

Heart Development and Congenital Heart Disease



Sally Dunwoodie

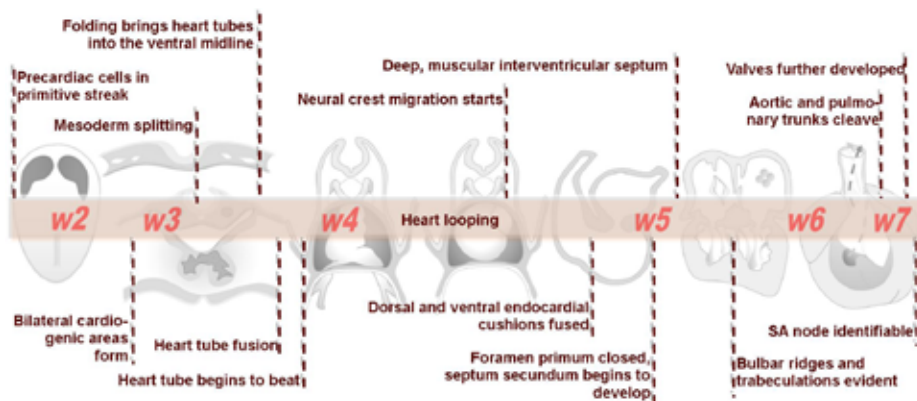
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Developmental and Stem Cell Biology Division
Victor Chang Cardiac Research Institute

for the heart of Australia



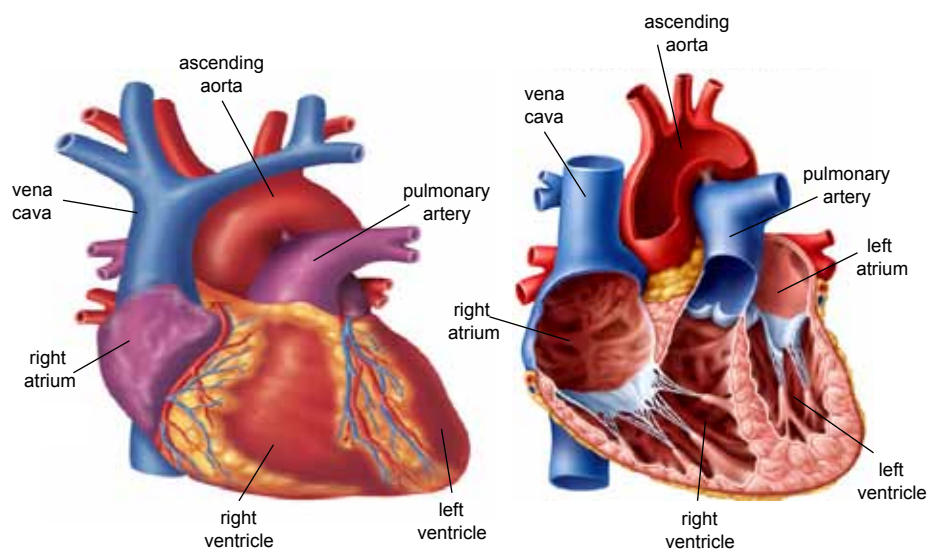
human cardiac development- timeline



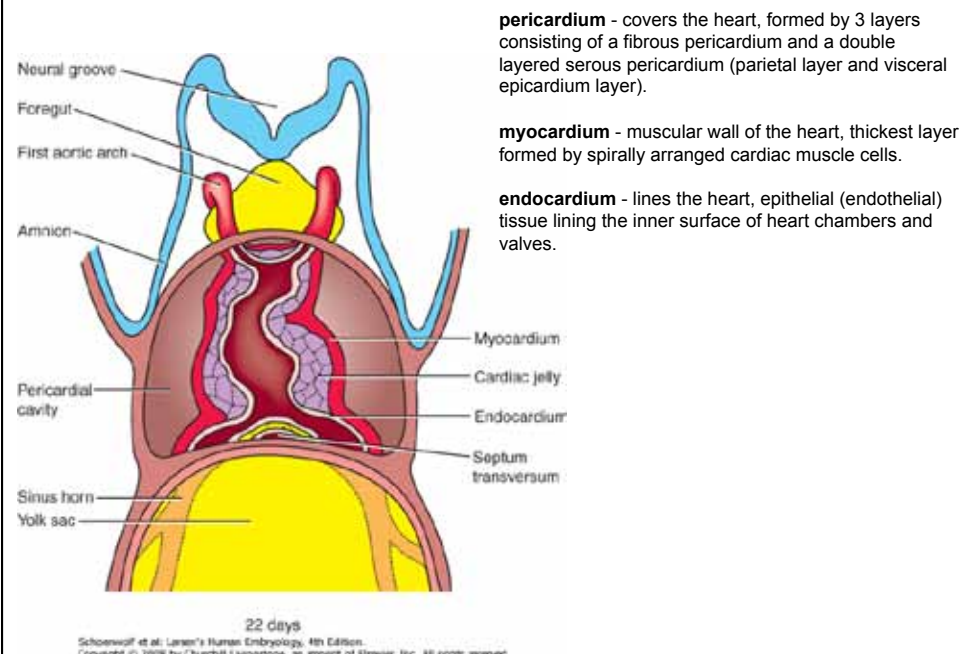
lecture objectives

- ♥ 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.

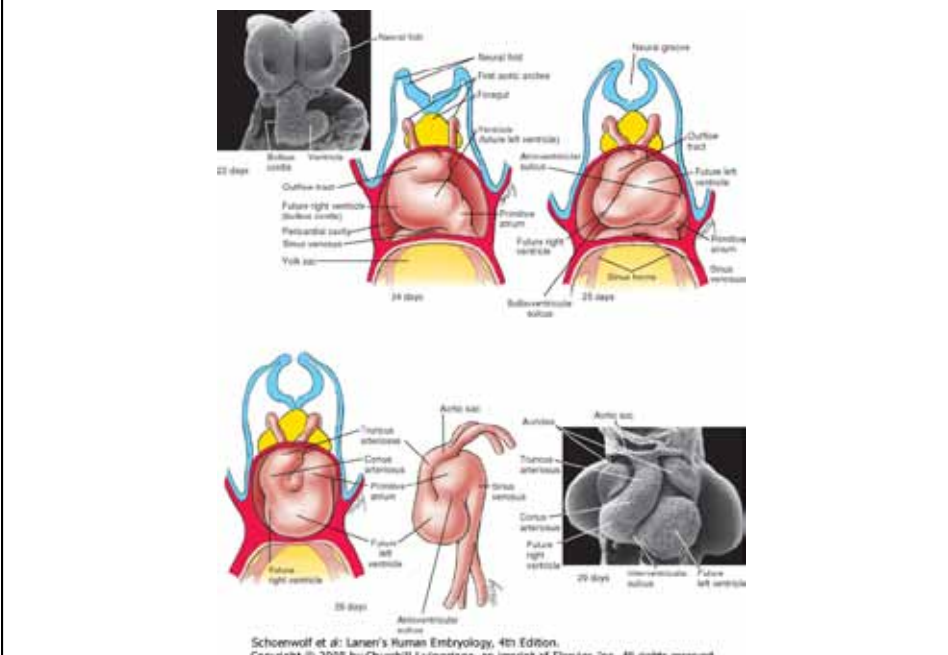
four chambered heart



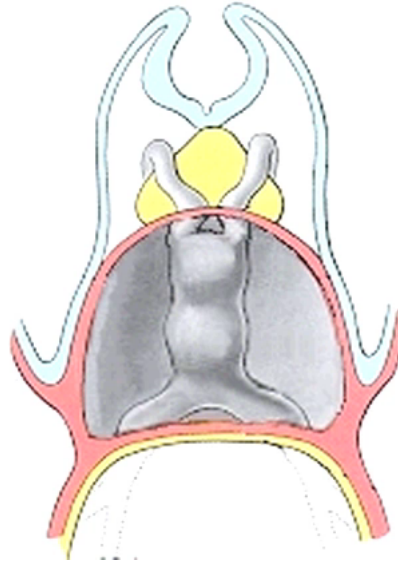
linear heart tube and layers of heart



heart tube looping and regionalisation

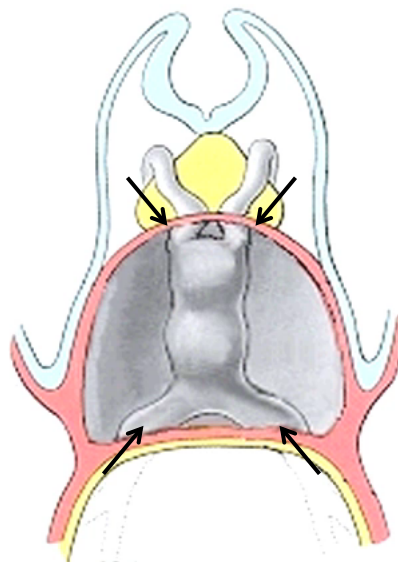


heart tube looping and regionalisation



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

heart tube looping and regionalisation



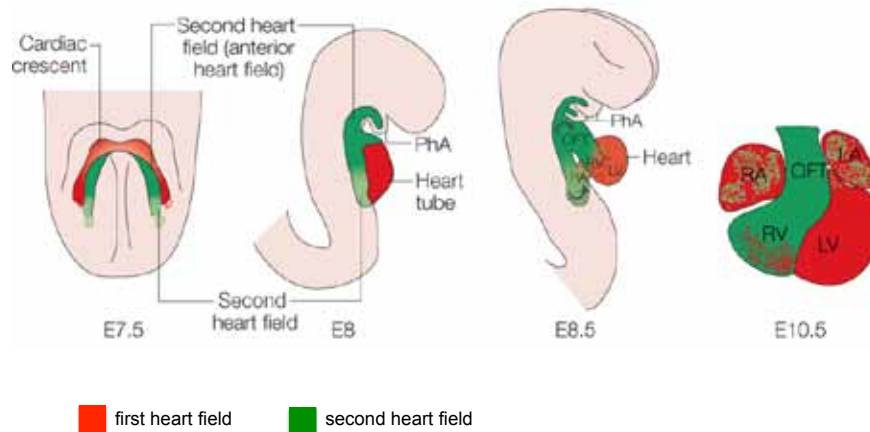
first and second heart fields

two main cardiac progenitor populations

first heart field
(primary, anterior)

second heart field
(secondary)

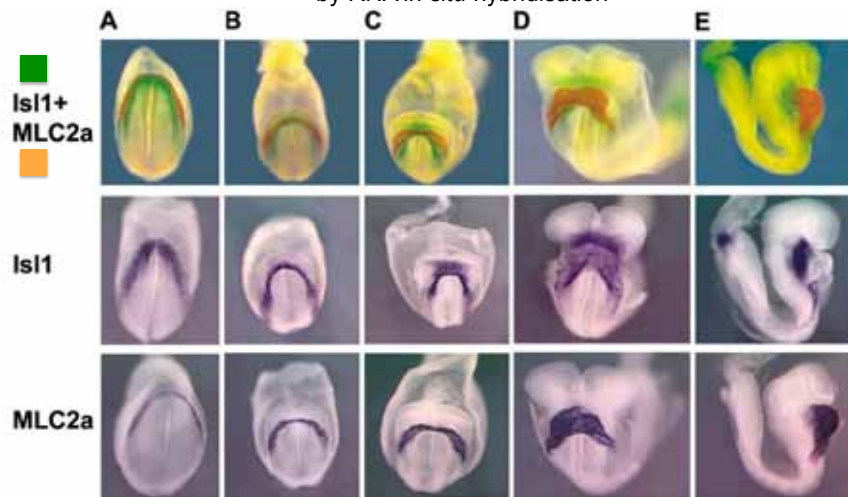
first and second heart fields



Buckingham et al (2005) Nat Rev Genet

first and second heart fields

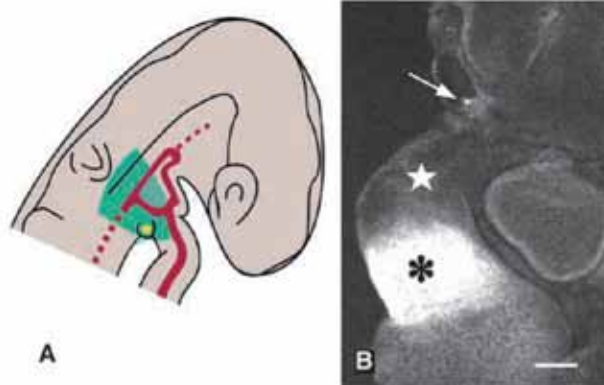
examine transcript localisation
by RNA *in situ* hybridisation



Cai et al Dev Cell 2003

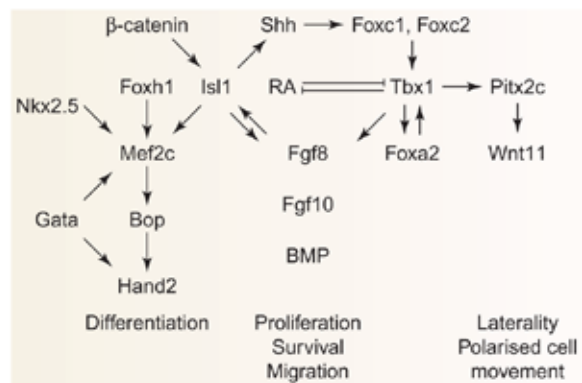
first and second heart fields

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

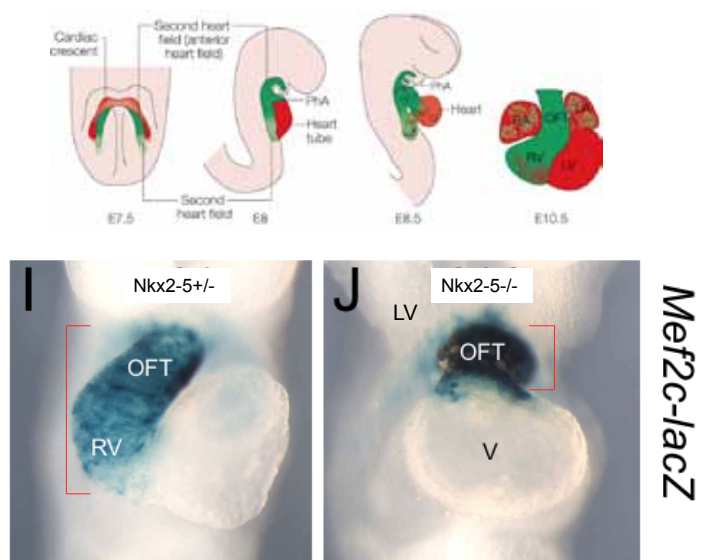


Waldo et al Dev 2001

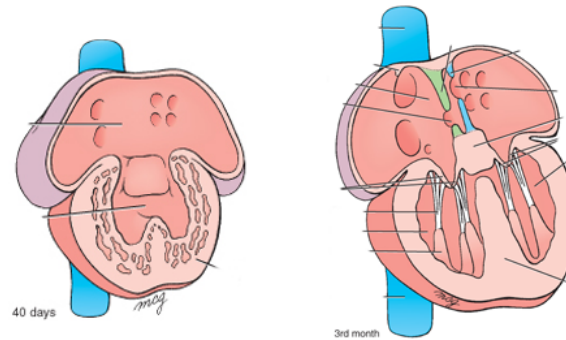
second heart field



Nkx2-5 required for deployment of second heart field

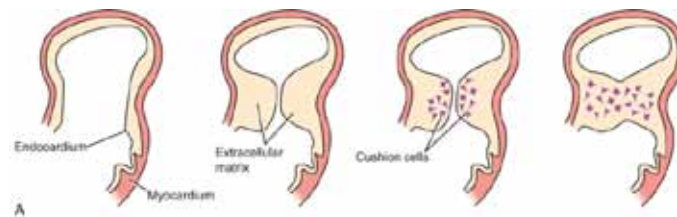


septation



- 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

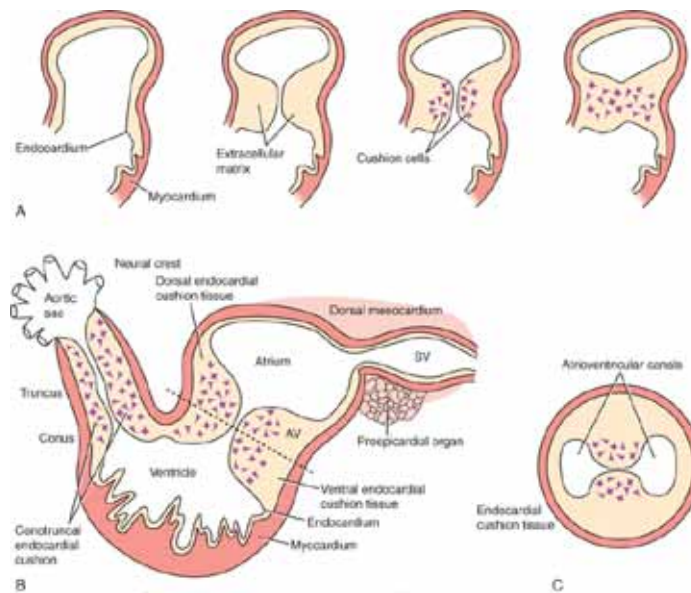


Endocardial Cushions

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

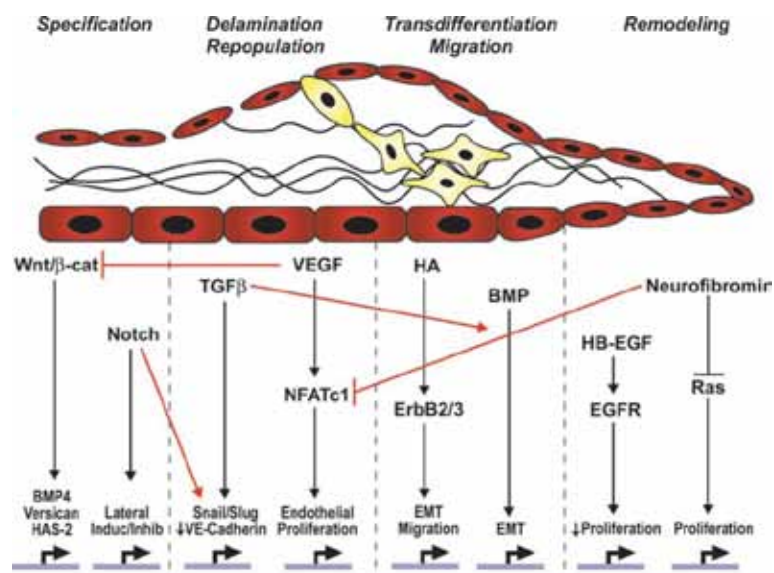
Schoenwolf et al. Larner's Human Embryology, 4th Edition.
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septation- endocardial cushion



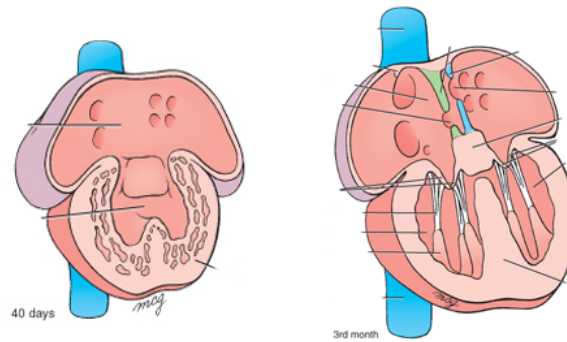
Schoenwolf et al: *Larney's Human Embryology*, 4th Edition.
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signaling network model for heart valve development and remodeling



Armstrong and Bischoff (2004) *Circulation Research*

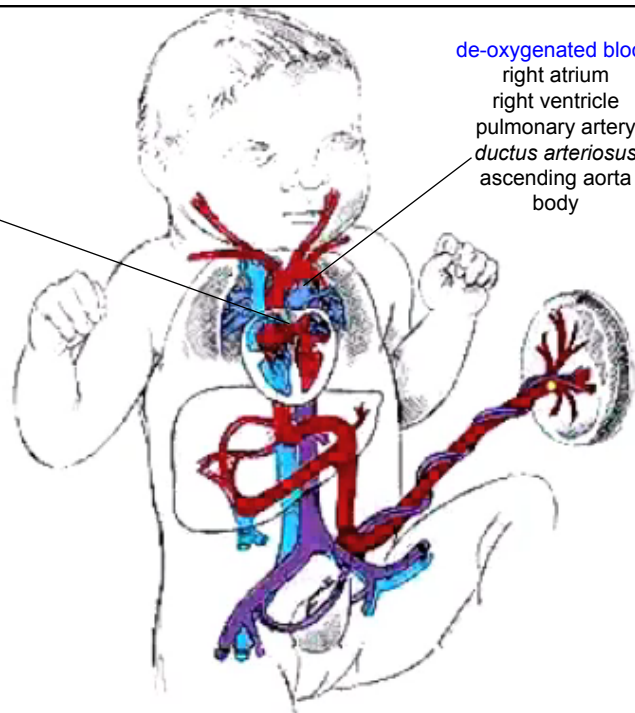
septation- atrial septation



- 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.

prenatal blood flow

oxygenated blood
right atrium
foramen ovale
left atrium
left ventricle
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

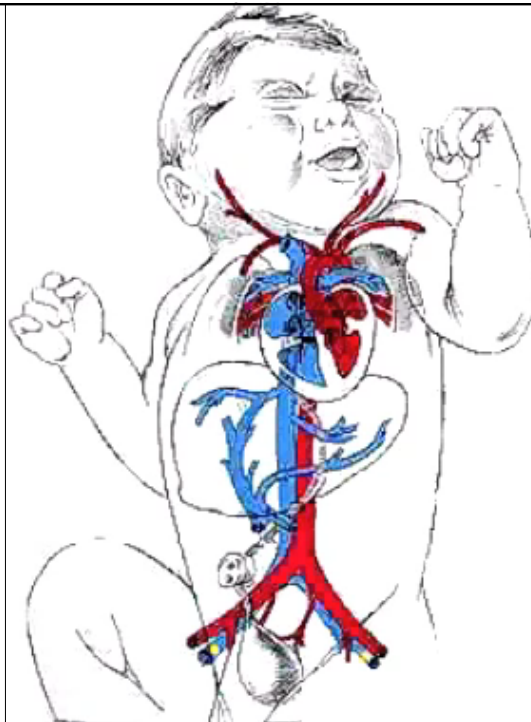
postnatal blood flow

de-oxygenated blood

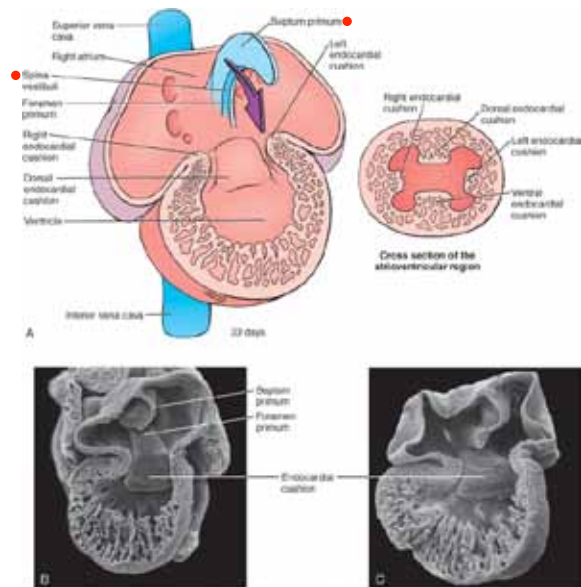
right atrium
right ventricle
pulmonary artery
lungs

oxygenated blood

pulmonary veins
left atrium
left ventricle
ascending aorta
body

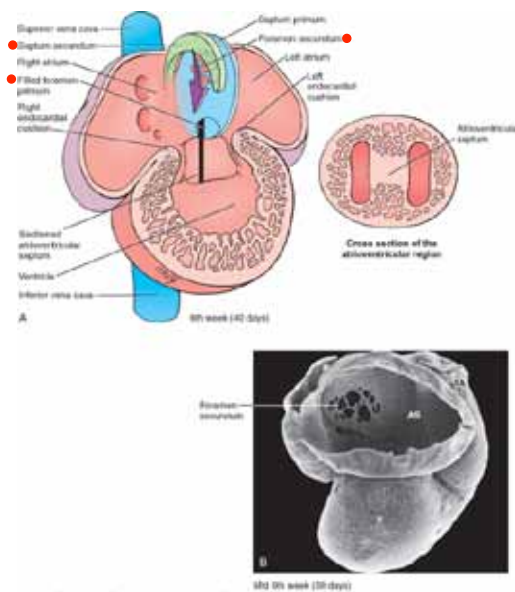


septation- atrial septation



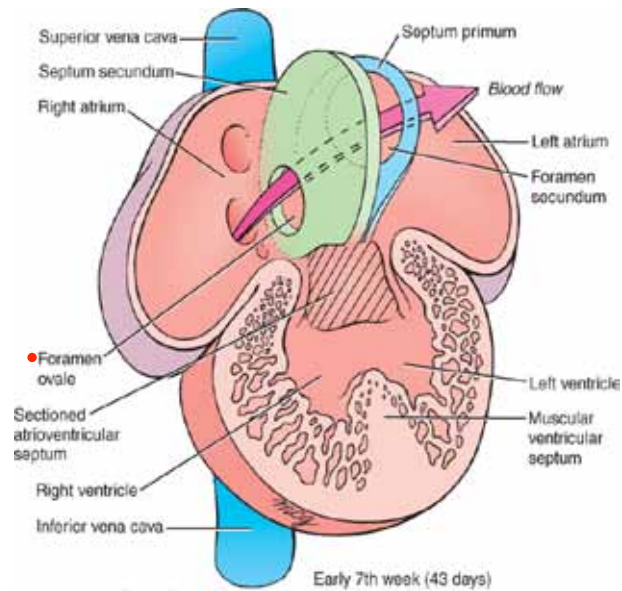
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septation- atrial septation



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septation- atrial septation



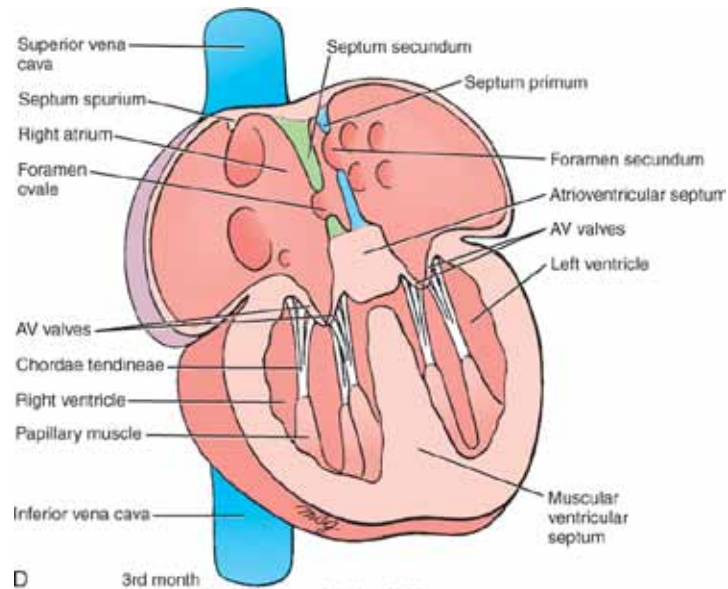
septation- atrial septation

poor understanding of
genes required for atrial
septation

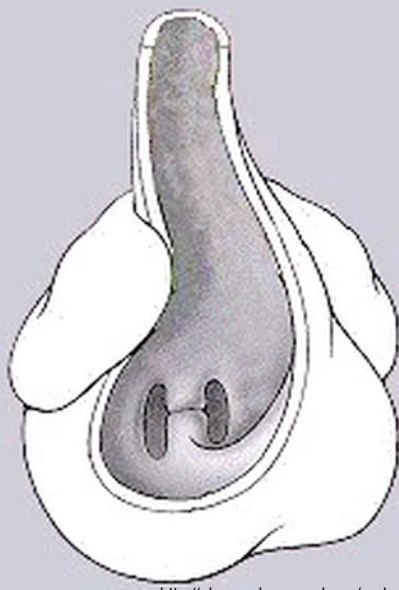


http://php.med.unsw.edu.au/embryology/index.php?title=Development_Animation_-_Heart_Atrial_Septation

four chambered heart



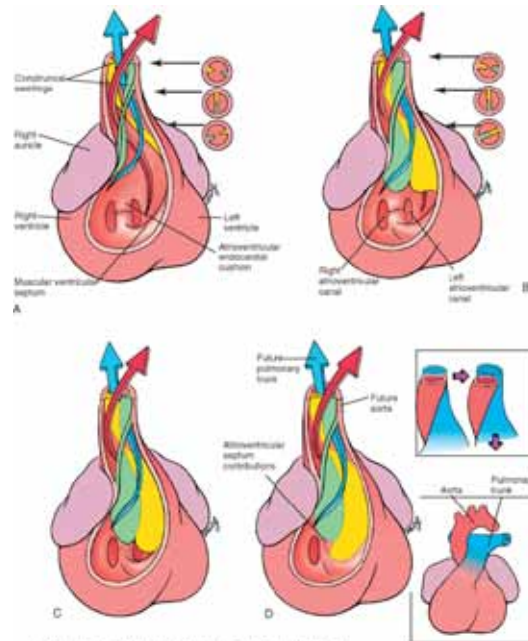
outflow tract septation



- initially outflow tract is a single tube, the bulbus cordis
- elongates to form proximal conus arteriosus and distal truncus arteriosus
- 2 growths 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



Schoenwolf et al; Larsen's Human Embryology, 4th Edition.
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congenital heart disease (CHD)

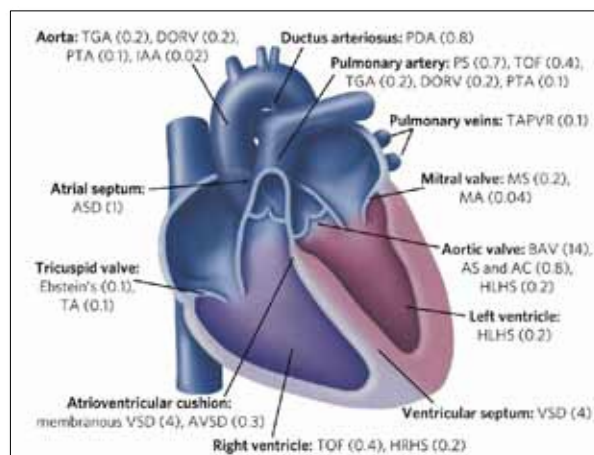
6-27 per 1,000 live birth

**Australia
2009**

72,800 fetal deaths
3066 CHDs

274,000 live births
1650-7400 CHDs

4 children
die each week



44 per 1,000 fetal deaths

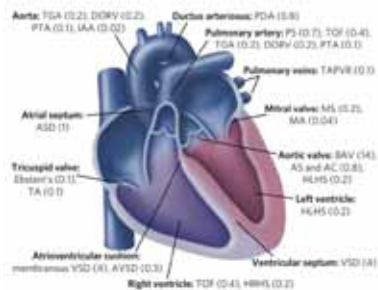
Australia

62,000 with CHD
50% >18yo

recurrence risk
to offspring
up tp 6.7%

Bruneau (2008) Nature
Hoffman (1995) Pediatr Cardiol

congenital heart disease (CHD)



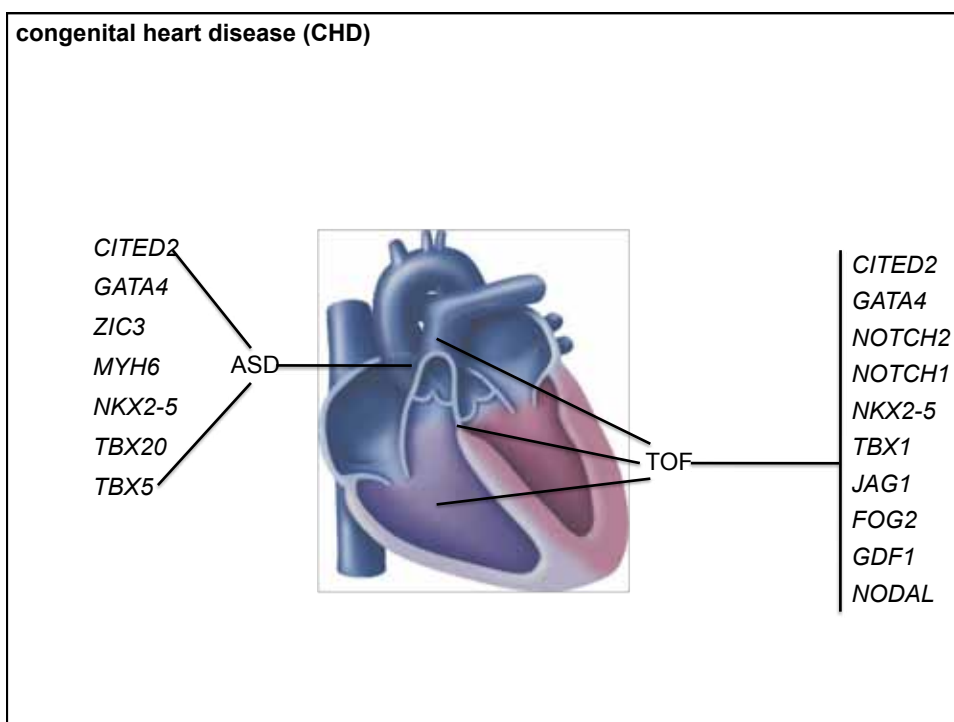
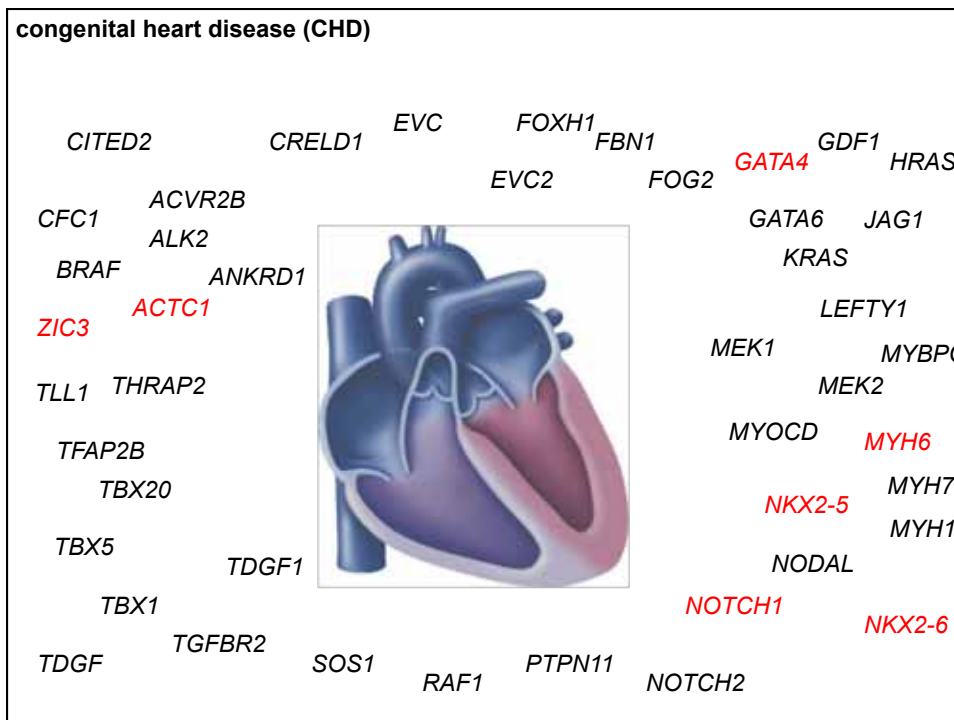
How do we identify the genes associated with these defects?

- 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 ASD in mice
- understand developmental processes eg. SHF – OFT – aorta + pulmonary artery

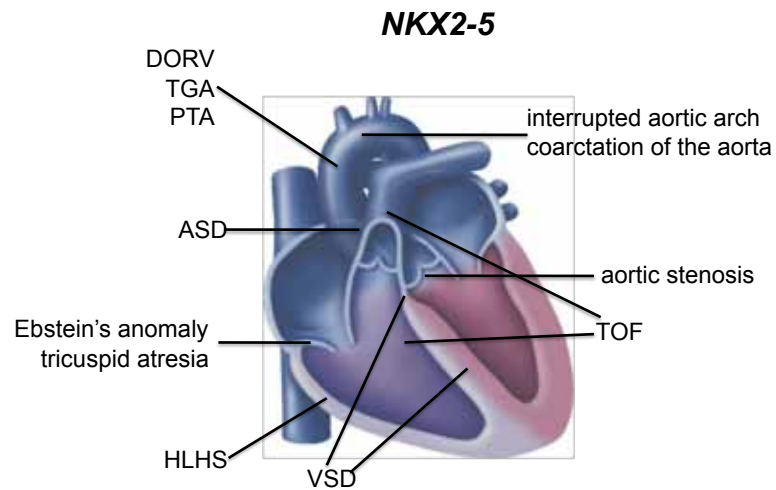
Bruneau Nature 2008

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
- for unselected CHD, the frequency of these gene variants ranges from 0.77% for *CITED2* to 2% for *NKX2-5*



congenital heart disease (CHD)



congenital heart disease (CHD)

