his work and has brought a flood of light from the comparative standpoint to this phase of the work. That the formation of pathological embryos, anomalies and monsters are due to environment as well

[22] Granville, A. B., Graphic Illustrations of Abortion, [etc.]. London, J. Churchill, 1834.

[23] Giacomini, C., *Ergebnisse der Anatomie*, 1894, *4*, 617-649.

[24] His, W., Anatomie menschlicher Embryonen. 2 vol., Leipzig. F. C. W. Vogel, 1882, and Festschrift, Rudolph Virchow, gewidmet zur Vollendung seines 70. Lebensjahres. *Internationale Beiträge zur wissenschaftlichen Medicin*. Berlin, August Hirschwald, 1891, *1*, 177-193.

as to heredity is one of the discoveries of modern medicine of far-reaching value to human welfare. Mall credited this important discovery to the experimental embryologists and estimated that the work started in 1888 with the observations of F. Vejdovsky [25] who noted that the eggs of Lumbricus produce more monsters in warm than in cool weather and thought that this was due to the change in temperature. Then followed the work of Driesch [26] who submitted sea urchins' eggs to high temperatures in the two cell stage and obtained double monsters; and of O. Hertwig [27] who produced spina bifida experimentally; and finally the work of Stockard.[28] In his paper on Monsters (71), in the report on Cyclopia (98), and in Chapter VII of the final paper (104), Mall analyzed the history of experimental embryology, giving the results of submitting eggs to different chemical environments, of treating them with X-rays, or of operative procedures, giving most credit with respect to cyclopia to the experiments of Stockard who found that by treating fish eggs with substances of the nature of anaesthetics at certain critical stages, he could produce anomalies at will. For example, by adding magnesium chloride to the sea water in which were fish eggs at the time of marked cell division which precedes the formation of the optic cup, fifty per cent of the eggs developed into cyclopia. Of these experiments, Mall said (See 98, page 9): "The remarkable experiments of Stockard set at rest all germinal theories of cyclopia and prove that every egg has in it the power to develop cyclopian monsters." With wider application, it is clear that an abnormal environment, when the anlage of different organs are in a critical state, accounts for other abnormalities. Mall's final conclusions (104, page 200) were that the study of pathological embryos and the recent experiments in embryology set at rest for all time the question of the causation of monsters. He said, "It has been my aim to demonstrate that the embryos

[25] Vejdovsky, F., Entwickelungsgeschichliche Untersuchungen, Prag, 1888.

[26] Driesch, H., *Zeitschrift für wissenschaftliche Zoölogie*, 1892, *55*, 1-62.

[27] Hertwig, O., *Archiv für mikroscopische Anatomie*, 1892, *39*, 353.

[28] Stockard, C. R., *Archiv Entwcklungsmechn. Organ.*, 1907, *27*, 249.

found in pathological human ova and those obtained experimentally in animals are not merely analogous or similar, but identical. A double-monster fish or a cyclopian fish is identical with the same condition in human beings. Monsters are produced by external influences which act upon the ovum, as, for instance, varnishing the shell of a hen's egg or changing its temperature, traumatic and mechanical agencies, magnetic and electrical influences, as well as alteration of the character of the surrounding gases, or the injection of poisons into the white of an egg. In aquatic animals monsters may be produced by similar methods."

In the study of his own material, it was necessary to formulate some basis for classification, which Mall regarded as only tentative because it had to be based on the nature of the pathological process rather than on etiology.

In developing fertilized ovum, the materials that are to form the mechanism of implantation and the enveloping membranes are segregated early. During the process of cleavage, these trophoblastic elements take their place as a surface layer of cells which undergo rapid division and precocious differentiation. Soon after arrival in the uterus, the trophoblastic elements can be recognized morphologically and as they begin to function, the ovum becomes converted into a blastocyst, the greater part of whose wall is of trophoblastic origin, only the inner cell mass giving rise to the embryo proper. Thus Mall was able to classify pathological ova in accordance with the degree of their attained development. He recognized seven groups: the first two had trophoblast alone; while the other five had both trophoblast and embryo. The first group comprised those having only a partially developed trophoblast while the second consisted of a complete chorion and an exocoelomic cavity. The rest were classified by the size of the embryo into those in which it was a mere nodular rudiment, or with embryos in progressive states of completeness.

The conditions which produce pathological ova, in so far as they originate in the environment act through the trophoblast. Before implantation the nutrition of the embryo passes through the chorion into the fluid of the exocoelom; after implantation, the interchange of materials is through the blood vessels. Mall

summed up the process by which an abnormal environment can affect the embryo under the term *faulty implantation.* When the abnormal environment was brought to bear on the very early stages, there resulted the complete disappearance of the embryo, as in the first two groups in his classification. Likewise the other stages corresponded to conditions in which the abnormal factors were applied later. Dr. Mall probably went too far in his stressing of the environment as the cause of all pathologic ova. Had he lived ten years longer, he would certainly have modified this emphasis. At least it was a demonstrable cause, and so much better than prenatal impressions which it supplanted, that one does not wonder at Mall's enthusiasm.

The most imporatant work of Mall in connection with the subject of pathological embryos was his analysis of the nature of the changes in the embryo itself. He found that these embryos did not show the same type of lesions to be found under abnormal conditions in the adult. Two factors bring about marked differences; first, the early embryos have no leucocytes, for the first blood cells are all red blood cells. This at once eliminates all of the processes of inflammation of the adult which are associated with the migration of leucocytes, both their presence in the tissues and the effects of their enzymes. This means that the reactions in the connective tissues are those of the primitive mesenchyme cells, fibroblasts, and macrophages. Secondly, during development, there are hormones which control and regulate the relative growth of the different tissues and organs. Mall found that the most striking effect of pathological conditions was an interference with this regulation. In his earliest descriptions of the phenomenon, he referred to the effects as a "dissociation" of the tissues. In his final report, he recognized that this phenomenon received its explanation in the experiments of Harrison on tissue culture. In tissue culture, cells grow outside the body, wholly released from the regulating mechanisms which integrate growth in normal development; and Mall saw that the phenomenon which he had called "dissociation" in pathological embryos was a growth of cells in the embryo exactly like that of tissue cultures. Besides these fundamental principles of the pathology of

embryos, Mall's reports give the most extensive accounts of pathological embryos in existence. The nature of the abnormalities in the environment was the point on which he was working at the time of his death, and the importance of this study is indicated in the fact that fully 20 per cent of all pregnancies end in abortion (77, Vol. I, page 203).

It is probable that the best known work of Mall's mature years is that on the spleen, the liver, and the heart. All of these studies represent years of work and they call to mind the words of Councilman [29] about Mall: "Mall was a great scientific investigator. As such his work was thorough; he touched no subject on which his investigations did not throw light and in most cases he left the subject standing clearly, the obscurities gone."

The work on the spleen began with his study of the reticular framework already referred to and the introduction to his second paper on this subject published in 1900, with the interesting title "The Architecture and Blood-Vessels of the Dog's Spleen," shows the direct continuation of his thought, for he said, "In reworking the entire trabecular and vascular systems of the spleen, I have employed all methods at my disposal in order to obtain a clear picture of the whole organ. Throughout the work my aim has been to study the coarser structures first, then in order the finer and finer, hoping in this way to find some histological unit which repeats itself a great many times to produce the whole organ. That the use of a variety of methods is required to unravel this difficult organ in a satisfactory manner is clear to all who have studied this subject. It may not be out of place to state that I have worked a considerable time upon the spleen each year during the last fourteen years." The most outstanding discovery in this paper is that the veins of the splenic pulp have an incomplete endothelial lining, a discovery which is often credited to Mollier some years later. This establishes the fact of an open circulation in the spleen. Mall described the histological unit of the spleen with the artery and its lymphoid follicle in the center and the trabeculae with the interlobular veins and their remark-

[29] Councilman, W. T., Franklin Paine Mall (1862-1917), *Proceedings American Academy of Arts and Sciences*, 1922, *57*, 495-499.

able longitudinal muscles on the periphery. These units were about one millimeter in diameter and the average number for the dog's spleen was 80,000. In this paper and then later in 1903, Mall was interested in what has long been the major problem in connection with the spleen, namely, the nature of its circulation. The second paper was published shortly after Weidenreich's, with whose conclusions Mall was in agreement. Mall devised many types of injections, arterial and venous, especially methods for filling the pulp spaces. For many years the main question at issue was whether there were special channels between artery and veins of the pulp distinct from the route from artery through the pulp spaces into the veins. By means of injections with asphalt, Mall showed that the route from artery to vein was through the pulp spaces. Thus the circulation of the spleen is an open one; the walls of the artery are open except where they pass through the Malpighian follicles, and from the openings blood passes into the pulp spaces. Mall made what he regarded as the crucial experiment for demonstrating the circulation through the spleen; he tied the splenic veins of the hilus in two dogs under anaesthesia, and then returned the spleen to the body cavity for a half hour. At the end of this time, when the spleen showed maximum distention, he tied the arteries in one animal, cut out the spleen, and fixed the organ in formalin for twenty-four hours with the capsule intact and then in frozen sections found the pulp spaces engorged with blood. In the other animal he cut the veins, watched the contraction of the organ, which took a few seconds, and produced a spleen entirely free of corpuscles. He also obtained the spleen in its psysiological state by paralyzing its muscle by injecting nitrites into the arteries. His work on the framework showed how the spleen was constructed in order to bring about the emptying of the pulp spaces into the veins of the pulp, for when the longitudinal muscles in the veins of the trabeculae contract, the entire lobule becomes smaller and its veins compressed, while the veins within the trabeculae open up to receive the blood flow. Thus the spleen is an organ in which the blood readily flows into the tissue spaces, the so-called pulp; but unlike other organs it has an efficient

mechanism, the smooth muscle of the trabeculae, for speedily bringing the blood back into the circulation. These concepts of the open circulation of the spleen have been fully confirmed by the physiological work, especially of Barcroft (1926), in recent years.

Mall's interest in the architecture of the heart began with his reading of the paper of Gerdy [30] on the architecture of the heart. When, in 1891, Krehl [31] of Leipzig, showed that the auriculoventricular rings were really the tendons for the bands of the heart muscle, Mall saw that with this foundation another step forward could be taken and suggested to one of his most brilliant students, John Bruce MacCallum, that he try to unravel the heart muscle bands. This MacCallum did in the brief period of three weeks, using the embryo pig, and the material showed that the main bands started in the right atrioventricular ring, made a vortex at the apex, then passed through the septum from front to back and ended through the chordae tendineae in the auriculoventricular ring of the opposite side. Those which started on the front of the heart ended on the back of the opposite side. By cutting one small bundle, MacCallum found that he could unroll the foetal pig's heart into a single sheet or scroll of fibres.

Some years later, after MacCallum's death, Mall carried this work to completion by unrolling the adult human heart. He showed that there are two primary spiral bundles, which he termed sino- and bulbo-spiral, which make the vortices at the apex of the heart and empty the heart by a contraction which one might term spiral, but in simpler words, is like the wringing out of a cloth. Later he studied the development of these primary bundles and the origin of the atrioventricular bundle, but he recognized that our knowledge of both of these subjects is far from complete.

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[30] Gerdy, P. N., Recherches, discussions et propositions, [etc.] *Thèse*, Paris, 1823.

[31] Krehl, L., Abhandlungen der mathematisch-physischen Klasse der königlichen sächsischen Gesellschaft der Wissenschaften, Leipzig, 1891, *17*, 341-362.

Mall's paper on the structure of the liver shows his powers at their full. This paper represents the work of years; he said that when he started with the study of this organ he had thought that its unit would be the easiest to determine, but he had found it the most difficult. Starting with the work of His on the origin of the liver in its earliest stages, Mall followed through the complete development of the vascular channels through their complex changes, with the venous blood coming first through the omphalomesenteric vessels and then through the umbilical vein, and finally through the portal vein. The introduction to this paper contains an analysis of Thoma's hypothesis on the laws of growth of blood vessels which leads up to the principle that the capillary is the primary unit of the vascular system. In Mall's words (58, page 252): "The anlage, then, of the vascular system is the capillary; artery and vein are secondary and are differentiated out of them by the flow of blood set in motion by the heart." This is one of the fundamental generalizations that came from Mall's laboratory, that throughout the vascular system, including the lymphatics, endothelium is the essential tissue, muscle coats and connective tissue coats are accessory, or as their name suggests adventitial.

The question Mall attempted to solve in the liver was the nature of its structural unit; by means of corrosions of hepatic and portal veins, he could reconstruct the pattern of this organ and determine that the so-called lobule, with its center at the hepatic vein, can not be considered a structural unit, since the lobules vary so greatly in size. On the other hand, the portal units, as had been noted years before, in 1888, by Sabourin[32] met all the conditions of a structural unit, since all of them are of the same size. The portal units also have the artery and bile ducts in the center, as well as the portal vein, and have a size that is determined by the length of the capillary bed of the organ. To obtain a picture of the portal units of the liver in three dimensions is of such difficulty that it probably cannot be gained from pictures alone, but the study of the corrosions of the vessels which

[32] Sabourin, C., Recherches sur l'anatomie normale et pathologique de la glande billiare de l'homme, Paris, F. Alcan, 1888.

Mall left in his laboratory makes this possible. Mall showed that this concept was essential for following the development of the liver; it also clarifies all the pathological changes involving congestion. In this study of the liver Mall brought to its fullest fruition the concept of structural units, which he first formulated in the study of the villus in Ludwig's laboratory. The concept is that there is a structural unit for each organ which is a unit of function.

These pages have not exhausted the story of Mall's scientific work but they have touched upon his most important studies. In summary, he established the endodermal origin of the thymus; demonstrated the vascular patterns of organs; discovered the vasomotor nerves of the portal vein; clarified the structure of organs by his concept of structural units; threw light on the laws of growth of the nervous system; followed the development of certain organs to the adult state; laid the foundations for the study of the pathology of embryos, discovering why these abnormal processes differ from those of the adult. He was an investigator, an educator and a leader; and when the history of medical education in this country is written, it will appear that his thought was a significant contribution to its advance.

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