Histology of the Cardiovascular System

(The Heart and Blood Vessels)

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Histology of the Heart

- The wall of the heart is formed of 3 layers, from the inside-out:

1. Endocardium
2. Myocardium
3. Epicardium (visceral pericardium)

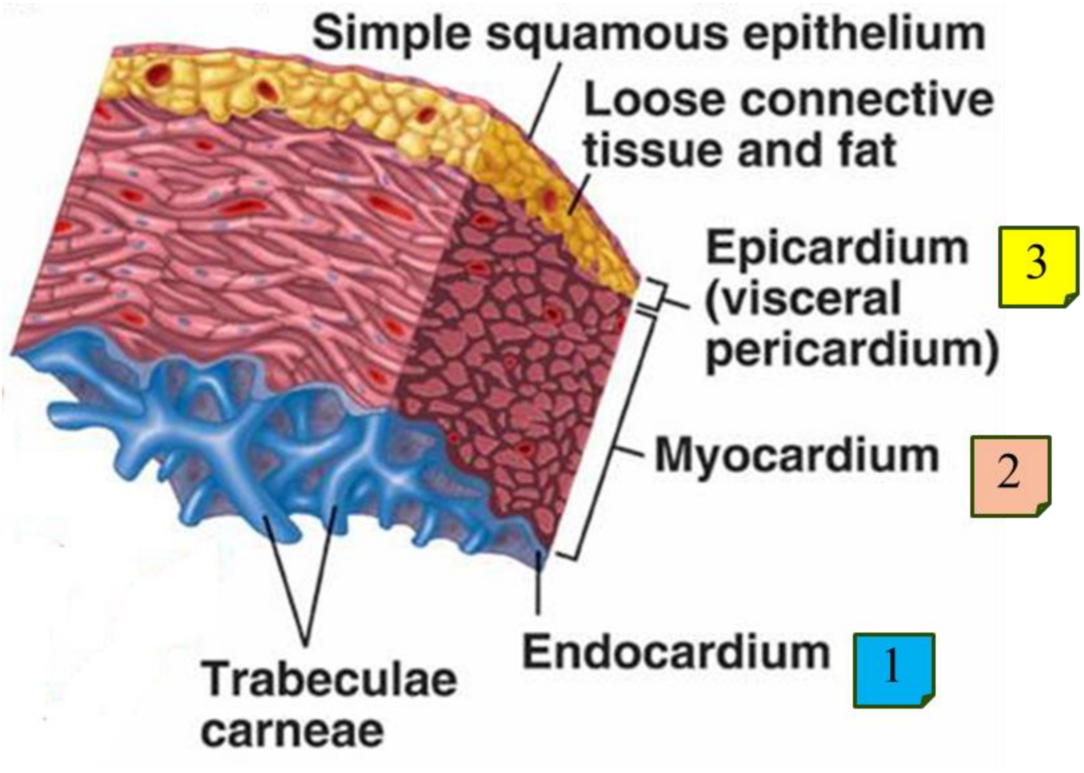


Fig.1: The layers of the heart wall.

The Endocardium:

- Formed of:
  - *Endothelium*: simple squamous epithelium in contact with the blood.
  - *Subendothelium*: connective tissue with fibers and fibroblasts.
  - *Subendocardium*: loose areolar connective tissue continuous with the connective tissue of the myocardium. Contains Purkinje fibers and blood vessels.

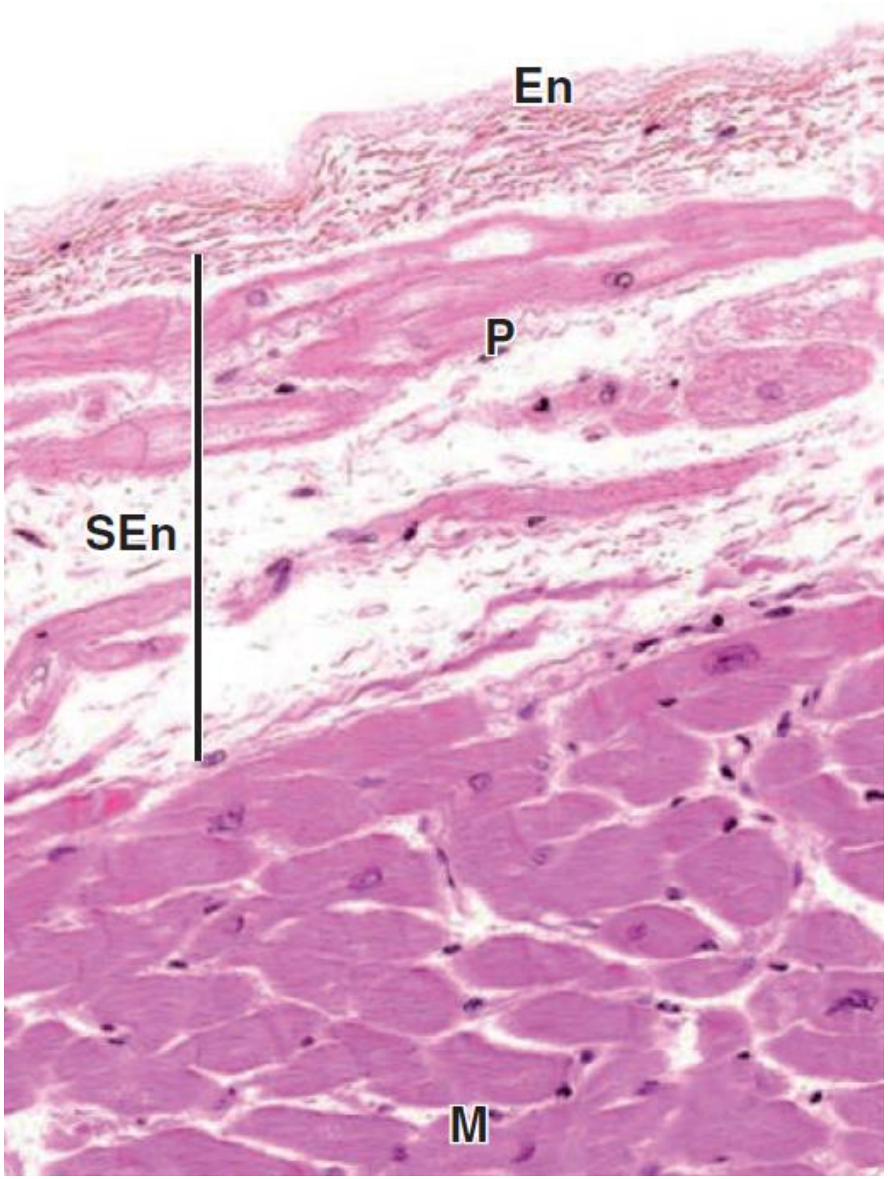


Fig.2: The endocardium. En, endothelium; SEn, subendocardium; P, Purkinje fibers; M, myocardium.

The Myocardium:

- The thickest layer of the heart wall. It’s thicker in the ventricles, and thickest in the left ventricle.
- Composed of cardiac muscle fibers that spiral around the heart chambers and that are attached to the fibrous skeleton of the heart.
- Between the cardiac muscle fibers, we have loose areolar connective tissue (the endomysium).

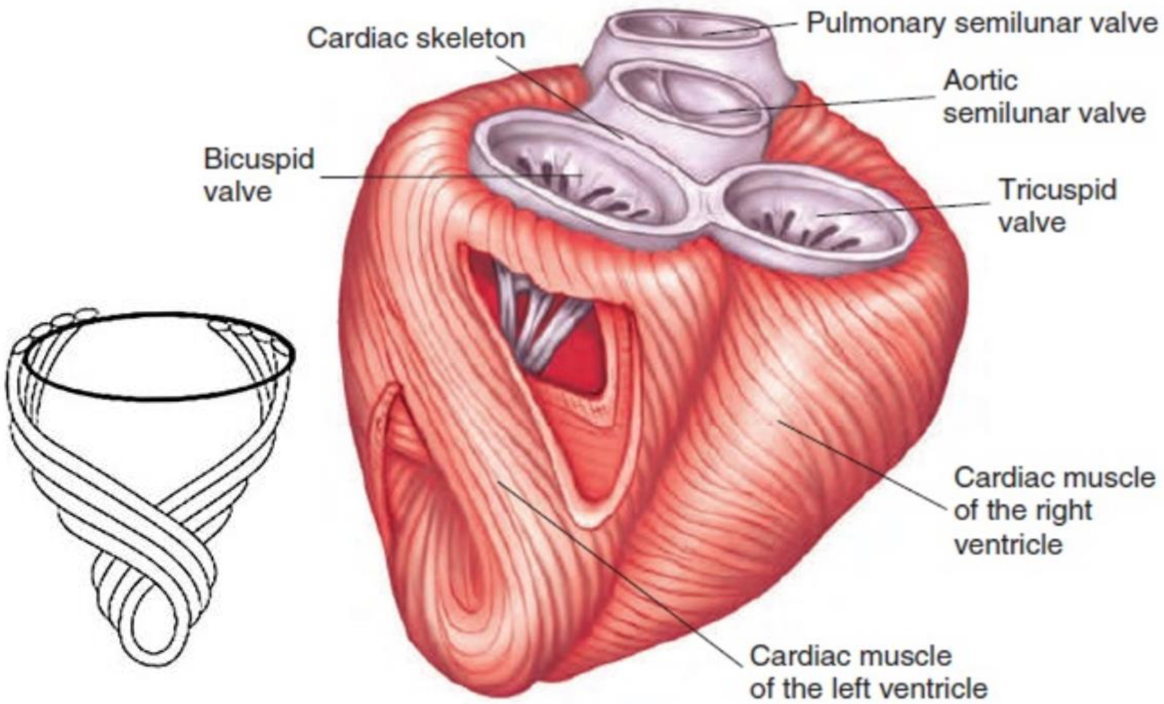


Fig.3: The spiral arrangement of the cardiac muscle fibers and their attachment to the fibrous skeleton.

Cardiac muscle fibers

1) Cells are branched.
2) Centrally located nucleus.
3) Cross-striation.
4) Branches are connected to each at the intercalated discs, where we have desmosomes and gap junctions.
5) Numerous mitochondria.
6) Lipofuscin and glycogen granules.

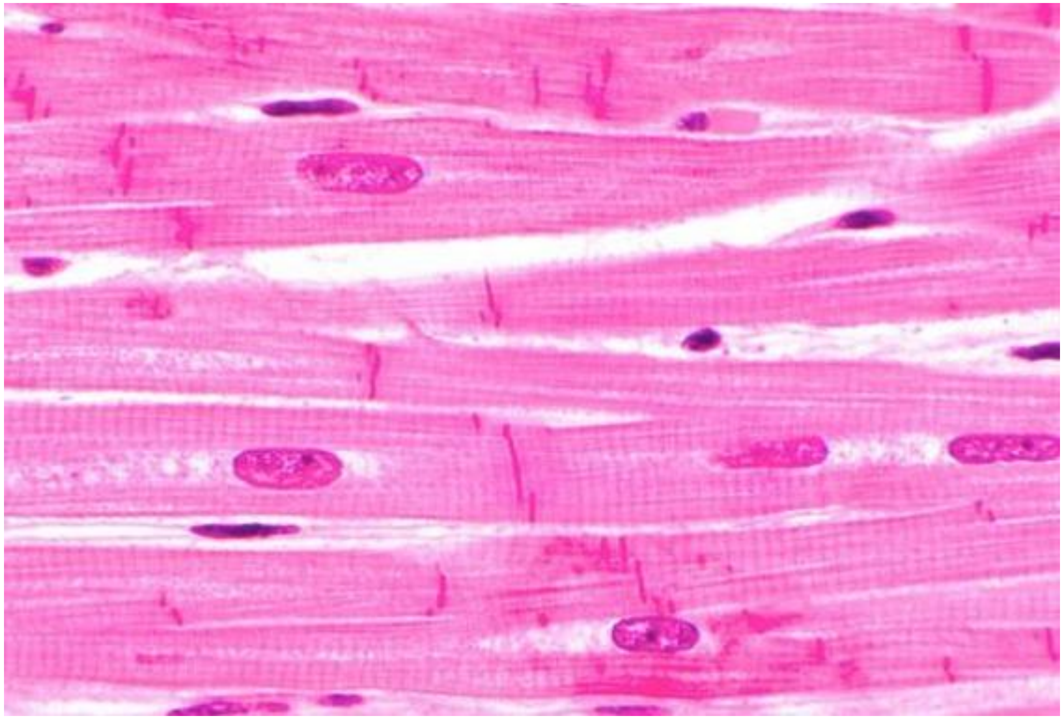


Fig.4: Cardiac muscle cells.

The Epicardium:

- Formed of an outer layer of simple squamous mesothelium, with an underlying connective tissue containing fat cells.
- The mesothelial cells produce a lubricant fluid (the pericardial fluid) into the pericardial cavity to prevent friction. The major vessels and nerves of the heart lie within the fatty connective tissue.
- The epicardium correspond to the visceral pericardium and is continuous with the parietal pericardium.

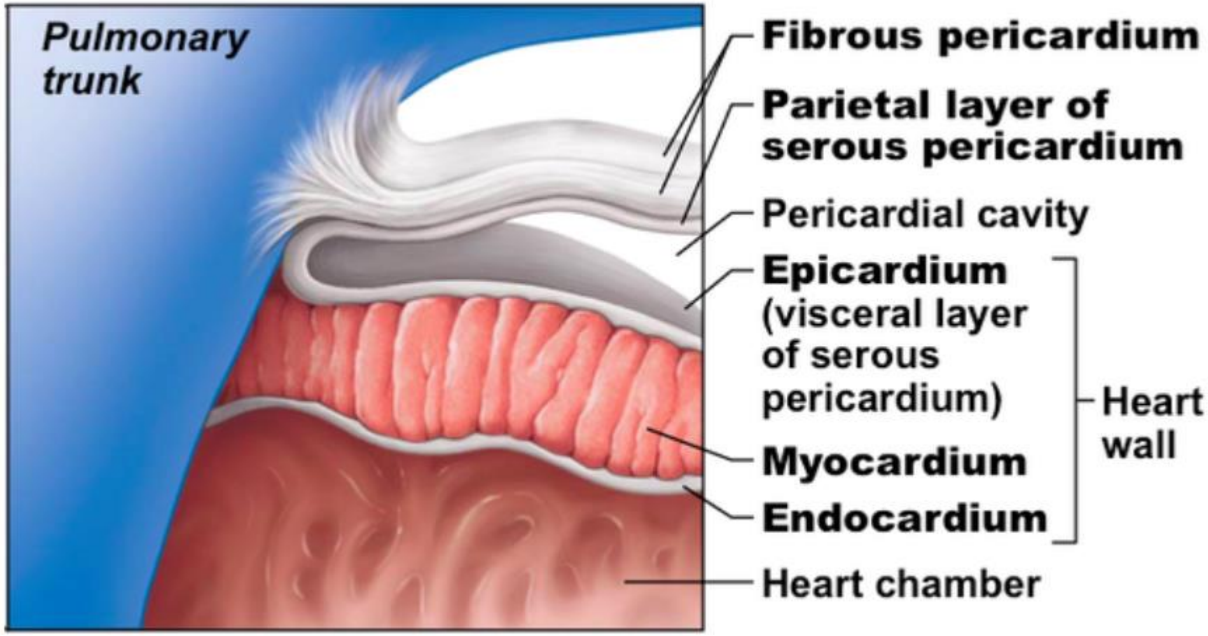


Fig.5: The various layers of the pericardium.

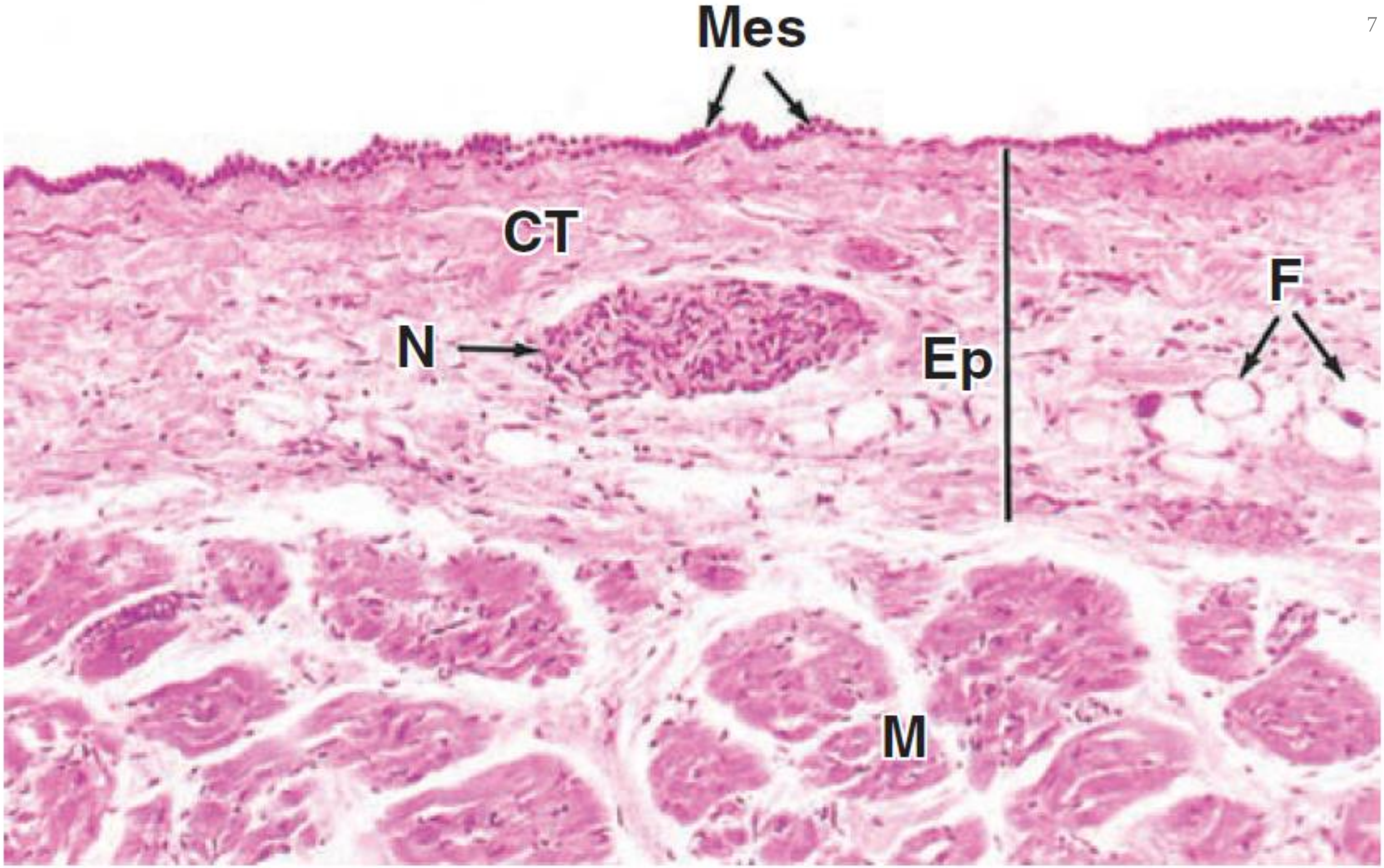


Fig.6: The epicardium. Ep, epicardium; Mes, mesothelium; CT, connective tissue; F, fat cells; N, nerve; M, myocardium.

Other structures in the heart

a) Purkinje fibers:

- Part of the conducting system of the heart. Found in the ventricles.
- Located in the subendocardial tissue.
- These are large, pale-staining cardiac muscle fibers with less myofibrils and more glycogen granules.

b) Fibrous skeleton of the heart:

- Dense collagenous irregular connective tissue in the endocardium that serves as:
  - Base for the heart valves
  - Site for attachment of cardiac muscle fibers
  - Electrical insulator between atria and ventricle.

c) ***Heart valves:***

- Valve leaflets are formed of a fibrous core of connective tissue continuous with that of the fibrous skeleton, surrounded on both sides by endothelium.
- They are avascular. They obtain nutrients from the blood in the heart or blood vessels in the base of the valve.

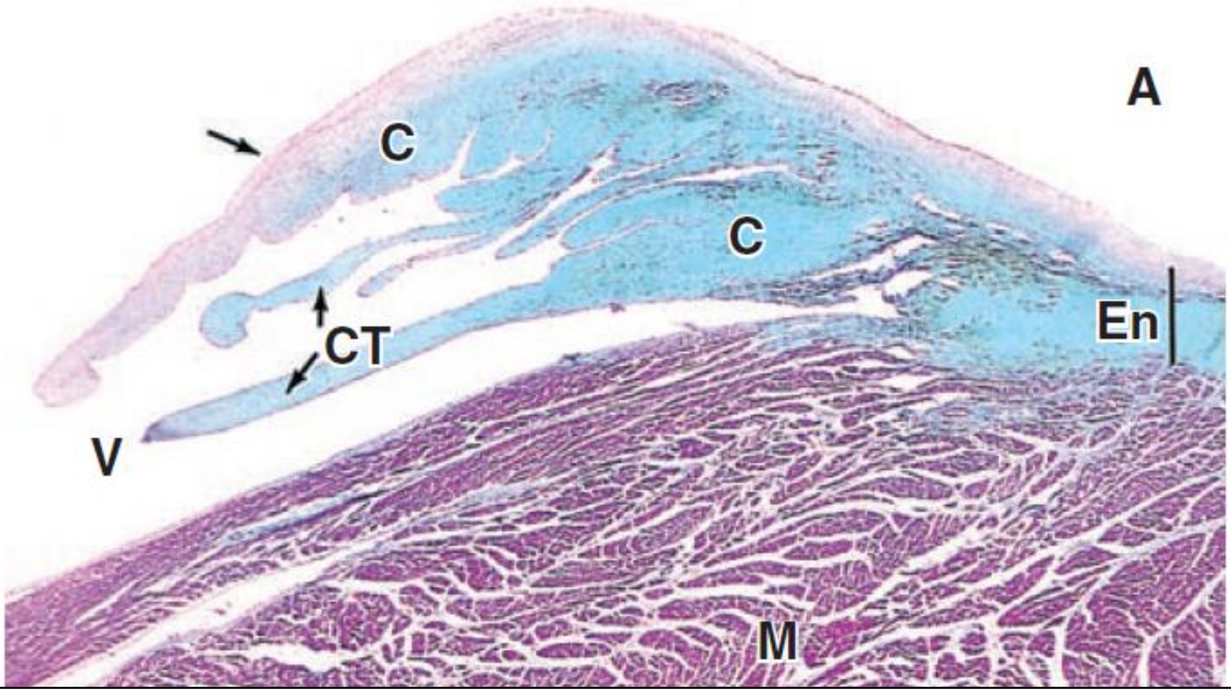


Fig.7: Atrioventricular valve (arrow) between atria (A) and ventricle (V). Note the core of fibrous connective tissue (C) which extends into the chordae tendinea (CT). En, endocardium; M, myocardium.

Histology of the Vessels

General layout of vessel wall

- All blood vessels (except capillaries) have the same general layout of their walls. From inside out:
  1. Tunica intima (interna)
  2. Tunica media
  3. Tunica adventitia (externa)

- The difference between the vessels is in the relative composition and thickness of these layers.

Tunica intima (interna)

- The *internal* layer of the vessel wall in *intimate* contact with blood.
- Formed of:
  - Endothelium (simple squamous epithelium)
  - Subendothelial loose connective tissue with some smooth muscle cells
  - Internal elastic lamina – a sheet of elastic fibers

Tunica media

- The middle layer of the wall.
- Formed of:
  - Smooth muscle cells with connective tissue
  - Elastic fibers
  - External elastic lamina

Tunica adventitia (externa)

- The external layer. Usually bound to the surrounding connective tissue
- Formed of:
  - Dense irregular connective tissue adventitia
  - Vasa vasorum (vessels of the vessel). These supply nutrients and oxygen to the adventitia and outer media. The inner media and intima are supplied by direct diffusion from the blood inside the vessel.
  - Nervi vasorum (nerves of the vessel). Control the diameter of the vessel by vasodilation or constriction.

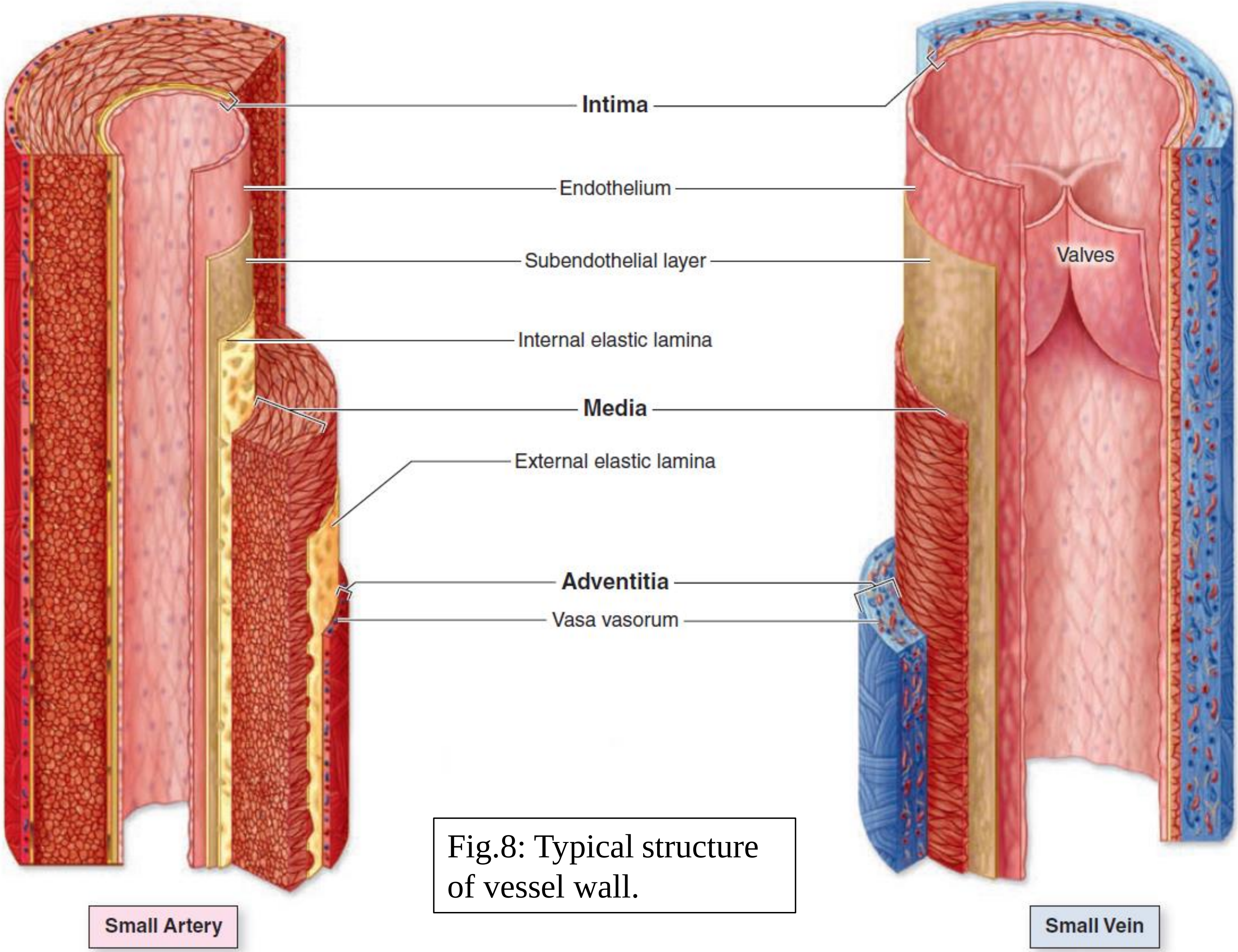


Fig.8: Typical structure of vessel wall.

Histology of the Vessels - Arteries

Elastic arteries

- These include the aorta and the pulmonary trunk and their main branches.
- They are '*conducting arteries*' that carry blood to the smaller arteries.
  - ***Tunica intima***: typical structure with smooth muscle cells. The internal elastic lamina may not be clearly recognized.
  - ***Tunica media***: the thickest layer. Contains numerous fenestrated elastic laminae alternating with layers of smooth muscle fibers. The fenestrations allow nutrient to pass through.
  - ***Tunica adventitia***: typical structure with prominent vasa vasorum due to thick walls.

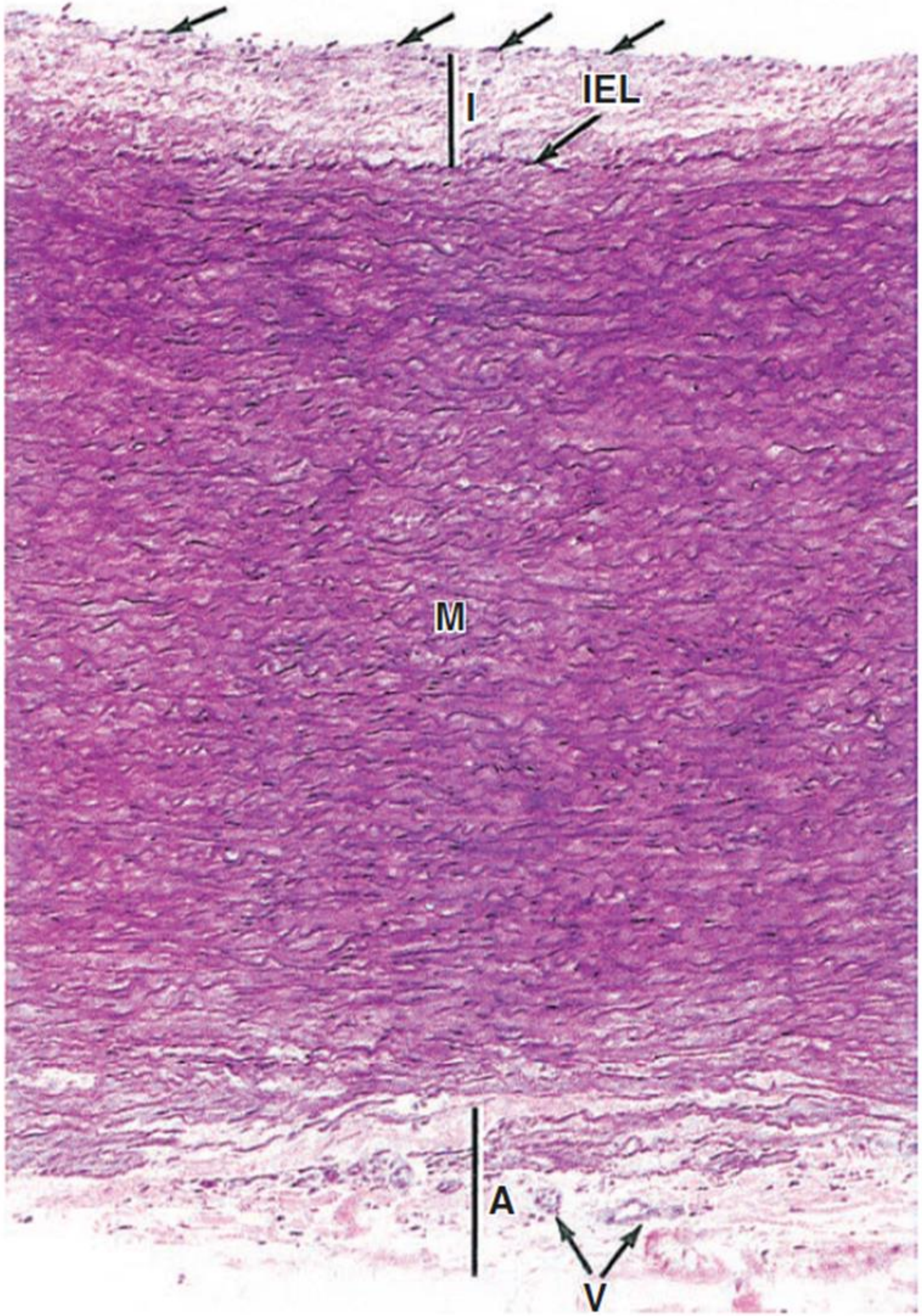


Fig.9: Elastic artery (aorta). Note the three layers of the wall: intima (I), media (M), and adventitia (A). Arrows at the top indicate the endothelium. The internal elastic lamina (IEL) can be seen in this image. V, vasa vasorum. Special stain was used to show the elastic fibers.

Muscular arteries

- These are '*distributing arteries*' that distribute blood to the organs.
  - ***Tunica intima***: thin with typical structure. The internal elastic lamina is prominent.
  - ***Tunica media***: the thickest layer. Contains numerous layers of smooth muscle fibers, with some elastic laminae. The external elastic lamina is prominent.
  - ***Tunica adventitia***: typical structure.

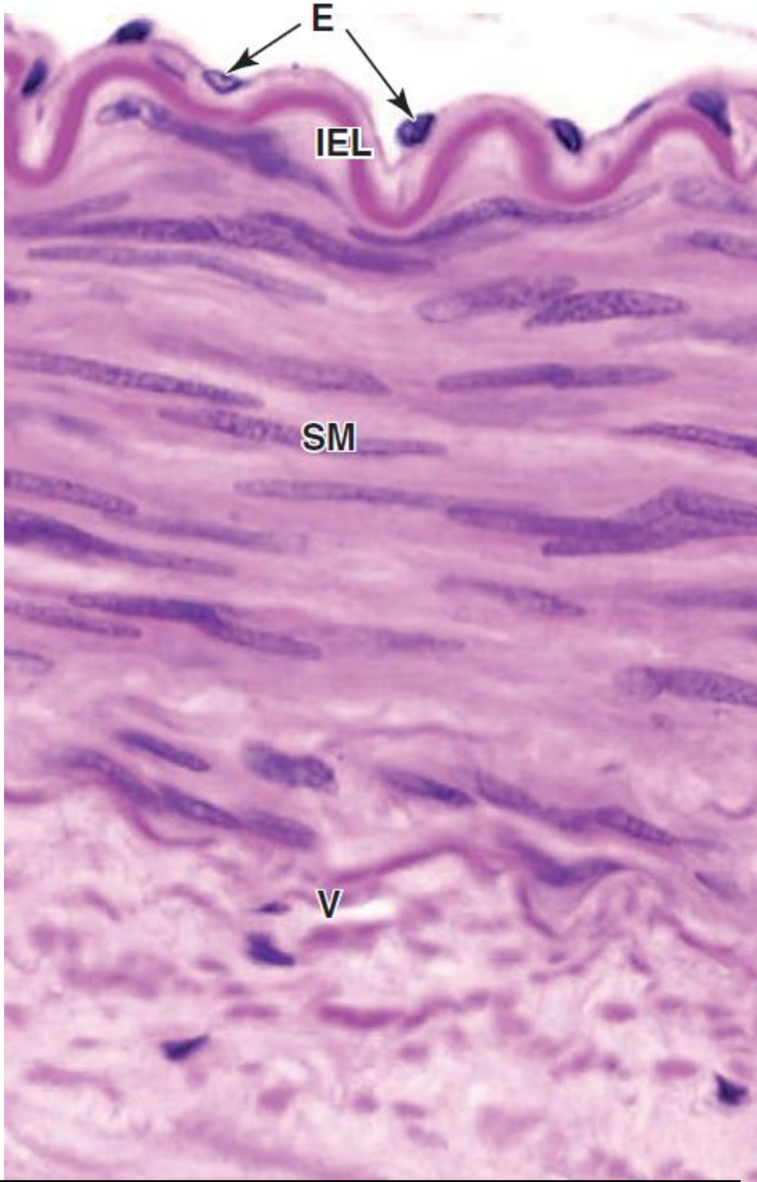
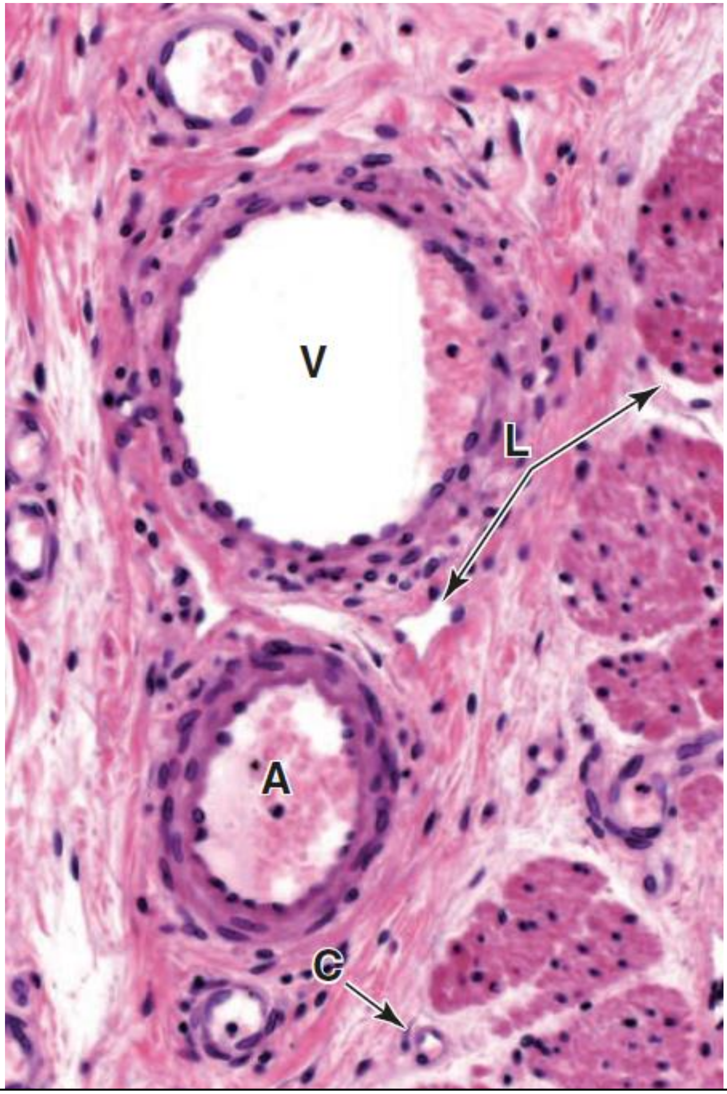


Fig.10: Muscular artery. Note the thin intima with the lining endothelium (E) and the prominent internal elastic lamina (IEL). The media is mostly smooth muscle fibers (SM). The adventitia is external with vasa vasorum (V).

Arterioles

- Arterial branches that are <0.1mm in diameter. It's the beginning of the microvasculature of the organ.
  - *Tunica intima*: very thin with no elastic lamina.
  - *Tunica media*: formed of only 1-3 layers of smooth muscle fibers, with no elastic laminae.
  - *Tunica adventitia*: thin.



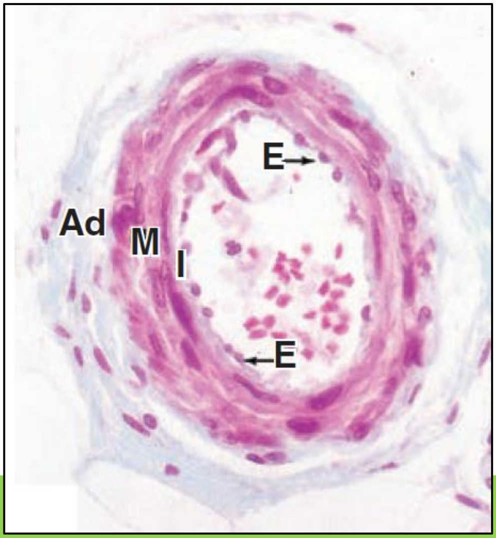


Fig.11: Microvasculature of an organ. A, arteriole. These give rise to capillaries (C), which then drain into a venule (V). Also shown are lymphatic vessels (L). To the left, wall of an arteriole: intima (I), media (M), and adventitia (Ad). E, endothelium.

- Capillaries arise from arterioles. The smooth muscles of the arterioles act as sphincters to control the flow of blood into the capillaries.

- Arterioles, also, give rise to '***thoroughfare channels***' that connect the arterioles to the ***postcapillary venules***. Capillaries arise from the initial segment of these channels, which are called ***metarterioles***. The flow of blood into the capillaries from the metarterioles is controlled by smooth muscle '***precapillary sphincters***'.

- Capillaries drain into the venous side of the thoroughfare channel which lacks smooth muscles.

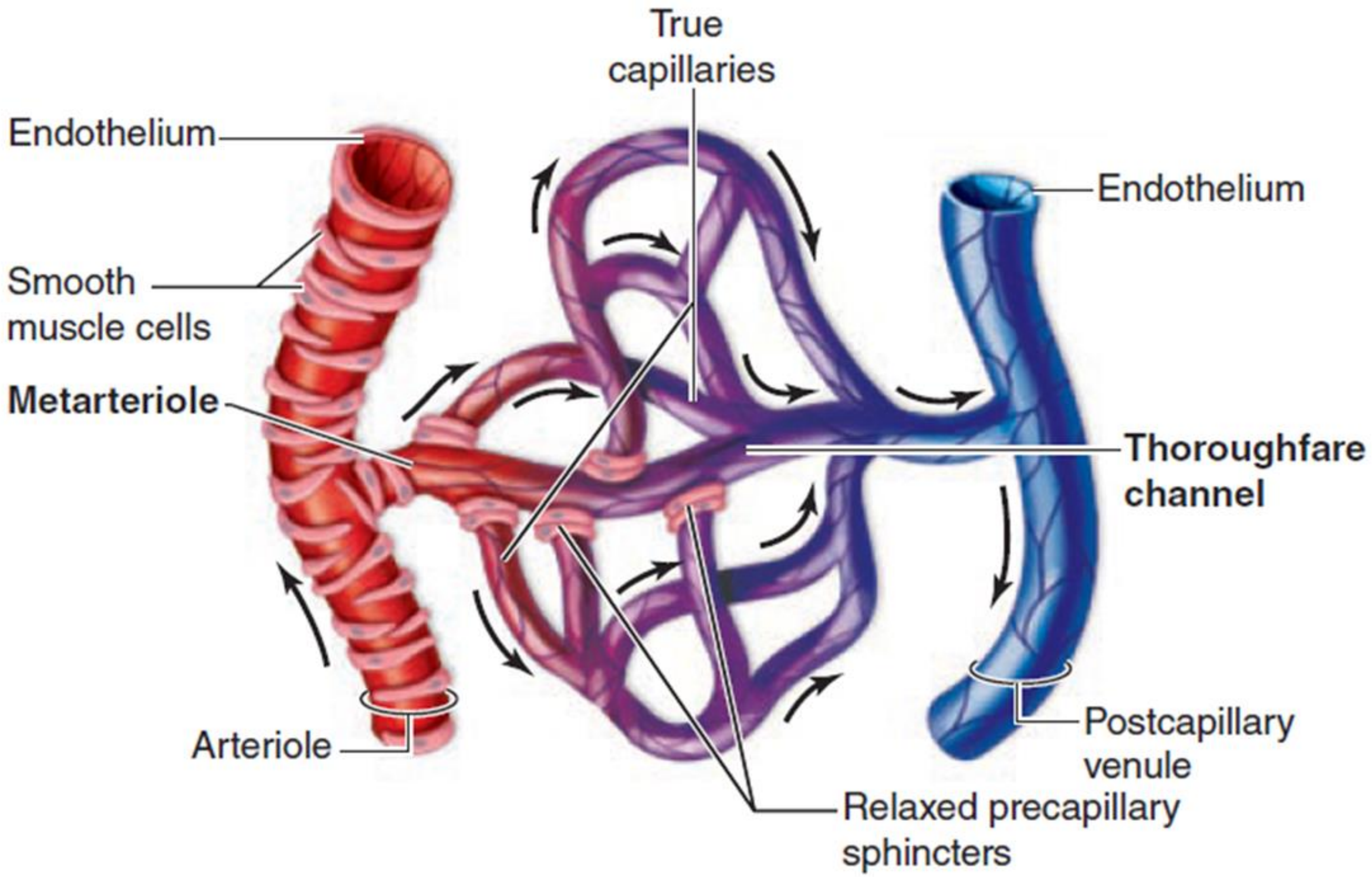


Fig.12: Microvasculature of an organ. The flow of blood through the capillaries is controlled by the contraction and relaxation of the precapillary sphincters.

Histology of the Vessels - Capillaries

- Capillaries are the smallest vessels in the body. With a diameter of 4-10μm, blood cells can pass only one at a time.
- Exchange of gases and nutrients occur through the thin capillary walls. The density of the capillaries depends on the metabolic activity of the organ.
- They are formed of simple squamous endothelium rolled up in a tube surrounded by basal lamina and pericytes. The endothelial cells:
  - Are connected by tight junctions
  - Contain pinocytotic vesicles
  - Release substance that prevent coagulation of blood, control passage of WBC into tissues, and affect vessels diameter

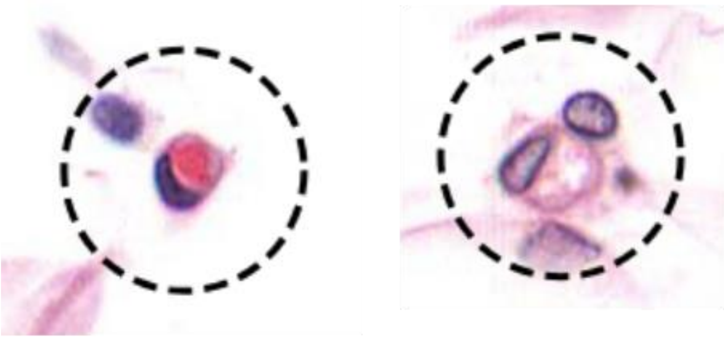
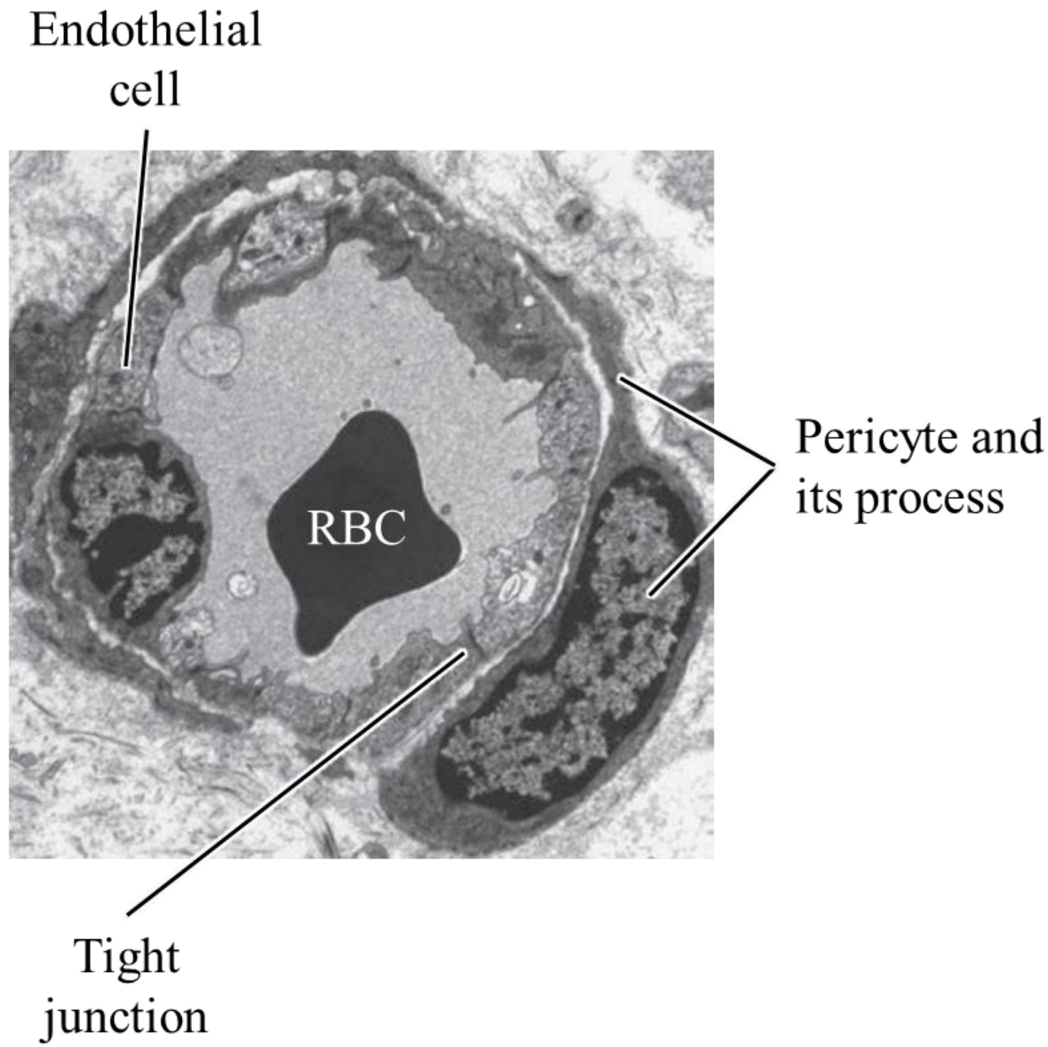


Fig.13: Capillaries. Above, light microscope images. In the top-left image, a red blood cell is filling the capillary. In the top-right image, the nucleus just outside the capillary belongs to a pericyte. To the right, electron microscope image of a capillary.



Types of capillaries

a) Continuous capillaries

- Many tight junctions between slightly overlapping endothelial cells. This allows well-regulated exchange across the cells.
- The most common type of capillary. Found in muscle, connective tissue, lungs, exocrine glands, and nervous tissue.

b) Fenestrated capillaries

- Have a sieve-like structure in which the endothelial cells are penetrated by numerous small circular fenestrations that allows more extensive exchange.
- Some fenestrations are covered by very thin diaphragms of proteoglycans; others may represent membrane invaginations that temporarily involve both sides of the very thin cells. The basement membrane however is continuous.
- Fenestrated capillaries are found in some organs, such as the kidneys, intestine, choroid plexus, and endocrine glands.

c) Discontinuous capillaries (sinusoids)

- The endothelium has large perforations without diaphragms and irregular intercellular clefts. In addition, the basement membranes is highly discontinuous.
- These features and larger diameter of these capillaries permit maximal exchange of macromolecules as well as allow easier movement of cells between tissues and blood.
- Sinusoidal capillaries of this type are found in the liver, spleen, and bone marrow.

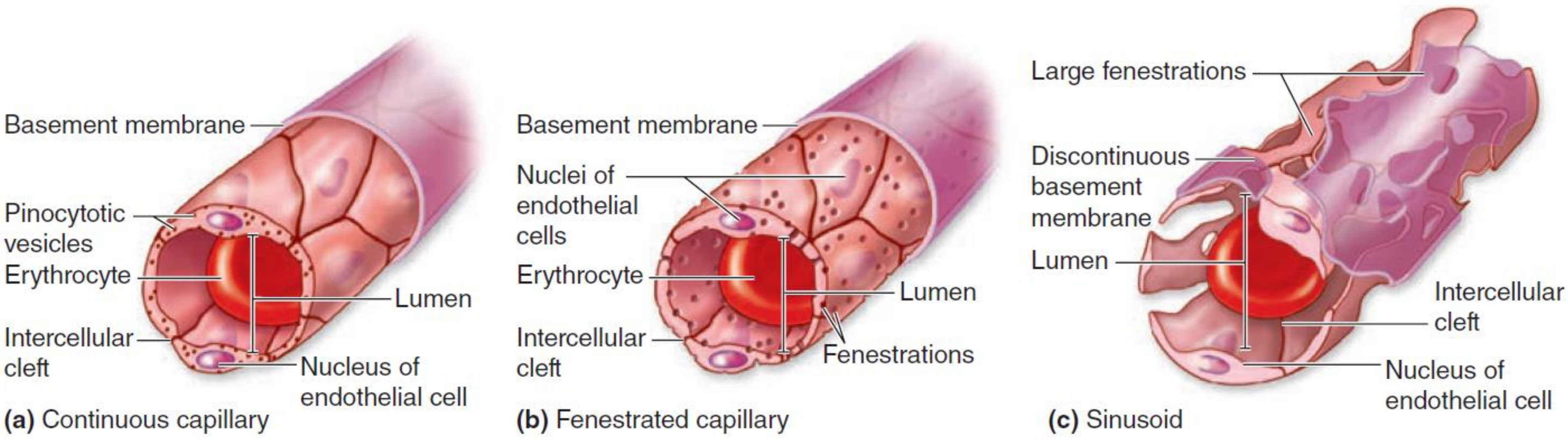


Fig.14: Types of capillaries.

Pericytes

- Mesenchymal cells with long cytoplasmic processes that surround continuous capillaries and post-capillary venules.
- They are surrounded by a basal lamina that merges with the basal lamina of the capillary.
- They have well-developed networks of myosin, actin, and tropomyosin indicating that pericytes dilate or constrict capillaries, helping to regulate blood flow.
- They help form new capillaries after injury.

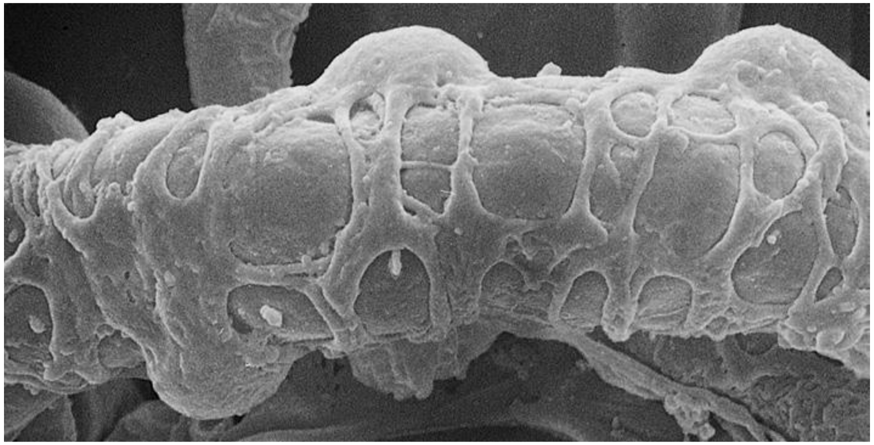


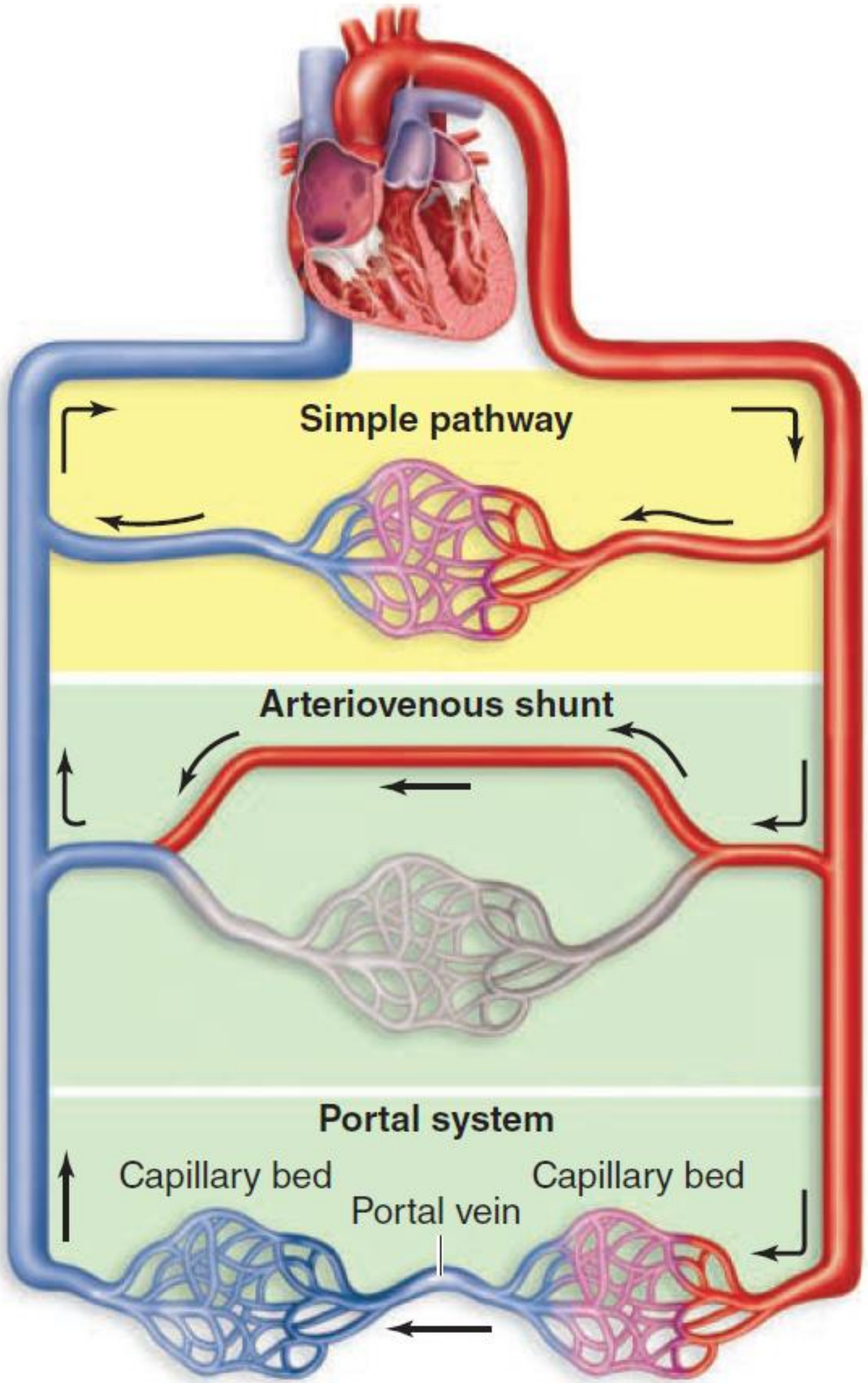
Fig.15: SEM of a capillary surrounded by pericytes.

Types of circulations

Simple pathway: Arteriole → Capillary bed → Venule --- Most common

Arteriovenous shunts: blood is shunted directly from arterial to venous side bypassing capillaries --- Skin

Portal systems: capillary bed 1 → portal vein → capillary bed 2 --- Hepatic portal systems



Histology of the Vessels - Veins

Venules

- *Postcapillary venules*
  - Similar to capillaries (endothelium and basal lamina) surrounded by pericytes. Lager diameter.
  - Site where white blood cells leave the circulation to enter inflamed tissue.
- *Collecting and muscular venules*
  - Have distinct tunica media with only 2-3 layers of smooth muscles.

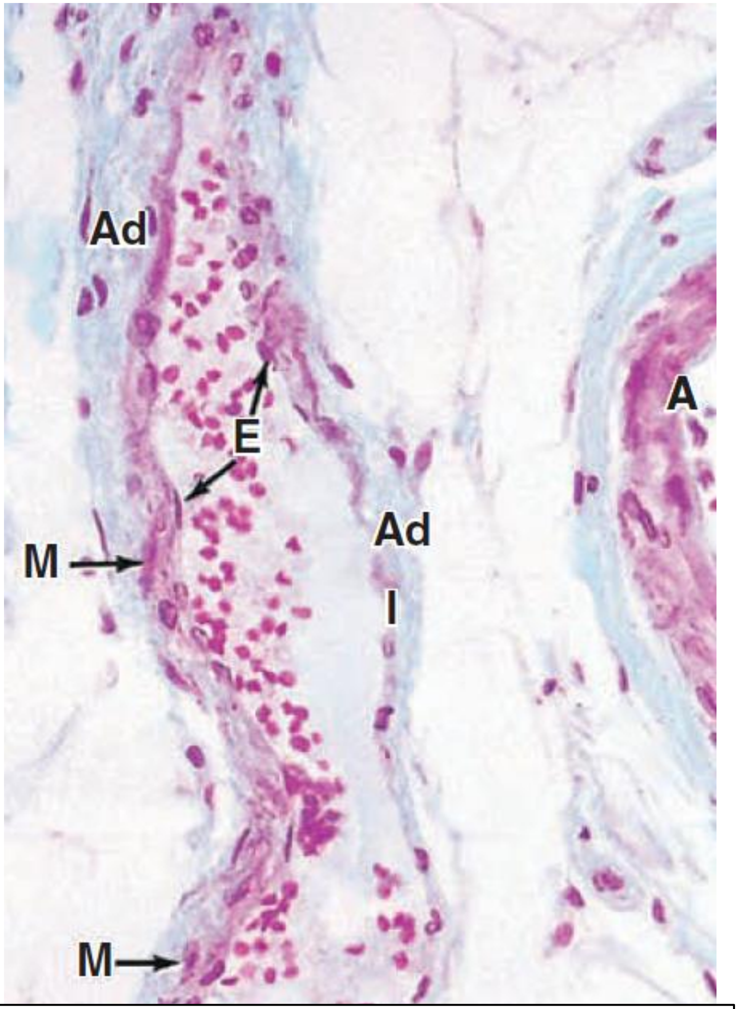


Fig.16: Muscular venule. I, intima. E, endothelium. M, media. Ad, adventitia. Note the large lumen and the thin wall (compare with the arteriole A).

Small and medium veins

- Accompany the muscular arteries.
- The tunica intima is usually thin. The media has small bundles of smooth muscle cells (3-5 layers) mixed with a network of reticular fibers and delicate elastic fibers. The adventitia is thick and well developed with several collagen fibers.
- Medium veins posses valves.

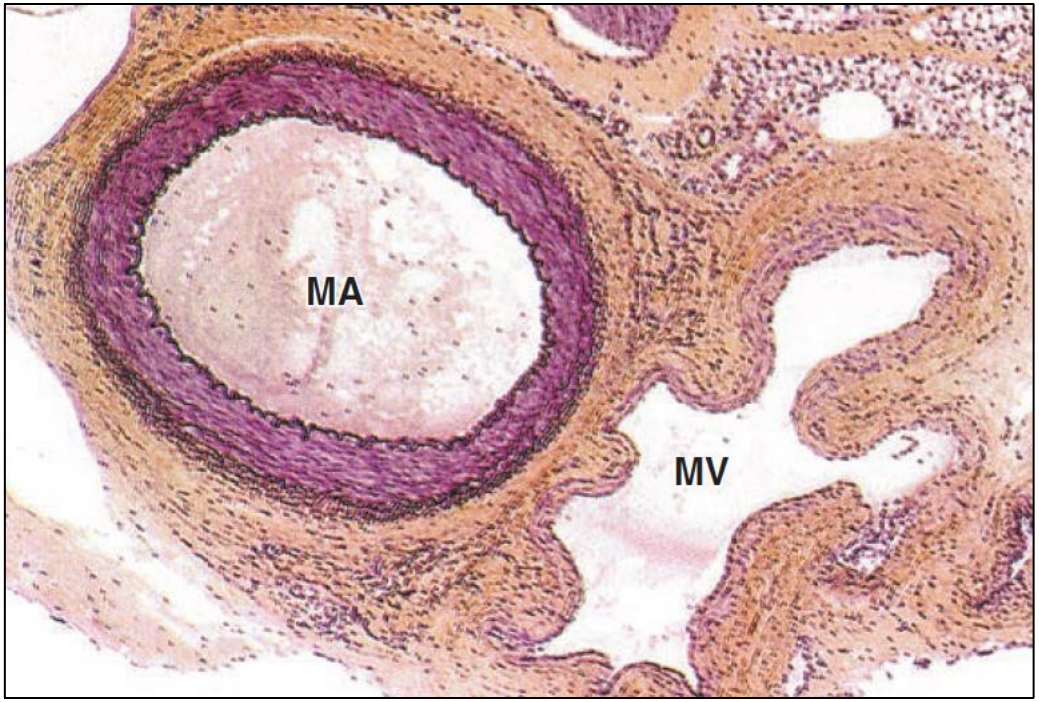


Fig.17: Medium vein (MV) accompanying a muscular artery (MA).

Large venous trunks

- Accompany the large elastic arteries.

- Intima is well-developed. Media has alternating layers of smooth muscle (>5) and connective tissue. The tunica adventitia is thicker than the media in large veins and frequently contains longitudinal bundles of smooth muscle. Both the media and adventitia contain elastic fibers, and an internal elastic lamina may be present.
- Possess valves which are folds of the tunica intima that prevent backflow of blood. They are most numerous in the veins of the leg.

- Vasa vasorum are numerous in the large veins because blood in the lumen is deoxygenated.

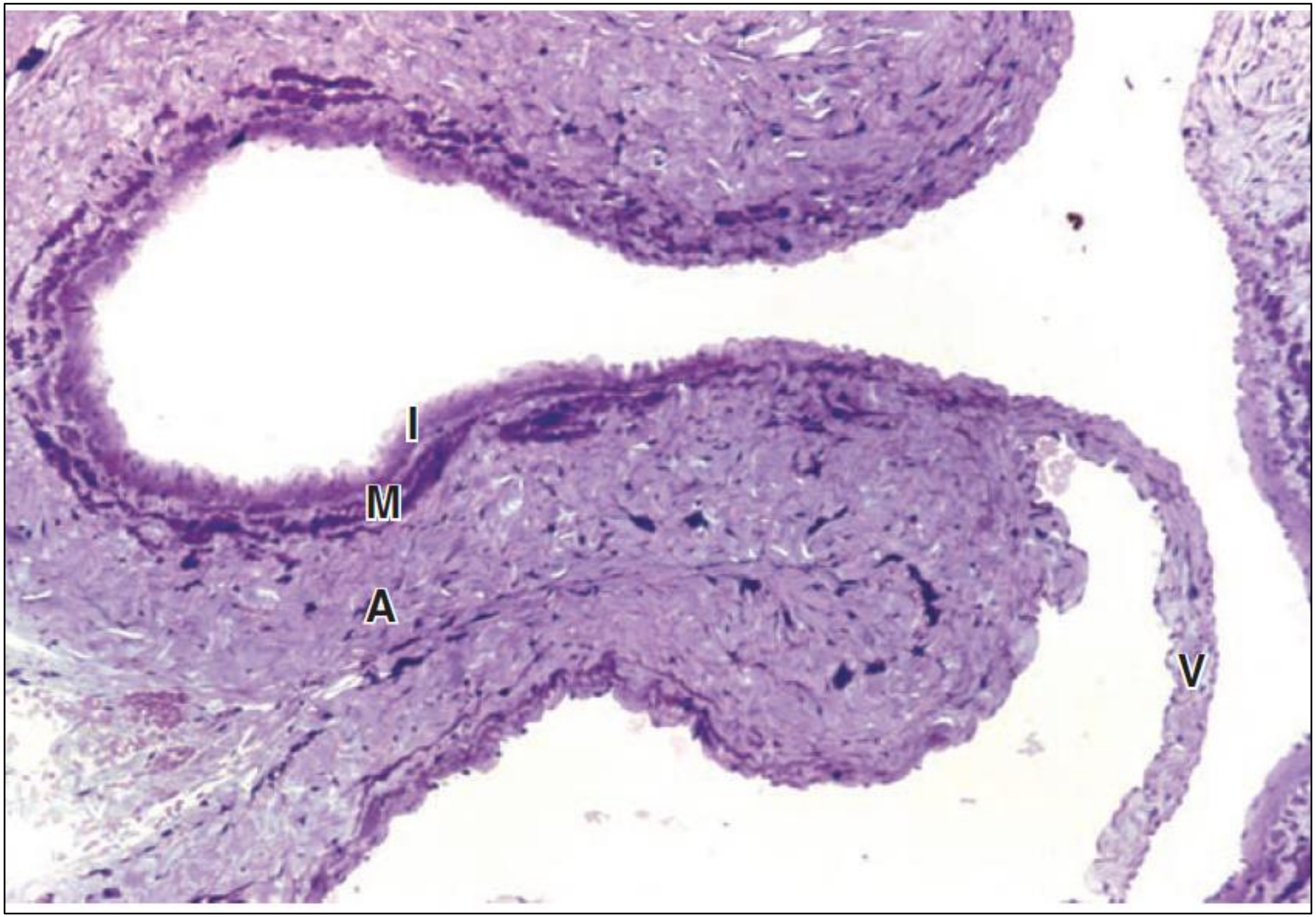
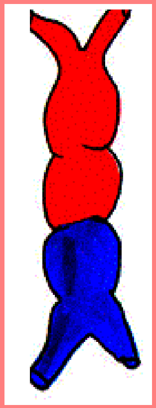


Fig.18: Large vein with distinct intima (I), media (M), and adventitia (A). Note the valve (V).

Development of the Cardiovascular System



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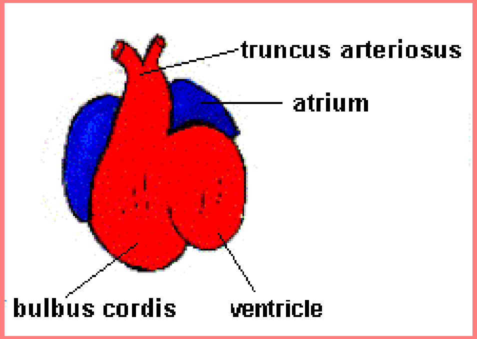


Highlights

- ***The cardiovascular system is the first major system to function in the embryo.***

- The primordial heart and vascular system start to develop in the ***middle of the third week*** of development.

- The heart begins to beat about day 22 or 23. The adult form of the heart is obtained by the 8th week.

- *This early development is necessary because the rapidly growing embryo can no longer satisfy its nutritional and oxygen requirements by diffusion alone.*

Development of the Heart

- Mesodermal cells derived from the primitive streak form a crescent-shaped region in the splanchnic layer of the lateral mesoderm. This is called the ***primary heart field***.
- Later in the third week, cells from the pharyngeal mesoderm and some cells from the neural crest will form the ***secondary heart field*** just medial to the primary.

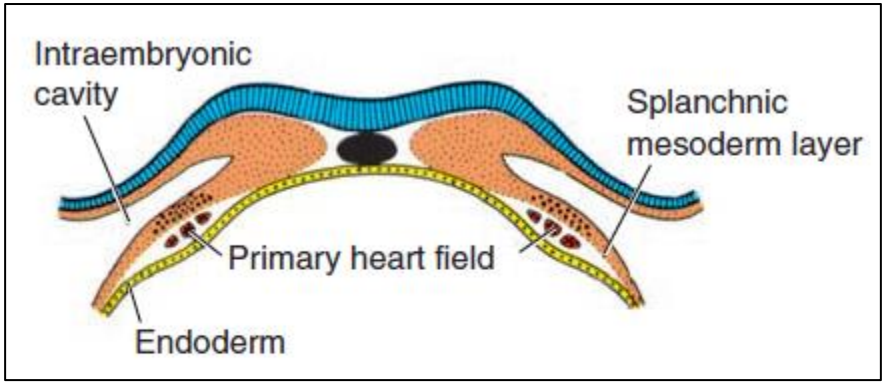


Fig.1: Cross-section through embryo showing site of heart formation.

- Which part of the heart these cells will form is already determined at this early stage. In the embryo, this is controlled by ***retinoic acid***. The right-left sidedness (laterality) is controlled by a complex pathway that involves ***serotonin***.

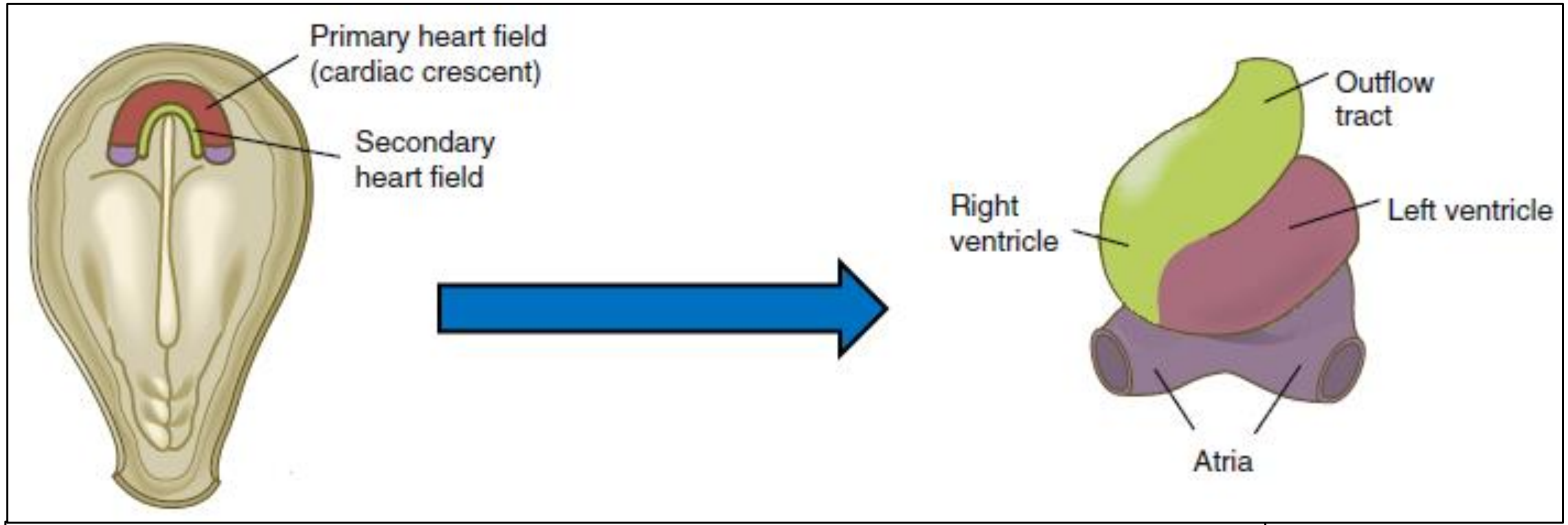


Fig.2: Heart fields and the parts of the heart they form.

Clinical Correlation
• Drugs based on retinoic acid (like some used for treating acne), may cause congenital heart disease if taken by a pregnant woman.

The Heart Tube

- By vasculogenesis, the heart field will be converted into two endothelial-lined tubes in the splanchnic layer of the lateral mesoderm, one on each side. These ***heart tubes*** will form the endocardium of the heart.

- Nearby mesodermal cells will form the ***primordial myocardium*** around the endothelial heart tubes. This myocardium will release a gelatinous-matrix connective tissue, the ***cardiac jelly***, that separates it from the endothelial tube.

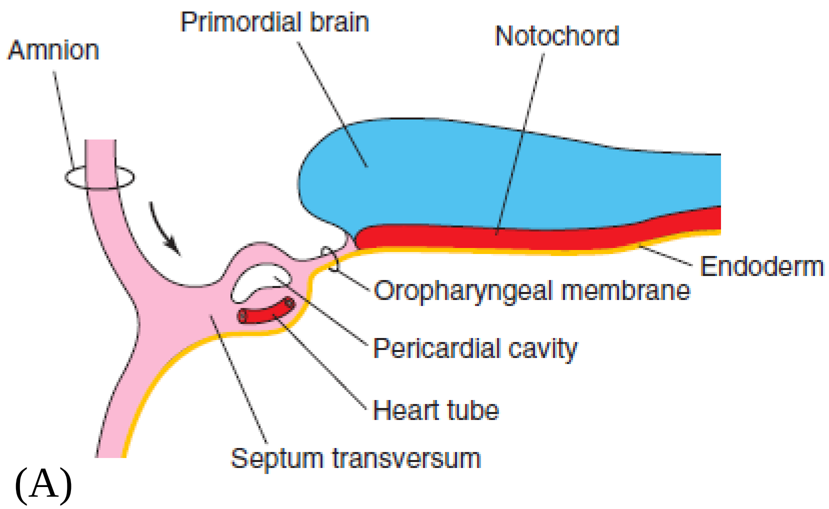
- Mesothelial cells covering the inflow and outflow tracts of the tubes move over the heart tubes to form the ***epicardium***.

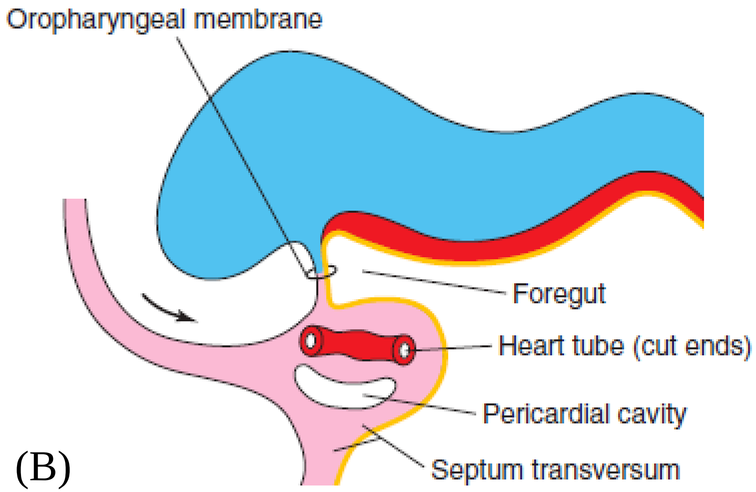
- Thus the heart wall is formed of three layers: endocardium, myocardium, and epicardium all derived from mesoderm.

- The heart tube is initially located cranial to the neural tube and the oropharyngeal membrane. As the brain grows and the embryo folds, the heart tube will assume its position ventral to the foregut, caudal to the oropharyngeal membrane (Fig.3).

- Lateral folding of the embryo will bring the two heart tubes together ultimately resulting in their fusion (except the cranial ends). Thus a single heart tube is formed (Fig.4).

- The heart tube bulges more and more into the nearby intraembryonic cavity, the ***pericardial cavity***. However, it remains attached posteriorly by a ***dorsal mesocardium*** (Figs.4d and 5a). Later on, this mesocardium disappears forming the ***transverse pericardial sinus*** (Fig.5). Thus the heart tube becomes suspended in the pericardial cavity by the vessels at its cranial and caudal ends.





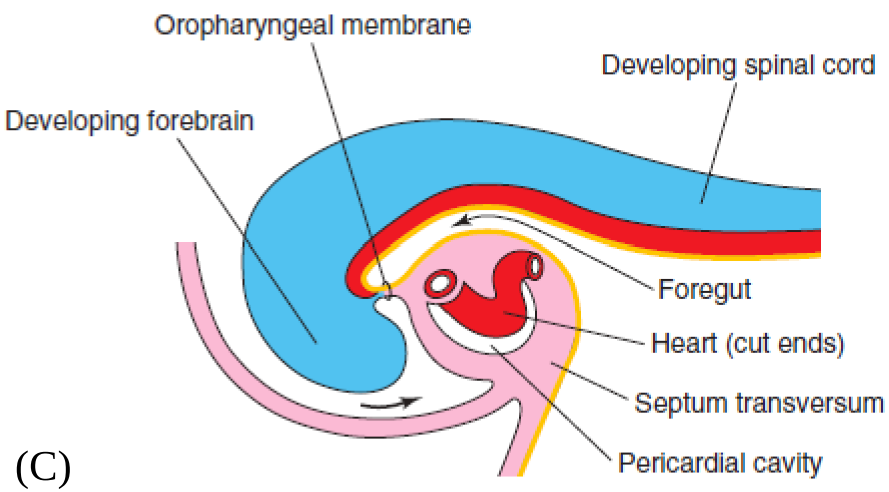


Fig.3: Longitudinal sections through the cranial part of the embryo during the fourth week, showing the effect of the head fold (arrows) on the position of the heart and other structures.

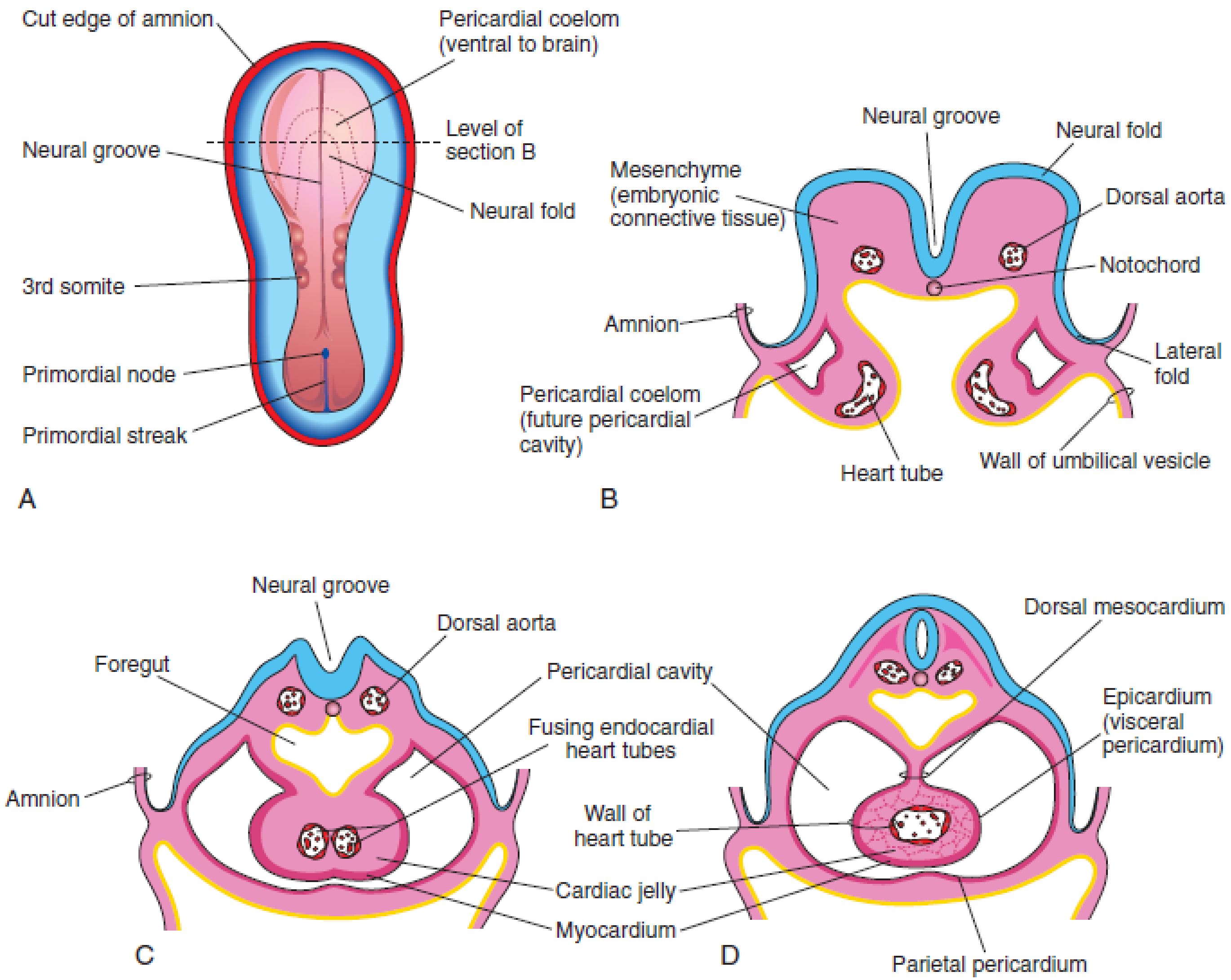
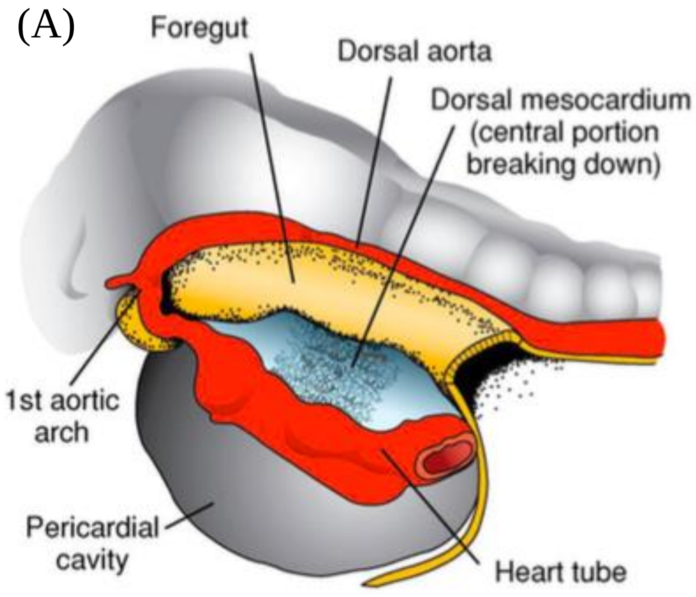
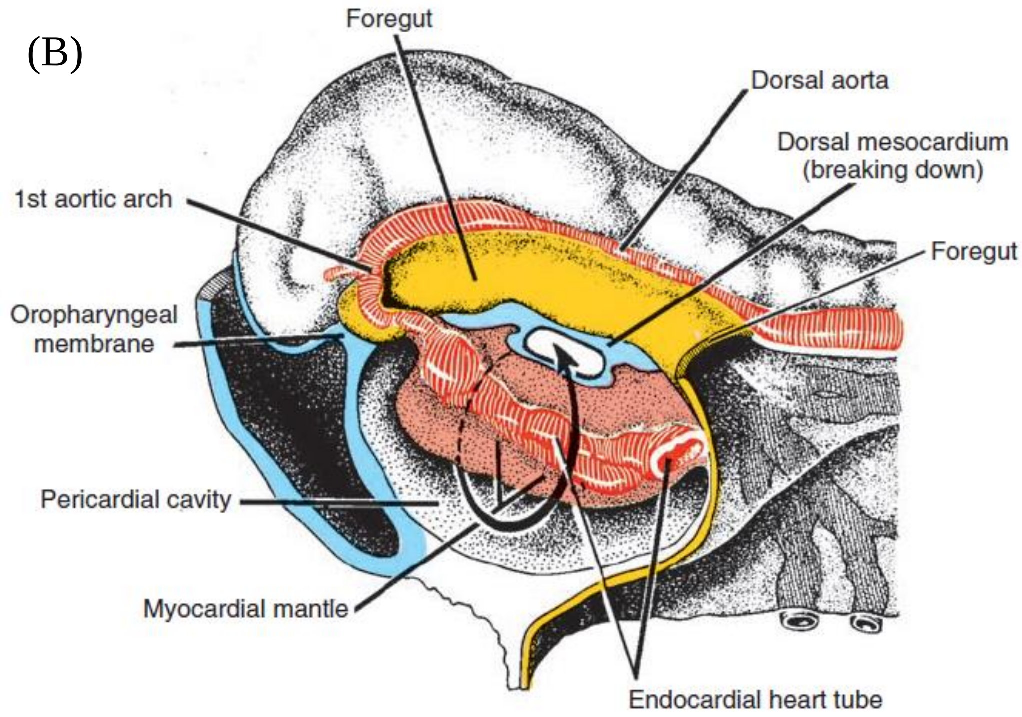


Fig.4: A, dorsal view of embryo showing level of the sections. B-D, cross-sections through the embryo showing the effect of lateral folding on the development of heart tubes.

(A)



(B)



(C)

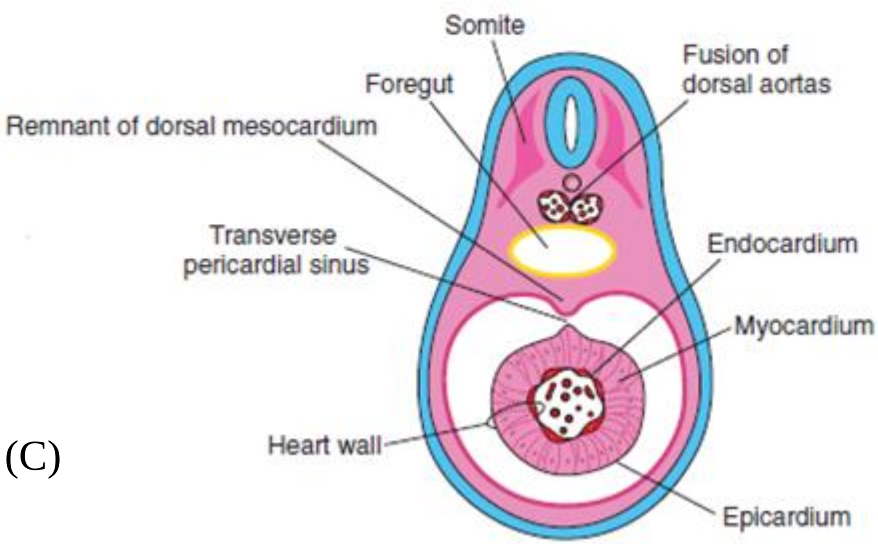


Fig.5: A and B, cranial part of the embryo showing the dorsal mesocardium and the transverse pericardial sinus. C, cross section through the embryo; note how the two halves of the pericardial cavity communicate through the transverse sinus.

- The straight heart tube will elongate and develop a series of dilation and constrictions (Fig.6).

- These dilations are (cranial → caudal):

1. Bulbus cordis (3 parts)
   a. Truncus arteriosus
   b. Conus cordus
   c. Part of right ventricle
2. Ventricle
3. Atrium
4. Sinus venosus

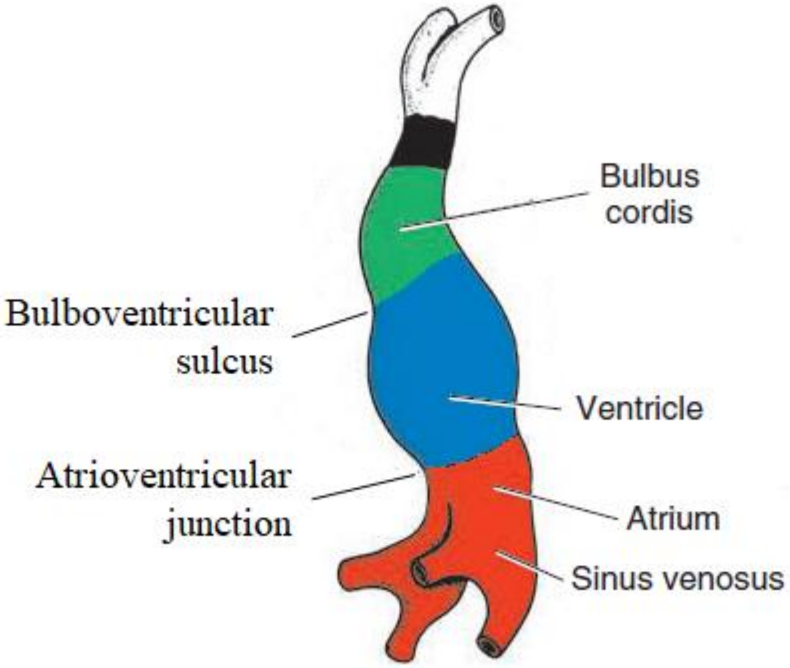


Fig.6: The heart tube and its parts.

- The truncus arteriosus is attached to the ***aortic sac*** which gives rise to the pharyngeal arteries. The sinus venosus receives the common cardinal, vitelline, and umbilical veins.

Table 1: Derivatives of the various parts of the heart tube.

	Dilation		Derivative
1	Bulbus cordis	Truncus arteriosus	Proximal parts of the aorta and the pulmonary trunk
		Conus cordis	Outflow tracts of the right ventricle (RV) and left ventricle (LV)
		Proximal third of the bulbus	Trabeculated part of the right ventricle
2	Ventricle		Trabeculated part of the left ventricle
3	Atrium		Trabeculated part of the right atrium (RA) and left atrium (LA)
4	Sinus venosus		• Smooth part of the right atrium • Venous derivatives

Looping of the Heart Tube

- The cranial (arterial) end of the heart is fixed to the pharyngeal arches and the caudal (venous) end is fixed to the septum transversum. The bulbus and the ventricle grow more rapidly than the other parts of the tube. Because of these reasons, the tube will bend on itself forming the U-shaped bulboventricular loop (Figs.7 and 8).

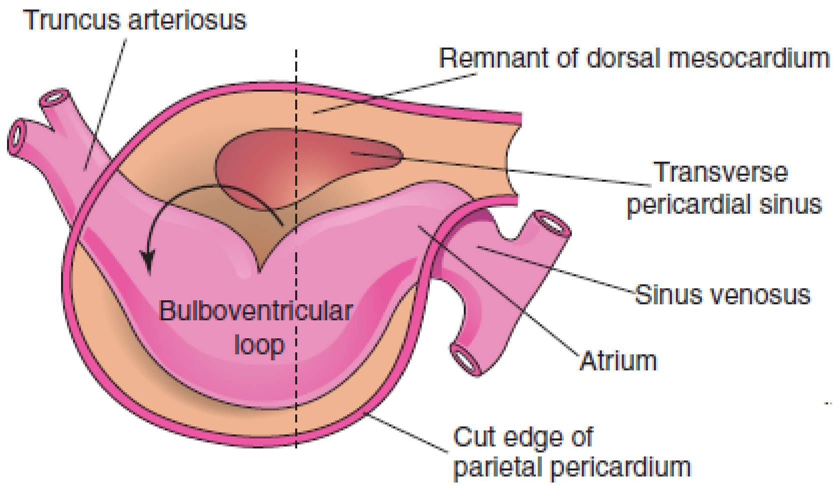


Fig.7: The bulboventricular loop.

- With further growth, the cranial part of the tube moves ventrocaudally and to the right; whereas the caudal part moves dorsocrainally (Fig.9).
- The atrium is initially outside the pericardial cavity. With looping, it becomes inside. The sinus venosus develops two extensions, the ***sinus horns***.

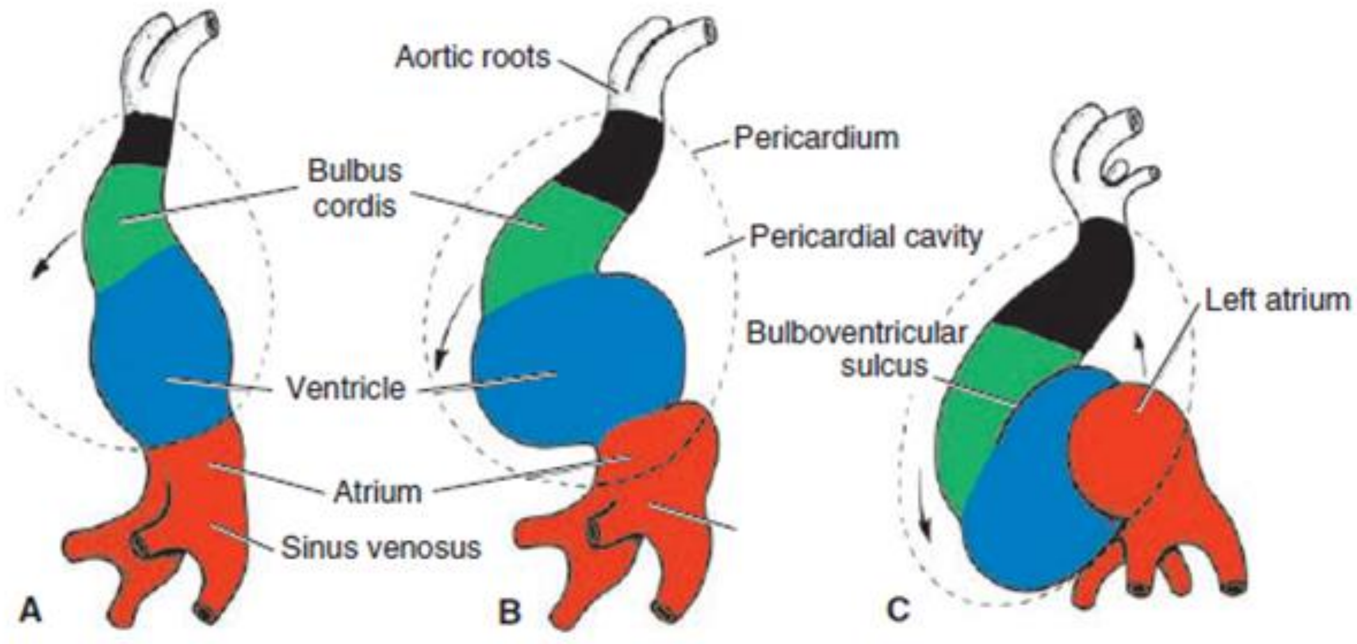


Fig.8: The looping of the heart tube.

- Looping of the heart starts on day 23 and ends by day 28.

- Between the bulbus and the ventricle, there's a groove on the outside called the ***bulboventricular sulcus*** corresponding to a narrow ***primary interventricular foramen***. The ventricular and atrial dilations are connected to each other by the narrow ***atrioventricular (AV) canal***.

- After looping of the tube, trabeculae start to appear around the bublboventricular sulcus. The trabeculated ventricular dilation is now called the ***primitive left ventricle***. Similarly, the trabeculated proximal third of the bulbus is now called the ***primitive right ventricle*** (Fig.9).

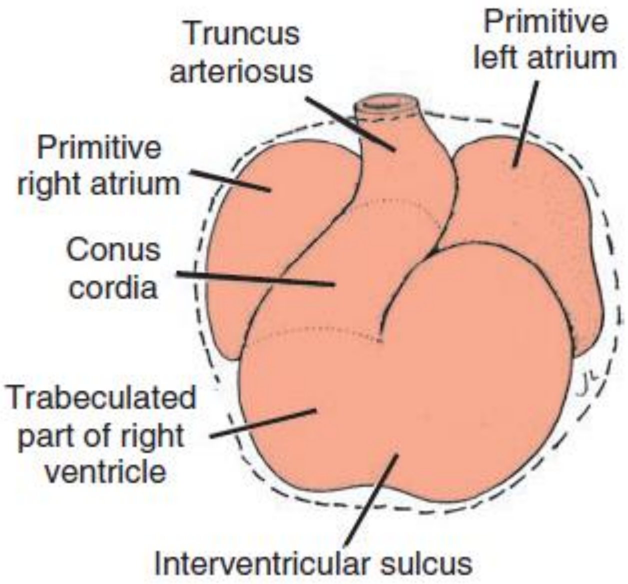
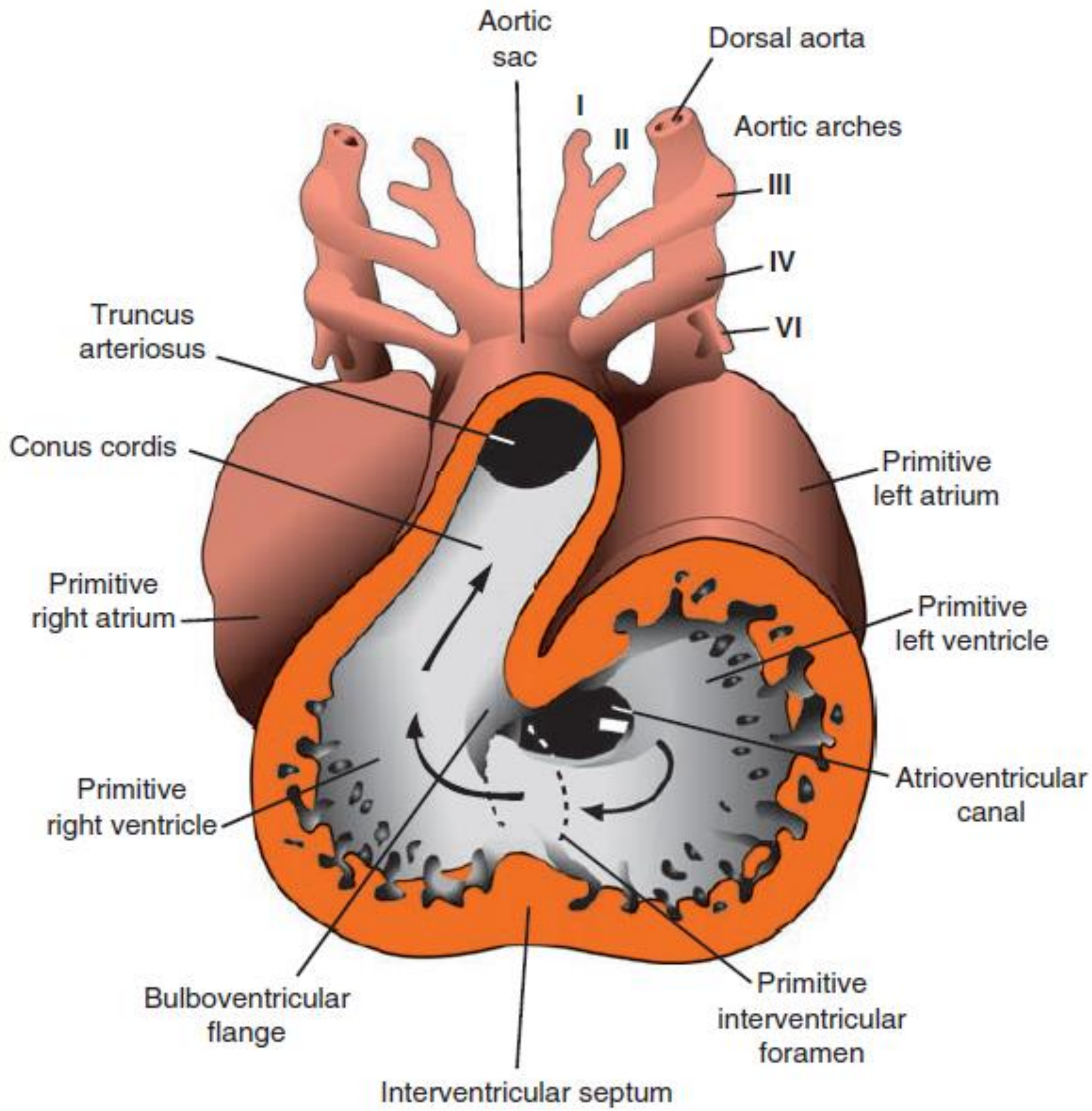


Fig.9: Above, the heart after looping. Note how the atria became posterior. Right, the same as above but sectioned to show the trabeculae in the ventricles.

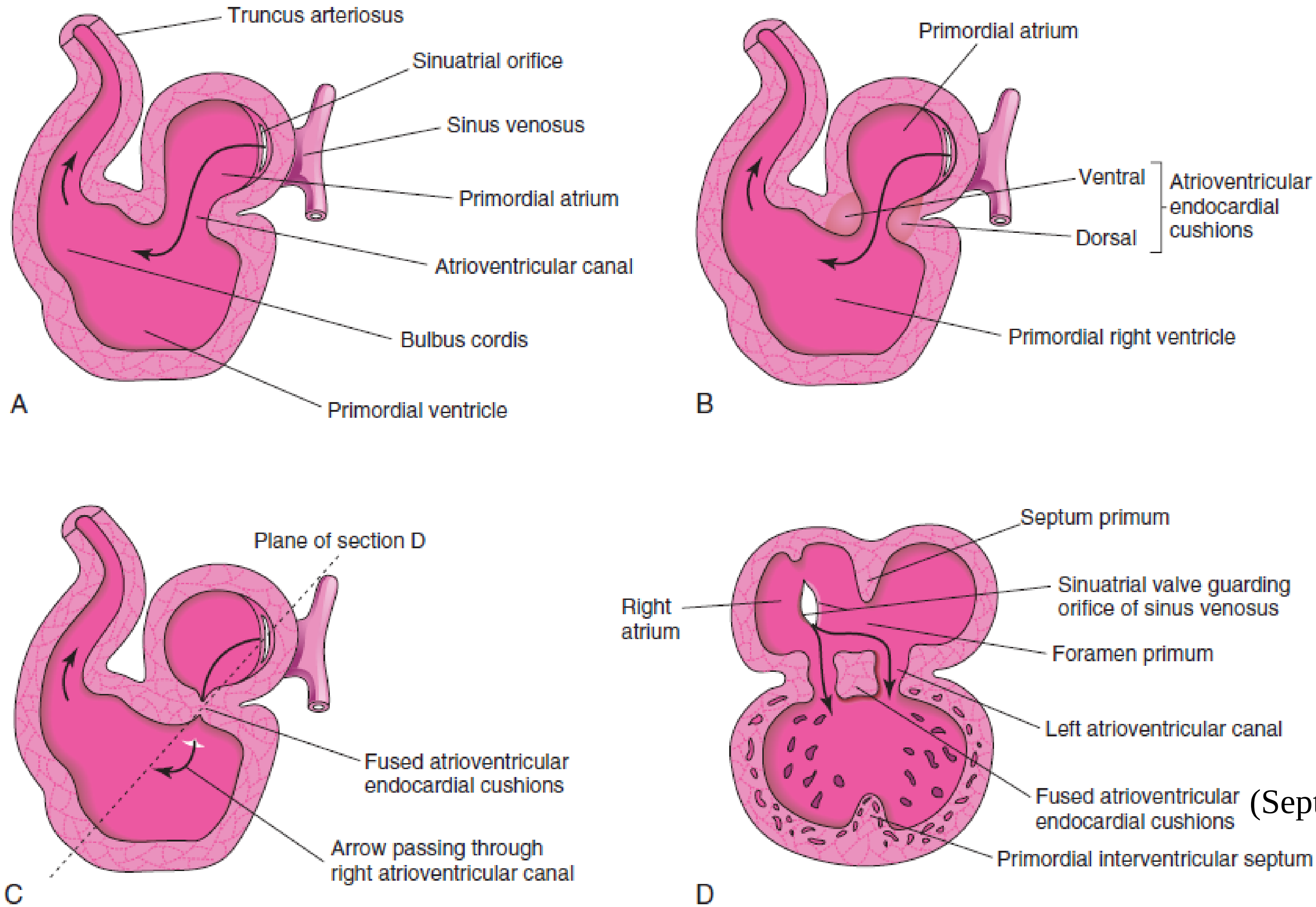


Partitioning of the Atrioventricular Canal

- During the fourth week, atrioventricular endocardial cushions appear on the dorsal and ventral walls of the atrioventricular canal (Fig.10)

- These cushions meet and fuse with each other forming the ***septum intermedium*** dividing the atrioventricular canal into right and left halves.

- These cushions are made of extracellular matrix released by the myocardium (cardiac jelly) and neural crest and mesenchymal cells.



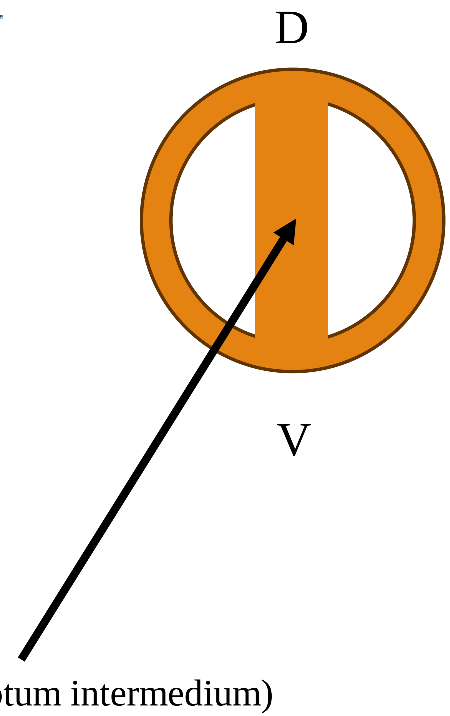


Fig.10: A-C, sagittal sections through the heart showing the partitioning of the atrioventricular canal. D, Coronal section through the heart showing the two atrioventricular orifices. The animated diagram to the right shows this process.

Formation of the Interatrial Septum

- The primordial atrium is divided into right and left atria by the formation, and subsequent modification and fusion, of two septa: the septum primum and septum secundum (Figs.11 and 12).

- The thin, crescent-shaped ***septum primum*** grows toward the fusing AV endocardial cushions from the roof of the primordial atrium.

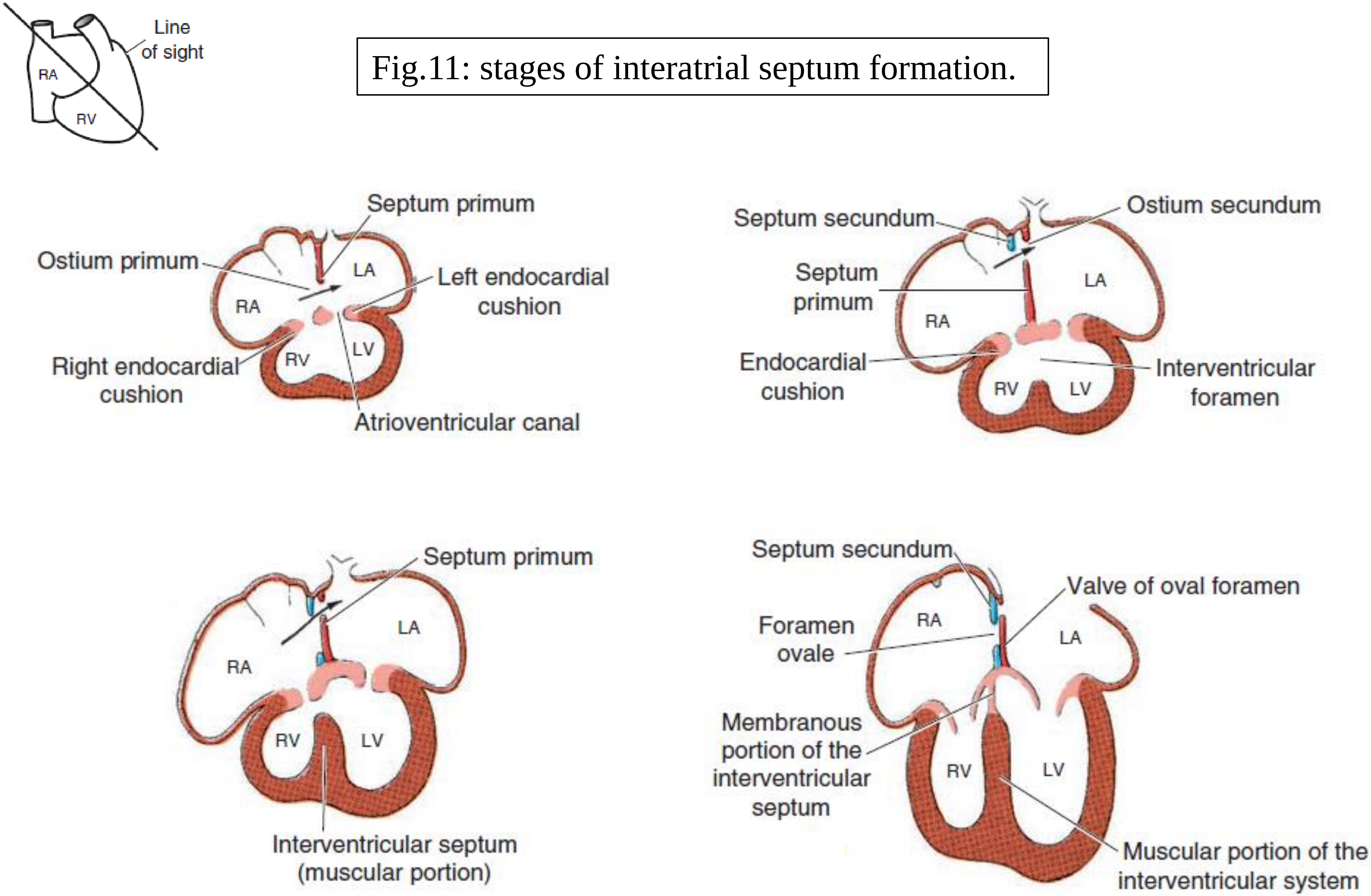
- As the septum primum grows, a large opening, the ***ostium primum***, is located between its free edge and the endocardial cushions. This foramen shunts oxygenated blood from the right to the left atrium. The foramen becomes progressively smaller and disappears as the septum primum fuses with the fused AV endocardial cushions.

- Before the ostium primum disappears, perforations appear in the central part of the septum primum. As the septum fuses with the endocardial cushions, these perforations fuse to form another opening in the septum primum, the ***ostium secundum***, which ensures continued shunting of oxygenated blood from the right to the left atrium.

- The thick ***septum secundum*** grows from the the right atrium, immediately adjacent to the septum primum. As this septum grows, it gradually overlaps the ostium secundum in the septum primum. The septum secundum forms an incomplete partition between the atria leaving a foramen called the ***foramen ovale***.

- The cranial part of the septum primum gradually disappears. The remaining part of this septum, attached to the fused endocardial cushions, acts as a valve for the foramen ovale.

Fig.11: stages of interatrial septum formation.



- Before birth, the foramen ovale shunts oxygenated blood from the right to the left atrium. The valve of the foramen (septum primum) prevents the returning of blood in the opposite direction.
- After birth, the pressure in the left atrium becomes higher pressing the septum primum against the septum secundum leading to their subsequent fusion and closure of the foramen ovale. The site of the foramen ovale is indicated in the heart by a depression called the ***fossa ovalis***.

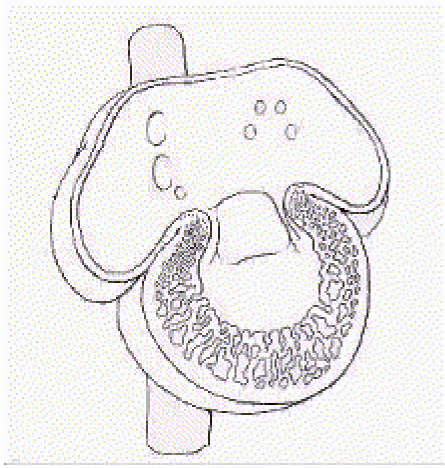


Fig.12: Animation showing interatrial septum formation.

Changes in the Sinus Venosus and Right Atrium

- The sinus venosus has two extension, the right and left sinus horns. On each side, they receive venous blood through the:

1. ***Common cardinal vein*** (formed by union of anterior and posterior cardinal veins) from the body of the embryo.
2. ***Vitelline vein*** from the umbilical vesicle.
3. ***Umbilical vein*** from the placenta.

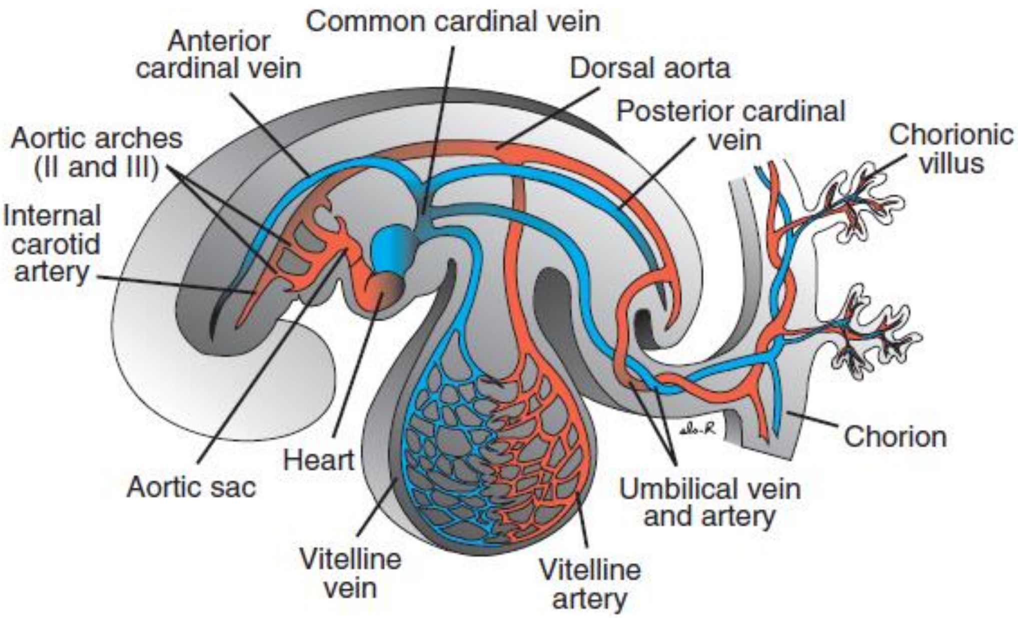


Fig.13: Veins draining into the heart of a 4-week old embryo.

- At first, communication between the sinus and the atrium is wide. Soon, however, this entrance shifts to the right. This is caused by left-to-right shift which occur in the venous system during development.

- As a result of this shift, the ***left sinus horn*** and its tributaries will lose their importance. Eventually, all that remains of the left sinus horn is the ***oblique vein of the left atrium*** and the ***coronary sinus*** (Fig.14).

- The ***right sinus horn***, on the other hand, will enlarge and becomes incorporated into the right atrium forming its smooth-walled part, the ***sinus venarum***, which is separated from the trabeculated part by a ridge called the ***crista terminalis***.

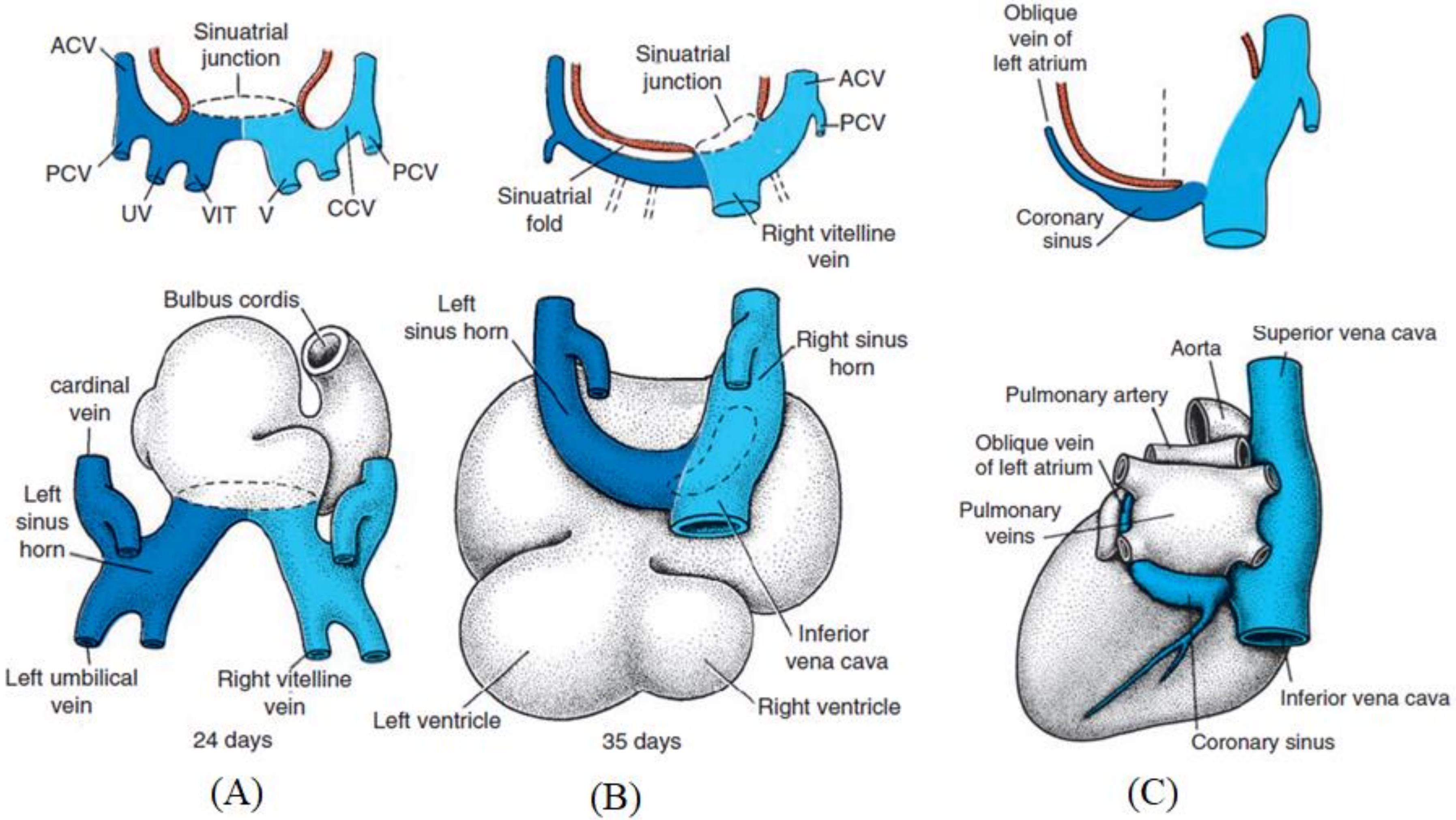


Fig.14: Dorsal view of various stages in the development of the sinus venosus. ACV, anterior cardinal vein; PCV, posterior cardinal vein; CCV, common cardinal vein; VIT V, vitelline vein; UV, umbilical vein.

- The opening of the right sinus horn into the atria, the ***sinuatrial orifice***, is guarded by the right and left venous valves. Dorsocranially, the valves fuse forming a ridge known as the ***septum spurium*** (Fig.15a).

- Initially the valves are large, but when the right sinus horn is incorporated into the wall of the atrium, the left venous valve and the septum spurium fuse with the developing atrial septum.

- The superior portion of the right venous valve disappears entirely. The inferior portion develops into two parts: **(1)**the valve of the inferior vena cava and **(2)**the valve of the coronary sinus (Fig.15b).

Changes in the Left Atrium

- A single pulmonary vein arises from the dorsal wall of the atrium just to the left of the septum primum. As the atrium expands, the primordial pulmonary vein and its main branches are incorporated into the wall of the left atrium. As a result, four pulmonary veins and the smooth part of the left atrial wall are formed (Fig.16).

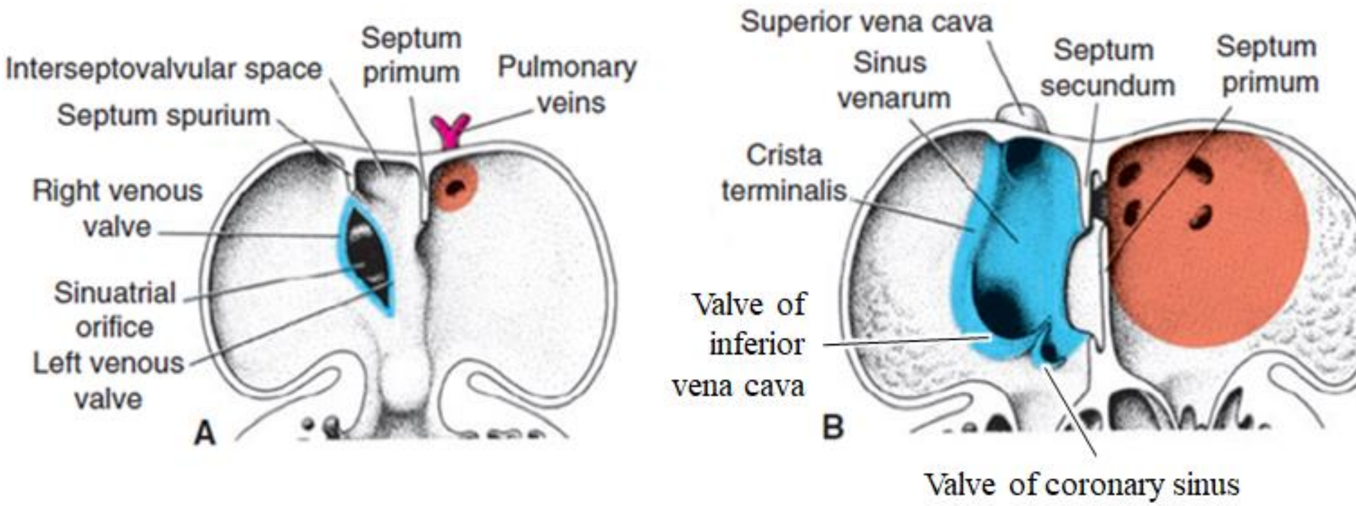


Fig.15: Coronal sections through the heart showing the development of the smooth-walled portions of the right and left atria.

Pericardial Sinuses

- The ***transverse sinus*** is formed when the arterial and venous ends of the heart tube come together after looping.
- The ***oblique sinus*** is formed as an expansion of the visceral pericardium due to the incorporation of the right sinus horn and the pulmonary veins into the atria.

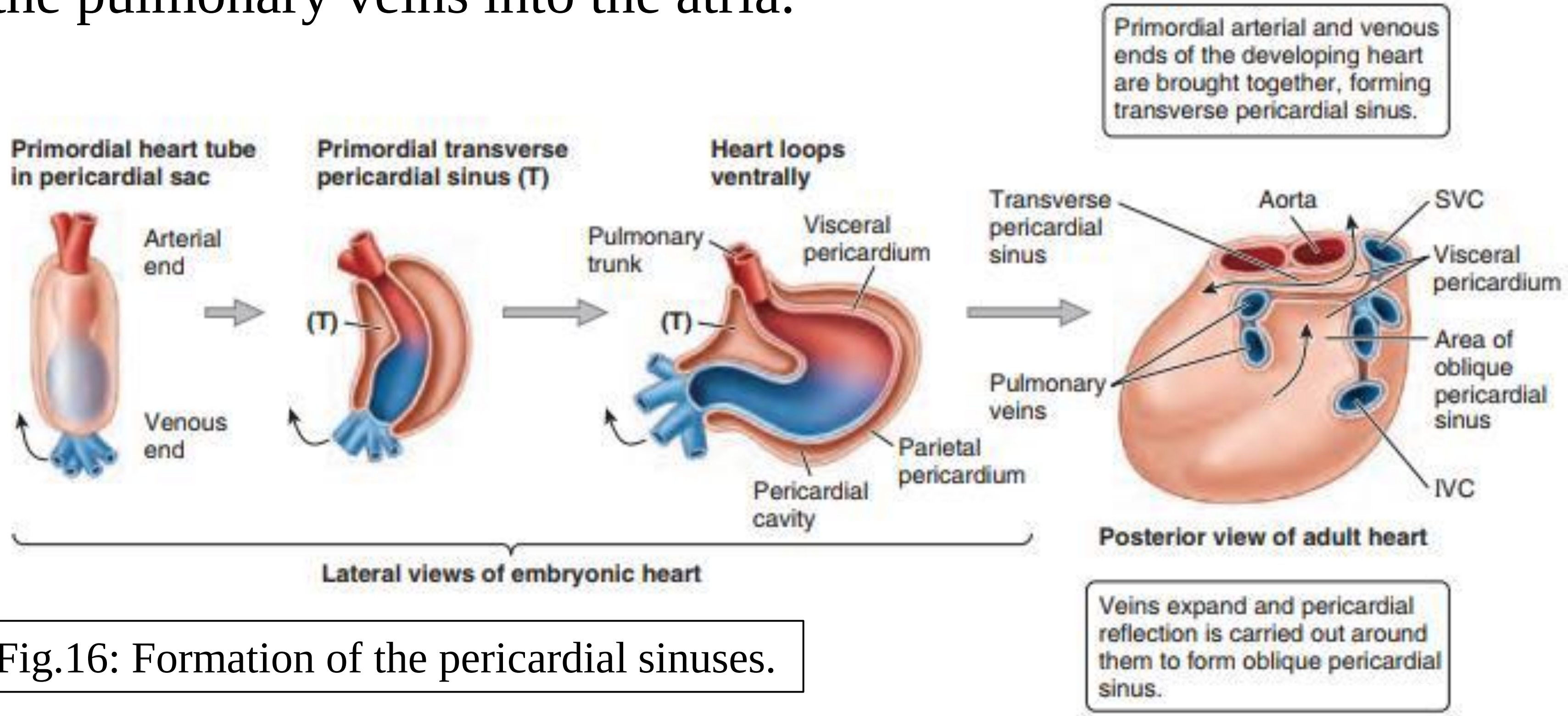


Fig.16: Formation of the pericardial sinuses.

Formation of the Interventricular Septum

- During the fourth week, a muscular median ridge arises from the floor of the primordial ventricle (Figs.11 and 18).

- The height of this muscular interventricular septum increases due to (1)growth of the right and left ventricles and (2)active proliferation of myoblasts in the septum.

- Until the seventh week, there is a crescent-shaped interventricular foramen between the concave free edge of the interventricular septum and the fused AV endocardial cushions. This foramen permits communication between the right and left ventricles.

- By the end of the seventh week, the conotruncal ridges fuse with endocardial cushions leading to the formation of a membranous septum that closes the interventricular foramen.

- The membranous part of the interventricular septum is formed by fusion of tissues from three sources: (1)right conotruncal ridge, (2)left conotruncal ridge, and (3)AV endocardial cushions.

- After closure of the interventricular foramen, the pulmonary trunk is in communication with the right ventricle and the aorta communicates with the left ventricle.

- Cavitation in the ventricular wall forms a spongy mass of muscular tissue, the ***trabeculae carnae***. Some of them become prominent to form the ***papillary muscles*** (Fig.19).

Formation of the Conotruncal Septum

- During the fifth week, two ridges appear in the truncus arteriosus: the right and left truncal ridges. As these ridges grow, they will spiral around each other.
- When the truncal ridges fuse, a spiral ***aorticopulmonary septum*** is formed (Figs.17 and 18). This septum divides the truncus arteriosus into two arterial channels, the ascending aorta and the pulmonary trunk.

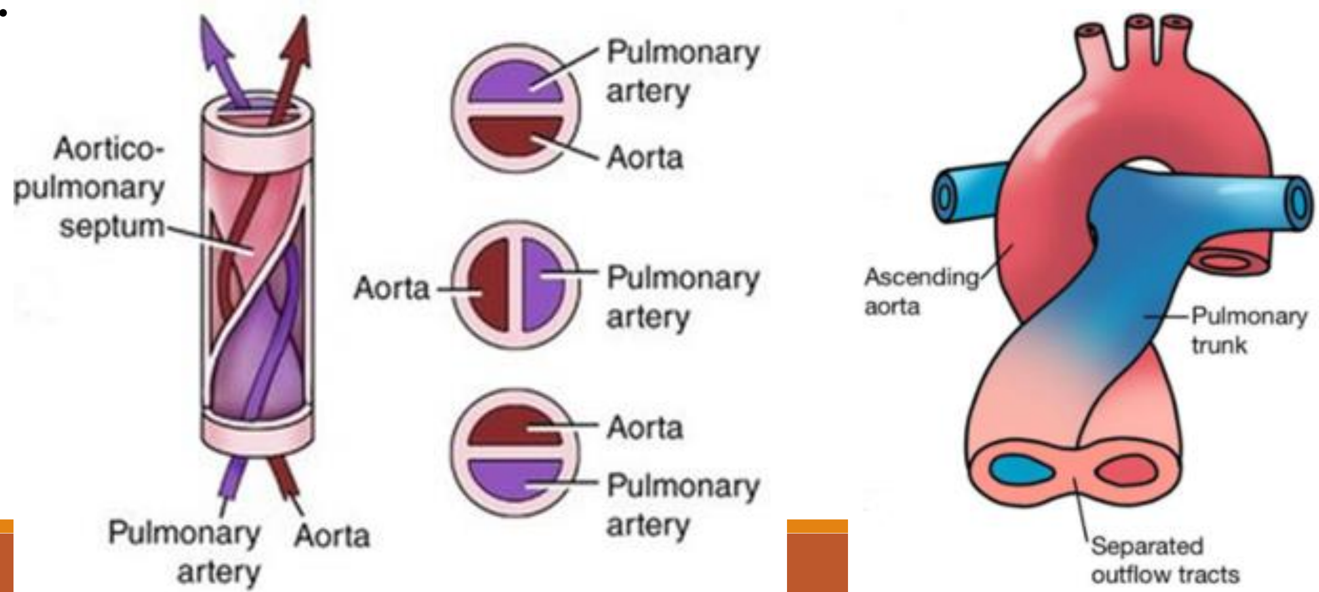


Fig.17: The spiral aorticopulmonary septum.

- Two similar ridges appear in the conus cordis. These fuse with each other and with the truncal ridges.

- When the two conal swellings have fused, the septum divides the conus into two portions:

1. The outflow tract of the right ventricle, the ***conus arteriosus*** (infundibulum), which is the origin of the pulmonary trunk.
2. The outflow tract of the left ventricle, the ***aortic vestibule***, the part of the ventricular cavity just inferior to the aortic valve.

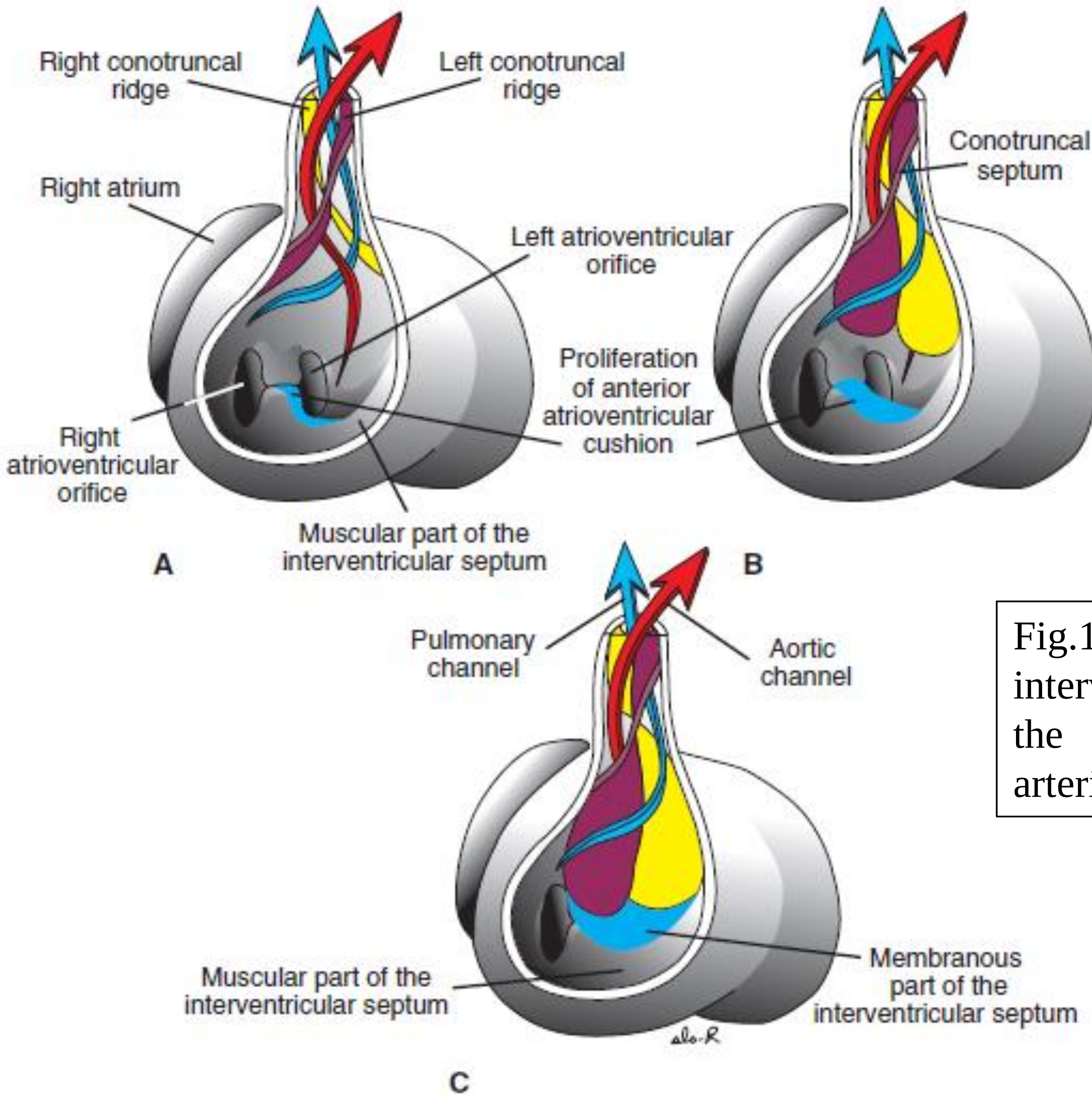


Fig.18: The formation of the interventricular septum and the division of the truncus arteriosus and conus cordis.

Formation of the Cardiac Valves

The atrioventricular valves

- The ventricular surface of the AV endocardial cushions becomes hollowed out forming the thin cusps of the AV valves and the chordae tendinae, which attach the cusps to the papillary muscles (Fig.19).

- On the right side, there are three cusps forming the right atrioventricular (tricuspid) valve. On the left, we have two cusps forming the left (bicuspid, mitral) valve.

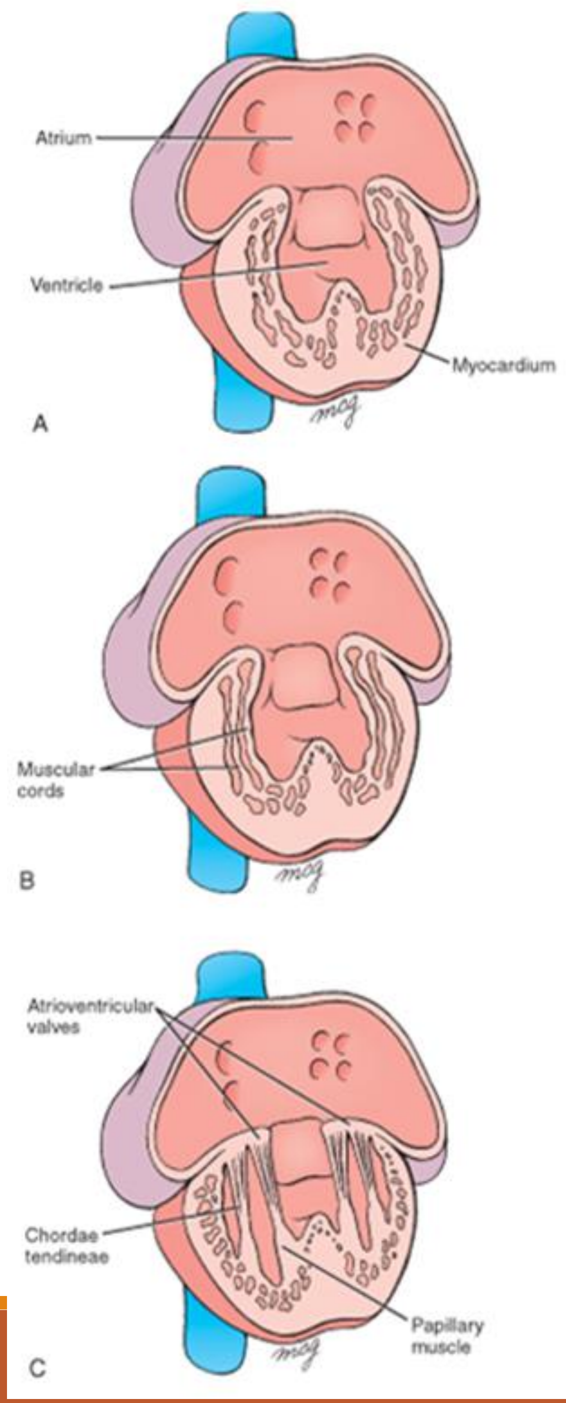


Fig.19: The formation of the atrioventricular valves. Note sponge-like appearance of the ventricular wall, these are the trabeculae carnae.

The semilunar valves

- After the formation of the aorticopulmonary septum, swellings appear at the orifices of both the aorta and the pulmonary artery (Fig.20).
- Gradually, the swellings become excavated on their upper surfaces to form the semilunar valves (three cusps for each valves).

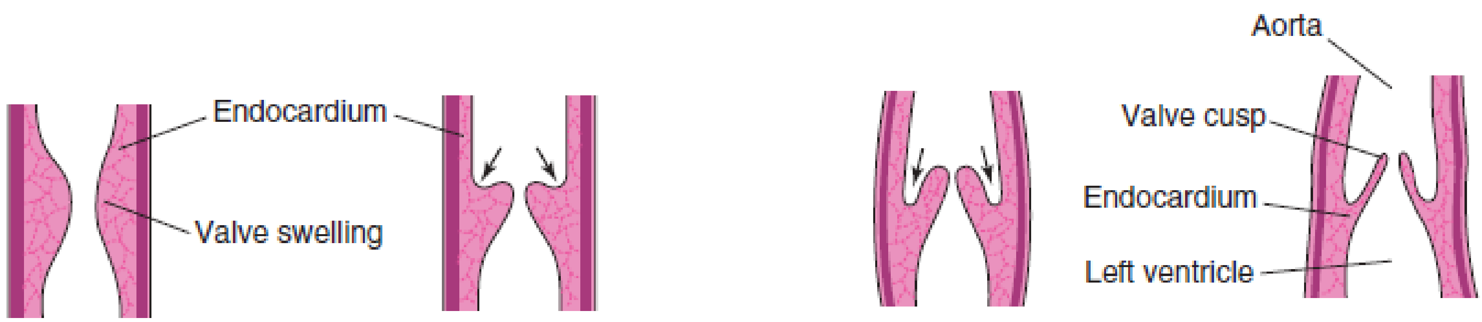


Fig.20: The formation of the semilunar valves.

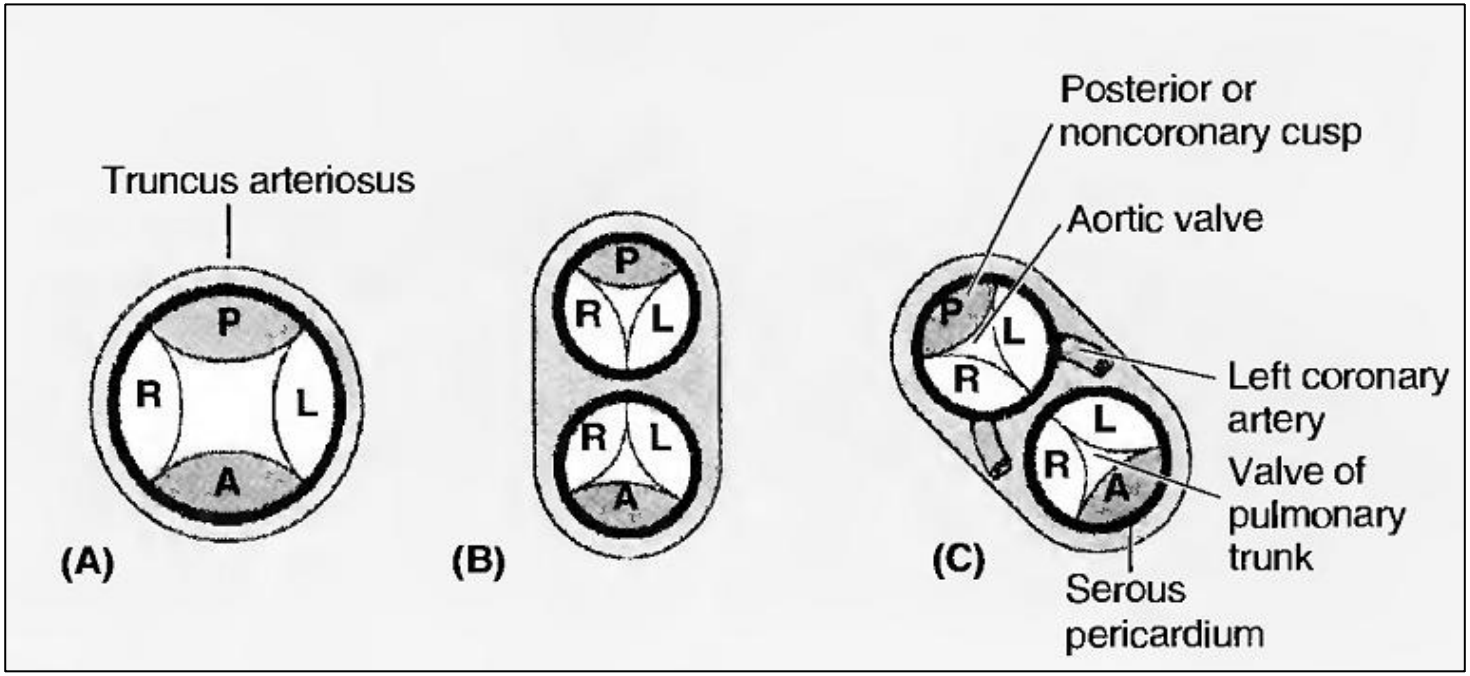


Fig.21: The position of the cusps of the semilunar valves. R and L are the right and left truncal swellings, respectively. A and P are the anterior and posterior truncal swellings. After formation of the aorticopulmonary septum, the A and P swellings divide into two pairs, one for each artery. In later development (C), the truncus will rotate and the cusps will obtain their adult position.

Development of the Vessels

- Blood vessels are formed by two mechanisms:

1. ***Vasculogenesis***. In addition to the ***heart tubes***, two longitudinal tubes are formed by vasculogensis on each side of the embryo's midline dorsally; these are called the ***right and left dorsal aortae*** (Fig.4). As lateral folding of embryo occurs, the two dorsal aortae fuse caudally to form a single midline dorsal aorta (Figs.5c). Cranially, the right and left dorsal aortae remain separate. The ***cardinal veins*** are also formed by vasculogenesis.

2. ***Angiogenesis***, by which new vessels arise from existing vessels. All other vessels in the body are formed by angiogenesis.

Development of the Arterial System

- The dorsal aortae are related to three groups of arteries (Fig.23):

1. ***Aortic arches***. These pass through the developing pharyngeal arches and connect the right and left dorsal aortae to the aortic sac.
2. ***Intersegmental arteries***. These are 30 paired branches of the dorsal aortae that supply the somites.
3. ***Splanchnic arteries***. Lateral and ventral branches that supply various organs of the body.

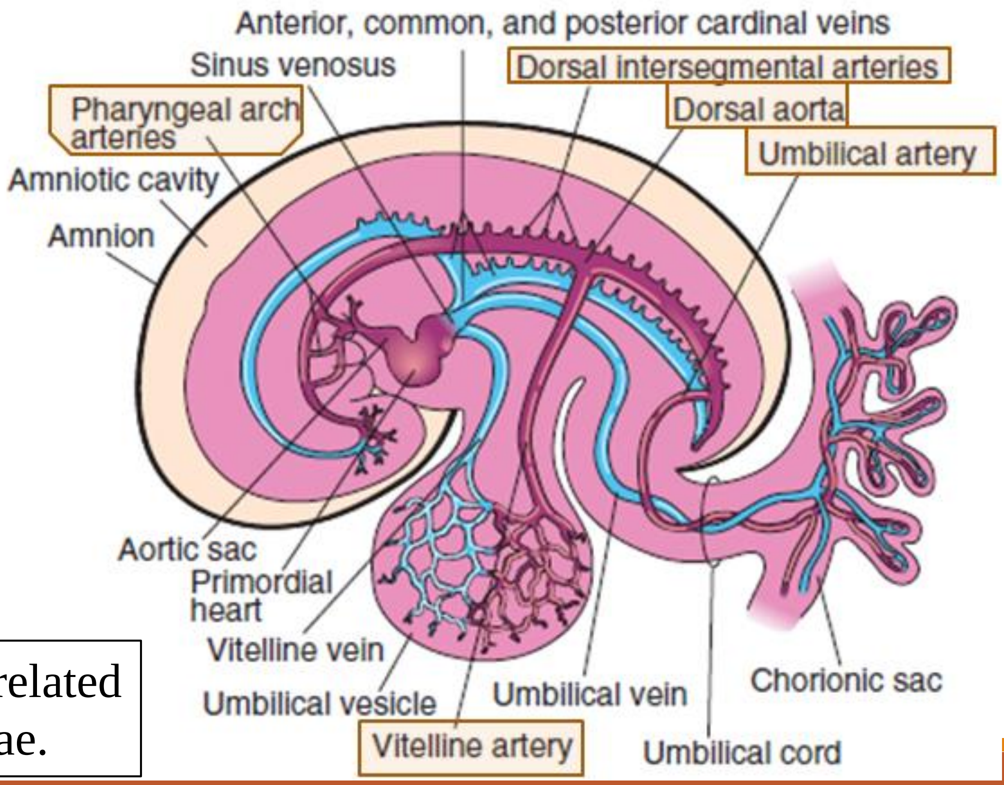


Fig.22: Arteries related to the dorsal aortae.

The Aortic Arches

- As the pharyngeal arches form during, they receive their own blood supply through the aortic arches which connect the aortic sac to the dorsal aortae.

- The arches appear in a cranial-to-caudal sequence, thus not all the aortic arches appear at the same time.

- Six arterial arches appear. The fifth arch, however, soon disappears (or may never form at all).

- The aortic arches give rise to various vessels in the thorax, neck, and head (Fig.23).

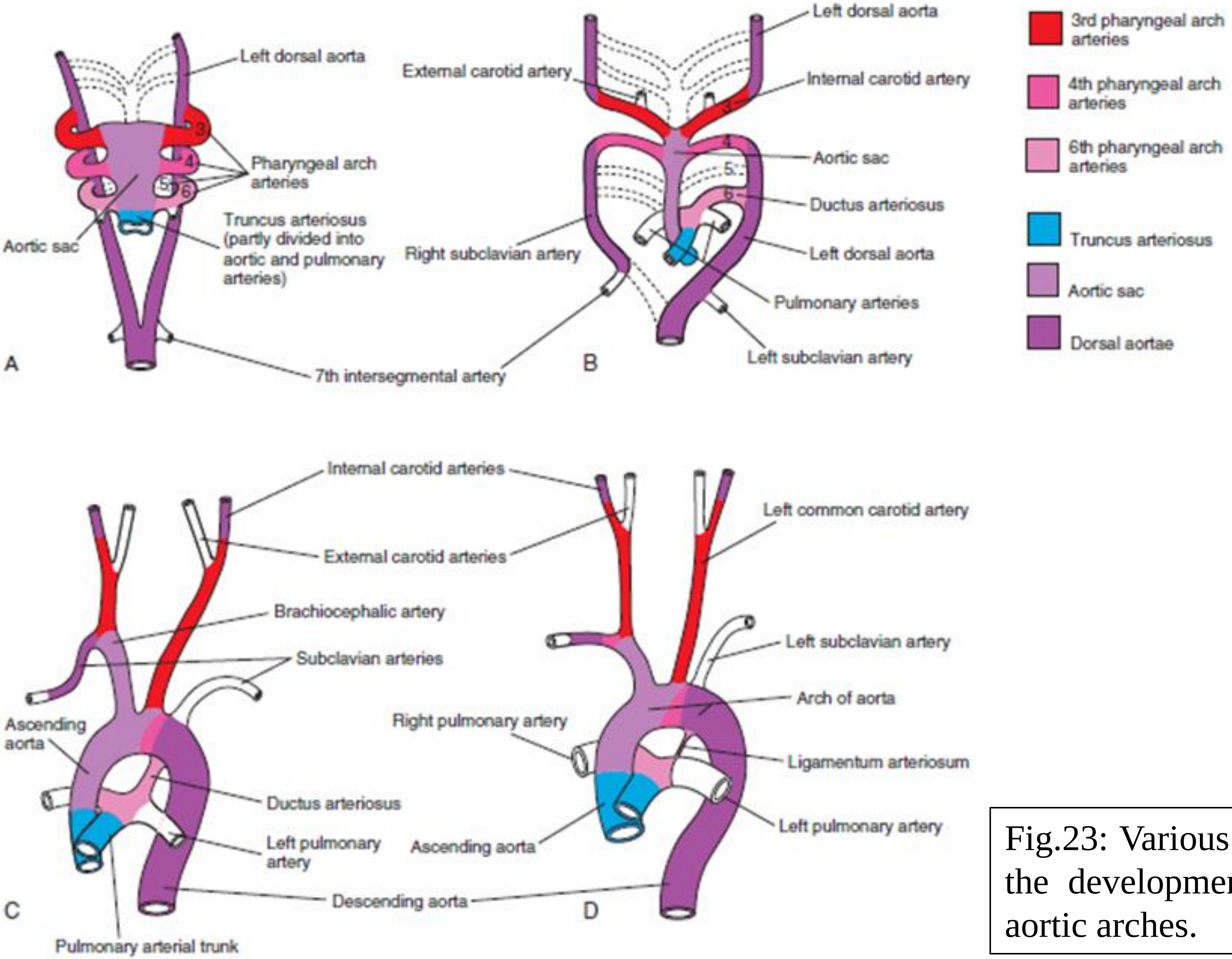


Fig.23: Various stages in the development of the aortic arches.

Clinical Correlation

- The recurrent laryngeal nerve hooks around the 6^{th} aortic arch.
- On the right side, the distal part of the 6^{th} arch and the 5^{th} arch disappear. The nerve becomes hooked around the 4^{th} aortic arch.
- On the left, the whole 6^{th} arch remains and the nerve becomes hooked around the ductus arteriosus.
- Because of this, when the adult derivatives of the arches are formed, the recurrent laryngeal nerve hooks around the subclavian artery on the right and the ligamentum arteriosum on the left.

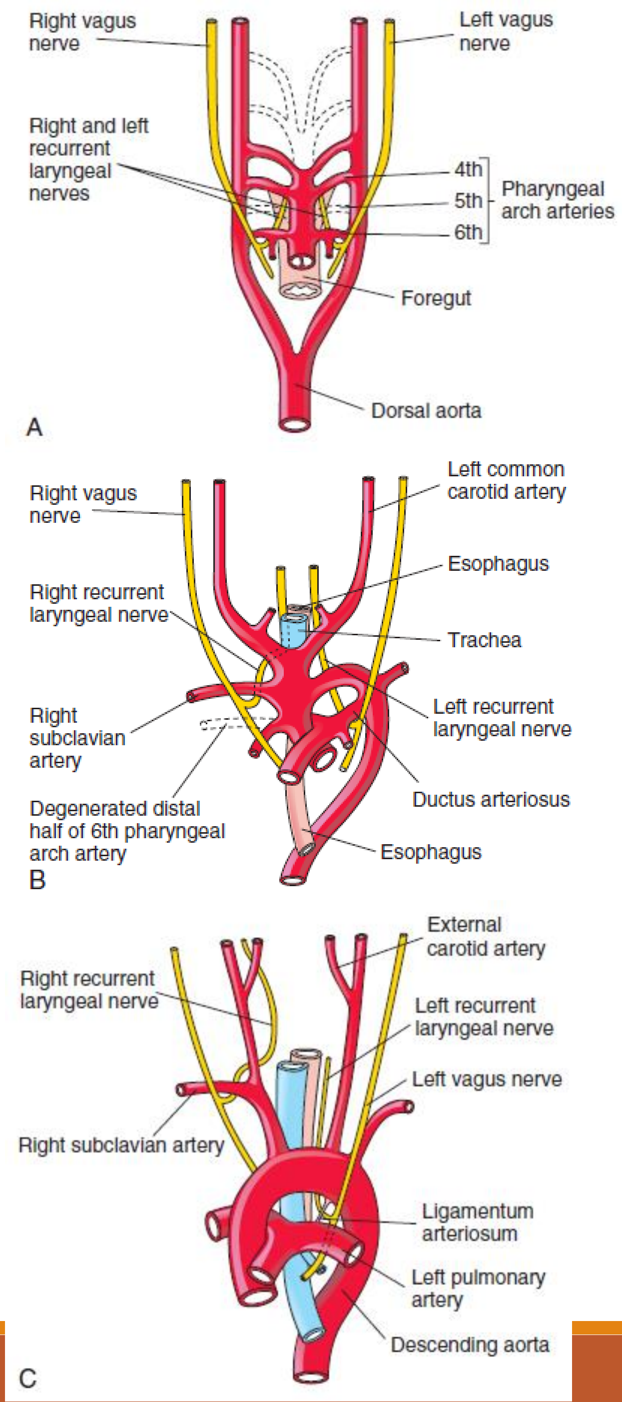


Fig.24: Relation of the recurrent laryngeal nerve to the aortic arches.

The Intersegmental Arteries

- Thirty branches of the dorsal aorta that carry blood to the somites and their derivatives.

- The arteries in the ***neck*** (the first 6) join to form a longitudinal artery on each side that is attached to the 7th intersegmental artery. This longitudinal artery will form the ***vertebral artery***. The original connections of the arteries to the dorsal aorta disappear (Fig. 25).

- In the ***thorax***, the intersegmental arteries persist as the ***intercostal arteries***.

- The lumbar and sacral intersegmental arteries form various arteries in those regions.

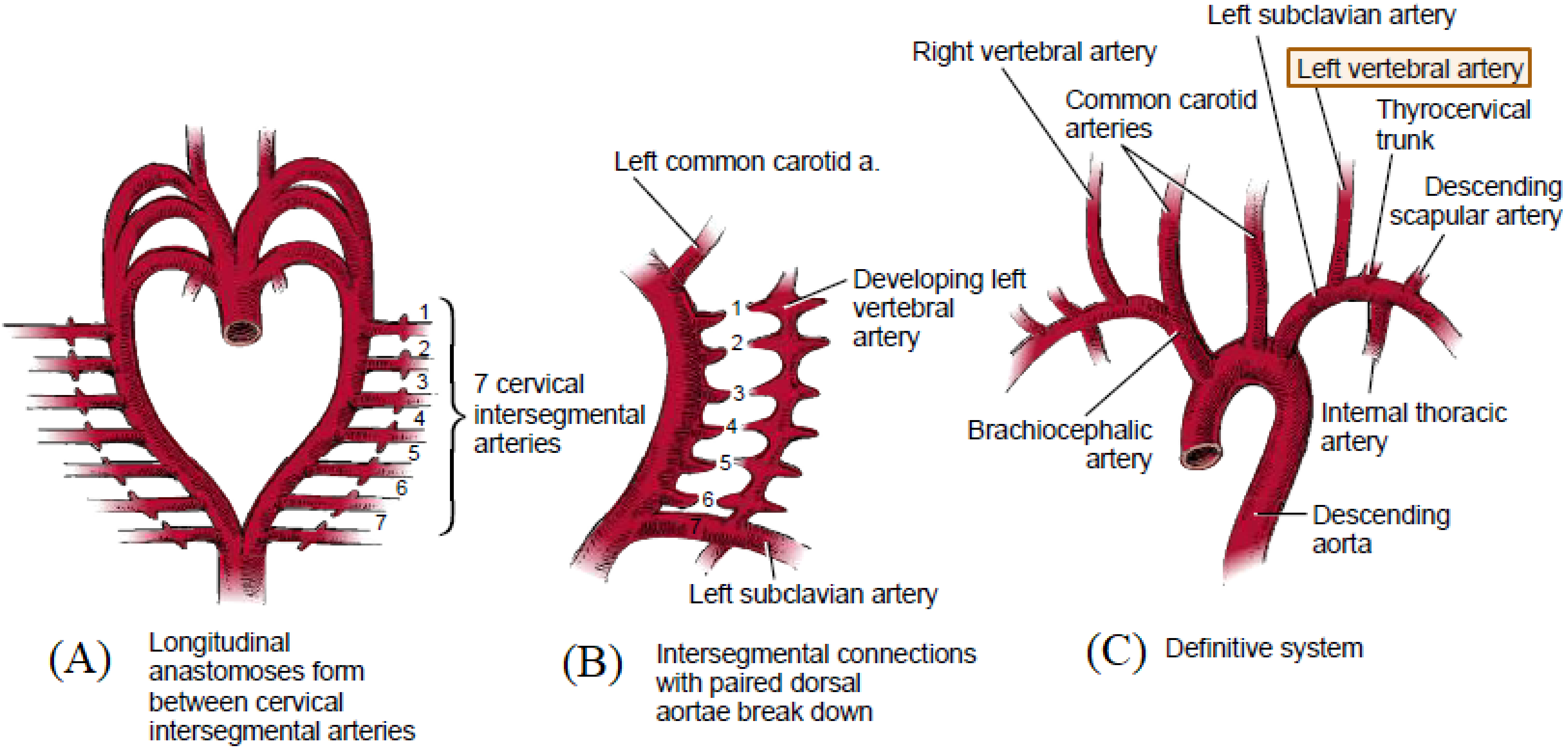


Fig.25: Development of the vertebral artery from the cervical intersegmental arteries. Notice in (C) how the vertebral artery is a branch of the subclavian.

Splanchnic Arteries

- The ***vitelline arteries*** pass to the umbilical vesicle and later to the primordial gut. Most of these arteries fuse to form three single ventral branches of the aorta: the ***celiac trunk***, the ***superior mesenteric artery***, and the ***inferior mesenteric artery***.

- The paired ***umbilical arteries*** pass ventrally through the connecting stalk (primordial umbilical cord) and become continuous with vessels in the chorion. Soon these arteries will lose their connection to the aorta and become connected to the common iliac arteries. The proximal parts of these arteries become the ***internal iliac*** and ***superior vesical arteries***. The distal parts of the umbilical arteries become modified and form the ***medial umbilical ligaments***.

- ***Lateral splanchnic branches*** form the ***phrenic***, ***suprarenal***, ***renal***, and ***gonadal*** arteries.

Development of the Venous System

- The heart receives venous blood through 3 pairs of veins: (1)vitelline veins, (2)umbilical veins, and (3)common cardinal veins (Fig.13).

- Later in development, two more venous systems develop: (1)supracardinal and (2)subcardinal.

- Venous anastomoses are formed between the right and left sides of these systems and between each other.

- Most of the veins on the left will disappear and venous blood is shifted to the right side.

Vitelline Veins

- The right and left vitelline veins carry deoxygenated blood from the umbilical vesicle and later the gut tube. They form a plexus around the duodenum (Fig.26a), then pass through the septum transversum before entering the sinus venosus.
- As the liver grows in this region, it will interrupt these veins leading to the formation of a network of venous spaces, the ***hepatic sinusoids***, which are drained through the right and left ***hepatocardiac channels*** into the sinus venosus (Fig.26b).
- With reduction of the left sinus horn, the left hepatocardiac channel will become smaller and form the ***left hepatic vein***. The prehepatic part of the left vitelline vein will disappear (Fig.26c,d).
- The right hepatocardiac channel will enlarge and form the ***right hepatic vein*** and the ***terminal part of the inferior vena cava***. The prehaptic part of the right vitelline vein will form the ***portal vein*** (Fig.26d).

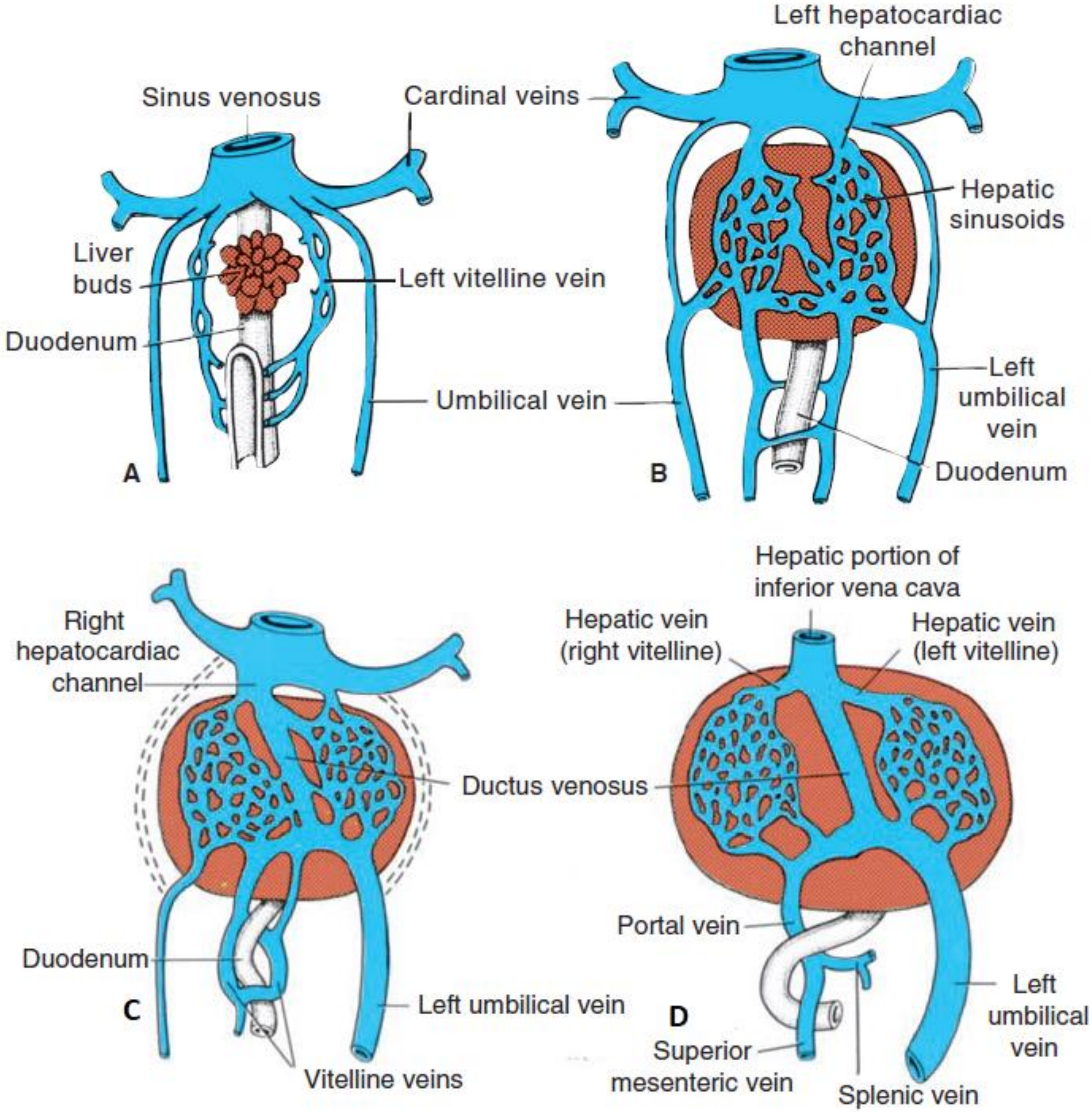


Fig.26: Development of the portal circulation from the vitelline veins.

Umbilical Veins

- The right and left umbilical veins carry well-oxygenated blood from the placenta. They pass through the septum transversum to drain into the sinus venosus.

- Initially, the umbilical veins pass on each side of the liver, with some connections to the hepatic sinusoids (Fig.26a,b).
- With further development, the entire right umbilical vein and the cranial part of the left umbilical vein disappear. The caudal part of the left vein persists becoming the only vessel to carry blood from the placenta to the liver (Fig.26c,d).
- A direct communication forms between the left umbilical vein and the right hepatocardiac channel, the ***ductus venosus*** (Fig.26d).

- After birth, the left umbilical vein and the ductus venosus will form the ***ligamnetum teres*** and ***ligamentum venosum***, respectively.

Cardinal Veins

- These carry deoxygenated blood from the body of the embryo.
- The anterior and posterior cardinal veins carry blood from the cranial and caudal parts of the embryo, respectively. They unite to form the common cardinal veins which open into the sinus venosus.

- An ***oblique anastomosis*** is formed between the anterior cardinal veins that shunts the blood from the left to the right. This shunt will form the ***left brachiocephalic vein***. The ***anterior cardinal veins*** will form the ***internal jugular veins***. The ***right common cardinal and part of the right anterior cardinal veins*** will form the ***superior vena cava*** (SVC).

- The ***posterior cardinal veins*** will largely disappear.

- The ***supracardinal*** and ***subcardinal*** veins will form various veins in the body.

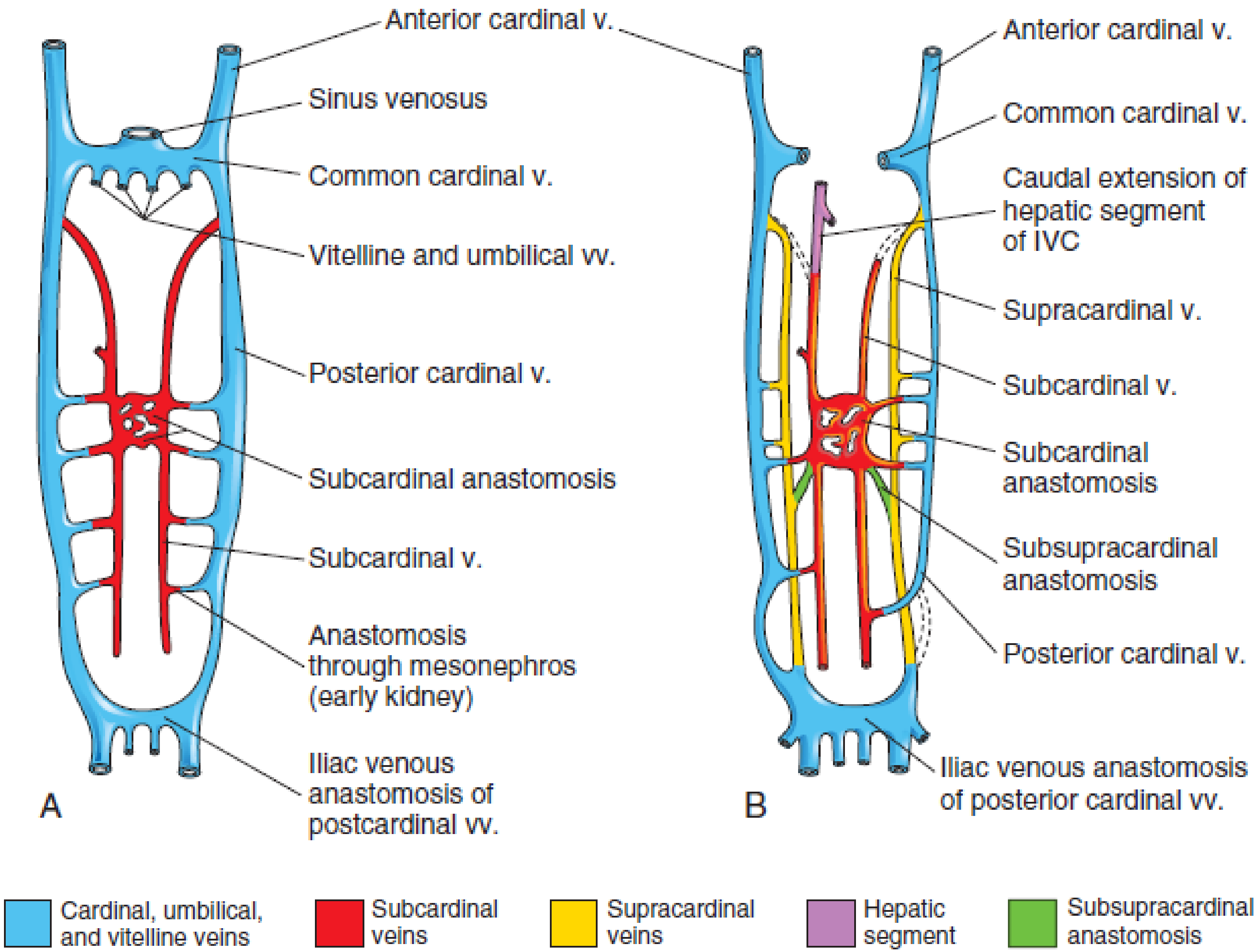


Fig.27: Development of the cardinal veins. Continued on next slide.

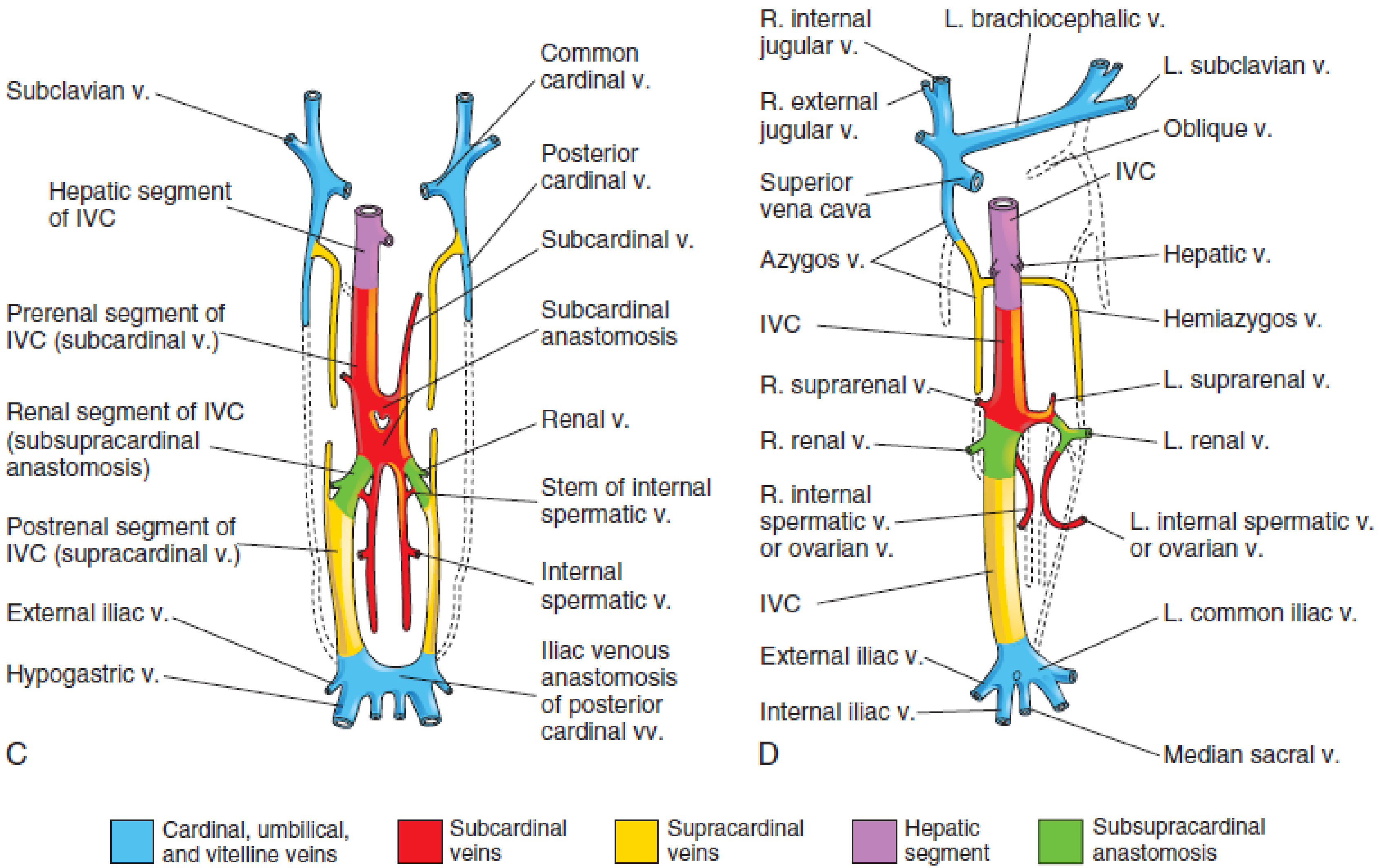


Fig.27: Continued from previous slide. Note in (D), the various parts of the inferior vena cava.

Fetal Circulation

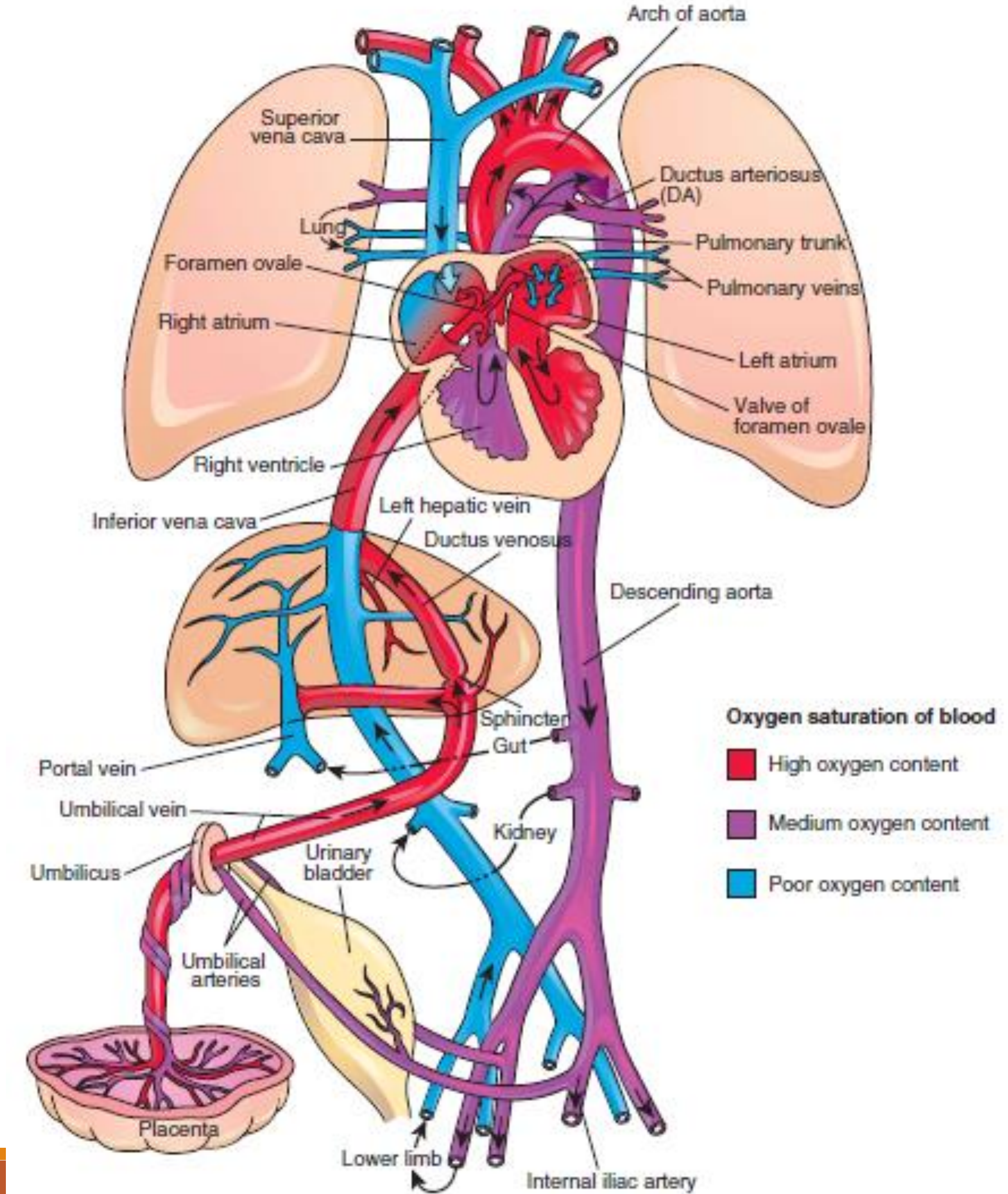
- Highly oxygenated, nutrient-rich blood returns under high pressure from the placenta in the umbilical vein. On reaching the liver, most of the blood passes through the ductus venosus into the IVC, bypassing the liver. This is controlled by a sphincter. The rest of the blood passes into the liver sinusoids to enter the IVC through the hepatic veins. *In the liver there's a mixture with poorly-oxygenated blood coming through the portal vein*.
- After a short course in the IVC, the blood enters the RA of the heart. *In the IVC, blood is mixed with poorly oxygenated blood from the lower limbs, abdomen, and pelvis*.
- In the RA, most of the blood is directed by the valve of the IVC into the LA through the foramen ovale. *In the LA*, *it's mixed with small amount of poorly oxygenated blood from the lungs through the pulmonary veins*.

- This blood, still with good oxygenation, passes into the LV and then into the aorta where it supplies the head, neck, and upper limbs. After that, it reaches the descending aorta.

- Some of the blood in the RA, stays in the RA and is *mixed with poorly oxygenated blood coming through the SVC*. This, then, passes into the RV and the pulmonary trunk. Due to high resistance in the pulmonary vessels, most of this blood passes through the ductus arteriosus to enter the descending aorta.

- Medium-oxygenated blood in the descending aorta supplies the trunk and lower limbs.

- Blood leaves the fetus through the umbilical arteries to enter the placenta to be oxygenated.



In the fetal circulation, well oxygenated and poorly oxygenated blood are mixed in the:

- Liver
- IVC
- RA
- LA

Fig.28: Fetal circulation.

Changes after birth

1. When the neonate takes a breath, the resistance in the pulmonary vessels decreases and more blood passes through the lung. This increases pressure in the LA. At the same time, the umbilical vein is cut reducing blood flow and pressure in the RA. This will push the septum primum against the septum secundum closing the foramen ovale. Anatomical fusion will occur later forming the fossa ovalis.

2. Hypoxia in the lungs keeps the ductus arteriosus open during fetal life. When oxygen enters the lungs after birth, the ductus will constrict and later become fibrosed to form the ligamentum arteriosum.

3. The umbilcal vein becomes the ligamentum teres and the ductus venosus becomes the ligamentum venosum.

4. The distal parts of the umbilical arteries form the medial umbilical ligaments with the proximal parts forming the superior vesical arteries.

Thank You