6. HEART AND CIRCULATORY SYSTEM I

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RECOMMENDED READING: Larsen Human Embryology, 3rd Edition, pp. 195-199; 157-169 top left; 172-174; bottom 181-182; 187-top 189, Simbryo-cardiovascular system

SUMMARY: The circulatory system, consisting of heart, blood vessels, and blood cells is the first functional organ to develop. This lecture will focus on the formation of the embryonic vasculature, the origin and formation of the early heart tube and primitive cardiac chambers, cardiac looping, and the primitive circulation. Between the 5^{th} - 8^{th} week of embryonic development, the tubular heart is remodeled into a four chambered structure. We will see how right and left atrioventricular canals connect each atrium with its respective ventricle, and how the atrial septum and definitive right and left atria form. We will also see why the great veins deliver blood to the right atrium while the pulmonary veins empty into the left.

GLOSSARY:

Angioblasts: precursors of blood vessels
Angiogenesis: lengthening, branching, sprouting and remodeling of embryonic blood vessels
Aortic arches: paired arteries surrounding the pharynx; portions will contribute to formation of the great arterial vessels
Blood islands: clusters of cells in the yolk sac, connecting stalk and chorionic villi that form primitive blood vessels
Cardiac jelly: gelatinous extracellular matrix that forms the middle layer of the heart tube
Ductus venosus: shunts most of the blood in the umbilical vein into the inferior vena cava (IVC) (by-passing the liver sinusoids)
Hemangioblasts: earliest precursors of blood cells
Intussusception: incorporation of one structure into another
Vasculogenesis: formation of blood vessels in the embryonic disk

LEARNING OBJECTIVES:

At the end of the lecture you should be able to:

1) Describe the origin and morphogenesis of the primitive embryonic cardiovascular system, including the formation of embryonic blood vessels, the heart tube, cardiac looping, formation of primitive heart chambers and the early embryonic circulatory system.
2) Describe the structural remodeling of the primitive heart and circulatory system.

3) Explain why the inferior and superior vena cavae, as well as the coronary sinus, empty into the right atrium and the pulmonary veins empty into the left atrium.
4) Describe the origin and role of endocardial cushions, the formation of the right and left atrioventricular canals as well as the septum intermedium.
5) Discuss the formation, structure and function of the fetal atrial septum.

INTRODUCTION: Formation of the cardiovascular system begins during the 3rd week of gestation and is completed by the end of the 8th week (<u>refer to the chronological table in Chapter 7</u>). The ventricular and atrial cardiac musculature, the endocardial cushions, the Purkinje conducting fibers and the endothelial lining of the heart (endocardium) are derived from mesoderm. Portions of the aorta, pulmonary trunk, and vascular walls of the aortic arch derivatives are formed from neural crest.

<u>The first trimester:</u>

a) Vitelline stage (3^{rd} – 4^{th} week): Formation of blood and blood vessels begins in the mesodermal wall of the yolk sac as well as in the wall of the chorion outside the embryo proper (**Figure 6-1**). The yolk sac (the first hematopoietic region) provides nutrients via vitelline vessels while the placenta is forming. Vasculogenesis begins in the splanchnic mesoderm of the embryonic disc.

b) By the beginning of the 5th week, the placenta provides nutrients, O_2, etc. Cardiogenesis is well underway and the embryonic circulation is functional. The liver takes over the role of hematopoiesis.

c) Structures designed to facilitate separate systemic and pulmonary circulations form between the 5^{th} and 8^{th} weeks of gestation, although a dual pump is not operational until immediately after birth.

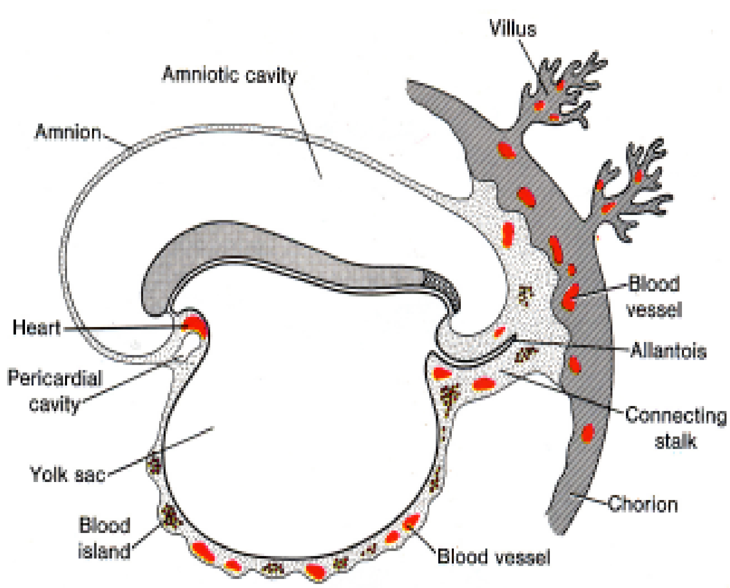

Fig. 6-1. Extra-embryonic blood vessel formation in the chorion, the connecting stalk, and the wall of the yolk sac in a presomite embryo of approximately 19 days (modified from Keibel and Elze). Note the position of the pericardial cavity and developing heart.

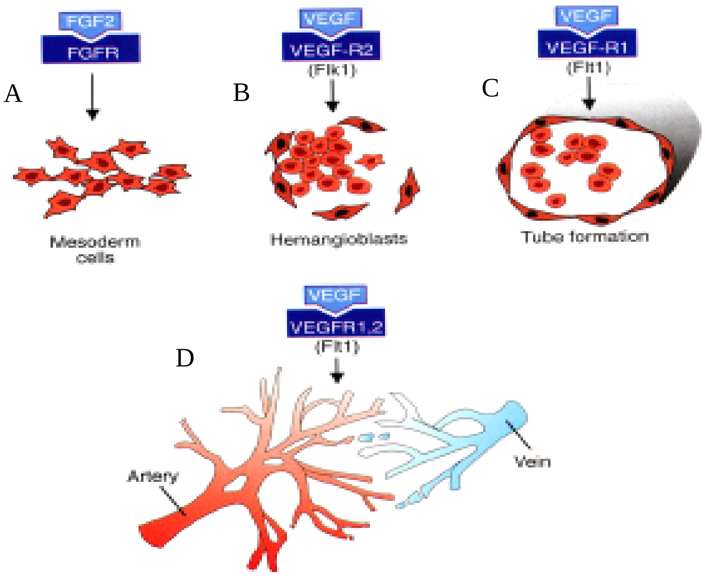

Fig. 6-2, A-C. Vasculogenesis: blood vessels and blood cells form de novo. **D.** Angiogenesis: new vessels sprout from existing ones.

I. Blood vessel formation

During the third week of development, blood vessels form in blood islands in the extra-embryonic regions of the chorion, the connecting stalk, and the wall of the yolk sac, which is the first hematopoietic region in the embryo (**Figure 6-1**). The primitive blood vessels bring nutrients to the embryo and transport gases to and from sites of respiratory exchange. Blood vessel formation begins in the embryonic disc prior to somite formation. Extra-embryonic blood vessels eventually merge with those of the embryo.

Blood vessels develop in three ways.

a) Vasculogenesis: Fibroblast growth factor 2 (FGF-2) binds to its receptor (FGFR) on subpopulations of mesoderm cells and induces them to form pluripotent **hemangioblasts (Figure 6-2A)**. Under the influence of vascular endothelial growth factor (VEGF) acting through two different receptors, the hemangioblasts segregate into an inner core of primitive nucleated blood cells **(Figure 6-2B)** surrounded by presumptive endothelial cells **(Figure 6-2C)** that coalesce to form primitive blood vessels.

b) Angiogenesis: VEGF stimulates proliferation of endothelial cells at places where vessels sprout from existing ones **(Figure 6-2D)**.

c) Vascular precursors called angioblasts migrate into organs from other regions.

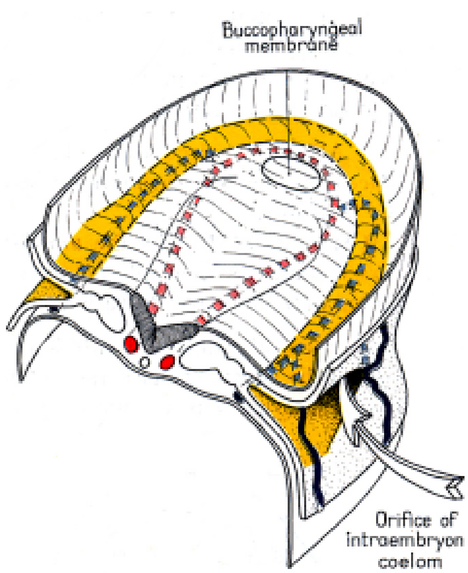

Fig. 6-3. Cleavage of the lateral plate by the coelom reaches the cardiac region, bringing about differentiation of the splanchnopleure and the somatopleure. These form the walls of the future pericardial cavity.

II. <u>Formation of heart tube:</u>

REVIEW (See lecture 2). **Precardiac mesoderm** emerges from the early primitive streak just posterior to the primitive node and reaches a position rostral and anterior to the prochordal plate (future buccopharyngeal membrane) forming a **cardiac primordium (cardiac crescent) (Figure 6-5A)**. The intraembryonic coelom divides the mesoderm into splanchnopleure and somatopleure. The cardiac primordium is included in splanchnopleure (**Figure 6-3**).

<u>The primitive heart tube:</u>
Vasculogenesis occurs within the cardiac primordium creating bilateral **endocardial tubes**. Formation of the **dorsal aortae** occurs simultaneously, close to the notochord. Transverse (**Figure 6-4**) and cephalo-caudal flexion (**Figure 6-5**) results in formation of the foregut and intraembryonic coelom. During this process, the two endocardial tubes are carried ventral to the closing gut tube.

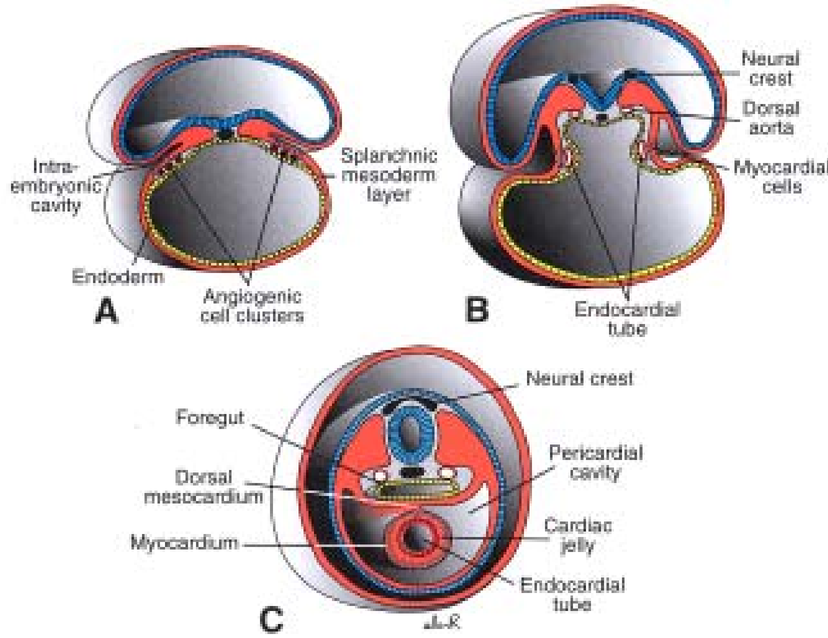

Fig. 6-4. Transverse sections through embryos at different stages of development, showing formation of a single heart tube from paired primordia. A. Early presomite embryo (17 days). B. Late presomite embryo (18 days). C. Eight-somite stage (22 days).

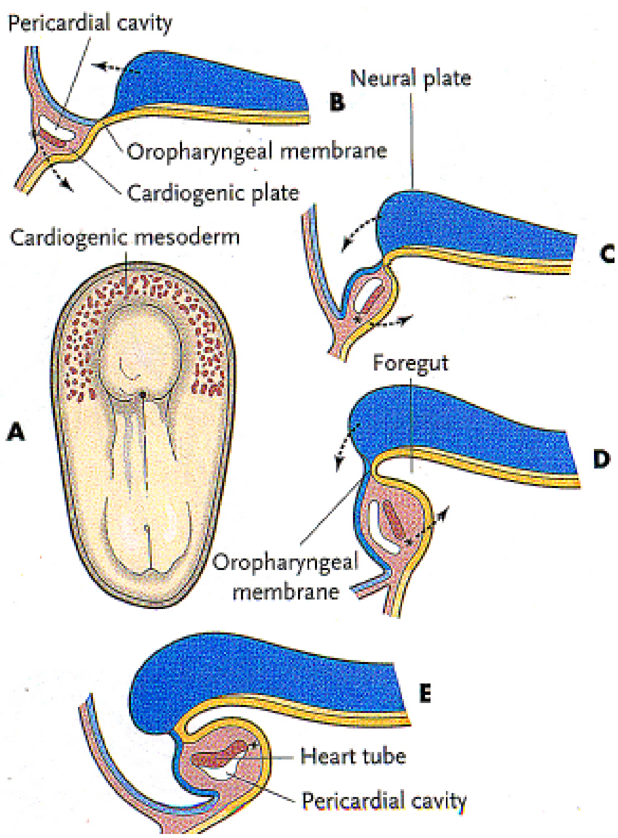

Fig.6-5. A, Dorsal view of a late presomite embryo (about 18 days) after removal of the amnion. Vasculogenesis, occurring in cell clusters formed in the splanchnic mesoderm in front of the neural plate on each side of the embryo, is visible through the overlying ectoderm and somatic mesoderm layer. B, Cephalocaudal section through a similar embryo showing the position of the presumptive pericardial cavity and cardiogenic area (18 days). C-E, Changes in the position of the heart and pericardial cavity during head folding. The heart tube rotates 180^{o} to reach a position ventral to the foregut, caudal to the oropharyngeal membrane and suspended in the dorsal portion of the pericardial cavity (20-22 days).

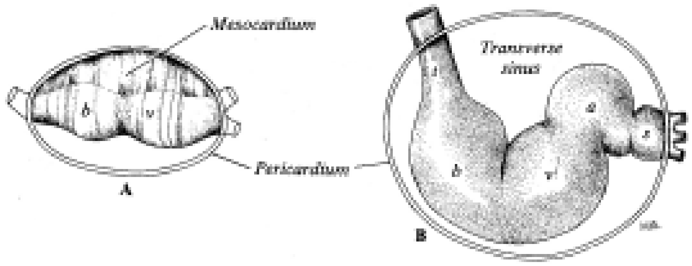

Fig. 6-6. Slide views of the heart: A, before, B, following loss of the mesocardium. a, common atrium; b, bulbus cordis; s, sinus venosus; t, truncus arteriosus; v, ventricle.

Apoptosis in portions of each of the tubes results in their fusion to form a **single heart tube** suspended by a temporary dorsal mesocardium in the newly formed **pericardial cavity (Figure 6-4)**. Fusion occurs in a cranial-caudal direction. Rapid growth of the central nervous system causes rotation of the heart tube and pericardial cavity 180^{o} ventral and caudal to the oropharyngeal membrane (**Figure 6-5**).

b) The straight cardiac tube consists of an inner endocardocardial lining (endothelium) separated from the cardiac mesoderm (future myocardium) by a gelatinous hyaluronate-rich **cardiac jelly (Figure 6-4C)**. Cardiac mesoderm secretes the **cardiac jelly** that provides structural support and nutrients for the endocardial lining. **BMP signaling** promotes cardiac myogenesis (muscle formation)and is required later, during cardiac morphogenesis. Interestingly, the epicardium is derived from the **proepicardial** primordium, located near the dorsal mesocardium, and not from the heart tube. Cells migrating from the proepicardium cover the surface of the tubular heart. The dorsal mesocardium breaks down creating the **transverse sinus** of the pericardial cavity (**Figure 6-6**). The heart tube is now attached to the pericardial cavity only at its caudal and rostral ends. At its caudal end, the endocardial tubes do not fuse, but extend toward the posterior part of the embryo as the venous (afferent) inflow tracts of the heart. At its cranial end, the endothelial tube leading out from the heart produces pairs of vascular **aortic arch arteries** that loop from the ventral to the dorsal side of the pharynx.

c) A series of dilations and constrictions appear in the wall of the straight heart tube (Figure **6-7A**). Starting at the caudal (venus) end, these are: the **sinus venosus**, a **primitive atrium** (both still

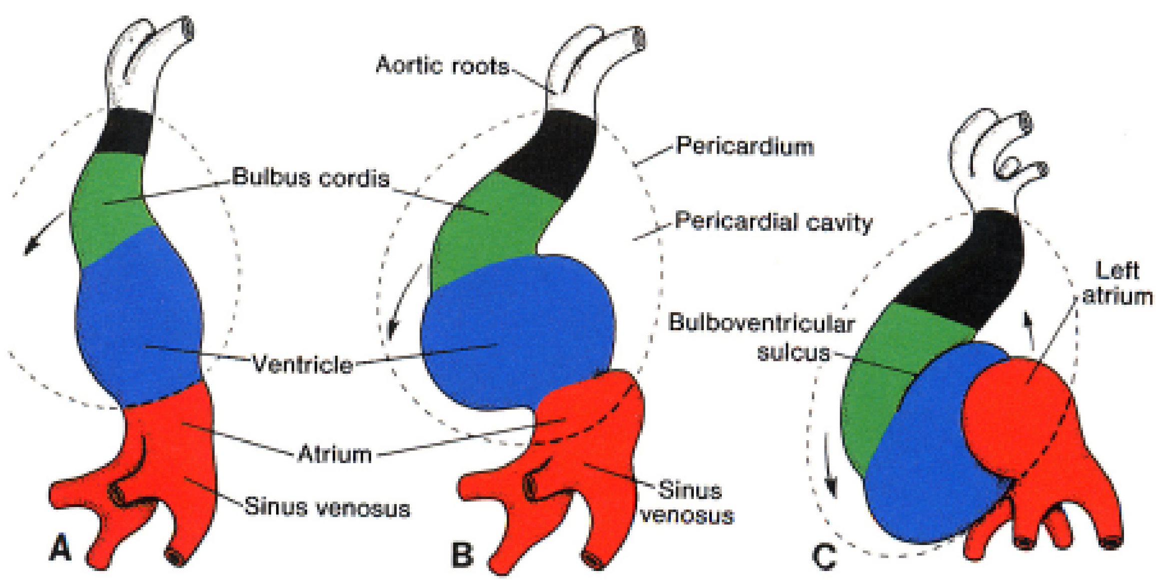

Fig. 6-7. Formation of the cardiac loop. (A) At 8 somites, (B) 11 somites**,** and (C) 16 somites. Broken line indicates pericardium. Note how the atrium gradually assumes an intrapericardial position.(Modified from Kramer (2).

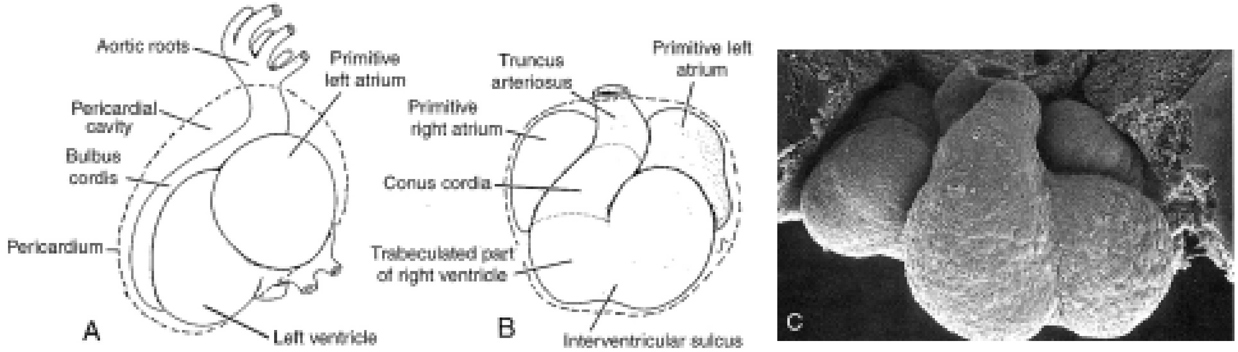

Fig. 6-8. The heart of a 5-mm embryo (approximately 28 days). (A) Seen from the left, (B) in frontal view. (Modified from Kramer (2). Note that the bulbus cordis is divided into: (a) the truncus arteriosus, (b) the conus cordis, and (c) the trabeculated part of the right ventricle.

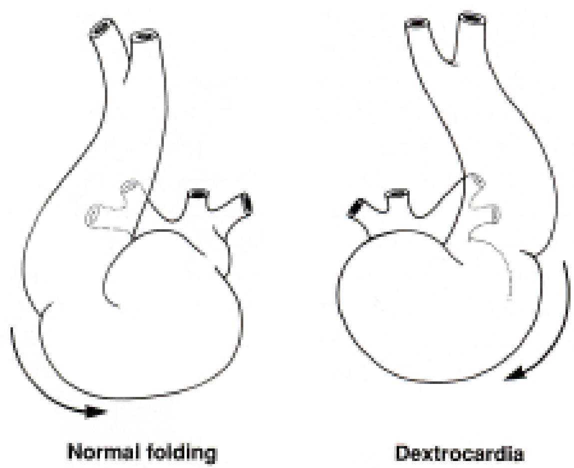

Fig. 6-9.

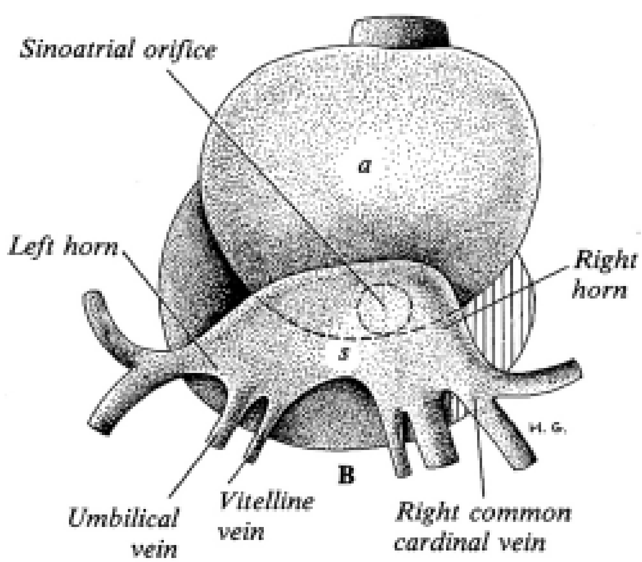

Fig.6-10. The heart at four weeks: dorsal view. a, common atrium; S, sinus venosus; v, ventricle. (Adapted from Kramer TC: Am J Anat 71:343, 1942)

exterior to the pericardial cavity) a **primitive ventricle**, the **bulbus cordis** and **aortic sac** from which the **first aortic arches** emerge.

III. Cardiac Looping (Figures 6-7, 8, 9)

The heart is the first organ system to acquire an asymmetrical shape. On about day 23, portions of the heart tube elongate and loop (fold) toward the left (**normal dextral looping**) to form an S shape). The bulbus cordis elongates and is displaced to the right (inferior and anterior) of the primitive ventricle which is displaced to the left. The proximal end of the bulbus cordis forms the **primitive right ventricle**. The mid portion of the bulbus forms the **conus cordis** (future aortic vestibule and infundibulum). The distal portion of the bulbus forms the **truncus arteriosus**, (future ascending aorta and

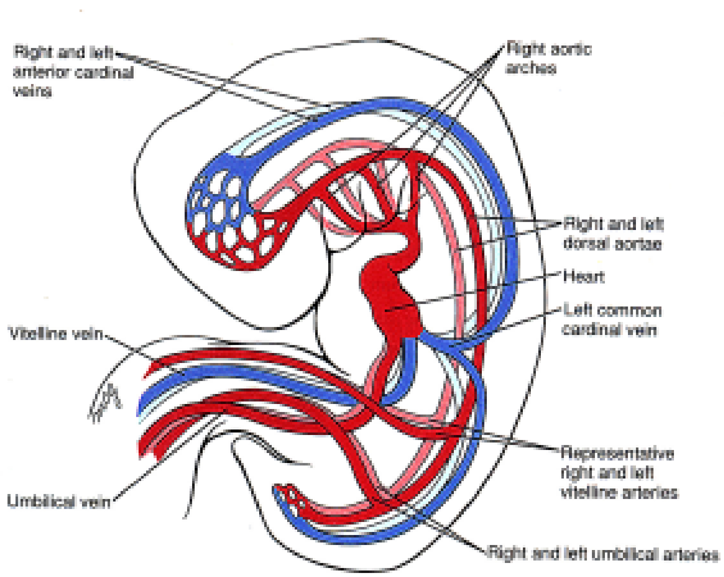

Fig. 6-11. Schematic depiction of the embryonic vascular system in the middle of the fourth week. The heart has begun to beat and to circulate blood. The outflow tract of the heart now includes four pairs of aortic arches and the paired dorsal aortae that circulate blood to the head and trunk. Three pairs of veins—the umbilical, vitelline, and cardinal veins—deliver blood to the inflow end of the heart.

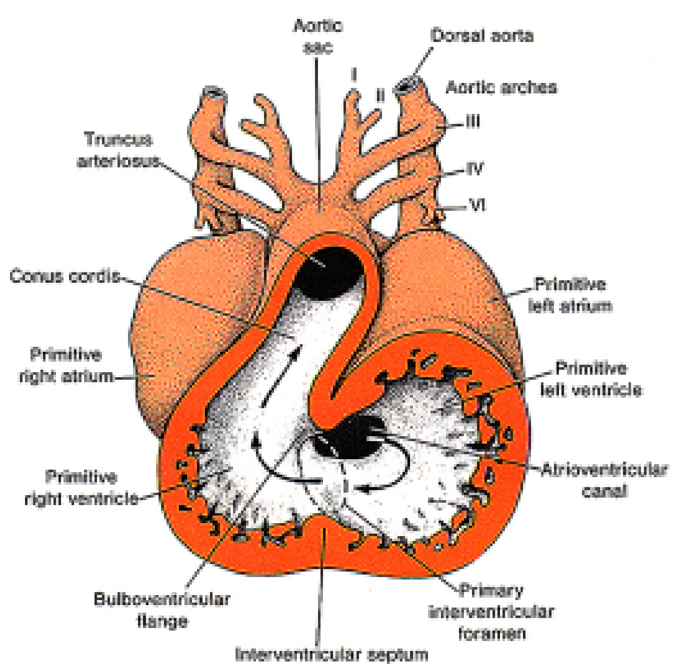

Fig. 6-12

pulmonary trunk). As the heart loops, the primitive atrium and sinus venosus ascend and enter the pericardial cavity (**Figures 6-7C &6-8A**) posteriorly and superiorly to the primitive ventricle. The single atrium then dilates on either side of the of the truncus arteriosus (**Figures 6-8B,C**). If the heart loops in reverse, i.e. loops right instead of left, the left ventricle is displaced to the right, a condition known as **dextrocardia (Figure 6-9)**. Left-right patterning proteins (Nodal, Lefty-2) and several transcription factors (e.g. Nkx-2-5, MEF-2, HAND 1 and HAND 2) are required for correct dextral looping. Null mutations of these transcription factors block heart development at the stage of looping.

As the heart loops, **myofibrils** begin to form and beating begins (Day 22-23). At first this beat is irregular; functional circulation and rhythmic beating occurs between Days 27-29. The pacemaker for this contraction is located in the sinus venosus. Research on chick embryos has shown that endothelin-1, secreted by the coronary arteries, stimulates cardiacmyocytes to transform into cells of the conducting system. In mice, cells of the conducting system appear very early and may begin functioning before septation of the heart is completed.

IV. <u>The primitive cardiovascular system at the end of the 4th week</u> (Figures 6-10, 11, 12, 13)

a) Although the heart now resembles its future exterior shape, it is still an unpartitioned tube through which blood flows in a single stream. Oxygenated blood returning from the placenta enters both horns of the sinus venosus via paired left and right **umbilical veins**. Paired **vitelline veins** deliver blood from the yolk sac. The **anterior cardinal veins (CV)** drain the head and neck; the **posterior CVs** drain the body wall and developing kidneys. These bilateral embryonic vessels enter the **right**

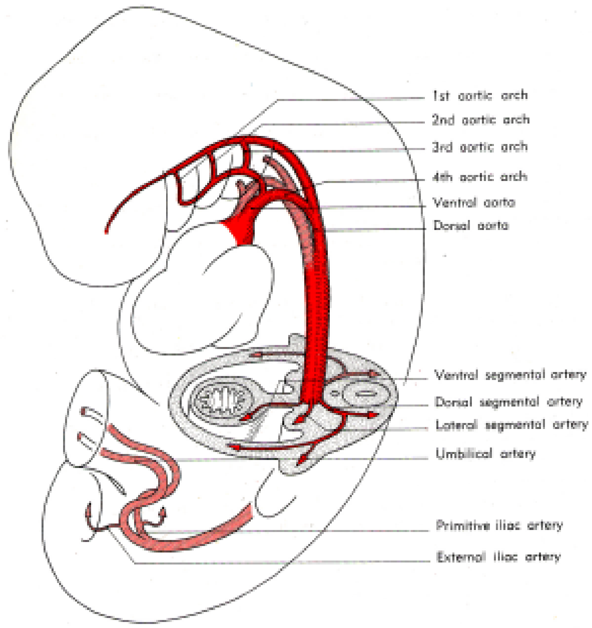

Fig. 6-13. Arterial system of a human embryo of 30 days.

and left sinus horns of the sinus venosus via the **right and left common CVs**, respectively. From the sinus venosus, blood enters the primitive atrium via the **sinoatrial orifice** and then after passing through the **atrioventricular canal (AV canal)**, enters first the primitive left and then the right ventricle. Blood then flows through the conus cordis and truncus arteriosus to emerge from the aortic sac and aortic arches. **Aortic arches 3, 4**, and **6** develop sequentially (aortic arches 1 and 2 regress, 5 never exists) (**Figure 6-12**). The 4th aortic arches are continuous with 2 **dorsal aortae**, which merge from T4 to L4 and send branches to the developing embryonic tissues and organs (**Figure 6-13**). Two **umbilical arteries** return blood to the developing placenta where it will be re-oxygenated, etc. (**Figures 6-11, 6-13**).

<u>SEPTATION AND REMODELING</u> These topics will be introduced during the remainder of this lecture and will continue to be described during the next one (HD 7). Briefly, the CV is totally remodeled between the 30th and 49th days of gestation (E30-E49) and the heart is partitioned into four chambers (a process sometimes referred to as **septation**). Although described separately, septation of the heart chambers occurs more-or-less concurrently. During this time the system is functional, supplying the growing embryo and its developing organs with nutrients and oxygen and collecting metabolic wastes. Moreover, although it is redesigned to form separate systemic and pulmonary circulations, the latter is not required in utero where maternal blood, and not the lungs, is the source of oxygen. The two circulations become functionally distinct at birth although anatomical separation may not occur until several months later.

V. <u>Formation of the great veins and smooth walled portions of both atria.</u> (Figures 6-10, 6-14, 6-15, 8-16)

Recall that at the end of the 4th week, 3 pairs of veins enter the right and left horns of the sinus venosus via the common cardinal veins: the vitelline veins, the umbilical veins, and the cardinal veins. Blood passes from the sinus venosus to the common atrium through the sinoatrial orifice **(Figure 6-10).**

a) **(Figure 6-14)** At the time atrial septation begins (see IV below), 3

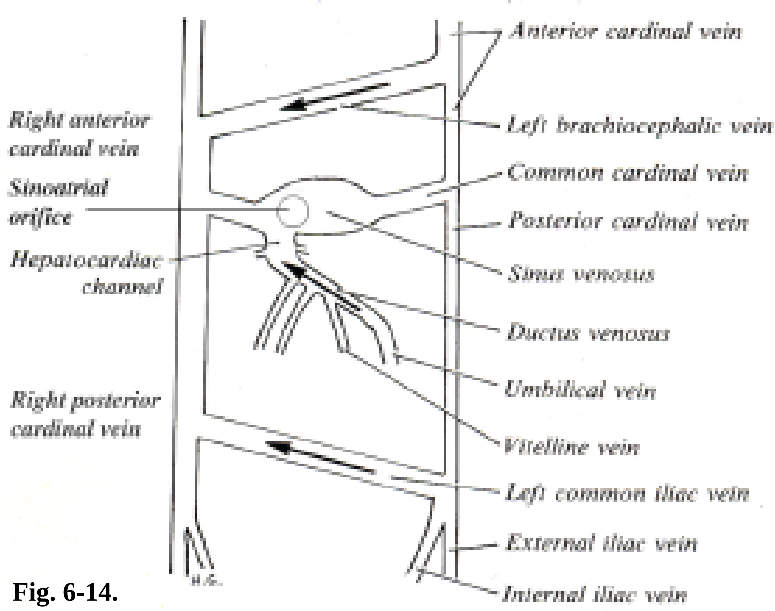

Fig. 6-14.

major shunts develop that divert venus blood from the left side of the heart to the right.

(i) The left brachiocephalic vein diverts blood from the left to the right anterior cardinal vein.

(ii) The left common iliac vein diverts blood from the left to the right posterior cardinal vein.

(iii) **(Figures 6-14, 6-15)** The superior portion of the right vitelline vein receives venus blood from the developing liver, portal vein, and the **ductus venosus**. In the fetus, the latter structure transports blood that has been oxygenated in the placenta, from the umbilical vein, through the liver (bypassing the liver sinusoids) and delivers it directly into the inferior vena cava (IVC) which then empties into the right atrium. The hepatic portion of the IVC widens to form the hepatocardiac channel, and will eventually form the **terminal portion of the inferior vena cava (IVC)**.

(iv) Portions of the right anterior and right common cardinal veins participate in the formation of the **superior vena cava (SVC).**

(v) In the trunk a pair of **subcardinal veins** arises in the developing mesonephros. These veins are connected with the posterior cardinal veins and to each other through numerous anastomoses. When the mesonephric kidneys regress, a pair of **supra-cardinal veins** appears in the body wall dorsal to the subcardinal veins. Over time, all three sets of cardinal veins in the body break up to varying degrees, with surviving remnanats incorporated into the **inferior vena cava.**

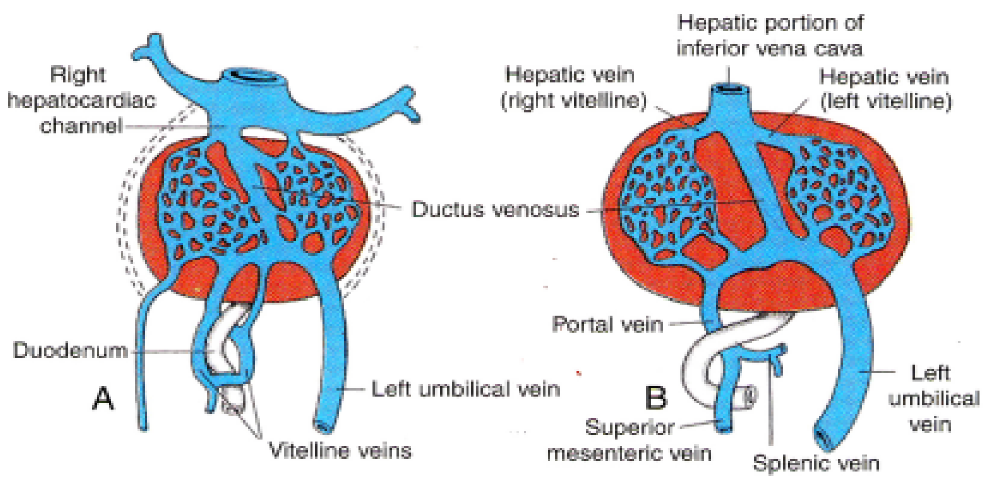

Fig. 6-15. Development of vitelline and umbilical veins in the (A) second and (B) third months. Note formation of the ductus venosus, portal vein, and hepatic portion of the inferior vena cava. The splenic and superior mesenteric veins enter the portal vein.

b) **<u>The right atrium</u> (Figure 6-16)** The increased blood flow in the right sinus horn is accompanied by a shift of the sinoatrial orifice to the right half of the common atrium (**Figure 6-14**). Blood from the IVC, SVC and coronary sinus, is now delivered to the right atrium. The right sinus horn, which is now the only communication between the original sinus venosus and atrium, is gradually incorporated (by intussusception) into the right atrium to form the **sinus venarum** (smooth walled part of the right atrium). The **crista terminalis** is the dividing line between the original trabeculated part of the right atrium, the **right auricle** (the trabeculated atrial appendage), and the smooth walled sinus venarum. The sinoatrial node (pacemaker of the conducting system), originally positioned in the right sinus horn, is incorporated into the wall of the right atrium. The left sinus horn is reduced to the **coronary sinus** and the left common cardinal vein forms the oblique vein of the left atrium.

c) **<u>The left atrium</u> (Figure 6-16)**. A pulmonary vein grows from the left side of the primitive atrium towards the developing lungs. It branches twice to produce 4 pulmonary veins. These are gradually incorporated into the posterior wall of the left atrium, by intussusception, forming the smooth walled portion of the left atrium. The original primitive left atrium becomes the vestigial **left auricle**.

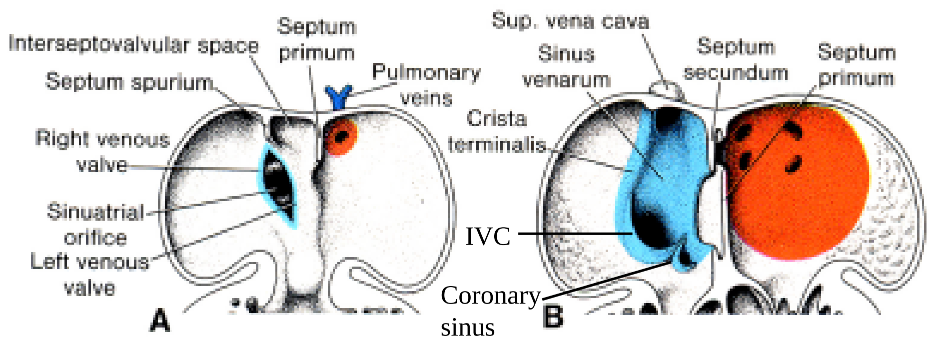

Fig. 6-16. Coronal sections through the heart to show the development of the smooth-walled portions of the right and left atrium. Both the wall of the right sinus horn (blue) and the pulmonary veins (red) are incorporated into the heart to form the smooth-walled parts of the atria.

VI. <u>Centering the Atrioventricular (AV) Canal</u> (Figure 6-17)

Initially, the AV canal gives access only from the common atrium to the left ventricle (**Figure 6-12**). Blood is then diverted from the left ventricle to the primitive right ventricle by an internal **bulbo-ventricular flange (fold)**. At the beginning of the 5th week the bulbo-ventricular flange recedes, the AV canal enlarges, and becomes centered above the two primitive ventricles so that blood passing through the AV orifice now has direct access to both ventricles (**Figure 6-17**).

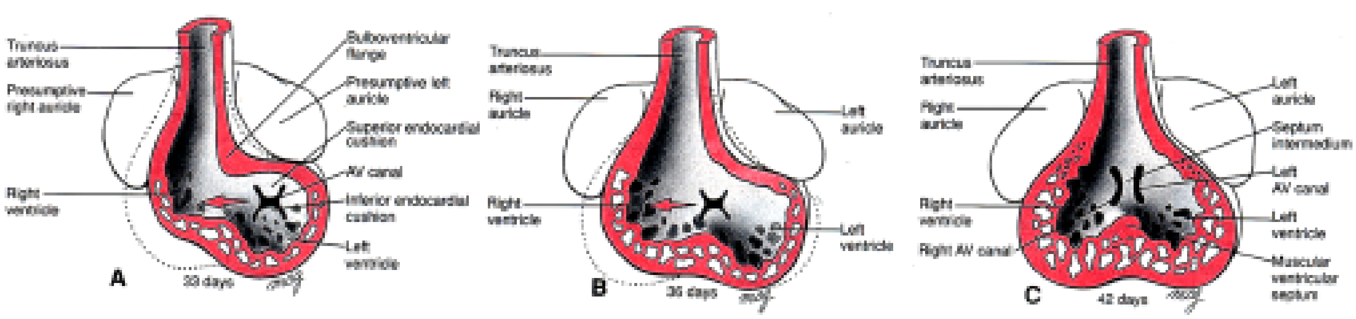

Fig. 6-17. (A-C) Realignment of the heart. As the septum intermedium forms during the fifth and sixth weeks, the heart is remodeled to align the developing left atrioventricular canal with the left atrium and ventricle and the right atrioventricular canal with the right atrium and ventricle.

VII. <u>The Endocardial Cushions: partitioning the AV Canal - formation of Septum Intermedium</u> (Figures 6-17, 6-18)

On the superior, inferior, and lateral walls of the AV canal, thickenings known as **endocardial cushions (EC)** appear. These mesenchymal thickenings form when some cells from the

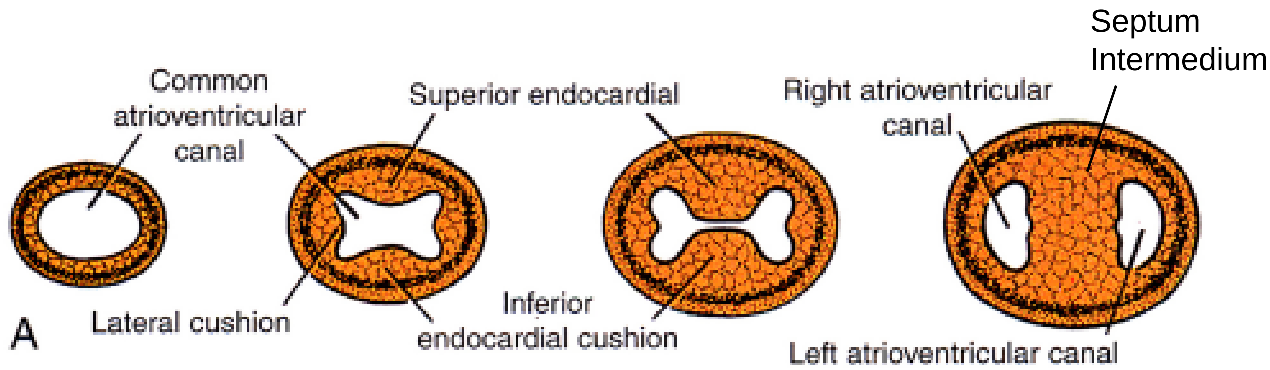

Fig. 6-18. Formation of the septum intermedium in the atrioventricular canal. From left to right, 4-, 6-, 9", and 12-mm stages, respectively. The initial circular opening becomes gradually widened in transverse direction.

endocardium in two circumscribed areas respond to inductive signals (adherons and TGFβ 1 and 3) from the underlying myocardium, loose their epithelial character, and transform into mesenchymal cells. The mesenchymal cells migrate into the cardiac jelly that separates the endocardium and myocardium to produce mesenchyme that ultimately differentiates into connective tissue. Endocardial cells respond to these induction signals only in the atrioventricular region (and conus cordis; lecture 7). Once formed, the **superior and inferior cushions** fuse to form the **septum intermedium**. The atrioventricular canal is now divided into a right AV canal (between the right primitive atrium and primitive right ventricle) and a left AV canal (between the left atrium and the left ventricle). The early endocardial cushions serve as primitive valves that assist in the forward propulsion of blood through the heart. The fate of the endocardial cushions and the consequence(s) of malformation will be discussed during this and lecture HD 7.

VIII. **<u>Partitioning the primitive atrium</u> (Figure 6-19, also see Figure 6-16)**

a) At the end of 4th week, a sickle shaped crest, the **septum primum**, grows from the roof of the common atrium into the lumen towards the EC in the AV canal. The opening between the lower limb of septum primum and the EC is the **ostium (or foramen) primum**.
b) Extensions of the superior and inferior EC grow towards septum primum and eventually would obliterate communication between the right and left atria. Before this happens, perforations in septum primum coalesce to form a new opening, called **ostium (foramen) secundum**.
c) A new partition, the **septum secundum** appears to the right of septum primum but never forms a complete partition. The opening left in septum secundum is the **oval foramen (foramen ovale)**. The passage between the two atria consists of an obliquely elongated cleft (**Figure 6-19g**). During fetal life, blood flows from the right to the left atrium through this cleft. The septum primum acts as a valve controlling blood flow from the right to the left atrium **(Figure 6-19h)**