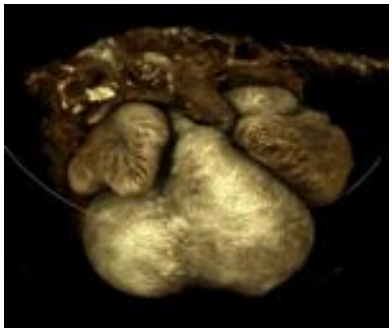
Victor Chang
Cardiac Research Institute

Heart Development and Congenital Heart Disease



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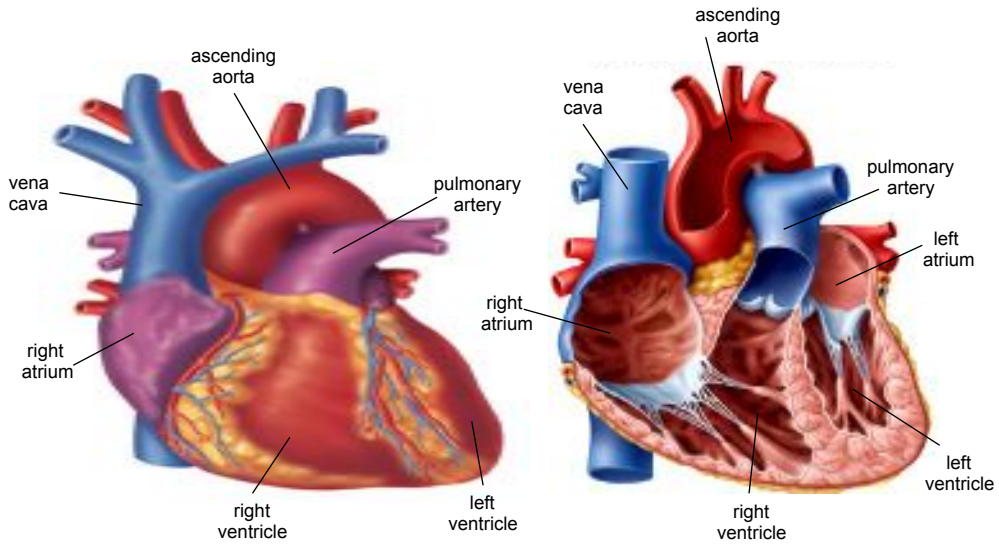
Faculty of Medicine, UNSW

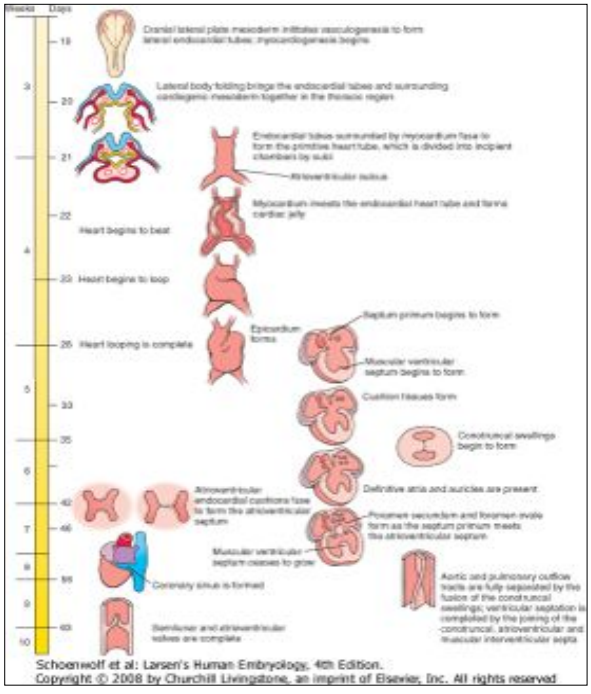
for the heart of Australia ....

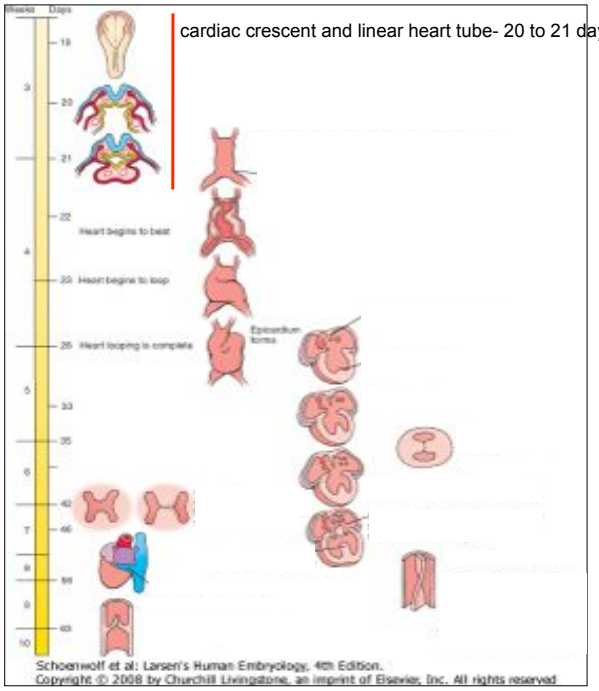
four chambered heart



Lecture objectives

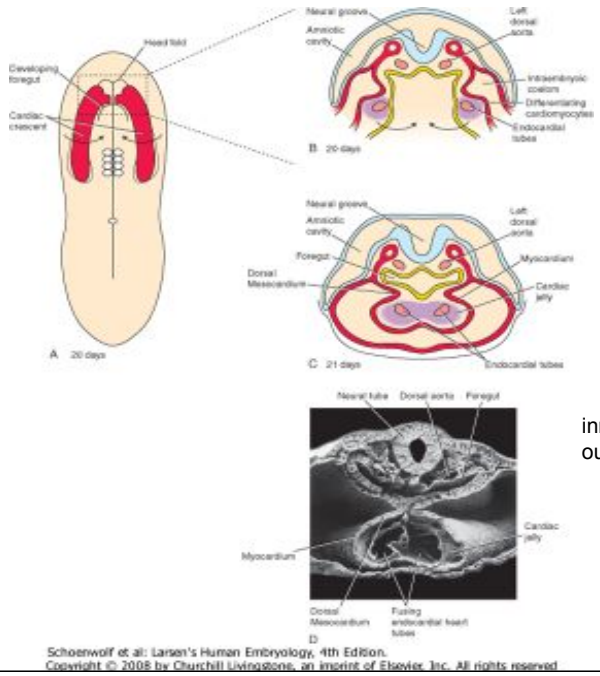
- Describe how the first and second heart fields contribute to the heart
- Explain how endocardial cushion formation contributes to chamber formation
- Describe the development of primary and secondary atrial septa and the ventricular septum
- Compare prenatal and postnatal blood flow and the changes that occur at birth
- Explain the changes occurring in the outflow tract as it transforms from a single to a double tube
- Describe the major cardiovascular developmental abnormalities.



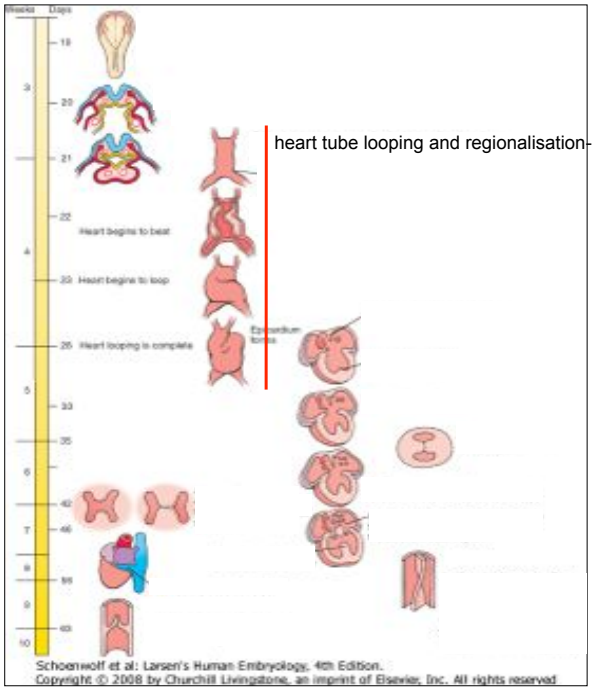


cardiac crescent and linear heart tube- 20 to 21 days

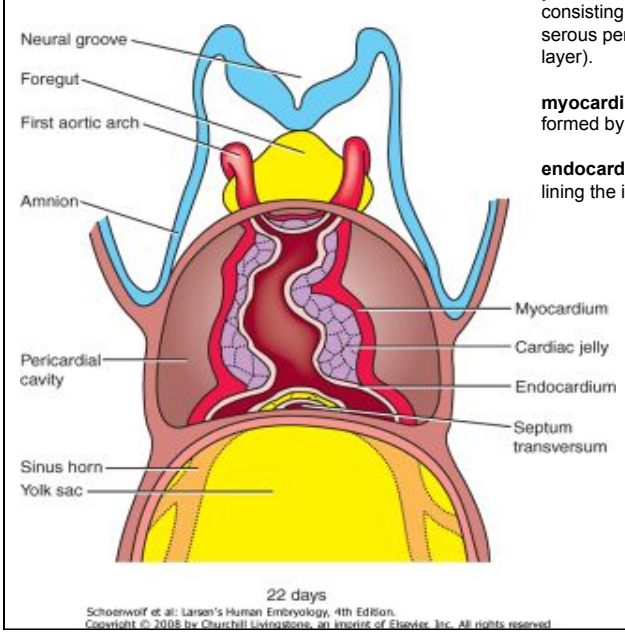
cardiac crescent and linear heart tube



inner endocardium
outer myocardium



linear heart tube and layers of heart

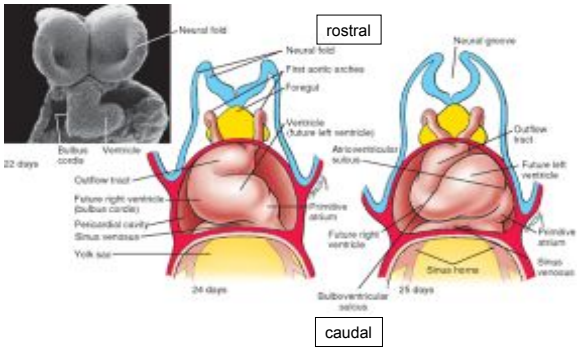


pericardium - covers the heart, formed by 3 layers consisting of a fibrous pericardium and a double layered serous pericardium (parietal layer and visceral epicardium layer).

myocardium - muscular wall of the heart, thickest layer formed by spirally arranged cardiac muscle cells.

endocardium - lines the heart, epithelial (endothelial) tissue lining the inner surface of heart chambers and valves.

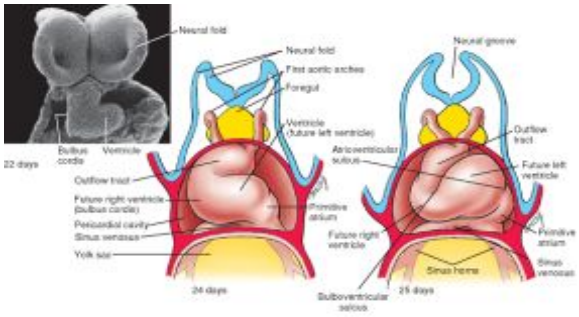
heart tube looping and regionalisation



Constrictions (sulci) and expansions form over 5 weeks as tubular heart lengthens. Expansions contribute to the chambers.

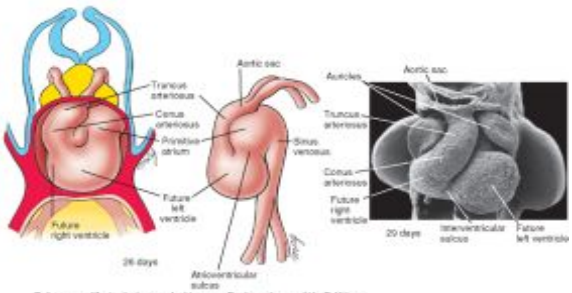
rostral		*rostral*	*rostral*
outflow tract	→	conus & truncus arteriosus	truncus arteriosus
bulbus cordis	→	right ventricle	-split into ascending aorta
primitive ventricle	→	left ventricle	& pulmonary artery
primitive atrium	→	right & left atrium	
sinus venosus		sinus venosus	conus arteriosis
cardinal veins		cardinal veins	-incorporated into ventricle
blood inflow		blood inflow	
caudal		*caudal*	

heart tube looping and regionalisation



truncus arteriosus
-split into ascending aorta
& pulmonary artery

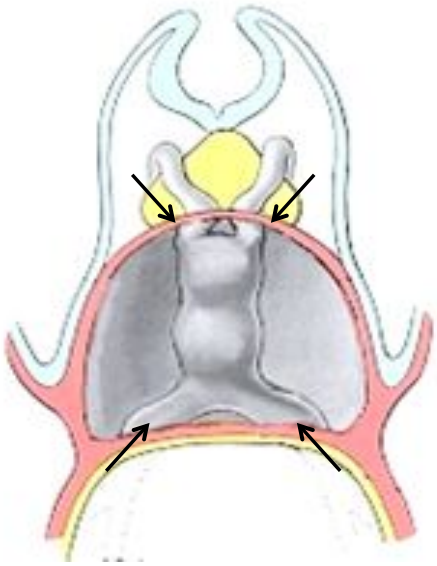
conus arteriosis
-incorporated into ventricle



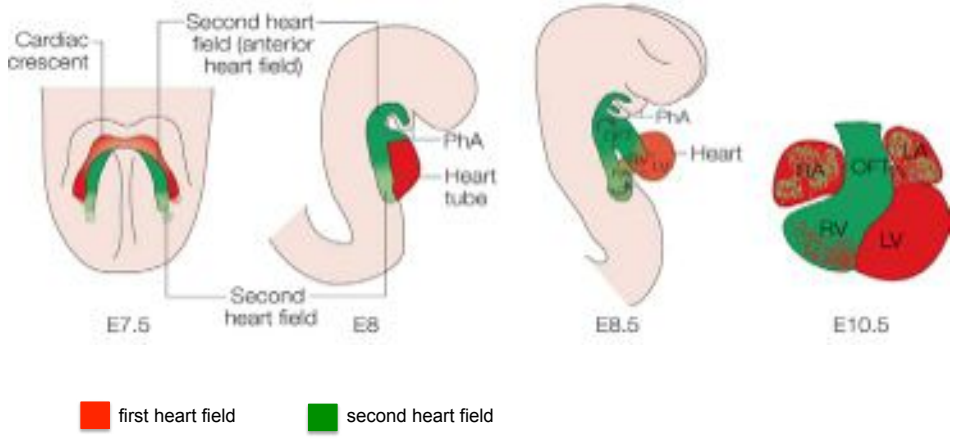
first and second heart fields- cardiac progenitor populations

first heart field (primary)
= linear heart tube

second heart field (secondary)
=dorsal to heart tube ⟶



first and second heart fields

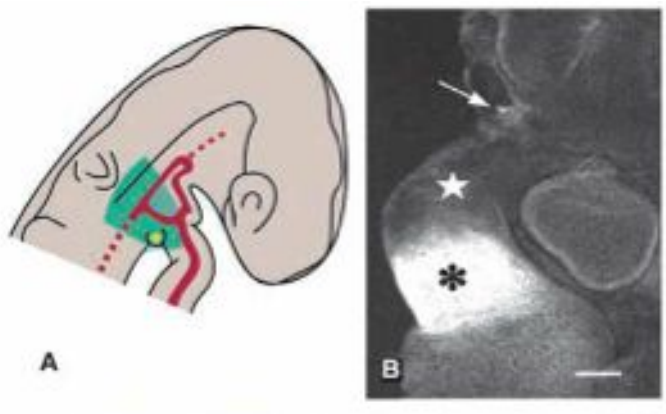


How was this worked out?

Buckingham et al (2005) Nat Rev Genet

first and second heart fields

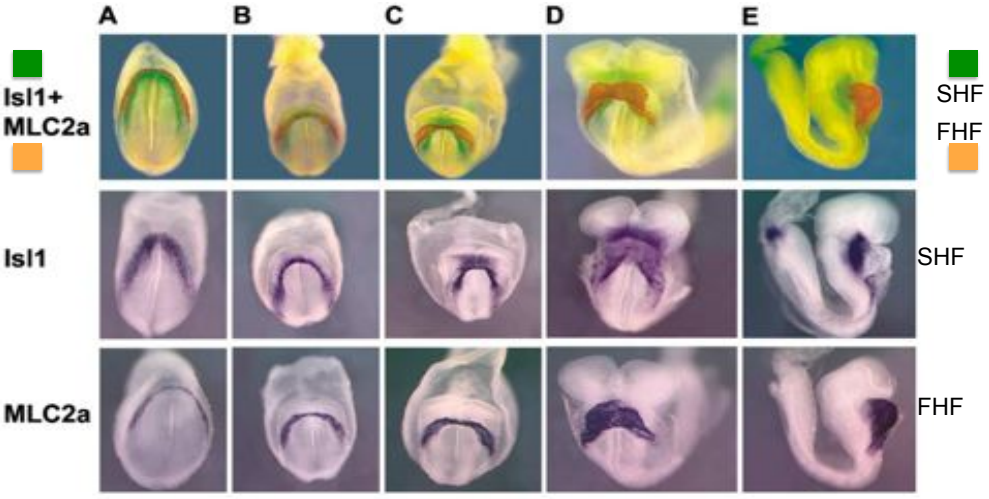
label cells with lipophilic dye
culture embryo
see where these labelled cells and their progeny end up



Waldo et al Dev 2001

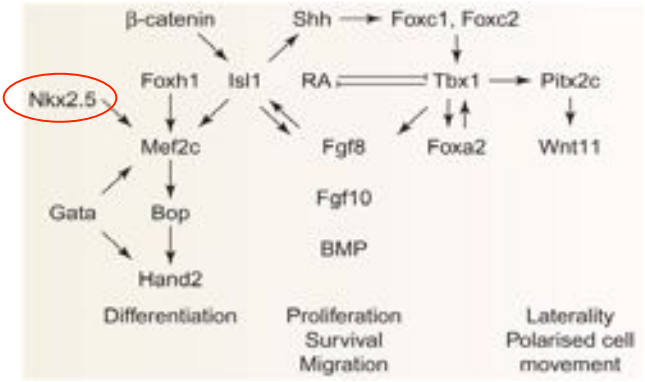
first and second heart fields

examine transcript localisation
by RNA *in situ* hybridisation



Cai et al Dev Cell 2003

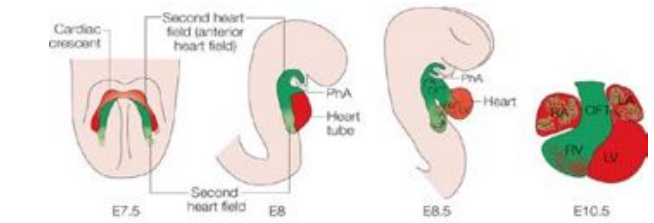
second heart field

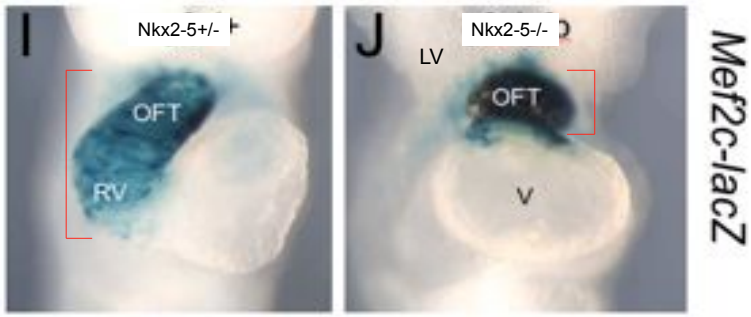


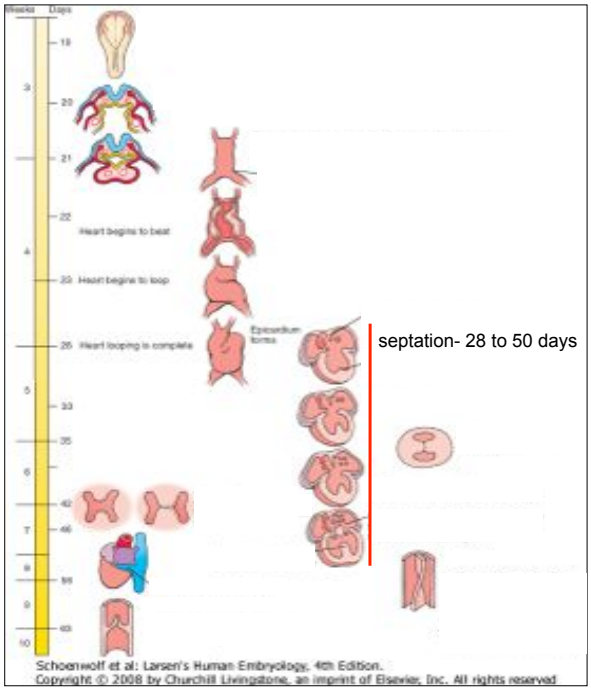
growth factor=
Fgf8
Fgf10
BMP
Wnt11
Shh

transcription factors

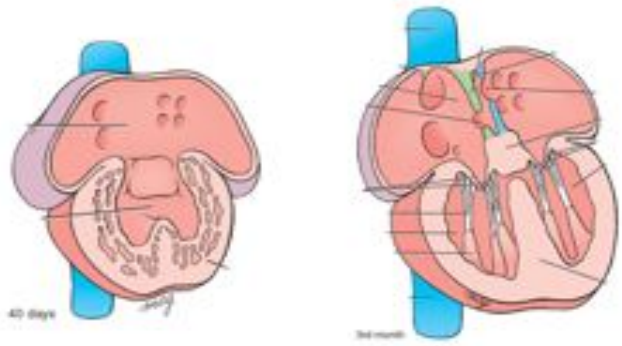
Nkx2-5 required for deployment of second heart field





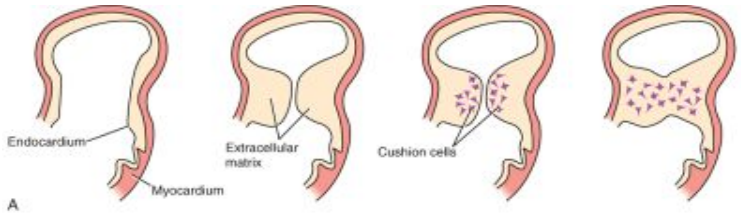


septation



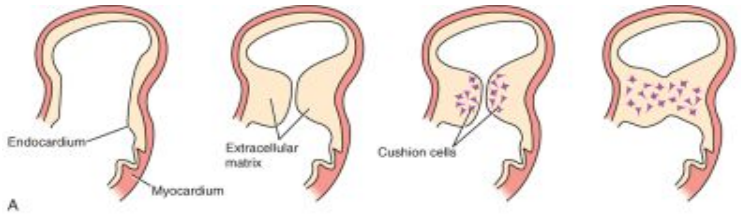
- Septation is necessary to separate the systemic and pulmonary circulations
- Partial separation of definitive atria, ventricles and division of the atrioventricular canal into right and left canals
- Endocardial cushions and muscular septum

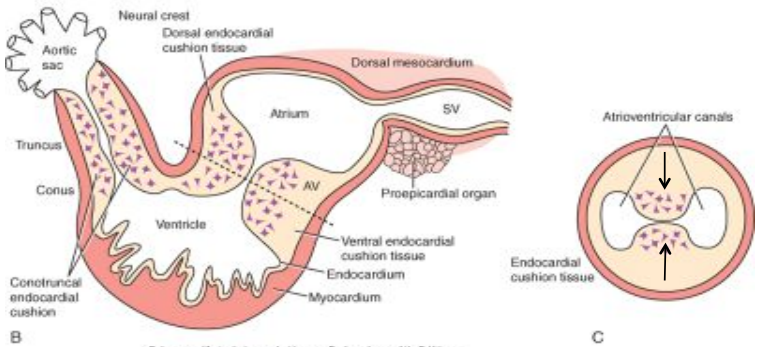
septation- endocardial cushion



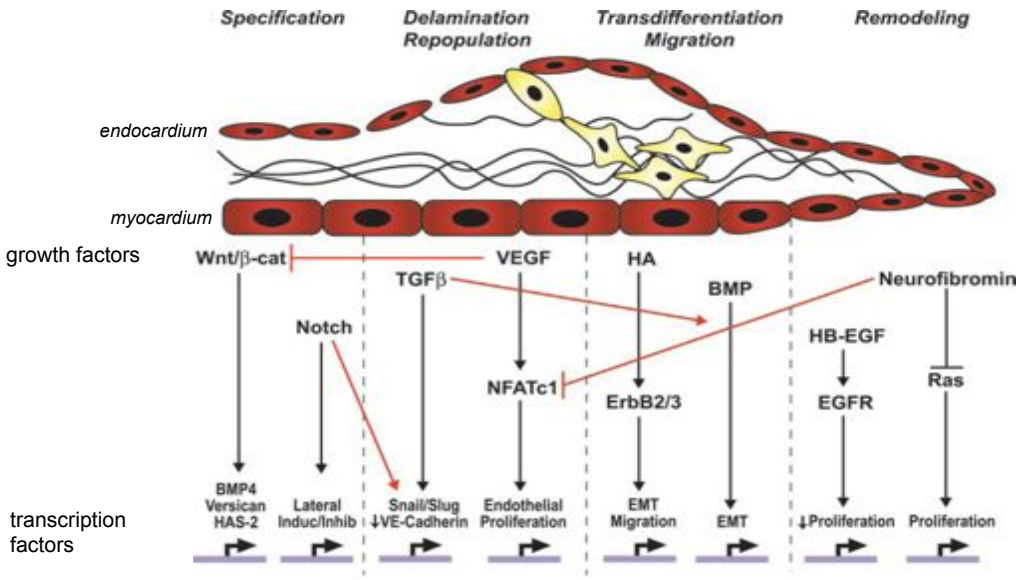
Endocardial Cushions
- form initial division of atria and ventricles
- form on dorsal and ventral wall of atrioventricularcanals
- grow into canal - meet and fuse to separate atrioventricular canal into right and left channels
- anterior and posterior cushions fuse; lateral cushions remain unfused

septation- endocardial cushion



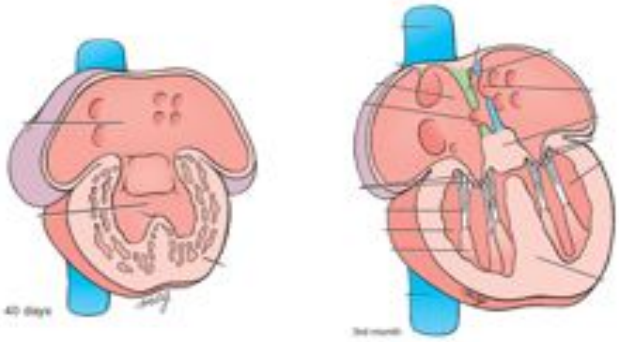


signaling network model for heart valve development and remodeling



Armstrong and Bischoff (2004) Circulation Research

septation- atrial septation



• Mature interatrial septum is formed by fusion of two muscular septum (primum and secundum). Thus blood does not pass from the right atrium to the left atrium.

• Each has large openings allowing right-to-left shunting of blood throughout gestation.

• Shunting permits oxygenated blood from the umbilicus to bypass the developing pulmonary system and enter the systemic system.

septation- atrial septation

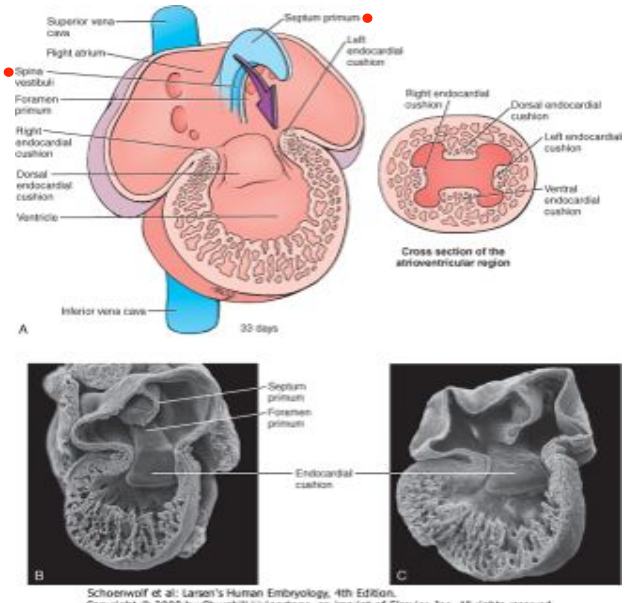
poor understanding of genes required for atrial septation

right left

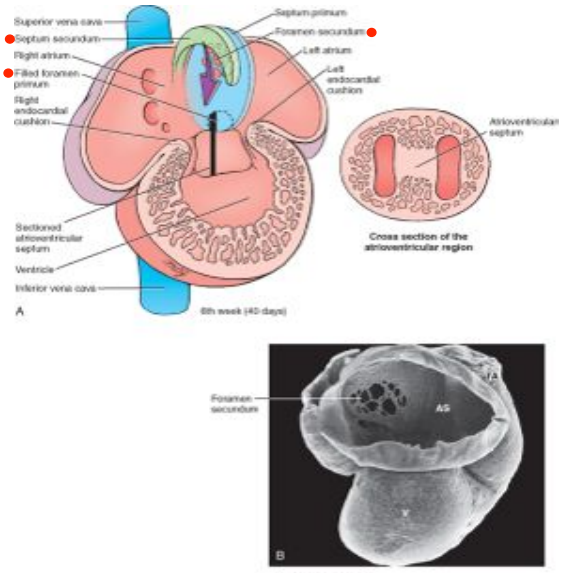
septum primum

septum secundum

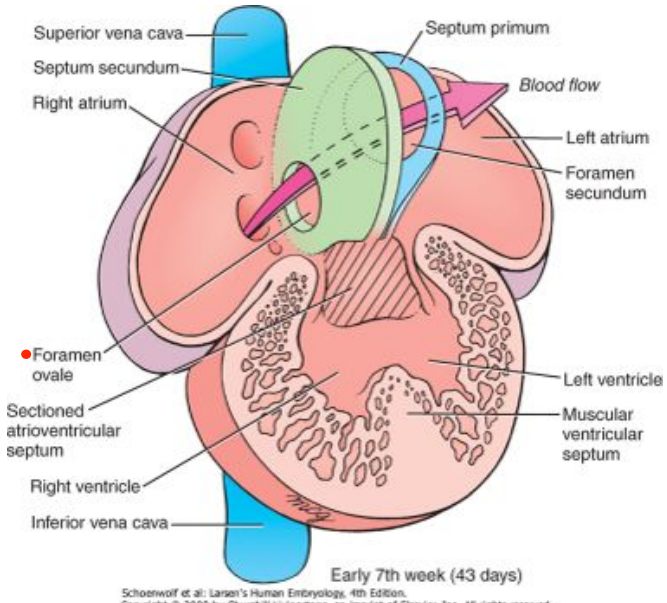
septation- atrial septation



septation- atrial septation

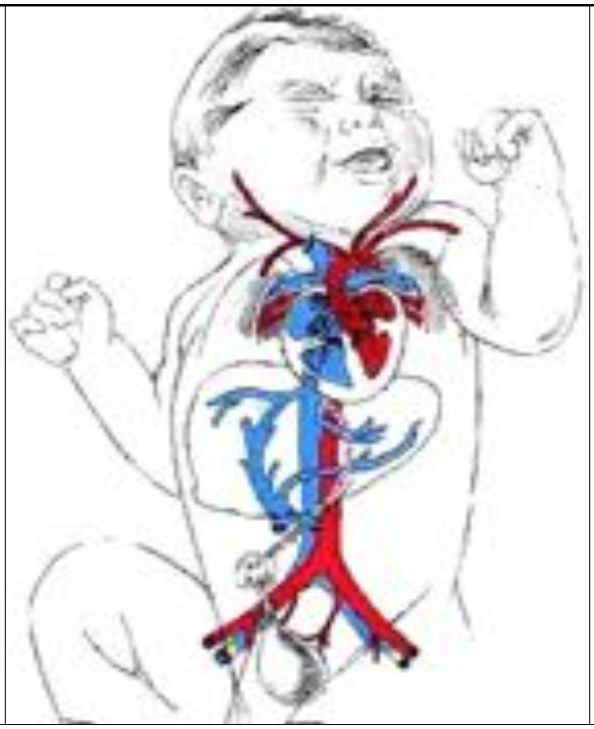


septation- atrial septation



postnatal blood flow

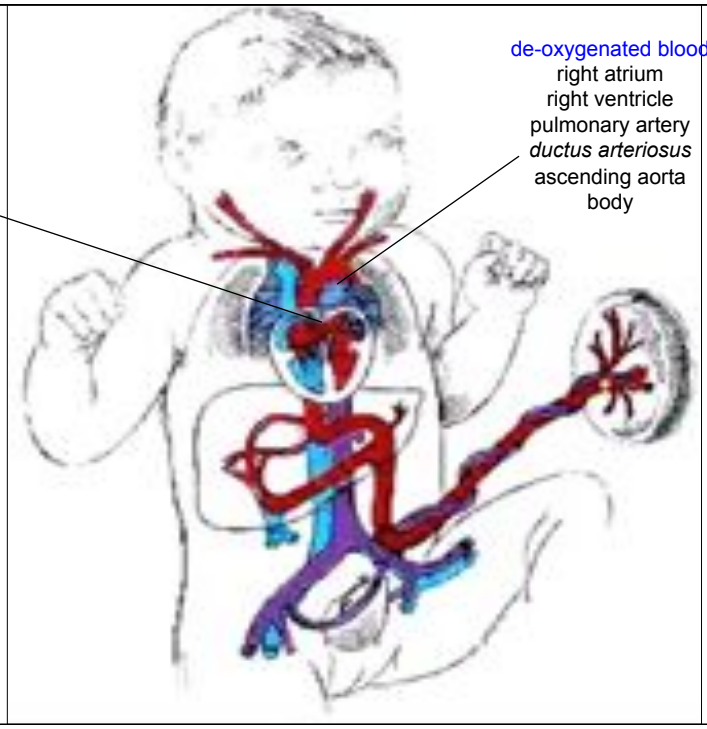
de-oxygenated blood
right atrium
right ventricle
pulmonary artery
lungs
oxygenated blood
pulmonary veins
left atrium
left ventricle
ascending aorta
body



prenatal blood flow

oxygenated blood
right atrium
foramen ovale
left atrium
left ventricle
ascending aorta
body

de-oxygenated blood
right atrium
right ventricle
pulmonary artery
ductus arteriosus
ascending aorta
body

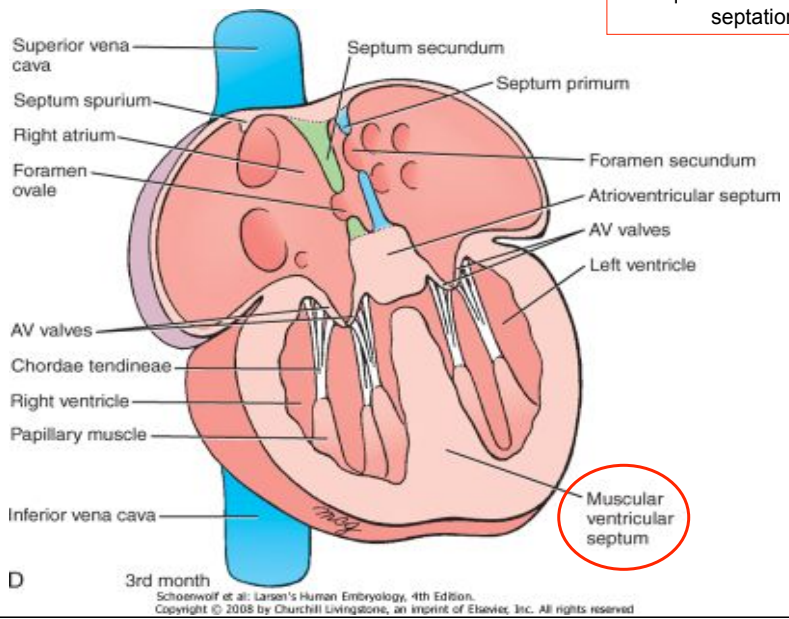


changes at birth

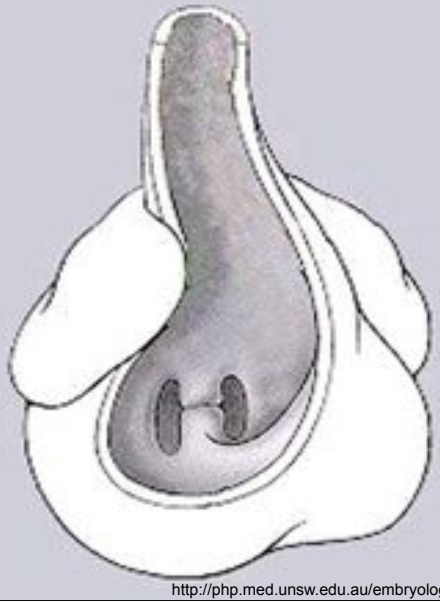
- at birth, cutting the umbilical cord and changes in the lungs after the first breaths trigger major functional adaptations in the fetal circulatory system
- blood flow through ductus venosus is eliminated
- pulmonary circulation bed expands - reducing blood flow through ductus arteriosus
- physiological closure of interatrial shunt
- closure of ductus venosus in liver is prolonged

ventricular septation four chambered heart

poor understanding of genes required for ventricular septation



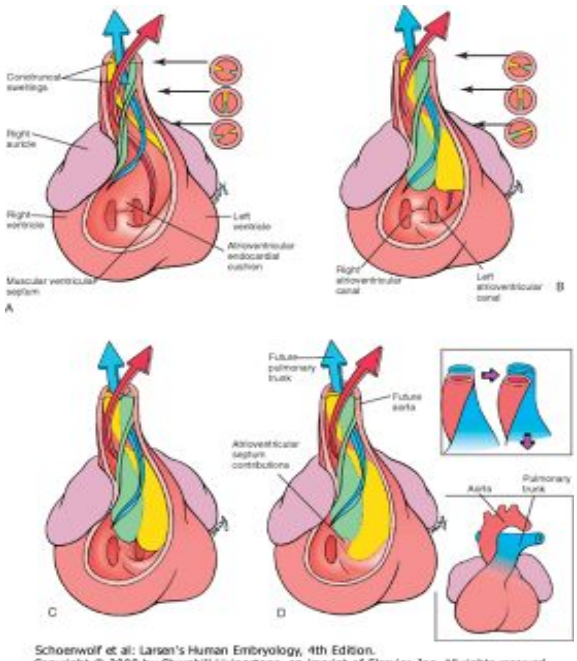
outflow tract septation



- initially outflow tract is a single tube, the bulbus cordis
- elongates to form proximal conus arteriosus and distal truncus arteriosus
- 2 growths (endocardial cushion) from wall in spiral pattern, inferior upwards - separate tract into 2 channels
- mesenchyme and neural crest contribute to this septation process
- fusion of outgrowths separate aortic and pulmonary outflow

http://php.med.unsw.edu.au/embryology/index.php?title=Development_Animation_-_Heart_Outflow_Septation

outflow tract septation



Congenital Heart Disease (CHD)

ASD: atrial septal defect

VSD: ventricular septal defect

AVSD: atrioventricular septal defect

DORV: double outlet right ventricle

TGA: transposition of the great arteries

PTA: persistent truncus arteriosus

TOF: tetralogy of Fallot

HLHS: hypoplastic left heart syndrome

http://www.rch.org.au/cardiology/heart_defects/

congenital heart disease (CHD)

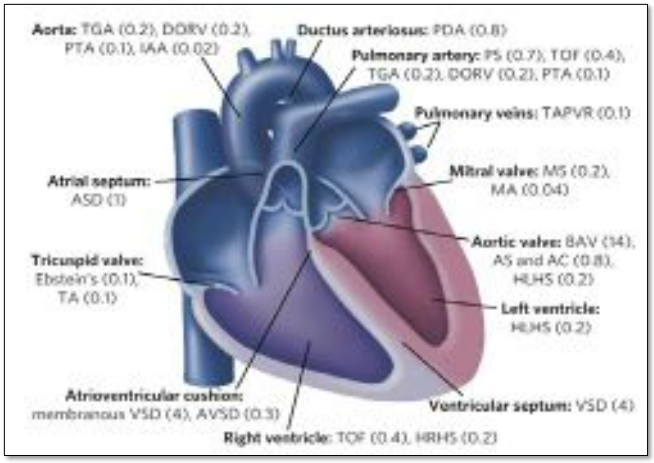
6-27 per 1,000 live birth

Australia 2009

72,800 fetal deaths
3066 CHDs

274,000 live births
1650-7400 CHDs

4 children
die each week



Australia

62,000 with CHD
50% >18yo

recurrence risk
to offspring
up tp 6.7%

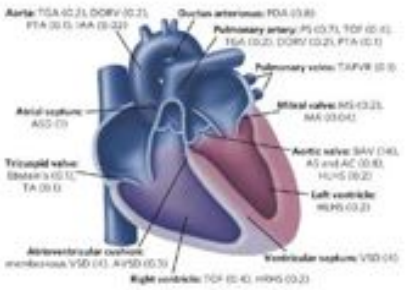
44 per 1,000 fetal deaths

Bruneau (2008) Nature
Hoffman (1995) Pediatr Cardiol

genetic causes of CHD

- Chromosomal (11.9%) and Mendelian syndromes (7.4%) account for CHD
- Non-syndromic large families with Mendelian inheritance patterns have identified CHD genes: *ZIC3* (heterotaxy), *NOTCH1* (aortic stenosis and bicuspid aortic valve), *NKX2.5* (ASD), *NKX2.6* (PTA/CAT), *MYH6* (ASD), *MYH11* (PDA), *JAG1* (TOF), *ACTC1* (ASD) and *GATA4* (ASD)
- Non-Mendelian/non-chromosomal "sporadic" CHD account for the remaining 80%, the increased risk of CHD recurrence in siblings and offspring indicates a genetic component

congenital heart disease (CHD)



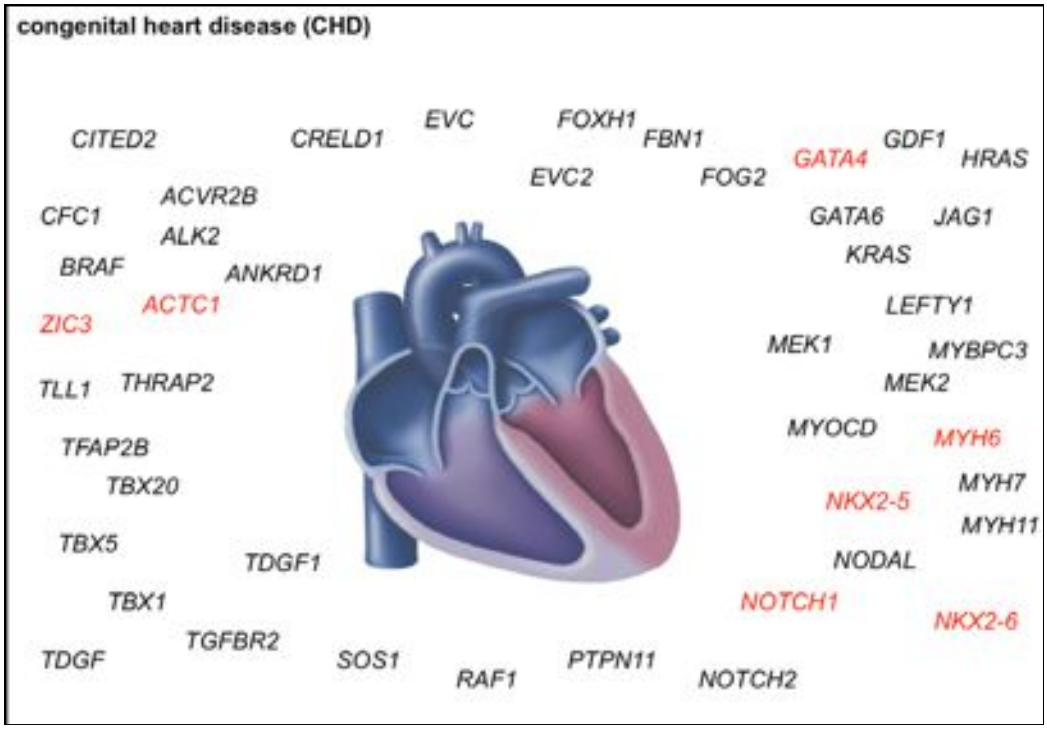
How do we identify the genes associated with these defects?

• familial: gene mapping

• non-familial: candidate gene
- 316 genes associated with heart defects in mice
- 276 genes associated with ASD in mice
- 143 genes associated with VSD in mice

• understand developmental processes eg. SHF – OFT – aorta + pulmonary artery

Bruneau Nature 2008


congenital heart disease (CHD)
CITED2
CRELD1
EVC
FOXH1
FBN1
GDF1
HRAS
GATA4
EVC2
FOG2
ACVR2B
CFC1
ALK2
GATA6
JAG1
KRAS
BRAF
ANKRD1
ACTC1
ZIC3
LEFTY1
MEK1
MYBPC3
MEK2
TLL1
THRAP2
MYOCD
MYH6
TFAP2B
TBX20
MYH7
NKX2-5
MYH11
TBX5
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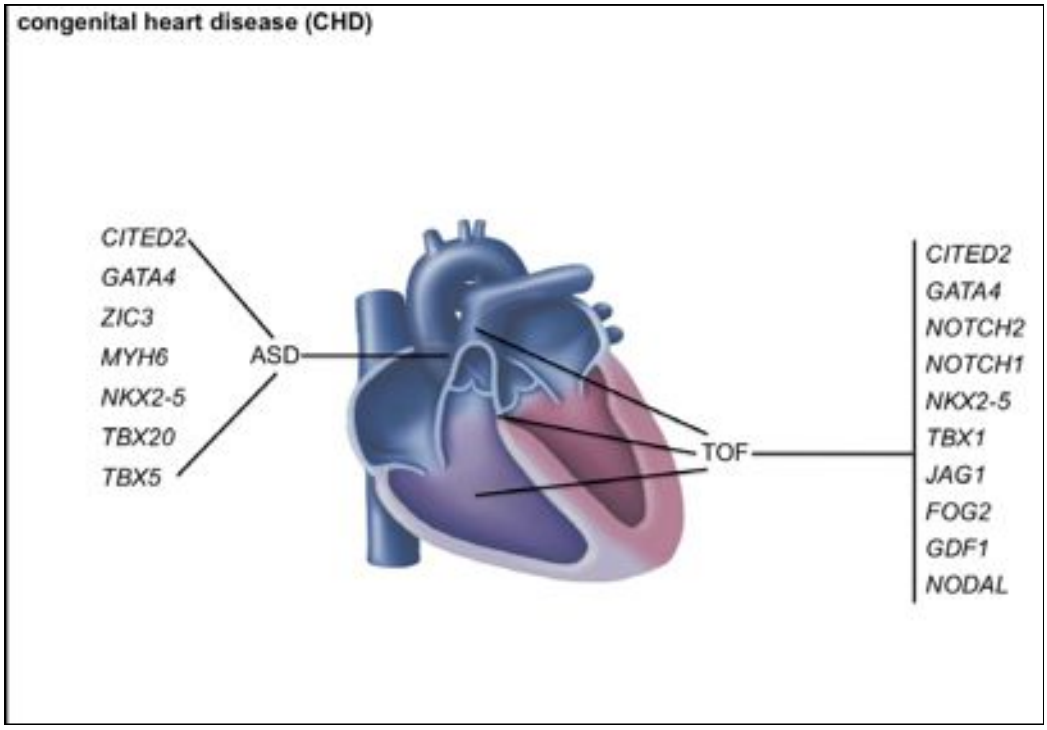
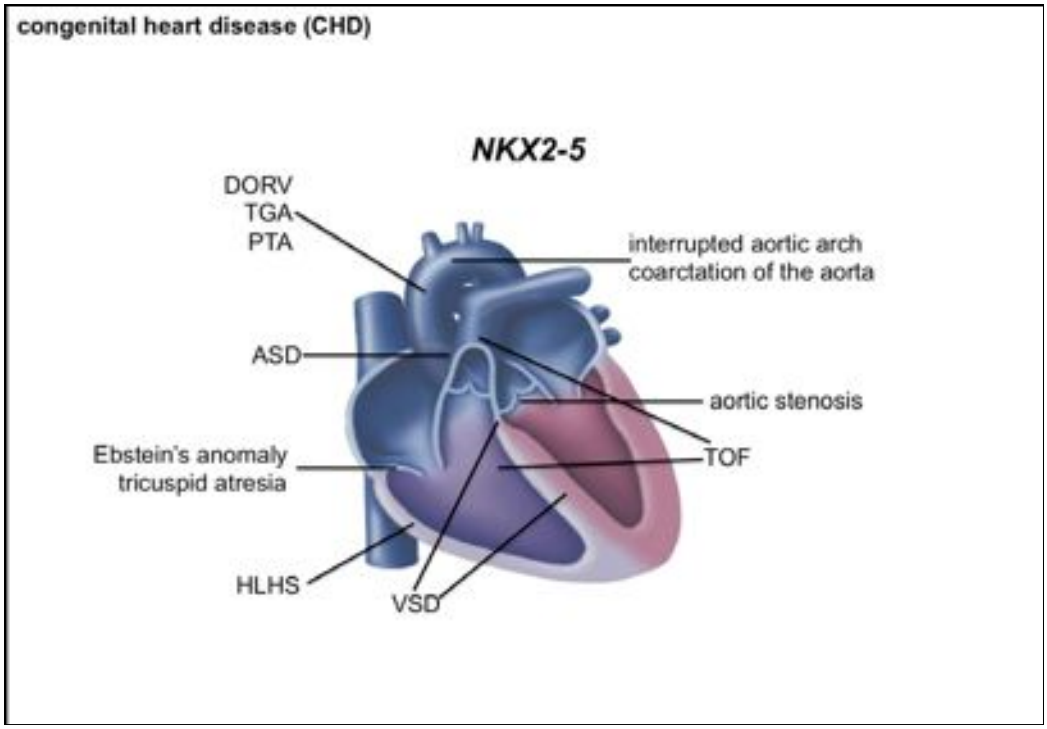
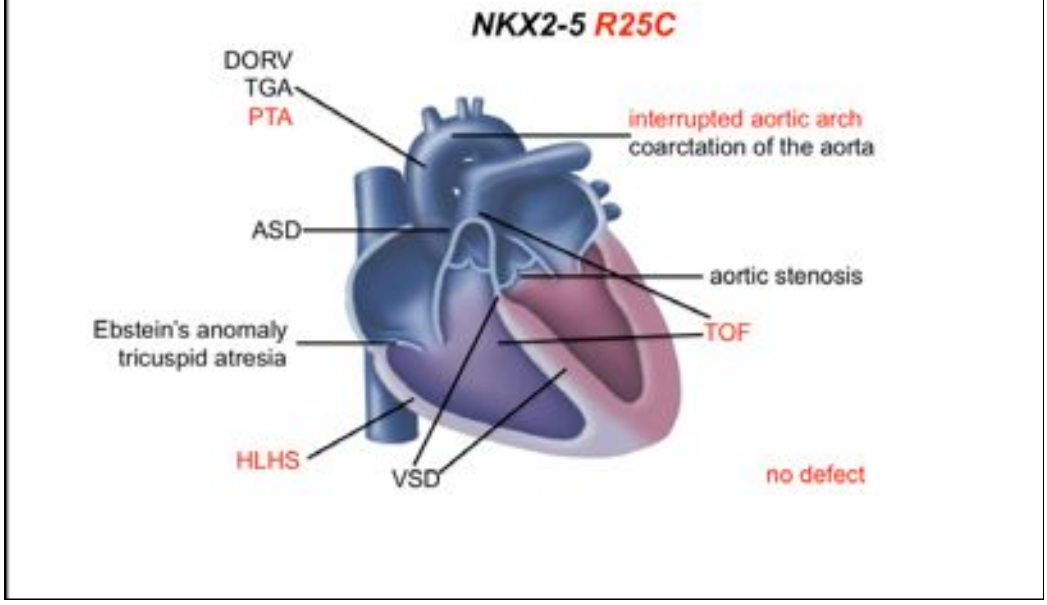
TGFBR2
TDGF
SOS1
RAF1
PTPN11
NOTCH2


congenital heart disease (CHD)
CITED2
GATA4
ZIC3
MYH6
NKX2-5
TBX20
TBX5
ASD
TOF
CITED2
GATA4
NOTCH2
NOTCH1
NKX2-5
TBX1
JAG1
FOG2
GDF1
NODAL

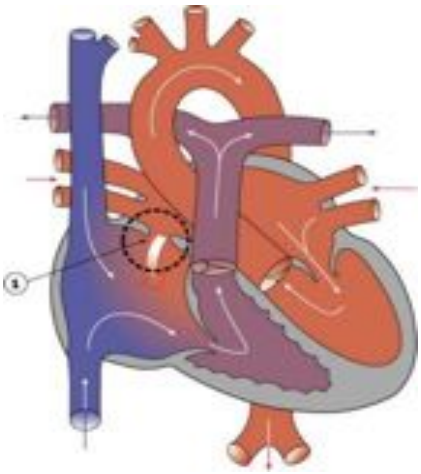
congenital heart disease (CHD)



congenital heart disease (CHD)



atrial septal defect



Atrial Septal Defects (ASD) are a group of common (1% of cardiac) congenital anomalies defects occurring in a number of different forms and more often in females.

• patent foramen ovale - allows a continuation of the atrial shunting of blood, in 25% of people a probe patent foramen ovale (allowing a probe to bypassed from one atria to the other) exists.

• ostium secundum defect.

• endocardial cushion defect involving ostium primum

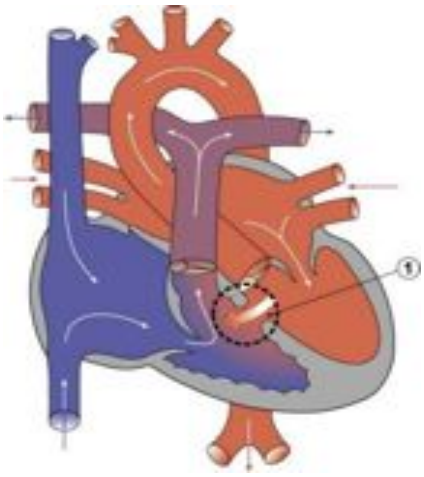
• sinus venosus defect - contributes about 10% of all ASDs and occurs mainly in a common and less common form. Common ("usual type") - in upper atrial septum which is contiguous with the superior vena cava. Less common - at junction of the right atrium and inferior vena cava.

• common atrium

1/1,000 live births

http://fromyourdoctor.com/topic.do?title=Atrial+Septal+Defect+ASD&t=7958

ventricular septal defect



The Ventricular Septal Defect (VSD) usually occurs in the membranous (perimembranous) (70%) rather than muscular interventricular septum, and is more frequent in males than females.

• Perimembranous defects are located close to the aortic and tricuspid valves and adjacent to atrioventricular conduction bundle.

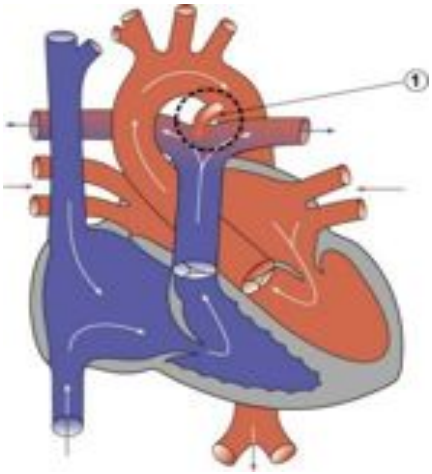
• The defect allows left-right shunting of blood, this shunting depends upon the size of the defect.

• Small defects may close spontaneously, larger defects result in infant congestive heart failure.

• Clinically repaired by coils or tissue-adapted devices like muscular or perimembranous occluders.

8/1,000 live births

patent ductus arteriosus

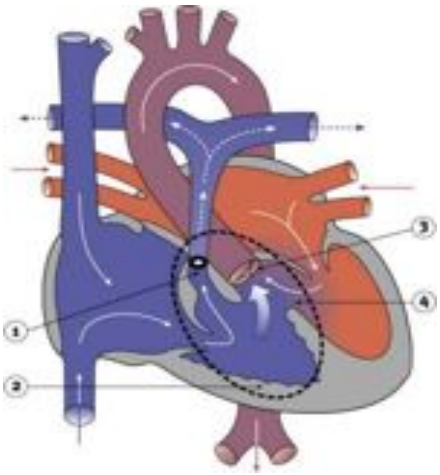


Patent Ductus Arteriosus (PDA) occurs commonly in preterm infants, can close spontaneously (by day three in 60% of normal term neonates) the remainder are ligated simply and with little risk.

The operation is always recommended even in the absence of cardiac failure and can often be deferred until early childhood.

0.81/1,000 live births

tetrology of Fallot



Named after Etienne-Louis Arthur Fallot (1888) who described it as "la maladie blue" and is a common developmental cardiac defect.

The syndrome consists of a number of a number of cardiac defects possibly stemming from abnormal neural crest migration.

The basic defect in a tetralogy of Fallot is an asymmetrical fusion of the truncoconal ridges and a malalignment of the aortic and pulmonary valves. This results in the typical 4 features seen in this defect:
1. pulmonary stenosis,
2. overriding aorta,
3. ventricular septal defect
4. right ventricular hypertrophy.

0.4/1,000 live births

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