BRAUNWALD

HEART DISEASE

A Textbook of Cardiovascular Medicine

5TH EDITION

VOLUME 2

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Edited by

EUGENE BRAUNWALD A.B., M.D., M.A. (hon.), M.D. (hon.), Sc.D. (hon.), F.R.C.P.

Vice President for Academic Programs, Partners HealthCare System; Distinguished Hersey Professor of Medicine, Faculty Dean for Academic Programs at Brigham and Women's Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

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Congenital Heart Disease in Infancy and Childhood

WILLIAM F. FRIEDMAN

GENERAL CONSIDERATIONS

DEFINITION

Congenital cardiovascular disease is defined as an *abnormality in cardiocirculatory structure or function that is present at birth, even if it is discovered much later.* Congenital cardiovascular malformations usually result from altered embryonic development of a normal structure or failure of such a structure to progress beyond an early stage of embryonic or fetal development. The aberrant patterns of flow created by an anatomical defect may, in turn, significantly influence the structural and functional development of the remainder of the circulation. For instance, the presence in utero of mitral atresia may prohibit normal development of the left ventricle, aortic valve, and ascending aorta. Similarly, constriction of the fetal ductus arteriosus may result directly in right ventricular dilatation and tricuspid regurgitation in the fetus and newborn, contribute importantly to the development of pulmonary arterial aneurysms in the presence of ventricular septal defect and absent pulmonic valve, or, further, result in an alteration in the number and caliber of fetal and newborn pulmonary vascular resistance vessels.

POSTNATAL EVENTS. These may markedly influence the clinical presentation of a specific "isolated" malformation. The infant with Ebstein's malformation of the tricuspid valve may improve dramatically as the magnitude of tricuspid regurgitation diminishes with normal fall in pulmonary vascular resistance after birth; the infant with hypo-

plastic left heart syndrome or interrupted aortic arch may not exhibit circulatory collapse; and the baby with pulmonic atresia or severe stenosis may not become cyanotic until normal spontaneous closure of a patent ductus arteriosus occurs. Ductal constriction many days after birth also may be a central factor in some infants in the development of coarctation of the aorta. Still later in life the patient with a ventricular septal defect may experience spontaneous closure of the abnormal communication, or develop right ventricular outflow tract obstruction and/or aortic regurgitation or pulmonary vascular obstructive disease. These selected examples serve to emphasize that anatomical and physiological changes in the heart and circulation may continue indefinitely from prenatal life in association with any specific congenital cardiocirculatory lesion.

Certain congenital defects are not apparent on gross inspection of the heart or circulation. Examples include the electrophysiological pathways for ventricular preexcitation or interruptions in the cardiac conduction system giving rise to paroxysmal supraventricular tachycardia or congenital complete heart block, respectively. Similarly, abnormalities in the development of myocardial autonomic innervation or in the ultrastructure of myocardial cells may ultimately prove to contribute to asymmetrical septal hypertrophy and left ventricular outflow tract obstruction. These examples make clear that occasional difficulties arise in distinguishing between congenital anomalies that are readily apparent at or shortly after birth and lesions that may have as their basis a subtle or undetectable abnormality that is present at birth.

INCIDENCE. The true incidence of congenital cardiovascular malformations is difficult to determine accurately, partly because of the difficulties in definition discussed above. About 0.8 per cent of live births are complicated by a cardiovascular malformation.[1] This figure does not take into account what may be the two most common cardiac anomalies: the congenital, nonstenotic bicuspid aortic valve[2] and the leaflet abnormality associated with mitral valve prolapse.[3] Moreover, the widely quoted 0.8 per cent incidence figure fails to include small preterm infants, almost all of whom have persistent patent ductus arteriosus. Further, if the calculations were to include stillbirths and abortuses, the incidence would be greatly increased. Cardiac malformations occur 10 times more often in stillborn than in liveborn babies, and many early spontaneous abortions are associated with chromosomal defects (see Chapter 49).[1] Thus, it is clear that past statistical analyses have seriously *underestimated* the incidence of congenital heart disease.

Precise data concerning the frequency of individual congenital lesions also are lacking, and the results of many analyses differ, depending on the source (living or dead) and the selection of the study population. Table 29–1 is a compilation from both clinical and pathological studies that approximates the frequency of occurrence of specific cardiovascular malformations.[4,5,5a]

Taken in toto, children with congenital heart disease are predominantly male. Moreover, specific defects may show a definite gender preponderance; patent ductus arteriosus, Ebstein's anomaly of the tricuspid valve, and atrial septal defect are more common in *females,* whereas valvular aortic stenosis, coarctation of the aorta, hypoplastic left heart, pulmonary and tricuspid atresia, and transposition of the great arteries are more common in *males.*[6]

Extracardiac anomalies occur in about 25 per cent of infants with significant cardiac disease,[7] and their presence may significantly increase mortality. The extracardiac anomalies often are multiple, in part involving the musculoskeletal system; one third of infants with both cardiac and extracardiac anomalies have some established syndrome.

TABLE 29–1 RELATIVE FREQUENCY OF OCCURRENCE OF CARDIAC MALFORMATIONS AT BIRTH

DISEASE	PERCENTAGE
Ventricular septal defect	30.5
Atrial septal defect	9.8
Patent ductus arteriosus	9.7
Pulmonic stenosis	6.9
Coarctation of the aorta	6.8
Aortic stenosis	6.1
Tetralogy of Fallot	5.8
Complete transposition of the great arteries	4.2
Persistent truncus arteriosus	2.2
Tricuspid atresia	1.3
All others	16.5

Data based on 2310 cases.

ETIOLOGY

Malformations appear to result from an interaction between multifactorial genetic and environmental systems too complex to allow a single specification of cause[8]; in most instances, a causal factor cannot be identified. Maternal rubella, ingestion of thalidomide and isoretinoin early during gestation, and chronic maternal alcohol abuse are environmental insults known to interfere with normal cardiogenesis in humans.[9–11] *Rubella syndrome* consists of cataracts, deafness, microcephaly, and, either singly or in combination, patent ductus arteriosus, pulmonic valvular and/or arterial stenosis, and atrial septal defect. *Thalidomide* exposure is associated with major limb deformities and, occasionally, with cardiac malformations without predilection for a specific lesion. Tricuspid valve anomalies are associated with the ingestion of *lithium* during pregnancy. The *fetal alcohol syndrome* consists of microcephaly, micrognathia, microphthalmia, prenatal growth retardation, developmental delay, and cardiac defects. The latter—often defects of the ventricular septum—occur in about 45 per cent of affected infants. *Maternal lupus erythematosus* during pregnancy has been linked to congenital complete heart block (see p. 949). Animal experiments have incriminated hypoxia, deficiency or excess of several vitamins, intake of several categories of drugs, and ionizing irradiation as teratogens capable of causing cardiac malformations. The precise relation of these animal teratogens to human malformations is not clear.

The genetic aspects of congenital heart disease are discussed extensively in Chap. 49. A single gene mutation may be causative in the familial forms of atrial septal defect with prolonged AV conduction, mitral valve prolapse, ventricular septal defect, congenital heart block, situs inversus, pulmonary hypertension, and the syndromes of Noonan, LEOPARD, Ellis–van Creveld, and Kartagener. In recent years, the genes responsible for several defects have either been mapped (e.g., long QT syndrome, Holt-Oram syndrome) or identified (e.g., Marfan syndrome, hypertrophic cardiomyopathy, supravalvular aortic stenosis). Contiguous gene defects on the long arm of chromosome 22 likely underlie the conotruncal malformations of the DiGeorge and velocardiofacial syndromes.[12,13] Table 29–2 provides a partial list of syndromes in which cardiovascular anomalies may be manifestations of the pleiotropic effects of single genes or examples of gross chromosomal defects. Less than 10 per cent of all cardiac malformations can be accounted for by chromosomal aberrations or genetic mutations or transmission.

The finding that, with some exceptions, only one of a pair of monozygotic twins is affected by congenital heart disease indicates that the vast majority of cardiovascular malformations are not inherited in a simple manner.[14] However, this observation may have led, in the past, to an underestimation of genetic contribution, because most recent twin studies reveal more than double the incidence of heart defects in monozygotic twins but usually only one of the pair.[15] Family studies indicate a twofold to tenfold increase in the incidence of congenital heart disease in siblings of affected patients or in the offspring of an affected parent. Malformations often are concordant or partially

concordant within families.[16,17] Because the incidence of congenital heart disease in the offspring or siblings of an index patient is only 2 to 10 per cent, it is seldom wise to discourage the parents of one affected child from having additional children if either parent is free of a cardiovascular anomaly.[1] Moreover, the low recurrence rate and the increasing possibilities for effective treatment for nearly all cardiac lesions usually justify a positive approach to family counseling. When two or more members of the family are affected, the recurrence risk may be quite high, and a pedigree should be obtained before further counseling. If a dominant or recessive mendelian pattern is established, the mendelian laws apply, and the risk of recurrence in each pregnancy is equal.

PREVENTION

The feasibility of preventive programs depends on what is learned in the future about the 90 per cent or more of cardiovascular anomalies for which no cause currently is known. Strict testing in animals of new drugs that may be teratogenic when taken during pregnancy may be expected to reduce the chances of another thalidomide tragedy. In this regard, the dictum cannot be emphasized too strongly that no medication should be taken during pregnancy without prior consultation with a physician. Physicians who deal with pregnant women should be aware of known teratogens as well as drugs that may have a functional rather than a structural damaging influence on the fetal and newborn heart and circulation, and should recognize that drugs abound for which there is inadequate information concerning their teratogenic potential. Similarly, appropriate radiological equipment and techniques for reducing gonadal and fetal radiation exposure should always be used to reduce the potential hazards of this likely cause of birth defects.

Detection of abnormal chromosomes in fetal cells obtained from amniotic fluid or chronic villus biopsy (Chap. 49) may predict cardiac malformation as one component of the multisystem involvement that may exist in such syndromes as Down, Turner, or trisomy 13–15 (D1) or 16–18 (E). Similarly, identification in such cells of the enzyme disorders observed in the mucopolysaccharidoses, homocystinuria, or type II glycogen storage disease may allow one to predict the ultimate presence of cardiac disease. Finally, immunization of children with rubella vaccine will avoid the effects of maternal rubella and its cardiac consequences.

EMBRYOLOGY

NORMAL CARDIAC DEVELOPMENT. Correlation of anatomical features of malformed hearts and embryonic cardiac morphology allows a developmental analysis of various anomalies. Detailed accounts of the normal development of the cardiovascular system are provided elsewhere.[18–20] In brief, during the first month of gestation the primitive, straight cardiac tube is formed, comprising the sinuatrium, the primitive ventricle, the bulbus cordis, and the truncus arteriosus in series, from cephalad to caudad. In the second month of gestation this tube doubles over on itself to form two parallel pumping systems, each with two chambers and a great artery. The two atria develop from the sinuatrium; the atrioventricular canal is divided by the endocardial cushions into tricuspid and mitral orifices; and the right and left ventricles develop from the primitive ventricle and bulbus cordis. Differential growth of myocardial cells causes the straight cardiac tube to bear to the right, and the bulboventricular portion of the tube doubles over on itself, bringing the ventricles side by side. Migration of the atrioventricular canal to the right and of the ventricular septum to the left serves to align each ventricle with its appropriate atrioventricular valve. At the distal end of the cardiac tube the bulbus cordis divides into a subaortic muscular conus and a subpulmonic muscular conus; the subpulmonic conus elongates and the subaortic conus resorbs, allowing the aorta to move posteriorly and connect with the left ventricle.

ABNORMAL DEVELOPMENT. A host of anomalies may result from defects in this basic developmental pattern. Thus, double-inlet left ventricle (see p. 944) is observed if the tricuspid orifice does not align over the right ventricle. The various types of persistent truncus arteriosus (p. 907) result from failure of the truncus to divide into main pulmonary artery and aorta. Double-outlet anomalies of the right ventricle (p. 941) are produced by failure of either the subpulmonic or subaortic conus to resorb, whereas resorption of the subpulmonic instead of the subaortic conus may be central to transposition of the great arteries (p. 935).

THE ATRIA. The primitive sinuatrium is separated into right and left atria by the downgrowth from its roof of the septum primum toward the atrioventricular canal, thereby creating an inferior intraatrial ostium primum opening (Fig. 29–1). Multiple perforations form in the anterosuperior portion of the septum primum as the septum secundum begins to develop to the right of the former. The coalescence of these perforations forms the ostium secundum. The septum secundum completely separates the atrial chambers except for a central opening—the fossa ovalis—which is covered by tissue of the septum primum, forming the valve of the foramen ovale.

Fusion of the endocardial cushions anteriorly and posteriorly divides the atrioventricular canal into tricuspid and mitral inlets (Fig. 29–2). The inferior portion of the atrial septum, the superior portion of the ventricular septum, and portions of the septal leaflets of both the tricuspid and mitral valves are formed from the endocardial cushions. The integrity of the atrial septum depends on growth of the septum primum and septum secundum and proper fusion of the endocardial cushions. Atrial septal defects (see p. 896) and varying degrees of endocardial cushion defect (see p. 898) are the result of developmental deficiencies of this process.

THE VENTRICLES. Partitioning of the ventricles occurs as cephalic growth of the main ventricular septum results in its fusion with the endocardial cushions and the infundibular or conus septum. Defects in the ventricular septum may occur owing to a deficiency of septal substance; malalignment of septal components in different planes, preventing their fusion; or an overly long conus, keeping the septal components apart. Isolated defects probably result from the first mechanism, whereas the latter two appear to generate the ventricular defects seen in tetralogy of Fallot (p. 929) and transposition complexes (p. 935).

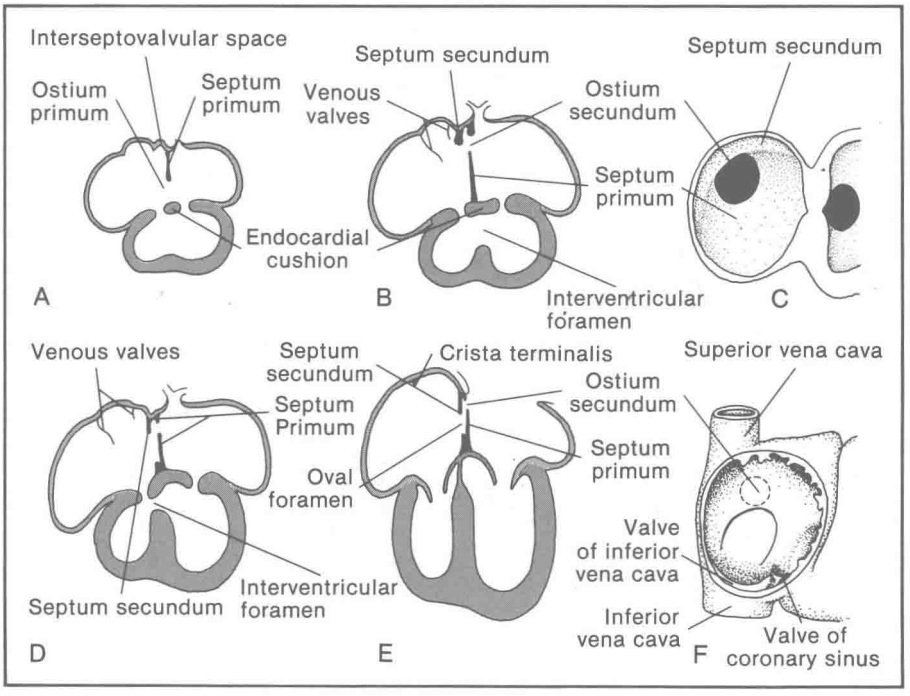

FIGURE 29–1. Diagrammatic representation of the atrial septa at 30 days *(A)*, at 33 days *(B)*, at 33 days (seen from the right side) *(C)*, at 37 days *(D)*, and in the newborn *(E)*; the newborn atrial septum viewed from the right *(F)*. (From Clark, E. B., and Van Mierop, L. H. S.: Development of the cardiovascular system. *In* Moss' Heart Disease in Infants, Children, and Adolescents. Baltimore, © Williams and Wilkins, 1989.)

TABLE 29–2 SYNDROMES WITH ASSOCIATED CARDIOVASCULAR INVOLVEMENT

SYNDROME	MAJOR CARDIOVASCULAR MANIFESTATIONS	MAJOR NONCARDIAC ABNORMALITIES
Heritable and Possibly Heritable		
Ellis–van Creveld	Single atrium or atrial septal defect	Chondrodystrophic dwarfism, nail dysplasia, polydactyly
TAR (thrombocytopenia–absent radius)	Atrial septal defect, tetralogy of Fallot	Radial aplasia or hypoplasia, thrombocytopenia
Holt-Oram	Atrial septal defect (other defects common)	Skeletal upper limb defect, hypoplasia of clavicles
Kartagener	Dextrocardia	Situs inversus, sinusitis, bronchiectasis
Laurence-Moon-Biedl-Bardet	Variable defects	Retinal pigmentation, obesity, polydactyly
Noonan	Pulmonic valve dysplasia, cardiomyopathy (usually hypertrophic)	Webbed neck, pectus excavatum, cryptorchidism
Tuberous sclerosis	Rhabdomyoma, cardiomyopathy	Phakomatosis, bone lesions, hamartomatous skin lesions
Multiple lentigines (LEOPARD)	Pulmonic stenosis	Basal cell nevi, broad facies, rib anomalies, deafness
Rubinstein-Taybi	Patent ductus arteriosus (others)	Broad thumbs and toes, hypoplastic maxilla, slanted palpebral fissures
Familial deafness	Arrhythmias, sudden death	Sensorineural deafness
Weber-Osler-Rendu	Arteriovenous fistulas (lung, liver, mucous membranes)	Multiple telangiectasias
Apert	Ventricular septal defect	Craniosynostosis, midfacial hypoplasia, syndactyly
Crouzon's	Patent ductus arteriosus, aortic coarctation	Ptosis with shallow orbits, craniosynostosis, maxillary hypoplasia
Hypertrophic cardiomyopathy	Asymmetric septal hypertrophy	Family history of sudden death
Incontinentia pigmenti	Patent ductus arteriosus	Irregular pigmented skin lesions, patchy alopecia, hypodontia
Alagille (arteriohepatic dysplasia)	Peripheral pulmonic stenosis, pulmonic stenosis	Biliary hypoplasia, vertebral anomalies, prominent forehead, deep-set eyes
DiGeorge	Interrupted aortic arch, tetralogy of Fallot, truncus arteriosus	Thymic hypoplasia or aplasia, parathyroid aplasia or hypoplasia, ear anomalies
Friedreich's ataxia	Cardiomyopathy and conduction defects	Ataxia, speech defect, degeneration of spinal cord dorsal columns
Muscular dystrophy	Cardiomyopathy	Pseudohypertrophy of calf muscles, weakness of trunk and proximal limb muscles
Cystic fibrosis	Cor pulmonale	Pancreatic insufficiency, malabsorption, chronic lung disease
Sickle cell anemia	Cardiomyopathy, mitral regurgitation	Hemoglobin SS
Conradi-Hünermann	Ventricular septal defect, patent ductus arteriosus	Asymmetrical limb shortness, early punctate mineralization, large skin pores
Cockayne	Accelerated atherosclerosis	Cachectic dwarfism, retinal pigment abnormalities, photosensitivity dermatitis
Progeria	Accelerated atherosclerosis	Premature aging, alopecia, atrophy of subcutaneous fat, skeletal hypoplasia
Connective Tissue Disorders		
Cutis laxa	Peripheral pulmonic stenosis	Generalized disruption of elastic fibers, diminished skin resilience, hernias
Ehlers-Danlos	Arterial dilatation and rupture, mitral regurgitation	Hyperextensible joints, hyperelastic and friable
Marfan	Aortic dilatation, aortic and mitral incompetence	Gracile habitus, arachnodactyly with hyperextensibility, lens subluxation
Osteogenesis imperfecta	Aortic incompetence	Fragile bones, blue sclerae
Pseudoxanthoma elasticum	Peripheral and coronary arterial disease	Degeneration of elastic fibers in skin, retinal angioid streaks
Inborn Errors of Metabolism		
Pompe disease	Glycogen storage disease of heart	Acid maltase deficiency, muscular weakness
Homocystinuria	Aortic and pulmonary artery dilatation, intravascular thrombosis	Cystathionine synthetase deficiency, lens subluxation, osteoporosis

TABLE 29–2 SYNDROMES WITH ASSOCIATED CARDIOVASCULAR INVOLVEMENT—*Continued*

SYNDROME	MAJOR CARDIOVASCULAR MANIFESTATIONS	MAJOR NONCARDIAC ABNORMALITIES
Inborn Errors of Metabolism, *continued*		
Mucopolysaccharidoses: Hurler; Hunter	Multivalvular and coronary and great artery disease; cardiomyopathy	Hurler: Deficiency of α-L-iduronidase, corneal clouding, coarse features, growth and mental retardation Hunter: Deficiency of L-idurano-sulfate sulfatase, coarse facies, clear cornea, growth and mental retardation
Morquio; Scheie; Maroteaux-Lamy	Aortic regurgitation	Morquio: Deficiency of *N*-acetylhexosamine sulfate sulfatase, cloudy cornea, severe bone changes involving vertebrae and epiphyses Scheie: Deficiency of α-L-iduronidase, cloudy cornea, normal intelligence, peculiar facies Maroteaux-Lamy: Deficiency of arylsulfatase B, cloudy cornea, osseous changes
Chromosomal Abnormalities		
Trisomy 21 (Down syndrome)	Endocardial cushion defect, atrial or ventricular septal defect, tetralogy of Fallot	Hypotonia, hyperextensible joints, mongoloid facies, mental retardation
Trisomy 13(D)	Ventricular septal defect, right ventricle patent ductus arteriosus, double-outlet right ventricle	Single midline intracerebral ventricle with midfacial defects, polydactyly, nail changes, mental retardation
Trisomy 18(E)	Congenital polyvalvular dysplasia, ventricular septal defect, patent ductus	Clenched hand, short sternum, low arch dermal ridge pattern on fingertips, mental retardation
Cri du chat (short-arm deletion-5)	Ventricular septal defect	Cat cry, microcephaly, antimongoloid slant of palpebral fissures, mental retardation
XO (Turner)	Coarctation of aorta, bicuspid aortic valve, aortic dilatation	Short female, broad chest, lymphedema, webbed neck
XXXY and XXXXX	Patent ductus arteriosus	XXXY: Hypogenitalism, mental retardation, radial-ulnar synostosis XXXXX: Small hands, incurving of fifth fingers, mental retardation
Sporadic Disorders		
VATER association	Ventricular septal defect	Vertebral anomalies, anal atresia, tracheoesophageal fistula, radial and renal anomalies
CHARGE association	Tetralogy of Fallot (other defects common)	Colobomas, choanal atresia, mental and growth deficiency, genital and ear anomalies
Williams	Supravalvular aortic stenosis, peripheral pulmonic stenosis	Mental deficiency, elfin facies, loquacious personality, hoarse voice
Cornelia de Lange	Ventricular septal defect	Micromelia, synophrys, mental and growth deficiency
Shprintzen (velocardiofacial)	Ventricular septal defect, tetralogy of Fallot, right aortic arch	Cleft palate, prominent nose, slender hands, learning disability
Long Q-T (Jervell and Lange-Nielsen, Romano-Ward)	Long Q-T interval, ventricular arrhythmias	Family history of sudden death, congenital deafness (not in Romano-Ward)
Teratogenic Disorders		
Rubella	Patent ductus arteriosus, pulmonic valvular and/or arterial stenosis, atrial septal defect	Cataracts, deafness, microcephaly
Alcohol	Ventricular septal defect (other defects)	Microcephaly, growth and mental deficiency, short palpebral fissures, smooth philtrum, thin upper lip
Dilantin	Pulmonic stenosis, aortic stenosis, coarctation, patent ductus arteriosus	Hypertelorism, growth and mental deficiency, short phalanges, bowed upper lip
Thalidomide	Variable	Phocomelia
Lithium	Ebstein's anomaly, tricuspid atresia	None

Modified from Friedman, W. F.: Congenital heart disease. *In* Isselbacher, K. I., Braunwald, E. et al. (eds.): Harrison's Principles of Internal Medicine. 13th ed. New York, McGraw-Hill Book Co., 1994, p. 1038.

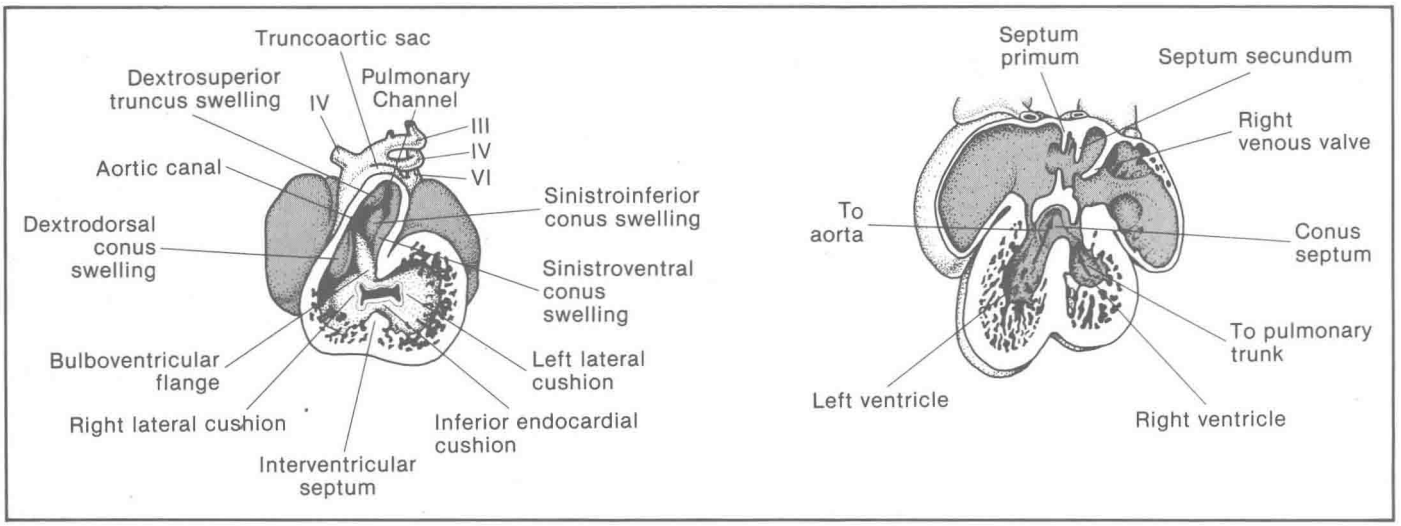

FIGURE 29–2. Frontal section through the heart of a 9-mm embryo (left panel) and 15-mm embryo (right panel). At 9 mm, development is noted of the cushions in the atrioventricular canal, and the truncus and conus swellings are visible. At 15 mm, the conus septum is completed; note the septation in the atrial region. (From Clark, E. B., and Van Mierop, L. H. S.: Development of the cardiovascular system. *In* Moss' Heart Disease in Infants, Children, and Adolescents. Baltimore, © Williams and Wilkins, 1989.)

THE LUNGS. These structures arise from the primitive foregut and are drained early in embryogenesis by channels from the splanchnic plexus to the cardinal and umbilicovitelline veins. An outpouching from the posterior left atrium forms the common pulmonary vein, which communicates with the splanchnic plexus, establishing pulmonary venous drainage to the left atrium. The umbilicovitelline and anterior cardinal vein communications atrophy as the common pulmonary vein is incorporated into the left atrium. Anomalous pulmonary venous connections (see p. 946) to the umbilicovitelline (portal) venous system or to the cardinal system (superior vena cava) result from failure of the common pulmonary vein to develop or establish communications to the splanchnic plexus. Cor triatriatum (see p. 923) results from a narrowing of the common pulmonary vein–left atrial junction.

THE GREAT ARTERIES. The truncus arteriosus is connected to the dorsal aorta in the embryo by six pairs of aortic arches. Partition of the truncus arteriosus into two great arteries is a result of the fusion of tissue arising from the back wall of the vessel and the truncus septum. Rotation of the truncus coils the aorticopulmonary septum and creates the normal spiral relation between aorta and pulmonary artery. Semilunar valves and their related sinuses are created by absorption and hollowing out of tissue at the distal side of the truncus ridges. Aorticopulmonary septal defect (see p. 906) and persistent truncus arteriosus (see p. 907) represent varying degrees of partitioning failure.

Although the six aortic arches appear sequentially, portions of the arch system and dorsal aorta disappear at different times during embryogenesis (Fig. 29–3). The first, second, and fifth sets of paired

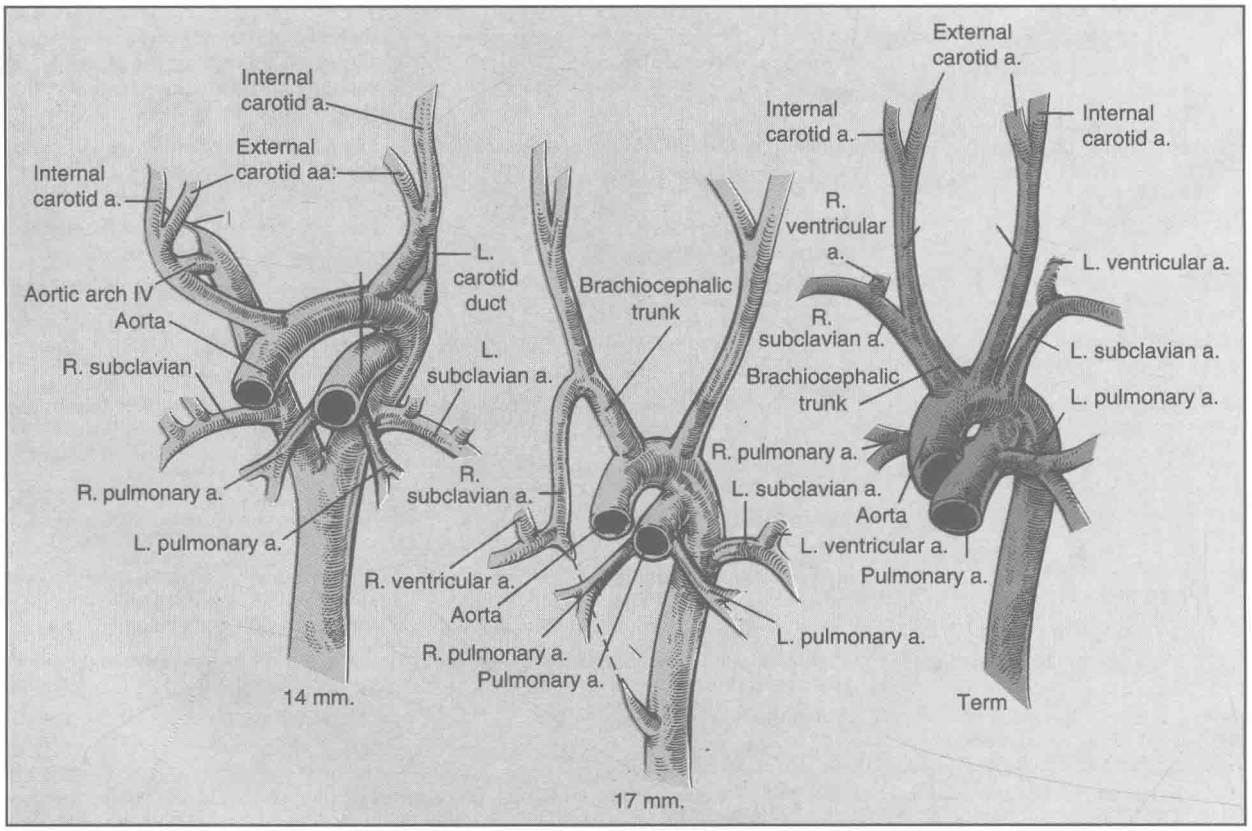

FIGURE 29–3. Transformation of the aortic arches and dorsal aortae into the definitive vascular pattern is a process of fusion and segmental resorption of the paired first to sixth branchial arches with the paired dorsal aortae. (From Castaneda, A., et al.: Cardiac Surgery of the Neonate and Infant. Philadelphia, W.B. Saunders Company, 1994, p. 398.)

arches regress completely. The proximal portions of the sixth arches become the right and left pulmonary arteries and the distal left sixth arch becomes the ductus arteriosus. The third aortic arch forms the connection between internal and external carotid arteries, while the left fourth arch becomes the arterial segment between left carotid and subclavian arteries; the proximal portion of the right subclavian artery forms from the right fourth arch. An abnormality in regression of the arch system in a number of sites can produce a wide variety of arch anomalies, whereas a failure of regression usually results in a double aortic arch malformation.

FETAL AND TRANSITIONAL CIRCULATIONS

Although the illness created by the presence of a cardiac malformation is almost always recognized only after an affected baby is born, important effects on the circulation have existed from early in pregnancy until the time of delivery. Thus knowledge of the changes in cardiocirculatory structure, function, and metabolism that accompany development is central to a systematic comprehension of congenital heart disease.

FETAL CIRCULATORY PATHWAYS. Dynamic alterations occur in the circulation during the transition from fetal to neonatal life when the lungs take over the function of gas exchange from the placenta. The single fetal circulation consists of parallel pulmonary and systemic pathways (Fig. 29–4) in contrast to the two-circuit system in the newborn and adult, in whom the pulmonary vasculature exists in series with the systemic circulation. Prenatal survival is not endangered by major cardiac anomalies as long as one side of the heart can drive blood from the great veins to the aorta; in the fetus, blood can bypass the nonfunctioning lungs both proximal and distal to the heart.

Oxygenated blood returns from the placenta through the umbilical vein and enters the portal venous system. A variable amount of this stream bypasses the hepatic microcirculation and enters the inferior vena cava by way of the ductus venosus. Inferior vena caval blood is composed to flow from the ductus venosus, hepatic vein, and lower body venous drainage, which is summarily deflected to a significant extent across the foramen ovale into the left atrium. Almost all superior vena caval blood passes directly through the tricuspid valve entering the right ventricle. Most of the blood that reaches the right ventricle bypasses the high-resistance, unexpanded lungs and passes through the ductus arteriosus into the descending aorta. The right ventricle contributes about 55 per cent and the left 45 per cent to the total fetal cardiac output. The major portion of blood ejected from the left ventricle supplies the brain and upper body, with lesser flow to the coronary arteries; the balance passes across the aortic isthmus to the descending aorta, where it joins with the large stream from the ductus arteriosus before flowing to the lower body and placenta.

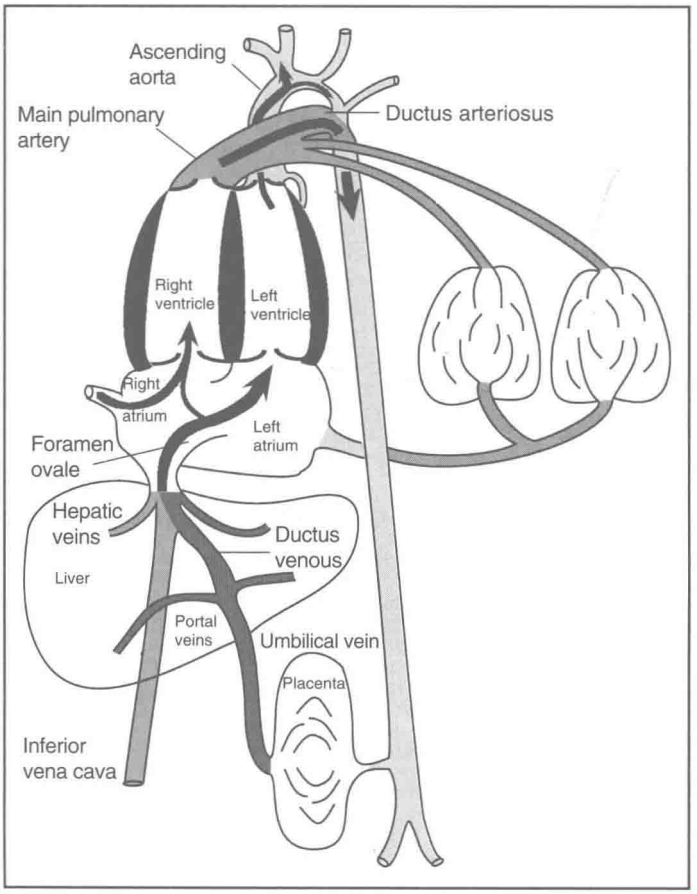

FIGURE 29–4. The fetal circulation with arrows indicating the directions of flow. A fraction of umbilical venous blood enters the ductus venosus and bypasses the liver. This relatively low-oxygenated blood flows across the foramen ovale to the left heart, preferentially perfusing the coronary arteries, head, and upper trunk. The output of the right ventricle flows preferentially across the ductus arteriosus and circulates to the placenta as well as to the abdominal viscera and lower trunk. (Courtesy of David Teitel, M.D.)

FETAL PULMONARY CIRCULATION. In fetal life, pulmonary arteries and arterioles are surrounded by a fluid medium, have relatively thick walls and small lumina, and resemble comparable arteries in the systemic circulation. The low pulmonary blood flow in the fetus (7 to 10 per cent of the total cardiac output) is the result of high pulmonary vascular resistance. Fetal pulmonary vessels are highly reactive to changes in oxygen tension or in the pH of blood perfusing them as well as to a number of other physiological and pharmacological influences.

EFFECTS OF CARDIAC MALFORMATIONS ON THE FETUS. Although fetal somatic growth may be unimpaired, the hemodynamic effects in utero of many cardiac malformations may alter the development and structure of the fetal heart and circulation.[21] Thus, total anomalous pulmonary venous connection in utero may result in underdevelopment of the left atrium and left ventricle (see p. 944), and premature closure of the foramen ovale may result in hypoplasia of the left ventricle. Moreover, postnatally, the caliber of the aortic isthmus may be reduced (see p. 913) in the presence of lesions in utero that create left ventricular hypertrophy and impede filling because of reduced compliance of that chamber. It may also be reduced in the presence of a lesion that interferes with left ventricular filling directly (e.g., mitral stenosis) or indirectly by diverting a proportion of left ventricular output away from the ascending aorta while increasing right ventricular output and ductus arteriosus flow (e.g., atrioventricular septal defect with left ventricular–right atrial shunt or aortic or subaortic stenosis with ventricular septal defect). Similarly, obstruction in utero to right ventricular outflow is associated with an increase in proximal aortic flow and diameter and almost never with aortic coarctation (see p. 965). In these and other examples it is important to recognize that malformations compatible with fetal survival may nonetheless result in abnormal development of the circulation in utero and also affect circulatory adjustments after birth.

FUNCTION OF THE FETAL HEART. Compared with the adult heart, the fetal and newborn heart is unique with respect to its ultrastructural appearance,[22] its mechanical and biochemical properties,[23–27] and its autonomic innervation.[24,27] During late fetal and early neonatal development there is maturation of the excitation-contraction coupling process[25,26,30,31] and the biochemical composition of the heart's energy-utilizing myofibrillar proteins and of adenosine triphosphate and creatine phosphate energy-producing proteins.[27] Moreover, fetal and neonatal myocardial cells are small in diameter and reduced in density, so that the young heart contains relatively more noncontractile mass (primarily mitochondria, nuclei, and surface membranes) than later in postnatal life. As a result, force generation and the extent and velocity of shortening are decreased, and stiffness and water content of ventricular myocardium are increased in the fetal and early newborn periods.

The diminished function of the young heart is reflected in its limited ability to increase cardiac output in the presence of either a volume load or a lesion that increases resistance to emptying.[32] Although functional integrity exists of efferent and afferent cardiac autonomic pathways early in life, fetal and newborn myocardium lacks the complete development of sympathetic but not cholinergic innervation. Thus, adaptation to cardiocirculatory stress in fetal or early newborn life may be less effective than in adulthood.

CHANGES AT BIRTH. The fundamental change that normally occurs at birth is a division of the single parallel fetal circulation into separate, independent circulations. Inflation of the lungs at the first inspiration produces a marked reduction in pulmonary vascular resistance owing partly to the sudden suspension in air of fetal pulmonary vessels previously supported by fluid media. The reduced extravascular pressure assists new vessels to open and already patent vessels to enlarge. The rapid decrease in pulmonary vascular resistance is related more importantly to vasodilatation owing to the increase in oxygen tension to which pulmonary vessels are exposed rather than to physical expansion of alveoli with gas. Great interest exists currently in defining the role of nitric oxide in the mediation of changes in pulmonary vascular tone in these events.[22,33] Pulmonary arterial pressure falls, and pulmonary blood flow increases greatly. Systemic vascular resistance rises when clamping of the umbilical cord removes the low-resistance placental circulation. Increased pulmonary blood flow increases the return of blood to the left atrium and raises left atrial pressure, which in turn closes the foramen ovale.

The shift in oxygen dependence from the placenta to the lungs produces a sudden increase in arterial blood oxygen tension, which, in concert with alterations in the local prostaglandin milieu, initiates constriction of the ductus arteriosus.[35] Pulmonary pressure falls further as the ductus constricts. In healthy mature infants the ductus

arteriosus is profoundly constricted at 10 to 15 hours and is closed functionally by 72 hours, with total anatomical closure following within a few weeks by a process of thrombosis, intimal proliferation, and fibrosis. A high incidence exists in preterm infants of persistent patency of the ductus arteriosus because of an immaturity of those mechanisms responsible for constriction (see p. 905). In surviving preterm infants the ductus arteriosus spontaneously closes within 4 to 12 months of birth.

The ductus venosus, ductus arteriosus, and foramen ovale remain potential channels for blood flow after birth. Thus persistent patency of the ductus venosus may mask the most marked signs of pulmonary venous obstruction in infants with total anomalous pulmonary venous connection below the diaphragm (see p. 944). Similarly, lesions producing right or left atrial volume or pressure overload may stretch the foramen ovale and render incompetent the flap valve mechanism for its closure. Anomalies that depend on patency of the ductus arteriosus for preserving pulmonary or systemic blood flow remain latent until the ductus arteriosus constricts. A common example is the rapid intensification of cyanosis observed in the infant with tetralogy of Fallot when the magnitude of pulmonary hypoperfusion is unmasked by spontaneous closure of the ductus arteriosus. Moreover, there is increasing evidence that ductal constriction is a key factor in the postnatal development of coarctation of the aorta (see p. 965). Lastly, it should be recognized that because the ductus arteriosus is potentially patent after birth and the pulmonary resistance vessels are hyperreactive, hypoxic pulmonary vasoconstriction of diverse causes may result in a right-to-left shunt through the ductus.

PATHOLOGICAL CONSEQUENCES OF CONGENITAL CARDIAC LESIONS

CONGESTIVE HEART FAILURE

Although the basic mechanisms of cardiac failure, as outlined in Chapter 13, are similar for all ages, the pediatric cardiologist should clearly recognize that the common causes, time of onset, and often the approach to treatment vary with age.[36–38] The development of fetal echocardiography has allowed the diagnosis of intrauterine cardiac failure.[39–41] The cardinal findings of fetal heart failure are scalp edema, ascites, pericardial effusion, and decreased fetal movements. Although abnormalities in several organ systems may result in nonimmunological fetal hydrops, cardiac causes include a host of structural, functional, rhythm, and metabolic disturbances of the heart. Infants under 1 year of age with cardiac malformations account for 80 to 90 per cent of pediatric patients who develop congestive failure. Moreover, cardiac decompensation in the infant is a medical emergency necessitating immediate treatment if the patient is to be saved.

CAUSES OF HEART FAILURE. In the preterm infant, especially under 1500 gm birthweight, persistent patency of the ductus arteriosus is the most common cause of cardiac decompensation, and other forms of structural heart disease are rare.[42] In the full-term newborn the earliest important causes of heart failure are the hypoplastic left heart and coarctation of the aorta syndromes, sustained tachyarrhythmia, cerebral or hepatic arteriovenous fistula, and myocarditis. Among the lesions commonly producing heart failure beyond age 1 to 2 weeks, when diminished pulmonary vascular resistance allows substantial left-to-right shunting, are ventricular septal and atrioventricular septal defects, transposition of the great arteries, truncus arteriosus, and total anomalous pulmonary venous connection, often with pulmonary venous obstruction. Although heart failure usually is the result of a structural defect or of myocardial disease, it should be recognized that the newborn myocardium may be severely depressed by such abnormalities as hypoxemia and acidemia, anemia, septicemia, marked hypoglycemia, hypocalcemia, and polycythemia. In the older child, heart failure often is due to acquired disease (Chap. 31) or is a complication of open-heart surgical procedures. In the acquired category are rheumatic and endomyocardial diseases, infective endocarditis, hematological and nutritional disorders, and severe cardiac arrhythmias.

CLINICAL MANIFESTATIONS IN THE INFANT. The clinical expression of cardiac decompensation in the infant consists of distinctive signs of pulmonary and systemic venous congestion and altered cardiocirculatory performance that resemble, but often are not identical to, those of the older child or adult (Table 29–3).[36,43] These reflect the interplay between the hemodynamic burden and adaptive responses. Common symptoms and signs are feeding difficulties and failure to gain weight and grow, tachypnea, tachycardia, pulmonary rales and rhonchi, liver enlargement, and cardiomegaly. Less frequent manifestations include peripheral edema, ascites, pulsus alternans, gallop rhythm, and inappropriate sweating. Pleural and pericardial effusions are exceedingly rare. The distinction between left and right heart failure is less obvious in the infant than in the older child or adult because most lesions that create a left ventricular pressure or volume overload also result in left-to-right shunting of blood through the foramen ovale and/or patent ductus arteriosus as well as pulmonary hypertension owing to elevated pulmonary venous pressures. Conversely, augmented filling or elevated pressure of the right ventricle in the infant reduces left ventricular compliance disproportionately when compared with the older child or adult and gives rise to signs of both systemic and pulmonary venous congestion.[37]

Fatigue and dyspnea on exertion express themselves as a feeding problem in the infant. Characteristically, the respiratory rate in heart failure is rapid (50 to 100 breaths/min). In the presence of left ventricular failure, interstitial pulmonary edema reduces pulmonary compliance and results in tachypnea and retractions. Excessive pulmonary blood flow by way of significant left-to-right shunts may further decrease lung compliance. Moreover, upper airway obstruction may be produced by selective enlargement of cardiovascular structures. In patients with large left-to-right shunts and left atrial and main pulmonary artery enlargement, the left main stem bronchus may be compressed, resulting in emphysematous expansion of the left upper or lower lobe or left lower lobe collapse.[44] Respiratory distress with grunting, flaring of the alae nasi, and intercostal retractions is observed when failure is severe and especially when pulmonary infection precipitates cardiac decompensation, which often is the case. Under these circumstances pulmonary rales may be due to the infection or failure, or both. A resting heart rate with little variability is also characteristic of heart failure. Hepatomegaly is regularly seen in infants in failure, although liver tenderness is uncommon. Cardiomegaly may be assessed roentgenographically, but it

TABLE 29–3 FEATURES OF HEART FAILURE IN INFANTS

Poor feeding and failure to thrive
Respiratory distress—mainly tachypnea
Rapid heart rate (160 to 180 beats/min)
Pulmonary rales or wheezing
Cardiomegaly and pulmonary edema on radiogram
Hepatomegaly (peripheral edema unusual)
Gallop sounds
Color—ashen pale or faintly cyanotic
Excessive perspiration
Diminished urine output

must be recognized that in the normal newborn infant, the cardiac diameter may be as much as 60 per cent of the thoracic diameter, and the large thymus gland in infants occasionally interferes with evaluation of heart size. Two-dimensional and Doppler echocardiography provide a good estimate of cardiac performance and chamber dimensions, and values may be compared with data derived from normal infants.[45–49]

Cardiac decompensation may progress with extreme rapidity in the first hours and days of life, producing a clinical picture of advanced cardiogenic shock and a profoundly obtunded infant. The presence of marked hepatomegaly and gross cardiomegaly usually allows distinction from noncardiac causes of diminished systemic perfusion.

The management of the infant with congenital heart disease and heart failure is described on p. 889.

CYANOSIS

Cyanosis is produced by reduced hemoglobin in cutaneous vessels in excess of approximately 3 gm/dl (see p. 891). Peripheral cyanosis usually reflects an abnormally great extraction of oxygen from normally saturated arterial blood, commonly the result of peripheral cutaneous vasoconstriction. Central cyanosis is a result of arterial blood oxygen unsaturation, most often in patients with congenital heart disease caused by shunting of systemic venous blood into the arterial circuit. Infants especially (as compared with adults) may appear cyanotic when in heart failure because of both peripheral and central factors[50]; the latter may include severe impairment of pulmonary function that commonly exists with alveolar hypoventilation, ventilation-perfusion inequality, or impaired oxygen diffusion.

In patients with central cyanosis owing to arterial oxygen unsaturation, the degree of cutaneous discoloration depends on the absolute amount of reduced hemoglobin, the magnitude of the right-to-left shunt relative to systemic flow, and the oxyhemoglobin saturation of venous blood. The last of these depends in turn on the tissue extraction of oxygen. Commonly, cyanosis appears or intensifies with physical activity or exercise as the saturation of systemic venous blood declines concurrent with an increase in right-to-left shunting across a defect as peripheral vascular resistance decreases. Oxygen transfer to the tissues is affected by shifts in the oxygen hemoglobin dissociation relation, which may be altered by blood pH and levels of red blood cell 2,3-diphosphoglycerate concentration.

The clinical approach to the infant with cyanosis is discussed on pp. 890 to 894.

CLUBBING AND POLYCYTHEMIA/ERYTHROCYTOSIS. Prominent accompaniments of arterial hypoxemia are polycythemia and clubbing of the digits. The latter is associated with an increased number of capillaries with increased blood flow through extensive arteriovenous aneurysms and an increase of connective tissue in the terminal phalanges of the fingers and toes. Polycythemia is a physiological response to chronic hypoxemia that stimulates erythrocytosis. The extremely high hematocrits observed in patients with arterial oxygen unsaturation cause a progressive increase in blood viscosity. Because the relationship is nonlinear between hematocrit and blood viscosity, relatively small increases beyond packed blood cell volumes of 60 per cent result in large increases in viscosity. Also, the apparent viscosity of blood increases in the microcirculation where lower shear rates exist, an increasingly important factor as the hematocrit exceeds 70 per cent.

Both the hematocrit and the circulating whole blood volume are increased in polycythemia accompanying cyanotic congenital heart disease; the hypervolemia is the result of an increase in red cell volume. The augmented red blood cell volume provoked by hypoxemia provides an increased oxygen-carrying capacity and enhanced oxygen supply to the tissues. The compensatory polycythemia often is of such severity that it becomes a liability and produces such adverse physiological effects as hyperviscosity, cellular aggregation, and thrombotic lesions in diverse organs and a hemorrhagic diathesis.[51] In this regard, oral steroid contraceptives are contraindicated in the adolescent cyanotic female because of the enhanced risk of cerebral thrombosis.

Management. Red cell volume reduction and replacement with plasma or albumin (erythrophoresis) lower blood viscosity and increase systemic blood flow and systemic oxygen transport, and thus may be helpful in the management of patients with severe hypoxic polycythemia (hematocrit ≥ 65 per cent). A final hematocrit of 55 to 63 per cent should be achieved; the higher level is necessary in patients with low initial oxygen saturation to avoid a severe reduction in arterial oxygen content. Acute phlebotomy without fluid replacement is contraindicated.

CEREBRAL AND PULMONARY COMPLICATIONS. Cerebrovascular accidents and brain abscesses occur particularly in cyanotic patients with substantial arterial desaturation.[52,53] *Cerebral thrombosis* is most common under age 2 years in severely cyanotic children, even in the presence of relatively low hematocrits, and occurs especially in a clinical setting in which oxygen requirements are raised by fever or, if blood viscosity is increased, dehydration.

Brain Abscess. This is an important complication of cyanotic heart disease.[53] Such abscesses are rare under 18 months of age and commonly are of insidious onset marked by headache, low-grade fever, vomiting, and a change in personality. Seizures or paralysis less frequently herald the onset of a brain abscess. Abscess must be suspected in any cyanotic child with focal neurological signs. Morbidity and mortality are related inversely to oxygen saturation levels. Brain abscess is thought to occur in about 2 per cent of the population with cyanotic congenital heart disease; a mortality rate of 30 to 40 per cent often is related to delay in diagnosis and treatment.

Paradoxical Embolus. This is a rare complication of cyanotic heart disease, usually observed only at necropsy.[54] Emboli arising in systemic veins may pass directly to the systemic circulation, because right-to-left intracardiac shunts allow venous blood to bypass the normal filtering action of the lungs.

Retinopathy. Dilated tortuous vessels progressing to papilledema, and retinal edema occasionally are observed in cyanotic patients, and appear to be related to decreased arterial oxygen saturation and/or to erythrocytosis but not to hypercapnia.

Hemoptysis. This is an uncommon but major complication in cyanotic patients with congenital heart disease, and occurs most often in the presence of pulmonary vascular obstructive disease or in patients with an extensive bronchial collateral circulation or pulmonary venous congestion.[55] Massive hemoptysis almost always represents rupture of a dilated bronchial artery.

SQUATTING. After exertion, patients with cyanotic heart disease, especially tetralogy of Fallot, typical assume a squatting posture to obtain relief from breathlessness.[56] Squatting appears to improve arterial oxygen saturation by increasing systemic vascular resistance, thereby diminishing the right-to-left shunt, and also by the pooling of markedly desaturated blood in the lower extremities. In addition, systemic venous return, and therefore pulmonary blood flow, may increase.

HYPOXIC SPELLS. Hypercyanotic or hypoxemic spells commonly complicate the clinical course in younger children with certain types of cyanotic heart disease, especially tetralogy of Fallot (see p. 929).[56] The spells are characterized by anxiety, hyperpnea, and a sudden marked increase in cyanosis; they are the result of an abrupt reduction in pulmonary blood flow. Unless terminated, the hypercyanotic episodes may lead to convulsions and may even be fatal. The sudden reduction in pulmonary blood flow may be precipitated by fluctuations in arterial pCO_2 and pH, a sudden fall in systemic or increase in pulmonary vascular resistance, or an acute increase in the severity of right ventricular outflow tract obstruction either by augmented contraction of the hypertrophied muscle in the right ventricular outflow tract or by a decrease in right ventricular cavity volume owing to tachycardia.

Treatment. This consists of oxygen administration, placing the child in the knee-chest position, and administration of morphine sulfate. Additional medications that may prove of value include the intravenous administration of sodium bicarbonate to correct the accompanying acidemia, alpha-adrenoceptor stimulants such as phenylephrine hydrochloride (Neo-Synephrine) or methoxamine to raise peripheral resistance and diminish right-to-left shunting, and beta-adrenoceptor blocking agents, which reduce cardiac sympathetic tone and depress cardiac contractility directly and increase ventricular volume by reducing heart rate.

ACID-BASE IMBALANCE

Disturbances in blood gas and acid-base equilibrium are noted particularly in infants with either congestive heart failure or cyanosis.[57] Large-volume left-to-right shunts, especially with pulmonary edema, may be associated with moderate respiratory acidemia and a lowering of arterial oxygen tensions, reflecting an increase in the alveolar-arterial oxygen tension gradient and ventilation-perfusion imbalance. Interference with carbon dioxide transport implies moderate to severe failure in these infants. Lesions associated with a reduced systemic cardiac output, such as severe coarctation of the aorta or critical aortic stenosis in infancy, often present as cardiac failure complicated by a severe metabolic acidemia and relatively high values of arterial oxygen tension. The latter finding, even in the presence of right-to-left shunting across a patent ductus arteriosus, is a result of diminished systemic perfusion and an elevated pulmonary-systemic blood flow ratio.