7. HEART AND CIRCULATORY SYSTEM II

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SUMMARY:

During this lecture we will continue to describe the development of the fetal heart. Topics will include septation of the ventricles, formation of the atrioventricular valves, and formation of the cardiac outflow tracts. The derivation of the great vessels leading out of the heart will also be described briefly. We will see the course of the fetal circulation, whose task is to pump and maintain the flow of blood from the placenta through the fetal body and back to the placenta where wastes can be exchanged for nutrients and oxygen. The structural and functional changes in the cardiovascular system that occur at birth when the placental circulation is abruptly interrupted and breathing begins will also be discussed. Finally, several congenital cardiac malformations will be discussed from the perspective of abnormal cardiac development.

GLOSSARY:

Aortic arches: paired arteries surrounding the pharynx; portions will contribute to formation of the great vessels

Aorticopulmonary septum: the portion of the conotruncal septum that divides the truncus arteriosus into the ascending aorta and the pulmonary trunk

Bulbar ridges: another name for the truncoconal ridges or conus swellings that ultimately separate the conotrucal outflow tract

Conotruncal septum: the septum that divides the conus cordis into the outflow tracts (infundibulum of the right ventricle [conus arteriosus] and aortic vestibule) as well as the truncus arteriosus

Ductus arteriosus: shunts blood from the left pulmonary artery to the descending aorta, by-passing the lungs

Ductus venosus: shunts most of the blood in the umbilical vein into the inferior vena cava (IVC) (by-passes the liver sinusoids)

Membranous interventricular septum: outgrowth of tissue from the inferior endocardial cushion, which fuses with the conus swellings and the muscular septum and closes the foramen between the right and left ventricles

Semilunar valves: the aortic and pulmonary valves

LEARNING OBJECTIVES:

The student should be able to:
1) Discuss the formation and remodeling of the primitive embryonic ventricles and their respective outflow tracts.
2) Know the derivation of the great vessels.
3) Explain the structural and functional design of the fetal circulation.
4) Discuss origin of some well known cardiac malformations.

REVIEW: (Figs. 7-1, 7-2) The single common atrium is incompletely divided into a right and left atrium. The superior vena cava as well as the coronary sinus deliver blood to the right atrium and the pulmonary veins enter the left atrium. Oxygenated blood from the placenta is transported in the inferior vena cava (IVC) to the right atrium. The primitive ventricle gives rise to the left ventricle; the proximal portion of the bulbus cordis gives rise to the right ventricle. Blood flows from the sinus venosus into the common atrium. It passes through the common atrioventricular (AV) canal into the primitive ventricle, through the bulbus cordis (primitive right ventricle, conus cordis and truncus arteriosus), into the aortic sac, and is then distributed to cranial structures and dorsal aortae via the aortic arches. After the AV canal expands and shifts to the right, it communicates with both ventricles. When the AV endocardial cushions (EC) fuse, the left AV canal opens into the primitive left ventricle and the right AV canal opens into the primitive right ventricle. The muscular interventricular (IV) septum incompletely separates the 2 ventricles. Blood flows from the left to
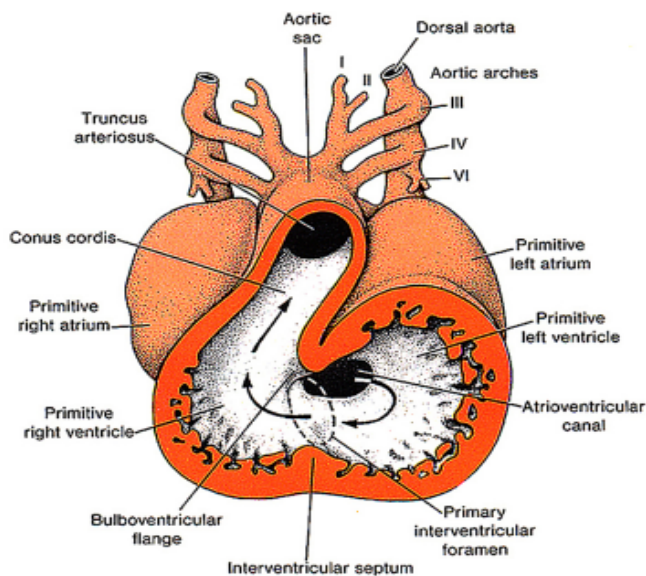

Fig. 7-1. Frontal section through the heart of a 6-mm embryo showing the primary interventricular foramen and the entrance of the atrium into the primitive left ventricle. Note the bulboventricular flange. *Arrows* indicate direction of blood flow.
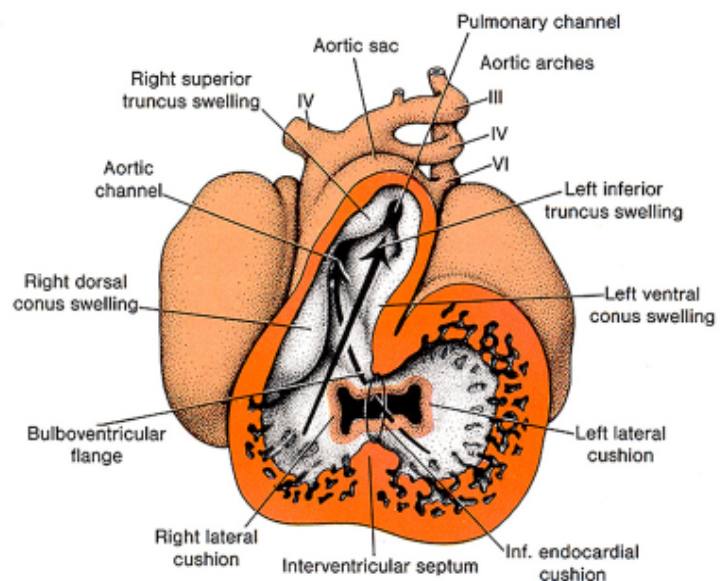
Fig. 7-2. Fronted section through the heart of a 9-mm embryo. At this stage of development blood from the atrial cavity enters the left primitive ventricle as well as the right primitive ventricle. Note the development of the cushions in the A-V canal. The swellings in the truncus and conus are clearly visible. The ring indicates the primitive interventricular foramen. *Arrows* indicate blood flow.

the right ventricle through the primary IV foramen. The conus cordis and truncus arteriosus shift to the left. Both ventricles now have access to the truncus arteriosus by way of the conus cordis **(Fig 7-3)**. The following events will be described separately although they occur concurrently.
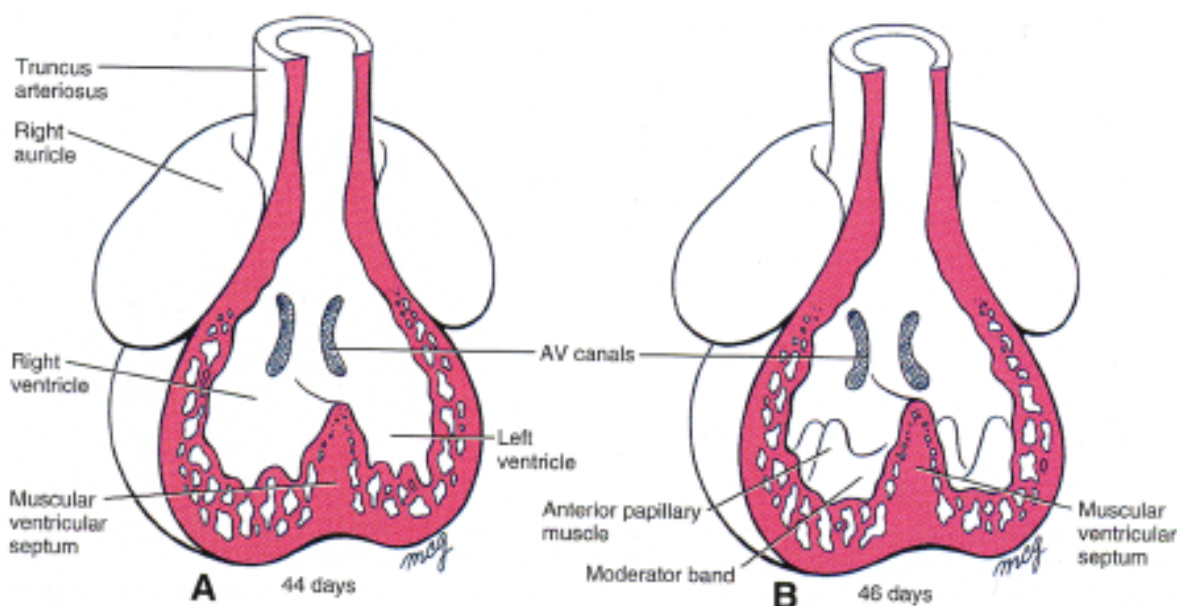

Fig. 7-3. A, B, Initial septation of the ventricles. The muscular interventricular septum enlarges in the region of the interventricular sulcus between weeks 4 and 7 (Larsen p.174, Fig 7-18).

I. **Formation of the muscular portion of the interventricular (IV) septum (Fig. 7-3).** At the end of 4th week the two primitive ventricles begin to dilate. The myocardium grows on the outside and diverticulates and trabeculates on the inside. The medial walls form an incomplete **muscular (primary) interventricular septum**. The ventricles communicate with each other through the **interventricular foramen**.

II. **Formation of the atrioventricular valves.** The atrioventricular valves begin to form between the fifth and eighth week. Undermining of the myocardium surrounding the right and left atrioventricular canals forms the leaflets or cusps **(Fig. 7-4)** . The free edge of each leaflet is attached to the ventricular walls by thin sinews, the **chordae tendineae,** which insert into small hillocks of myocardium, the papillary muscles **(Fig. 7-5).**
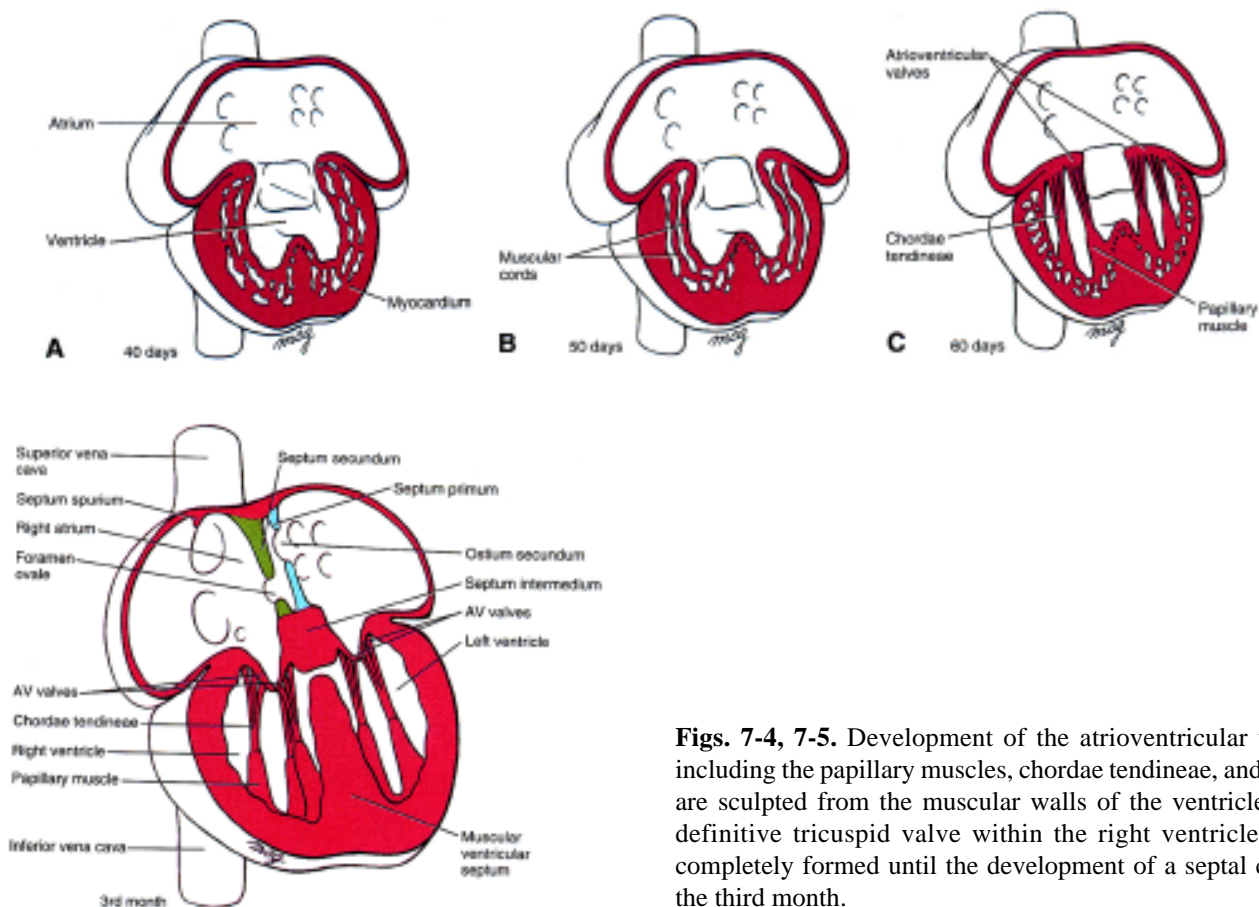
Figs. 7-4, 7-5. Development of the atrioventricular valves, including the papillary muscles, chordae tendineae, and cusps, are sculpted from the muscular walls of the ventricles. The definitive tricuspid valve within the right ventricle is not completely formed until the development of a septal cusp in the third month.

III. **Partitioning the truncus arteriosus and conus cordis. Formation of the outflow tracts from the right and left ventricles.**

    a)   Septum formation in truncus arteriosus. During the 5th week, **truncus swellings** appear on opposite walls of the truncus arteriosus **(Fig. 7-2)**. The right truncus swelling grows superiorly and to the left; the left truncus swelling grows superiorly and to the right in the direction of the aortic sac. Fusion of the two swellings forms a helical **truncus septum (aorticopulmonary septum) (Fig. 7-6A)** that twists 180° counterclockwise and divides the truncus into an **aortic** and a **pulmonary channel**. The aortic channel communicates with the 3rd and 4th aortic arches. The pulmonary channel communicates with the 6th aortic arches **(Fig. 7-7B)**. The subsequent split in the aortico-pulmonary septum creates the **ascending aorta** and **pulmonary trunk (Fig. 7-6B)**.

    b)   Septum formation in the conus cordis (outflow tracts from the ventricles) and formation of the **conotruncal septum**. Two **conus swellings (Fig. 7-2),** also referred to as **bulbar ridges (Fig. 7-7B),** appear on opposite walls of the conus cordis just inferior to the truncus swellings. The conus swellings fuse as they grow inferiorly toward the muscular interventricular septum. The conus (bulbar) portion of the **conotruncal septum** divides the conus into an anterolateral portion that descends into the right ventricle to become the **conus arteriosus (infundibulum)** (smooth walled portion) of the right
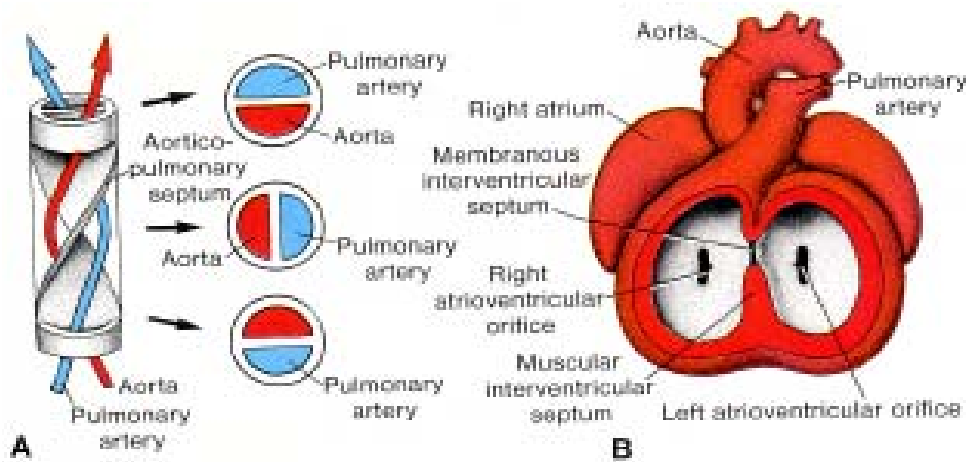
Fig. 7-6. (A) Diagram to show the spiral shape of the aortico-pulmonary septum. (B) Position of aorta and pulmonary artery at 25-mm stage (eighth week).Note how the aorta and pulmonary artery twist around each other.
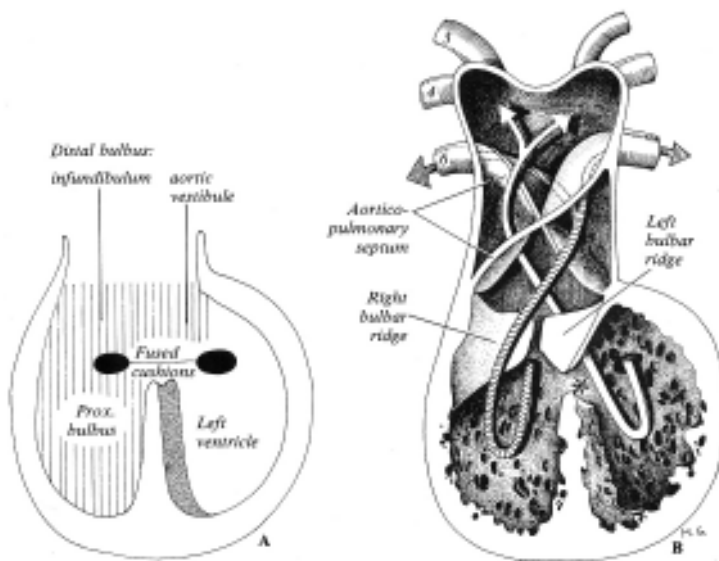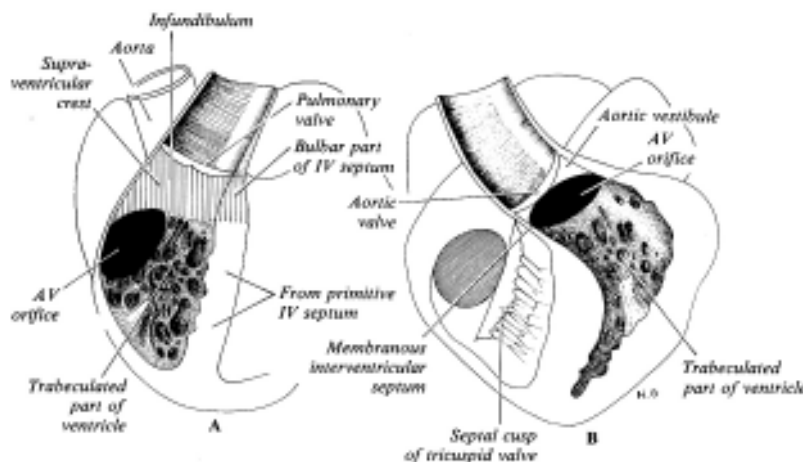

Fig. 7-7.

Fig. 7-8. (A) Interior of the adult right ventricle. (B) Interior of the adult left ventricle.

ventricle, and a posteromedial portion that descends into the left ventricle forming the **aortic vestibule** (smooth walled portion) of the left ventricle **(Fig. 7-8)**.

c) The **aortic and pulmonary valves (semilunar valves)** develop in the inferior portions of the truncus swellings. Each valve is derived from 3 tubercles: 2 lateral tubercles that divide when the aorta and pulmonary trunk separate and a third tubercle that develops in the wall in each valve **(Fig. 7-9)**.

IV. Formation of the membranous portion of the interventricular (IV) septum. At the end of the 4th week the medial walls form an incomplete **muscular (primary) interventricular septum**. The ventricles communicate with each other through the **interventricular foramen.** The two primitive ventricles dilate further as a result of continuous growth of the myocardium on the outside and diverticulation and
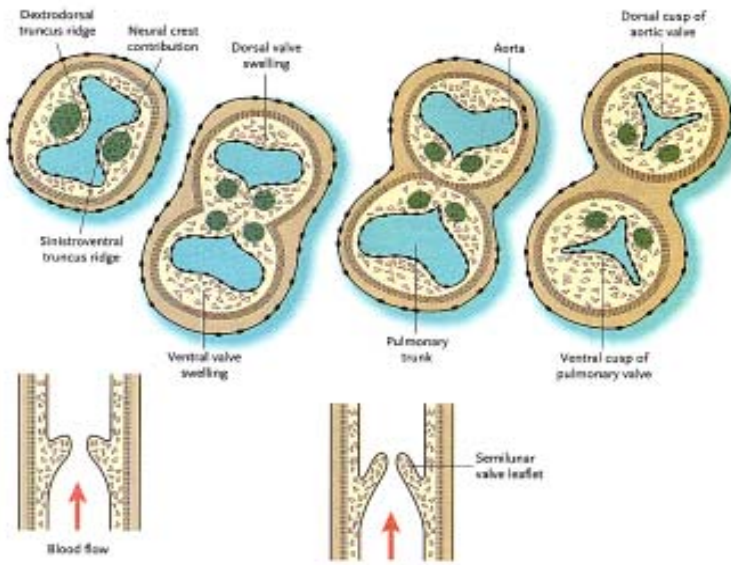
Fig. 7-9. Formation of the semilunar valves in the outflow tract of the heart. Neural crest cells (green areas) may contribute in part to the formation of the valvular leaflets.

trabecular formation on the inside **(Fig. 7-7)**. The IV foramen, between the free rim of the muscular ventricular septum and the fused EC, permits communication between the 2 ventricles. When the two conus swellings fuse this space is reduced **(Fig. 7-7B and Fig. 7-10B)**. It is obliterated by an outgrowth of tissue from the inferior EC forming the membranous portion of the IV septum **(Fig. 7-10B, C)**.

V. **Development of the great arteries.** Derivatives of the 3rd, 4th and 6th aortic arches **(Figs. 7-11 and 7-12)**. The 3rd arch participates in formation of the carotid arteries; the 4th forms the
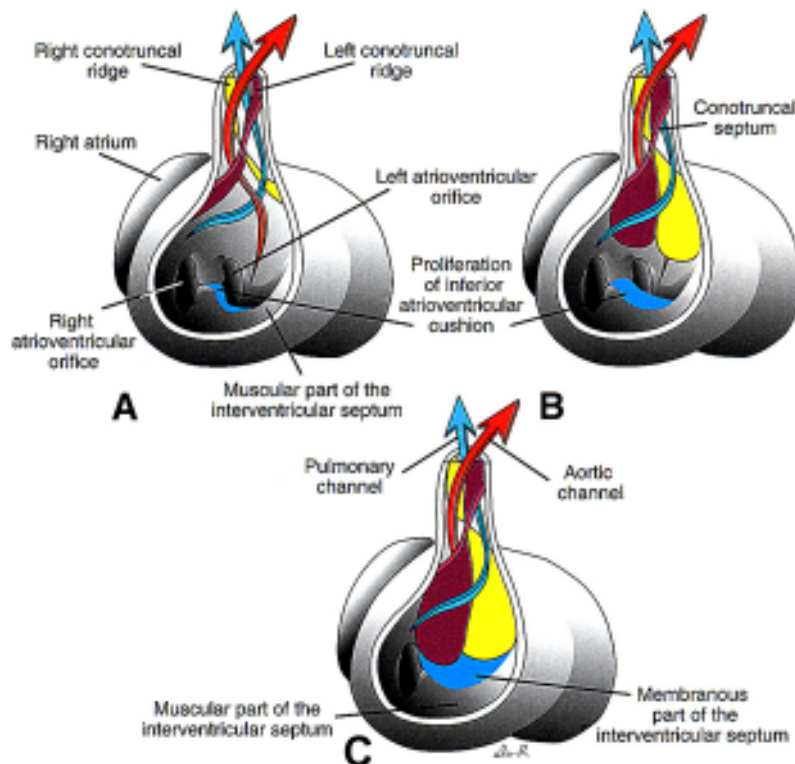

**Fig. 7-10.** Development of the conotruncal ridges (swellings) and closure of the interventricular foramen. Proliferations of the right and left conus swellings, combined with proliferation of the inferior endocardial cushion, close the interventricular foramen and form the membranous portion of the interventricular septum. A. 6 weeks (12 mm). B. Beginning of the seventh week (14.5 mm). C. End of the seventh week (20 mm).

aortic arch on the left side and a portion of the subclavian on right; the 6th arch forms the proximal parts of pulmonary arteries and the **ductus arteriosus**, a fetal vessel that shunts blood from the pulmonary trunk to the descending aorta, bypassing the fetal lungs **(Fig. 7-13).** The ductus arteriosus closes after birth when the lungs become functional.
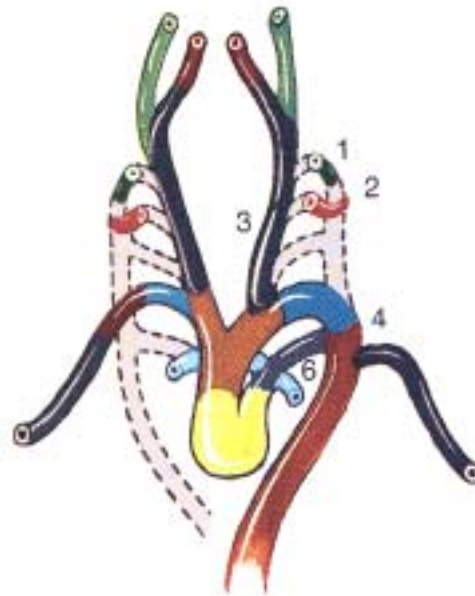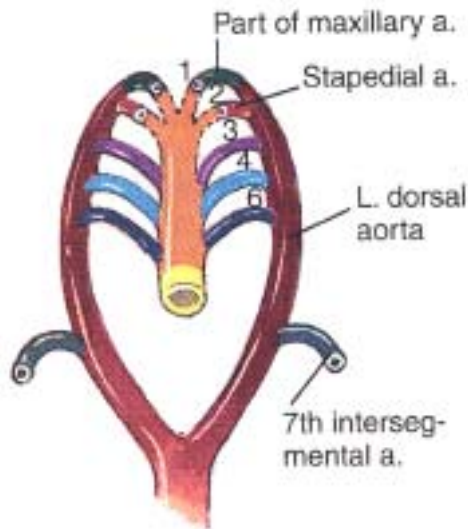
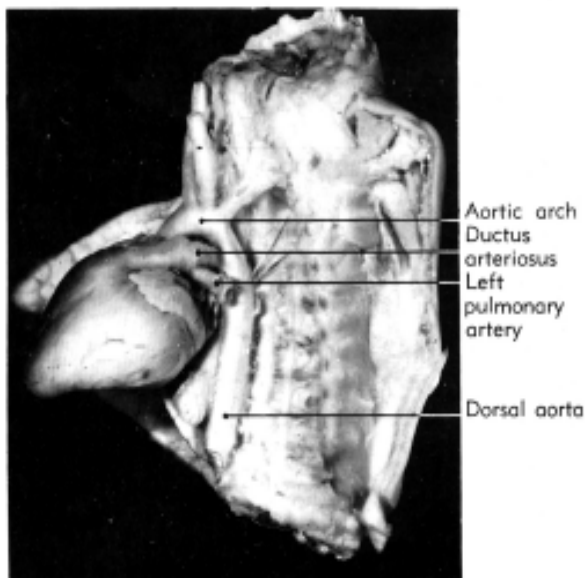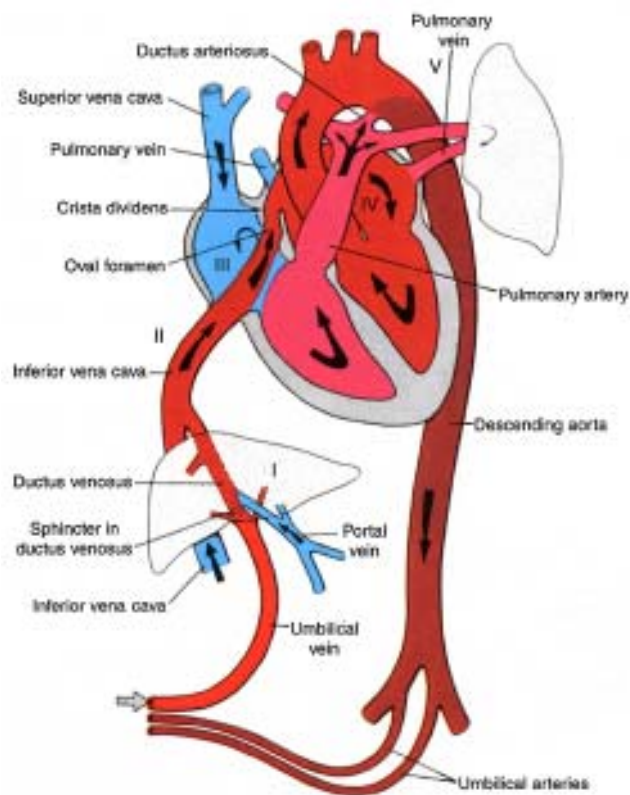**Figs. 7-11, 7-12**. Development of the aortic system.

Fig. 7-13.

VI. Fetal circulation (Fig. 7-14).

a) Oxygenated blood from placenta, (~80% saturated), is delivered to the heart by way of the umbilical vein. The main portion of blood flows through ductus venosus into the IVC. A smaller portion enters the liver sinusoids and mixes with blood from the portal circulation. A functional sphincter (not observed anatomically) is thought to regulate blood flow through the liver sinusoids.

b) In the IVC, the still highly oxygenated blood mixes with a small amount of deoxygenated blood from the lower limbs and enters the right atrium. Most of it passes from the right atrium, through the foramen ovale, to the left atrium where it mixes with a small amount of blood returning from the lungs. From the left atrium, blood enters the left ventricle and ascending aorta. Since the coronary and carotid arteries are the first branches of the ascending aorta, the heart musculature and the brain receive well oxygenated blood. Blood in the descending aorta is delivered to the trunk and lower limbs.

c) Desaturated blood from the SVC and a small

Fig. 7-14. Plan of the human circulation before birth. Arrows indicate the direction of the blood flow. Note where the oxygenated blood mixes with deoxygenated blood: (I) in the liver, (II) in the inferior vena cava, (III) in the right atrium, and (IV) at the entrance of the ductus arteriosus into the descending aorta.

portion of oxygenated IVC blood that is diverted into the right atrium by the lower edge of septum secundum flows by way of the right ventricle into the pulmonary trunk. Since resistance in the pulmonary vessels of the collapsed lungs is high, the main portion of blood from the pulmonary trunk passes through ductus arteriosus directly into the descending aorta, where it mixes with the blood from the proximal aorta. From there the blood stream flows towards the placenta by way of 2 umbilical arteries. Oxygen saturation is now reduced to ~58%.
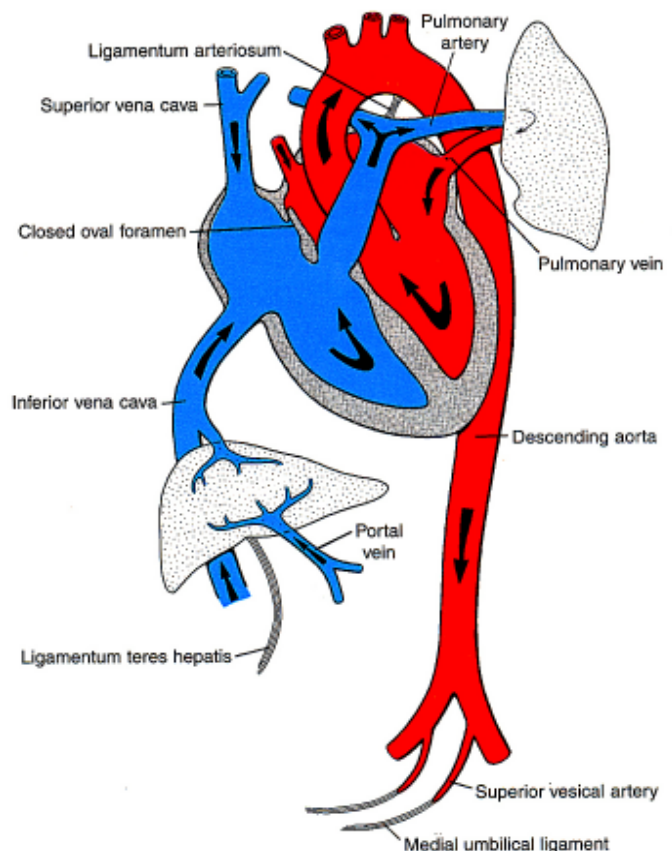

Fig. 7-15. Plan of the human circulation after birth. Note the changes occurring as a result of the beginning of respiration and the interruption of the placental blood flow.

7-8

VII. <u>Circulatory changes at birth</u> (**Figs. 7-14, 7-15**). The sudden changes occurring in the vascular system at birth are caused by the initiation of lung respiration and by cessation of the placental flow. These dramatic changes convert the fetal circulation to separate pulmonary and systemic circulations, arranged in series.

a) Closure of the umbilical arteries. This is accompanied by contraction of the smooth muscle and is probably caused by thermal and mechanical stimuli and a change in oxygen tension. Actual obliteration may take 2 to 3 months. The distal parts of the umbilical arteries form the **medial umbilical ligaments** while the proximal parts remain open as the **superior vesical arteries**.

b) Closure of the umbilical vein and ductus venosus. This occurs shortly after closure of the umbilical arteries. Hence, blood from the placenta may enter the newborn for some time after birth. After obliteration, the umbilical vein forms the **ligamentum teres hepatis**. Ductus venosus is also obliterated and forms **ligamentum venosum**.

c) Closure of ductus arteriosus. Immediately after birth the muscular wall of ductus arteriosus contracts. This is thought to be due to local changes in oxygen tension during inflation of the lungs. However, during the first days after birth, a left-to-right shunt is not unusual. Anatomical closure is thought to take from 1 to 3 months. In the adult, the obliterated ductus arteriosus forms the **ligamentum arteriosum**. During fetal life, ductus arteriosus and ductus venosus are kept open by circulating **prostaglandins**. Ductus arteriosus is kept patent in infants born with malformations by administration of prostaglandins. Premature infants are sometimes injected with prostaglandin inhibitors to stimulate closure of ductus arteriosus.

d) Closure of the oval foramen is caused by increased pressure in the left atrium (opening of pulmonary vasculature) combined with a decrease in pressure in the right atrium (cessation of umbilical flow). With the first good breadth, the septum primum is pressed against the septum secundum. During the first days of life, this closure is reversible. Crying creates a shunt from right to left, thus accounting for the cyanotic periods of the new born. Constant apposition gradually leads to fusion of the 2 septa in approximately 1 year. In 20-25% of all individuals, perfect closure never occurs, a condition known as probe patent foramen ovale.

VIII. <u>Malformations of the Heart</u>

Chronologic Table 7-1.

Normal time	Developmental events	Malformation arising during period
18 days	Horseshoe-shaped cardiac primordium appears.	Lethal mutants
20 days	Bilateral cardiac primordia fuse.	Cardia bifida (experimental)
	Cardiac jelly appears.	-
	Aortic arch is forming	-
22 days	Heart is looping into S shape.	Dextrocardia
	Heart begins to beat.	-
	Dorsal mesocardium is breaking down.	-

	Aortic arches I and II are forming.	-
24 days	Atria are beginning to bulge.	-
	Right and left ventricles act like two pumps in series.	-
	Outflow tract is distinguishable from right ventricle.	-
Late fourth week	Sinus venosus is becoming incorporated into right atrium.	Venous inflow malformations
	Endocardial cushions appear.	Persistent atrioventricular canal
	Early septum I appears between left and right atria.	Common atrium
	Muscular interventricular septum is forming.	Common ventricle
	Truncoconal ridges are forming.	Persistent truncus arteriosus
	Aortic arch I is regressing.	-
	Aortic arch III is formed.	-
	Aortic arch IV is forming.	-
Early fifth week	Endocardial cushions are coming together, forming right and left atrioventricular canals.	Persistent atrioventricular canal
	Further growth of interatrial septum I and muscular interventricular septum occurs.	Muscular ventricular septal defects
	Truncus arteriosus is dividing into aorta and pulmonary artery.	Transposition of great vessels
		Aortic and pulmonary stenosis or atresia
	Atrioventricular bundle is forming; there is possible neurogenic control of heart beat.	-
	Pulmonary veins are becoming incorporated into left atrium.	Aberrant pulmonary drainage
	Aortic arches I and II have regressed.	-
	Aotic arches III and IV have formed.	-
	Aortic arch VI is forming.	-
Late fifth to early sixth week	Endocardial cushions fuse.	-
	Interatrial foramen II is forming.	-
	Interatrial septum I is almost contacting endocardial cushion.	Low atrial septal defects
	Membranous part of interventricular septum starts to form.	Membranous interventricular septal defects
	Semilunar valves begin to form.	Aortic and pulmonary valvular stenosis
Late sixth week	Interatrial foramen II is large.	High atrial septal defects
	Interatrial septum II starts to form.	-
	Atrioventricular valves and papillary muscles are forming.	Tricuspid or mitral valvular stenosis or atresia
	Interventricular septum is almost complete.	Membranous interventricular septal defects
	Coronary circulation is becoming established.	-
Eighth to ninth week	Membranous part of interventricular septum is completed.	Membranous interventricular septal defects

a) <u>Normal Heart:</u> In the normal adult heart (**Fig. 7-15**) blood from the inferior vena cava (**IVC**) and superior vena cava (**SVC**) enters the right atrium, traverses the tricuspid valve, and is pumped from the right ventricle through the pulmonary trunk (regulated by the pulmonary valve) to the lungs. It then passes to the left atrium via the pulmonary veins, through the mitral valve to the left ventricle, and is pumped into the ascending aorta

(regulated by the aortic valve). Considering the complicated formation and critical timing for the correct formation and alignment of multiple cardiac structures, it is not surprising that defects arise. A few examples will be discussed during the lecture. These malformations are also described in Larsen.

b) <u>Malformation of cardiac looping:</u> Abnormalities in cardiac looping often result in incomplete formation of one of the ventricles. This leads to a functionally univentricular heart.

c) <u>Malformations of atrial septation</u> (**Fig. 7-16**). (i) Ostium secundum defect(ASD): excessive resorption of septum primum. (ii) Septum secundum fails to develop. (iii) Complete absence of the atrial septum; both septum primum and septum secundum fail to develop.
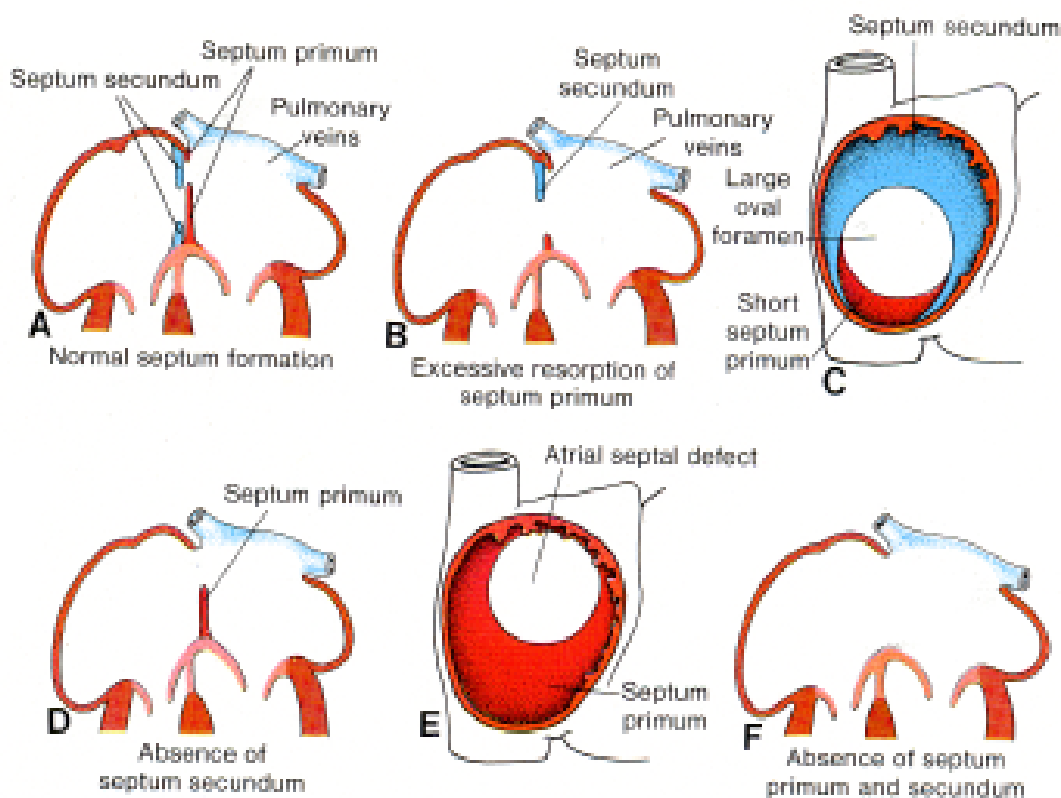

Fig. 7-16. (A) Normal atrial septum formation. (B and C) Ostium secundum defect caused by excessive resorption of the septum primum. (D and E) Similar defect caused by failure of development of the septum secundum. (F) Common atrium or cor trilocular biventriculare—complete failure of the septum primum and septum secundum to form.

d) <u>Malformations of ventricular septation</u> (**Figs. 7-17 and 7-18**). **Ventricular septal defect (VSD)**: Isolated defect in membranous interventricular septum: Blood from the left ventricle flows to the right through an open ventricular foramen.
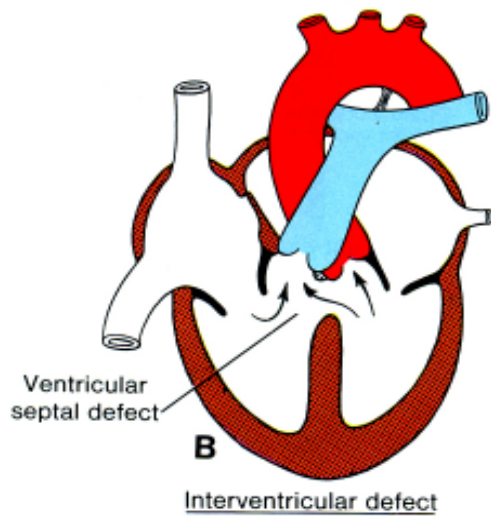
Ventricular septal defect

B

Interventricular defect

Interventricular defects.

Fig. 7-17

Subaortic

Inlet/Outlet

Inlet (Atrio-ventricular

Subpulmonary

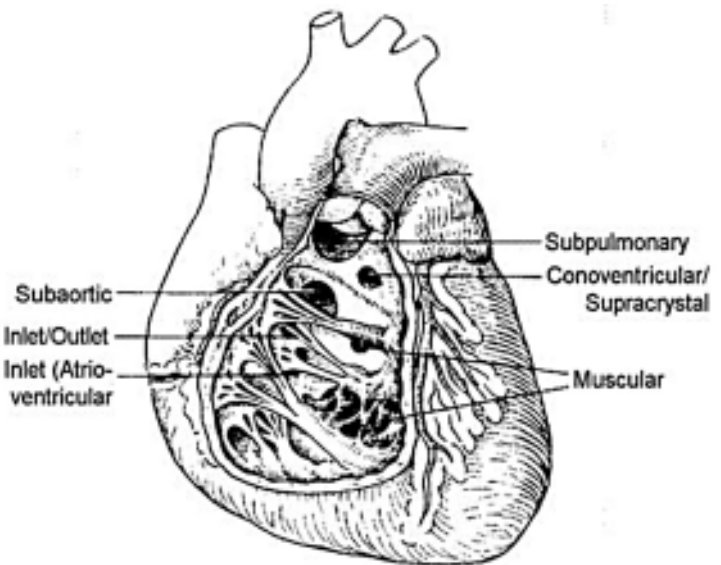Conoventricular/Supracrystal

Muscular

Fig. 7-18.

e)   Malformations of conotruncal septation (**Fig. 7-19**). **Tetralogy of Fallot (TOF):** Unequal division of the conus caused by anterior displacement of the conotruncal septum results in stenosis of the pulmonary trunk, hypertrophy of the right ventricle, overriding aorta, interventricular septal defect.
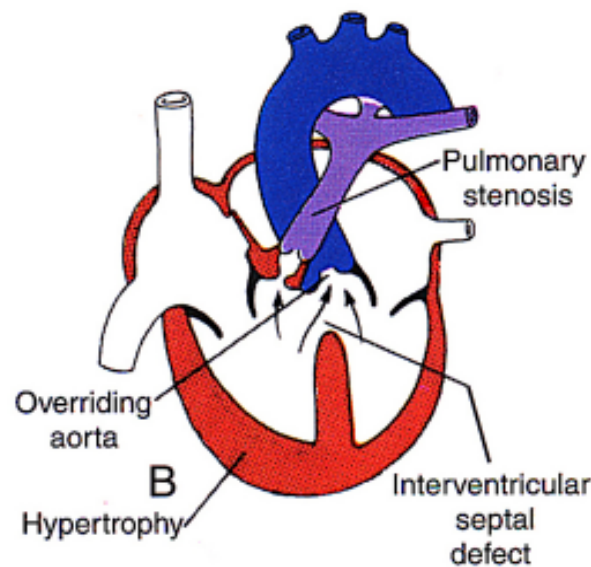

Pulmonary stenosis

Overriding aorta

B

Hypertrophy

Interventricular septal defect

Fig. 7-19. Tetralogy of Fallot.

f) Failure of conotruncal septum to spiral **(Fig.7-20). Transposition of the Great Arteries (TGA)**: Conotruncal septum fails to spiral and instead descends straight downward. The aorta originates from the right ventricle and the pulmonary artery from the left.
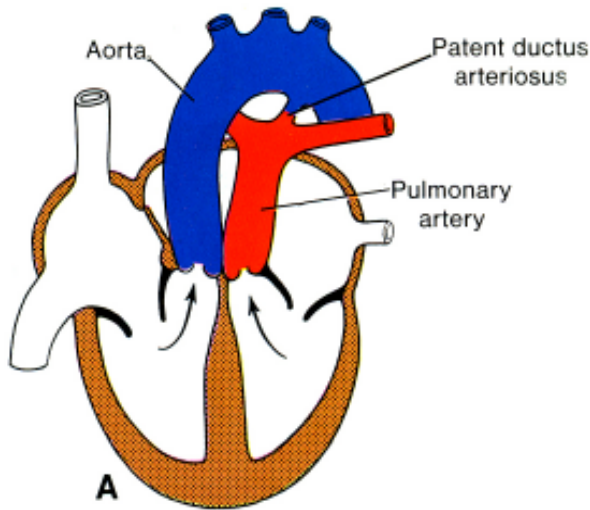

Fig. 7-20. Transposition of the Great Vessels.

Fig. 7-21. Persistent Truncus Arteriosus.

g) Absence of the conotruncal septum **(Fig. 7-21). Persistent Truncus Arteriosus:** The pulmonary artery originates from the common truncus arteriosus. Accompanied by a ventricular septal defect, the undivided outflow tract overrides both ventricles. Neural crest cells participate in formation of the conotruncal septum **(Fig. 7-22)**. The crest cells migrate through pharyngeal arches 4, and 6, and invade the conotruncal swellings. Persistent truncus arteriosus can be experimentally reproduced in chicks by ablating the cardiac neural crest.
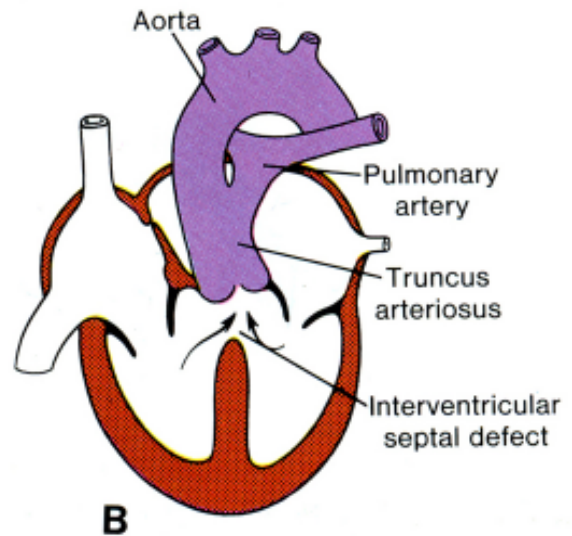

Fig. 7-22. Separation of the truncus arteriosus into the pulmonary artery and aorta. The truncoconal septa (between the aorta and the pulmonary trunk) forms from the cells of the cardiac neural crest. (A) Human cardiac neural crest cells migrate to pharyngeal arches 4 and 6 during the fifth week of gestation and enter the truncus arteriosus to generate the septa. (B) Quail cardiac crest cells were transplanted into the analogous region of a chick embryo, and the embryos were allowed to develop. The quail cardiac neural crest cells can be recognized by a quail-specific antibody, which stains them darkly. In the heart, these cells can be seen separating the truncus arteriosus (right) into the pulmonary artery and the aorta (left). (A after Kirby and Waldo 1990; B from Waldo et al. 1998, photographs courtesy of K. Waldo and M. L. Kirby.)