Lecture no.3

The Heart Embryology

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•The human heart is the first functional organ to develop.

•It begins beating and pumping blood around day 21 or 22, a mere three weeks after fertilization.

•This emphasizes the critical nature of the heart in distributing blood through the vessels and the vital exchange of nutrients, oxygen, and wastes both to and from the developing baby.

• The critical early development of the heart is reflected by the prominent **heart bulge** that appears on the anterior surface of the embryo.

Cardiogenesis takes place via a complex series of steps:

1. Determination of mesoderm- and neural crest cells for heart formation

2. Growth and differentiation processes to become cardiomyocytes

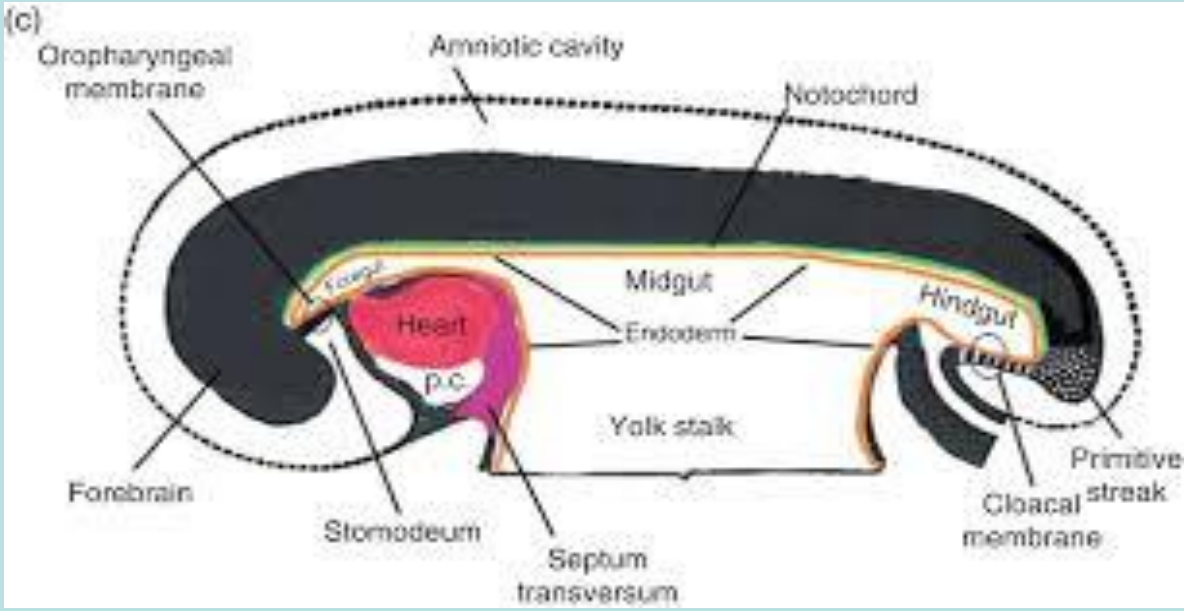
3. Migration and transformation processes in order to form the heart

The heart primordium arises predominantly from splanchnic mesoderm in the cardiogenic region of the trilaminar embryo.

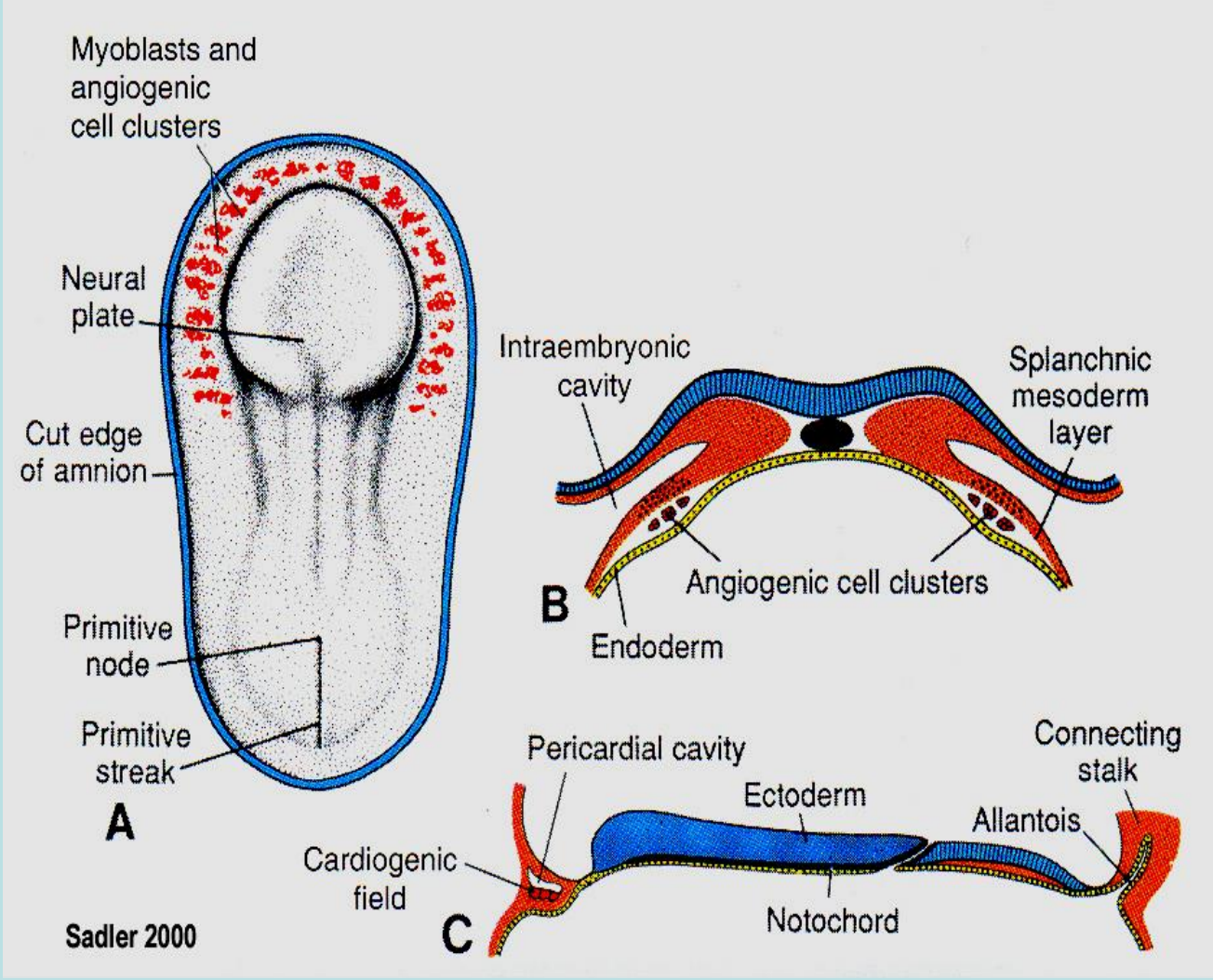
Blastodermal cardiogenic precursors have been located in the rostral epiblast either side of the primitive streak.

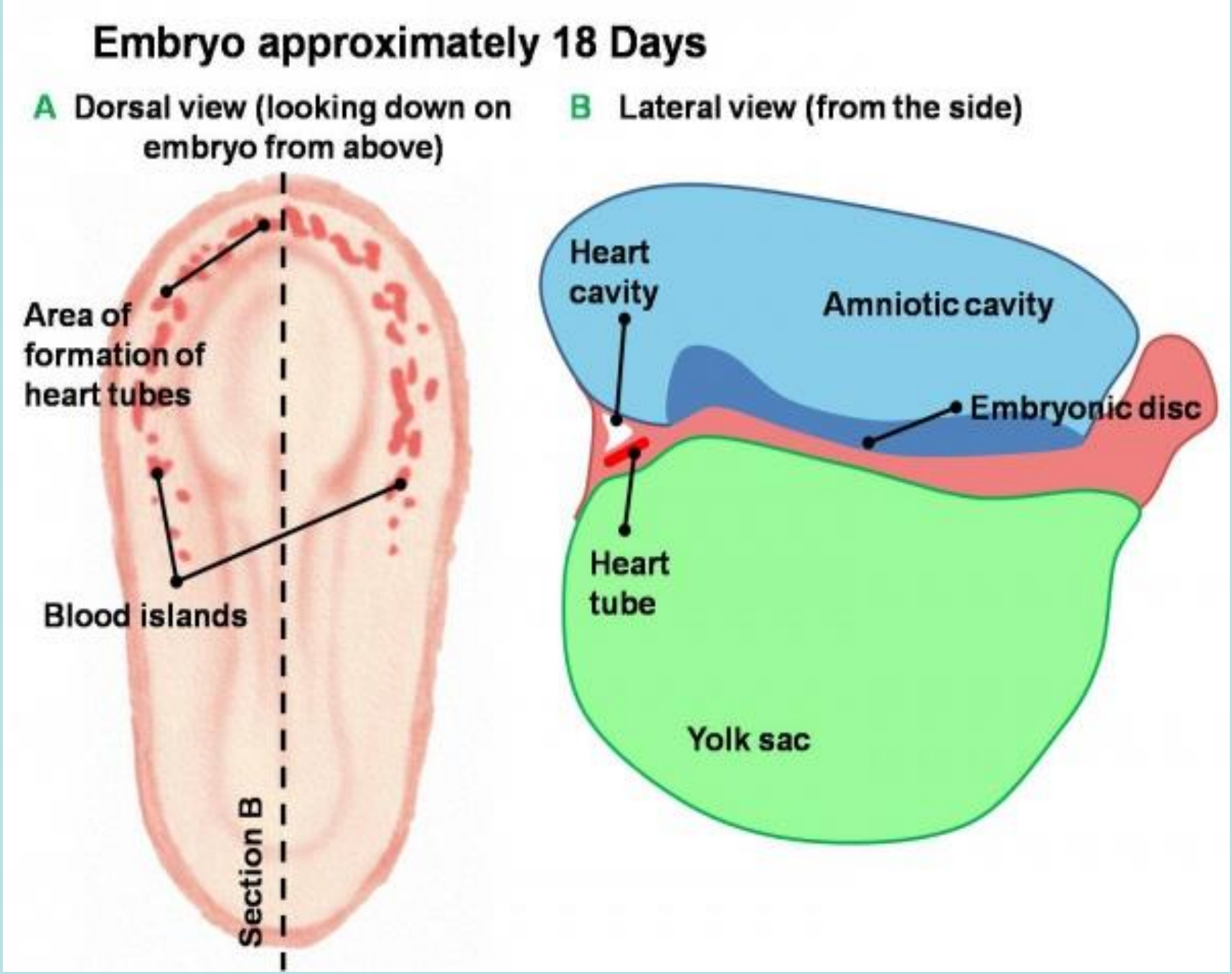
Cardiogenic precursors have also been located in the rostral primitive streak.

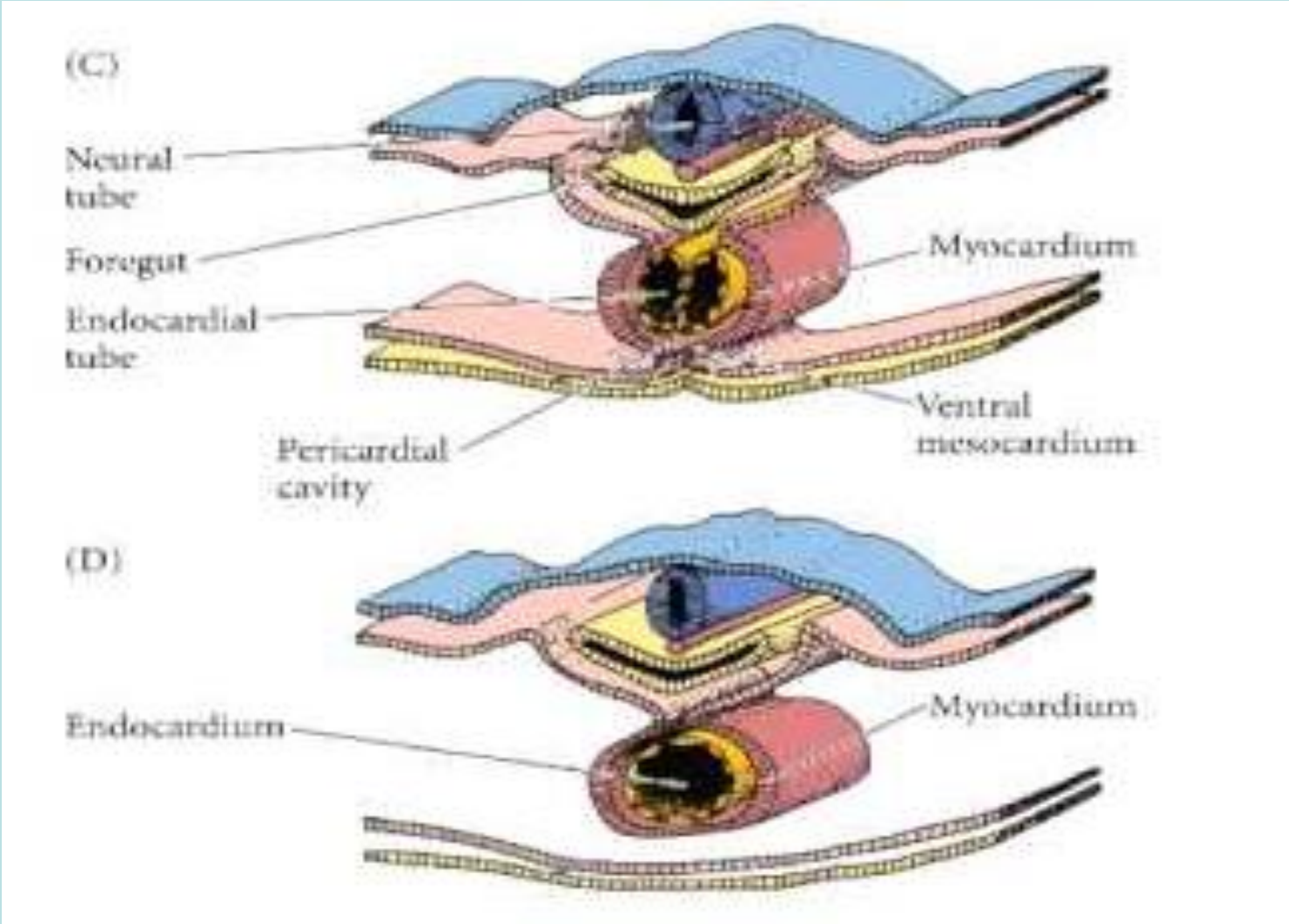
After ingression through the primitive streak, mesodermal cells rapidly move laterally and cranially until they reach the cardiogenic fields.

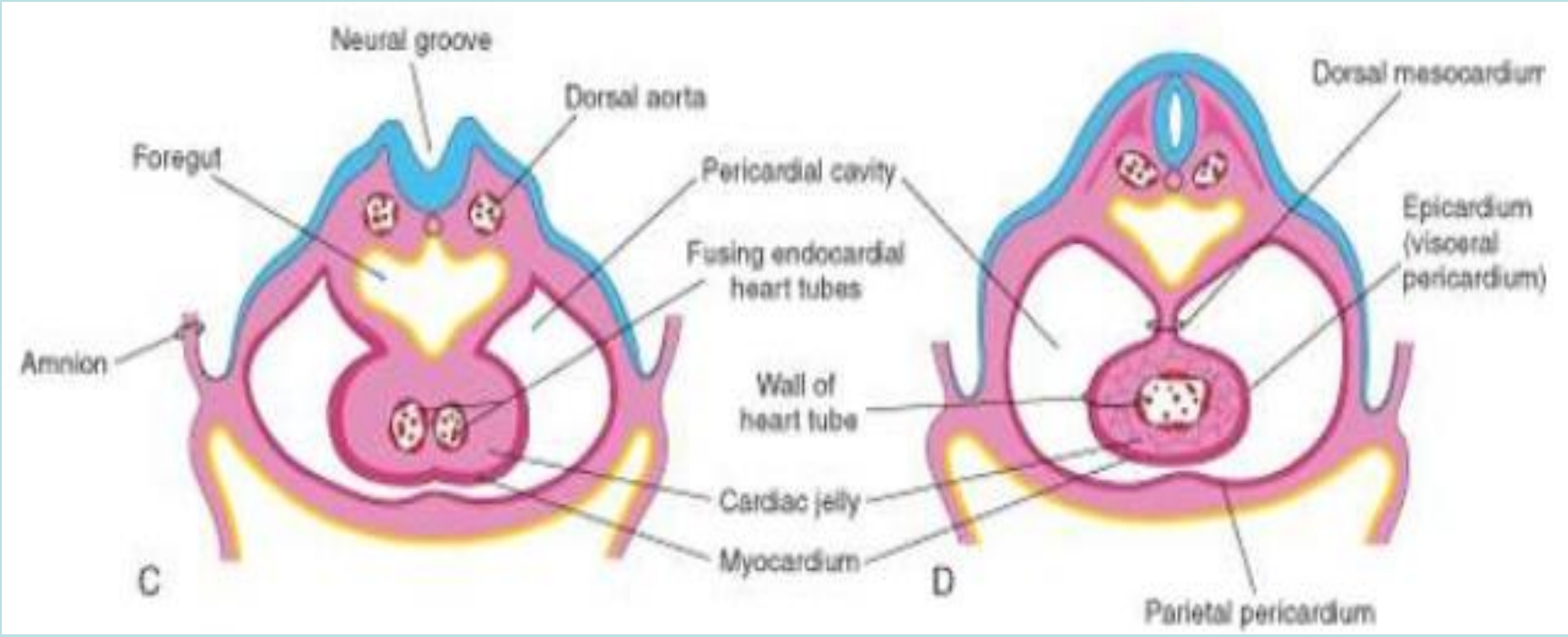


- Mesenchimal cells (splanchnic mesoderm) …..>cardiogenic cells>>>migrating cells between endoderm and mesoderm=>longitudinal cardiogenic cords=>>>endocardic tubes




Embryo approximately 18 Days
A Dorsal view (looking down on embryo from above)
B Lateral view (from the side)
Area of formation of heart tubes
Blood islands
Section B
Heart cavity
Amniotic cavity
Embryonic disc
Heart tube
Yolk sac


(C)
Neural tube
Foregut
Endocardial tube
Pericardial cavity
Myocardium
Ventral mesocardium
(D)
Endocardium
Myocardium


Neural groove
Dorsal aorta
Foregut
Pericardial cavity
Fusing endocardial heart tubes
Amnion
Wall of heart tube
Cardiac jelly
Myocardium
C
Dorsal mesocardium
Epicardium (visceral pericardium)
D
Parietal pericardium

The cardiovascular system begins to develop during week 3.

Mesenchymal cells derived from the mesoderm form **endothelial tubes** which join to form the primitive vascular system .

HEART DEVELOPMENT (WEEK 3)

Heart develops from splanchnic mesoderm in the **cardiogenic area**.

Bilateral **cardiogenic cords** are formed from the mesenchyme become canalized and form the paired **endocardial heart tubes**.

These fuse into a single **heart tube** forming **the primitive heart.**

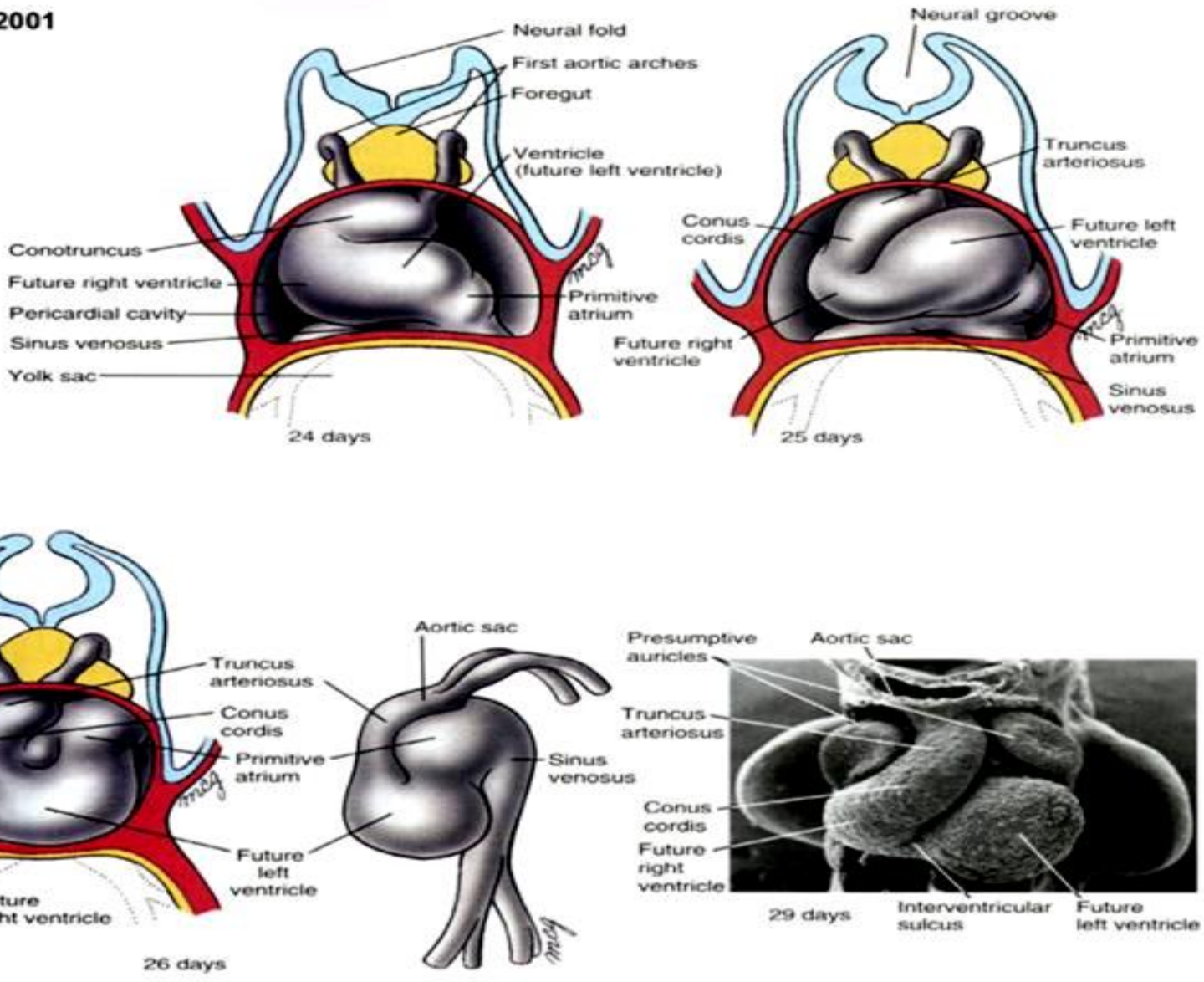
Surrounding mesenchyme thicken to form the **myoepicardial mantle** (future **myocardium** and **epicardium**) separated from the endothelial heart tube (future **endocardium**) by the gelatinous **cardiac jelly** .

The future heart develops dilatations and constrictions resulting in 4 chambers :

1. **sinus venosus**
2. **primordial atrium**
3. **ventricle**
4. **bulbus cordis**

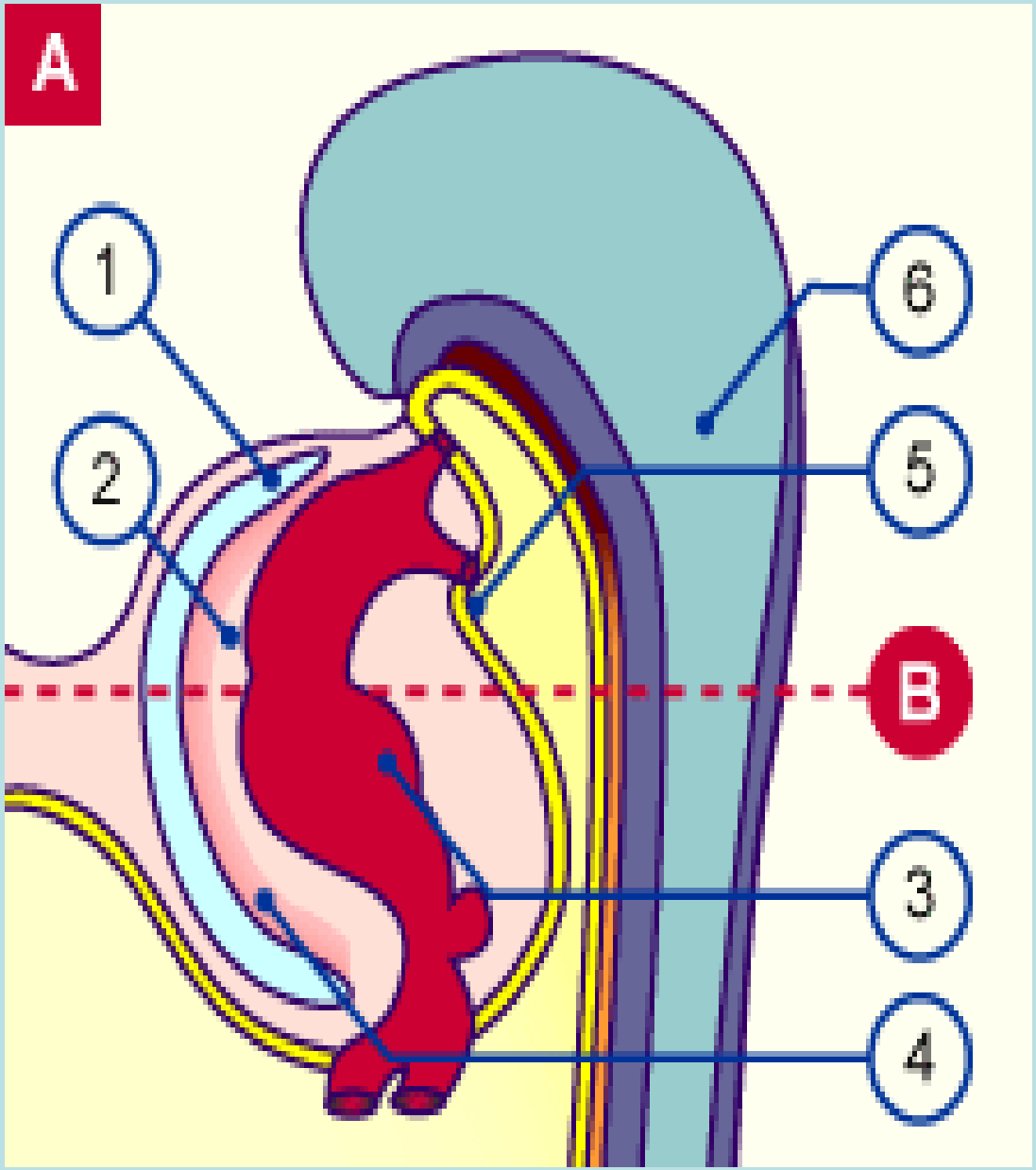
The **truncus arteriosus** is continuous caudally with the bulbus cordis, and enlarges cranially to form the **aortic sac** from which the **aortic arches** arise.

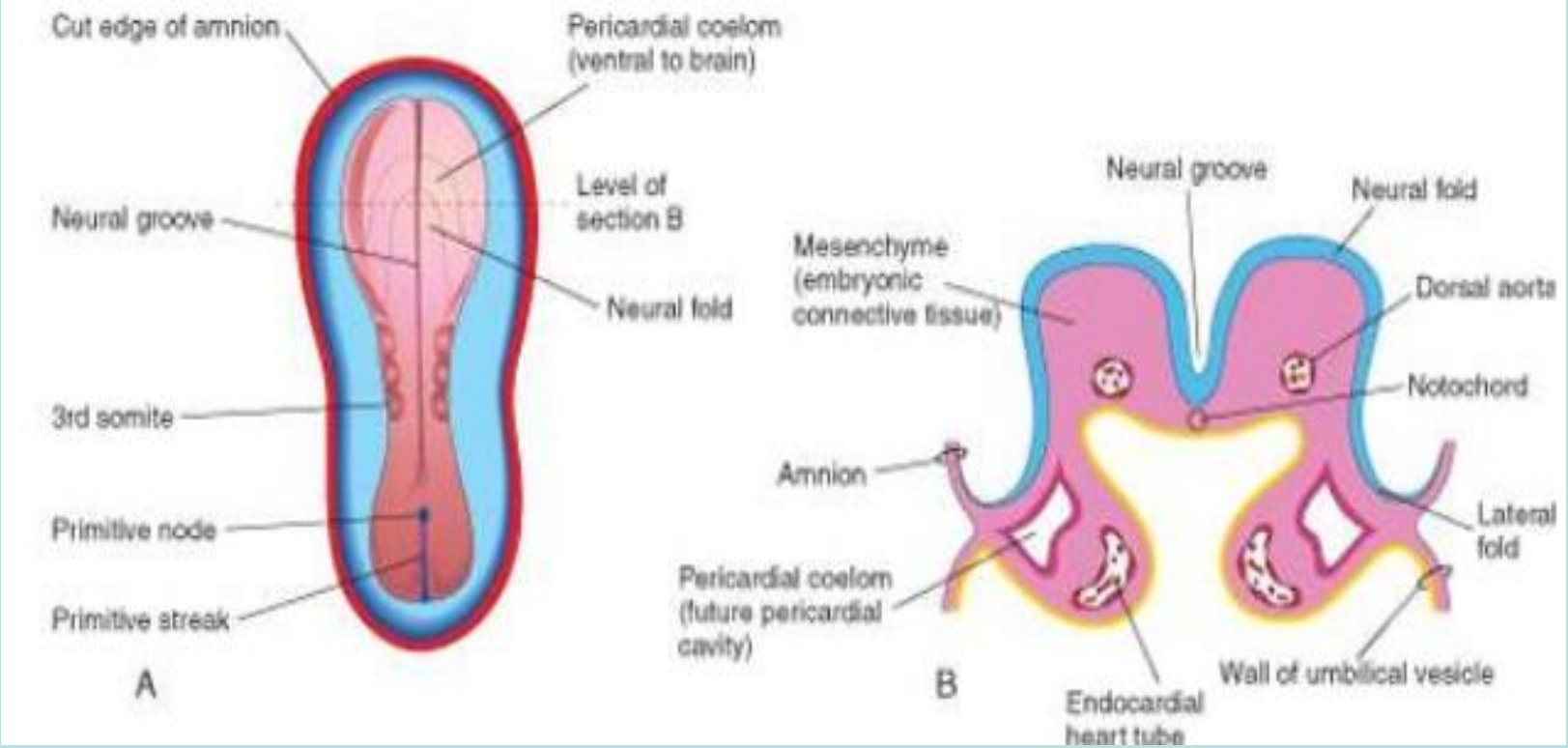
Larsen 2001


Neural fold
First aortic arches
Foregut
Ventricle
(future left ventricle)
Conotruncus
Future right ventricle
Pericardial cavity
Sinus venosus
Yolk sac
Primitive
atrium
24 days
Neural groove
Truncus
arteriosus
Conus
cordis
Future left
ventricle
Future right
ventricle
Primitive
atrium
Sinus
venosus
25 days
Truncus
arteriosus
Conus
cordis
Primitive
atrium
Future
left
ventricle
Future
right ventricle
26 days
Aortic sac
Sinus
venosus
Presumptive
auricles
Aortic sac
Truncus
arteriosus
Conus
cordis
Future
right
ventricle
29 days
Interventricular
sulcus
Future
left ventricle

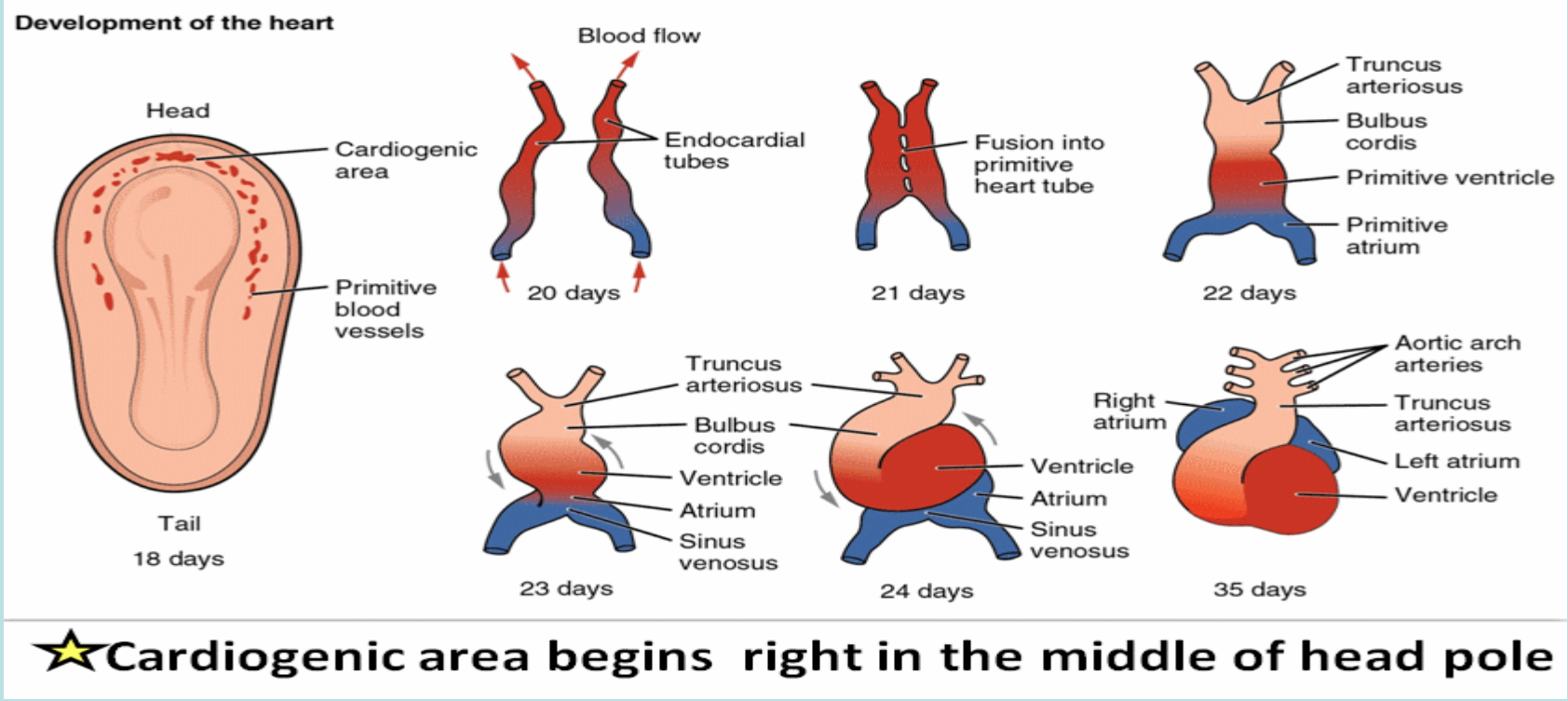
Sagittal section in a 28 days embryo

1. Pericardial cavity
2. Cardiac jelly
3. Endocardial tube
4. Myoepicardium
5. Pharyngeal pouch

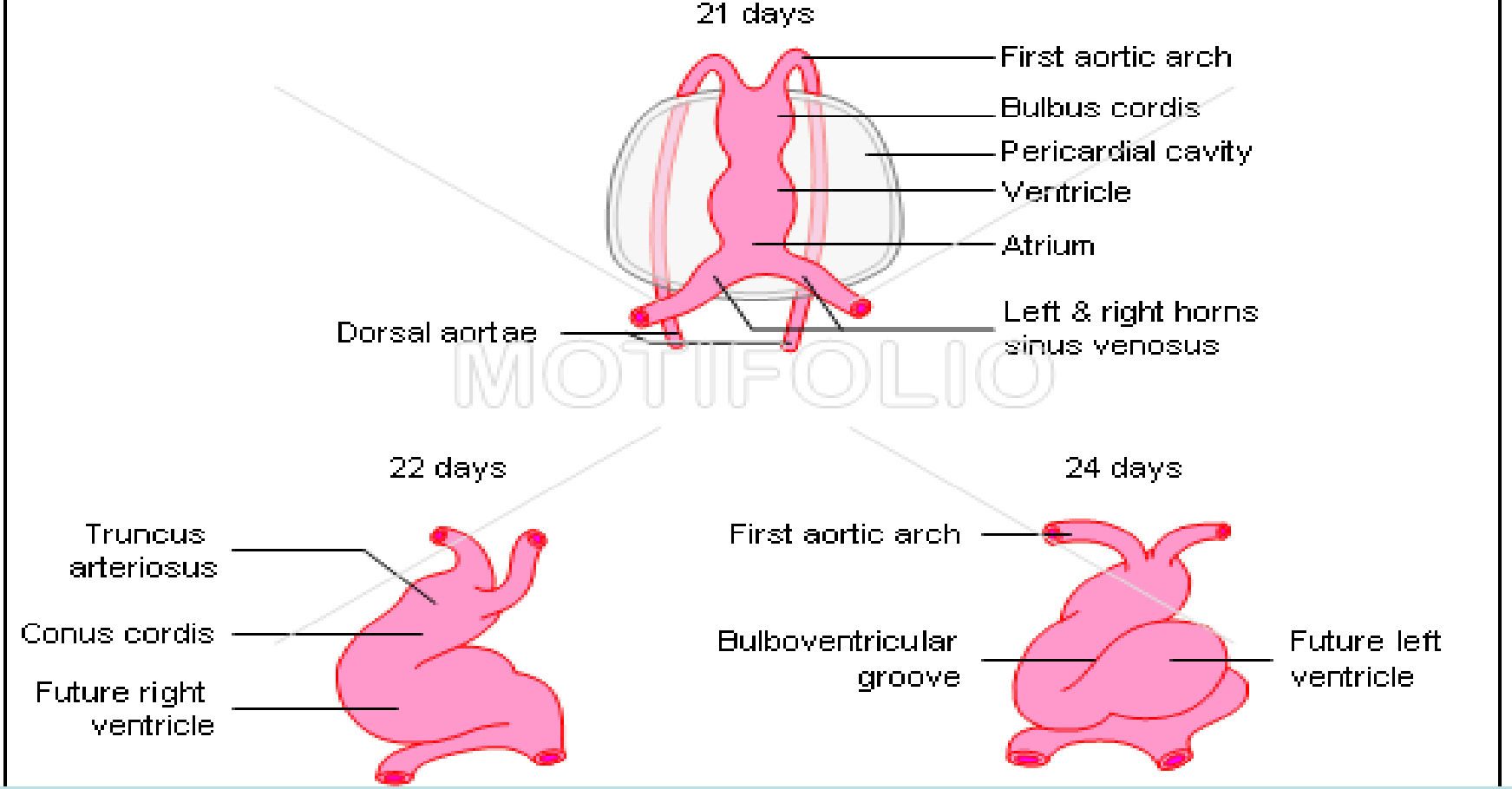




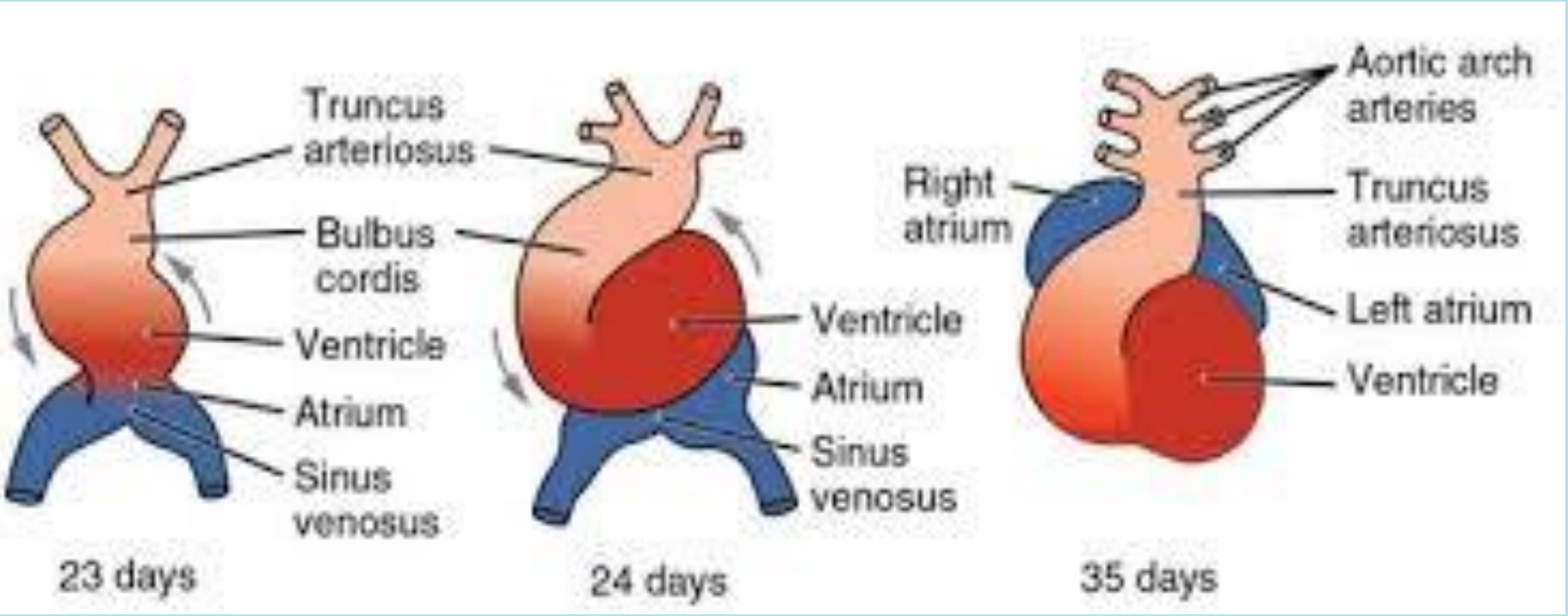
- The primordial myocardium forms from splanchnic mesoderm surrounding the pericardial coelom.
- It is separated from the endothelial heart tube by cardiac jelly (gelatinous connective tissue).
- The endothelium of the heart tube forms the internal endocardium, while the epicardium develops from mesothelial cells arising from the sinus venosus, which spread cranially over the myocardium.
- Recent knowledge shows that additional myocardial cells are added to the outflow tract during heart looping.
- Cardiac looping occurs from late in the fourth week to early in the fifth week .
- All of the partitioning of the primitive heart occurs between the middle of the fourth week and the end of the fifth week.



- The heart is the first organ to form and become functional, emphasizing the importance of transport of material to and from the developing infant.
- It originates about day 18 or 19 from the mesoderm and begins beating and pumping blood about day 21 or 22.
- It forms from the cardiogenic region near the head and is visible as a prominent heart bulge on the surface of the embryo.
- Originally, it consists of a pair of strands called cardiogenic cords that quickly form a hollow lumen and are referred to as endocardial tubes.
- These then fuse into a single heart tube and differentiate into:
- 1. the truncus arteriosus,
- 2. bulbus cordis,
- 3. primitive ventricle,
- 4. primitive atrium,
- 5. and sinus venosus, starting about day 22.
- The primitive heart begins to form an S shape within the pericardium between days 23 and 28.
- The internal septa begin to form about day 28, separating the heart into the atria and the ventricles, although the *foramen ovale* persists until shortly after birth.
- Between weeks five and eight, the atrioventricular valves form.
- The semilunar valves form between weeks five and nine.



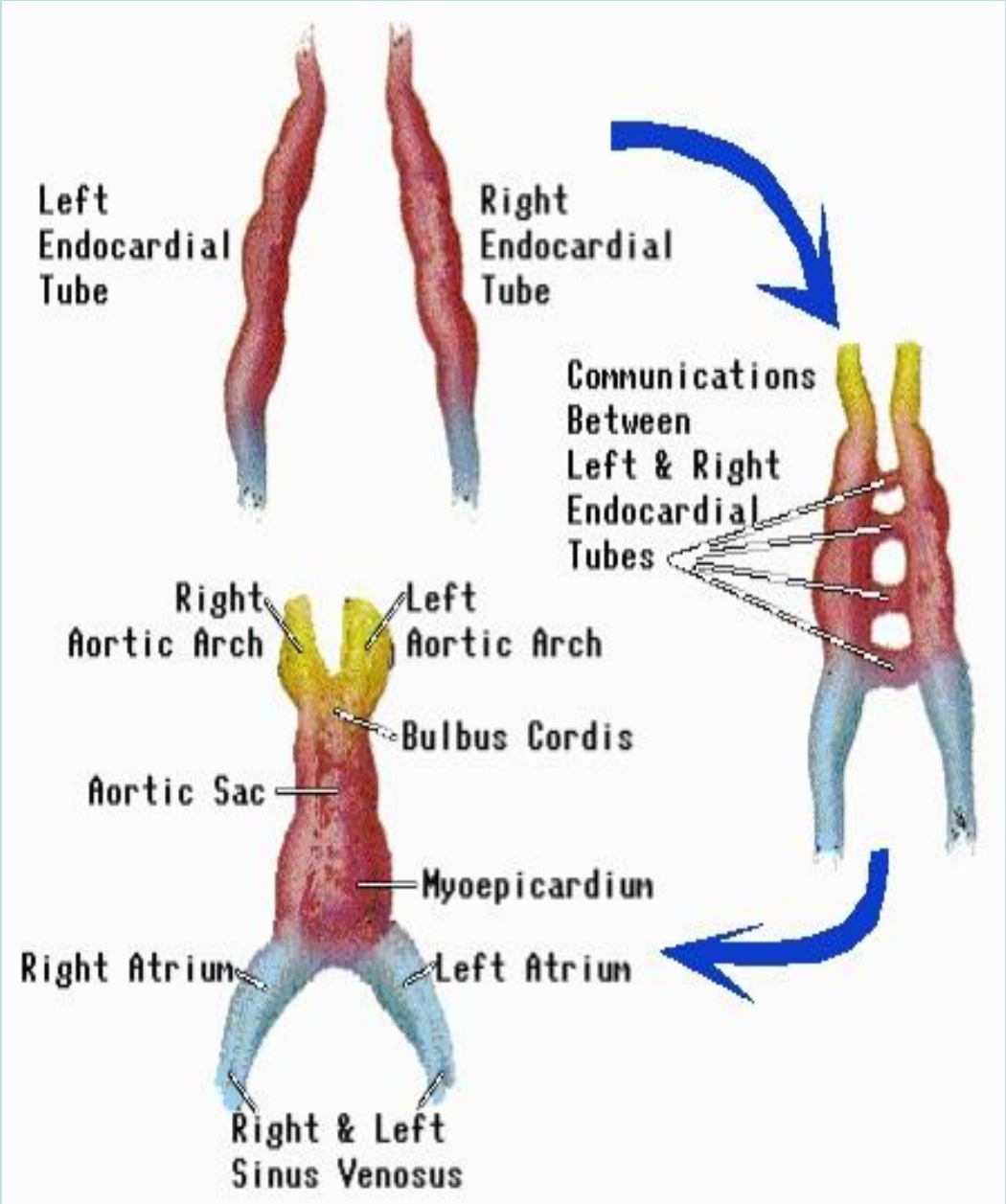
- The primitive streak forms the mesodermal cardiogenic fields.
- The cells in the primitive streak are organised rostrocaudally, while after migration to form the cardiogenic fields they are organised mediolaterally.
- The most cranial end of the cardiogenic field becomes the ventral midline of the later heart tube which becomes the right border during looping.
- At approximately day 19 the lateral plate mesoderm divides into dorsal (somatic) and ventral (splanchnic) layers, forming the pericardial coelom between them.
- Angioblastic cords develop in the splanchnic mesoderm and canalise to form bilateral heart tubes.
- Following lateral folding of the embryo, fusion of the heart tubes occurs, beginning cranially and extending caudally.
- Folding of the heart of the embryo during the fourth week brings the heart tube dorsal to the pericardial cavity.
- The precardiomyocytes differentiate to form the myocardial sleeve of the heart tube, allowing the heart tube to begin beating.
- By the beginning of the fourth week, coordinated contractions of the heart tube, which push blood cranially, are present.
- This function initiates as nutritional and oxygen embryologic demands can no longer be met by passive diffusion from the placenta.



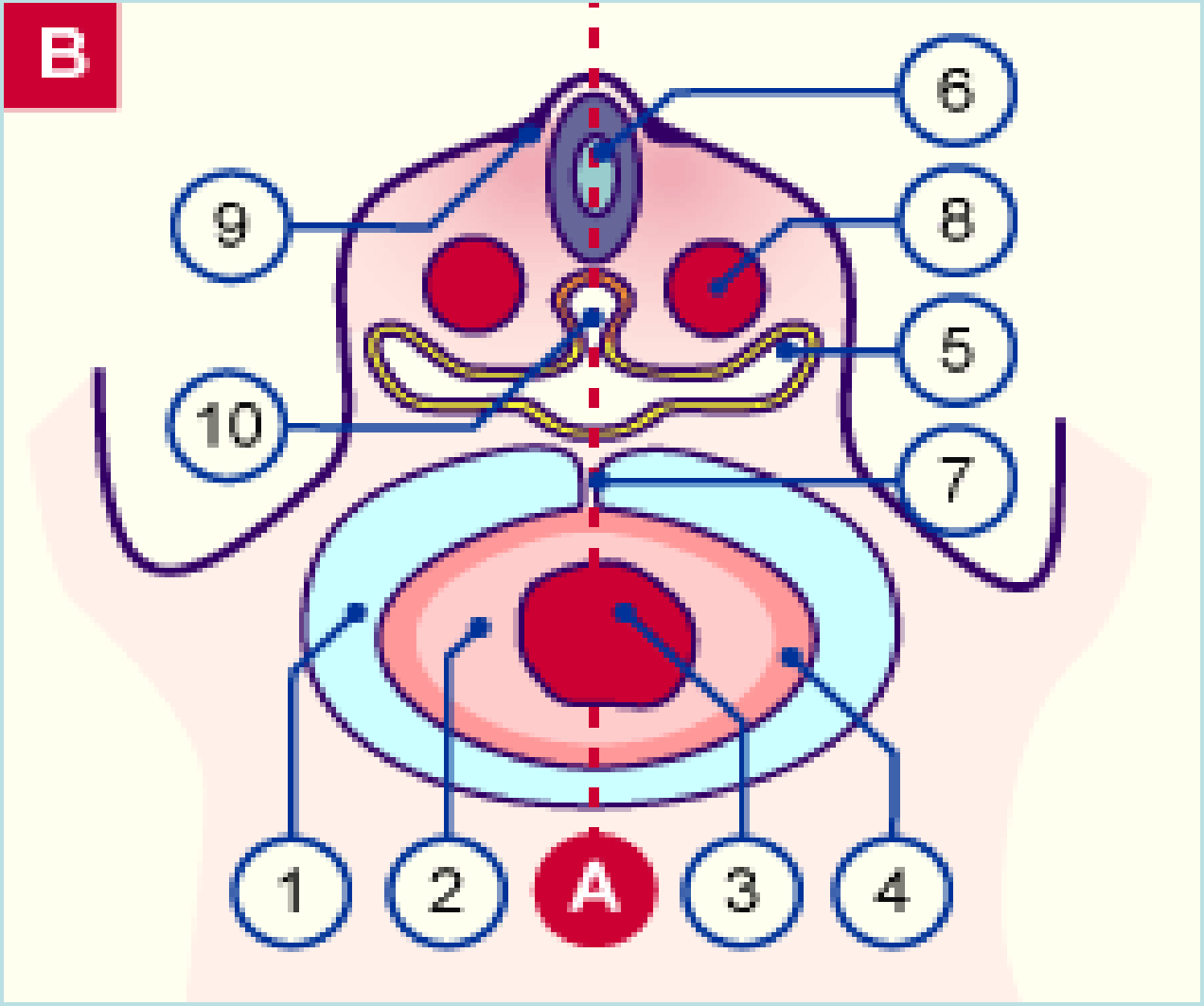
- The five regions of the primitive heart tube develop into recognizable structures in a fully developed heart.

1. The ***truncus arteriosus*** will eventually divide and give rise to the ascending aorta and pulmonary trunk.
2. The ***bulbus cordis*** develops into the right ventricle.
3. The **primitive ventricle** forms the left ventricle.
4. The **primitive atrium** becomes the anterior portions of both the right and left atria, and the two auricles.
5. The ***sinus venosus*** develops into the posterior portion of the right atrium, the SA node, and the coronary sinus.

- The heart forms from an embryonic tissue called **mesoderm** around 18 to 19 days after fertilization.
- Mesoderm is one of the three primary germ layers that differentiates early in development that collectively gives rise to all subsequent tissues and organs.
- The heart begins to develop near the head of the embryo in a region known as the **cardiogenic area**.
- Following chemical signals called factors from the underlying endoderm (another of the three primary germ layers), the cardiogenic area begins to form two strands called the **cardiogenic cords**.
- As the cardiogenic cords develop, a lumen rapidly develops within them.
- At this point, they are referred to as **endocardial tubes**.
- The two tubes migrate together and fuse to form a single **primitive heart tube**.
- The primitive heart tube quickly forms five distinct regions.
- From head to tail, these include:
- **1. *truncus arteriosus***
- ***2. bulbus cordis***
- **3. primitive ventricle**
- **4. primitive atrium**
- **5. *sinus venosus.***
- Initially, all venous blood flows into the *sinus venosus*, and contractions push the blood from tail to head, or from the *sinus venosus* to the *truncus arteriosus*.
- This is a very different pattern from that of an adult.



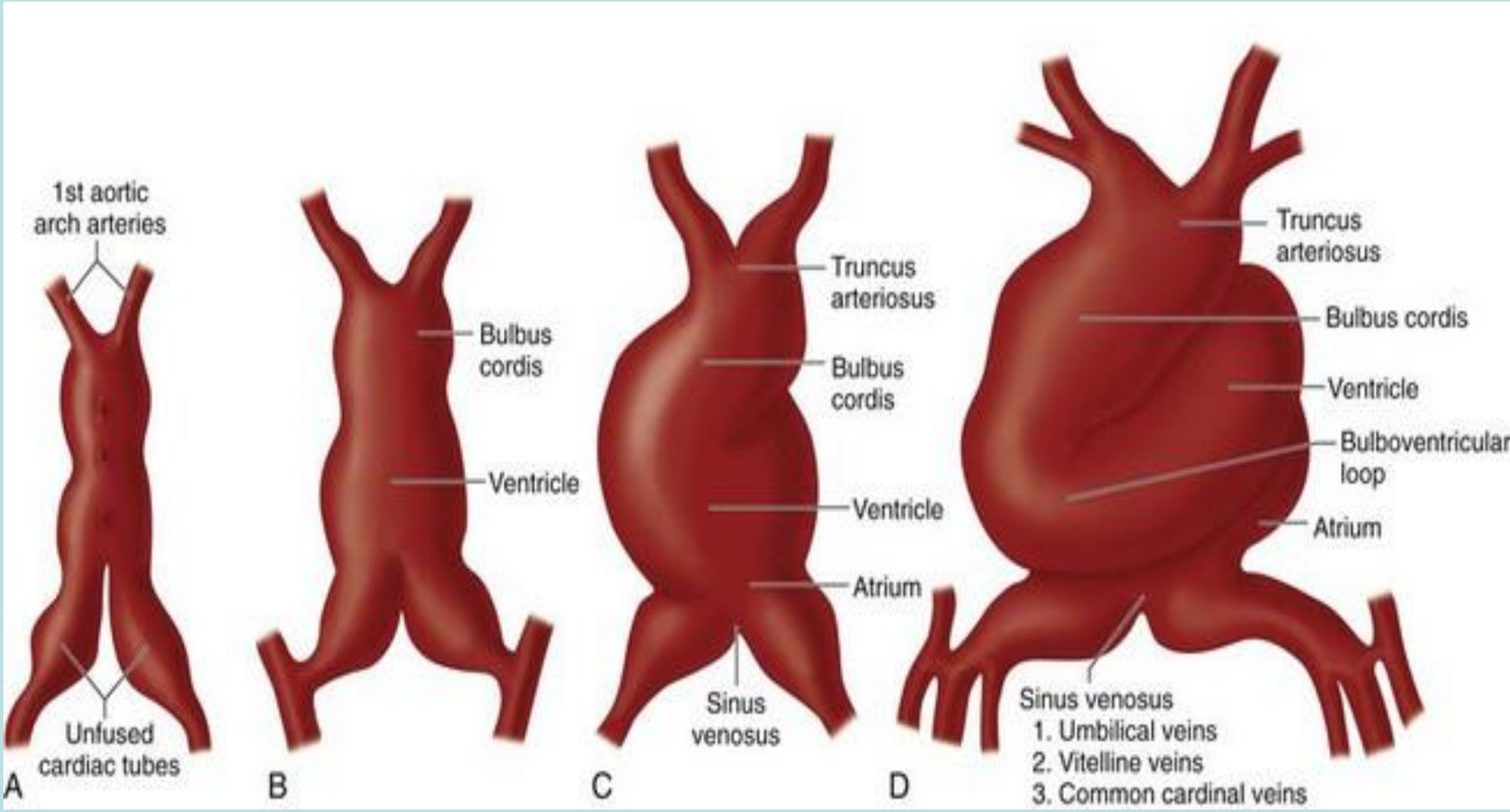
Transversal section in a 28 days embryo



6. Neural tube
7. Mesocardium
8. Aorta dorsalis
9. Neural crest
10. Notochord

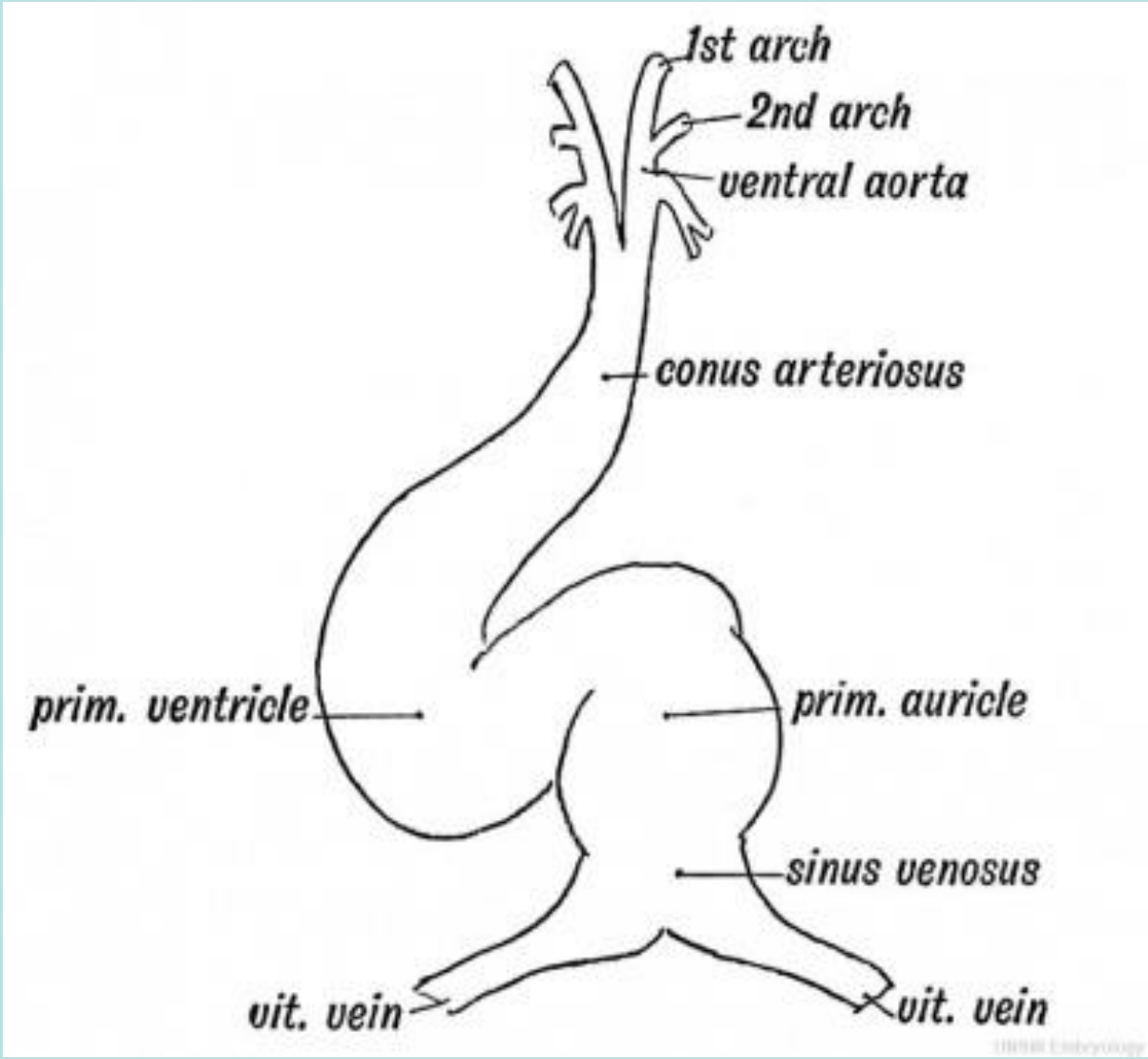
- As the primitive heart tube elongates, it begins to fold within the pericardium, eventually forming an S shape, which places the chambers and major vessels into an alignment similar to the adult heart.
- This process occurs between days 23 and 28.
- The remainder of the heart development pattern includes development of septa and valves, and remodeling of the actual chambers.
- Partitioning of the atria and ventricles by the interatrial septum, interventricular septum, and atrioventricular septum is complete by the end of the fifth week, although the foetal blood shunts remain until birth or shortly after. The atrioventricular valves form between weeks five and eight, and the semilunar valves form between weeks five and nine.

Cardiac tube enlargement



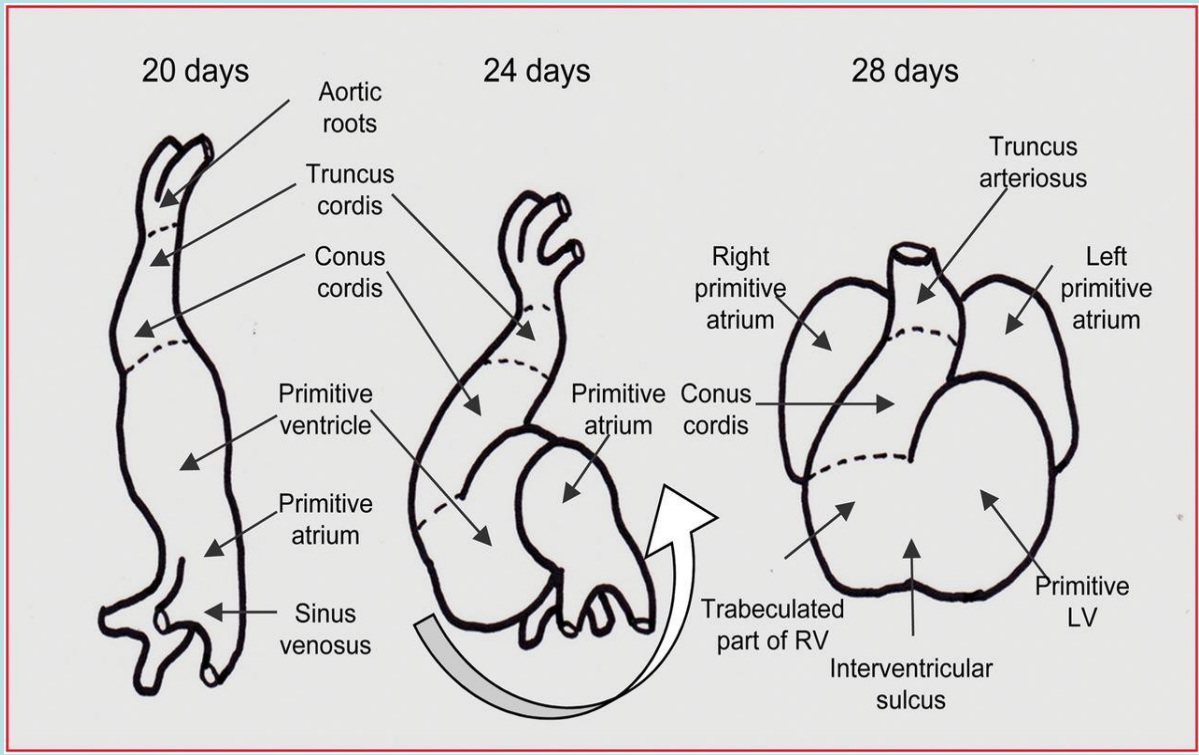
Cardiac tube folding

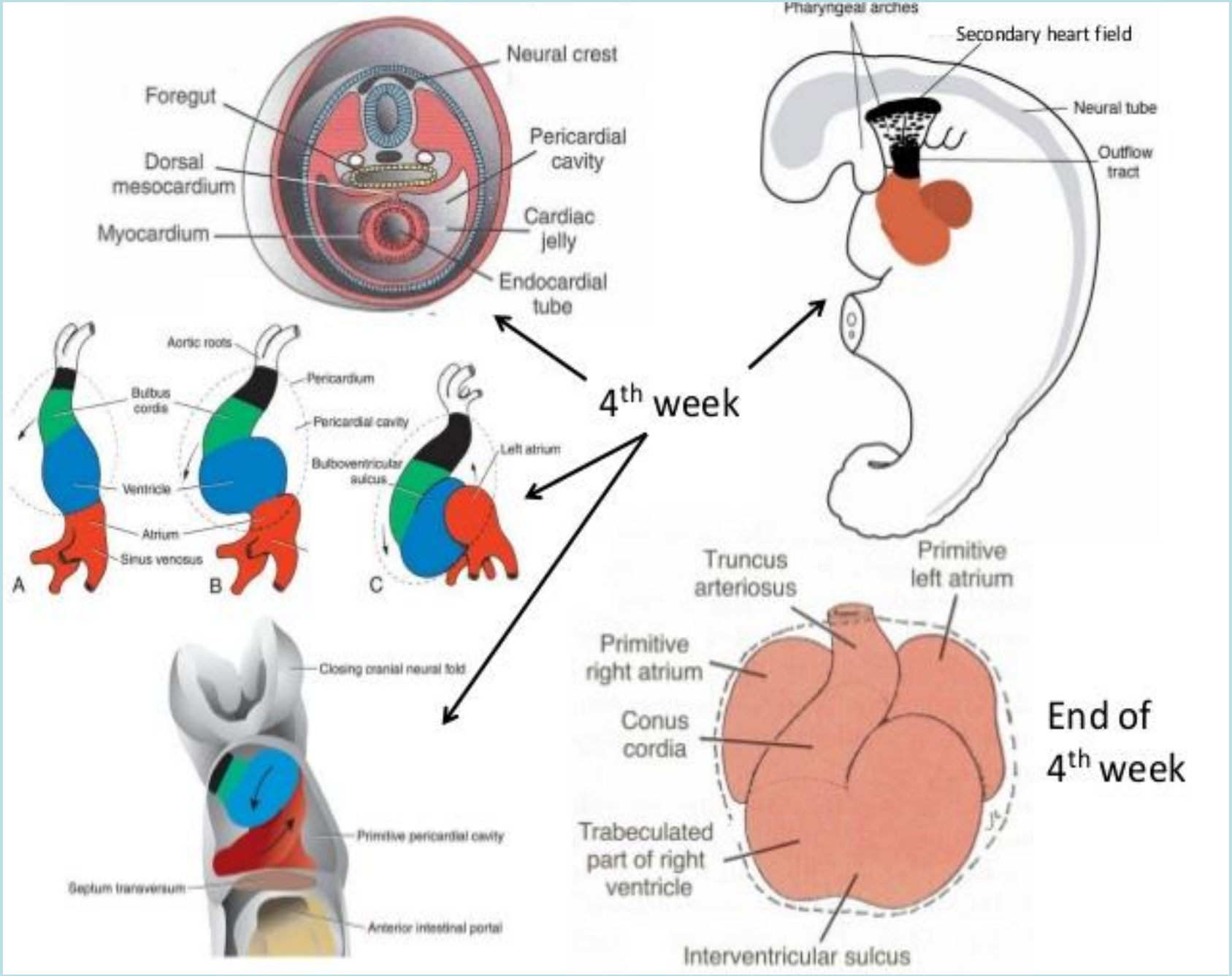
- **Venous extremity, primitive atrium and venous sinus are situated dorsal and cranially, the arterial extremity caudally and ventral.**
- **The primitive atrium takes a dorsal position, coming in relation anteriorly with bulbus arteriosus and dorsaly with sinus venosus.**



The torsion of the cardiac tube

- **By torsioning of the cardiac tube, mesenchimal structures which anchore anteriorly bulbus arteriosus to the roof of the pharynx and posteriorly the sinus venosus to the transverse septum, come in relation and between them , during the 3rd foetal month, the pericardial transverse sinus is formed.**




Neural crest
Foregut
Pericardial cavity
Dorsal mesocardium
Cardiac jelly
Myocardium
Endocardial tube
Pharyngeal arches
Secondary heart field
Neural tube
Outflow tract
4th week
Aortic roots
Pericardium
Bulbus cordis
Pericardial cavity
Left atrium
Bulboventricular sulcus
Ventricle
Atrium
Sinus venosus
A
B
C
Truncus arteriosus
Primitive left atrium
Primitive right atrium
Conus cordia
Trabeculated part of right ventricle
Interventricular sulcus
End of 4th week
Closing cranial neural fold
Primitive pericardial cavity
Septum transversum
Anterior intestinal portal

Septation of the heart cavities

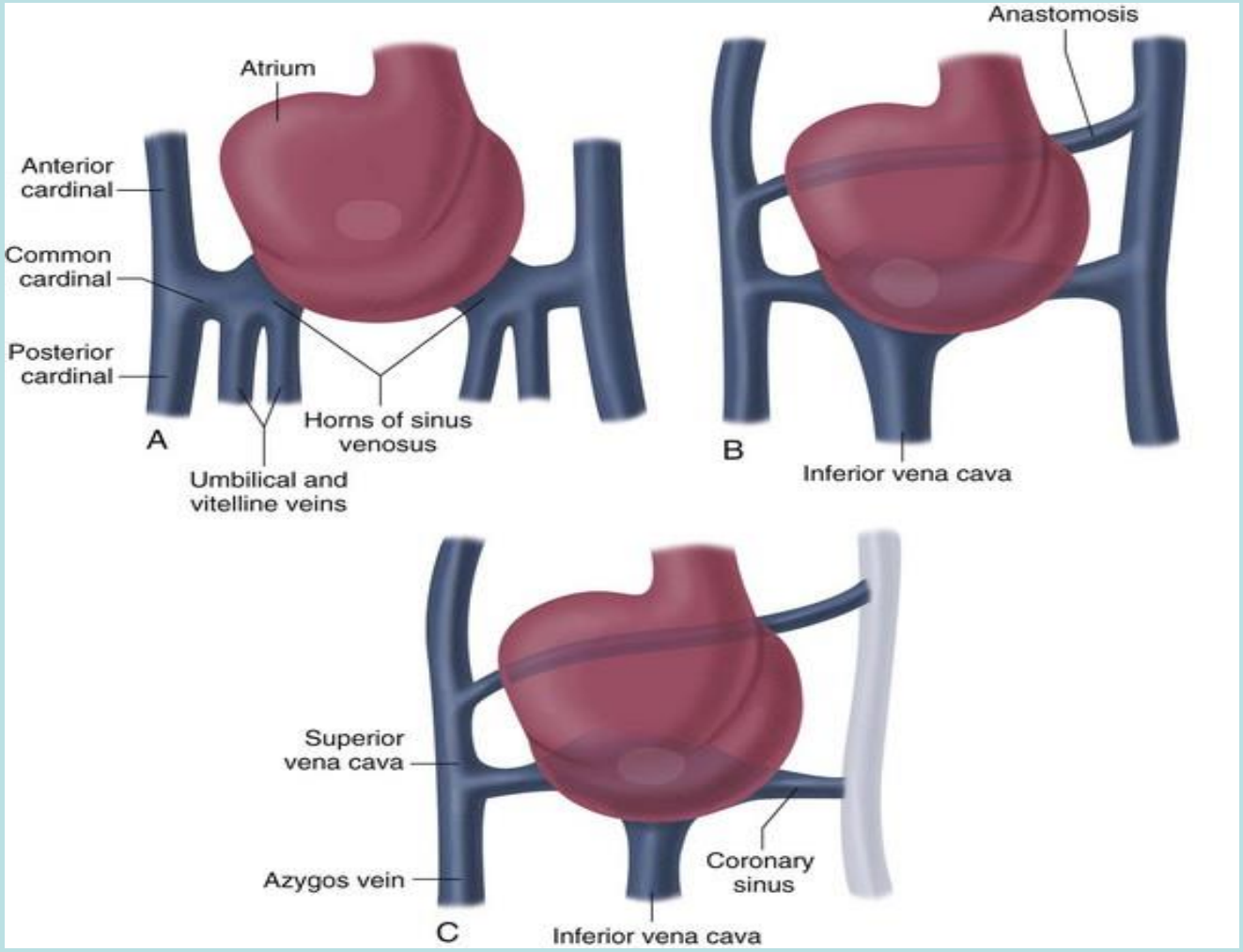
- **The process starts at the middle of the 4th week, and ends at the end of the 5th week.**

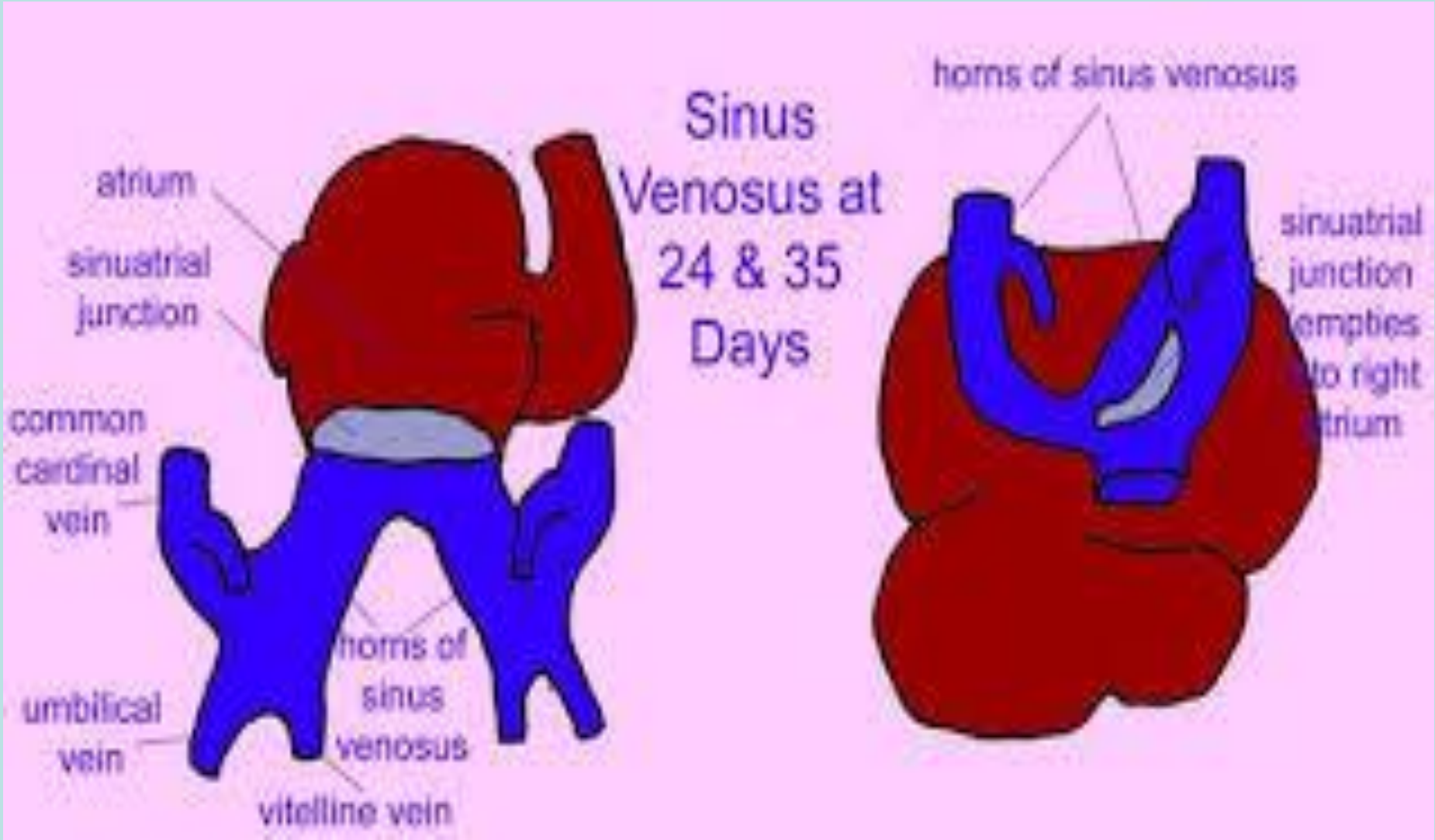
- **Stages:**

- **a. Inclusion of the sinus venosus in the wall of the future right atrium**
- **b. Septation of the primitive atrium, resulting the right atrium and the left atrium**
- **c. Septation of the atrioventricular canal in the 2 atrioventricular orifices, right and left**
- **d. Septation of the primitive ventricle in the 2 ventricles, right and left**
- **e. Inclusion of the proximal part of the bulbus arteriosus in the wall of the right ventricle**
- **f. Septation of the truncus arteriosus and the distal part of the bulbus arteriosus, resulting the separation of the ascending aorta and the pulmonary arterial trunk.**

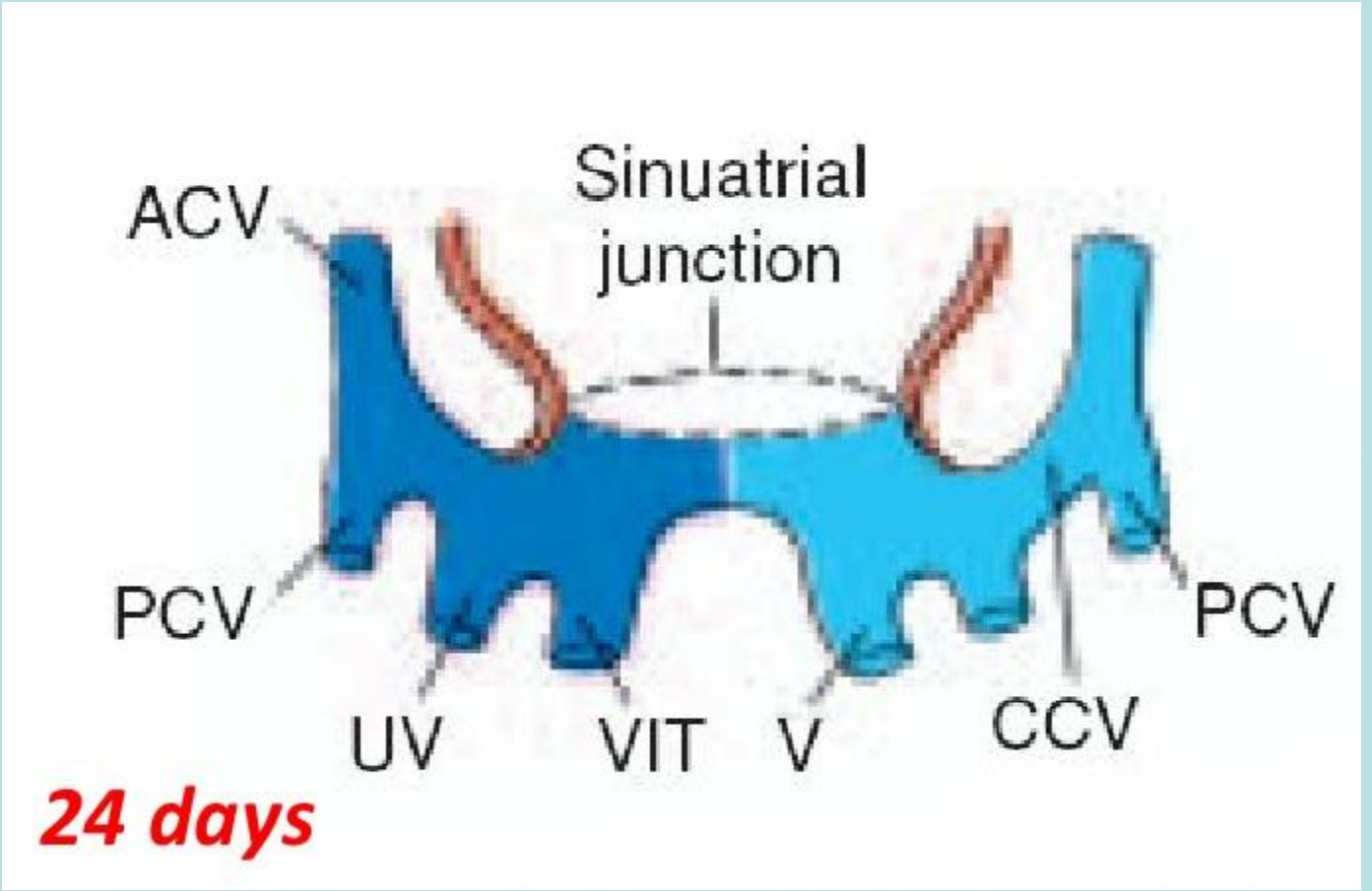
a. The evolution of the venous sinus

- Left Cuvier canal atrophies very much, giving birth to the oblique vein of the left atrium.
- From the left horn of the venous sinus emerges the coronary sinus, which opens into the right atrium.
- From the right Cuvier canal and additional segment of the right anterior cardinal vein emerges the superior vena cava, while the inferior vena cava comes from the right subcardinal vein, common hepatic vein and right sacrocardinal vein.

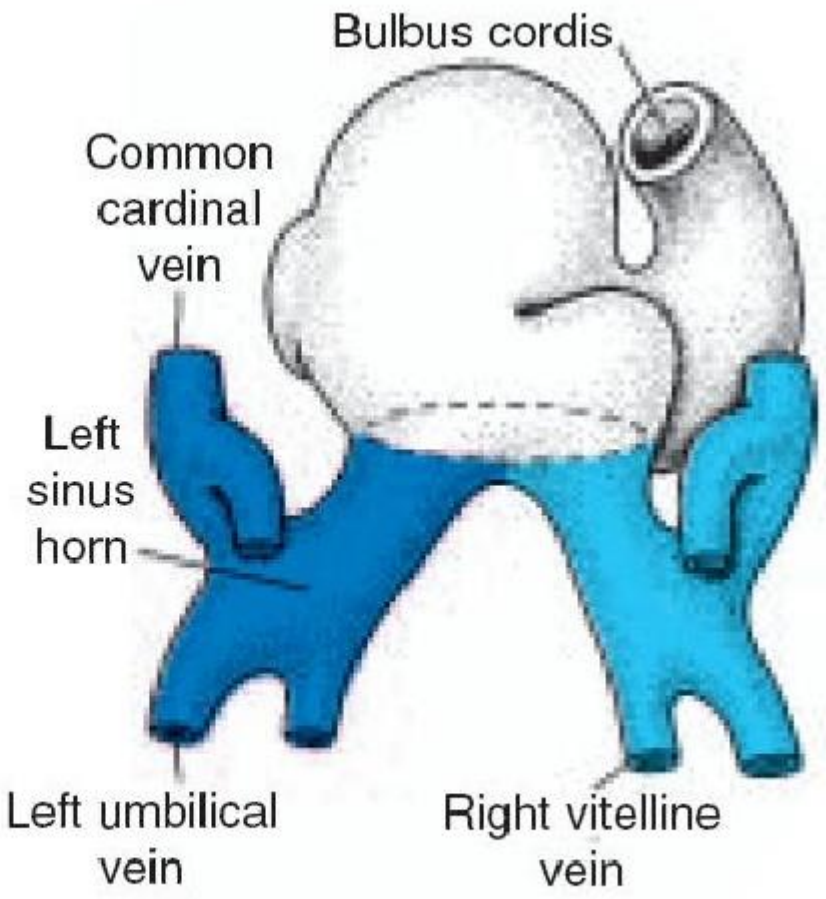



Sinus Venosus at 24 & 35 Days
atrium
sinuatrial junction
common cardinal vein
umbilical vein
horns of sinus venosus
vitelline vein
horns of sinus venosus
sinuatrial junction empties to right atrium

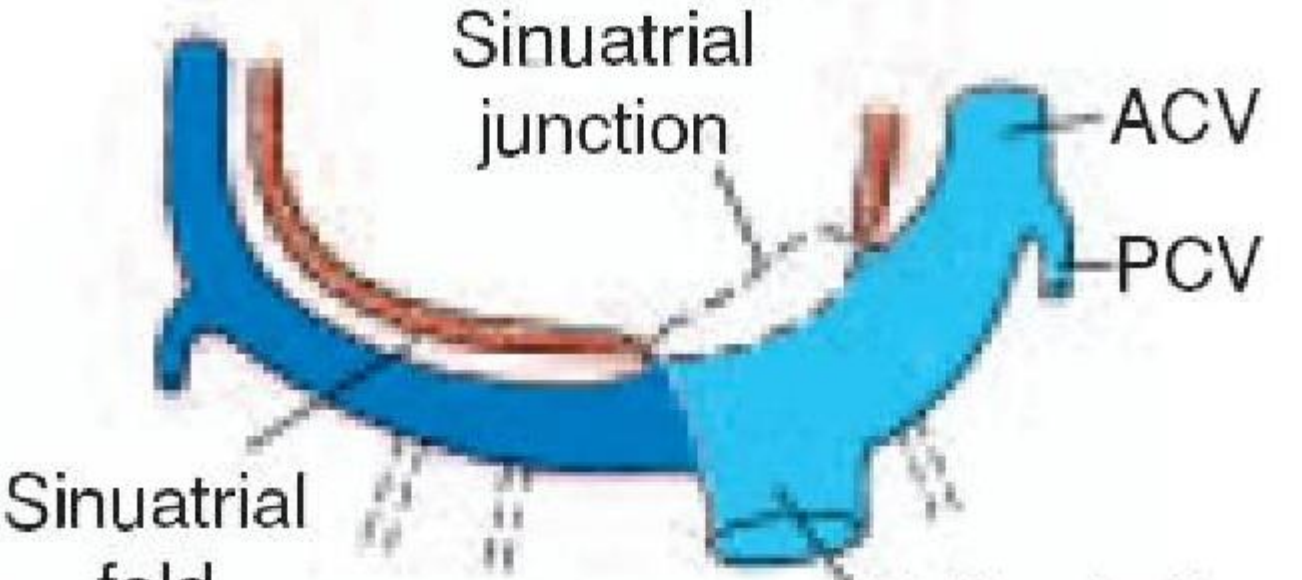
- **At the end of the 2nd month , by blossoming of the coronary sinus , the heart veins are formed.**
- **From the 3rd week the embryonic heart is functional, before the birth of the extrinsic innervation, which starts in the 4th week, by the presence in the heart of the vagi nerves.**
- **Between the atria and the ventricles an epicardic tissue forms the fibros skeleton of the heart, separating the atrial miocardium and the ventricular miocardium.**
- **Sinuatrial node differentiates in the right wall of the sinus venosus and is included in the right atrium, as well the sinus venosus.**
- **Later the atrioventricular node and His fascicle apear.**
- **Superficial cells of the external layer flattens and transform in a mesotelial way and form the epicard.**



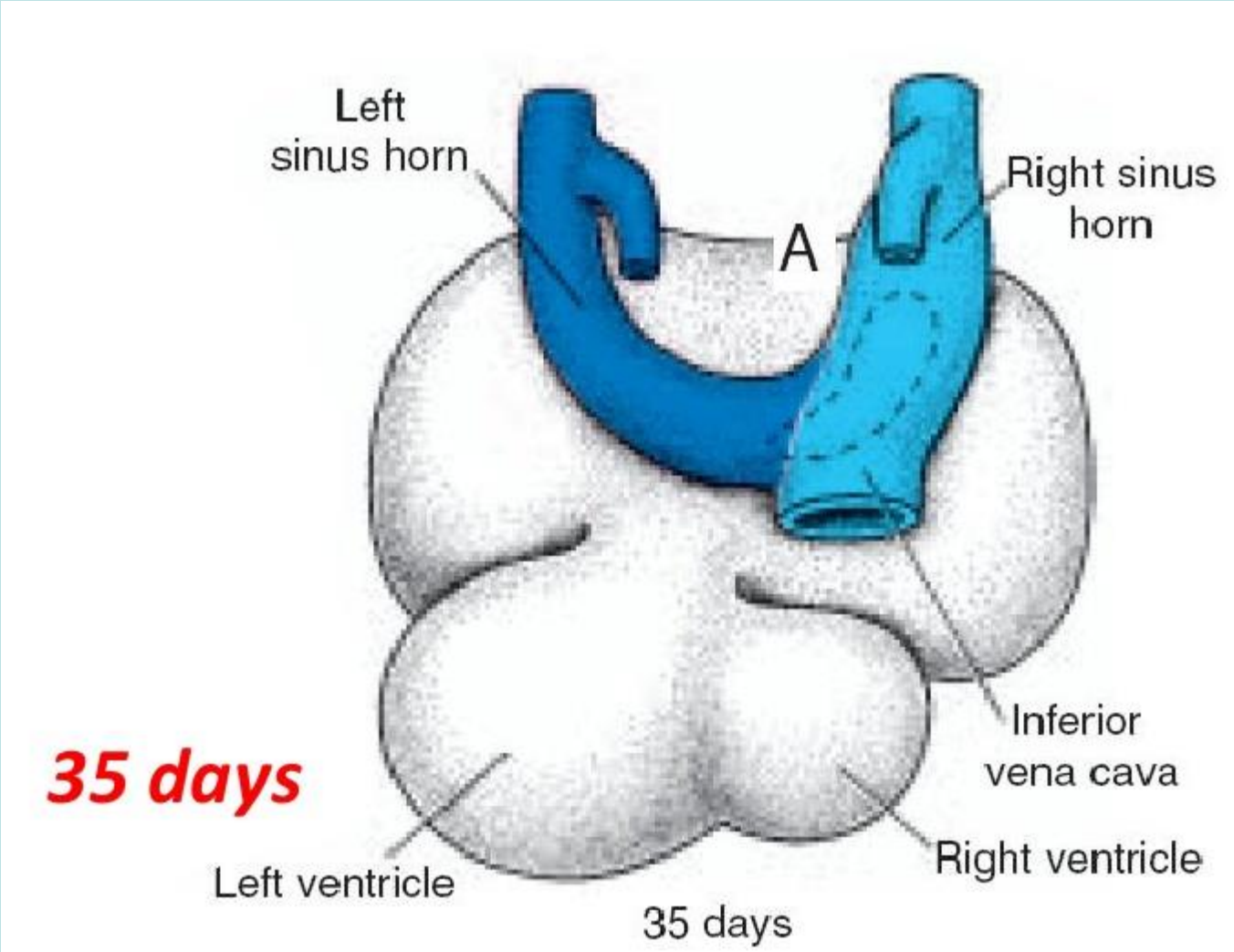
24 days



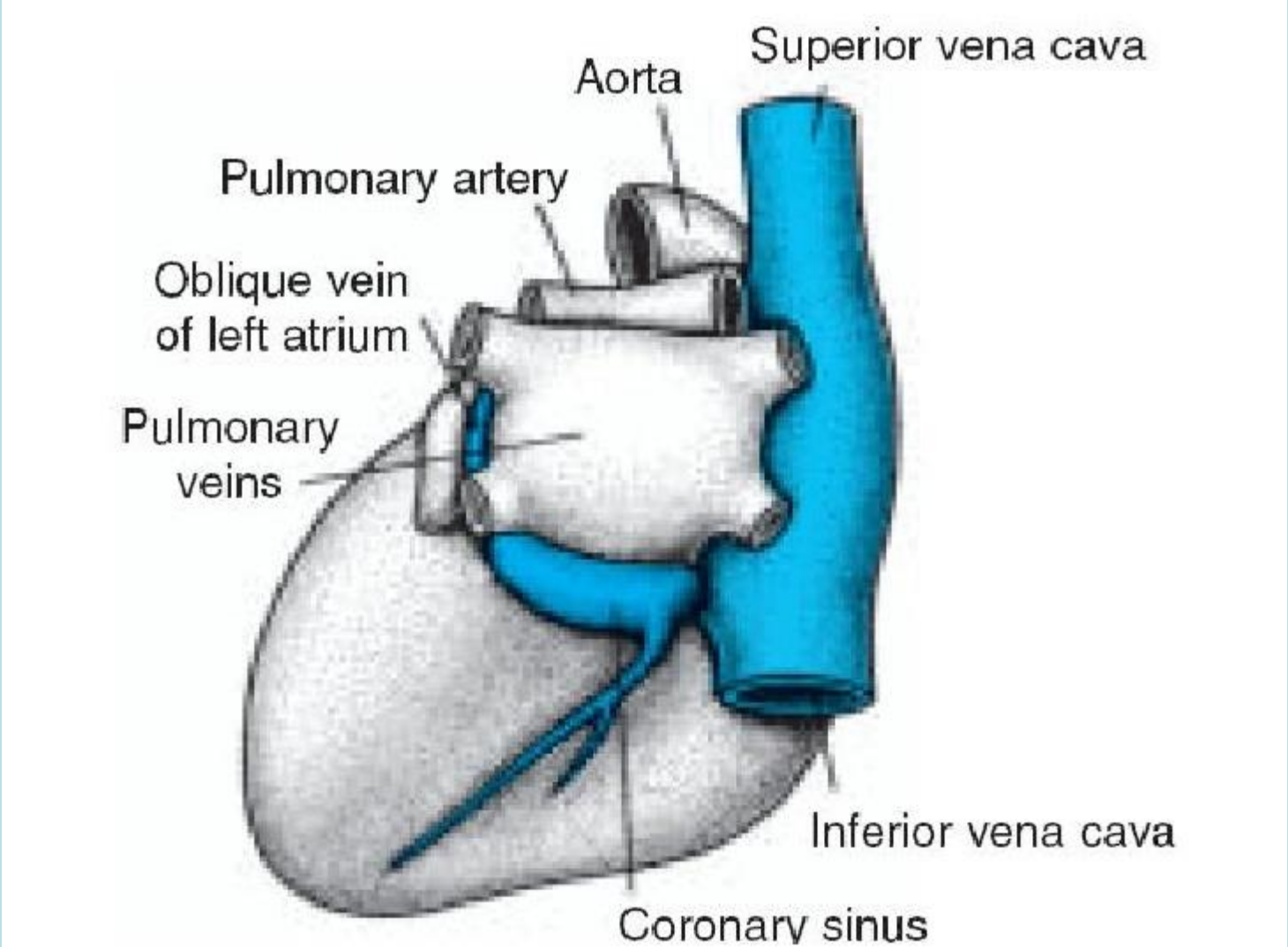
24 days


Sinuatrial
junction
ACV
PCV
Sinuatrial
fold
Right vitelline
vein

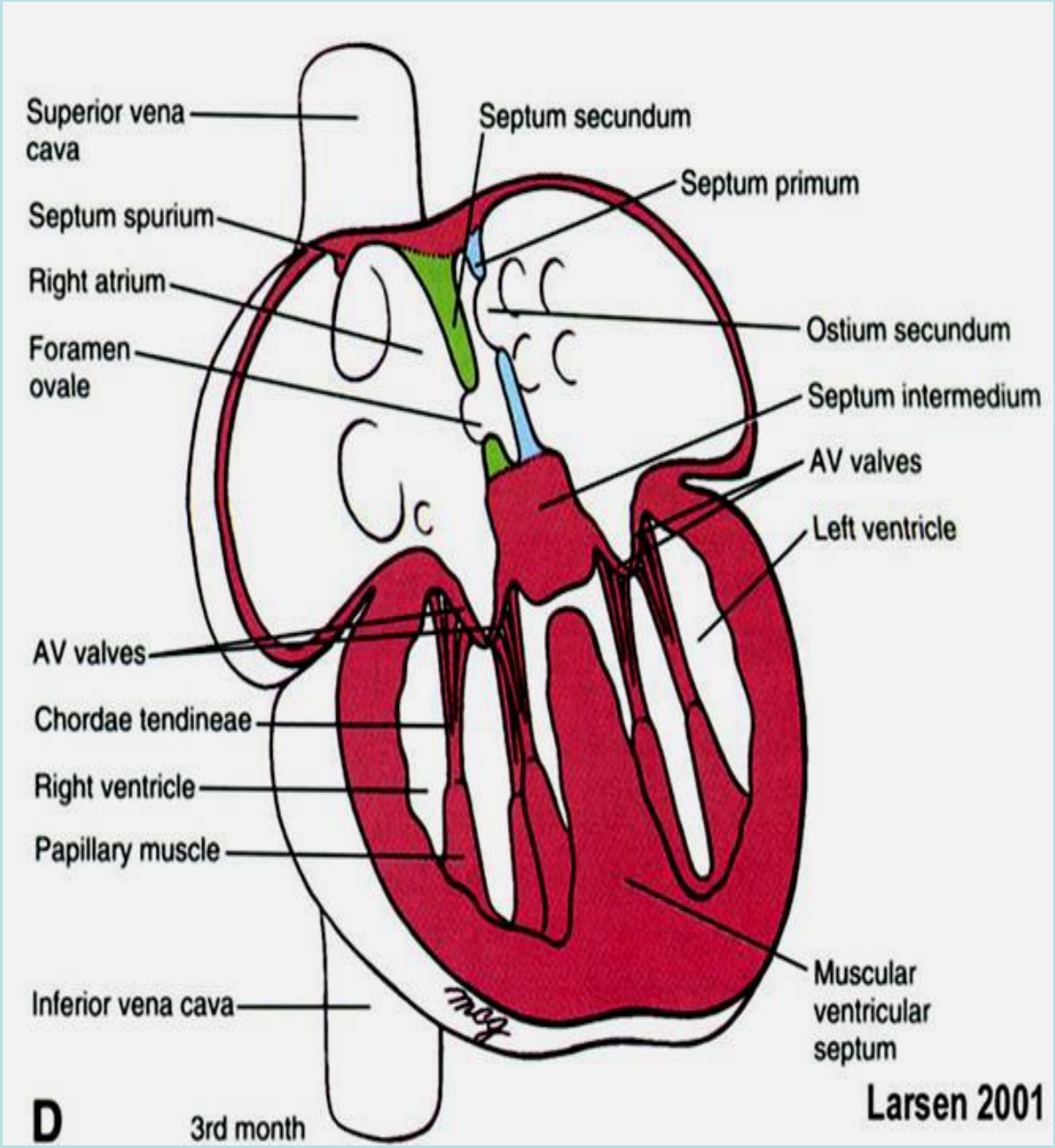
35 days

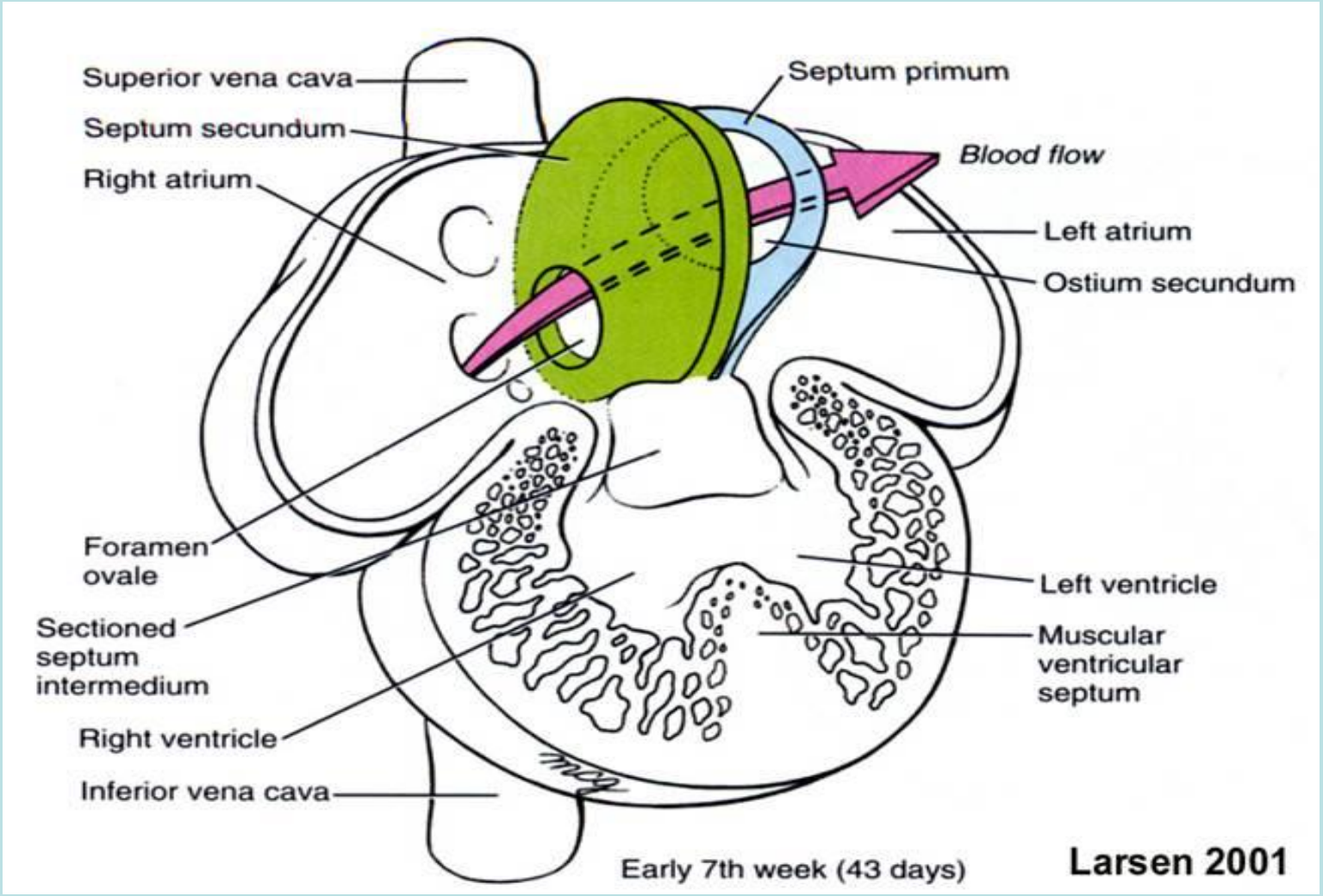

Left
sinus horn
A
Right sinus
horn
Inferior
vena cava
Right ventricle
Left ventricle
35 days

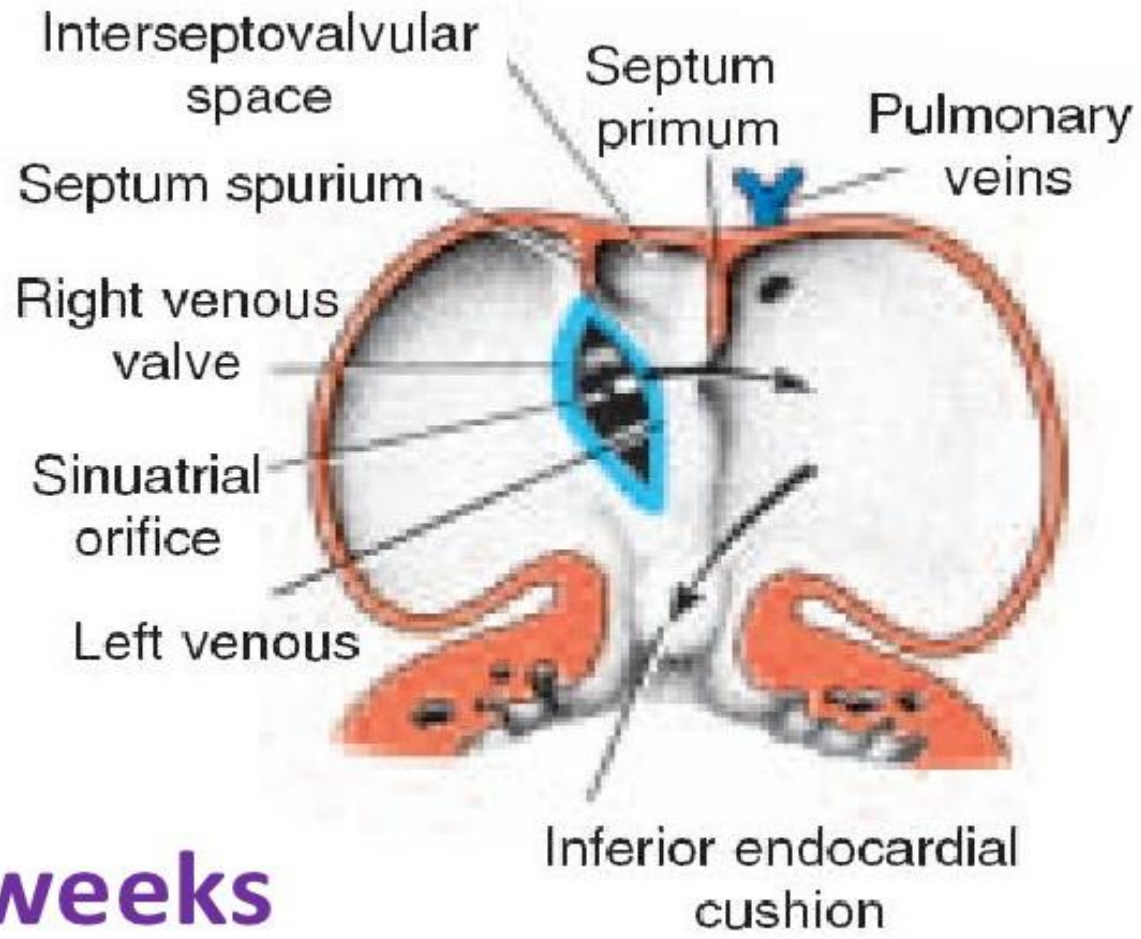
35 days


Superior vena cava
Aorta
Pulmonary artery
Oblique vein
of left atrium
Pulmonary
veins
Inferior vena cava
Coronary sinus

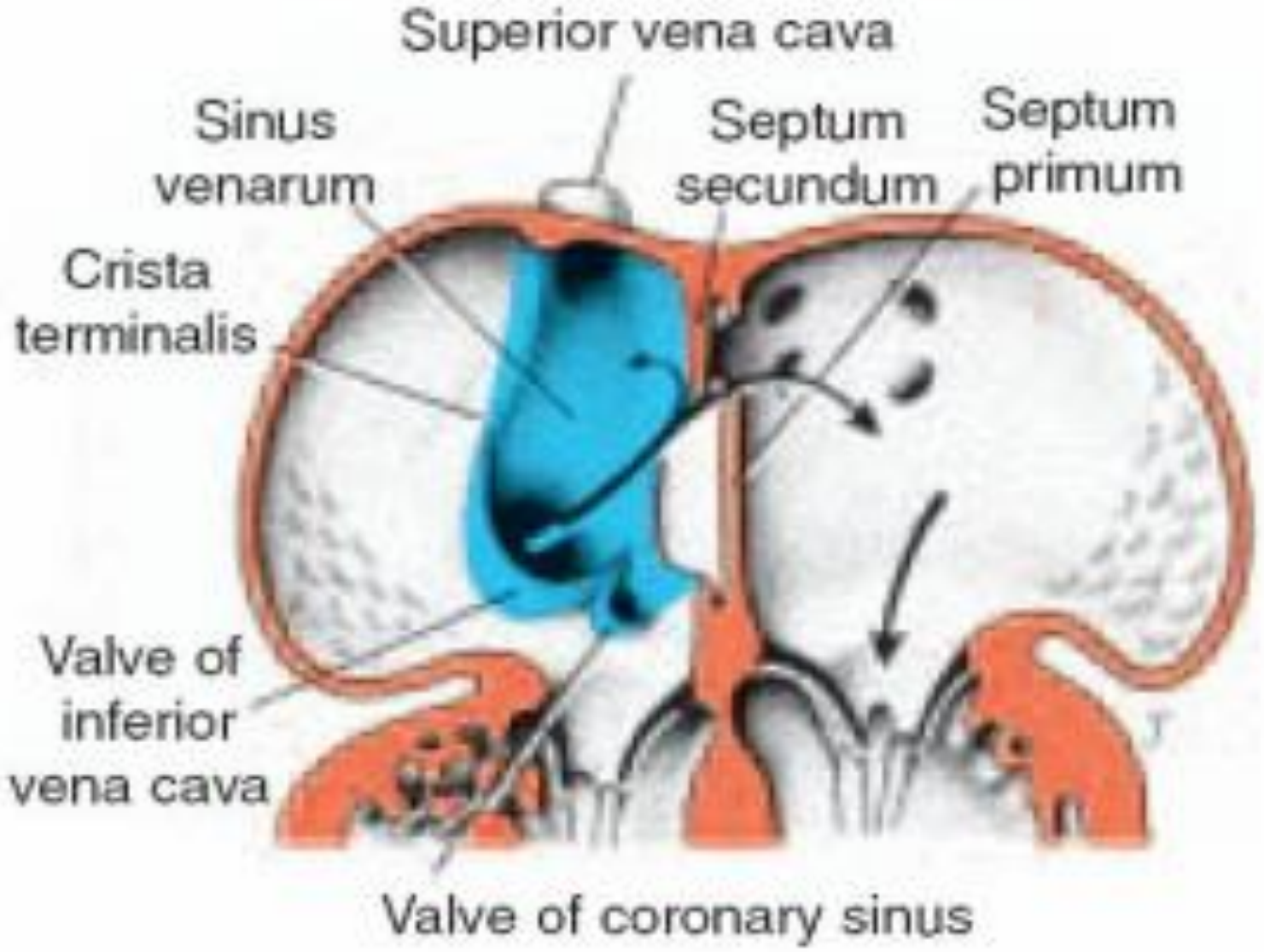
- **By inclusion of the sinus venosus into the wall of the right atrium, the 2 venae cavae open into the cavity.**
- **The opening place of the sinus venosus into the right atrium is marked by 2 valves: right and left.**
- **Superiorly the 2 valves fusion, forming a false septum *(septum spurium*), which eventually will disapear.**
- **The 2 valves are modified later.**
- **The right one divides and formes the valve of the inferior vena cava (Eustachio), and the valve of the coronary sinus (Thebesius).**
- **During the embryofoetal period the right valve redirectes the oxygenated blood from the right atrium to the left atrium , via interatrial orifice.**
- **The left valve atrophies and be weldded to the interatrial septum.**



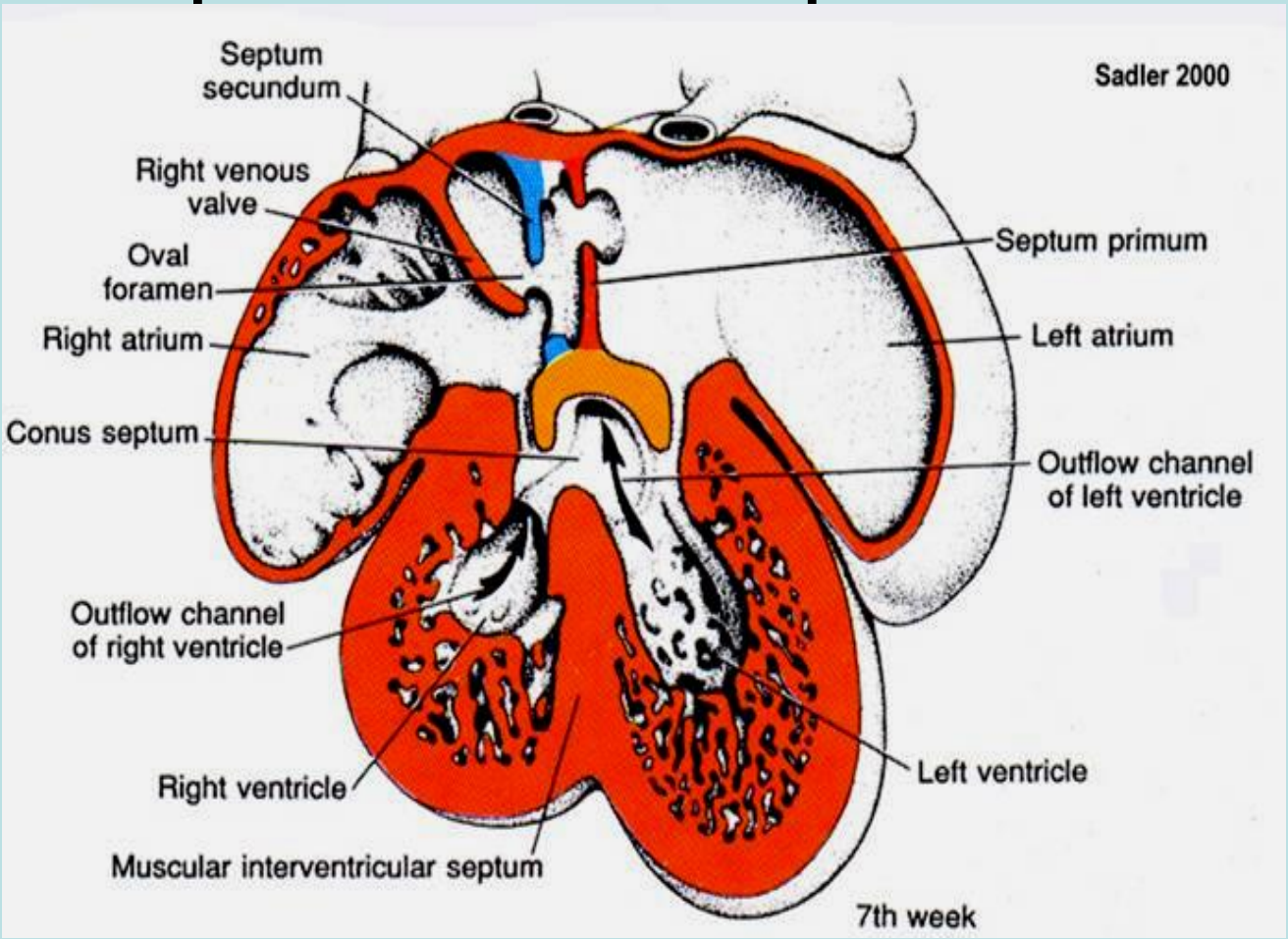

Superior vena cava
Septum secundum
Right atrium
Septum primum
Blood flow
Left atrium
Ostium secundum
Foramen ovale
Sectioned septum intermedium
Right ventricle
Inferior vena cava
Left ventricle
Muscular ventricular septum
Early 7th week (43 days)
Larsen 2001


Interseptovalvular space
Septum primum
Pulmonary veins
Septum spurium
Right venous valve
Sinuatrial orifice
Left venous
Inferior endocardial cushion

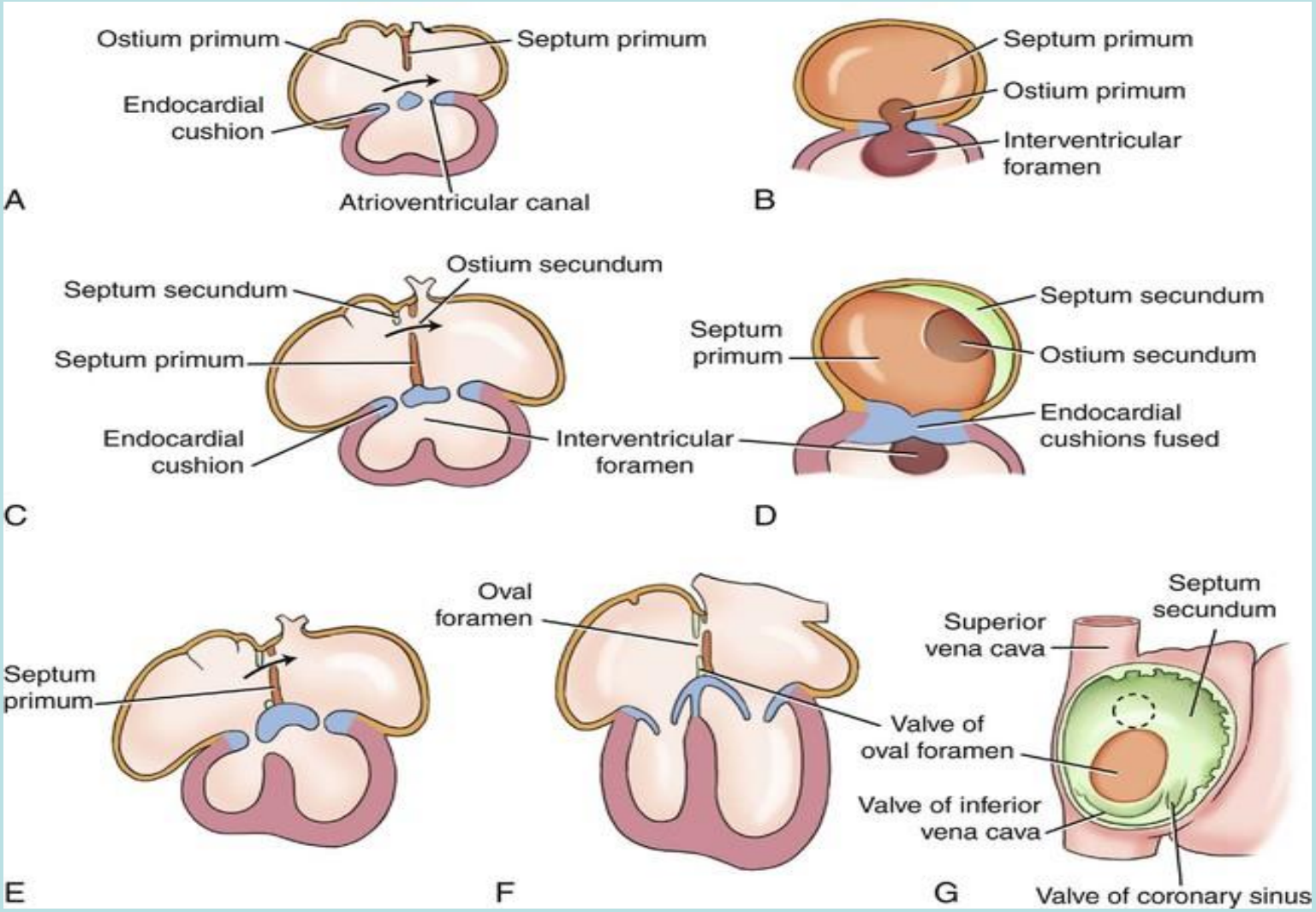
5 weeks


Superior vena cava
Sinus venarum
Septum secundum
Septum primum
Crista terminalis
Valve of inferior vena cava
Valve of coronary sinus

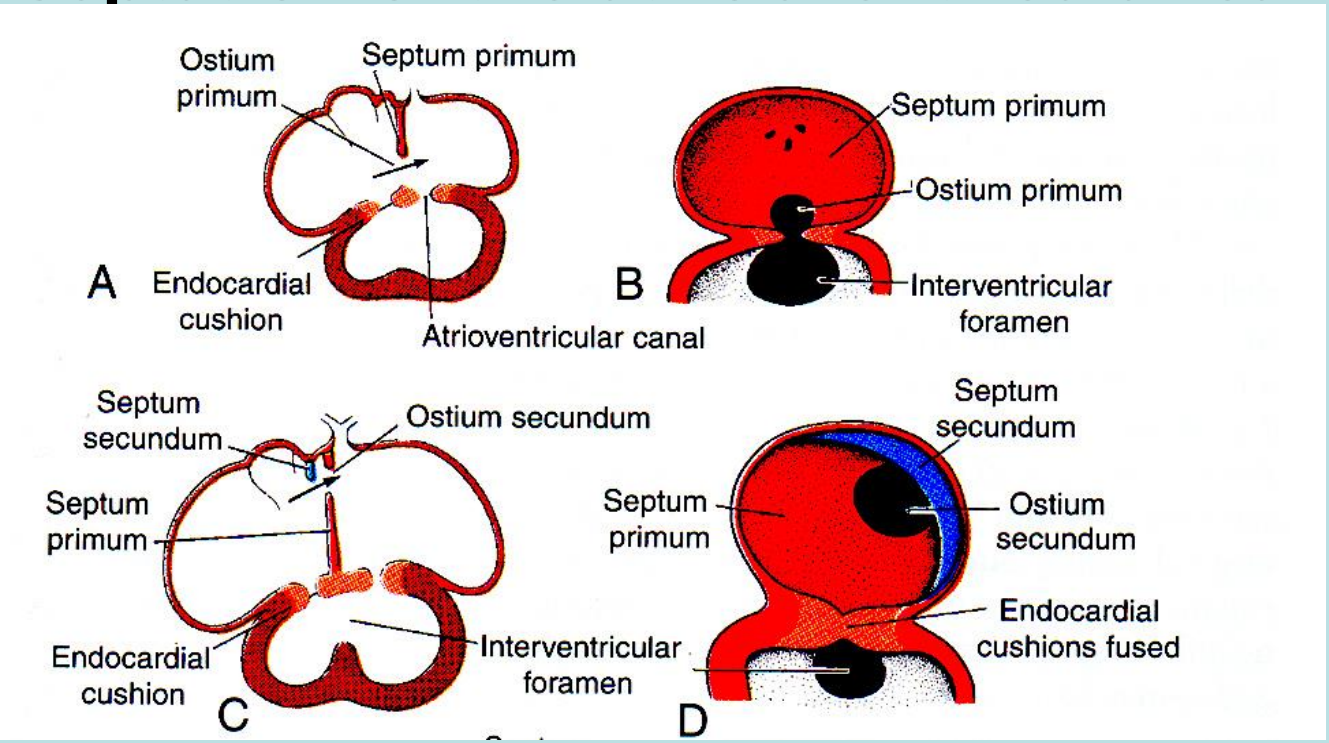
b. The primitive atrium - septa formation



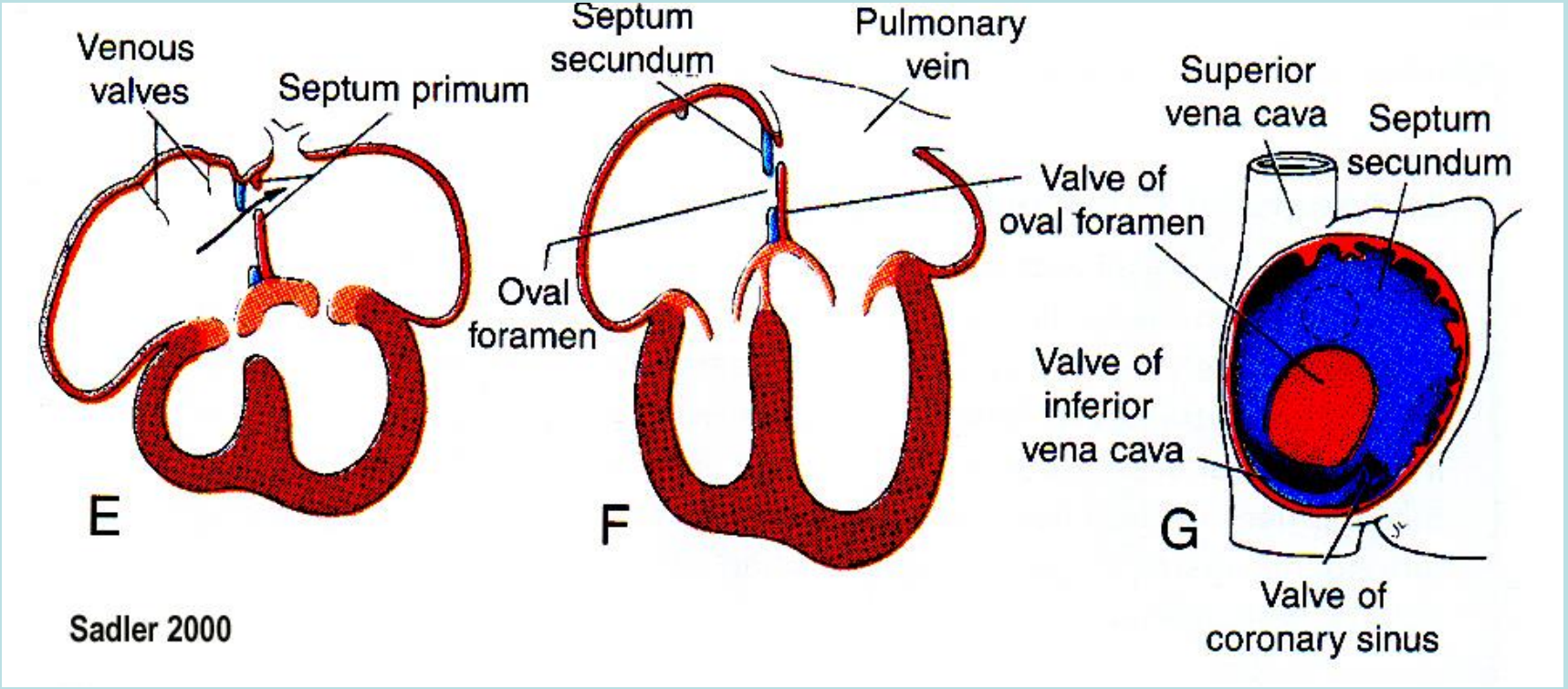
- **Begins in the 5th week, to the 6mm embryo, by the presence of the dorsocranial part of the septum primum *(septum primum*), semilunar in shape, which growths caudally to the left side of the septum spurium , toward the intermediate septum, which divides the atrioventricular canal into two orifices: bicuspid/ mitral and tricuspid.**
- **Septum primum, before reaching the intermediate septum, leaves the interatrial orifice, Born primary interatrial orifice *(ostium primum),* that eventually disappear.**
- **When the embryo has 7mm, the superior part of the septum primum undergoes a resorbtion process, that leads to a secondary interatrial orifice, (Botal foramen/ *ostium secundum*).**

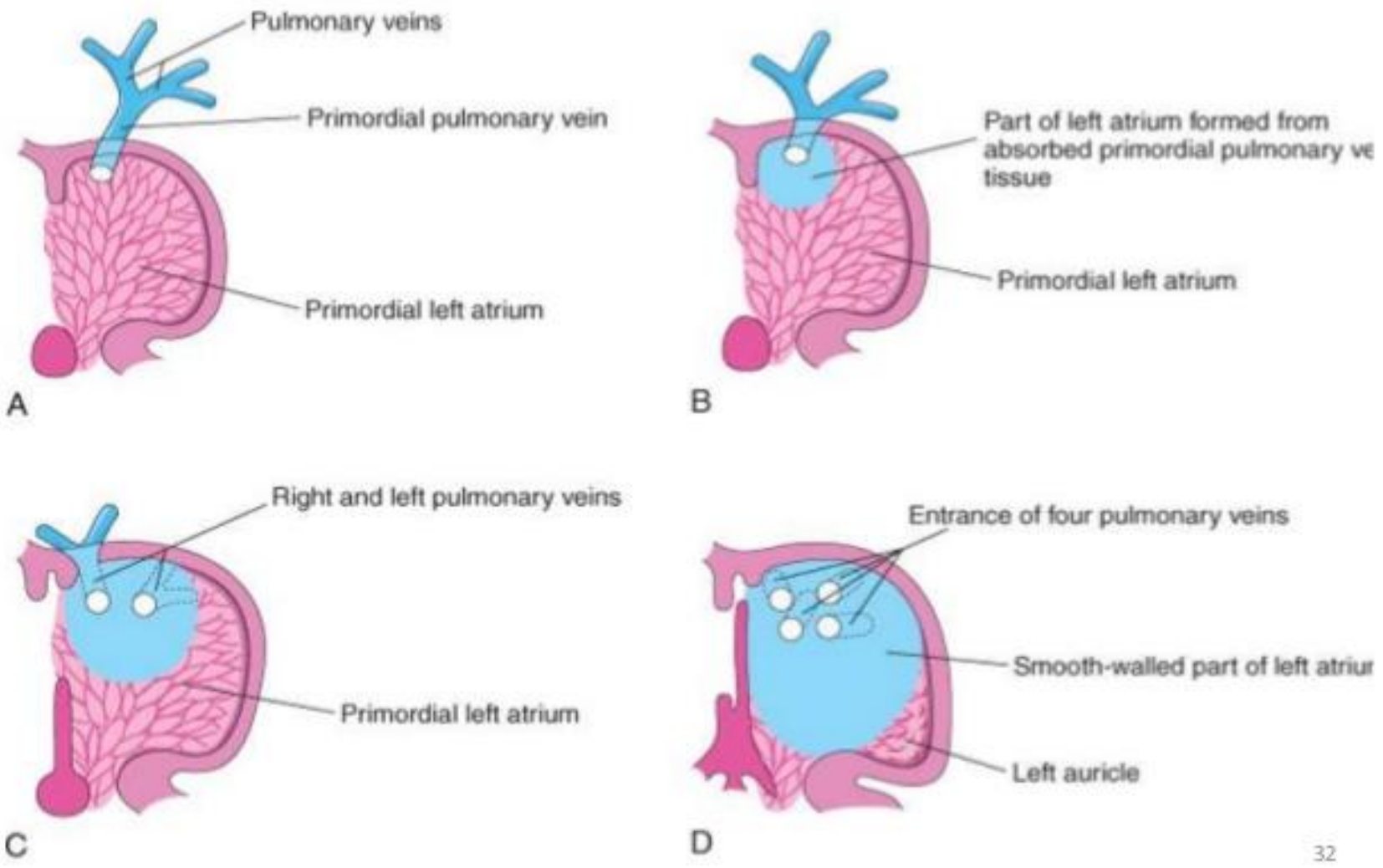

Ostium primum
Septum primum
Endocardial cushion
Atrioventricular canal
A
Septum primum
Ostium primum
Interventricular foramen
B
Ostium secundum
Septum secundum
Septum primum
Endocardial cushion
Interventricular foramen
C
Septum secundum
Septum primum
Ostium secundum
Endocardial cushions fused
D
Septum primum
E
Oval foramen
F
Septum secundum
Superior vena cava
Valve of oval foramen
Valve of inferior vena cava
Valve of coronary sinus
G

c. The septation of the atriobventricular canal



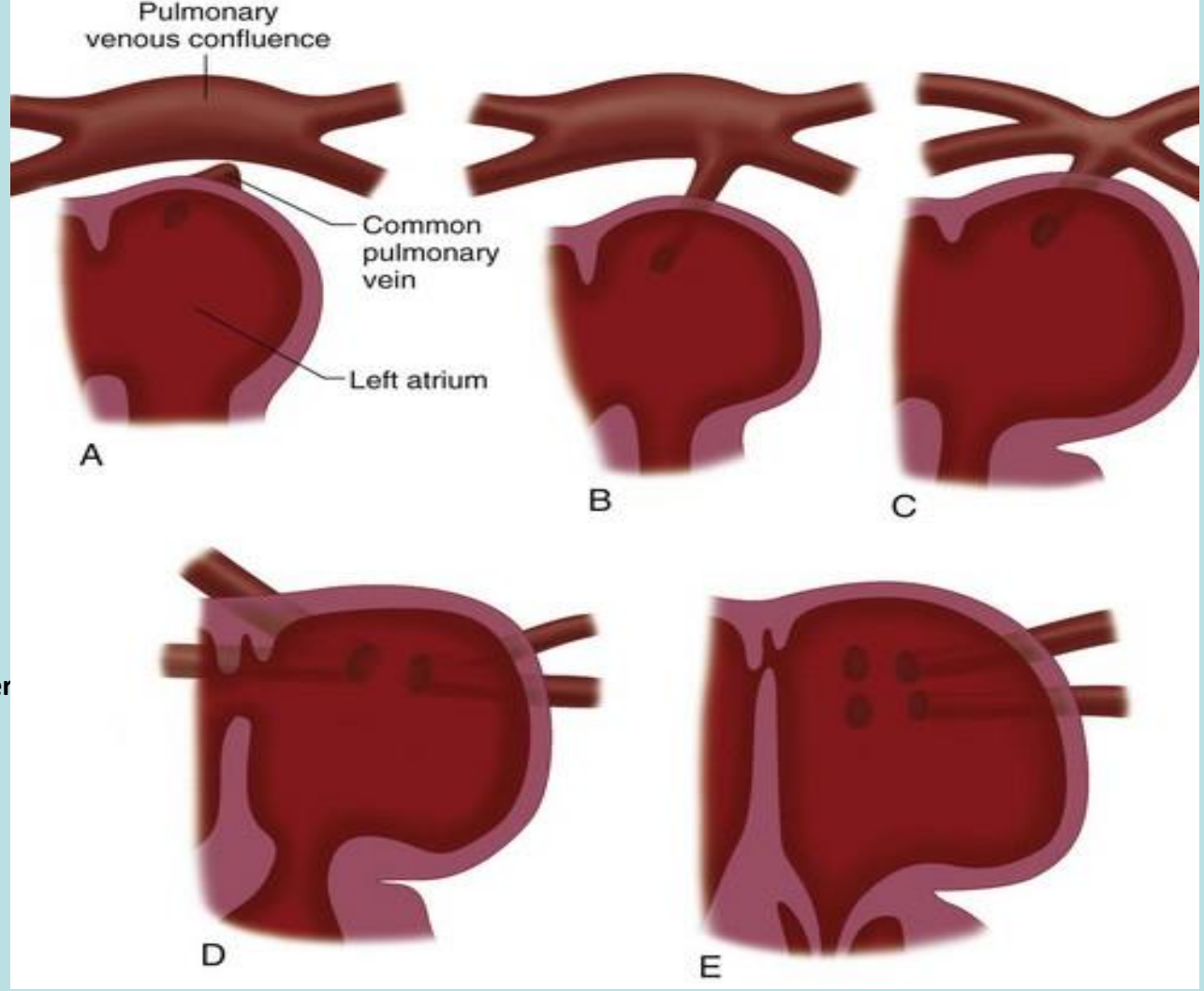
- **Takes place by the presence of 2 endocardic structures, ventral and dorsal.**
- **They fuse when the embryo has 11 mm, forming the intermediate septum, sagittally disposed.**
- **This septum divides the atrioventricular canal into a right and a left atrioventricular orifices.**
- **Initially the 2 oifices are small and surrounded by endocardic folds.**
- **They form the internal, membranous part of the atrioventricular valves.**
- **The main , fibrous part, is formed by the penetration of the ventricular muscular trabecules.**
- **In their vicinity these trabecules undergo a fibrosis process, forming the cordae tendinae, while the part from the ventricular wall formes the papillary muscles.**

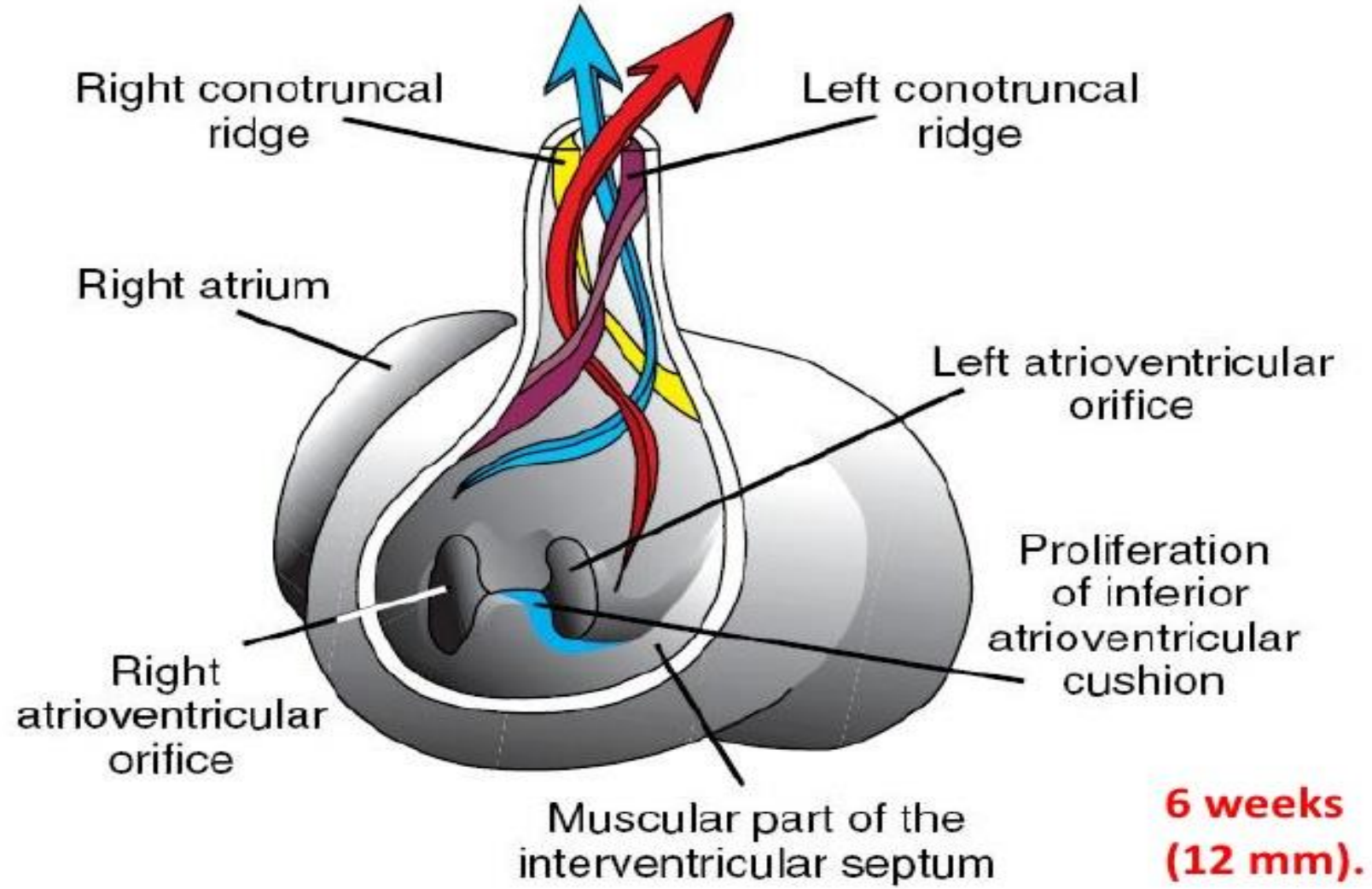

Venous valves
Septum primum
E
Septum secundum
Pulmonary vein
Oval foramen
F
Superior vena cava
Septum secundum
Valve of oval foramen
Valve of inferior vena cava
G
Valve of coronary sinus
Sadler 2000


Pulmonary veins
Primordial pulmonary vein
Primordial left atrium
A
Part of left atrium formed from absorbed primordial pulmonary ve tissue
Primordial left atrium
B
Right and left pulmonary veins
Primordial left atrium
C
Entrance of four pulmonary veins
Smooth-walled part of left atriu
Left auricle
D

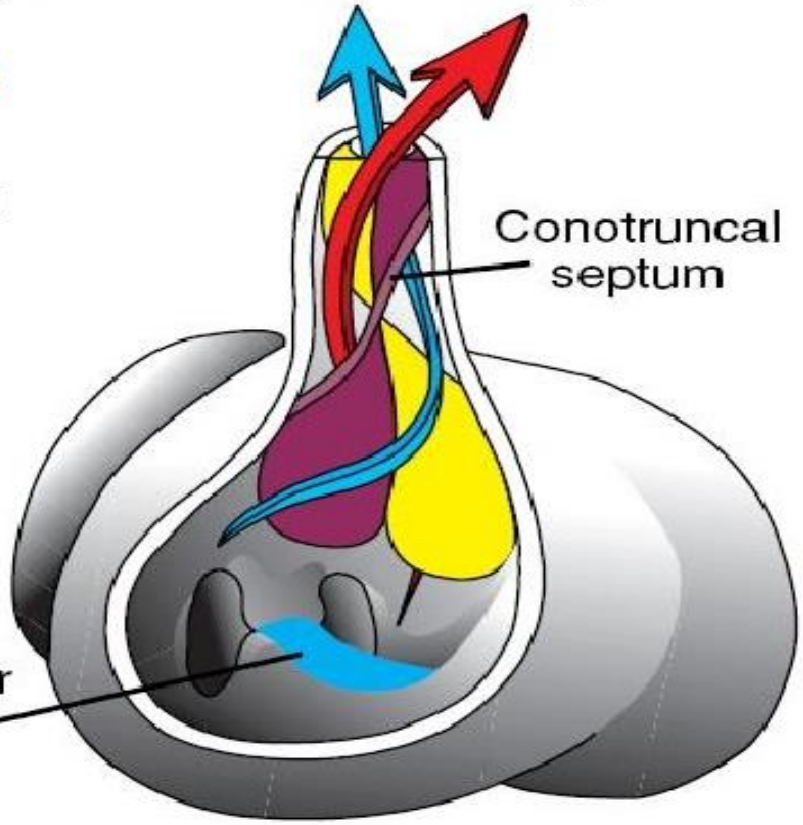
In the 6th week appears the secondary septum *(septum secundum*), which develops forward backward , on the right side of teh septum primum, covering the foramen of Botale.

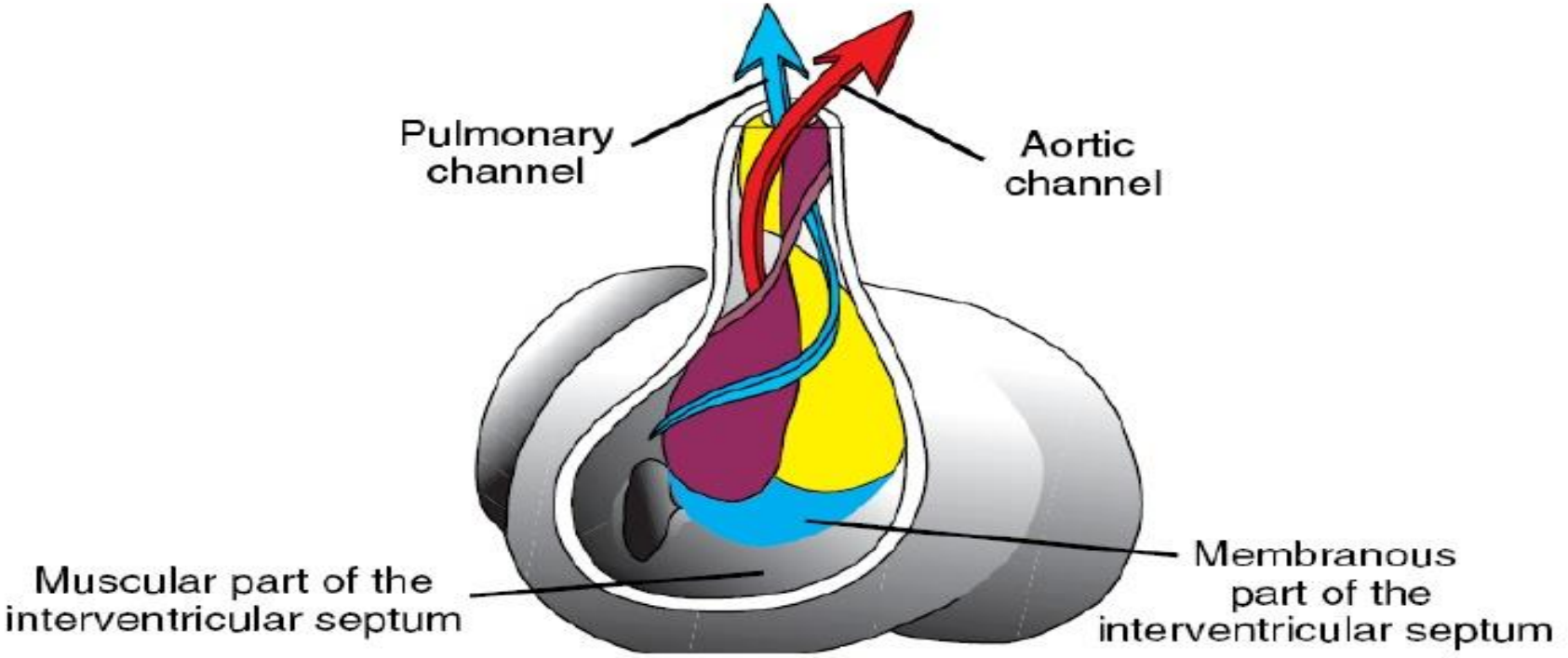
The posterior border of the secondary septum formes the fosa ovalis limbus, on the internal wall of the right atrium, while in the left atrium the anterosuperior border of the septum primum gives rise to the semilunar fold *(falx septi).*




Right conotruncal ridge
Left conotruncal ridge
Right atrium
Left atrioventricular orifice
Proliferation of inferior atrioventricular cushion
Right atrioventricular orifice
Muscular part of the interventricular septum
6 weeks (12 mm).

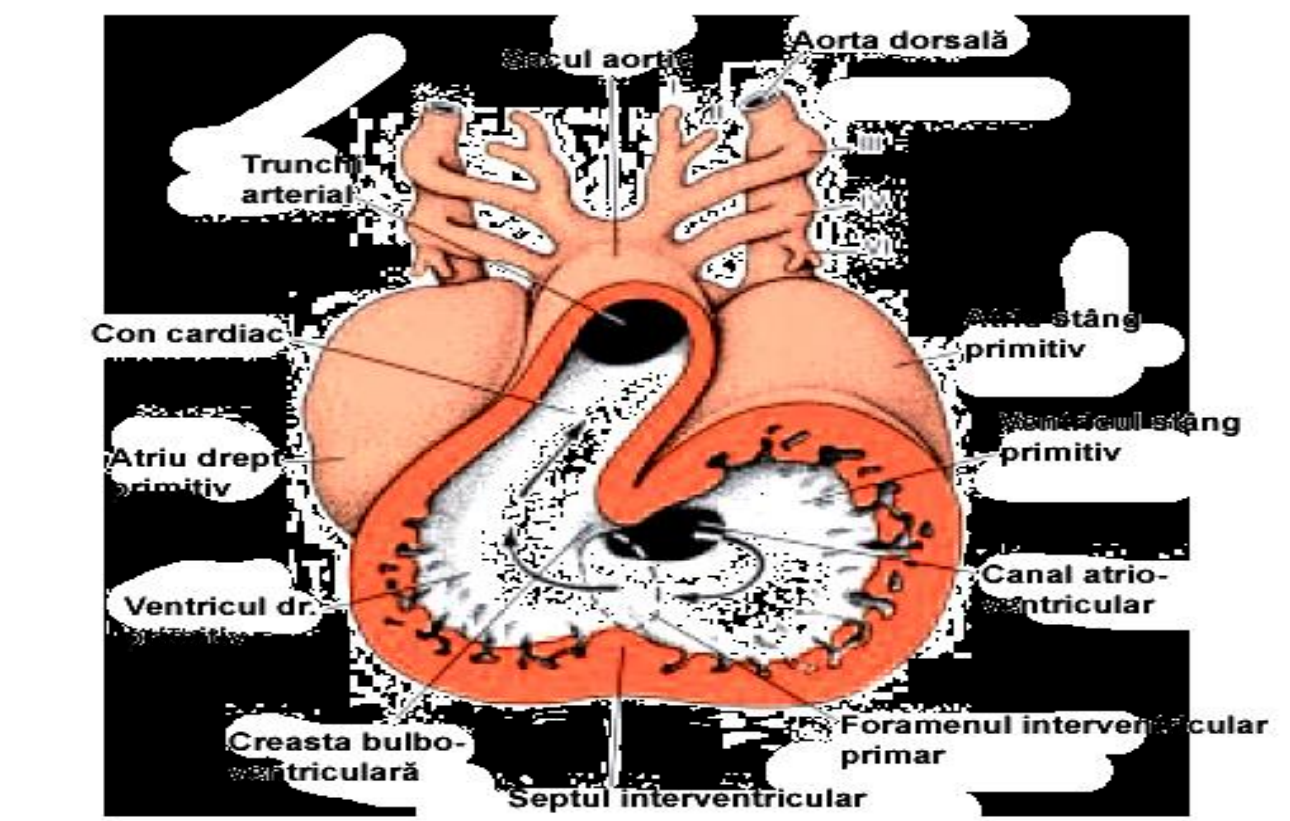
Development of the conotruncal ridges (cushions) and closure of the interventricular foramen. Proliferations of the right and left conus cushions, combined with proliferation of the inferior endocardial cushion, close the interventricular foramen and form the membranous portion of the interventricular septum.




Pulmonary channel
Aortic channel
Muscular part of the interventricular septum
Membranous part of the interventricular septum

d. The primitive ventricle-septa formation

- Begins after the 2nd month.
- The ventricular muscles are enlarged, filling the whole cavity of the primitive ventricle.
- The middle fibres fuse in the apex vicinity and form the primary muscular interventricular septum.
- At the end of the 8th week the muscular interventricular septum fuses with the bulbus arteriosus septum and the caudal prolongation of the intermediate septum.
- Results the membranous portion of the interventricular septum.

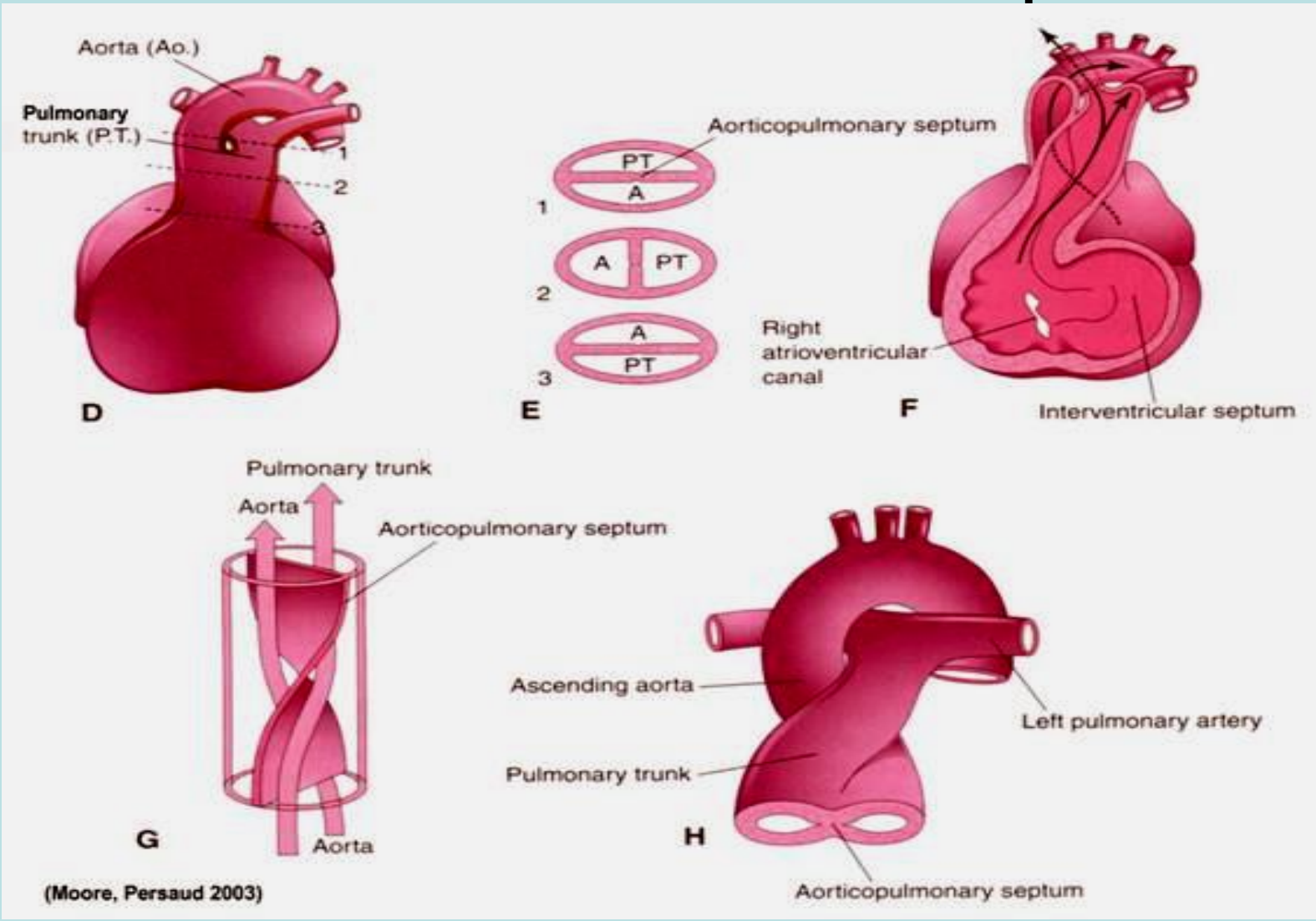


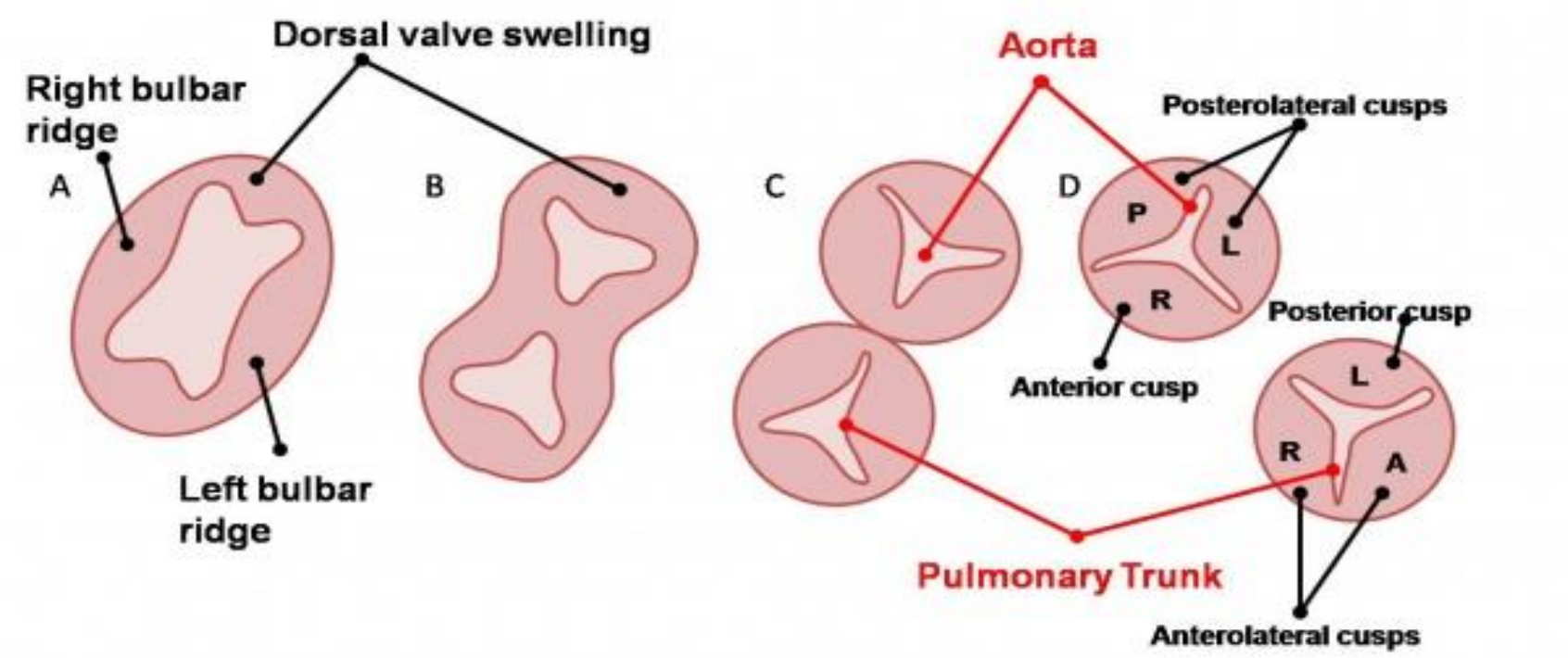
30 days embryo, primary interventricular foramen, communication of the left atrium with the left primitive ventricle

f. The bulbus arteriosus and truncus arteriosus septation

On the internal wall of the bulbus arteriosus and truncus arteriosus , on the 5 mm embryo, apear 2 longitudinal endocardiac cushions, right and left, having a helicoidal disposition.

This septum goes in the ventricles and joins with the muscular interventricular septum, forming its membranous part. This disposal makes the pulmonary trunk to surround the ascending aorta.

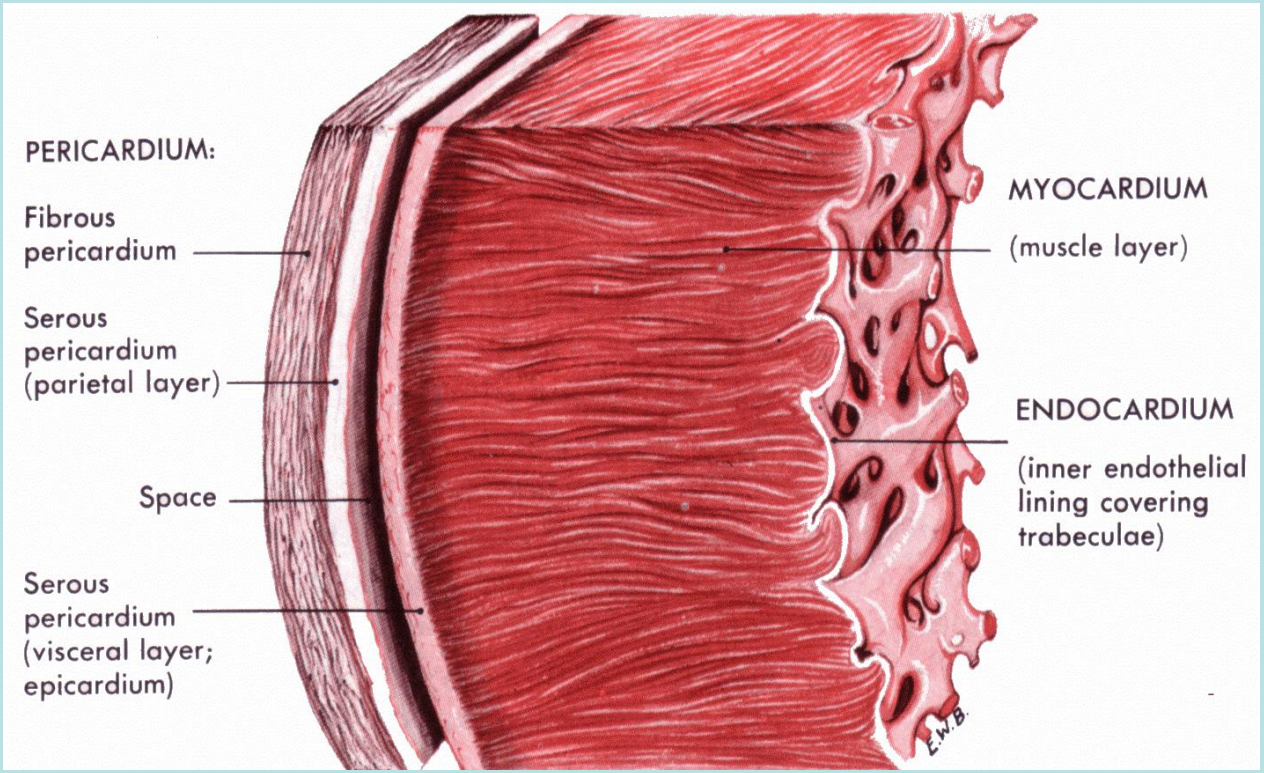


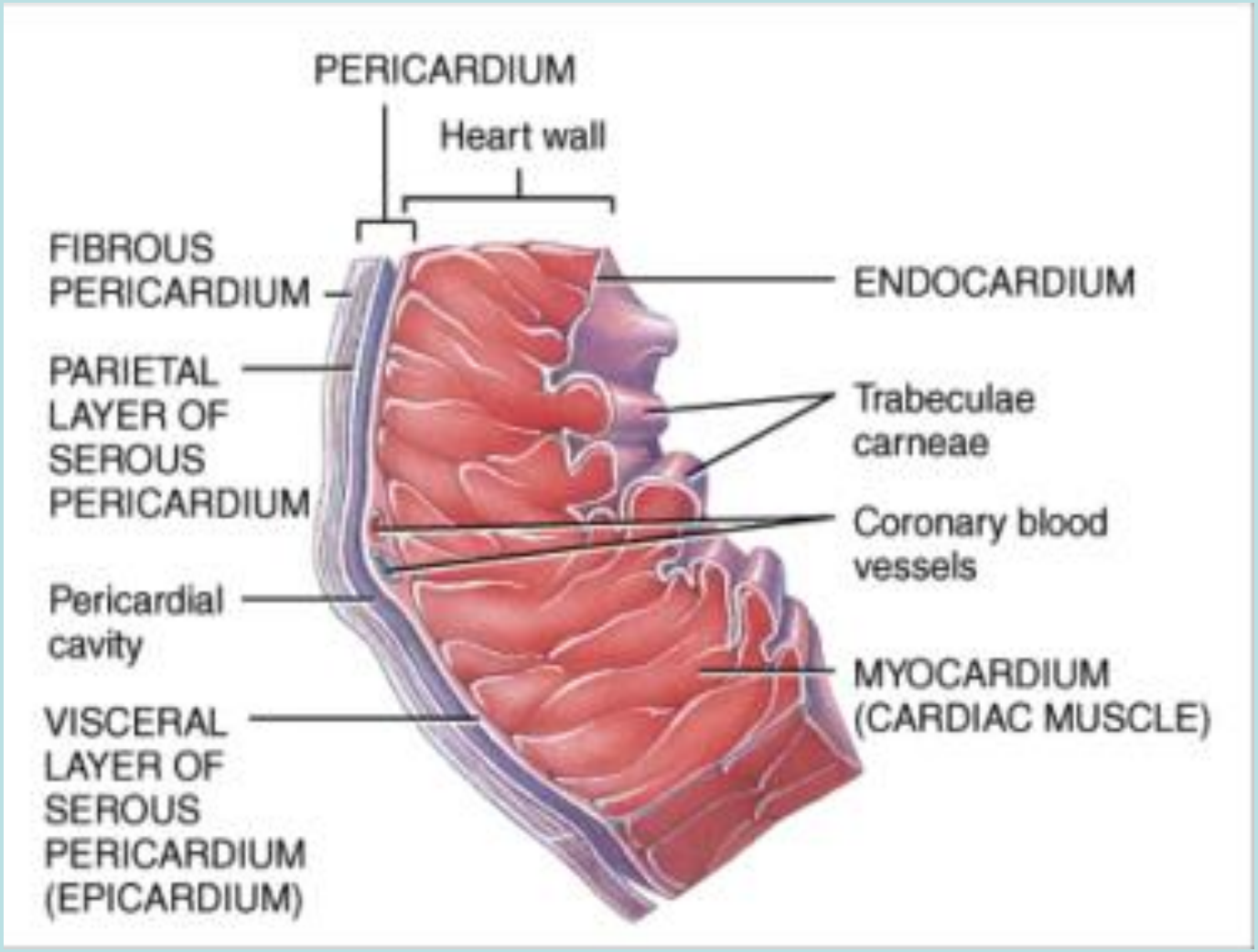


Weeks 6-7 = detorsion process
the aortic compartment comes in relation with the left ventricle and the pulmonary with the right ventricle.
Semilunar valves:anterior, posterior, right lateral and left lateral .
(pulmonary orifice:anterior, right, left; aorta= right , left, posterior leaflets).
20 mm embryo = the distal part of the bulbus arteriosus and the arterial trunk are complete separated.

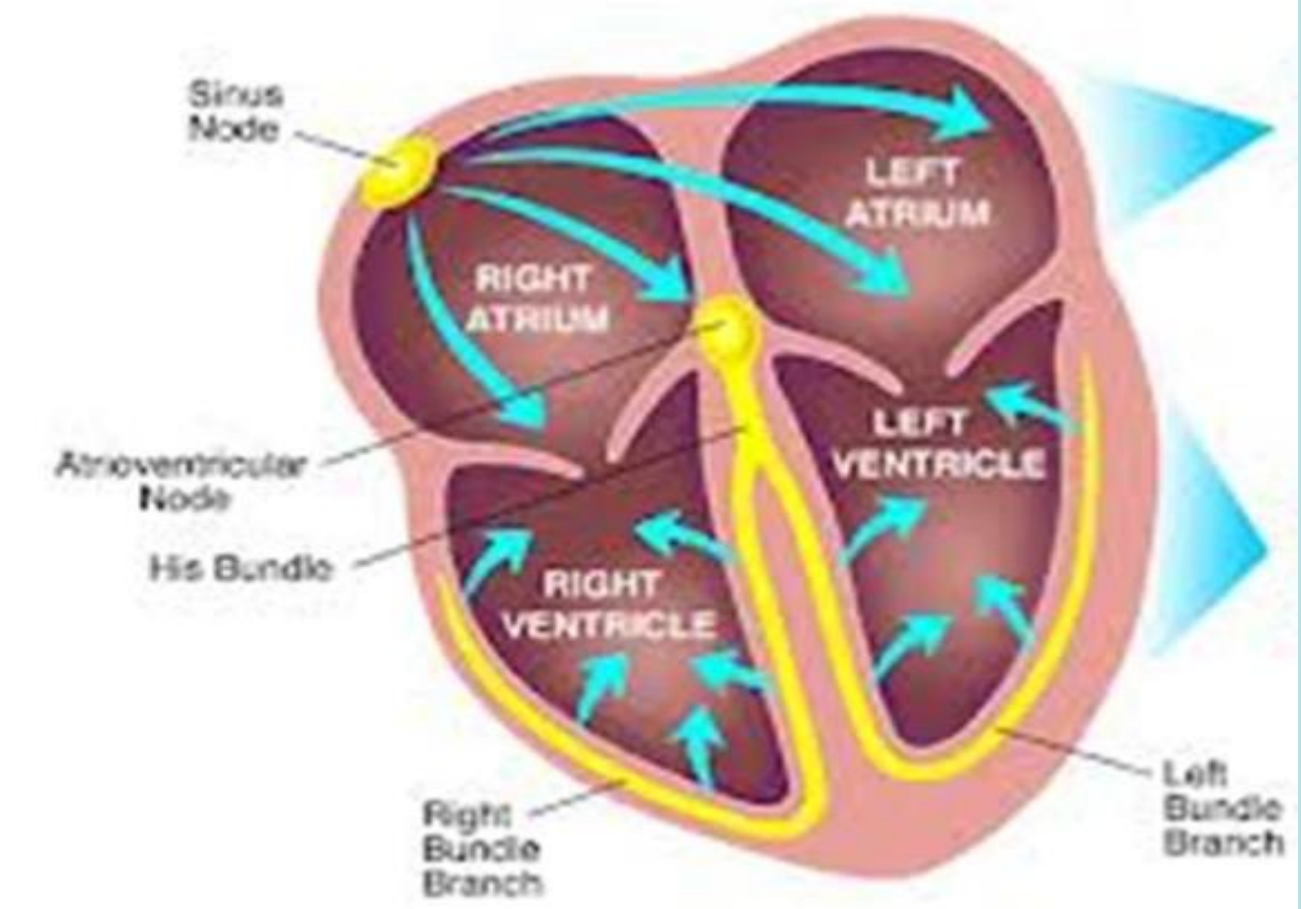
Developing of the heart walls

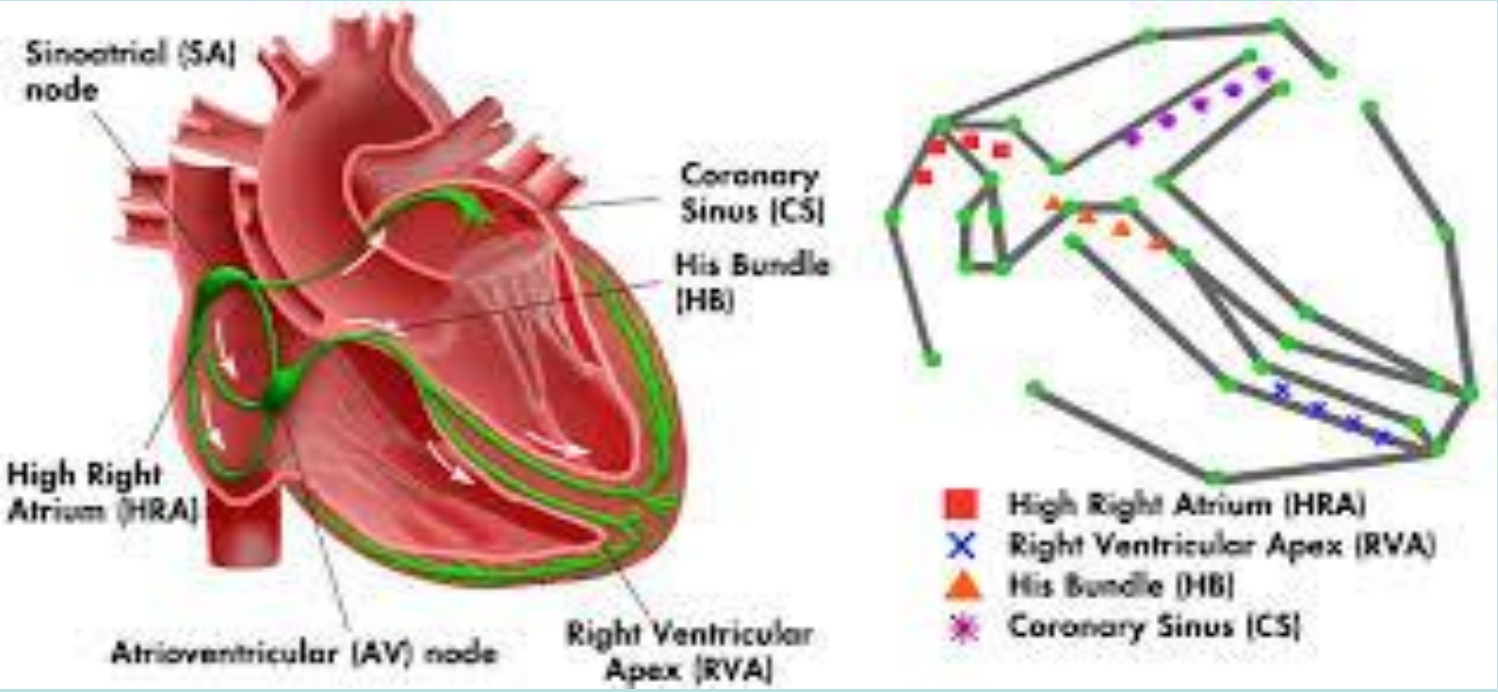
- **6th week = coronary arteries**



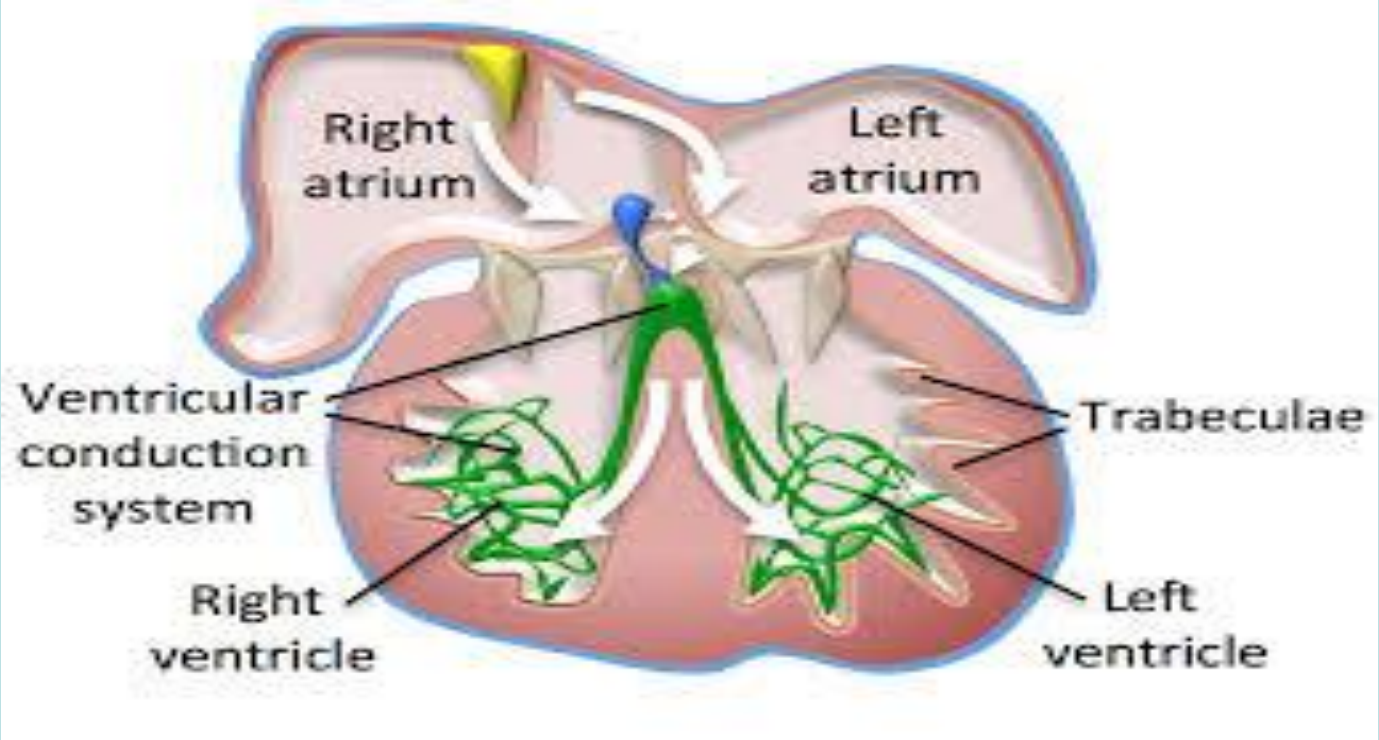

PERICARDIUM
Heart wall
FIBROUS PERICARDIUM
PARIETAL LAYER OF SEROUS PERICARDIUM
Pericardial cavity
VISCERAL LAYER OF SEROUS PERICARDIUM (EPICARDIUM)
ENDOCARDIUM
Trabeculae carneae
Coronary blood vessels
MYOCARDIUM (CARDIAC MUSCLE)

Heart pacemaker and conducting system development





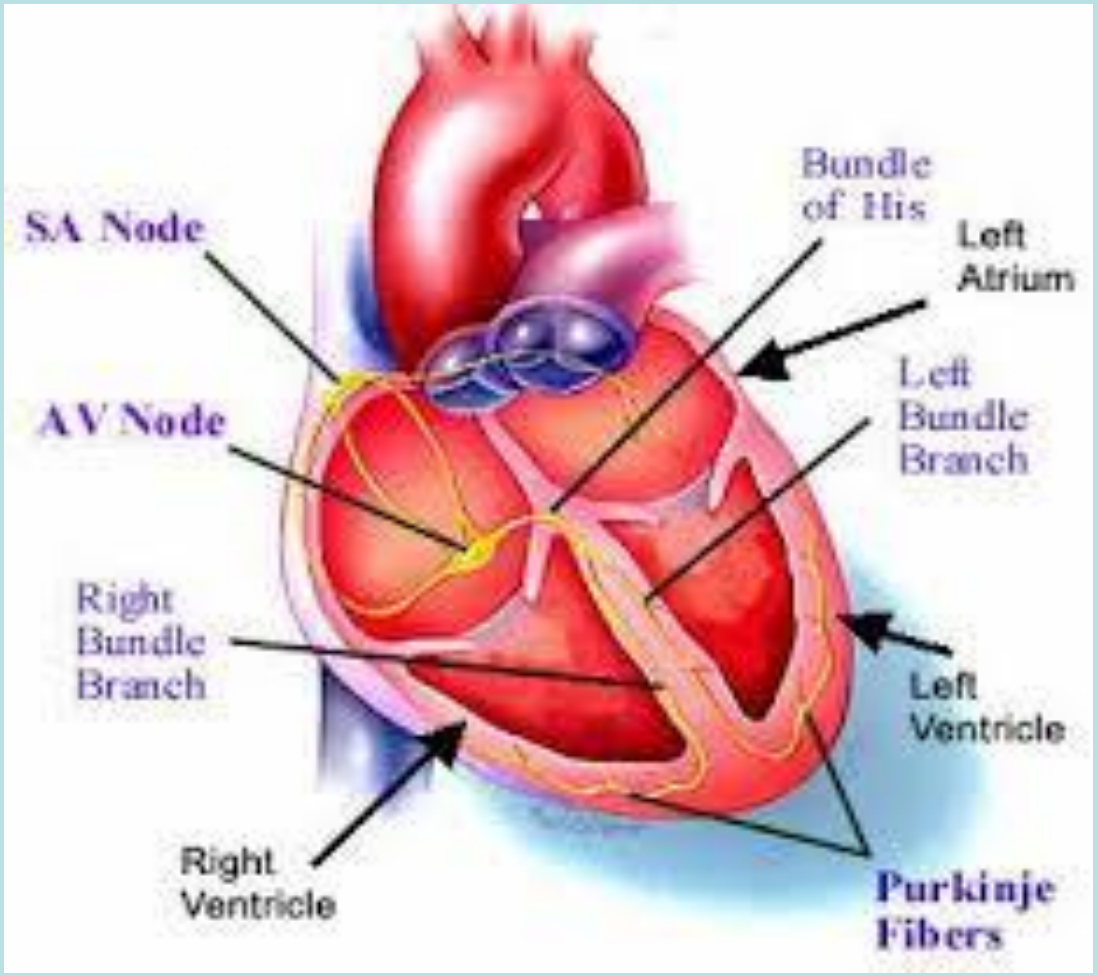
Primitive ventricle is the initial pacemaker.
Electric cellular depolarization= myocardiocites

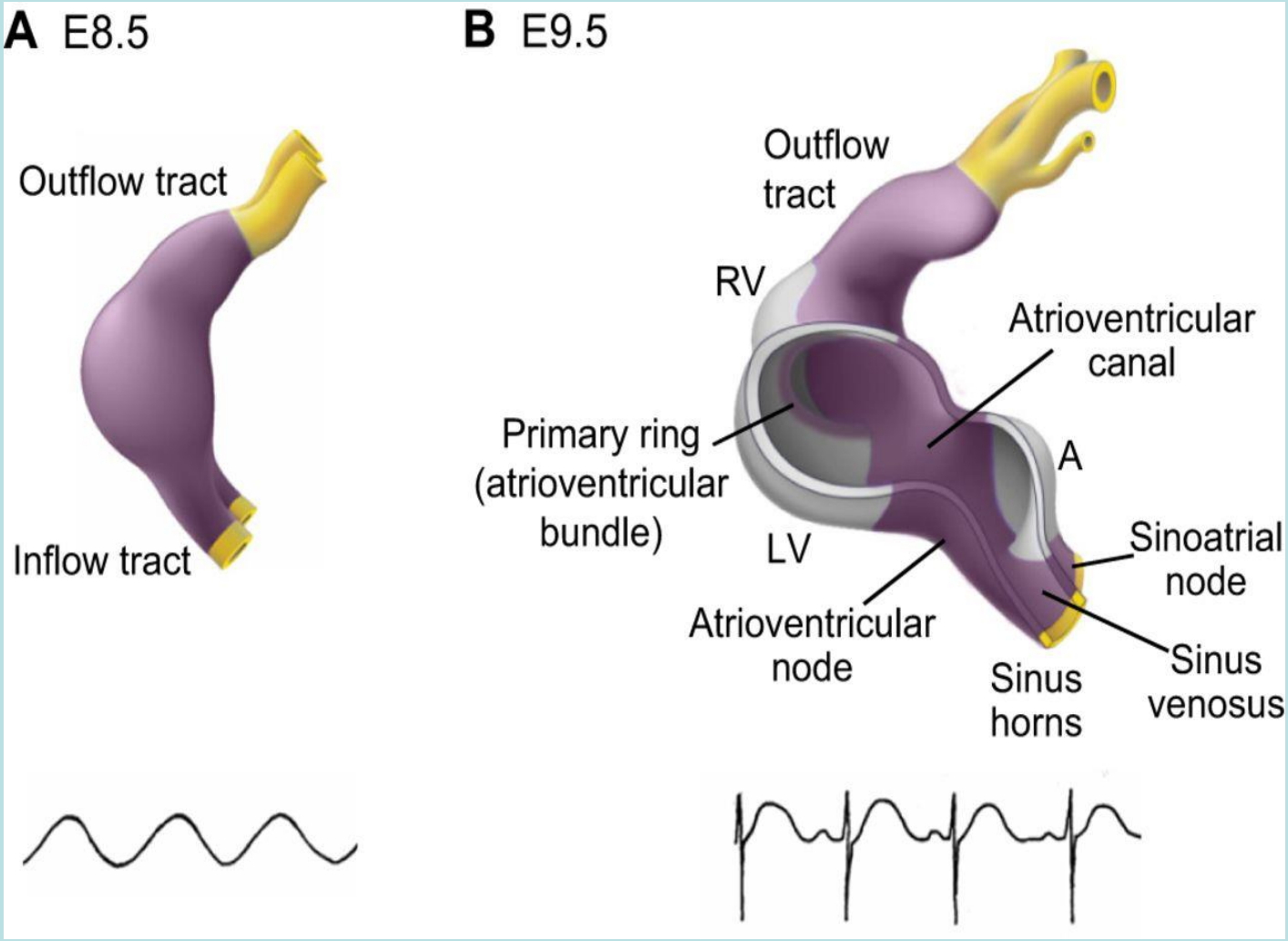

Right atrium
Left atrium
Ventricular conduction system
Trabeculae
Right ventricle
Left ventricle

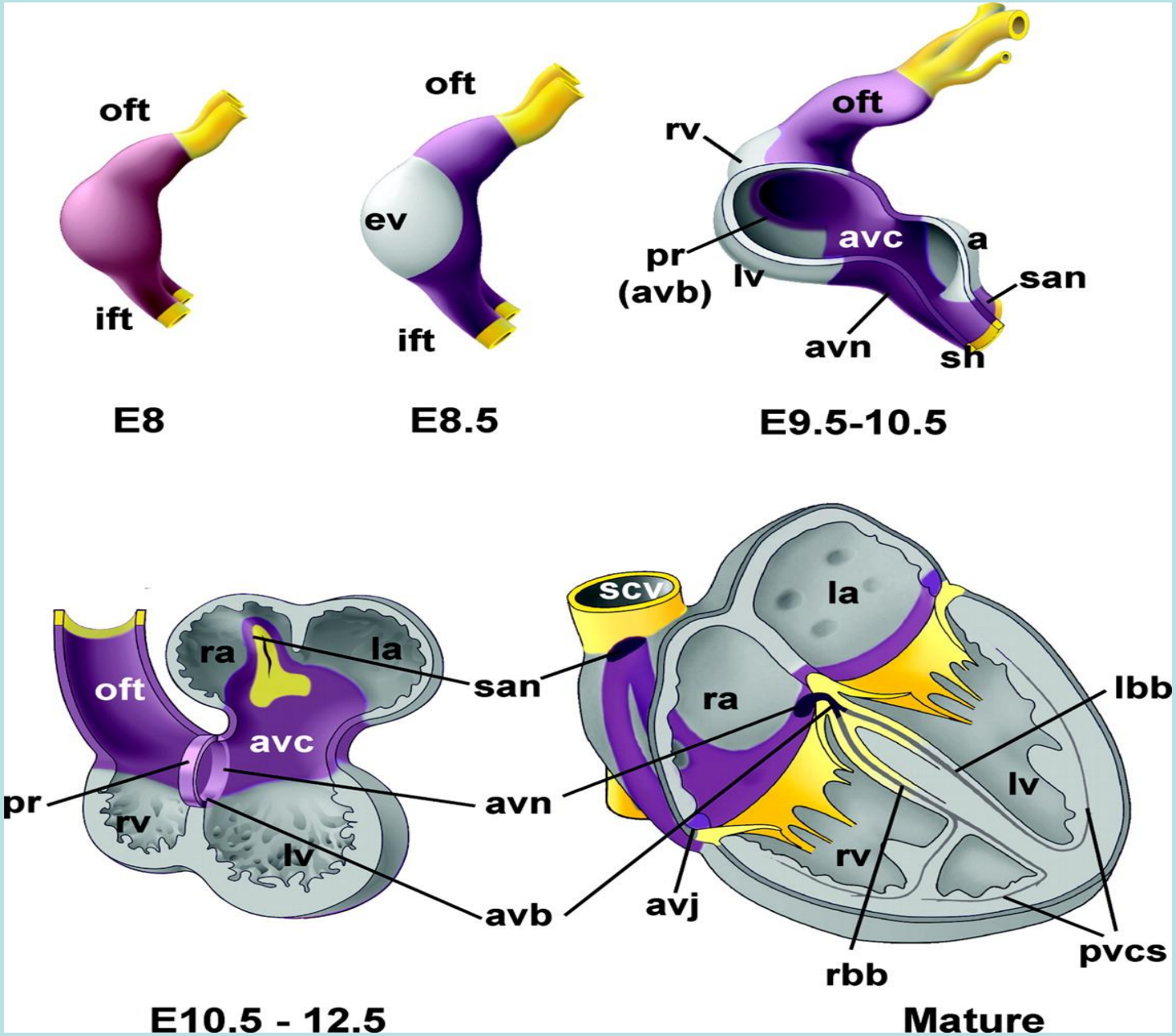
pacemaker= sinuatrial node

Week 5
75-80 beats/minute.
Peak= 165-185 b/min in the first 7 weeks.

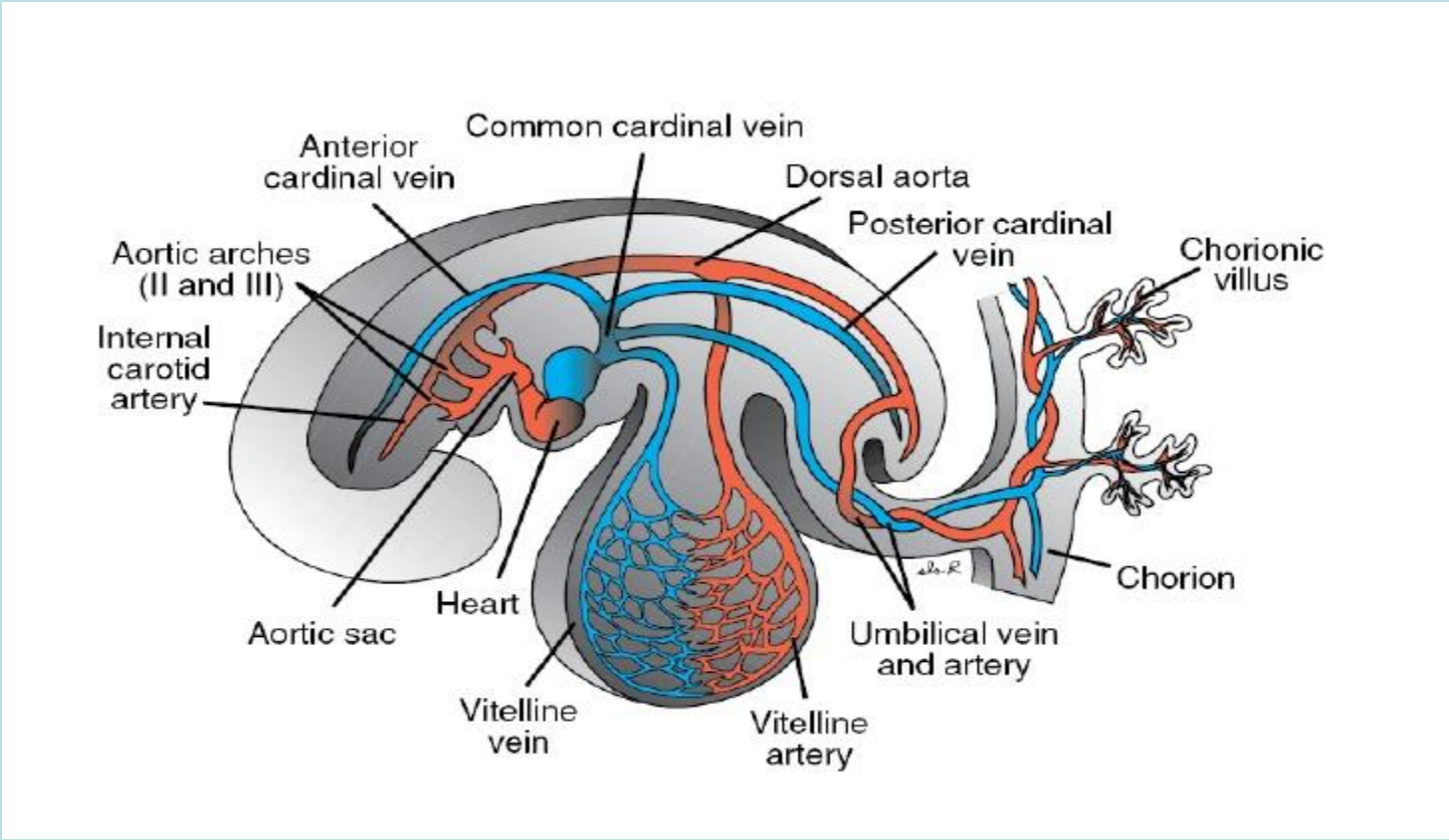
150 bts/min 15weeks.
finally-= 145 (+/-25).




A E8.5
Outflow tract
Inflow tract
B E9.5
Outflow tract
RV
Atrioventricular canal
Primary ring (atrioventricular bundle)
A
LV
Sinoatrial node
Atrioventricular node
Sinus horns
Sinus venosus

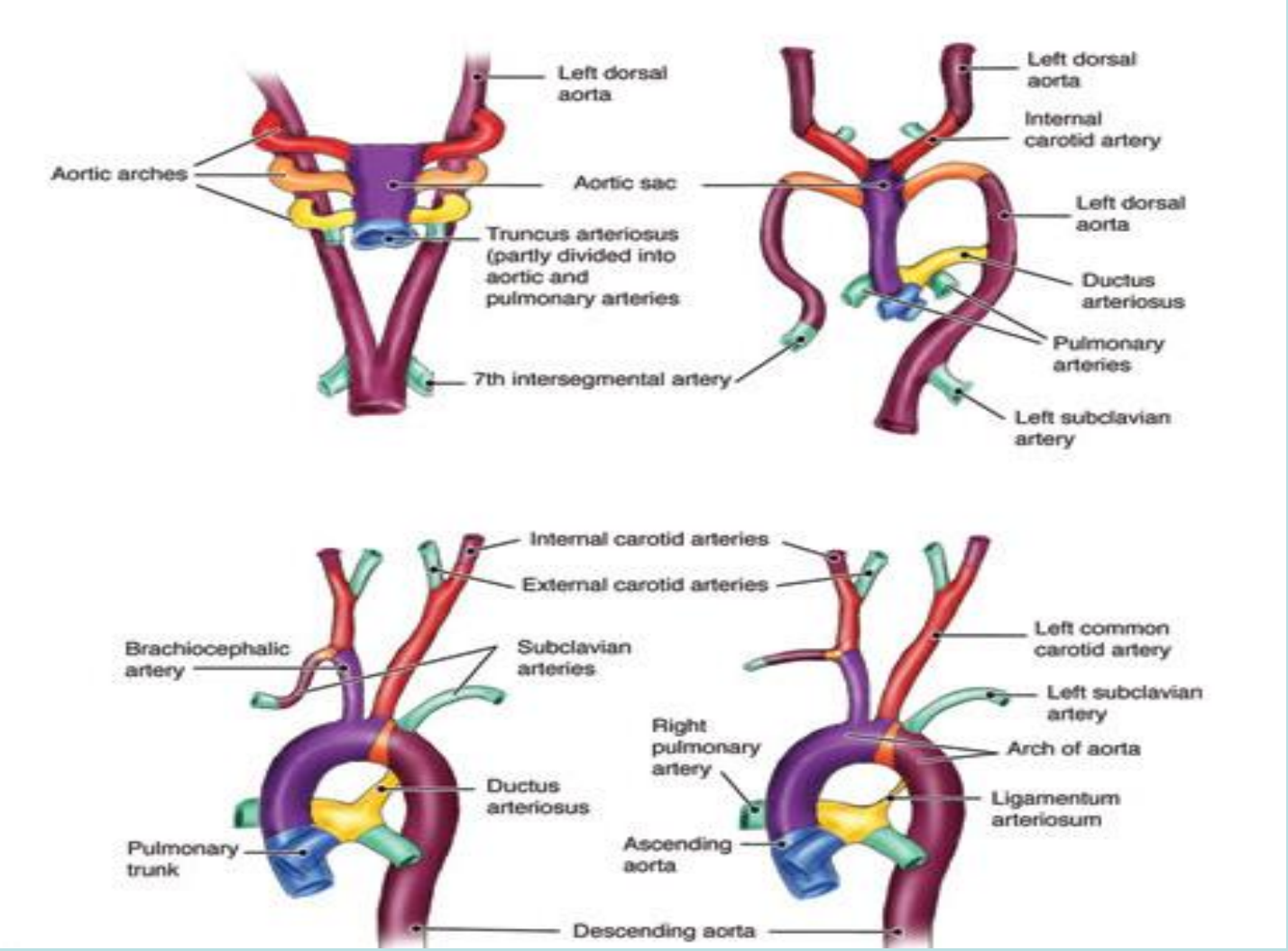

oft
ift
E8
oft
ev
ift
E8.5
oft
rv
pr
(avb)
lv
avc
a
san
avn
sh
E9.5-10.5
ra
la
oft
avc
san
pr
rv
lv
avn
avb
E10.5 - 12.5
scv
la
ra
lbb
lv
rv
avj
rbb
pvcs
Mature

Heart greater vessels development

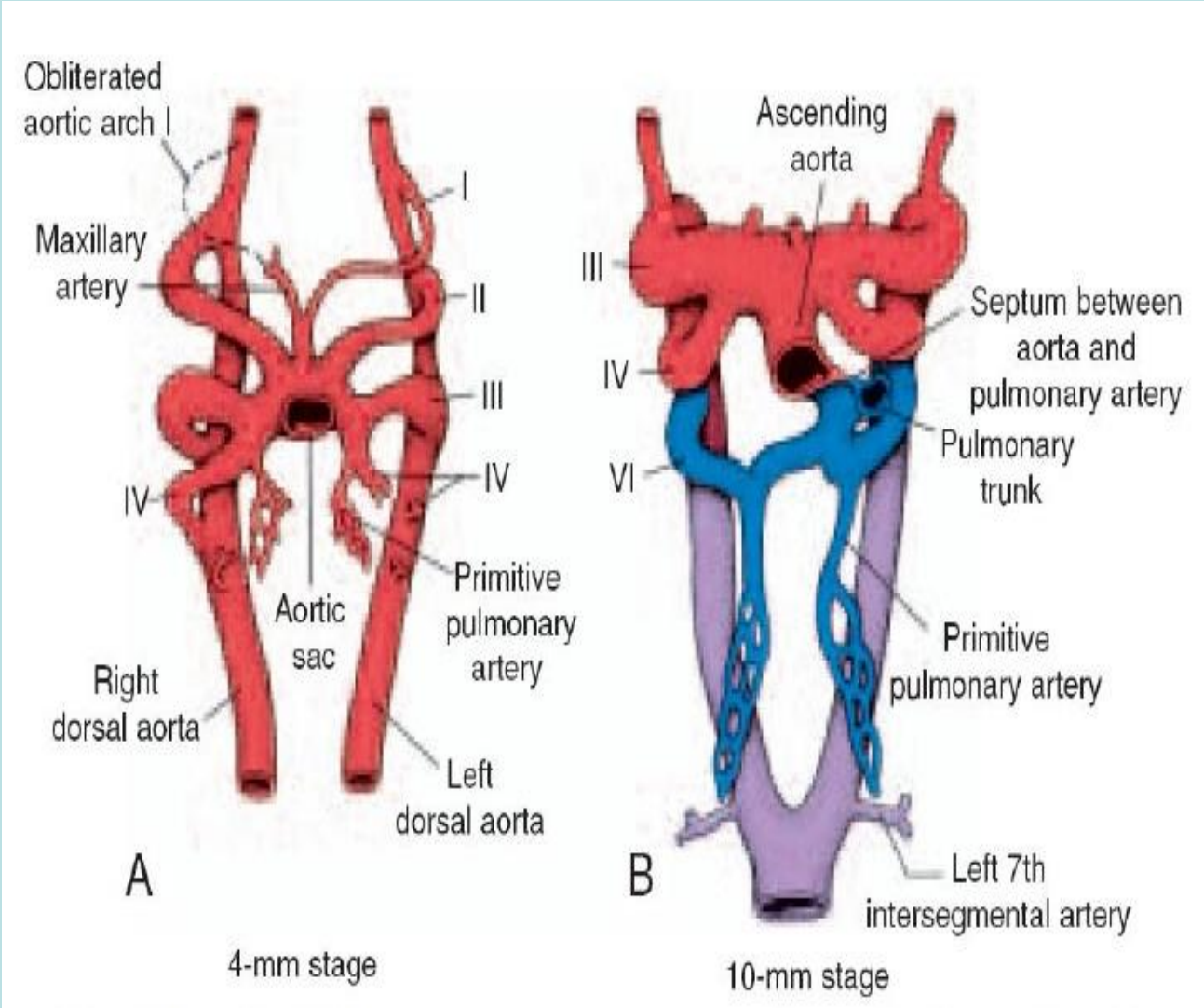


- **2 circulatory systems:**
- **A. vitelline/ omphalomesentericitelin,**
- **B. umbilical/uteroplacental.**

Arterial system – primitive aortic arches and primitive aorta development

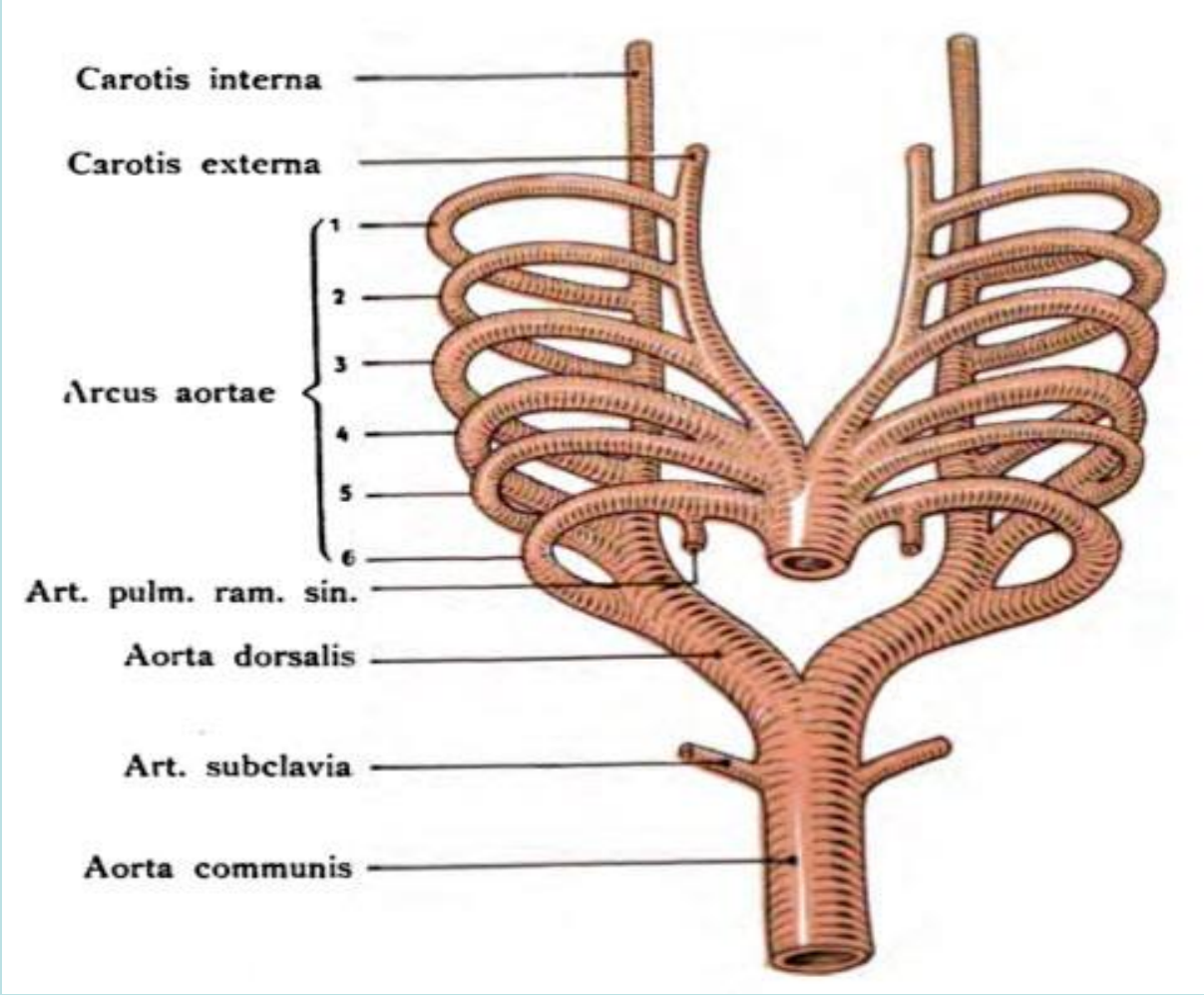


4,5 weeks


Obliterated aortic arch I
Maxillary artery
I
II
III
IV
IV
Aortic sac
Primitive pulmonary artery
Right dorsal aorta
Left dorsal aorta
A
4-mm stage
Ascending aorta
III
IV
VI
Septum between aorta and pulmonary artery
Pulmonary trunk
Primitive pulmonary artery
Left 7th intersegmental artery
B
10-mm stage

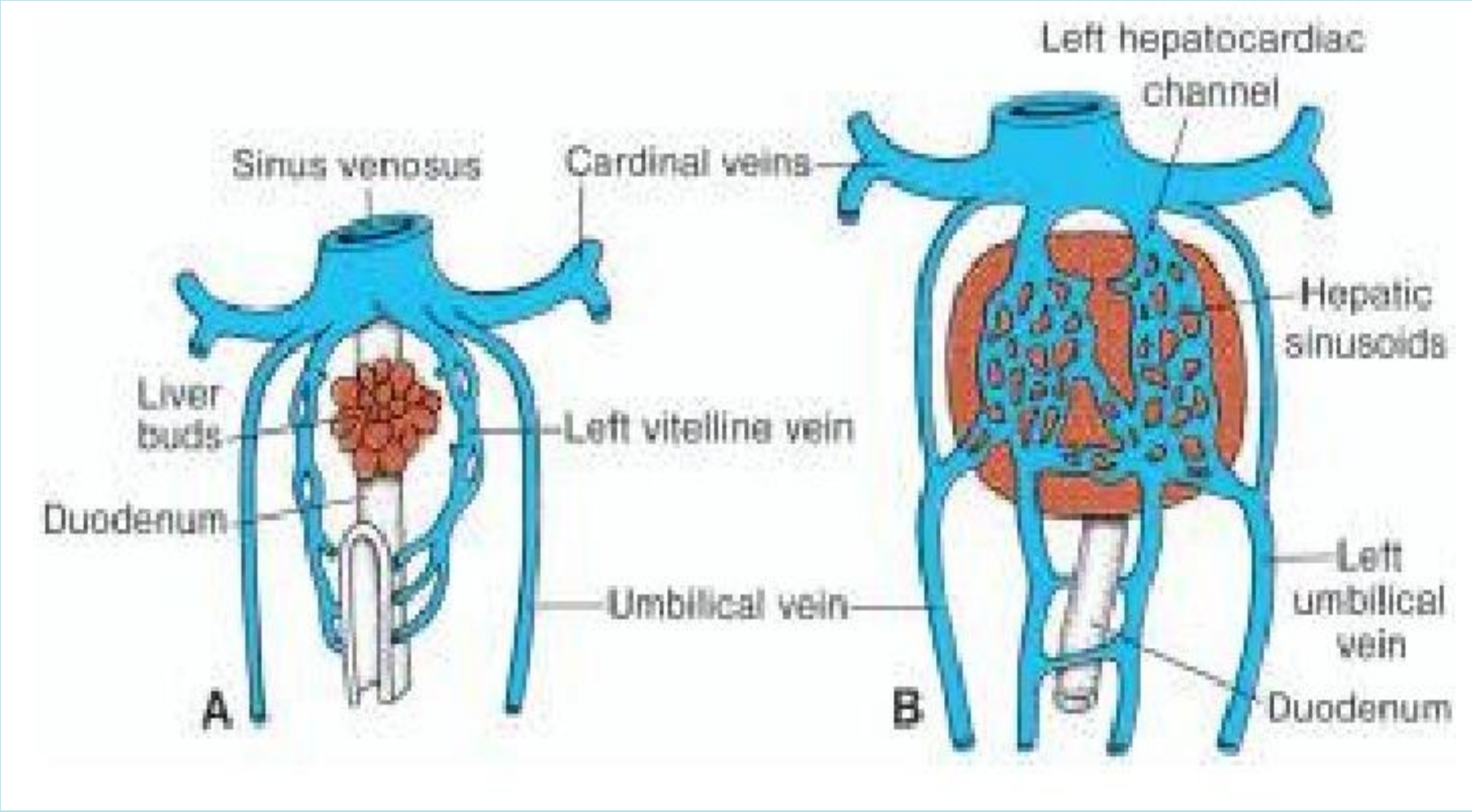
Aortic arches evolution

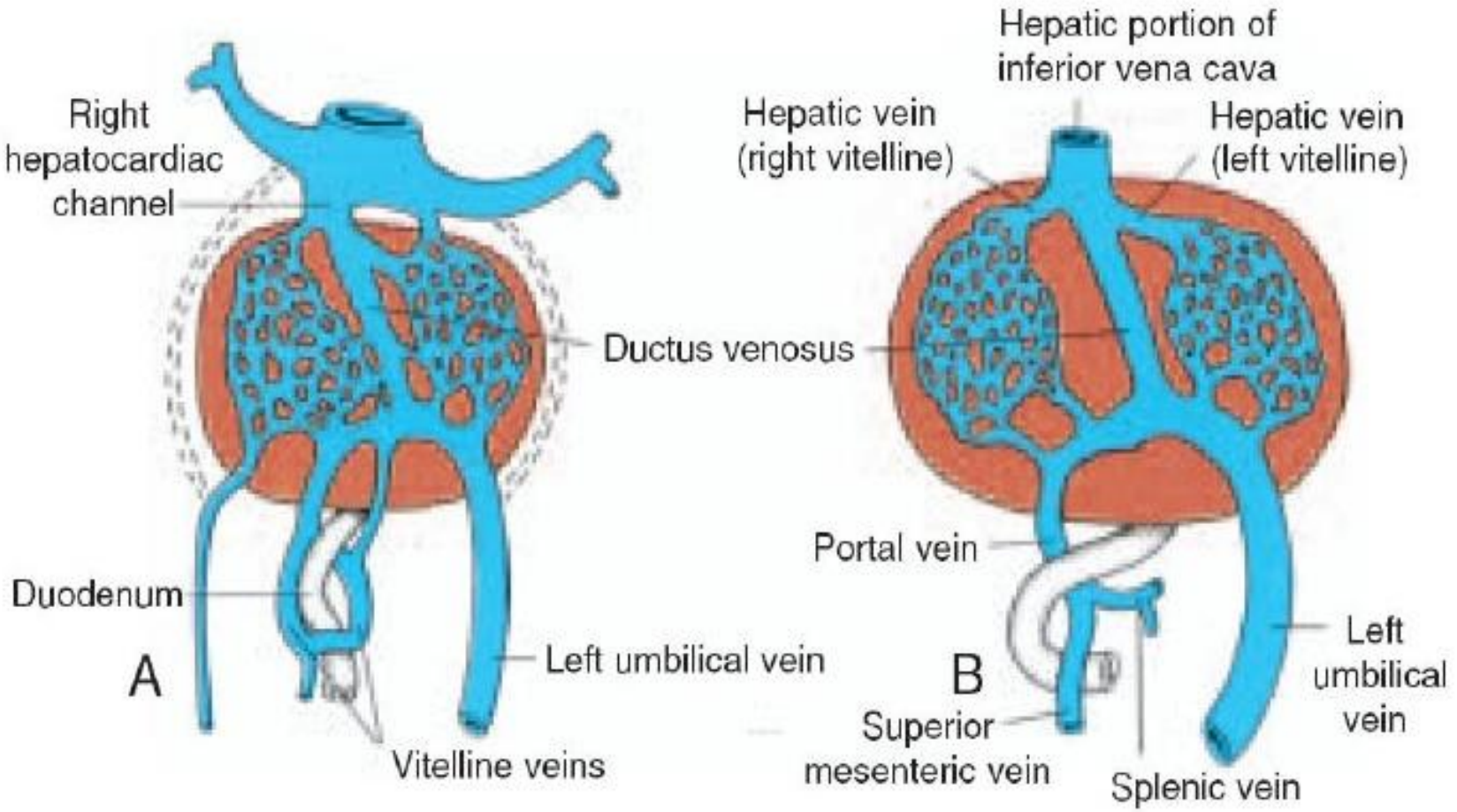
- 4th right aortic arch= right subclavian artery
- 4,5 right aortic arches= innominate artery
- 3,4 right common carotid artery
- 4th left aortic arch= left subclavian artery.



The venous system

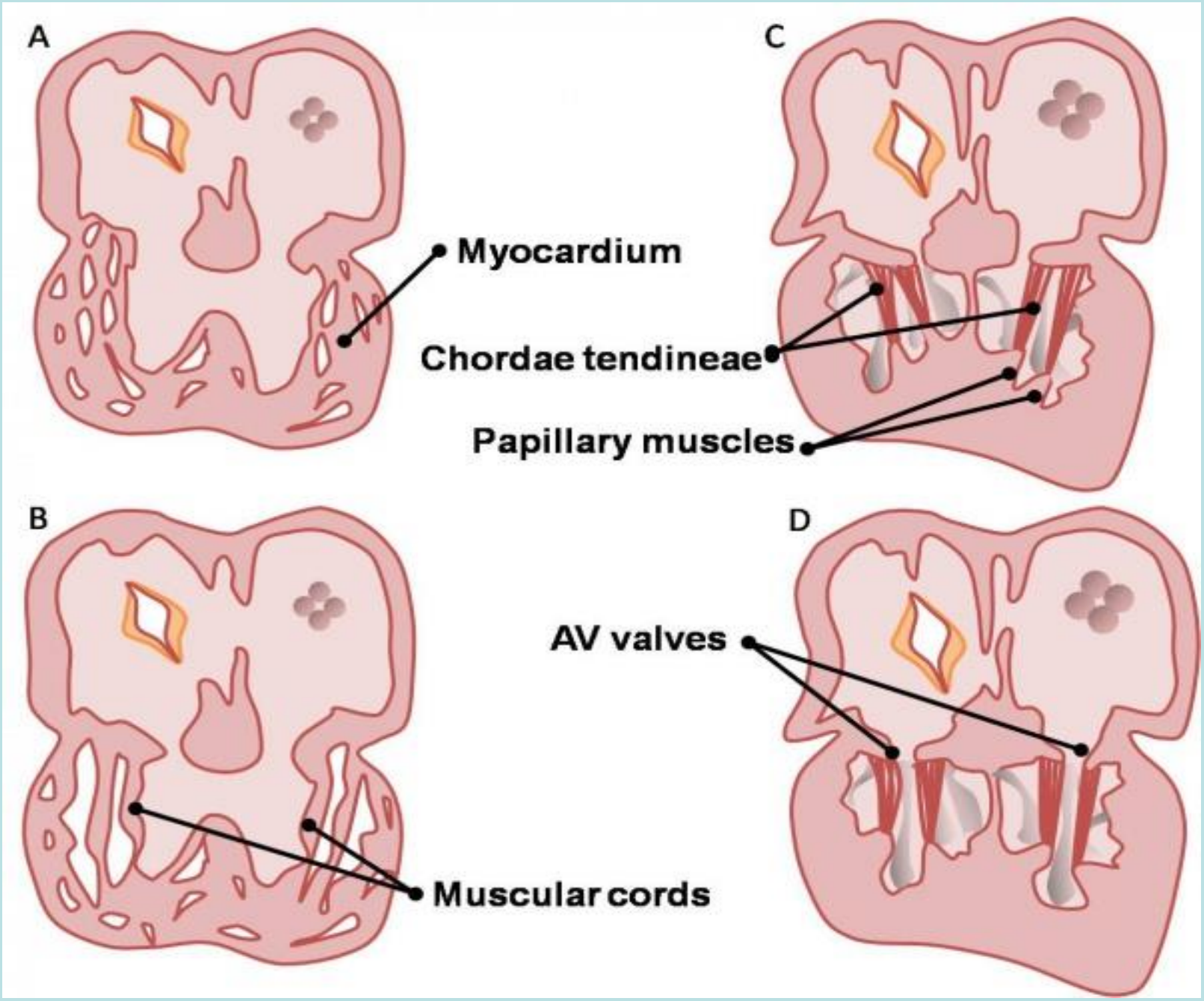
- **Vitelline veins**
- **Umbilical veins**
- **Cardinal veins**


Sinus venosus
Cardinal veins
Liver buds
Left vitelline vein
Duodenum
Umbilical vein
A
Left hepatocardiac channel
Hepatic sinusoids
Left umbilical vein
Duodenum
B

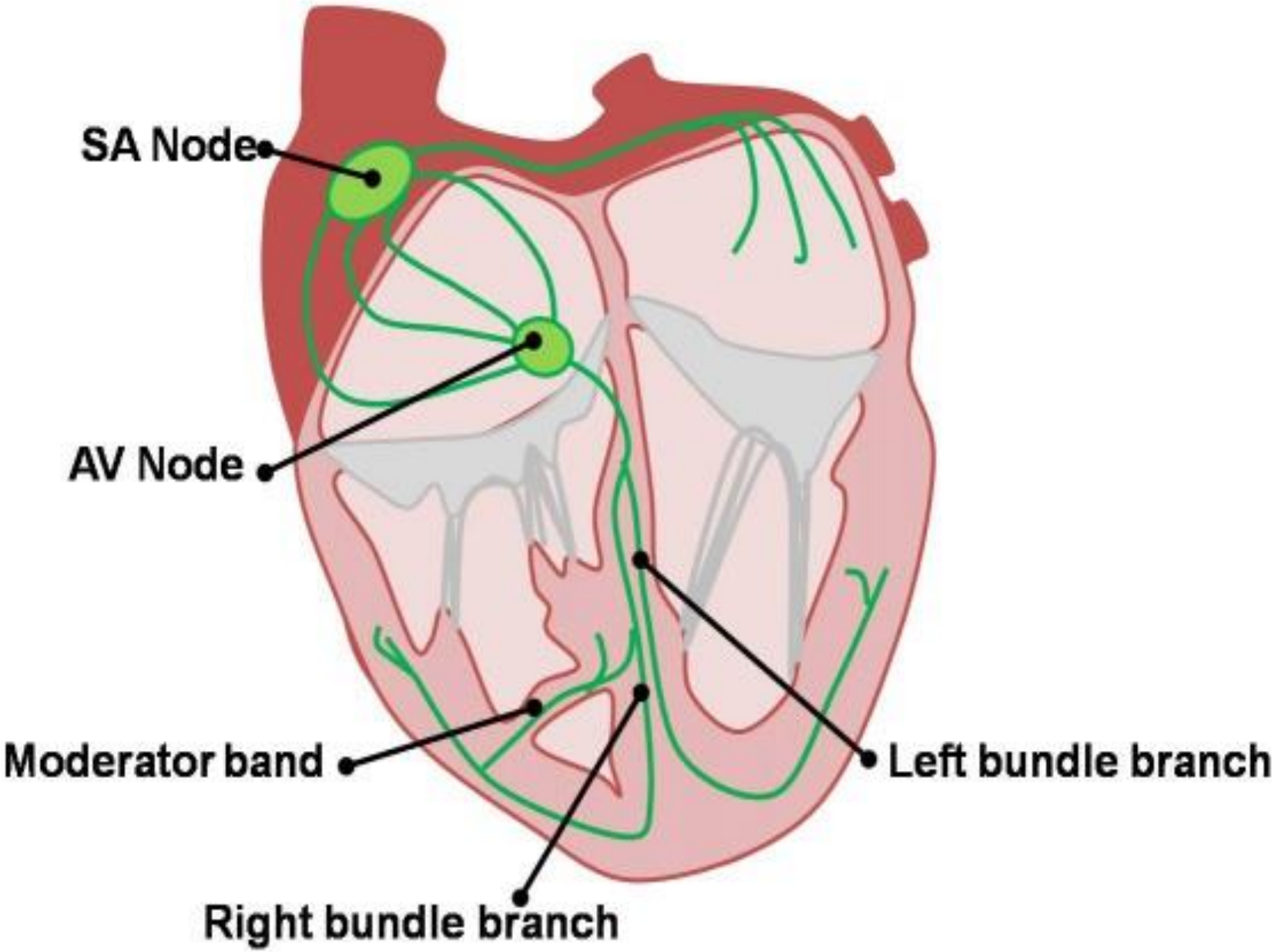

Right
hepatocardiac
channel
Ductus venosus
Duodenum
A
Left umbilical vein
Vitelline veins
Hepatic portion of
inferior vena cava
Hepatic vein
(right vitelline)
Hepatic vein
(left vitelline)
Portal vein
B
Left
umbilical
vein
Superior
mesenteric vein
Splenic vein

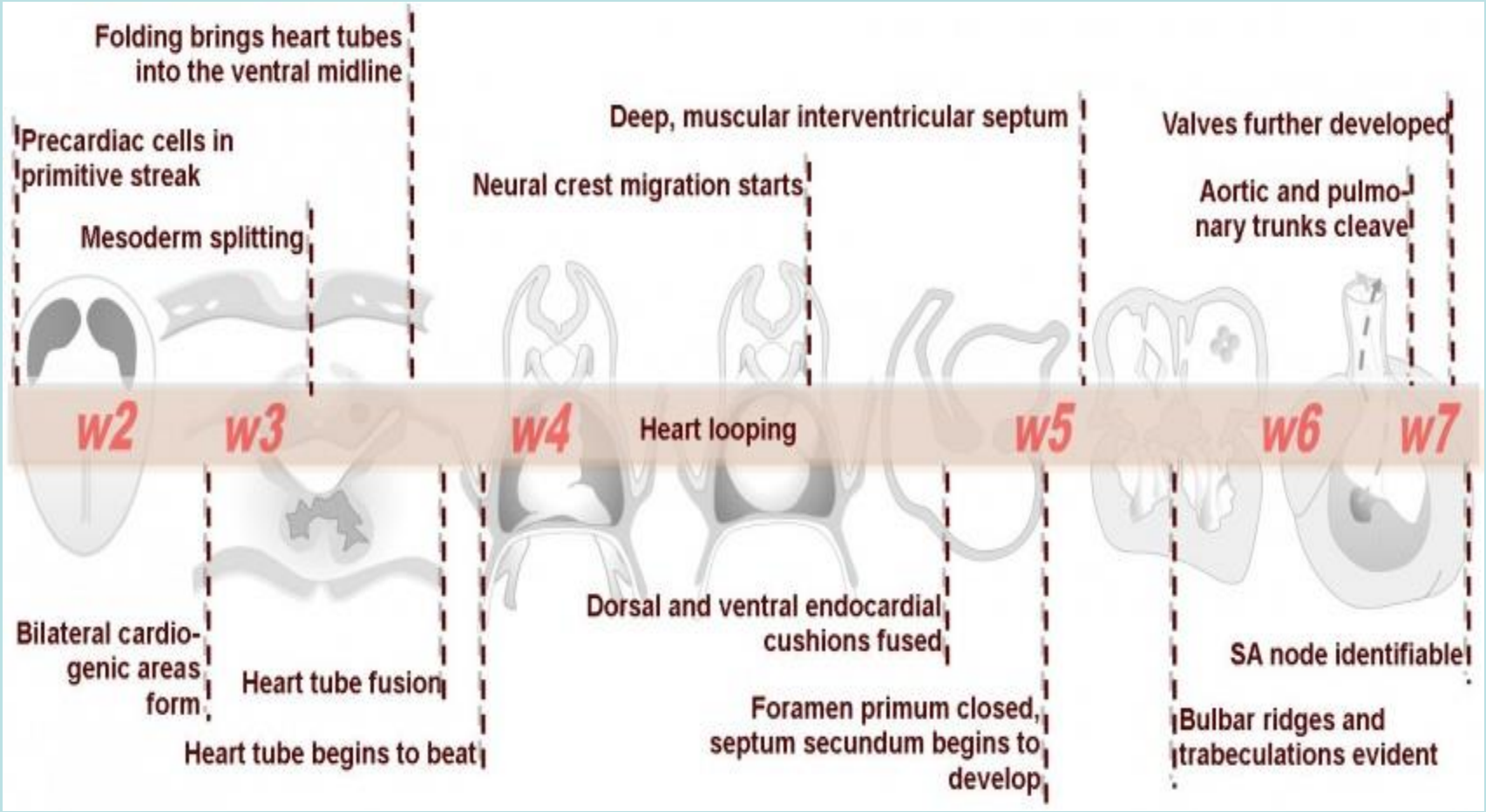
- The AV valves begin to form between the fifth and eighth weeks of development.
- The valve leaflets are attached to the ventricular walls by thin fibrous chords: the chordae tendineae, which insert into small muscles attached to the ventricle wall: the papillary muscles.
- These structures are sculpted from the ventricular wall.
- The left AV valve has anterior and posterior leaflets and is termed the bicuspid or mitral valve.
- The right AV valve has a third, small septal cusp and thus is called the tricuspid valve.

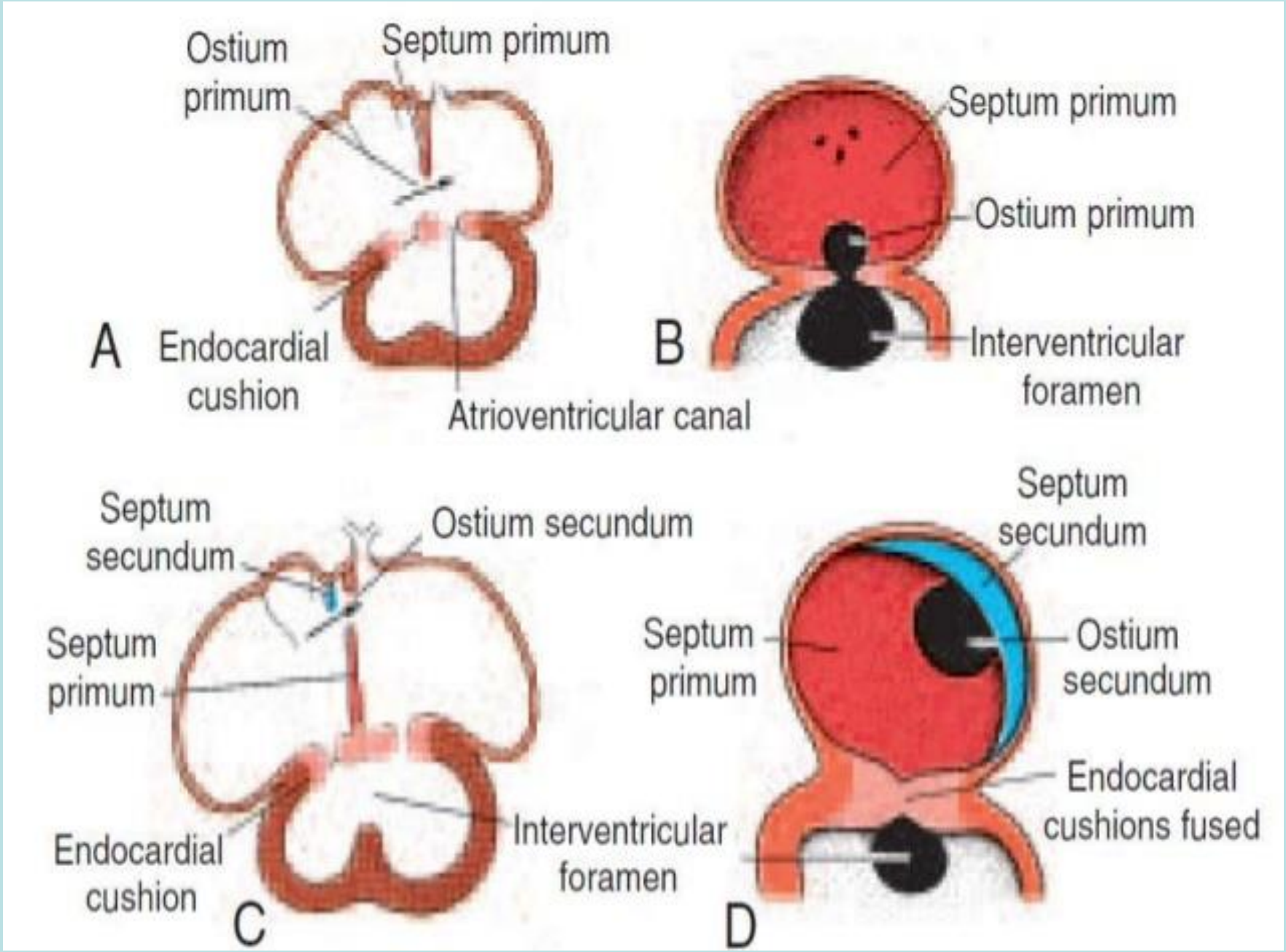
- **Development of the conduction system**
- Cardiomyocytes in the caudal heart tube are the first to become electrically active and become the “pacemaker”.
- The SA node, which develops during the fifth week, initially develops in the sinus venosus and then is incorporated into the RA.
- The AV node arises slightly superior to the endocardial cushions.
- Fibres forming the bundle of His develop from fast-conducting ventricular myocardium while the SA and AV nodes are formed from the slow-conducting myocardium of the inflow tract and AV canal.
- Connective tissue grows in from the epicardium, forming the cardiac skeleton that separates conduction in the atria and ventricles.

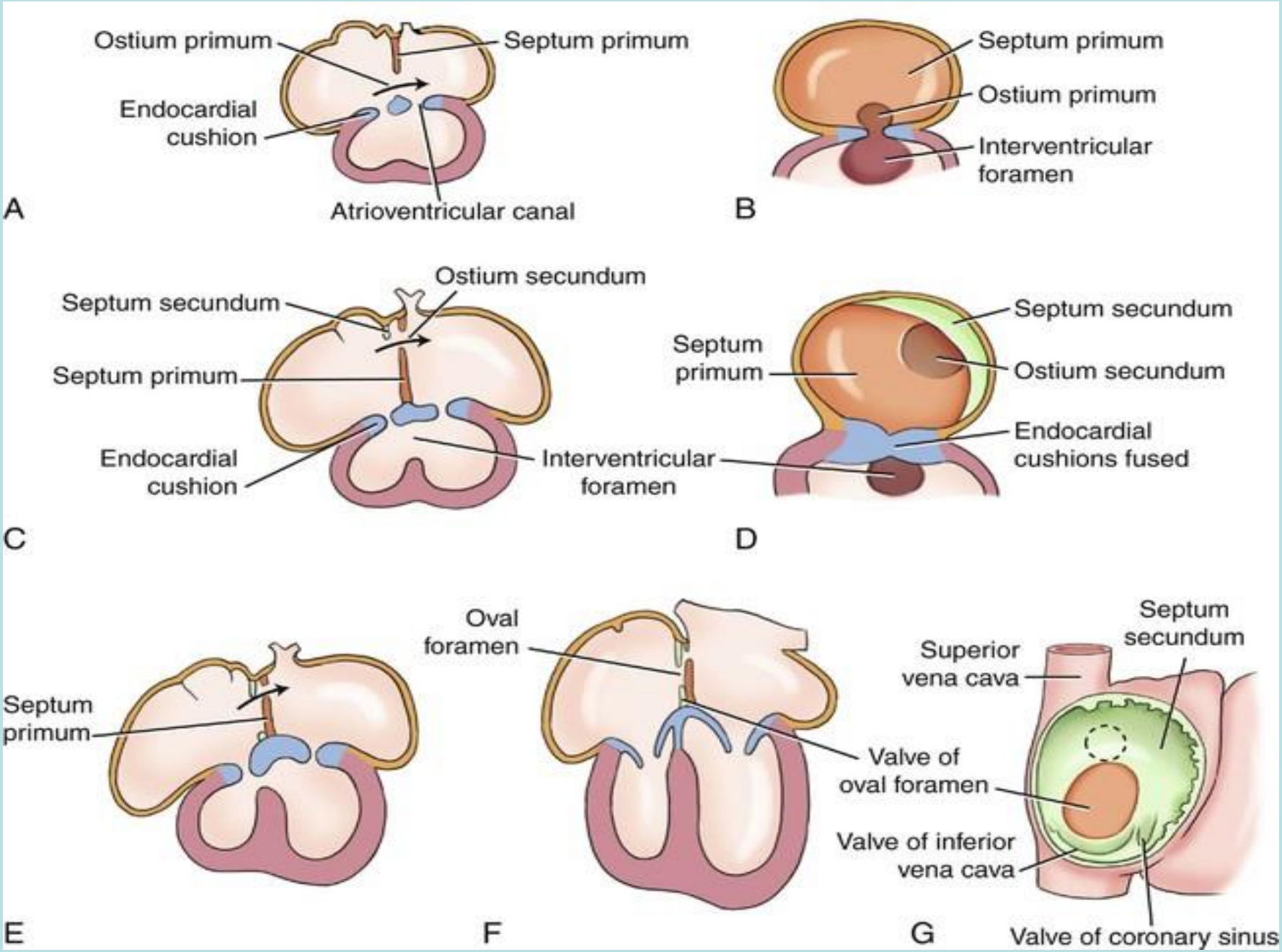

A
Myocardium
C
Chordae tendineae
Papillary muscles
B
Muscular cords
D
AV valves

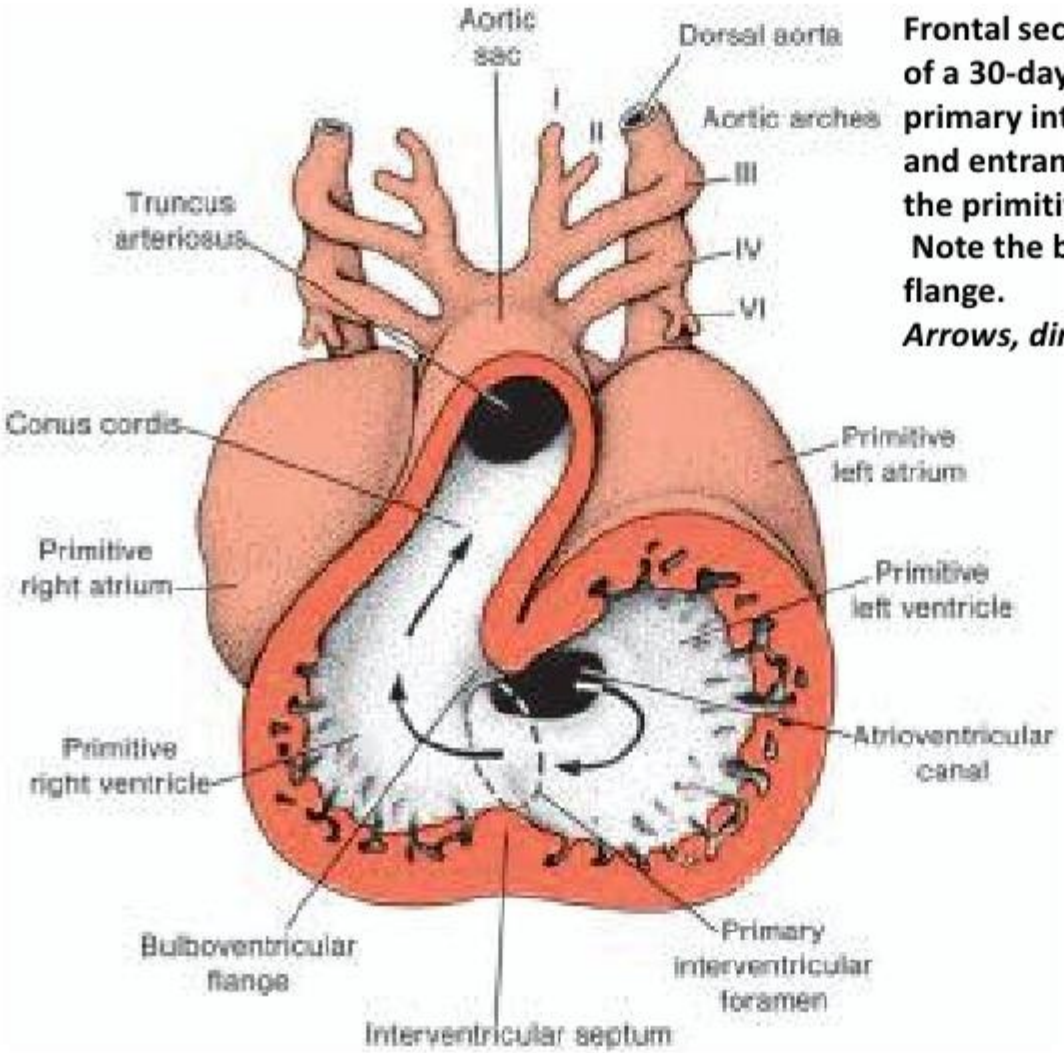
Cardiac Conduction System



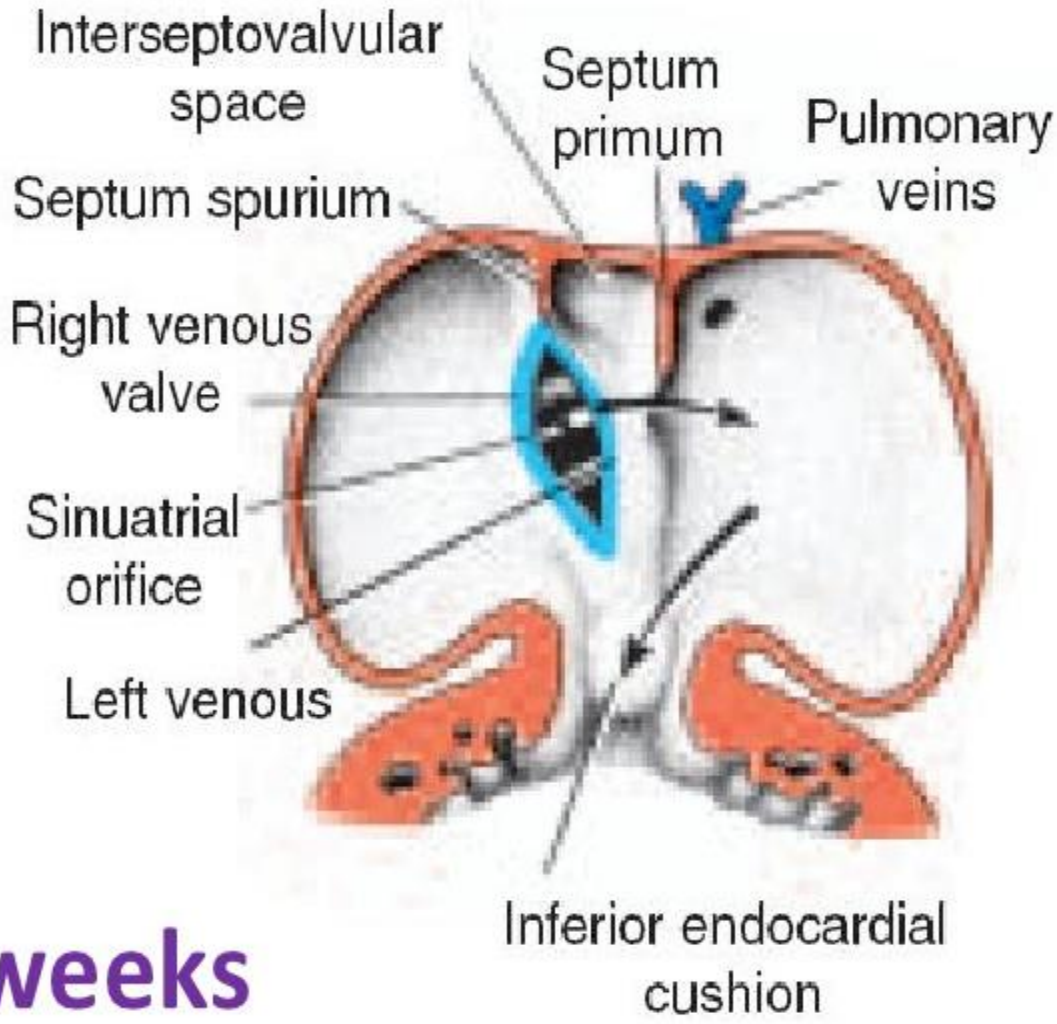

Folding brings heart tubes into the ventral midline
Precardiac cells in primitive streak
Mesoderm splitting
Deep, muscular interventricular septum
Neural crest migration starts
Valves further developed
Aortic and pulmonary trunks cleave
w2
w3
w4
Heart looping
w5
w6
w7
Bilateral cardiogenic areas form
Heart tube fusion
Heart tube begins to beat
Dorsal and ventral endocardial cushions fused
Foramen primum closed, septum secundum begins to develop
SA node identifiable
Bulbar ridges and trabeculations evident


Ostium primum
Septum primum
A
Endocardial cushion
Atrioventricular canal
B
Septum primum
Ostium primum
Interventricular foramen
Septum secundum
Ostium secundum
Septum primum
Endocardial cushion
Interventricular foramen
C
Septum secundum
Septum primum
Ostium secundum
Endocardial cushions fused
D


Ostium primum
Septum primum
Endocardial cushion
Atrioventricular canal
A
Septum primum
Ostium primum
Interventricular foramen
B
Ostium secundum
Septum secundum
Septum primum
Endocardial cushion
Interventricular foramen
C
Septum secundum
Septum primum
Ostium secundum
Endocardial cushions fused
D
Septum primum
E
Oval foramen
Valve of oval foramen
Valve of inferior vena cava
F
Septum secundum
Superior vena cava
Valve of coronary sinus
G



Frontal section through the heart of a 30-day embryo showing the primary interventricular foramen and entrance of the atrium into the primitive left ventricle.
Note the bulboventricular flange.
Arrows, direction of blood flow.


Interseptovalvular space
Septum primum
Pulmonary veins
Septum spurium
Right venous valve
Sinuatrial orifice
Left venous
Inferior endocardial cushion

5 weeks


Thank you!