Cardiovascular System

Establishment of the Cardiogenic Field

The vascular system appears in the middle of the third week, when the embryo is no longer able to satisfy its nutritional requirements by diffusion alone. Progenitor heart cells lie in the epiblast, immediately adjacent to the cranial end of the primitive streak. From there, they migrate through the streak and into the splanchnic layer of lateral plate mesoderm where they form a horseshoe-shaped cluster of cells called the primary heart field (PHF) cranial to the neural folds. As the progenitor heart cells migrate and form the PHF during days 16 to18, they are specified on both sides from lateral to medial to become the atria, left ventricle, and most of the right ventricle. Patterning of these cells occurs at the same time that laterality (left-right sidedness) is being established for the entire embryo and this process and the signaling pathway it is dependent upon is essential for normal heart development. The remainder of the heart, including part of the right ventricle and outflow tract (conus cordis and truncus arteriosus), is derived from the secondary heart field (SHF). This field of cells appears slightly later (days 20 to 21) than those in the PHF, resides in splanchnic mesoderm ventral to the posterior pharynx, and is responsible for lengthening the outflow tract. Cells in the SHF also exhibit laterality, such that those on the right side contribute to the left of the outflow tract region and those on the left contribute to the right. This laterality is determined by the same signaling pathway that establishes laterality for the entire embryo and explains the spiraling nature of the pulmonary artery and aorta and ensures that the aorta exits from the left ventricle and the pulmonary artery from the right ventricle.

Once cells establish the PHF, they are induced by the underlying pharyngeal endoderm to form cardiac myoblasts and blood islands that will form blood cells and vessels by the process of vasculogenesis. With time, the islands unite and form a horseshoe-shaped endothelial-lined tube surrounded by myoblasts. This region is known as the cardiogenic region; the intraembryonic (primitive body) cavity over it later develops into the pericardial cavity. In addition to the cardiogenic region, other blood islands appear bilaterally, parallel, and close to the midline of the embryonic shield. These islands form a pair of longitudinal vessels, the dorsal aortae.

Formation and Position of the Heart Tube

Initially, the central portion of the cardiogenic area is anterior to the buccopharyngeal membrane and the neural plate. With closure of the neural tube and formation of the brain vesicles, however, the central nervous system grows cephalad so rapidly that it extends over the central cardiogenic area and the future pericardial cavity. As a result of growth of the brain and cephalic folding of the embryo, the buccopharyngeal membrane is pulled forward, while the heart and pericardial cavity

move first to the cervical region and finally to the thorax. As the embryo folds cephalocaudally, it also folds laterally. As a result, the caudal regions of the paired cardiac primordia merge except at their caudal most ends. Simultaneously, the crescent part of the horseshoe-shaped area expands to form the future outflow tract and ventricular regions. Thus, the heart becomes a continuous expanded tube consisting of an inner endothelial lining and an outer myocardial layer. It receives venous drainage at its caudal pole and begins to pump blood out of the first aortic arch into the dorsal aorta at its cranial pole. The developing heart tube bulges more and more into the pericardial cavity. Initially, however, the tube remains attached to the dorsal side of the pericardial cavity by a fold of mesodermal tissue, the dorsal mesocardium. No ventral mesocardium is ever formed. With further development, the dorsal mesocardium disappears, creating the transverse pericardial sinus, which connects both sides of the pericardial cavity. The heart is now suspended in the cavity by blood vessels at its cranial and caudal poles. During these events, the myocardium thickens and secretes a thick layer of extracellular matrix, rich in hyaluronic acid, that separates it from the endothelium. In addition, mesothelial cells from the region of the sinus venosus migrate over the heart to form the epicardium. Thus the heart tube consists of three layers:

(*a*) the endocardium, forming the internal endothelial lining of the heart;

(*b*) the myocardium, forming the muscular wall; and

(*c*) the epicardium or visceral pericardium, covering the outside of the tube. This outer layer is responsible for formation of the coronary arteries, including their endothelial lining and smooth muscle.

Formation of the Cardiac Loop

The heart tube continues to elongate and bend on day 23. The cephalic portion of the tube bends ventrally, caudally, and to the right, and the atrial (caudal) portion shifts dorsocranially and to the left. This bending, which may be due to cell shape changes, creates the cardiac loop. It is complete by day 28. While the cardiac loop is forming, local expansions become visible throughout the length of the tube. The atrial portion, initially a paired structure outside the pericardial cavity, forms a common atrium and is incorporated into the pericardial cavity. The atrioventricular junction remains narrow and forms the atrioventricular canal, which connects the common atrium and the early embryonic ventricle. The bulbus cordis is narrow except for its proximal third. This portion will form the trabeculated part of the right ventricle. The midportion, the conus cordis, will form the outflow tracts of both ventricles. The distal part of the bulbus, the truncus arteriosus, will form the roots and proximal portion of the aorta and pulmonary artery. The junction between the ventricle and the bulbus cordis, externally indicated by the bulboventricular sulcus, remains narrow. It is called the primary interventricular foramen. Thus, the cardiac tube is organized by regions along its craniocaudal axis from the conotruncus to the right ventricle to the left ventricle to the atrial region, respectively.

Evidence suggests that organization of these segments is regulated by homeobox genes in a manner similar to that for the craniocaudal axis of the embryo. At the end of loop formation, the smooth-walled heart tube begins to form primitive trabeculae in two sharply defined areas just proximal and distal to the primary interventricular foramen. The bulbus temporarily remains smooth walled. The primitive ventricle, which is now trabeculated, is called the primitive left ventricle. Likewise, the trabeculated proximal third of the bulbus cordis may be called the primitive right ventricle. The conotruncal portion of the heart tube, initially on the right side of the pericardial cavity, shifts gradually to a more medial position. This change in position is the result of formation of two transverse dilations of the atrium, bulging on each side of the bulbus cordis .

Development of the Sinus Venosus

In the middle of the fourth week, the sinus venosus receives venous blood from the right and left sinus horns. Each horn receives blood from three important veins:

(*a*) the vitelline or omphalomesenteric vein,
(*b*) the umbilical vein, and
(*c*) the common cardinal vein.

At first communication between the sinus and the atrium is wide. Soon, however, the entrance of the sinus shifts to the right. This shift is caused primarily by left-to-right shunts of blood, which occur in the venous system during the fourth and fifth weeks of development. With obliteration of the right umbilical vein and the left vitelline vein during the fifth week, the left sinus horn rapidly loses its importance. When the left common cardinal vein is obliterated at 10 weeks, all that remains of the left sinus horn is the oblique vein of the left atrium and the coronary sinus. As a result of left-to-right shunts of blood, the right sinus horn and veins enlarge greatly. The right horn, which now forms the only communication between the original sinus venosus and the atrium, is incorporated into the right atrium to form the smooth-walled part of the right atrium. Its entrance, the sinuatrial orifice, is flanked on each side by a valvular fold, the right and left venous valves. Dorsocranially the valves fuse, forming a ridge known as the septum spurium. 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:

(*a*) the valve of the inferior vena cava, and
(*b*) the valve of the coronary sinus .

The crista terminalis forms the dividing line between the original trabeculated part of the right atrium and the smooth-walled part (sinus venarum), which originates from the right sinus horn.

Formation of the Cardiac Septa

The major septa of the heart are formed between the 27th and 37th days of development, when the embryo grows in length from 5 mm to approximately 16 to 17 mm. One method by which a septum may be formed involves two actively growing masses of tissue that approach each other until they fuse, dividing the lumen into two separate canals. Such a septum may also be formed by active growth of a single tissue mass that continues to expand until it reaches the opposite side of the lumen. Formation of such tissue masses depends on synthesis and deposition of extracellular matrices and cell proliferation. The masses, known as endocardial cushions, develop in the atrioventricular and conotruncal regions. In these locations they assist in formation of the atrial and ventricular (membranous portion) septa, the atrioventricular canals and valves, and the aortic and pulmonary channels. The other manner in which a septum is formed does not involve endocardial cushions. If, for example, a narrow strip of tissue in the wall of the atrium or ventricle should fail to grow while areas on each side of it expand rapidly, a narrow ridge forms between the two expanding portions. When growth of the expanding portions continues on either side of the narrow portion, the two walls approach each other and eventually merge, forming a septum. Such a septum never completely divides the original lumen but leaves a narrow communicating canal between the two expanded

Septum Formation in the Common Atrium

At the end of the fourth week, a sickle-shaped crest grows from the roof of the common atrium into the lumen. This crest is the first portion of the septum primum. The two limbs of this septum extend toward the endocardial cushions in the atrioventricular canal. The opening between the lower rim of the septum primum and the endocardial cushions is the ostium primum. With further development, extensions of the superior and inferior endocardial cushions grow along the edge of the septum primum, closing the ostium primum. Before closure is complete, however, cell death produces perforations in the upper portion of the septum primum. Coalescence of these perforations forms the ostium secundum, ensuring free blood flow from the right to the left primitive atrium. When the lumen of the right atrium expands as a result of incorporation of the sinus horn, a new crescent-shaped fold appears. This new fold, the septum secundum, never forms a complete partition in the atrial cavity. Its anterior limb extends downward to the septum in the atrioventricular canal. When the left venous valve and the septum spurium fuse with the right side of the septum secundum, the free concave edge of the septum secundum begins to overlap the ostium secundum. The opening left by the septum secundum is called the oval foramen (foramen ovale). When the upper part of the septum primum gradually disappears, the remaining part becomes the valve of the oval foramen. The passage between the two atrial cavities consists of an obliquely elongated cleft through which blood from the right atrium flows to the left side. After birth, when lung

circulation begins and pressure in the left atrium increases, the valve of the oval foramen is pressed against the septum secundum, obliterating the oval foramen and separating the right and left atria. In about 20% of cases, fusion of the septum primum and septum secundum is incomplete, and a narrow oblique cleft remains between the two atria. This condition is called **probe patency** of the oval foramen; it does not allow intracardiac shunting of blood. Further Differentiation of the Atria While the primitive right atrium enlarges by incorporation of the right sinus horn, the primitive left atrium is likewise expanding. Initially, a single embryonic pulmonary vein develops as an outgrowth of the posterior left atrial wall, just to the left of the septum primum. This vein gains connection with veins of the developing lung buds. During further development, the pulmonary vein and its branches are incorporated into the left atrium, forming the large smooth-walled part of the adult atrium. Although initially one vein enters the left atrium, ultimately four pulmonary veins enter as the branches are incorporated into the expanding atrial wall. In the fully developed heart, the original embryonic left atrium is represented by little more than the trabeculated atrial appendage, while the smooth-walled part originates from the pulmonary veins. On the right side the original embryonic right atrium becomes the trabeculated right atrial appendage containing the pectinate muscles, and the smooth-walled sinus venarum originates from the right horn of the sinus venosus.

Septum Formation in the Atrioventricular Canal

At the end of the fourth week, two mesenchymal cushions, the atrioventricular endocardial cushions, appear at the superior and inferior borders of the atrioventricular canal. Initially the atrioventricular canal gives access only to the primitive left ventricle and is separated from the bulbus cordis by the bulbo(cono)ventricular flange. Near the end of the fifth week, however, the posterior extremity of the flange terminates almost midway along the base of the superior endocardial cushion and is much less prominent than before. Since the atrioventricular canal enlarges to the right, blood passing through the atrioventricular orifice now has direct access to the primitive left as well as the primitive right ventricle. In addition to the superior and inferior endocardial cushions, the two lateral atrioventricular cushions appear on the right and left borders of the canal. The superior and inferior cushions, in the meantime, project further into the lumen and fuse, resulting in a complete division of the canal into right and left atrioventricular orifices by the end of the fifth week.

Atrioventricular Valves

After the atrioventricular endocardial cushions fuse, each atrioventricular orifice is surrounded by local proliferations of mesenchymal tissue. When the bloodstream hollows out and thins tissue on the ventricular surface of these proliferations, valves form and

remain attached to the ventricular wall by muscular cords. Finally, muscular tissue in the cords degenerates and is replaced by dense connective tissue. The valves then consist of connective tissue covered by endocardium. They are connected to thick trabeculae in the wall of the ventricle, the papillary muscles, by means of chordae tendineae. In this manner two valve leaflets, constituting the bicuspid, or mitral, valve, form in the left atrioventricular canal, and three, constituting the tricuspid valve, form on the right side.

SEPTUM FORMATION IN THE TRUNCUS ARTERIOSUS AND CONUS CORDIS

During the fifth week, pairs of opposing ridges appear in the truncus. These ridges, the truncus swellings, or cushions, lie on the right superior wall (right superior truncus swelling) and on the left inferior wall (left inferior truncus swelling). The right superior truncus swelling grows distally and to the left, and the left inferior truncus swelling grows distally and to the right. Hence, while growing toward the aortic sac, the swellings twist around eachother, foreshadowing the spiral course of the future septum. After complete fusion, the ridges form the aorticopulmonary septum, dividing the truncus into an aortic and a pulmonary channel. When the truncus swellings appear, similar swellings (cushions) develop along the right dorsal and left ventral walls of the conus cordis. The conus swellings grow toward each other and distally to unite with the truncus septum. When the two conus swellings have fused, the septum divides the conus into an anterolateral portion (the ouflow tract of the right ventricle) and a posteromedial portion (the outflow tract of the left ventricle). Neural crest cells, migrating from the edges of the neural folds in the hindbrain region, contribute to endocardial cushion formation in both the conus cordis and truncus arteriosus. Abnormal migration, proliferation, or differentiation of these cells results in congenital malformations in this region, such as tetralogy of Fallot, pulmonary stenoses, transposition of the great vessels and persistent truncus arteriosus. Since neural crest cells also contribute to craniofacial development, it is not uncommon to see facial and cardiac abnormalities in the same individual.

SEPTUM FORMATION IN THE VENTRICLES

By the end of the fourth week, the two primitive ventricles begin to expand. This is accomplished by continuous growth of the myocardium on the outside and continuous diverticulation and trabecula formation on the inside. The medial walls of the expanding ventricles become apposed and gradually merge, forming the muscular interventricular septum. Sometimes the two walls do not merge completely, and a more or less deep apical cleft between the two ventricles appears. The space between the free rim of the muscular ventricular septum and the fused endocardial cushions permits communication between the two ventricles. The interventricular foramen, above the muscular portion of the interventricular septum, shrinks on completion of the conus septum. During further development, outgrowth of tissue from the inferior endocardial cushion along the top of

the muscular interventricular septum closes the foramen. This tissue fuses with the abutting parts of the conus septum. Complete closure of the interventricular foramen forms the membranous part of the interventricular septum.

Semilunar Valves

When partitioning of the truncus is almost complete, primordia of the semilunar valves become visible as small tubercles found on the main truncus swellings. One of each pair is assigned to the pulmonary and aortic channels, respectively. A third tubercle appears in both channels opposite the fused truncus swellings. Gradually the tubercles hollow out at their upper surface, forming the semilunar valves. Recent evidence shows that neural crest cells contribute to formation of these valves.

Formation of the Conducting System of the Heart

Initially the pacemaker for the heart lies in the caudal part of the left cardiac tube. Later the sinus venosus assumes this function, and as the sinus is incorporated into the right atrium, pacemaker tissue lies near the opening of the superior vena cava. Thus, the sinuatrial node is formed. The atrioventricular node and bundle (bundle of His) are derived from two sources:

(*a*) cells in the left wall of the sinus venosus, and

(*b*) cells from the atrioventricular canal.

Once the sinus venosus is incorporated into the right atrium, these cells lie in their final position at the base of the interatrial septum.

Vascular Development

ARTERIAL SYSTEM

Aortic Arches

When pharyngeal arches form during the fourth and fifth weeks of development, each arch receives its own cranial nerve and its own artery. These arteries, the aortic arches, arise from the aortic sac, the most distal part of the truncus arteriosus. The aortic arches are embedded in mesenchyme of the pharyngeal arches and terminate in the right and left dorsal aortae. (In the region of the arches the dorsal aortae remain paired, but caudal to this region they fuse to form a single vessel.). The aortic sac contributes a branch to each new arch as it forms, giving rise to a total of five pairs of arteries. Consequently the five arches are numbered I, II, III, IV, and VI . During further development, this arterial pattern becomes modified, and some vessels regress completely. Division of the truncus arteriosus by the aorticopulmonary septum divides the outflow channel of the heart into the ventral aorta and the pulmonary artery. The aortic sac then forms right and left horns, which subsequently give rise to the brachiocephalic artery and the proximal segment of the aortic arch, respectively.

By day 27,

(1) most of the first aortic arch has disappeared, although a small portion persists to form the maxillary artery.

(2)Similarly, the second aortic arch soon disappears. The remaining portions of this arch are the hyoid and stapedial arteries.

The third arch is large; the fourth and sixth arches are in the process of formation. Even though the sixth arch is not completed, the primitive pulmonary artery is already present as a major branch. In a 29-day embryo, the first and second aortic arches have disappeared. The third, fourth, and sixth arches are large. The truncoaortic sac has divided so that the sixth arches are now continuous with the pulmonary trunk. With further development, the aortic arch system loses its original symmetrical form, This representationmay clarify the transformation from the embryonic to the adult arterial system. The following changes occur:

(3)The third aortic arch forms the common carotid artery and the first part of the internal carotid artery. The remainder of the internal carotid is formed by the cranial portion of the dorsal aorta. The external carotid artery is a sprout of the third aortic arch.

(4)The fourth aortic arch persists on both sides, but its ultimate fate is different on the right and left sides. On the left it forms part of the arch of the aorta, between the left common carotid and the left subclavian arteries. On the right it forms the most proximal segment of the right subclavian artery, the distal part of which is formed by a portion of the right dorsal aorta and the seventh intersegmental artery.

(5)The fifth aortic arch either never forms or forms incompletely and then regresses.

(6)The sixth aortic arch, also known as the pulmonary arch, gives off an important branch that grows toward the developing lung bud. On the right side the proximal part becomes the proximal segment of the right pulmonary artery. The distal portion of this arch loses its connection with the dorsal aorta and disappears. On the left the distal part persists during intrauterine life as the ductus arteriosus.

Vitelline and Umbilical Arteries

The vitelline arteries, initially a number of paired vessels supplying the yolk sac, gradually fuse and form the arteries in the dorsal mesentery of the gut. In the adult they are represented by the celiac, superior mesenteric, and inferior mesenteric arteries. These vessels supply derivatives of the foregut, midgut, and hindgut, respectively. The umbilical arteries, initially paired ventral branches of the dorsal aorta, course to the placenta in close association with the allantois. During the fourth week, however, each artery acquires a secondary connection with the dorsal branch of the aorta, the common iliac artery, and loses its earliest origin. After birth the proximal portions of the umbilical arteries persist as the internal iliac and superior vesical arteries, and the distal parts are obliterated to form the medial umbilical ligaments.

VENOUS SYSTEM

In the fifthweek, three pairs of major veins can be distinguished:
(*a*) the vitelline veins, or omphalomesenteric veins, carrying blood from the yolk sac to the sinus venosus;
(*b*) the umbilical veins, originating in the chorionic villi and carrying oxygenated blood to the embryo; and
(*c*) the cardinal veins, draining the body of the embryo proper.

Vitelline Veins

Before entering the sinus venosus, the vitelline veins form a plexus around the duodenum and pass through the septum transversum. The liver cords growing into the septum interrupt the course of the veins, and an extensive vascular network, the hepatic sinusoids, forms. With reduction of the left sinus horn, blood from the left side of the liver is rechanneled toward the right, resulting in an enlargement of the right vitelline vein (right hepatocardiac channel). Ultimately the right hepatocardiac channel forms the hepatocardiac portion of the inferior vena cava. The proximal part of the left vitelline vein disappears. The anastomotic network around the duodenum develops into a single vessel, the portal vein. The superior mesenteric vein, which drains the primary intestinal loop, derives from the right vitelline vein. The distal portion of the left vitelline vein also disappears.

Umbilical Veins

Initially the umbilical veins pass on each side of the liver, but some connect to the hepatic sinusoids. The proximal part of both umbilical veins and the remainder of the right umbilical vein then disappear, so that the left vein is the only one to carry blood from the placenta to the liver. With the increase of the placental circulation, a direct communication forms between the left umbilical vein and the right hepatocardiac channel, the ductus venosus. This vessel bypasses the sinusoidal plexus of the liver. After birth the left umbilical vein and ductus venosus are obliterated and form the ligamentum teres hepatis and ligamentum venosum, respectively.

Cardinal Veins

Initially the cardinal veins form the main venous drainage system of the embryo. This system consists of the anterior cardinal veins, which drain the cephalic part of the embryo, and the posterior cardinal veins, which drain the rest of the embryo. The anterior and posterior veins join before entering the sinus horn and form the short common cardinal veins. During the fourth week, the cardinal veins form a symmetrical system. During the fifth to the seventh week a number of additional veins are formed:
(*a*) the subcardinal veins, which mainly drain the kidneys;
(*b*) the sacrocardinal veins, which drain the lower extremities; and

(*c*) the supracardinal veins, which drain the body wall by way of the intercostal veins, taking over the functions of the posterior cardinal veins.

Formation of the vena cava system is characterized by the appearance of anastomoses between left and right in such a manner that the blood from the left is channeled to the right side. The anastomosis between the anterior cardinal veins develops into the left brachiocephalic vein. Most of the blood from the left side of the head and the left upper extremity is then channeled to the right. The terminal portion of the left posterior cardinal vein entering into the left brachiocephalic vein is retained as a small vessel, the left superior intercostal vein. This vessel receives blood from the second and third intercostal spaces. The superior vena cava is formed by the right common cardinal vein and the proximal portion of the right anterior cardinal vein. The anastomosis between the subcardinal veins forms the left renal vein. When this communication has been established, the left subcardinal vein disappears, and only its distal portion remains as the left gonadal vein. Hence the right subcardinal vein becomes the main drainage channel and develops into the renal segment of the inferior vena cava. The anastomosis between the sacrocardinal veins forms the left common iliac vein. The right sacrocardinal vein becomes the sacrocardinal segment of the inferior vena cava. When the renal segment of the inferior vena cava connects with the hepatic segment, which is derived from the right vitelline vein, the inferior vena cava, consisting of hepatic, renal, and sacrocardinal segments, is complete. With obliteration of the major portion of the posterior cardinal veins, the supracardinal veins assume a greater role in draining the body wall. The 4th to 11th right intercostal veins empty into the right supracardinal vein, which together with a portion of the posterior cardinal vein forms the azygos vein. On the left the 4th to 7th intercostal veins enter into the left supracardinal vein, and the left supracardinal vein, then known as the hemiazygos vein, empties into the azygos vein.

Circulation Before and After Birth

FETAL CIRCULATION

Before birth, blood from the placenta, about 80% saturated with oxygen, returns to the fetus by way of the umbilical vein. On approaching the liver, most of this blood flows through the ductus venosus directly into the inferior vena cava, short-circuiting the liver. A smaller amount enters the liver sinusoids and mixes with blood from the portal circulation. A sphincter mechanism in the ductus venosus, close to the entrance of the umbilical vein, regulates flow of umbilical blood through the liver sinusoids. This sphincter closes when a uterine contraction renders the venous return too high, preventing a sudden overloading of the heart. After a short course in the inferior vena cava, where placental blood mixes with deoxygenated blood returning from the lower limbs, it enters the right atrium. Here it is guided toward the oval foramen by the valve of the inferior vena cava, and most of the blood passes directly into the left atrium. A small amount is prevented from doing so by the lower edge of the septum secundum, the crista dividens,

and remains in the right atrium. Here it mixes with desaturated blood returning from the head and arms by way of the superior vena cava. From the left atrium, where it mixes with a small amount of desaturated blood returning from the lungs, 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 are supplied with welloxygenated blood. Desaturated blood from the superior vena cava flows by way of the right ventricle into the pulmonary trunk. During fetal life, resistance in the pulmonary vessels is high, such that most of this blood passes directly through the ductus arteriosus into the descending aorta, where it mixes with blood from the proximal aorta. After coursing through the descending aorta, blood flows toward the placenta by way of the two umbilical arteries. The oxygen saturation in the umbilical arteries is approximately 58%. During its course from the placenta to the organs of the fetus, blood in the umbilical vein gradually loses its high oxygen content as it mixes with desaturated blood. Theoretically, mixing may occur in the following places: in the liver (*I*), by mixture with a small amount of blood returning from the portal system; in the inferior vena cava (*II*), which carries deoxygenated blood returning from the lower extremities, pelvis, and kidneys; in the right atrium (*III*), by mixture with blood returning from the head and limbs; in the left atrium (*IV*), by mixture with blood returning from the lungs; and at the entrance of the ductus arteriosus into the descending aorta (*V*).

CIRCULATORY CHANGES AT BIRTH

Changes in the vascular system at birth are caused by cessation of placental blood flow and the beginning of respiration. Since the ductus arteriosus closes by muscular contraction of its wall, the amount of blood flowing through the lung vessels increases rapidly. This, in turn, raises pressure in the left atrium. Simultaneously, pressure in the right atrium decreases as a result of interruption of placental blood flow. The septum primum is then apposed to the septum secundum, and functionally the oval foramen closes. To summarize, the following changes occur in the vascular system after birth:

1-Closure of the umbilical arteries, accomplished by contraction of the smooth musculature in their walls, is probably caused by thermal and mechanical stimuli and a change in oxygen tension. Functionally the arteries close a fewminutes after birth, although the actual obliteration of the lumen by fibrous proliferation may take 2 to 3 months. Distal parts of the umbilical arteries form the medial umbilical ligaments, and the proximal portions remain open as the superior vesical arteries .

2-Closure of the umbilical vein and ductus vensus occurs shortly after that 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 in the lower margin of the falciform ligament. The ductus venosus, which courses from the ligamentum teres to the inferior vena cava, is also obliterated and forms the ligamentum venosum.

3-Closure of the ductus arteriosus by contraction of its muscular wall occurs almost immediately after birth; it is mediated by bradykinin, a substance released from the lungs during initial inflation. Complete anatomical obliteration by proliferation of the intima is thought to take 1 to 3 months. In the adult the obliterated ductus arteriosus forms the ligamentum arteriosum.

4-Closure of the oval foramen is caused by an increased pressure in the left atrium, combined with a decrease in pressure on the right side. The first breath presses the septum primum against the septum secundum. During the first days of life, however, this closure is reversible. Crying by the baby creates a shunt from right to left, which accounts for cyanotic periods in the newborn. Constant apposition gradually leads to fusion of the two septa in about 1 year. In 20% of individuals, however, perfect anatomical closuremay never be obtained (probe patent foramen ovale).

Lymphatic System

The lymphatic system begins its development later than the cardiovascular system, not appearing until the fifth week of gestation. The origin of lymphatic vessels is not clear, but they may form from mesenchyme in situ or may arise as saclike outgrowths from the endothelium of veins. Six primary lymph sacs are formed: two jugular, at the junction of the subclavian and anterior cardinal veins; two iliac, at the junction of the iliac and posterior cardinal veins; one retroperitoneal, near the root of the mesentery; and one cisterna chyli, dorsal to the retroperitoneal sac. Numerous channels connect the sacs with each other and drain lymph from the limbs, bodywall, head, and neck. Two main channels, the right and left thoracic ducts, join the jugular sacs with the cisterna chyli, and soon an anastomosis forms between these ducts. The thoracic duct then develops from the distal portion of the right thoracic duct, the anastomosis, and the cranial portion of the left thoracic duct. The right lymphatic duct is derived from the cranial portion of the right thoracic duct. Both ducts maintain their original connections with the venous system and empty into the junction of the internal jugular and subclavian veins. Numerous anastomoses produce many variations in the final form of the thoracic duct.

Heart and vascular abnormalities

Heart and vascular abnormalities make up the largest category of human birth defects, accounting for 1% of malformations among live-born infants. Classic examples of cardiovascular teratogens include **rubella virus** and **thalidomide.** Others include **isotretinoin** (**vitamin A**), **alcohol,** and many other compounds. Maternal diseases, such as insulin-dependent **diabetes** and **hypertension,** have also been linked to cardiac defects. Chromosomal abnormalities are associated with heart malformations.

1-Atrial septal defect ; One of the most significant defects is the **ostium secundum** defect, characterized by a large opening between the left and right atria. Occasionally, the oval foramen closes during prenatal life. This abnormality, **premature closure of the**

oval foramen, leads to massive hypertrophy of the right atrium and ventricle and underdevelopment of the left side of the heart. Death usually occurs shortly after birth.
2-Whenever the cushions fail to fuse, the result is a **persistent atrioventricular canal,** combined with a defect in the cardiac septum.
3-Tricuspid atresia, which involves obliteration of the right atrioventricular orifice, is characterized by the absence or fusion of the tricuspid valves. Tricuspid atresia is always associated with (*a*) patency of the oval foramen, (*b*) ventricular septal defect, (*c*) underdevelopment of the right ventricle, and (*d*) hypertrophy of the left ventricle.
4-Ventricular septal defect (**VSD**) involving the membranous portion of the septum is the most common congenital cardiac malformation, occurring as an isolated condition in 12/10,000 births.
5-Tetralogy of Fallot, the most frequently occurring abnormality of the **conotruncal** region, is due to an unequal division of the conus resulting from anterior displacement of the conotruncal septum.
6-Persistent truncus arteriosus results when the conotruncal ridges fail to fuse and to descend toward the ventricles
7-Transposition of the great vessels occurs when the conotruncal septum fails to follow its normal spiral course and runs straight down
8- Valvular stenosis of the pulmonary artery or aorta occurs when the semilunar valves are fused for a variable distance.
9-When fusion of the semilunar aortic valves is complete–**aortic valvular atresia**,the aorta, left ventricle, and left atrium are markedly underdeveloped
10-Ectopia cordis is a rare anomaly in which the heart lies on the surface of the chest. It is caused by failure of the embryo to close the ventral body wall

11-A patent ductus arteriosus, one of the most frequently occurring abnormalities of the great vessels.
12- In coarctation of the aorta, which occurs in 3.2/10,000 births, the aortic lumen below the origin of the left subclavian artery is significantly narrowed.
13- Abnormal origin of the right subclavian artery, double aortic arch,,,,,
14- A double inferior vena cava, Absence of the inferior vena cava, A double superior vena cava,,,,,,,