THE GENETICS OF CARDIOVASCULAR DISEASE

edited by

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PREFACE

Over the past 25 years, the growing importance of genetic factors in the basic understanding of human cardiovascular disease has become apparent. Prior to this time, there was an era when cardiovascular disease was first viewed at the diagnostic level followed by an era when cardiovascular disease was viewed at a treatment level. The first era occurred at the turn of the century with the first clinical recognition of symptoms and patterns for diagnosis of cardiovascular diseases. The development of diagnostic methodology, such as radiographic studies and electrocardiography, led to marked changes in our understanding of cardiovascular disease. This era was followed by improved methods of medical treatment, introduction of medication such as antibiotics, and more sophisticated surgical techniques.

Now we are in an era in which efforts are being made to prevent cardiovascular disease, prevention through methods such as risk factor identification for atherosclerosis, prophylactic antibiotics, and appropriate diagnosis. The prevention of cardiovascular disease has its basis in genetic counseling of the affected individual, of the family, of the physician, and of all allied health professionals. It is now possible to provide genetic counseling about many cardiovascular diseases because of the development of more sophisticated methods of detection of genetic disease, methods such as cytogenetics and chromosomal banding, biochemical genetic definition of enzyme activity, and molecular genetic techniques to identify the causal factors at the gene level. With these tools, the various forms of cardiovascular disease can be studied and many diseases whose cause is presently unknown will be recognized to have a genetic origin or at least a genetic component.

In this book, we have attempted to provide a textbook source of most cardiovascular conditions and their genetic basis. Some of these diseases are primarily cardiac, some involve other organs but have a major cardiac component, and some involve primarily other organ systems but have a minor component which is cardiovascular. We hope that by having this compilation of cardiovascular diseases in one source, it will be of value to all who are involved in the care of patients with cardiovascular disease or their families.

The first six chapters of this book delineate conditions related to congenital cardiac malformations. Their etiology is not precisely known, so we have included chapters that discuss many aspects of congenital cardiac malformations. The first chapter provides discussion of mechanisms of maldevelopment of the heart. We believe that these mechanisms provide a basis for understanding the genetic and environmental factors which operate to produce congenital cardiac malformations.

Chapter 2 describes the occurrence of congenital cardiac malformations in families and provides the current state of knowledge about recurrence risks for the major congenital cardiac malformations. The third chapter provides evidence that congenital cardiac malformations are an important component of syndromes associated with chromosomal aberrations. While some of these chromosomal conditions, such as Down syndrome, or Turner syndrome, are well known, the cardiac and other phenotypic features of more than 60 other chromosomal aberrations are described for handy reference. Knowledge of the presence and type of chromosomal abnormality and cardiac malformation provides valuable information for those who care for these children and for those who counsel the family.

Over the past 20 years, we have learned more about teratogenetic mechanisms and their relationship to the heart. We have included an extensive chapter (chapter 4) on teratogens and the heart. This chapter adds significantly to our understanding of the mechanisms of maldevelopment of the heart, although these malformations are largely due to environmental agents and, to a lesser degree, genetic susceptibility. We believe this chapter on teratogens will be useful for providing counseling to families when situations of fetal exposure have occurred,

and that this chapter will be a medical-legal reference in the future.

Congenital cardiac malformations occur in several multisystem diseases associated with a single gene abnormality. The clinical features and genetic implications of 14 syndromes are discussed in chapter 5. Congenital cardiac malformations may coexist with anomalies of other organ systems. We have the greatest knowledge about the major malformations of the gastrointestinal tract, since they are easily identified and very few escape detection. Chapter 6 provides information regarding the coexistent malformation of these two organ systems.

With the recent development of electrophysiologic techniques for diagnosis, cardiologists have developed the ability to define and classify cardiac rhythm disturbances in a more precise manner. This more detailed recognition will allow us to understand better the genetic aspects of important and occasionally life-threatening arrhythmias of the heart.

Our understanding of cardiac muscle disease remains at an elementary level. Many diseases which result in a cardiomyopathy or cardiac muscle dysfunction have a clear genetic basis (chapter 10, chapter 11). Yet there are many families in which cardiomyopathy occurs in numerous relatives and a known biochemical mechanism has not been defined. Chapter 8 summarizes the present state of knowledge of idiopathic cardiomyopathies.

There is an enormous variety of biochemical diseases which are clearly associated with specific laboratory and clinical findings in the cardiovascular system. These metabolic abnormalities may occur in lipid metabolism (chapter 9), intermediary metabolism (chapter 10), and a wide variety of storage disease (chapter 11). Our understanding of the biochemistry of these diseases is rapidly enlarging, and it is clear that many gains will be made with each passing year.

There are many forms of acquired cardiovascular disease. Many acquired cardiac diseases develop as a component of other conditions which primarily affect other organ systems, such as neuromuscular conditions with cardiac involvement. In chapter 12, we emphasize the potential relationship between abnormalities of skeletal muscle and cardiac muscles. For example, it is already well known that many individuals with major features of cardiomyopathy may also have minor evidence of skeletal muscle weakness.

Heritable diseases of connective tissue, which include the Marfan syndrome, are many and varied. This group of diseases primarily affects the cardiac valves and major blood vessels. Clinical recognition of the patient with this type of disorder will also lead to recognition of the specific patterns of cardiovascular abnormalities.

Hematologic conditions can have a profound affect on the function of the heart. Diseases such as thalassemia and sickle cell anemia have profound cardiovascular effects, not only through the creation of anemia but in the development of cardiac dysfunction. The application of molecular genetic techniques to the study of thalassemia and hemoglobinopathies represents a significant advance in our understanding of these diseases. Furthermore, our ability to provide accurate diagnosis has also been significantly improved.

Systemic hypertension (chapter 14) is a widely prevalent disease in the Western world and a major cardiovascular risk factor. Through satisfactory genetic techniques, many aspects of hypertension are being evaluated, and further development of this area may await the development of rapid molecular genetic diagnostic techniques.

The last two chapters of the book provide information regarding unusual conditions which primarily affect blood vessels and abnormalities of tissue growth. There are a large number of unusual conditions which primarily affect blood capillaries, arteries, veins, and lymphatic vessels. These conditions, such as Milroy disease and familial primary pulmonary hypertension, are discussed together in one chapter for the first time (chapter 16).

The final chapter of this book provides information regarding diseases with abnormal tissue growth (tuberous sclerosis, neurofibromatosis). This is particularly pertinent since neurofibromatosis is a very common genetic condition.

In all of these chapters, the clinical features are described and the cardiovascular manifestations presented. Furthermore, the use of prenatal diagnostic techniques is discussed, and it is clear that the use of new molecular genetic techniques is an important breakthrough in the understanding of many human diseases. We are presently at the threshold of understanding of the molecular biology of the heart. This book is intended as a source book, and periodic revision is planned.

CONTENTS

THE GENETICS OF CARDIOVASCULAR DISEASE

1. MECHANISMS IN THE PATHOGENESIS OF CONGENITAL CARDIAC MALFORMATIONS

Edward B. Clark

Human congenital cardiac malformations are traditionally classified by their anatomic characteristics. Ventricular septal defect, pulmonary valve stenosis, and atrial septal defect are all described according to the location of the abnormalities in the heart. While such a listing is important for physicians and surgeons who treat children with these malformations, a solely anatomic classification may obscure physiologic relationships important for identification of pathogenesis or etiology.

It seems reasonable to approach congenital cardiac malformations from a point of disordered mechanisms. There is a limited repertoire of developmental mechanisms in cardiac morphogenesis as in other developmental processes. Although epidemiologic investigation [1] suggests that etiologic relationships exist among congenital cardiac malformations, little research has been carried out on the basic mechanisms of cardiac morphogenesis. It is unclear how developmental mechanisms are controlled genetically or how they may be altered by environmental factors. An analysis of mechanisms may provide a new basis for assessing the genetics and recurrence risks of congenital heart disease. For some cardiac malformations, the proposed developmental mechanisms have a more convincing basis than for others. Theories of how these mechanisms may apply to human hearts are derived from experimental studies in mammals and chick embryos as well as from correlations with morphologic studies of human hearts.

Two theories have been proposed to explain the etiology and pathogenesis of human congenital cardiac malformations. The first theory views congenital cardiac malformations as phylogenetically determined because of the similarity of some human malformations to those of lower classes of animals. [2] However, we are unlikely ever to know what the hearts of our ancestors looked like. It is also incorrect to assume that the hearts of current amphibians and reptiles are similar to those of their phylogenetic ancestors, since most modern animals have evolved a more specialized and efficient cardiovascular system. Developmental arrest is the second theory. [3] It is valuable to attempt to find the critical time periods at which a teratogenic insult or genetic error may alter cardiac development. Invoking an arrest or cessation in development, however, does not identify the mechanism responsible for the malformations.

In the last 25 years, there has been a renewed interest in the developmental mechanisms of cardiac morphogenesis. [4–9] Most of this experimental work has been performed either in the rodent or the chick embryo. Therefore, application of the experimental information to the human cardiac development requires major extrapolation. In spite of the potential for some variance in mechanisms between species and

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classes of animals, there should be more similarities than differences.

The aim of this chapter is to develop a classification of congenital cardiac malformations according to pathogenic mechanisms. As discussed below, four developmental mechanisms (mesenchymal tissue migration, cardiac hemodynamics, cellular death, extracellular matrix abnormality), either singularly or in combination, likely play a major role in causing human cardiac malformations. Individual developmental mechanisms will be identified in lower animals and relation to specific human congenital cardiac malformations discussed.

Mesenchymal Tissue Migration

The early embryonic heart has insufficient cellular material to complete morphogenesis. Grohmann [10] reached this conclusion from his studies of the mitotic index of embryonic hearts which showed that the rate of cell division decreased during the time of rapid heart growth. Since there are not enough cells to account for the adult heart mass, he hypothesized that mesenchymal tissue moved into the heart during morphogenesis.

Branchial arch mesenchymal tissue is the logical source for the additional cellular mass which participates in cardiac development. Evidence to support this hypothesis comes from experiments in chick embryos by Rychter. [11] Carbon particle markers were placed in branchial arch mesenchyme prior to conotruncal septation and the markers then located in the aorticopulmonary septum after division of the conotruncus and aortic sac. The carbon particles were distributed asymmetrically. Particles from the left 4th and 6th branchial arches were located in the posterior septal wall while those placed in the right 4th and 6th branchial arches were located in the septum separating the lumen of the aorta and pulmonary artery. The difference in lateralization of the markers suggests that branchial arch mesenchymal tissue contributes asymmetrically to the developing outflow tract of the heart.

In the chick embryo, most of the tissue that forms the conotruncal region of the heart is outside of the cardiac mass early in development. Using Rychter's marking technique, de la Cruz and associates [12] demonstrated that carbon particles inserted in the aortic sac in the early cardiac loop stage embryos were located in the conal septum and right ventricular infundibulum at the completion of cardiac morphogenesis. Such in-migration of mesenchymal tissue to the arterial pole of the heart has been subsequently confirmed by other investigators. Thompson and Fitzharris [13] used computer-aided reconstruction to document the waves of cells which move from the branchial arch area into the embryonic heart.

Other experimental evidence suggests that altered cell migration can result in abnormal cardiac morphology. Okamoto and associates [14] irradiated pregnant rats and observed a spectrum of fetal cardiac abnormalities including double outlet right ventricle. Although they were concerned that radiation causes cellular death, radiation also slows cell migration. We [15] have placed a nylon loop around the outflow tract of chick embryos and observed an increase in the distance separating the aortic and mitral valve annuli. We have proposed that cells migrating into the heart were impeded by the nylon loop and contributed to the mass of the posterior conal tissue. We speculate that such mechanical alteration in cell migration is in part responsible for the spectrum of double outlet right ventricle following mechanical distortion of the conotruncus in the experiments of Gessner and VanMierop. [16]

The occipital neural crest contributes cells which participate in conotruncal septation. Using chick-quail chimeras, Kirby and co-workers [17] showed that neural crest cells destined to become components of the autonomic nervous system were located in the aorticopulmonary septum. They also showed that following removal of a portion of the occipital neural crest, embryos developed cardiac malformations similar to truncus arteriosus communis and double outlet right ventricle as well as hypoplasia of the thymus. It is unclear, however, whether these malformations were due to the absence of neural crest cells or a lack of interaction with branchial arch mesenchymal tissue.

CONOTRUNCAL CARDIAC MALFORMATIONS

Anomalies of the outflow tract of the heart are classified anatomically as conotruncal malformations. In humans, the pathogenesis of conotruncal malformations may be related to an abnormality of mesenchymal tissue and/or neural crest migration. Each of the conotruncal malformations occurs in the outflow tract of the

heart with or without other cardiac abnormalities.

A spectrum of human conotruncal malformations exists and varies from separation of the aortic and mitral annuli to complete absence of septation of the outflow pole of the heart (table 1–1). The "forme fruste" conotruncal malformation is a clinically insignificant increase in tissue mass separating the aortic and mitral valve annuli, the posterior conus. Rosenquist and associates [18] observed an increase in the mitral-aortic separation as great as one half the diameter of the aorta in otherwise normal hearts. The subarterial ventricular septal defect is located at the point where the proximal bulbar cushions fuse to separate the aortic and pulmonary outflow tracts. Aorticopulmonary window is an abnormality of conotruncal septation above the plane of the semilunar valves and is a failure of the distal bulbar cushion fusion. In double outlet right ventricle both great vessels originate from the right ventricular cavity; there is a ventricular septal defect and an increase in the posterior conus separating the aortic and mitral annuli. In tetralogy of Fallot, the aorticopulmonary septum is shifted to the right such that the infundibular or anterior conus is abnormal, and there is an associated infracristal ventricular septal defect. Abnormal positioning of the conotruncal cushions in a straight line, rather than in a spiral course, aligns the aorta with the right ventricle and is the probable pathogenic mechanism for d-transposition of the great vessels. [19] At the extreme end of the spectrum, truncus arteriosus communis is characterized by the lack of aorticopulmonary septation.

Several other cardiac anomalies are also probably conotruncal abnormalities. Interruption of the aortic arch between the left carotid and left subclavian arteries, type B interrupted aortic arch, is likely related to branchial arch mesenchymal tissue abnormalities. [20] Pulmonary atresia with ventricular septal defect is also likely a conotruncal defect. [21]

TABLE 1–1. Conotruncal Cardiac Malformations

Subarterial (type 1) ventricular septal defect
Aorticopulmonary window
Double outlet right ventricle
Tetralogy of Fallot
d-transposition of the great vessels
Truncus arteriosus communis
Interruption of aortic arch, type B (between the left carotid and the left subclavian arteries)
Pulmonary atresia with ventricular septal defect

CARDIAC MALFORMATIONS IN BRANCHIAL ARCH SYNDROMES

In humans, evidence linking conotruncal malformations with abnormal branchial arch/neural crest tissue migration is derived from analysis of branchial arch syndromes. Goldenhar syndrome, oculo-auriculo-vertebral dysplasia, is frequently associated with facial asymmetry and cardiac anomalies. [22] In 128 patients reported from the literature the incidence of cardiac anomalies was 36%. [23] The most common were tetralogy of Fallot, transposition of the great vessels, and unspecified types of ventricular septal defect. The prevalence of conotruncal malformations was 42%. Pierpont and others [24] reported that pulmonary hypoplasia lateralized with the facial asymmetry.

DiGeorge syndrome includes abnormalities of the third and fourth branchial arch derivatives, the thymus and parathyroid glands, facial abnormalities, and cardiac anomalies. The latter include truncus arteriosus communis, tetralogy of Fallot, transposition of the great vessels, double outlet right ventricle, and ventricular septal defect. In one report [25] an 80% prevalence of conotruncal malformations was found among 23 children with DiGeorge syndrome. In another report [26] 95% of cardiac anomalies in DiGeorge syndrome were conotruncal while common isolated anomalies such as atrial septal defect, ventricular septal defect, and coarctation of the aorta were not present.

CHARGE association consists of the nonrandom occurrence of choanal atresia, coloboma, cardiac malformations, ear abnormalities, and mental retardation as well as genital hypoplasia. [27,28] Among the children described with this syndrome, conotruncal anomalies including tetralogy of Fallot, type B interrupted aortic arch and pulmonary atresia with ventricular septal defects (VSD), occur frequently. Patients with the velo-cardio-facial syndrome have bifed uvula, typical facies with a wide nose, and conotruncal malformations including tetralogy of Fallot or double outlet right ventricle. [29,30]

Drug-induced teratogenic syndromes of isotretinoin and thalidomide characteristically have conotruncal abnormalities. Lammer and co-

workers [31] reported a spectrum of cardiac malformations including tetralogy of Fallot, d-transposition of the great vessels and type B interrupted aortic arch among 21 autopsies of infants whose mothers received isotretinoin in the first trimester of pregnancy. Cardiac disease occurs frequently in infants with thalidomide embryopathy. [32] Of those reported in sufficient detail, conotruncal malformations are predominant including tetralogy of Fallot, d-transposition of the great vessels and double outlet right ventricle (see chapter 3). Thus, thalidomide may influence cell migration leading to cardiac as well as extremity anomalies. These observations are consistent with McCredie's hypothesis [33,34] that neural crest injury plays an important role in multiple malformation syndromes.

Conotruncal malformations without facial abnormalities may be related to the long migration pathway of neural crest cells. Neural crest cells migrate in stages, although it is unclear which crest cells participate in conotruncal septation and which wave of crest cells participate in facial development. Disruption of one cluster of cells may only affect cardiac development, while disruption of adjacent clusters may result in both facial and cardiac malformations.

Cardiac Hemodynamics

Cardiac embryologists have long been intrigued with the interrelationship of function and form in the developing heart. The cardiovascular system is the only organ that provides support for the embryo while itself undergoing morphologic change. [35–37] In the late 19th century, Spitzer [38] proposed a theory of cardiac morphogenesis which relied heavily on the eroding effects of the blood stream on the cardiac shape. Much of this theory is doubtful because the blood stream of an embryo does not erode or deposit material as does a river. Nevertheless, lateral wall stress and the sheer force of blood flowing through the embryonic heart probably do affect cardiac formation in later stages of development.

In the chick heart [39] and probably in the human heart [40] two blood streams are present prior to septation. The blood flow molding hypothesis states that the cardiac septa form at the point of least flow and resistance between the streams, and as cardiac development proceeds the hemodynamic forces of the streams shape the cardiac chambers and valves. [41,42]

Blood flow and hemodynamic stress determine aortic arch selection, chamber volume, and valve orifice size rather than the initial position of the cardiac septa and great vessels. At the earliest stages, intracardiac blood flow is not necessary for normal cardiac development. Manasek and Monroe [43] showed that cardiac looping proceeds without blood flowing through the cardiac lumen. Photographic analysis of the developing chick heart suggests that the position of the cardiac streams does not coincide with the sites between the forming endocardial and conotruncal cushions. [44]

Aortic arch selection is related to the vector, volume, and direction of blood flow. Since arch vessel walls are a single cell thick and devoid of muscle tissue, vascular constriction is not possible. Yet, Pexieder [45] showed that aortic arch vessel blood pressure decreased as the arch vessels involute. His observations suggest that blood flow is directed away from the disappearing arch vessel. Experimental work in chick embryos by Rychter [46] supports this interpretation. He demonstrated that selective occlusion of aortic arches occlusion resulted in persistence of vessels which would otherwise disappear. He suggested that the volume of blood flow diverted toward the closing arches maintained their patency.

Blood volume also affects ventricular chamber size. Harh and co-workers [47] showed that nylon fibers inserted in the left atrioventricular orifice resulted in left ventricular chamber hypoplasia. Sweeney [48] found that reduction in left atrial volume produced a hypoplastic left ventricular chamber and abnormalities of the aortic arch. She also found that atrioventricular and semilunar valve area correlated directly with chamber volume.

HUMAN CARDIAC MALFORMATIONS CAUSED BY ALTERED HEMODYNAMICS

A group of human congenital cardiac malformations may be due to abnormal blood flow patterns (table 1–2). In coarctation of the aorta, a flange of tissue extends into the aortic lumen from the posterior lateral aortic wall at a point opposite the orifice of the ductus arteriosus. Hutchins [49] and Rudolph and co-workers [50] suggested that the tissue flange was formed by the divergence of the ductal stream with a portion flowing toward the head and neck vessels while the remainder of the stream

TABLE 1–2. Malformations Related To Altered Cardiac Hemodynamics

Coarctation of the aorta with intact ventricular septum
Hypoplastic left heart syndrome
Aortic valvular stenosis
Interruption of aortic arch — type A
Secundum atrial septal defect
Pulmonary atresia without ventricular septal defect
Perimembranous ventricular septal defect (type II)

courses toward the descending aorta and placenta. Interrupted aortic arch type A is also the consequence of abnormal vectorial blood flow during the process of aortic arch selection. [51] In addition, Moulaert and colleagues [52] demonstrated that the caliber of the transverse aortic arch correlated with the type of abnormality in aortic arch interruption.

Alteration of the distribution of intracardiac blood flow may be responsible for left and right heart hypoplasia (figure 1–1). In utero, most of the blood flow into the left heart crosses the atrial septum through the foramen ovale. Thus, the ratio of the foramen ovale/atrial septum is used as an index of transatrial blood flow. This ratio is smaller than normal in hearts with either coarctation of the aorta or aortic valvular stenosis and larger than normal in hearts with pulmonary valvular stenosis, pulmonary atresia, or secundum atrial septal defect. [53] These observations suggest that the volume of transatrial blood flow correlates directly with the site and severity of the cardiac lesion. Secundum atrial septal defect may not be a primary abnormality of atrial septation, but rather due to increased transatrial blood flow which enlarges the foramen ovale and erodes the flap valve.

Severe reduction in left heart blood flow would lead to a hypoplastic left heart. A transient decrease in blood flow through the aortic valve may result in only partial opening of the right and noncoronary aortic cusps and a subsequent fusion producing a bicuspid aortic valve.

Perimembranous ventricular septal defect may be the consequence of an imbalance of intracardiac blood flow affecting the heart prior to completion of ventricular septation. During septation of the ventricular chambers, an increase in left heart blood flow may deform the normal spatial relationships of the muscular and conotruncal septa resulting in a defect of the membranous ventricular septum.

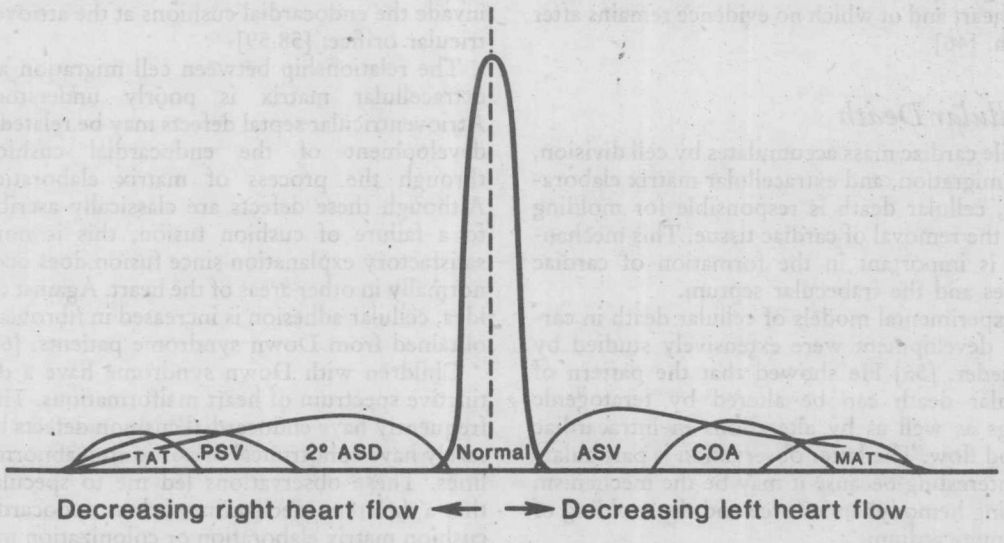

FIGURE 1–1. Spectrum of congenital cardiac malformations associated with decreased right or left heart blood flow. ASV = aortic stenosis valvular, 2°ASD = secundum atrial septal defect, COA = coarctation of the aorta, MAT = mitral atresia, PSV = pulmonary stenosis valvular, TAT = tricuspid atresia.

MECHANISM OF HEMODYNAMIC ALTERATION

After ventricular septation, the heart is a parallel circuit. Small changes in resistance in one limb of the circuit divert blood away from that limb and toward the other. Two variable resistance points, the ductus venosus and the ductus arteriosus, are present in the late embryonic and fetal stages of development. Each ductus is responsive to prostaglandins and prostaglandin inhibitors, although their relative sensitivity is unknown. Since vascular resistance is proportional to the 4th power of the radius, small changes in the caliber of the ductus arteriosus would have a large effect on the portion of blood flow. A transient decrease in the radius of the ductus arteriosus would increase resistance and decrease right heart blood flow. Long-term ductal obstruction may lead to pulmonary atresia with intact ventricular septum or pulmonary valvular stenosis.

Extracardiac as well as intracardiac events may also alter the balance of intracardiac blood flow. The association of congenital heart disease and neck webbing in Turner syndrome may be related to extrinsic aortic compression from dilated lymphatic vessels. [54] Intrauterine infection may alter vascular walls changing the proportion of blood flow. Some congenital cardiac malformations may be the consequence of changes in a vascular bed which is remote from the heart and of which no evidence remains after birth. [46]

Cellular Death

While cardiac mass accumulates by cell division, cell migration, and extracellular matrix elaboration, cellular death is responsible for molding and the removal of cardiac tissue. This mechanism is important in the formation of cardiac valves and the trabecular septum.

Experimental models of cellular death in cardiac development were extensively studied by Pexieder. [55] He showed that the pattern of cellular death can be altered by teratogenic drugs as well as by alterations in intracardiac blood flow. The latter observation is particularly interesting because it may be the mechanism linking hemodynamic force and the molding of the myocardium.

One can speculate that muscular ventricular septal defects form by excessive cellular death leading to septal perforation. Contrary to current embryologic teaching, there is no naturally occurring communication between the right and left ventricle at the level of the muscular septum. Ebstein's malformation, a failure of tricuspid valve separation from the ventricular wall, may also be related to abnormalities of cellular death.

Abnormalities of Extracellular Matrix

The role of extracellular matrix in cardiac development is receiving renewed attention. [56,57] Cardiac jelly, the amorphous glycosaminoglycans substrate which lies in a thick band between the endocardium and myocardium, has diverse functions. This material, produced by myocardial cells, accumulates in ridges to form the cardiac cushions at the atrioventricular orifice, and in the outflow tract. These cushions bridge the cardiac lumen to form the atrioventricular valve orifice and ventricular outflow tract respectively.

The cardiac cushions are important for embryonic cardiac function. They act as valves early in development so that aortic pressure has a distinct systolic and diastolic phase. [35] In addition, they serve as a medium through which cells migrate. Cellular mass moves in from the arterial pole of the heart and endocardial cells invade the endocardial cushions at the atrioventricular orifice. [58,59]

The relationship between cell migration and extracellular matrix is poorly understood. Atrioventricular septal defects may be related to development of the endocardial cushions through the process of matrix elaboration. Although these defects are classically ascribed to a failure of cushion fusion, this is not a satisfactory explanation since fusion does occur normally in other areas of the heart. Against this idea, cellular adhesion is increased in fibroblasts obtained from Down syndrome patients. [60]

Children with Down syndrome have a distinctive spectrum of heart malformations. They frequently have endocardial cushion defects but rarely have conotruncal or aortic arch abnormalities. These observations led me to speculate that a different mechanism such as endocardial cushion matrix elaboration or colonization may be responsible for the cardiac malformations. Supporting this speculation is the observation that the membranous interventricular septum is