Development of the heart

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Objectives:

- *Describe early angiogenesis.*
- *Describe the heart tube formation.*
- *Describe the partitioning into a 4-chambered heart.*
- *List the formation of heart valves and the conducting system in the heart.*
- *Explain the basis of congenital heart malformation.*

THE CARDIOVASCULAR SYSTEM
TIMELINE

Blastocyst

Day 20

Heart tubes and embryonic vessels develop

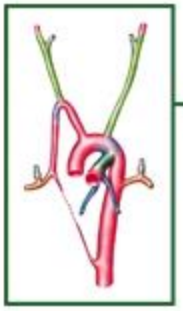
Day 25

Intraembryonic circulation established

1

Embryo

6 weeks



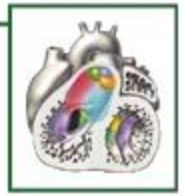
Aortic arches transform

4-5 weeks

Heart tube partitions into 4 heart chambers

2

8 weeks



Heart valves completed

Fetus

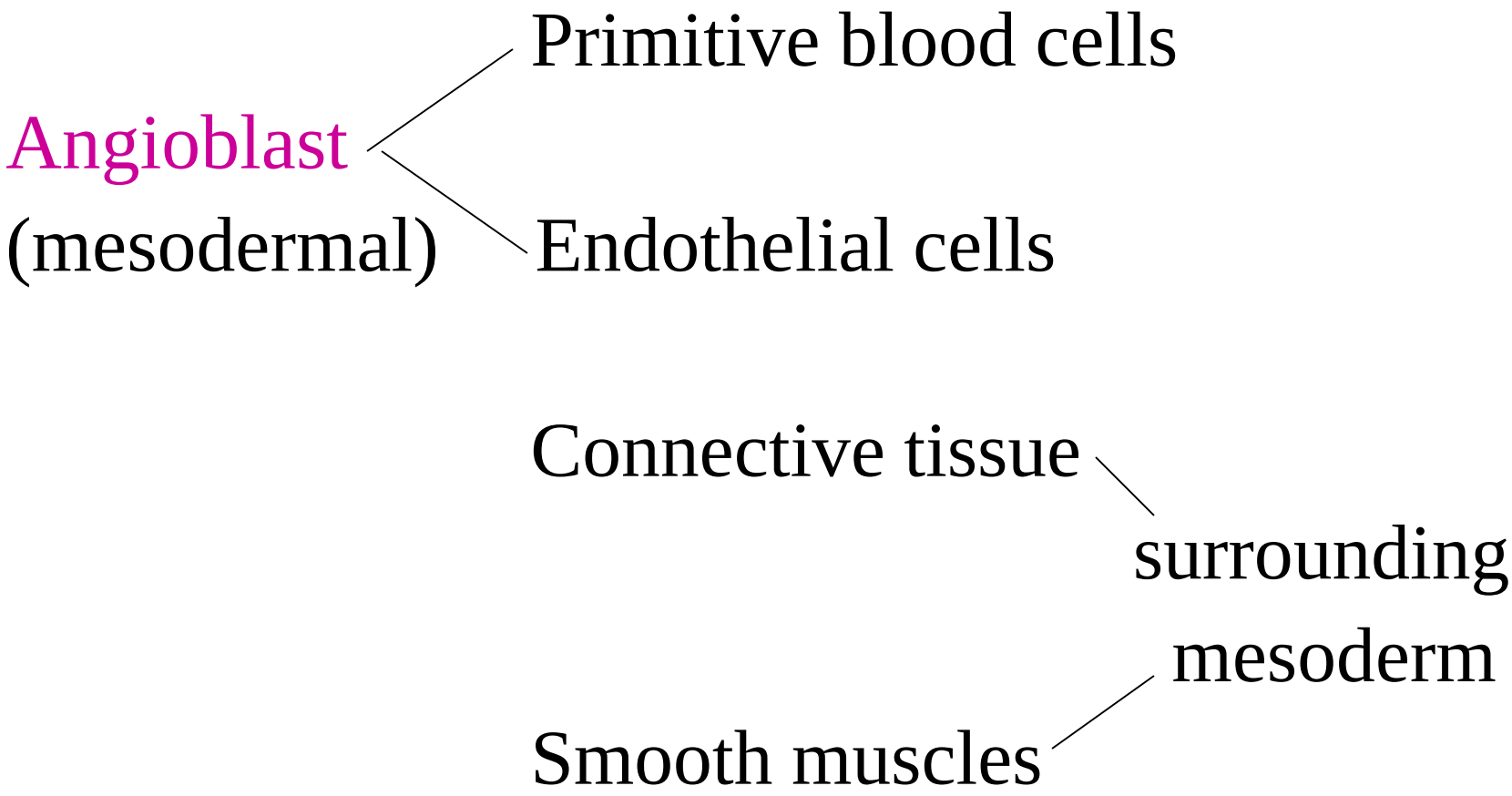
9

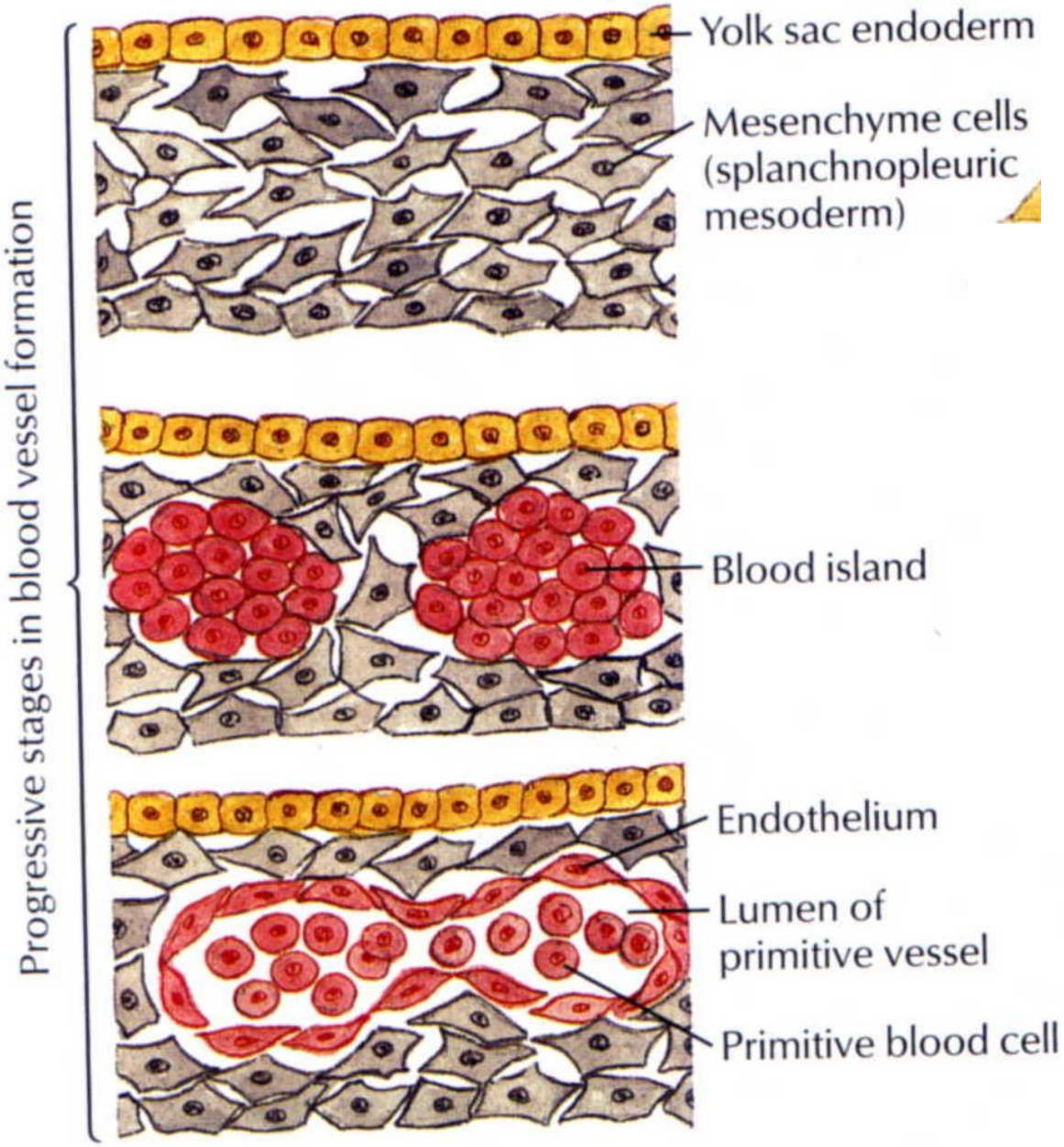
Birth

Birth

Foramen ovale closes with increased blood flow from lungs

Blood and blood vessels





Blood vessels formation

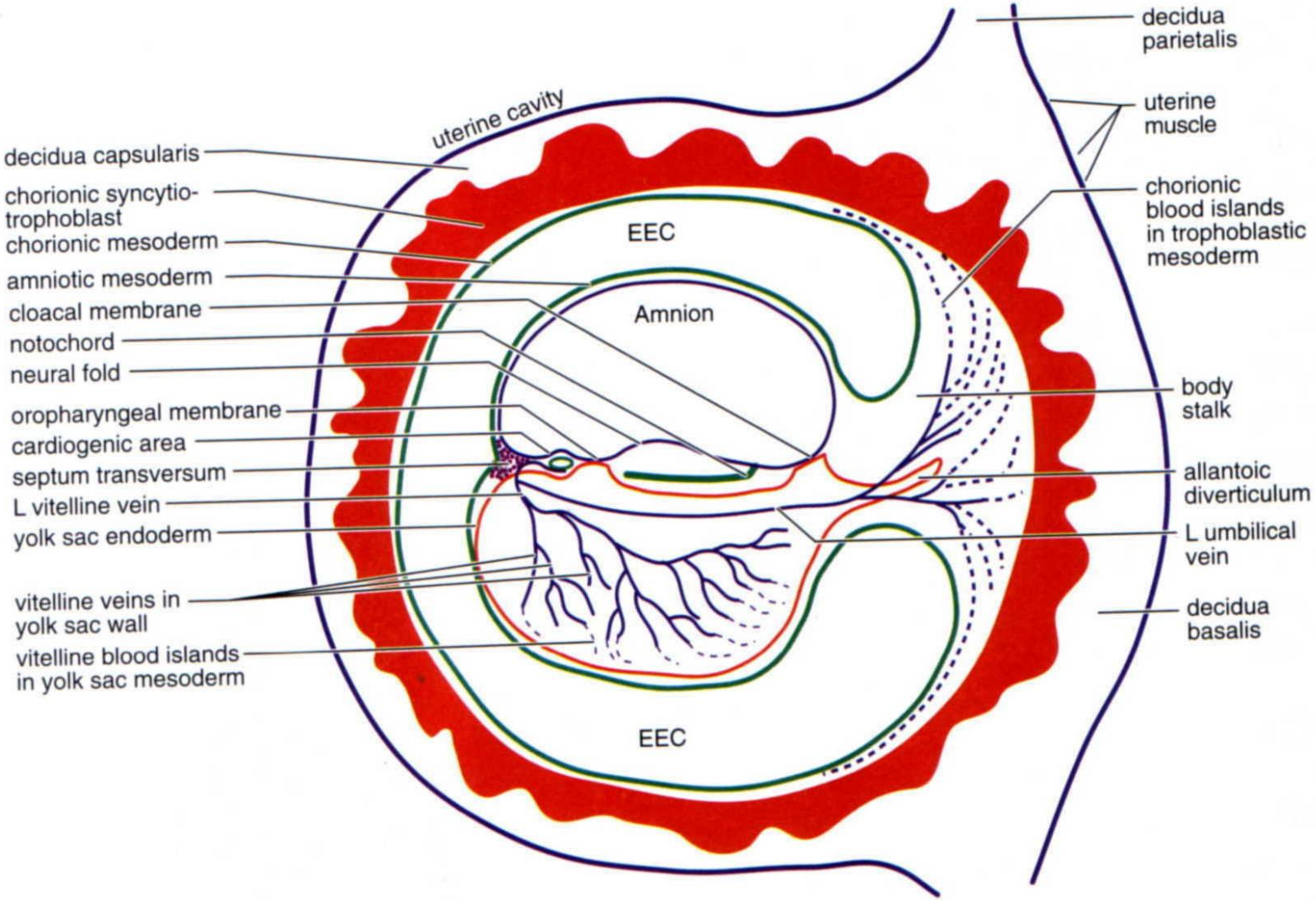
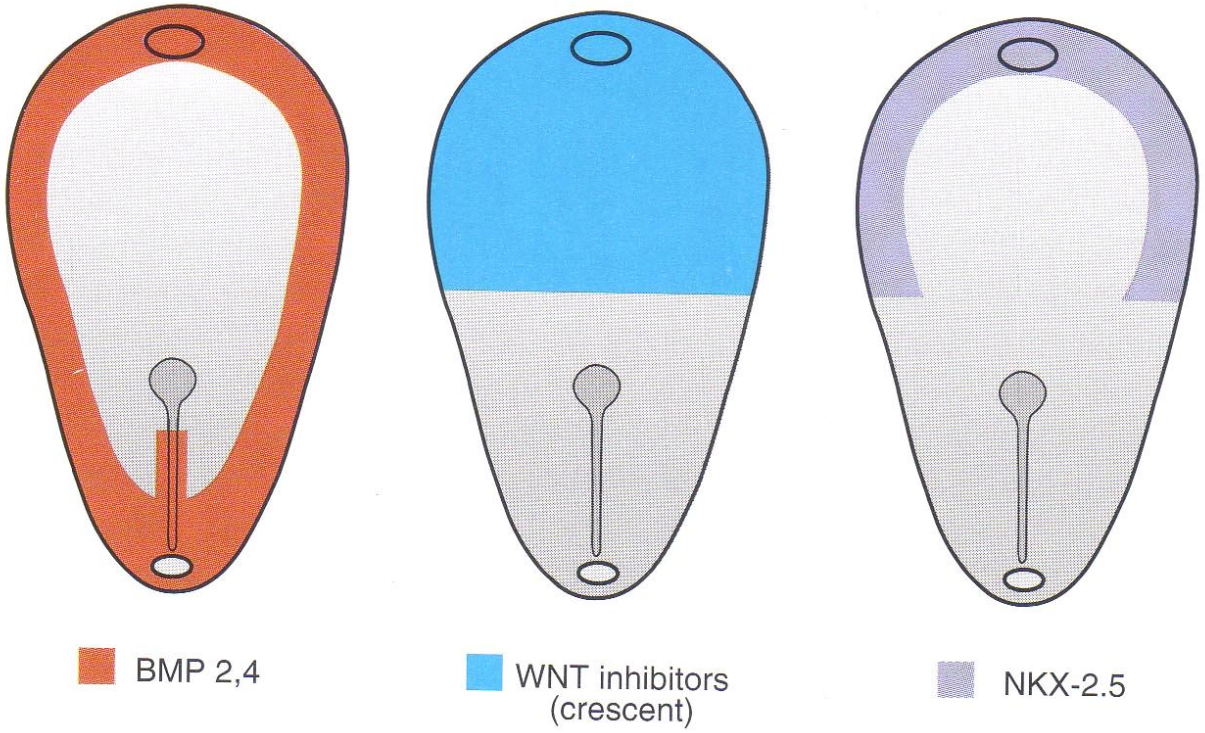


FIGURE 1 19-day human conceptus, implanted in the endometrium. Blood islands give rise to vitelline, chorionic, and umbilical veins.

The three parts of circulation: vitelline, chorionic & intraembryonic

Molecular regulation of cardiac development



- **Heart induction** – BMPs secreted by endoderm and lateral plate mesoderm together with inhibition of *WNT* in the anterior part of the embryo induce the expression of *NKX-2.5* in the heart -forming region .
- **Cardiac looping** - is induced by the *nodal* and *lefty2* genes. These two genes induce the transcription factor of *PITX2* in deposition of extracellular matrix in looping.

Development of the heart - 1

1. Cardiogenic plate appears around 3rd week
   Anterior to prochordal plate
   Pericardial coelom develop around heart tube
2. Rotation of heart primordia –180° rotation
3. Fusion of heart tubes around 4th week;
4. Differentiation of the heart tube tissue
   Epicardium – connective tissue
   Myocardium – cardiac muscle
   Subendocardium – spongy reticular tissue
   Endocardium - endothelium

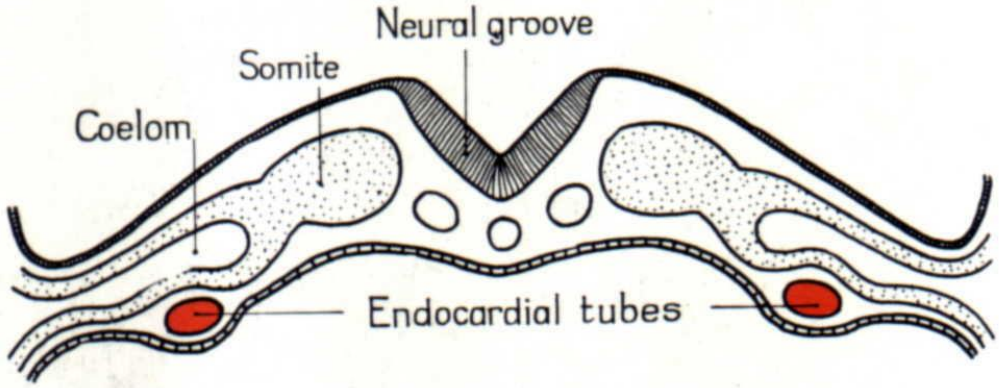


Fig. 2. — *Endocardial tubes in the splanchnopleure.*

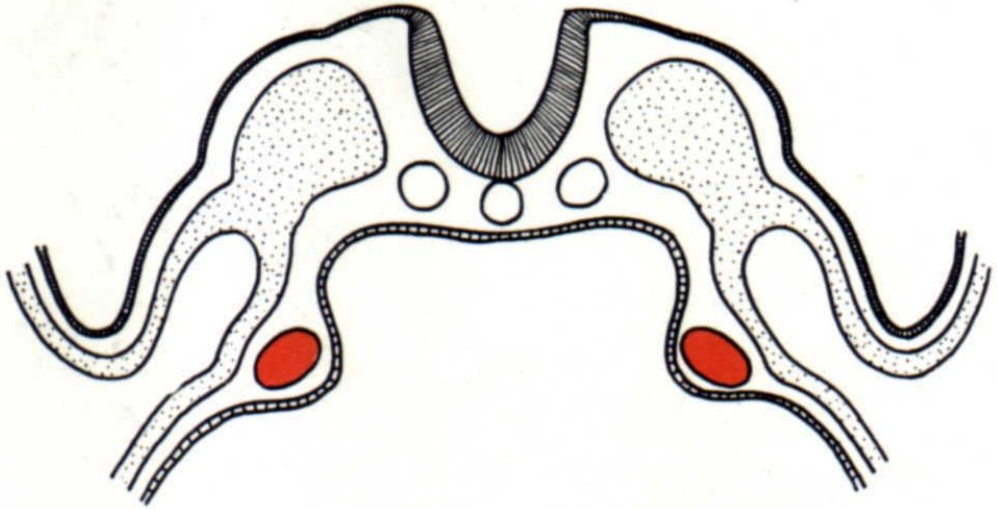


Fig. 3. — *Embryonic cephalocaudal flexion.*

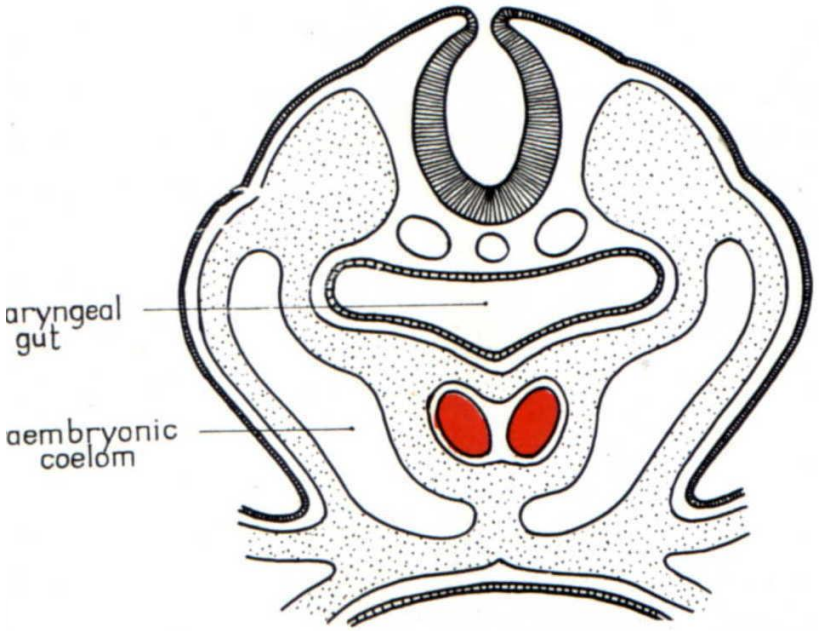


Fig. 4. — *Joining of tubes.*

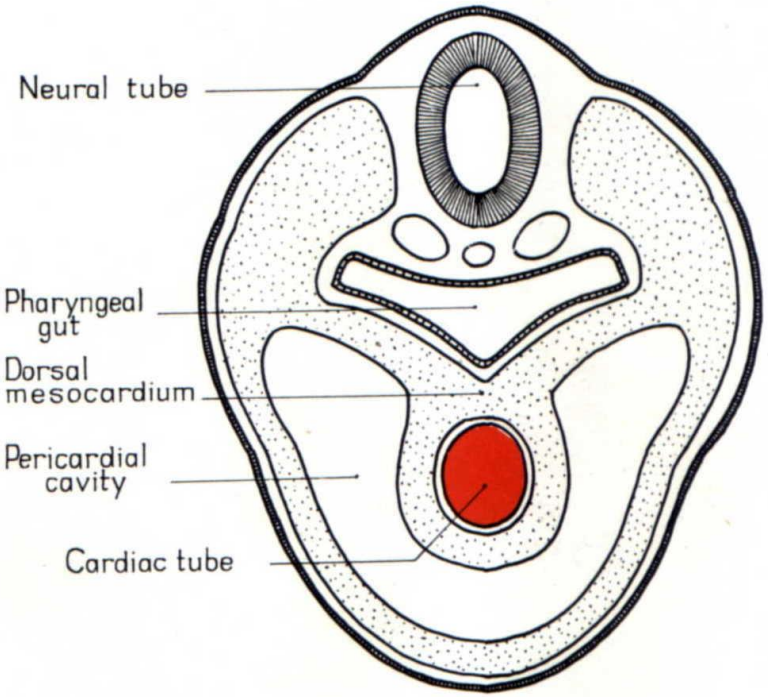
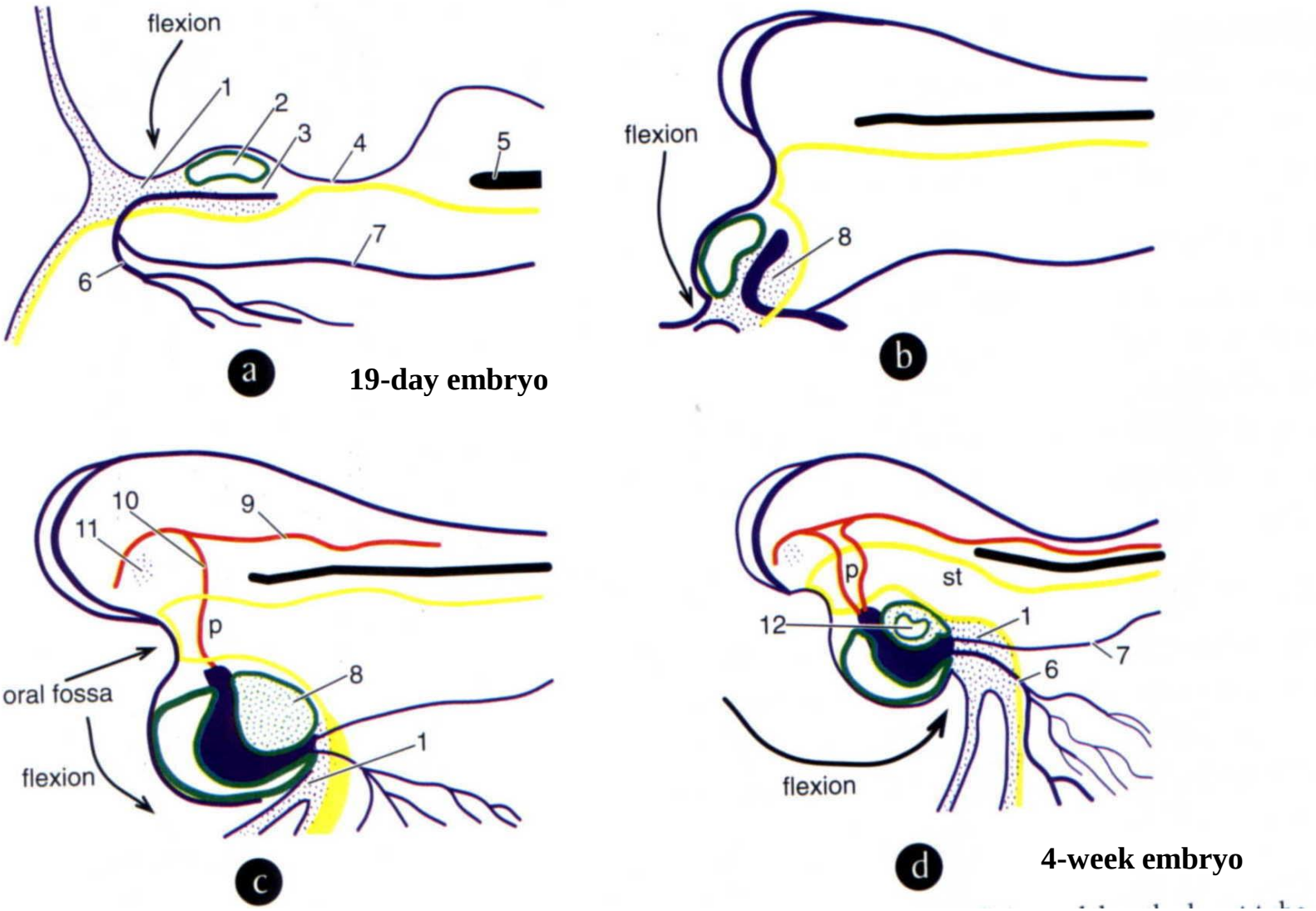


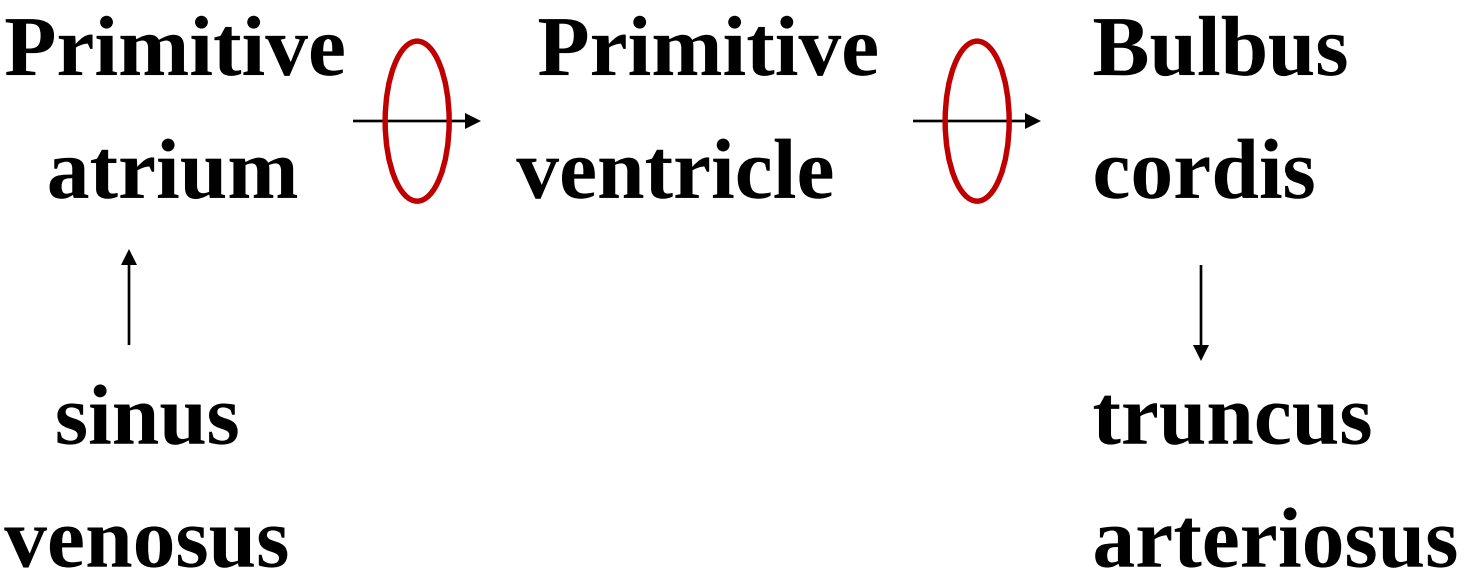
Fig. 5. — *Fusion into a median tube.*



Change of position of the heart in the developing embryo

Development of the heart - 2

5. Subdivision of the heart tube by 2 **rings**



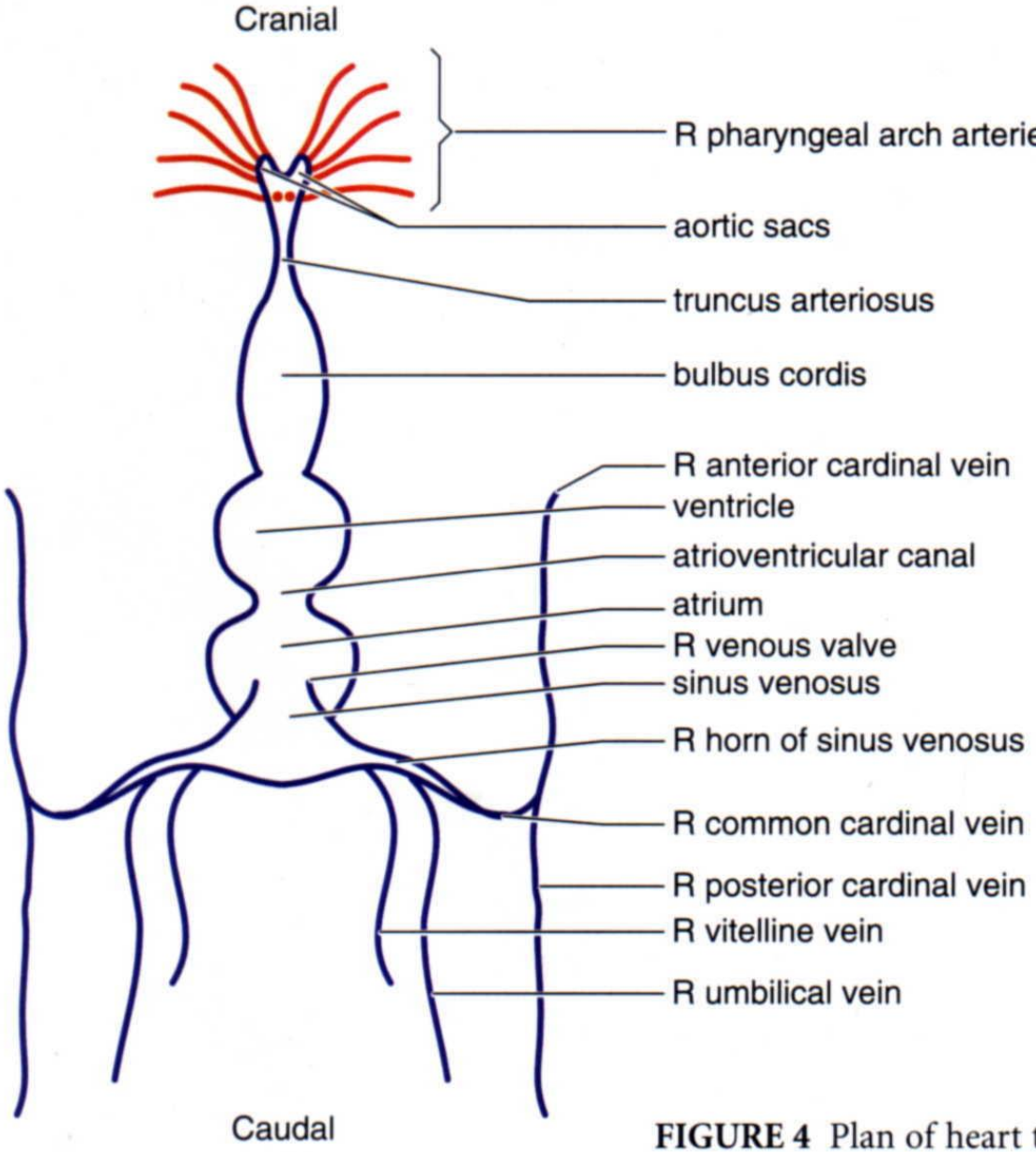


FIGURE 4 Plan of heart tube (4 weeks).

Development of the heart - 3

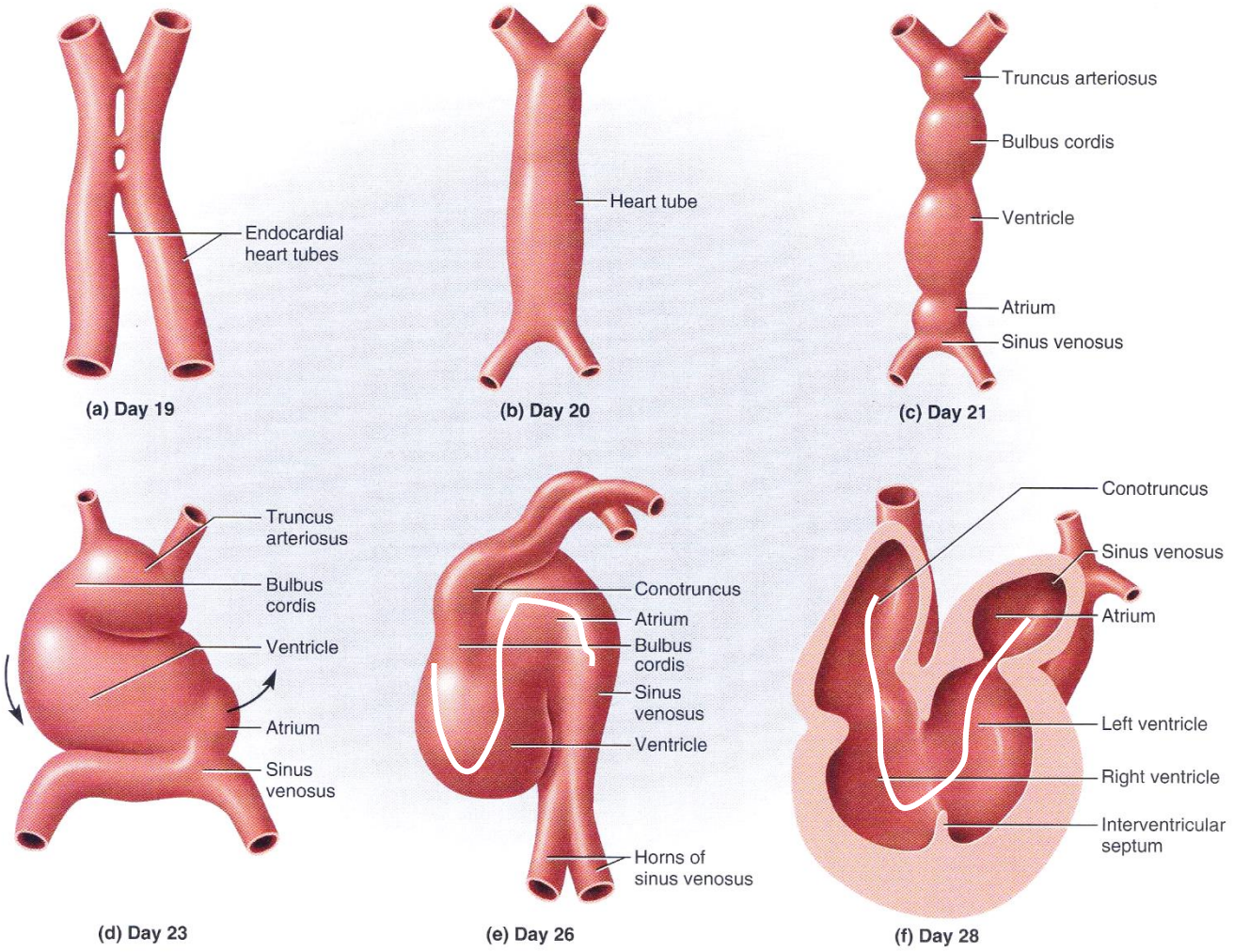
6. Bending of the heart tube

- dorsal mesocardium breaks (transverse sinus)
- S-bend (**bulboventricular bend** & **atrioventricular bend**)

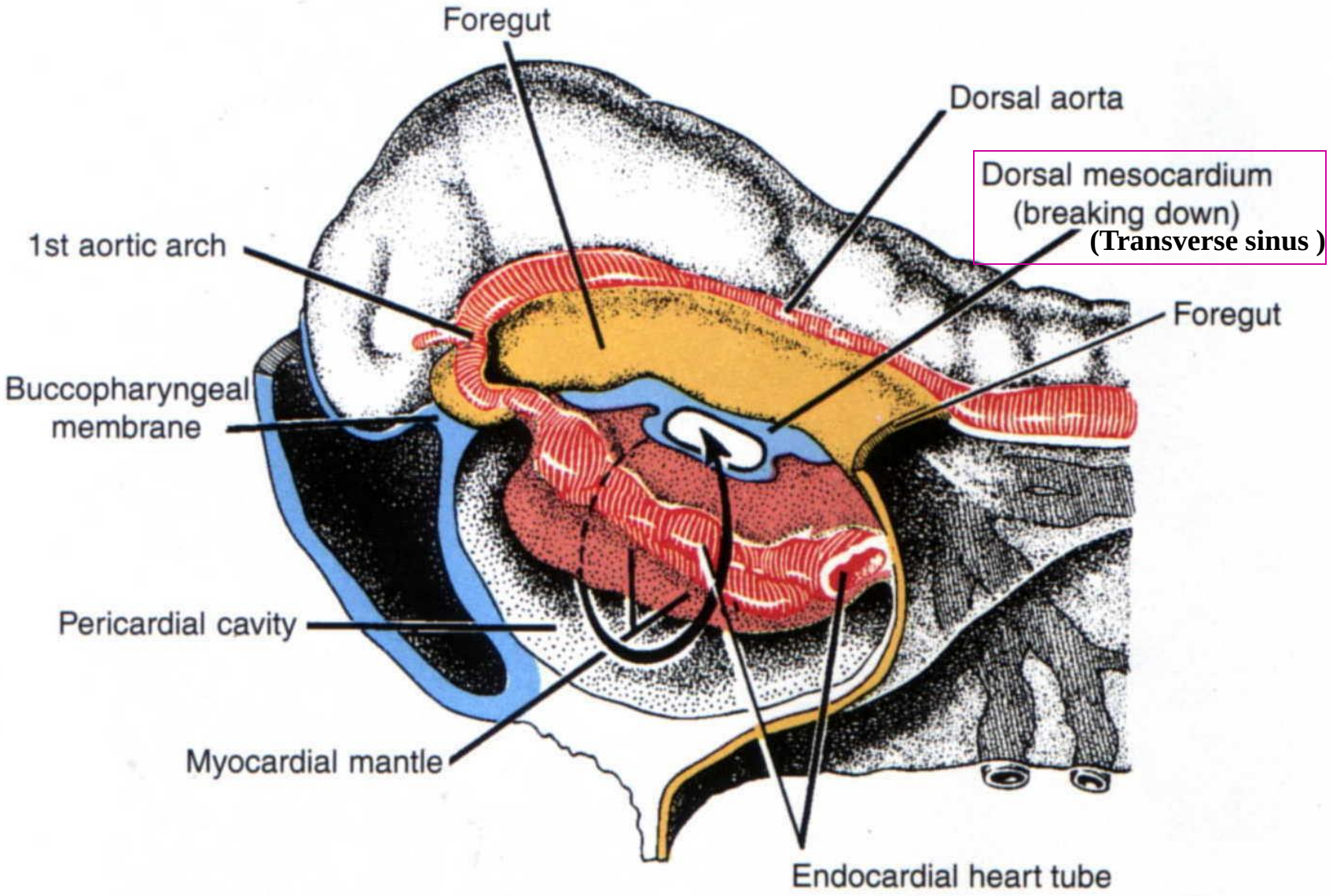
Straightening of atrioventricular bend

- Definitive relationship of atrium and ventricle (atria cranial to the ventricles)

Development of the Heart



(a) Endocardial heart tubes start to fuse, (b) Fusion of heart tubes complete, (c) Division of heart tube into dilated segments, (d) Looping of the heart tube, (e) Looping complete, (f) Frontal section of heart tube.


Foregut
Dorsal aorta
Dorsal mesocardium
(breaking down)
(Transverse sinus)
1st aortic arch
Foregut
Buccopharyngeal
membrane
Pericardial cavity
Myocardial mantle
Endocardial heart tube

Development of the heart - 4

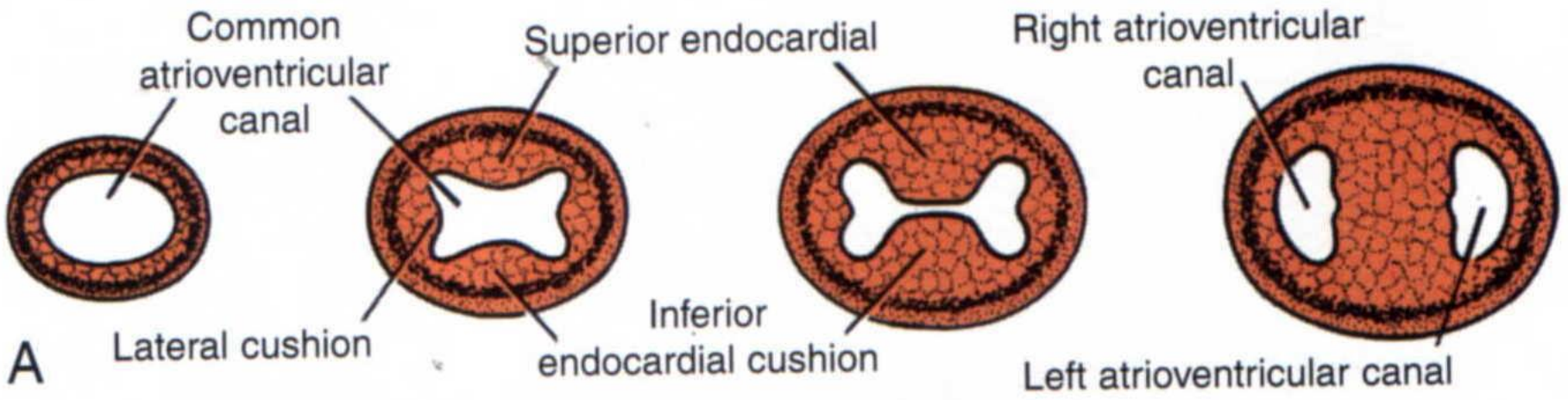
7. Partition & formation of 4-chambered heart

7.1 Partition of atrio-ventricular canal

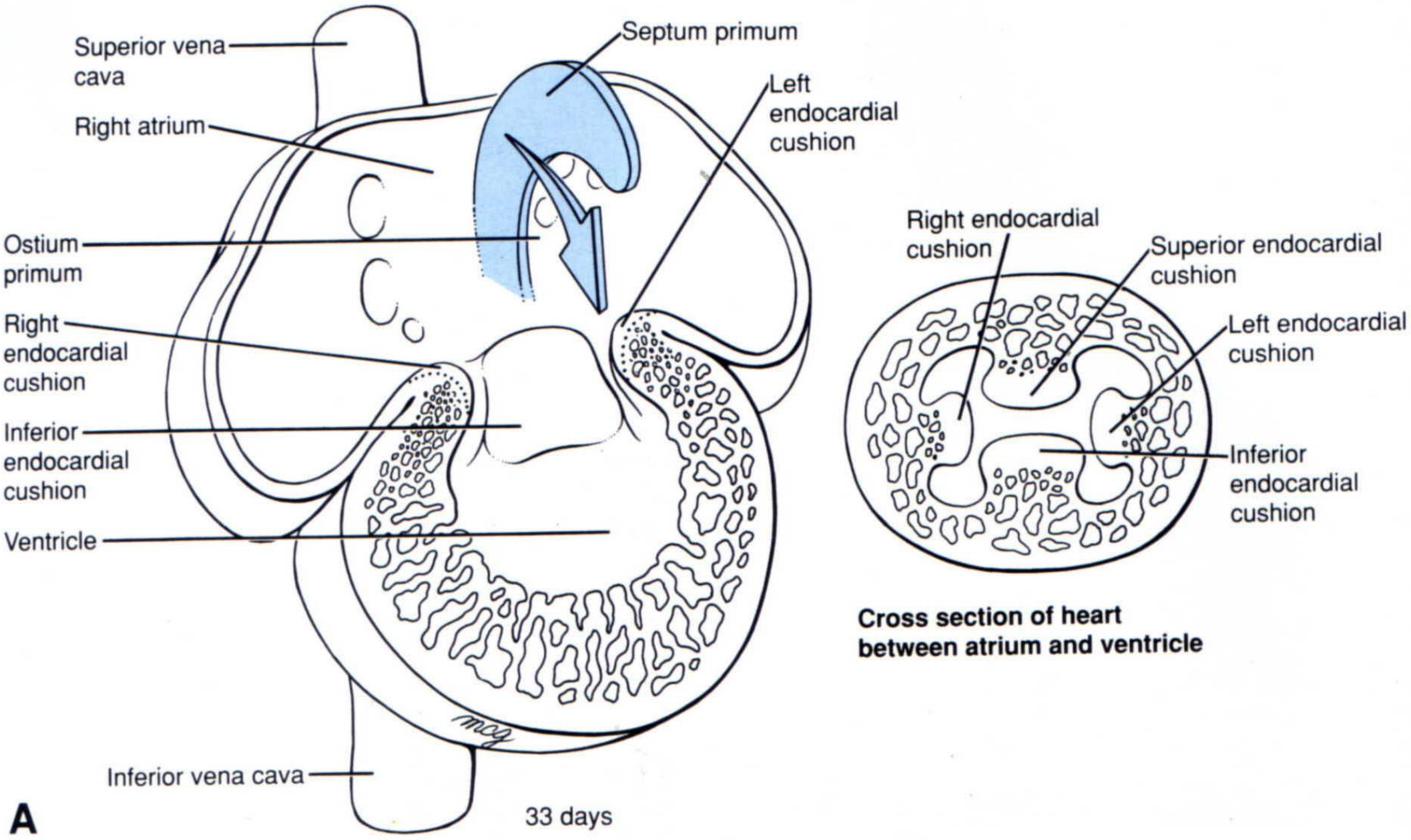
- Endocardial cushions
- Fusion of endocardial cushions (5^{th} wk)

7.2 Partition of primitive atrium

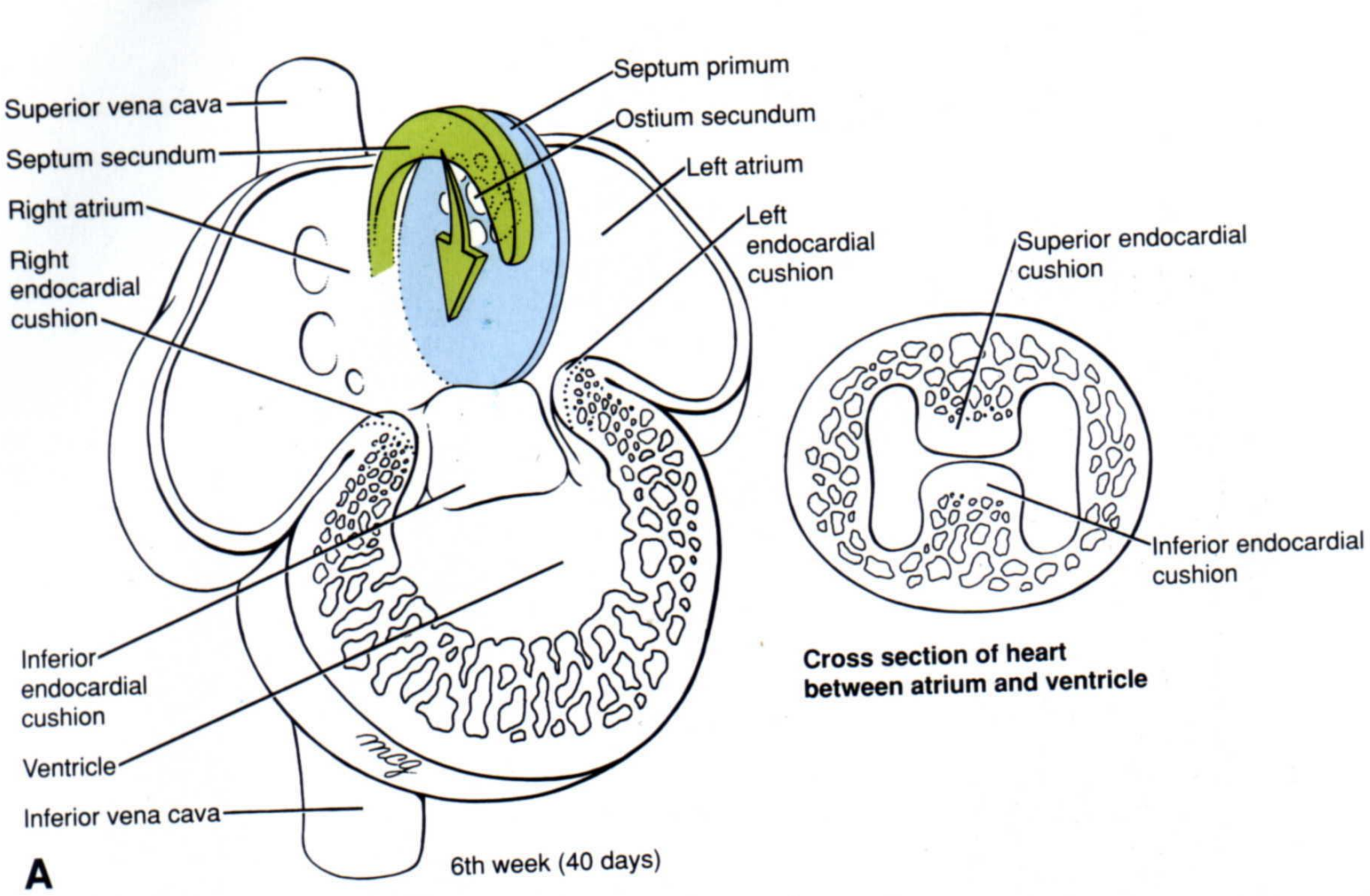
- **septum primum** (with foramen primum and foramen secundum)
- **Septum secundum** with foramen ovale (marked by fossa ovale in adult heart)



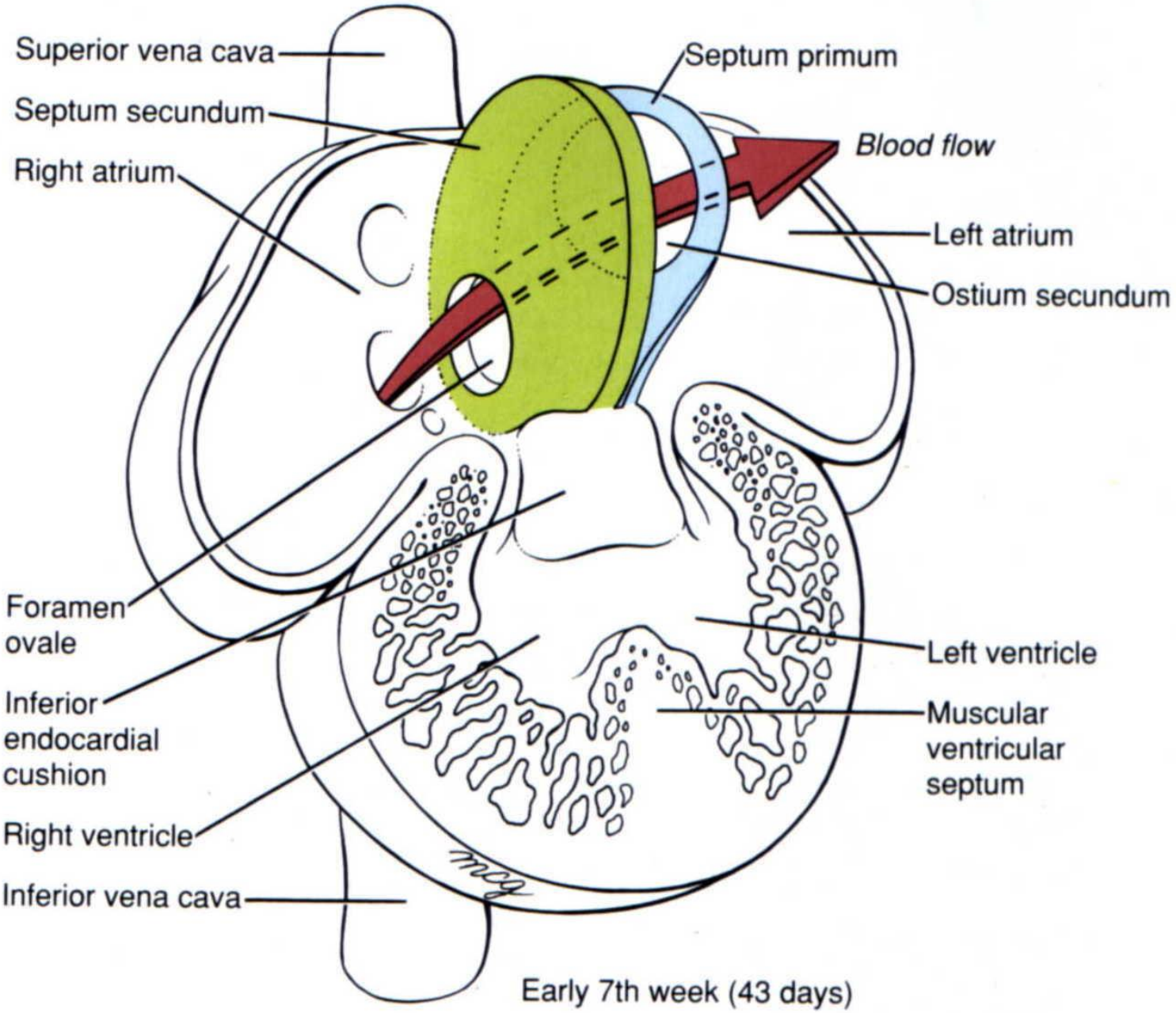
Formation of the septum in the atrioventricular canal



Development of the interatrial septum - 1



Development of the interatrial septum - 2



Development of the interatrial septum - 3

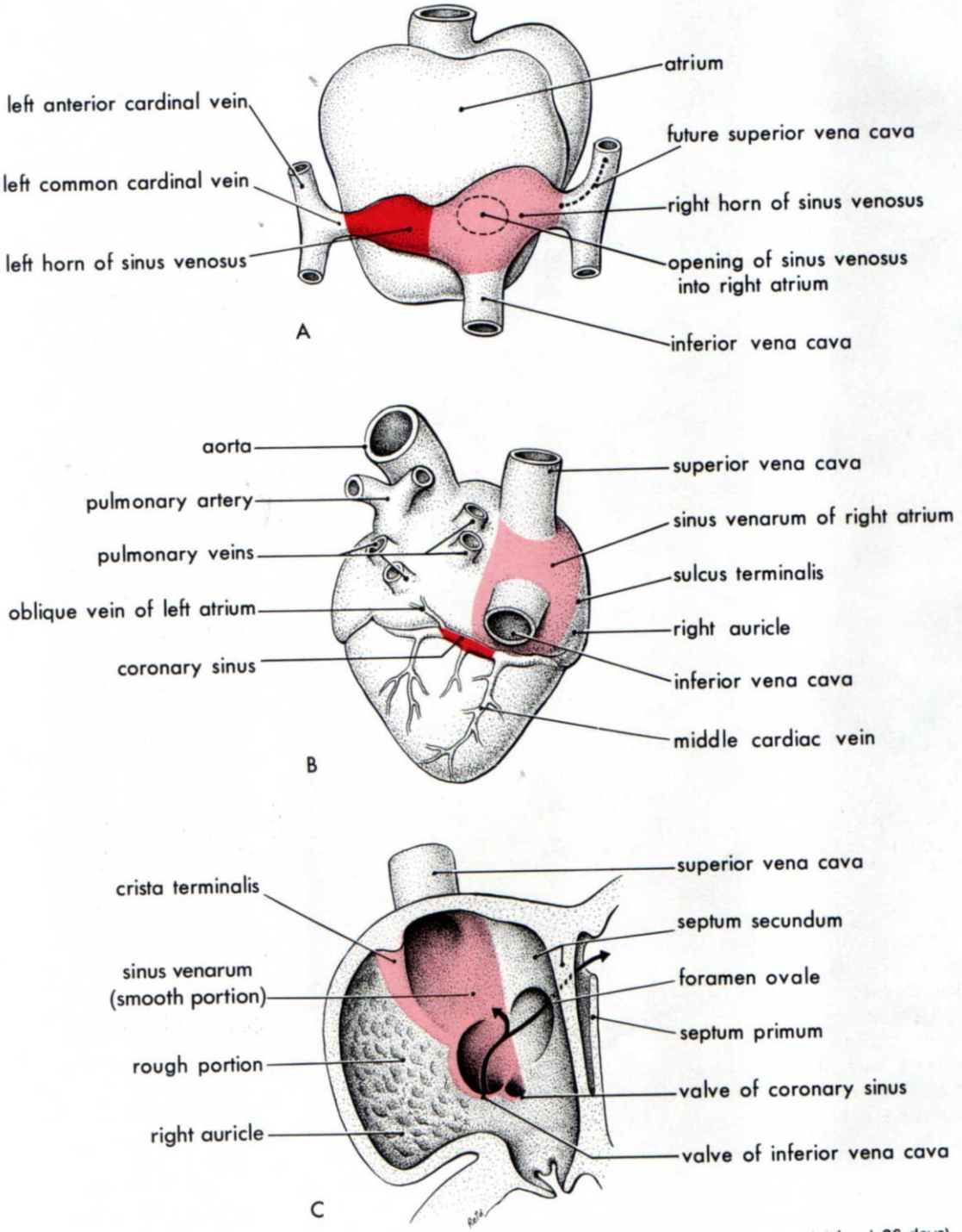
Development of the heart - 5

7.3 Changes in sinus venosus

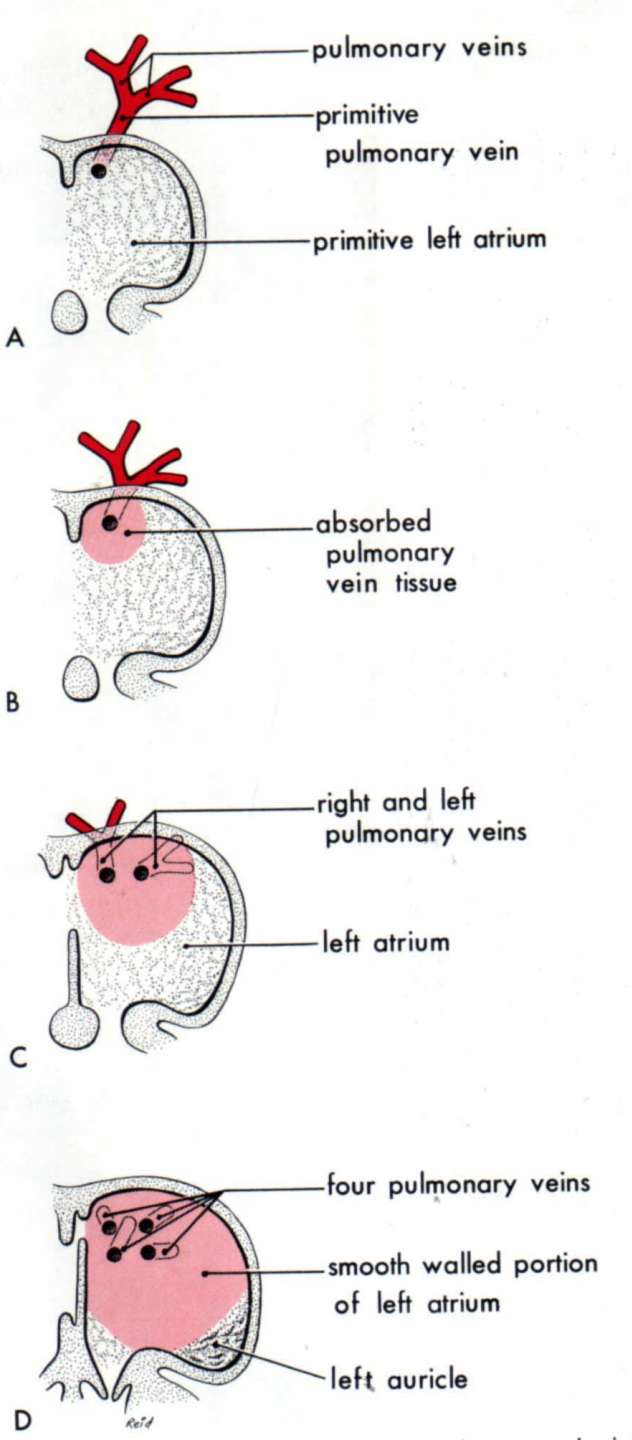
- Development of 2 left-to- right venous shunts
- Left sinus venosus reduces to **coronary sinus**
- Right sinus venosus enlarge and incorporate into the right atrium

7.4 Left atrium – incorporate the common pulmonary vein into left atrium.

Remodeling of the right atrium



Remodeling of the left atrium



Development of the heart - 6

7.5 Partition of primitive ventricle

- Muscular septum
- Membranous septum contributed by truncoconal septa and endocardial cushion

7.6 Fate of bulbus cordis and truncus arteriosus

- Bulbus incorporate into right ventricle
- Upper bulbus and truncus arteriosus separated by truncoconal septa into pulmonary trunk and aorta

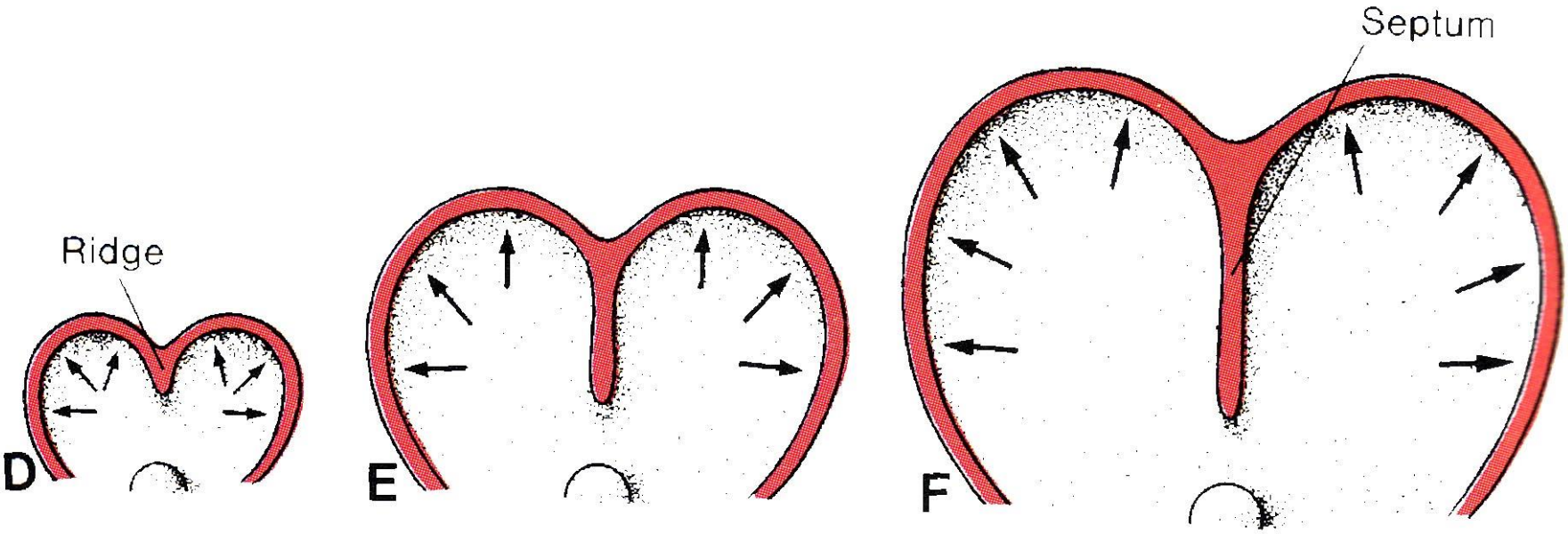
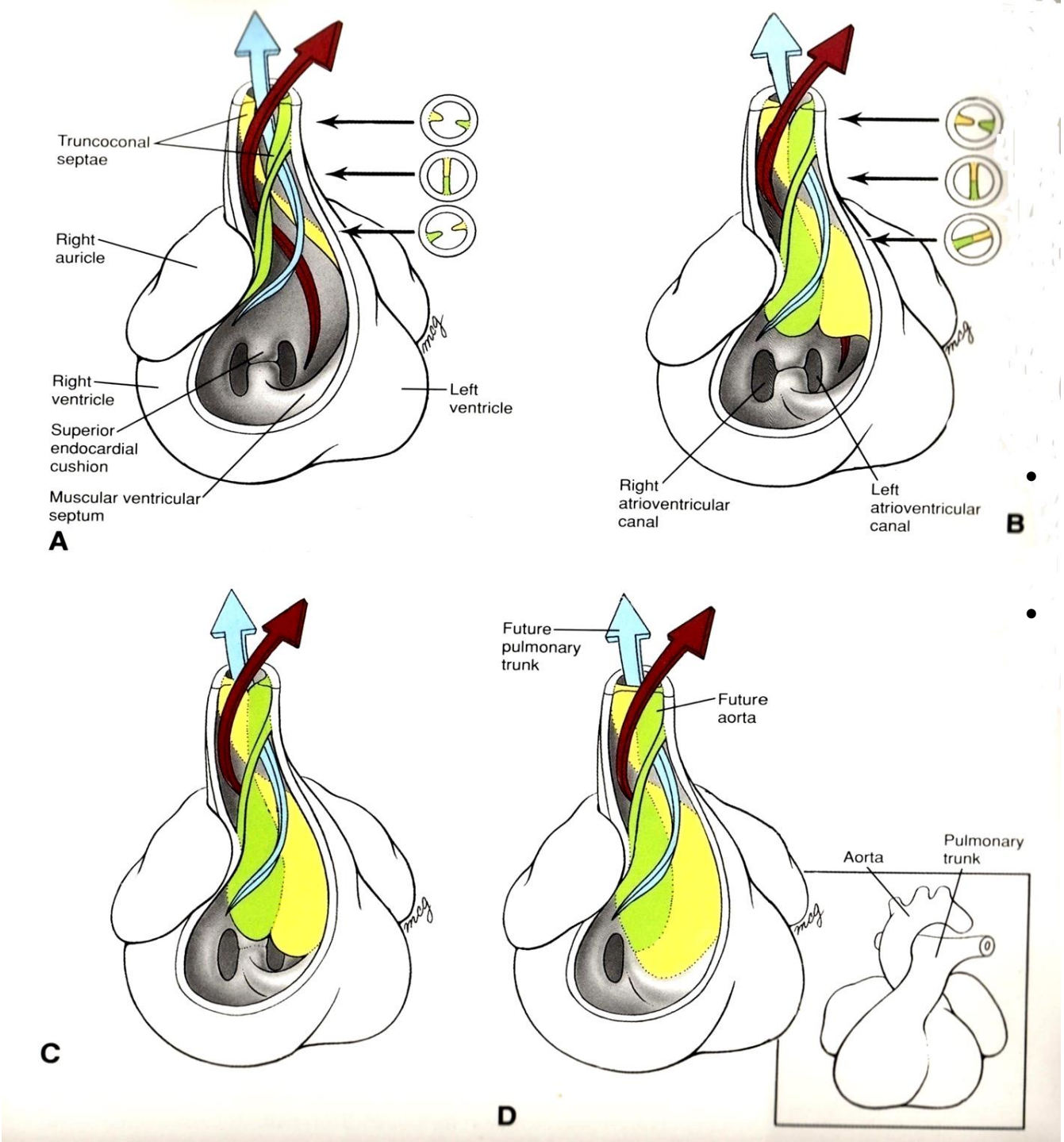


Diagram to illustrate the formation of muscular interventricular septum. Septum formed by two expanding portions of the wall of the heart. Such septum never completely separates two cavities.



- Formation of truncal and bulbar ridges
- When the spiral truncal and bulbar ridges fused, pulmonary trunk (PT) and aorta (Ao) are formed.

Larsen, 1996

Summary - Partition of the Heart

1. Endocardial cushion – dividing atrio-ventricular canal into left and right.

2. Formation of the interatrial septum

   - This is formed from two septa – septum primum and septum secundum.

   -Holes on the two septa – provide a shunt to allow blood to flow from right to left atrium before birth

3. Formation of the spiral conotruncal septa

   - Dividing the outgoing vessel into aorta and pulmonary trunk

4. Formation of the interventricular septum

   - Crescent shaped interventricular septum

   - Membranous interventricular septum contributed by cono-truncal septa and endocardial cushion to complete the septation.

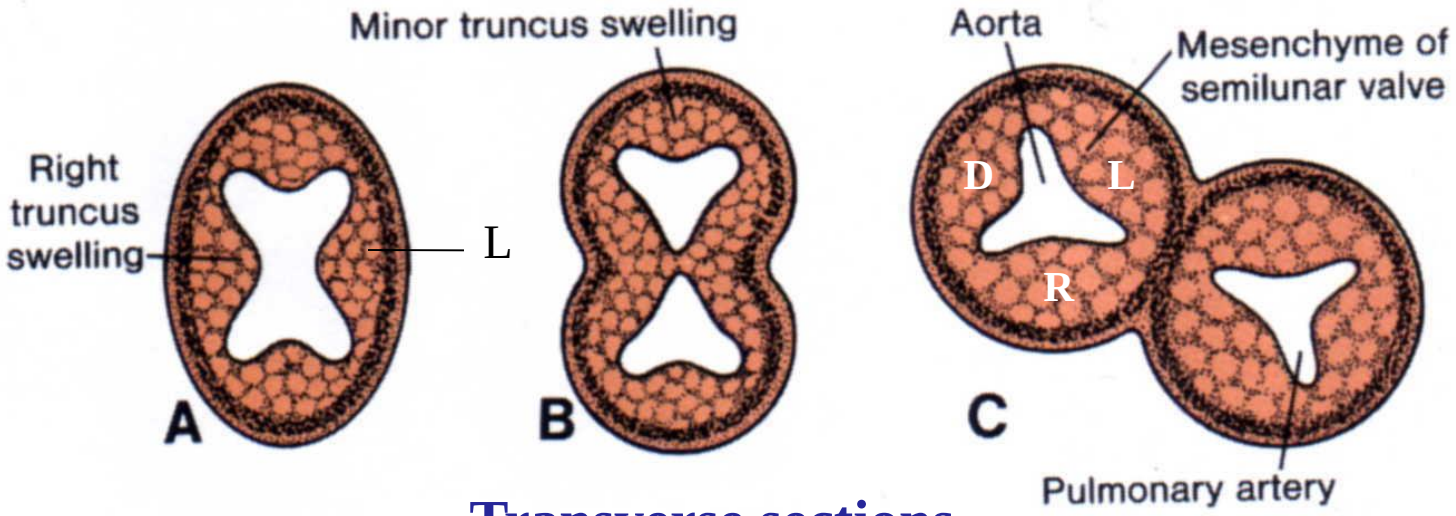
Development of the heart - 7

7.7 Cardiac valves

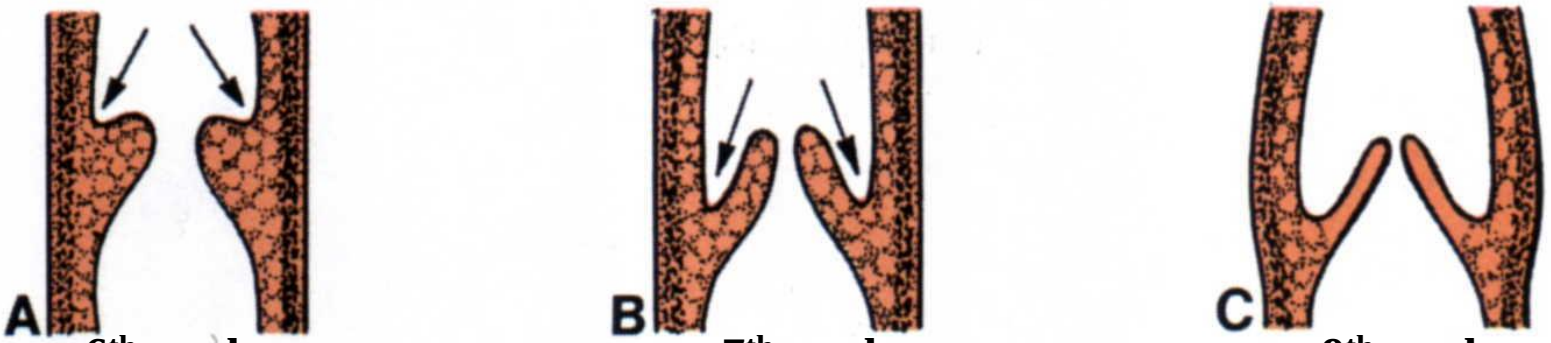
- Semilunar valves of aorta and pulmonary trunk
- Mitral and tricuspid valves

7.8 Conducting system

- **Primitive ventricle** (4^{th} week) controls the contraction
- **sinoatrial node** (**SAN**; 5^{th} week) originates from right wall of sinus venosus near opening of SVC
- **Atrioventricular node** (**AVN**) originates from (i) the left wall of sinus venosus and (ii) superior endocardial cushion of the atriventricular canal.
- **Bundle of His** develops in interventricular septum and bifurcates on septal ridge into L & R ventricles



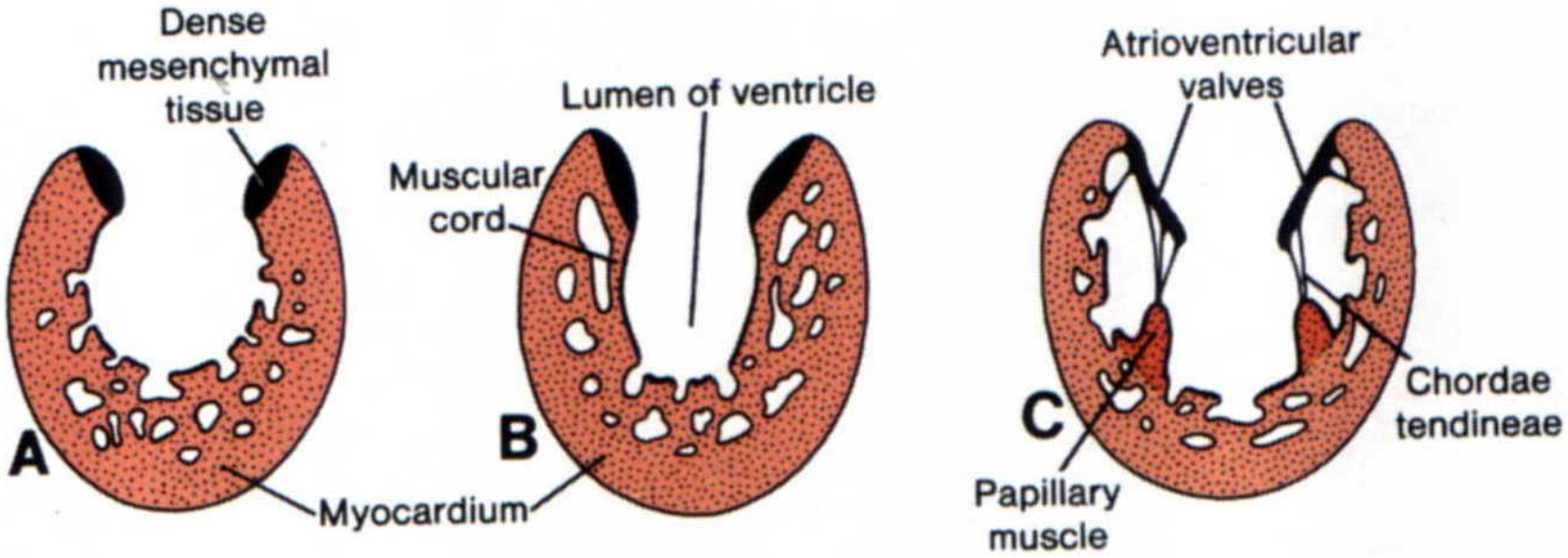
Transverse sections



6th week **7th week** **9th week**

Longitudinal sections

Development of semilunar valves of aorta and pulmonary trunk



Development of atrioventricular valves

(mitral and tricuspid valves)

Tissue of the ventricle are hollowed out and mesenchymal tissue at the atrioventricular remain attached to the ventricular wall by chordae tenineae.

Development of the heart - 7

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- Semilunar valves of aorta and pulmonary trunk
- Mitral and tricuspid valves

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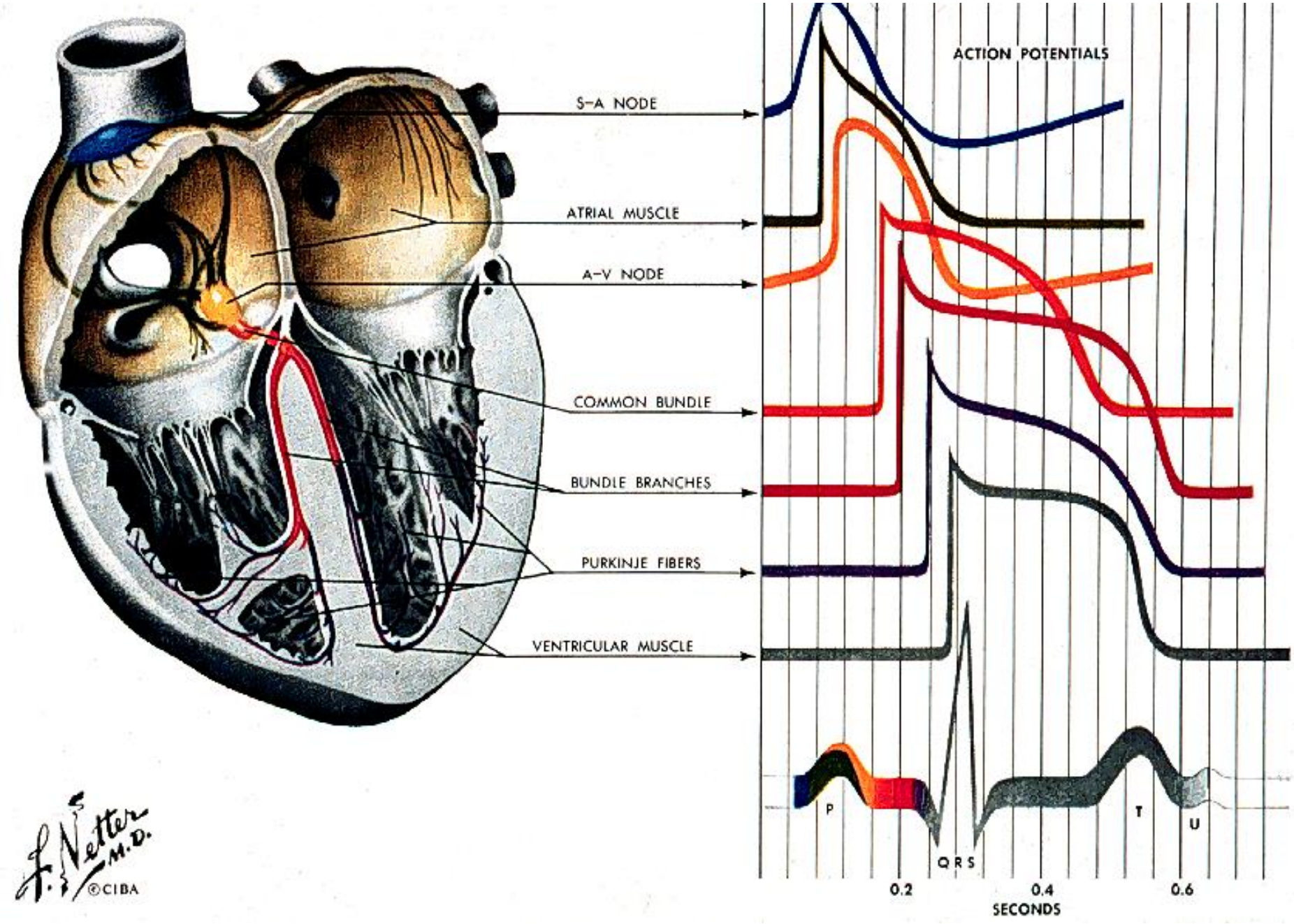
S–A NODE
ATRIAL MUSCLE
A–V NODE
COMMON BUNDLE
BUNDLE BRANCHES
PURKINJE FIBERS
VENTRICULAR MUSCLE
ACTION POTENTIALS
P
Q R S
T
U
0.2
0.4
0.6
SECONDS
F. Netter M.D.
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Development of the conducting system

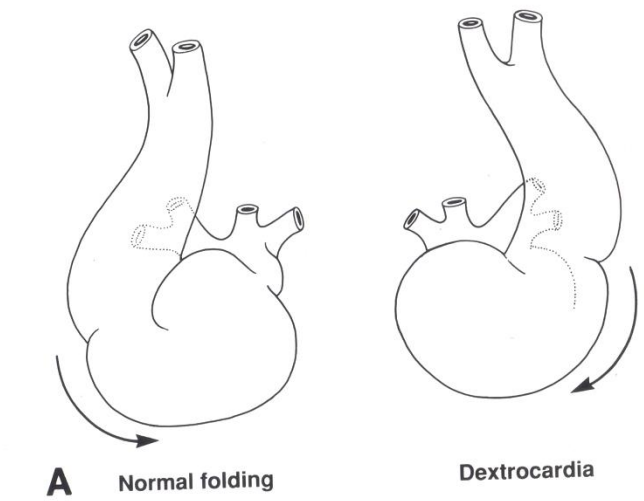
- The Purkinji cells in the heart arise from cardiogenic mesoderm and *develop in situ* from the myocardium

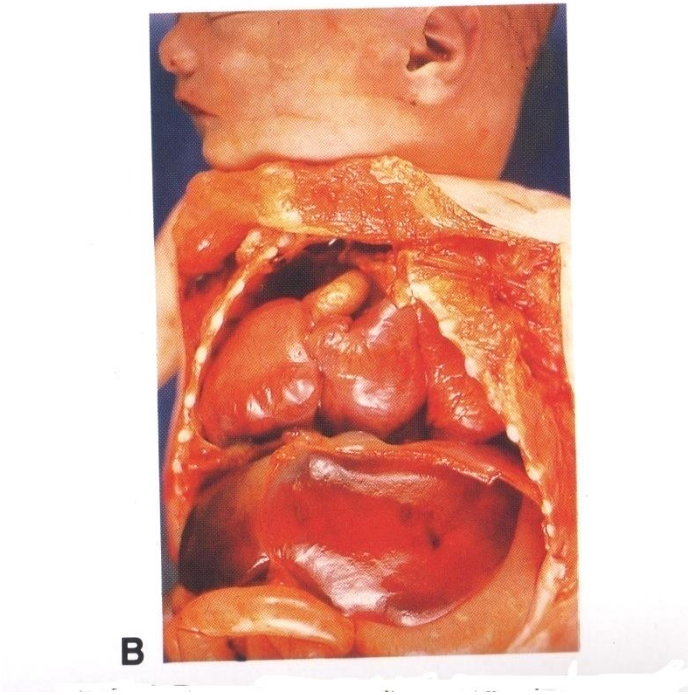
- In the cells of the conducting system, both nodes and all the conduction pathways develop from a series of rings of specialized cells that develop in the sulci of the truncoconal, bulboventricular, atrioventricular and sinoatrial junctions.

- According to this theory, these rings reshaped and rearranged during the folding of the heart tube so that they come into position to form nodes and pathways of the conducting system.

Mechanisms of Congenital Cardiac Pathogenesis

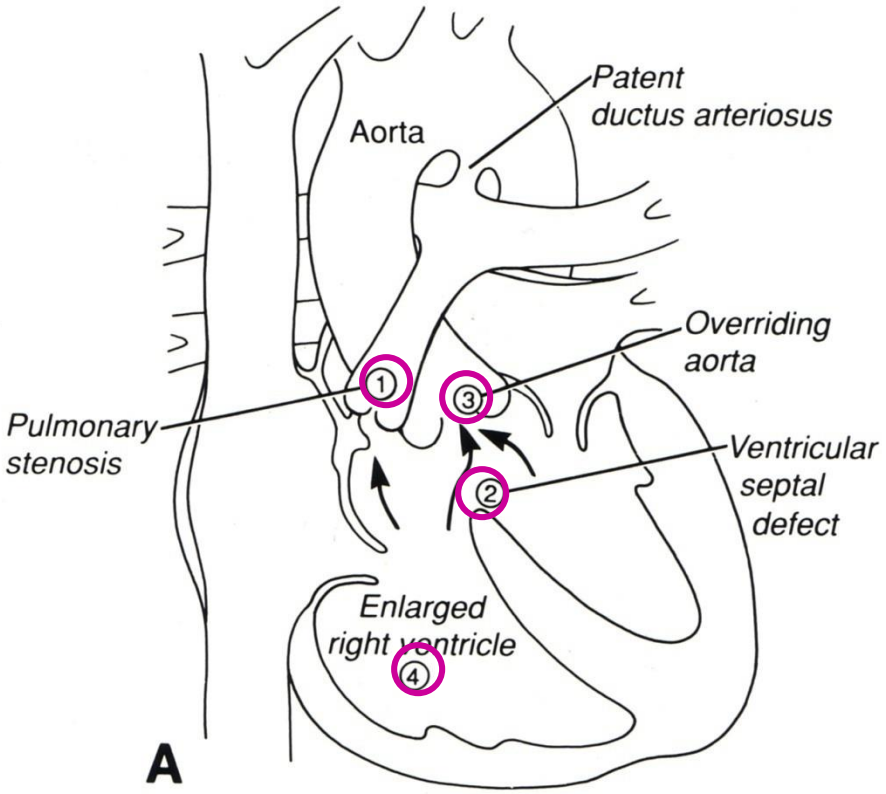
1. Left-right malformations, ***dextrocardia*****.** Most individuals with dextrocardia exhibit a general reversal in handedness and many organs, a condition known as ***situs inversus.***
2. **Neural crest cells** contribute to trunco-conal swelling Deficiency in neural crest cell leading to hypoplasia of truncoconal swelling, Tetralogy of Fallot, branchial arch IV deficiency, dextroposed aorta, tricuspid stenosis, e.g. **DiGeorge syndrome**.
3. Intracardic **haemodynamic forces** is important in morphogenesis
   - If shunting of blood from R to L is restricted, hypoplastic left heart results.
   - Obstruction of aortic blood flow results in ventricular membranous septal defect.

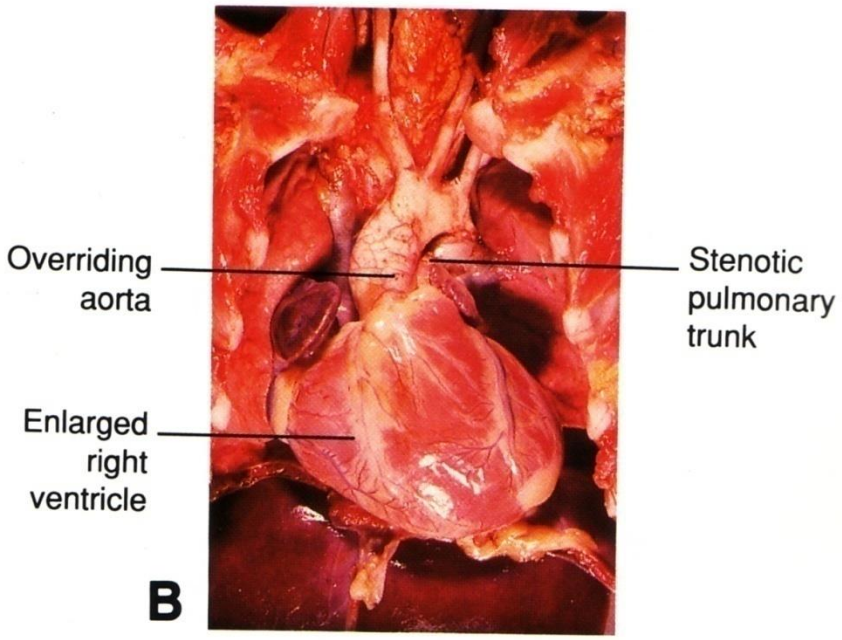




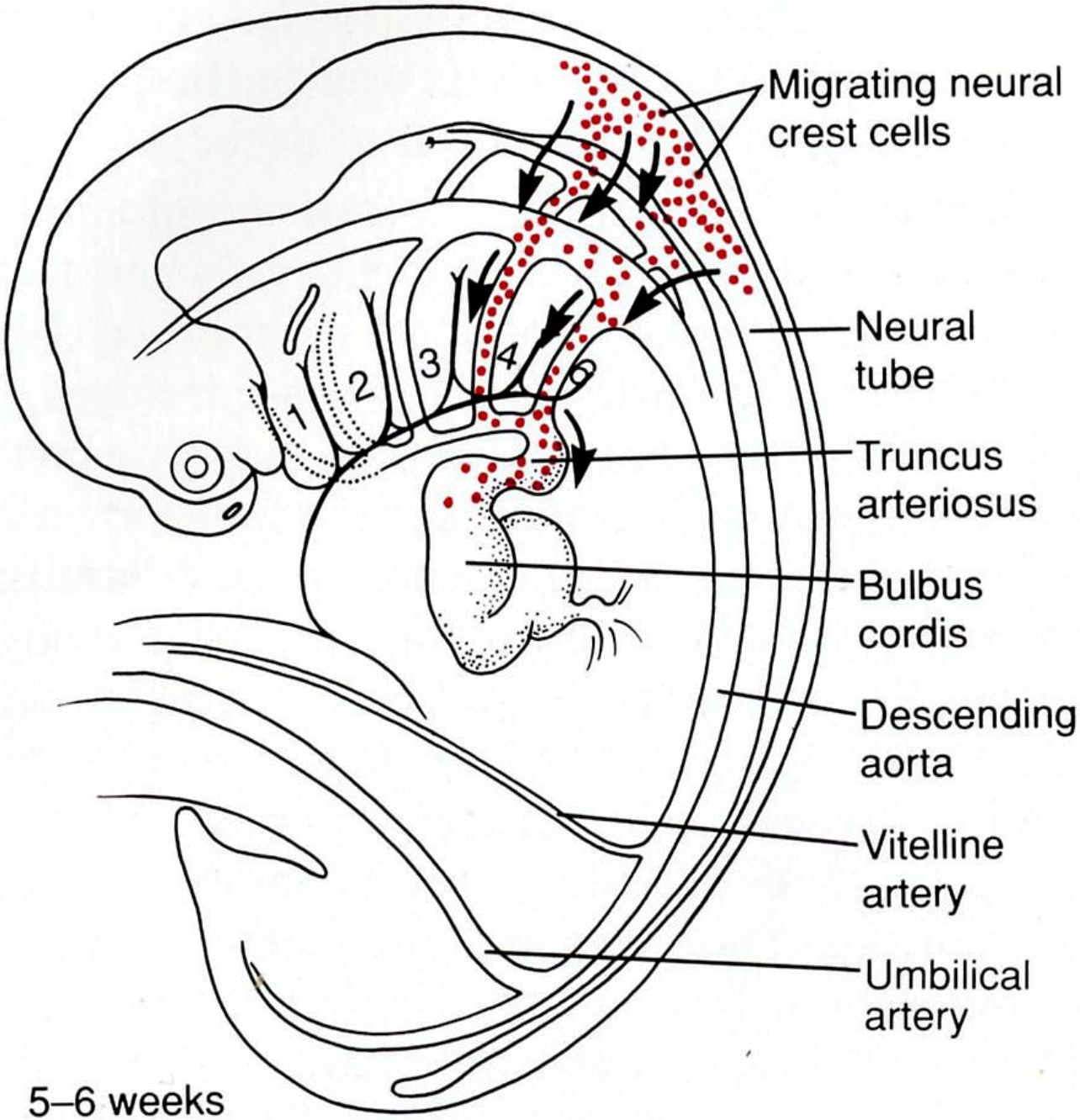
A In dextrocardia, the folding of the heart tube is reversed. The heart is normal in form, but is a mirror image of the normal heart.

B Infant with dextrocardia.





Tetralogy of Fallot


Migrating neural crest cells
Neural tube
Truncus arteriosus
Bulbus cordis
Descending aorta
Vitelline artery
Umbilical artery
1
2
3
4
6
5–6 weeks

Pierre Robin Sequence (Syndrome)

***Otolaryngological Manifestations*:**

Micrognathia (92%), cleft palalet (14-91%), retroglossoptosis (70-85%), otic anomaly (75%)

Systemic manifestations

Ocular anomalies (30% patients)

Cardiovascular findings benign murmurs, pulmonary stenosis, patent ductus arteriosus, patent foramen ovale, atrial septal defect, pulmonary hypertension (5-58%).

Anomalies in the musculoskeletal system (70-80%), e.g. UL-polydactyly, hyperextension of joints; LL – clubfeet, femoral, hip joint and knee anomalies; vertebral column anomalies.

Mechanisms of Congenital Cardiac Pathogenesis

4. Error in programmed cell death (**apoptosis**)
   - Fusion of endocardial tubes
   - Remodeling of ventricular muscular septum
   - Remodeling of conotruncus
   - Fusion of superior & inferior endocardial cushions
   - Development of atrioventricular valves

Circulation changes at birth

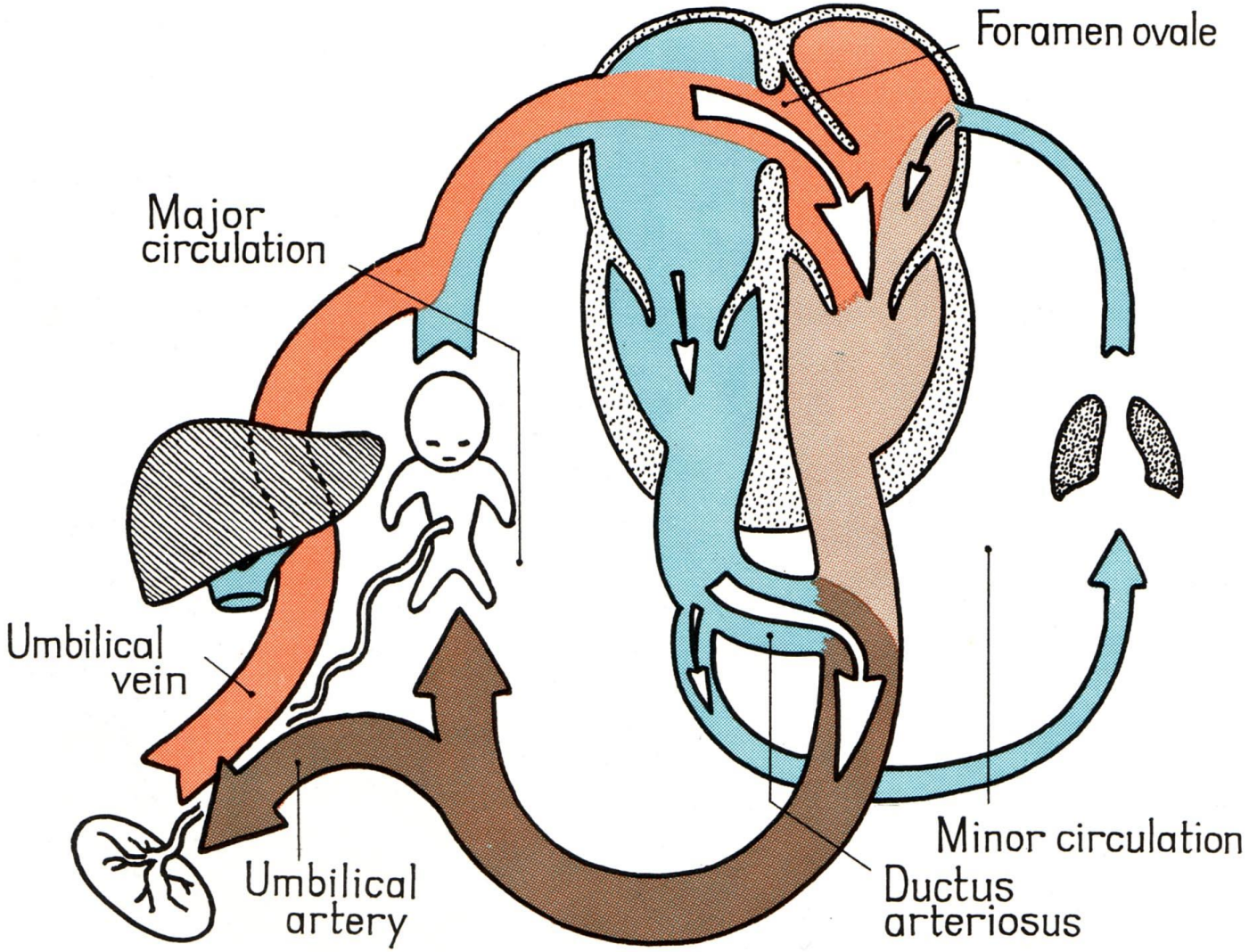
- ***Before birth*** – the fetal cardiovascular system is a single circulation bypassing the capillary network in the lung (high pressure in the amniotic fluid filled lung).

- ***After birth*** – the lungs are air filled reducing the resistance in the lung capillary. This leads to a series of changes in the newborn blood vascular system to establish a double circulation: pulmonary and systemic circulation.

Changes at birth -1

In utero development – gaseous and metabolite exchange depends on placenta, *two anatomical shunts* present in the blood circulation to avoid flowing through the lungs.

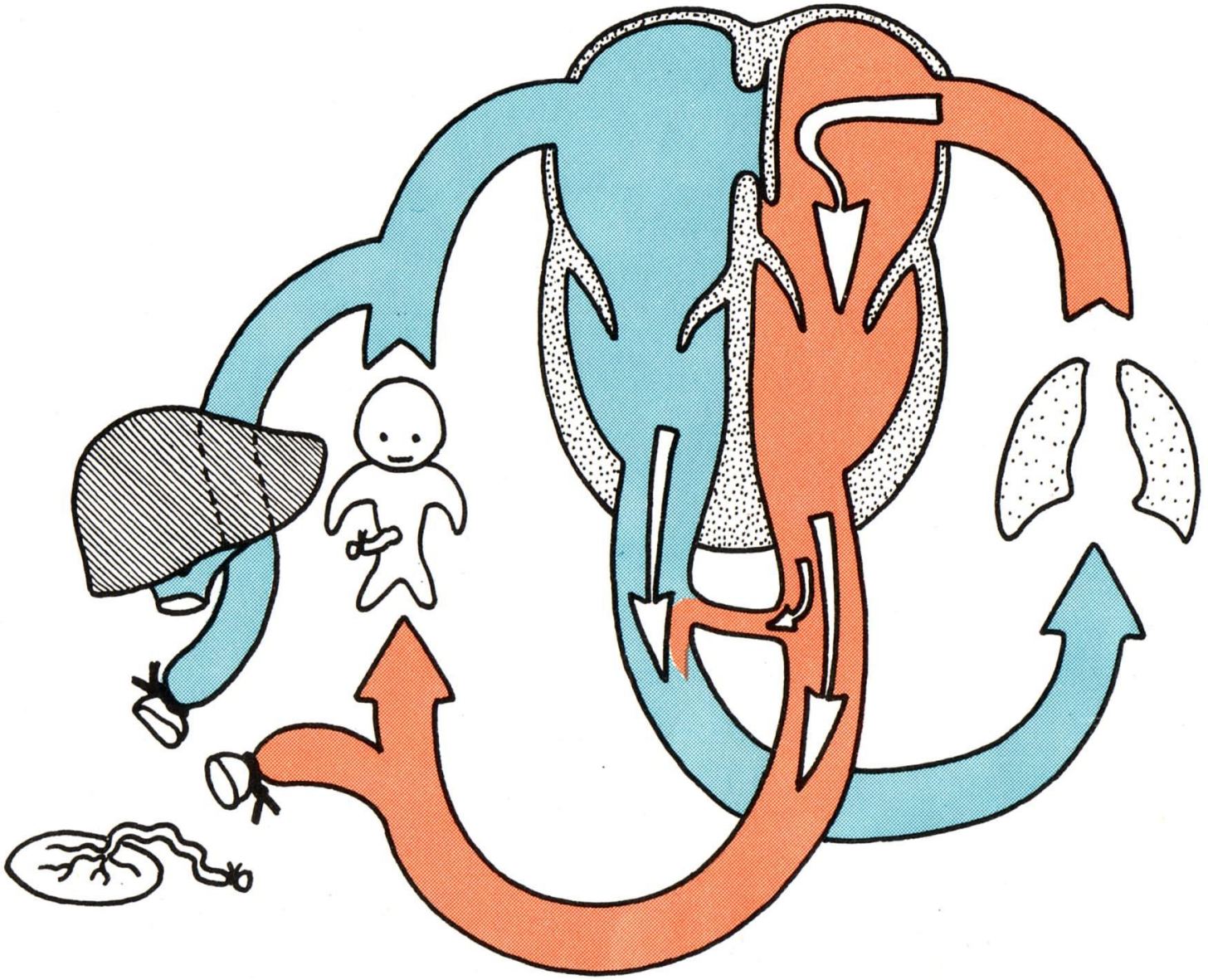
- **The openings in the interatrial septa** – allows blood to flow from right to left atria direct. Oxygenated blood from the umbilical vein flows into the right ventricle takes this bypass, flows into the left ventricle.
- **The ductus arteriosus** – allows blood to leave left pulmonary artery to the aorta. Most of the blood leaving the right ventricle takes this bypass route.



Fetal circulation

Changes at birth -2

- At birth, the lungs are inflated and resistance to blood flow drops sharply. Increase in left heart pressure closes the interatrial shunt, closes the foramen ovale physiologically..
- The lung inflation release bradykinin to cause contraction of the ductus arteriosus. It is effective to constrict 10-15 h after birth; it closes to blood flow within 2-4 days and the blood vessel becomes a fibrous cord (*ligamentum arteriosus*) by the age of 2-3 weeks.
- The double blood circulatory circuit (pulmonary circulation and systemic circulation) is established after birth.



Physiological separation of the circulation at birth

Tuchmann-Duplessis, 1972

Reference:

Sadler TW (2006) Langman's Medical Embryology. 10th edition, Lippincott Williams & Wilkins, Pennsylvania; pp.159-180.