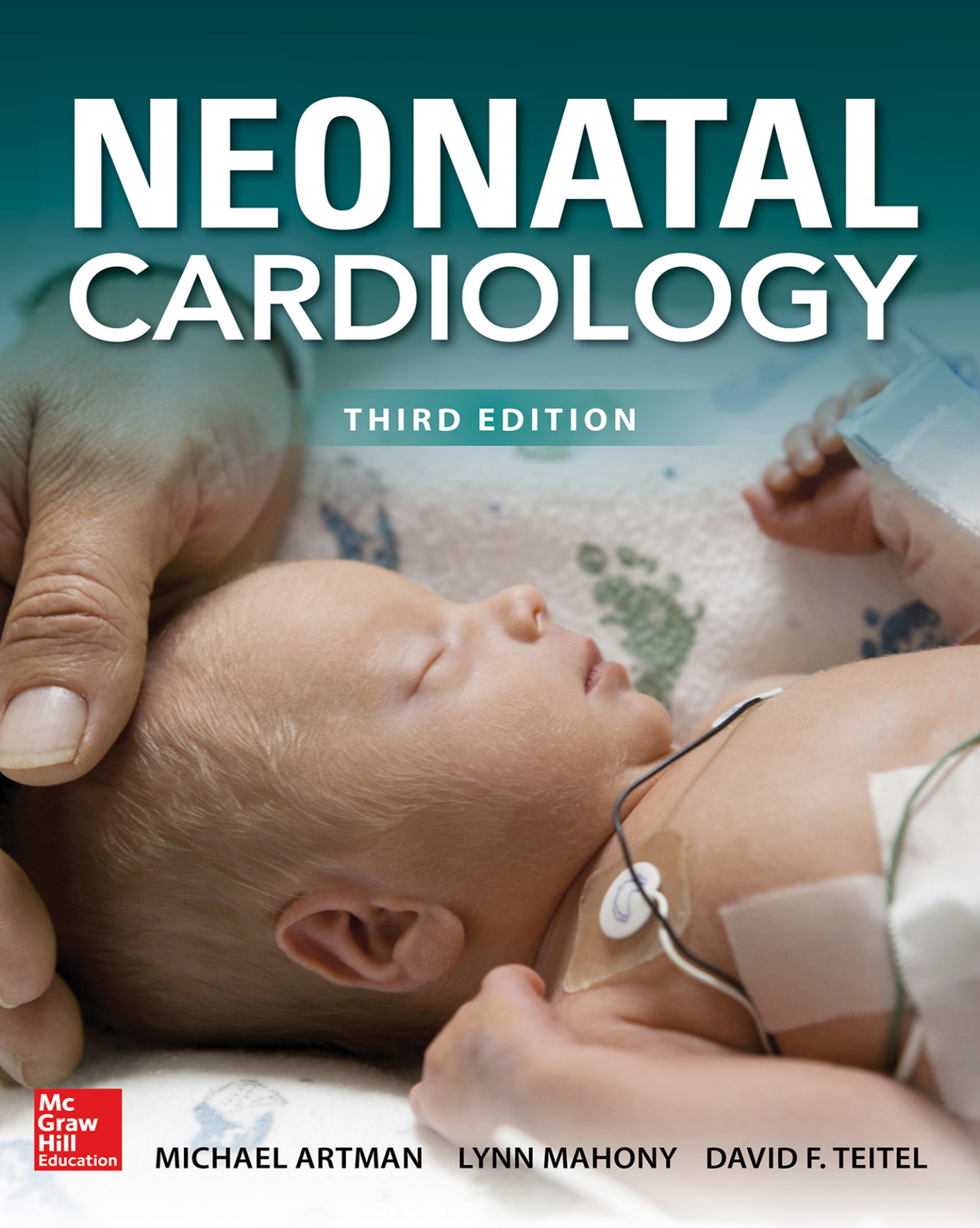
NEONATAL CARDIOLOGY

THIRD EDITION



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Mc Graw Hill Education

Neonatal Cardiology

Third Edition

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ISBN: 978-0-07-183451-3

MHID: 0-07-183451-6.

The material in this eBook also appears in the print version of this title: ISBN: 978-0-07-183450-6,
MHID: 0-07-183450-8.

eBook conversion by codeMantra
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This book is dedicated to our families for their unwavering support, understanding, and sacrifices.
It is from them that we gain our balance.

We are grateful to the many teachers from whom we were fortunate to learn more than mere facts.
Each of us continues to benefit from the wisdom of our mentors, who prepared us
so well for our lives, careers, and academic endeavors.

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Foreword to the Second Edition

During the 8 years since the publication of the first edition of *Neonatal Cardiology* in 2002, many remarkable advances in our understanding of normal cardiovascular development and of mechanisms, resulting in congenital cardiovascular malformations, have been achieved.

The concept that these malformations had little impact on normal fetal development was widely accepted; the influence of congenital cardiovascular malformations on fetal blood flow patterns and oxygenation, as well as their effect on fetal cardiac and vascular development, is increasingly being recognized. Furthermore, the potential effects of these defects on other organ systems, particularly the brain, has engendered great interest and study.

In this second edition, Drs. Michael Artman, Lynn Mahony, and David Teitel have continued the general philosophy of the first edition; they have presented clinical and hemodynamic manifestations of congenital and acquired cardiovascular disturbances, based on biological information regarding development and function. All chapters have been significantly modified to address the increased understanding of basic biology and factors affecting normal development and performance. As in the first edition, the graphic material largely presents diagrams that help to explain basic physiological concepts and pathophysiology. The quality of the diagrams has been greatly improved, making the information presented more readily assimilable.

The first chapter, on cardiac embryology, contributed by Dr. Kathleen Ruppel, reviews the advances in the understanding of genetic pathways involved in cardiac morphogenesis. Also, the revolutionary changes in our appreciation of the embryology of the heart and great vessels are presented. It was widely accepted that all structures developed from the primitive heart tube; it is now recognized that other primitive cells from the anterior or secondary heart field, as well as neural crest cells, are major contributors to cardiac and great vessel formation. Their importance in development of congenital cardiovascular malformations is now being explored.

The association of neurological abnormalities with congenital cardiovascular malformations has been recognized for many years; in many genetic syndromes, both developmental delay and cardiac defects are encountered. In recent years, concern has been raised regarding intellectual and behavioral impairment in children with several congenital cardiac anomalies. The possibility that this was related to surgical procedures during infancy was considered, but recent evidence suggests interference with brain development occurs during fetal life. In a most interesting new chapter, authored by Dr. Patrick McQuillen, neurological development and mechanisms by which congenital cardiovascular malformations could affect it are presented. This topic is of great importance, because it is suggested that in some infants with these cardiac lesions, correction during the neonatal period may not improve the neurological deficit. This would support the concept of intervention to correct the circulatory disturbance during fetal life.

The use of nonsurgical approaches to cardiac lesions has become standard practice over the past decade. Many of these procedures are not yet applicable to neonates, but as discussed in this edition, interventions to relieve aortic and pulmonary stenoses by balloon valvuloplasty have now become standard practice, thus avoiding the high risks of surgery in critically ill infants.

This edition of *Neonatal Cardiology* continues to provide pediatric cardiologists, neonatologists, and obstetricians with an invaluable resource for the differential diagnosis of cardiovascular disturbances and their management in newborn infants. The symptom-complex approach is particularly helpful to students and residents in understanding the mechanisms responsible for clinical manifestations.

Abraham M. Rudolph, MD

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Foreword to the Third Edition

Congenital heart disease is the most common serious congenital defect. It occurs in ~1% of all live births, and annually about 1.5 million children are born with congenital heart disease. (A similar number have bicuspid aortic valves, but these seldom cause problems in childhood.) Given the high potential early mortality and morbidity of these diseases, any book such as this one that improves the effectiveness of treatment will make a major contribution to world health.

Neonatal cardiology is concerned mainly with congenital heart disease. The period of transition from fetus to neonate is often difficult, and congenital or acquired disease at this age may, for many reasons, be more difficult to manage than at older ages. It is not surprising, therefore, that the highest mortality in children with congenital heart disease who are not treated occurs in the neonatal period. What is surprising is that so few books have concentrated on this critical period. This third edition of *Neonatal Cardiology* has gone a long way to correcting the deficiency.

With the advances in imaging methods, diagnostic cardiac catheterization has been replaced by echocardiography, CT, and MRI. As a result, the emphasis today is placed on anatomic abnormalities rather than on their physiological consequences, even though it is these consequences that often determine the outcome. The authors of this book, basing their work on the groundbreaking studies by Dr. Abraham Rudolph of abnormal fetal development and the physiological changes due to congenital heart disease, have shown how understanding the physiology as well as the anatomy of these lesions improves our ability to treat these patients.

In this third edition, Drs. Teitel, Mahony, and Artman have updated and expanded what was in the second edition with added information about myocytes, arrhythmias, and genetics. In addition, they have enlisted Dr. Gittenberger de Groot and her colleagues to discuss current concepts of cardiac embryology. Understanding embryology not only helps us understand how the anomaly formed but someday also will be integrated with genetics and perhaps lead to prevention of an anomaly. Furthermore, knowing how anomalies such as aortic atresia develop gives a guide to the best time for intrauterine treatment. In another chapter, Drs. McQuillen and Peyvandi discuss the relation between cardiac malformations and neurodevelopment. Now that most forms of congenital heart disease are treatable with low mortality, our concentration must be on the quality of life that results. Chief among these is neurological function, and recent studies have shown that fetuses with congenital heart disease often have neurological abnormalities before birth. Whether these changes are due to abnormal brain blood flow secondary to the congenital heart disease (and thus potentially amenable to treatment) or due to the same disturbance that has altered cardiac development remains to be determined.

Included in this book are discussions of arrhythmias and pharmacological treatment as they relate to congenital heart disease. Because pharmacology is used to manipulate physiology for the patient's benefit, knowing the basis of the physiological disturbance leads to more effective therapy.

Although knowledge of pathological anatomy is important in understanding congenital heart disease, knowledge of the associated pathophysiology is mandatory if we wish to provide optimal care. This book is one of the few to combine both aspects and represents a hallmark in the treatment of congenital heart disease.

Julien I.E. Hoffman, MD

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CHAPTER 1

Cardiac Morphogenesis: Implications for Congenital Cardiovascular Diseases

INTRODUCTION

Knowledge of the role of cardiac-specific genes and their modulating factors has increased tremendously over the last decade, although 85% of human congenital cardiovascular disease is still considered to be multifactorial in origin. Advances in the molecular biology of the developing heart have greatly contributed to our understanding of cardiac morphogenesis. Manipulation of conserved genes from a variety of model organisms has increased our understanding of how genetic factors and cellular interactions contribute to cardiac development. Transgenic mouse models have allowed time-specific tracing of cells and their role in heart formation. The problem of embryo-lethality after manipulating "cardiac-specific" genes has been overcome by inducible knockout strategies. Whole genome sequencing programs have also increased understanding of mutations in humans that lead to congenital cardiovascular disease.

This chapter summarizes the initial phases of cardiac development. We then describe in more detail how cardiac morphogenesis leads to formation of the four-chambered heart and how abnormal cardiogenesis contributes to congenital cardiovascular disease.

CARDIAC PROGENITORS AND THE CONCEPTS OF FIRST AND SECOND HEART FIELD

Heart development starts with two cardiogenic plates derived from the lateral splanchnic mesoderm. These plates fuse in the midline in the anterior (cranial) region of the embryo. The crescent of the cardiogenic plates is referred to as the first heart field (FHF) and is flanked

medially by the second heart field (SHF) mesoderm (Figure 1A). Upon fusion in the midline, the FHF forms the two-layered primary heart tube with myocardium on the outside lined by endocardium on the inside. The myocardium secretes a glycoprotein-rich layer, the cardiac jelly, toward the endocardium. The primary heart tube connects to the arterial pole cranially and to the venous pole caudally (Figure 1-1B) but does not contain all segments of the four-chambered heart. Venous tributaries abut on the small atrial component, followed downstream by the future atrioventricular canal and a primitive left ventricle. Finally, the outflow tract connects to the aortic sac at the arterial pole (Figure 1-1C). The various components can be distinguished soon after, as both the AV canal and the outflow tract contain an increasing amount of cardiac jelly that forms the endocardial cushions. The cushions become even more prominent as they acquire mesenchymal cells, derived from the endocardial lining as a result of endocardial-mesenchymal transition. Subsequently, the primary heart tube starts the developmentally determined rightward looping.

At the same time, the SHF adds progenitor cells to both the venous and the arterial poles, which ultimately form the essential components of the right ventricle (RV) and at least a part of the right side of the interventricular septum (Figure 1-1D). At the venous pole, the SHF forms cardiomyocytes encapsulating the sinus venosus and its tributaries. The sinus venosus is incorporated subsequently into the wall of the right and left atrium. Likewise, the walls of the great arteries, the embryonic pharyngeal arch arteries that connect to the aortic sac, are partly built from SHF-originating cells. Neural crest cells also contribute to formation of the great arteries, as will be explained below in this chapter.

Multiple specific transcription factors and signaling molecules are essential to the early stages of cardiogenesis. These include the earliest markers of the precardiac mesoderm, including the homeobox-containing gene *Nkx2.5* and the zinc-finger-containing *GATA4/5/6* subfamily. Members of the T-box family, *TBx1/5/18/20*, also have essential roles in SHF differentiation. Myocardial differentiation is regulated by several myocyte-specific genes, including myosin light and heavy chain, alpha-cardiac actin, and cardiac troponin I.

THE NEURAL CREST

The neural crest cells are an ecto-mesodermal derivative arising from the crest of the neural tube, migrating toward various parts of the embryo, including the heart. Cardiac neural crest cells differentiate into cells of the autonomic nervous system and into vascular smooth muscle cells of the pharyngeal arch arteries and contribute to the arterial pole of the heart entering the endocardial outflow tract cushions (Figure 1-1E). Neural crest cells within the heart are involved in modulation and induction of semilunar valve formation and generation of the myocardial component of the outflow tract septum. At the venous pole, where their contribution is less important, a similar effect is observed in the atrioventricular cushions. More recently, cardiac neural crest cells contributing smooth muscle cells to the coronary arteries have been identified.

THE EPICARDIUM

The epicardium (splanchnic mesodermal lining of the pericardial cavity) is a secondary layer covering the myocardial tube and the intrapericardial part of the arterial pole. During embryonic development, the epicardium originates from both the venous and the arterial poles (Figure 1-1E–G). The larger epicardial population derives from a protrusion of the coelomic wall, covering the sinus venosus and liver primordium (Figure 1-1F). The cells of the proepicardium spread along the outer wall of the ventricles and atria to the border of the myocardium at the arterial pole. Here, they join the arterial epicardium, which is derived from a much smaller arterial proepicardium exhibiting a slightly different phenotype (Figure 1-1G). On activation, the epithelial epicardium undergoes endocardial-mesenchymal transition, and the resulting mesenchymal cells fill the subepicardial space as epicardium-derived cells. These cells migrate between the myocardial cells of the heart tube, the atrioventricular cushions, and the future fibrous annulus. These epicardium-derived cells, in contrast to neural crest cells, differentiate into several cell lines including the majority of the cardiac fibroblasts and the vascular smooth muscle cells of the coronary vascular system (Figure 1-2).The endothelial lining of the coronary vascular system is derived from the endothelium of the sinus venosus/liver primordium adjacent to the proepicardium (Figures 1-1F, 1-2).

BREAKING SYMMETRY

Starting with the developmentally determined rightward looping, it is clear that the heart and its connections to the

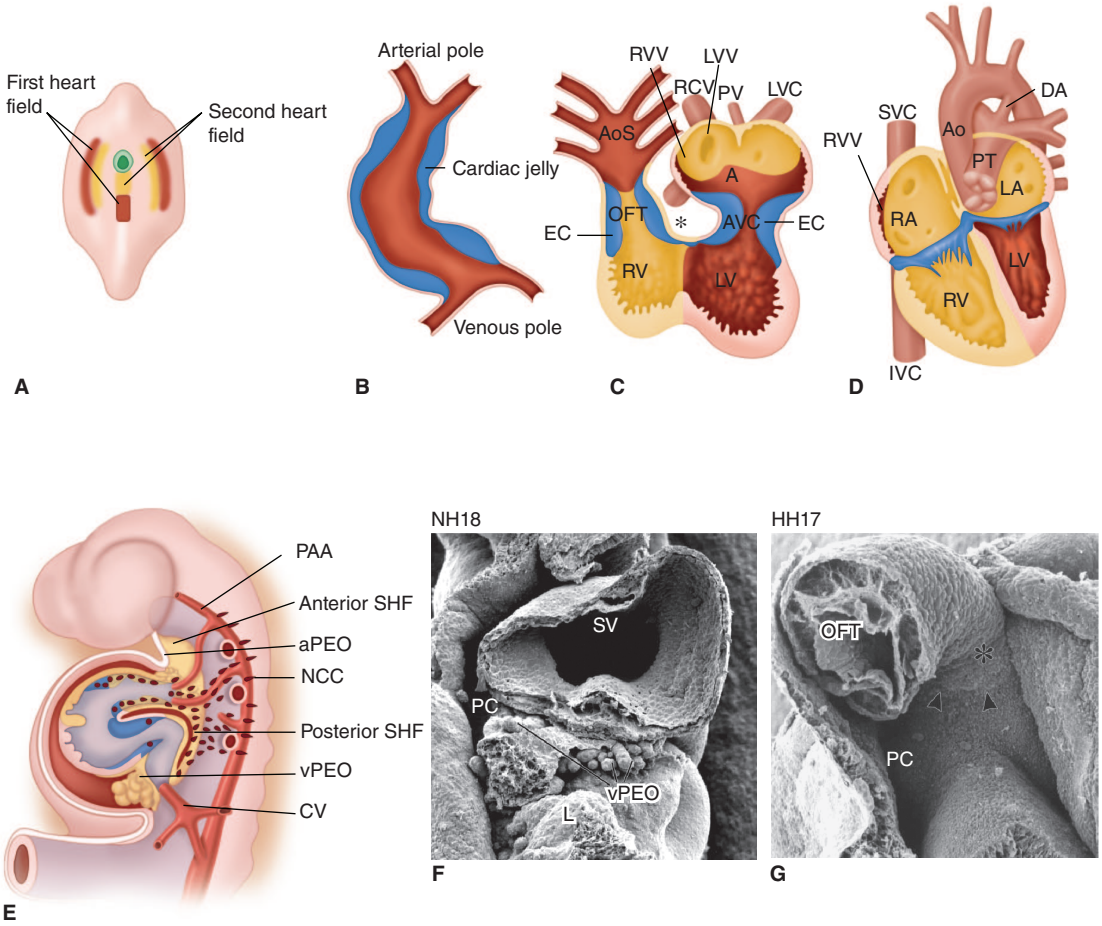

FIGURE 1-1. Cardiac development. **A**. Schematic depiction of the precardiac mesoderm in the primitive plate. The brown area reflects the mesoderm of the FHF, whereas the yellow area corresponds to the putative SHF mesoderm. **B**. Primary heart tube derived of FHF mesoderm. The tube consists of myocardium, lined by cardiac jelly. **C**. Heart tube after looping. The yellow areas reflect SHF-derived contributions. The SHF contributions to the outflow tract have not been depicted. Note that in this stage the atria are still positioned entirely above the primitive left ventricle, whereas the outflow tract is positioned above the primitive right ventricle. **D**. Advanced stage of heart development. Septation has now occurred at the level of the atria, ventricles, and outflow tract. **E**. Sagittal view of an embryo. The (anterior and posterior) SHF mesoderm and its derivatives are depicted in yellow. Contributions from neural crest cells are depicted in blue. A proepicardial organ can be distinguished at the venous pole as well as a smaller proepicardial organ at the arterial pole. **F**. Scanning electronic microscopic section at the level of the venous pole in a chick embryo, showing the venous pole of the proepicardial organ. **G**. Scanning electronic microscopic section at the level of the outflow tract in a chick embryo, showing the arterial pole of the proepicardial organ (arrowheads, asterisk). Abbreviations: A, atrium; Ao, aorta; AoS, aortic sac; aPEO, atrial pole of proepicardial organ; AVC, atrioventricular canal; EC, endocardial cushions; FHF, first heart field; HH, Hamburger and Hamilton; IVC, inferior vena cava; LA, left atrium; L, liver; LCV, left cardinal vein; LV, left ventricle; LVV, left venous valve; PAA, pharyngeal arch artery; PC, pericardial cavity; PT, pulmonary trunk; PV, pulmonary vein; RA, right atrium; RCV, right cardinal vein; RV, right ventricle; RVV, right venous valve; SHF, second heart field; SV, sinus venosus; SVC, superior vena cava; VPEO, venous pole of proepicardial organ. B–E: *Adapted from: Gittenberger-de Groot AC et al*. Ann Med. *2014;46(8):640-652.* F and G: *Adapted from: Gittenberger-de Groot AC et al*. Differentiation. *2012;84(1):41-53.*

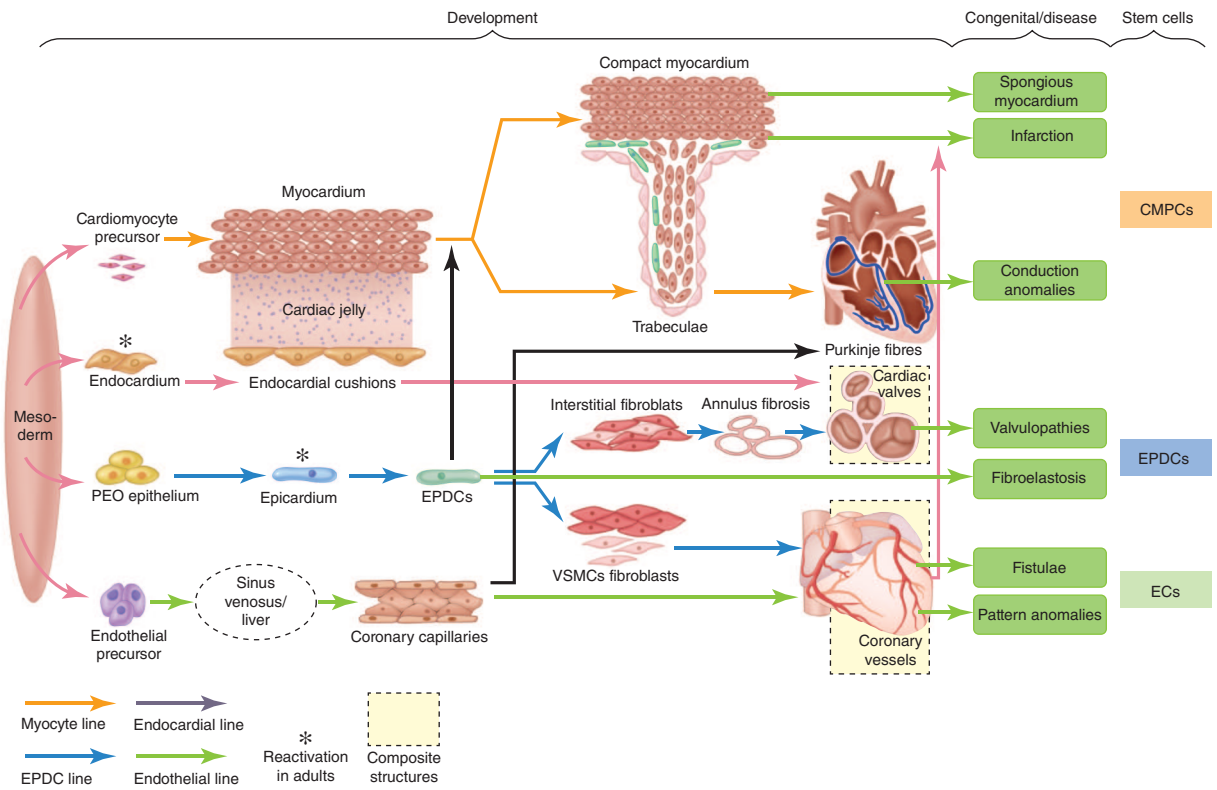

FIGURE 1-2. Cell lines contributing to the developing heart. Schematic representation of cardiac cell lines (cardiomyocytes, endocardium, epicardium, and endothelium) that are derived from the first and second heart field mesoderm and are the main contributors to the definitive heart and vessels. Epicardium-derived cells (in yellow) as well as inadequate interaction with other cardiac cell types may play a role in some cardiac malformations (green boxes). The second heart field and neural crest cell contribution to the great vessels is not represented. Abbreviations: CMPCs, cardiomyocyte progenitor cells; EPDCs, epicardium-derived cells; ECs, endothelial cells; VSMCs, vascular smooth muscle cells. *Adapted from: Gittenberger-de Groot AC et al*. Differentiation. *2012;84(1):41-53.*

lungs are not symmetric. Situs inversus and heterotaxy occur in humans; several mouse models have increased our knowledge on essential signaling factors related to determination of situs. It is remarkable that only the atrial situs and its contributing posterior SHF seem to be influenced by these factors, while right ventricle and left ventricle with their specific morphologies do not copy the atrial situs anomalies (eg, inversus or ambiguous).

CRITICAL DEVELOPMENTAL TIME WINDOWS

In the preceding paragraphs, the cellular building blocks of the cardiovascular system have been presented. Serious disturbances of one or more cell populations can lead to abnormal cardiac development and even early embryo-lethality. This results in early spontaneous abortion in humans. In homozygous mouse strains, 50% of spontaneous early embryo-lethality related to mutations is caused by cardiovascular abnormalities. In the usually non-homozygous human, the percent of spontaneous abortions caused by congenital cardiovascular disease cannot be determined unequivocally. The FHF lesions are considered to be the most critical for embryonic demise. Most of the cardiac malformations that clinicians encounter in the perinatal period occur during looping and events mediated by the SHF. Spontaneous abortion in the second trimester caused by congenital cardiovascular disease is less common, as most forms of cardiac malformations are compatible with intrauterine survival.

CARDIAC MORPHOGENESIS AND DYSMORPHOGENESIS

In the human embryo, the formation of the four-chambered heart occurs by about 8 weeks' gestation. Thereafter, maturation and remodeling of, eg, the pharyngeal arch arteries and valves are essential for ensuing proper functioning and postnatal survival. The most important elements of cardiac morphogenesis (summarized in Figure 1-3), including septation, valve formation, conduction system maturation, and coronary vascular development, will be presented.

Incorporation of the Sinus Venosus, Atrial Septation, and Pulmonary Vein Development

The precardiac mesoderm of the SHF at the venous pole develops uniquely from an *Nkx*2.5-negative but myosin light chain positive cell population, surrounding the lumen of the sinus venosus. This myocardial cell lineage is incorporated into the posterior wall of both the right and the left atria. The atrial appendages are probably related to the FHF.

The left and right cardinal veins (the embryonic superior and inferior caval veins) are incorporated into the right atrium and are flanked by the folds of the embryonic right and left venous valves (Figure 1-1C, D). The left inferior cardinal vein (future coronary sinus) and the left superior cardinal vein (regressing in the human heart as the ligament of Marshall) all drain into the cavity of the right atrium. A splanchnic vascular plexus surrounds the developing lung buds. During early developmental stages, the primary route of pulmonary drainage from this plexus is toward the systemic veins; a direct connection of the primitive pulmonary veins to the heart is achieved from different tissue later during development. The anlage of the primitive pulmonary vein, the so-called mid-pharyngeal endothelial strand, initially does not have a lumen and is connected to the sinus venosus.

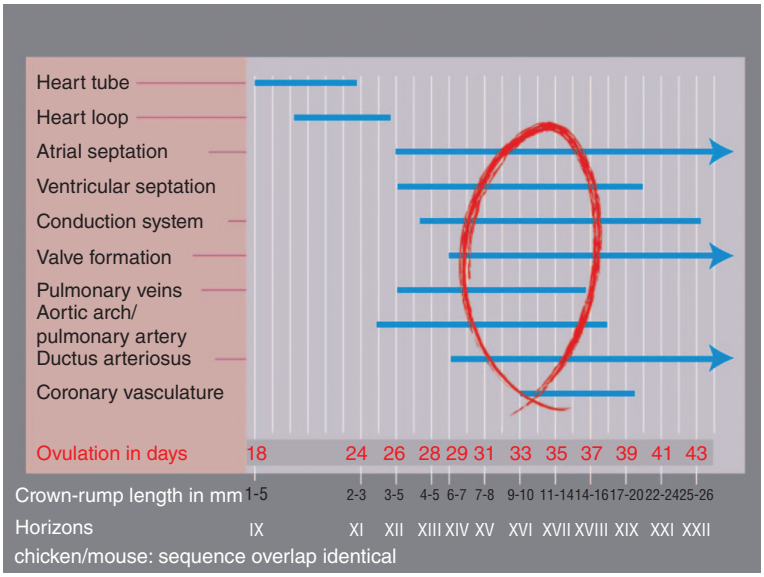

FIGURE 1-3. Cardiac morphogenesis. Schematic representation focusing on the time line and the major events during cardiac morphogenesis. Many processes essential to heart formation overlap during the 7 to 8 weeks of development, making it difficult to determine the separate molecular pathways or the primary insult that leads to congenital cardiovascular malformations, either isolated or complex. Valvulogenesis occurs relatively late in heart formation, while completion of atrial septation (closure of the foramen ovale) and ductus arteriosus differentiation (closure of the ductus arteriosus) naturally occur after birth because of the unique requirements of the fetal circulation. *Source*: Jongbloed MRM, et al. Development of the Cardiac Conduction System and the Possible Relation to Predilection Sites of Arrhythmogenesis, TheScientificWorldJOURNAL, vol. 8, pp. 239-269, 2008.

During atrial septation it connects to the dorsal wall of the left atrium. The splanchnic pulmonary venous connections with the systemic cardinal (putative caval) veins gradually disappear during normal development.

During atrial septation, four components deserve attention: the primary septum, the dorsal mesenchymal protrusion, the septum secundum, and the endocardial cushions. The initially two-layered myocardial primary atrial septum is positioned between the right and left atria. It partially disintegrates forming the ostium secundum, which is required for the formation of the embryonic foramen ovale (Figure 1-4A, B), the essential communication between the right and left atria during fetal life. Fusion of a mesenchymal cap on the free rim of the primary atrial septum with the atrioventricular endocardial cushion mass and with the dorsal mesenchymal protrusion closes the ostium primum. This structure is found at the right side of the primary atrial septum

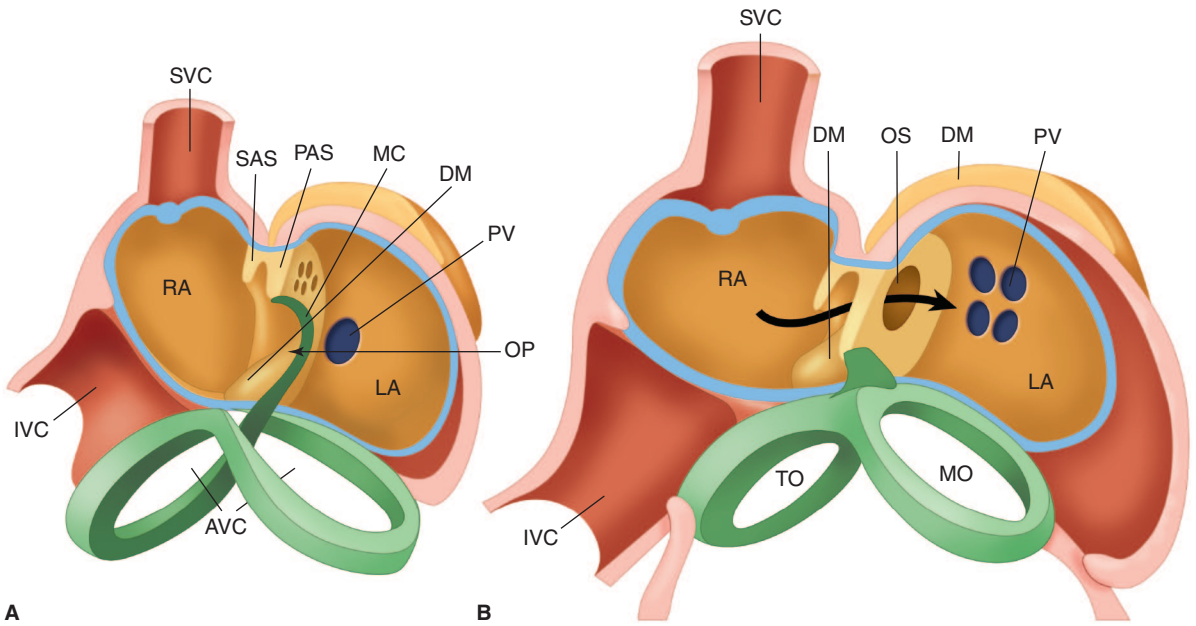

FIGURE 1-4. Atrial septation. **A**. Early development of the dorsal and cranial wall of the right and left atria. The gold indicates the contribution of the SHF to the incorporated sinus venosus myocardium. The appendages are not depicted. Both the inferior and the superior vena caval veins enter in the right atrium as well as the coronary sinus, which is derived from the left superior cardinal vein. A mesenchymal cap (green) under the rim of the primary atrial septum borders the ostium primum, which connects the right and left atria. The entrance of the primitive pulmonary vein is seen in the left atrium. The infolding of the superior wall of the right atrium that will form the secundum atrial septum is already seen merging with the dorsal mesenchymal protrusion. **B**. After completion of septation, the ostium primum is closed by fusion of the mesenchymal cap with the atrioventricular cushions, which have now divided the atrioventricular canal into a tricuspid and a mitral orifice. The perforations in the primary atrial septum have enlarged to form an ostium secundum that in combination with the free rim of the secundum atrial septum is part of the foramen ovale (arrow) that closes after birth. Abbreviations: AVC, atrioventricular canal; DM, dorsal mesocardium; IVC, inferior vena cava; LA, left atrium; MC, mesenchymal cap; MO, mitral orifice; OP, ostium primum; OS, ostium secundum; PAS, primary atrial septum; PV, pulmonary vein; RA, right atrium; SAS, secundum atrial septum; SVC, superior vena cava; TO, tricuspid orifice. *Used with permission from Gittenberger-de Groot AC, et al., (2011). Normal and Abnormal Cardiac Development. In: Pediatric Cardiovascular Medicine, Second Edition (eds JH Moller and JIE Hoffman), Wiley-Blackwell, Oxford, UK.*

as a thick mesenchymal mass (Figure 1-4A, B) and will develop into the muscular base of the atrial septum. At the right side of the primary septum and usually incorporating the left venous valve, a folding process of the atrial myocardial wall forms the crescent ridge of the atrial septum secundum (the limbus). During development, the free edge of the primary atrial septum (the valve of the foramen ovale) and the rim of the septum secundum (the limbus) will overlap, allowing blood to pass via the foramen ovale (Figure 1-4B). At a variable time after birth, these two rims often fuse, resulting in the closure of the foramen ovale, although this structure remains patent in up to 20% of normal adults.

Implications for Congenital Cardiovascular Disease

Abnormal pulmonary venous return. As described above, pulmonary drainage is initially via an extensive midsagittal splanchnic vascular network. Disturbance of the SHF can lead to misalignment and faulty incorporation of the primitive pulmonary veins into the dorsal left atrial wall. In case of absence or atresia of the midpharyngeal endothelial strand, either the early pulmonary to systemic connections will persist or abnormal connections will develop, leading to abnormal drainage of the pulmonary venous blood to three levels: subdiaphragmatic (eg, scimitar syndrome; Figure 1-5A), cardiac, and supracardiac (Figure 1-5B). The drainage of all the pulmonary veins can be abnormal (total anomalous pulmonary venous connection) or partial, with some pulmonary veins entering in into left atrium and some into either systemic veins (Figure 1-5B) or the right atrium. The few known genetic causes are linked to abnormalities of left/right asymmetry (heterotaxy) caused by mutations of the transcription factor *PITx2* or by more downstream signaling abnormalities (eg, *PDGFRα*).

Atrial septal defects. Several types of atrial septal defects occur. A primum atrial septal defect is caused by a deficient connection of the primary interatrial septum with the atrioventricular cushion complex. This anomaly is often seen in conjunction with an atrioventricular septal defect (see below) in which the dorsal mesenchymal protrusion is also underdeveloped. The most common anomaly of the atrial septum is a secundum atrial septal defect, in which there is deficiency of an atrial septal component. More rarely, a sinus venosus type of atrial septal defect is seen, which is related to the superior or inferior caval vein. Mutations in genes involved in posterior SHF differentiation, such as *TBx5* and *NKx2.5*, are linked to this relatively common group of malformations.

Atrioventricular septal defects. Data from animal models and humans suggest that most cases of atrioventricular septal defect (atrioventricular canal) are caused by a deficiency in the base of the atrial septum resulting from underdevelopment of the dorsal mesenchymal protrusion. Additionally, the posterior inlet ventricular septum is shorter than normal; in combination, this results in partial fusion to absence of the atrioventricular cushions, resulting in a common valve with either one- or two-valve ostia (depending on the amount of fusion). Portions of the atrioventricular cushions develop into the characteristic atrioventricular valve leaflets observed in atrioventricular septal defects (ie, superior and inferior bridging leaflets and left and right-sided mural leaflets).

Ventricular Inflow and Outflow Tract Septation

Viewed from the right, the ventricular septum is divided into several components, including the ventricular inlet septum, an apical trabeculated component, and an anterior ("infolding") component (Figure 1-6A, B). The outflow tract septum (Figure 1-6C) develops as a separate structure. The different components with their specific developmental history, boundaries, and origin are associated with varying congenital malformations of the ventricular septum.

To understand the process of ventricular septation and the aberrations in development that lead to the most common septal defects, it is helpful to first review several novel findings concerning the contribution of both the anterior SHF and the neural crest cells to the outflow tract septum and the trabecular portion of the right ventricle. Several tracing studies in mouse embryos employing surrogate markers for SHF-derived cells have shown an *asymmetric contribution* to both the myocardium and the vascular wall of the right ventricular outflow tract and the pulmonary trunk. In this process, which we have termed the "pulmonary push," the embryonic left (pulmonary) side of the outflow tract is expanded by a relatively large contribution of the SHF as compared to the right (aortic) side, eventually bringing the pulmonary orifice to its normal anterior and cranial position with respect to the aorta. This pulmonary push is responsible for the so-called rotation of the outflow tract and great arteries

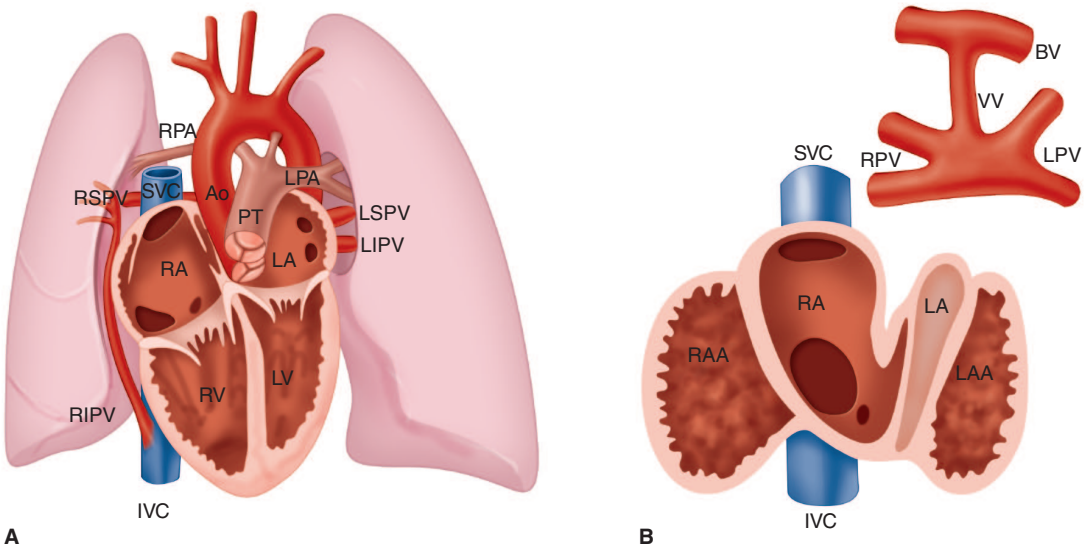

FIGURE 1-5. Anomalous pulmonary venous connection. A. Scimitar syndrome is characterized by a partial or complete right-sided anomalous venous connection to the inferior vena cava. In this case, the right inferior pulmonary vein has an anomalous connection to inferior vena cava. The other veins depicted all drain normally to the left atrium. Other characteristics of Scimitar syndrome include hypoplasia of the right pulmonary artery and lung, resulting in dextroposition of the heart. **B.** Total anomalous pulmonary venous connection, extracardiac type. The right and left pulmonary veins drain via a vertical vein into a systemic vein (eg, the left innominate vein, which drains into the superior vena cava). The absence of pulmonary venous connections and incorporation into the left atrium lead to a small left atrium that does not contain vessel wall tissue. Abbreviations: Ao, aorta; BV, brachiocephalic vein; IVC, inferior vena cava; LA, left atrium; LAA, left atrial appendage; LPA, left pulmonary artery; LIPV, left inferior pulmonary vein; LPV, left pulmonary vein; LSPV, left superior pulmonary vein; LV, left ventricle; PT, pulmonary trunk; RA, right atrium; RAA, right atrial appendage; RIPV, right inferior pulmonary vein; RPA, right pulmonary artery; RPV, right pulmonary vein; RSPV, right superior pulmonary vein; RV, right ventricle; SVC, superior vena cava; VV, vertical vein. *Panel B is Adapted from Douglas YL et al*. Int J Cardiol. *2009;134:302-312.*

and also explains the relatively deep position of the aortic orifice in the crux of the heart.

During this process, neural crest cells are incorporated by ingression into the aortic sac, creating the aorto-pulmonary septum, which separates the aorta and pulmonary artery. The aorto-pulmonary septum forms the central condensed mesenchyme, as well as two prongs extending into the septal and parietal endocardial cushions present in the outflow tract (Figure 1-6C). The neural crest cells have an induction effect on the outflow tract, recruiting myocardial cells into the cushions that form the posterior wall of the subpulmonary infundibulum, which also forms the septum between the right ventricular and the left ventricular outflow tracts. This outflow tract separation complex (distinguishable only as an outflow tract septum in specific cardiac anomalies) fuses by bringing together the septal and parietal cushion with the merged atrioventricular cushions, thereby closing the embryonic interventricular foramen and completing ventricular septation. During this process, an anterior folding septum is formed resulting from the expansion of the right and left ventricles, pushing the two outer faces of both ventricles together and trapping epicardium in between. Of note, the epicardium serves a similar function as the endocardial cushions inside the heart, bringing two myocardial faces together. The trapped epicardial cells will

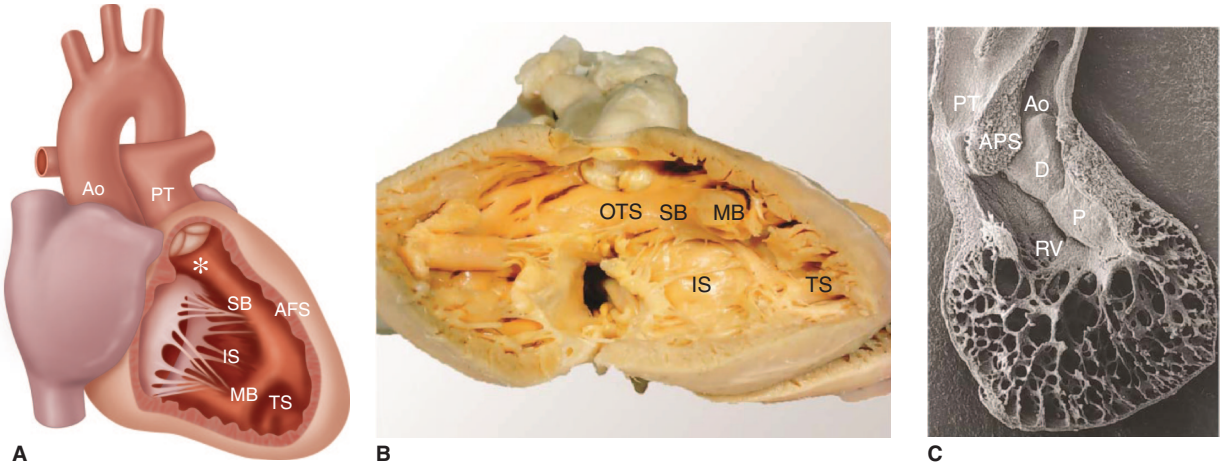

FIGURE 1-6. Ventricular septal components. A. Schematic representation showing the components of the interventricular septum including the inlet septum, the anterior folding septum, and the trabecular (apical) septum. The septal band that continues into the moderator band is related developmentally to the inlet septum. The posterior wall of the subpulmonary infundibulum contains the small outflow tract septum (asterisk). **B.** Postmortem specimen with the above-mentioned septal components. **C.** Scanning electron microscopic picture of the outflow tract of a chicken embryo. The aorto-pulmonary septum at the level between the aortic and pulmonary trunk orifices, which consists at this stage of condensed mesenchyme of neural crest cell origin, will merge with the distal endocardial outflow tract cushion and extend into the proximal outflow tract cushion. The distal level will remodel into the semilunar valves of the great arteries, while the proximal endocardial cushion will, by induction through the neural crest cell population, transform into myocardium and eventually form the small outflow tract septum. Abbreviations: AFS, anterior folding septum; Ao, aorta; APS, aorto-pulmonary septum; D, distal (endocardial outflow tract cushion); IS, inlet septum; MB, moderator band; OTS, outflow tract septum; P, proximal (outflow tract cushion); PT, pulmonary trunk; SB, septal band; TS, trabecular septum. ***A:*** *Adapted from Gittenberger-de Groot, AC, et al., (2012). Normal and Abnormal Cardiac Development, in Pediatric Cardiovascular Medicine, Second Edition (eds JH Moller and JIE Hoffman), Wiley-Blackwell, Oxford, UK.* ***B*** *and* ***C:*** *Used with persimmon from Gittenberger-de Groot, AC, et al., (2012). Normal and Abnormal Cardiac Development, in Pediatric Cardiovascular Medicine, Second Edition (eds JH Moller and JIE Hoffman), Wiley-Blackwell, Oxford, UK.*

differentiate into epicardium-derived cells, bringing these cells deep into the core of the septum.

Implications for Congenital Cardiovascular Disease

Ventricular septal defects. Muscular ventricular septal defects can be found within the anterior folding septum, within the inlet septum, and on the border of the septal band with the anterior folding septum, ie, central muscular ventricular septal defect.

Perimembranous ventricular septal defects and malalignment defects, tetralogy of Fallot, and double-outlet right ventricle. These malformations are caused primarily by an abnormal extension and malalignment of the outflow tract septal complex with the atrioventricular cushion mass. Since the fibrous connection between the tricuspid and mitral orifice and valves derives mainly from atrioventricular and outflow tract endocardial cushions, the ventricular septal defect will in part be flanked by fibrous tissue; hence, the term "perimembranous" is often used to describe these defects. The defect can extend more posteriorly toward the inlet septum or, in case of a malaligned or shortened outflow tract septum, toward the orifices of the great arteries. These are generally referred to as subarterial, but more specifically they are subaortic in tetralogy of Fallot and subpulmonary in Taussig-Bing malformation. From a developmental point of view, a double muscular subarterial infundibulum or conus has been proposed to be essential for the anomaly called double-outlet right ventricle.