Pediatric Cardiac Surgery
Contents

List of Contributors, vii
Preface, xiii

Chapter 1 Development of the Heart and Great Vessels, 1
Peter J. Gruber, Andy Wessels, and Steven W. Kubalak

Chapter 2 Nomenclature and Classification of Pediatric and Congenital Heart Disease, 27
Jeffrey P. Jacobs

Chapter 3 Physiology of the Fetal and Neonatal Circulations and Fetal Cardiac Surgery, 52
Ashok Muralidaran, Vadiyala Mohan Reddy, and Frank L. Hanley

Chapter 4 Preoperative Diagnostic Evaluation, 60

Chapter 5 Hybrid Procedures for Congenital Heart Disease, 84
Mark Galantowicz, John P. Cheatham, Alistair Phillips, Ralf J. Holzer, Sharon L. Hill, and Vincent F. Olshove

Chapter 6 Anesthesia for the Patient with Congenital Heart Disease, 103
H. Jay Przybylo

Chapter 7 Perioperative Care, 113
Carl L. Backer, John M. Costello, Jason M. Kane, and Constantine Mavroudis

Chapter 8 The Nurse Practitioner’s Role in Patient Management, 143
Nancy Benson, Denise Davis, Fejeania Hunter, Kim Teknipp, and Jamie Thomas

Chapter 9 Palliative Operations, 155
Carl L. Backer and Constantine Mavroudis

Chapter 10 Management of Pediatric Cardiopulmonary Bypass, 169
Darryl H. Berkowitz and J. William Gaynor

Chapter 11 Intraoperative Myocardial Protection, 214
Paul J. Chai

Chapter 12 Patent Ductus Arteriosus, 225
Muhammad Ali Muntaz, Athar Qureshi, Constantine Mavroudis, and Carl L. Backer

Chapter 13 Vascular Rings and Pulmonary Artery Sling, 234
Carl L. Backer and Constantine Mavroudis

Chapter 14 Coarctation of the Aorta, 256
Carl L. Backer, Sunjay Kaushal, and Constantine Mavroudis

Chapter 15 Interrupted Aortic Arch, 283
Richard A. Jonas

Chapter 16 Atrial Septal Defect, Partial Anomalous Pulmonary Venous Connection, and Scimitar Syndrome, 295
Carl L. Backer and Constantine Mavroudis

Chapter 17 Ventricular Septal Defect, 311
Constantine Mavroudis, Carl L. Backer, Jeffrey P. Jacobs, and Robert H. Anderson

Chapter 18 Atrioventricular Canal Defects, 342
Carl L. Backer and Constantine Mavroudis

Chapter 19 Truncus Arteriosus, 361
Constantine Mavroudis and Carl L. Backer

Chapter 20 Aortopulmonary Window and Aortic Origin of a Pulmonary Artery, 376
Stephanie Fuller and J. William Gaynor

Chapter 21 Isolated Right Ventricular Outflow Tract Obstruction, 385
John M. Karamichalis, Jeffrey R. Darst, Max B. Mitchell, and David R. Clarke

Chapter 22 Tetralogy of Fallot, 410
Robert D. Stewart, Constantine Mavroudis, and Carl L. Backer

Chapter 23 Surgical Treatment of Pulmonary Atresia with Ventricular Septal Defect, 428
Vadiyala Mohan Reddy and Frank L. Hanley
Chapter 24  Ventricular to Pulmonary Artery Conduits, 443
  John W. Brown, Osama M. Eltayeb,
  Mark Ruzmetov, Mark D. Rodefeld,
  and Mark W. Turrentine

Chapter 25  Double-Outlet Ventricles, 457
  Henry L. Walters III and Constantine Mavroudis

Chapter 26  Transposition of the Great Arteries, 492
  Constantine Mavroudis and Carl L. Backer

Chapter 27  Congenitally Corrected Transposition of
  the Great Arteries, 530
  Eric J. Devaney and Edward L. Bove

Chapter 28  The Functionally Univentricular Heart and
  Fontan’s Operation, 542
  Marshall L. Jacobs

Chapter 29  Ebstein Anomaly, 571
  Morgan L. Brown and Joseph A. Dearani

Chapter 30  Left Ventricular Outflow Tract
  Obstruction, 588
  Christo I. Tchervenkov, Pierre-Luc Bernier,
  Danny Del Duca, Samantha Hill, Noritaka Ota,
  and Constantine Mavroudis

Chapter 31  Hypoplastic Left Heart Syndrome, 619
  Jennifer C. Hirsch, Eric J. Devaney, Richard G.
  Ohye, and Edward L. Bove

Chapter 32  Aortico-Left Ventricular Tunnel, 636
  Stephanie Fuller and Thomas L. Spray

Chapter 33  Congenital Anomalies of the Mitral Valve, 640
  Richard D. Mainwaring and John J. Lamberti

Chapter 34  Total Anomalous Pulmonary Venous
  Connection, 659
  Nicola Viola and Christopher A. Caldarone

Chapter 35  Cor Triatriatum Sinister, Pulmonary Vein
  Stenosis, Atresia of the Common Pulmonary
  Vein, and Cor Triatriatum Dexter, 674
  Ralph E. Delius and Henry L. Walters III

Chapter 36  Anomalous Systemic Venous Connections, 685
  Henry L. Walters III and Ralph E. Delius

Chapter 37  Sinus of Valsalva Aneurysm, 704
  W. Steves Ring

Chapter 38  Coronary Artery Anomalies, 715
  Constantine Mavroudis, Ali Dodge-Khatami,
  Carl L. Backer, and Richard Lorber

Chapter 39  Cardiac Tumors, 744
  Rüdiger Lange and Thomas Günther

Chapter 40  Diseases of the Pericardium, 758
  Victor O. Morell and Ergin Kocyildirim

Chapter 41  Surgical Therapy of Cardiac
  Arrhythmias, 769
  Constantine Mavroudis, Barbara J. Deal, and
  Carl L. Backer

Chapter 42  Heart Transplantation, 813
  Joseph W. Rossano, David L.S. Morales, and
  Charles D. Fraser Jr

Chapter 43  Pediatric Lung and Heart-Lung
  Transplantation, 827
  Dewei Ren, George B. Mallory Jr, David L.S.
  Morales, and Jeffrey S. Heinle

Chapter 44  Infective Endocarditis, 845
  Muhammad Ali Mumtaz, Lara Danziger-
  Isakov, Constantine Mavroudis,
  and Carl L. Backer

Chapter 45  Pediatric Mechanical Circulatory
  Support, 856
  Brian W. Duncan

Chapter 46  Adult Congenital Heart Disease, 867
  Stamatis Prapa, Konstantinos Dimopoulos,
  Darryl F. Shore, Mario Petrrou, and Michael A.
  Gatzoulis

Index, 910

Color plate section facing p. 594
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Preface

This is the 4th Edition of Pediatric Cardiac Surgery. The first edition was published by Arciniegas in 1985, was followed by the 2nd Edition in 1994, and the 3rd Edition in 2003 by the present editors. Timely updates are important for any textbook as scientific intellectual curiosity, sentinel discoveries, and technological improvements have progressed at lightning speed. Even cardiac embryology, a field thought to be constant and thoroughly studied, has emerged with new findings of a second heart field, detailed results of syndromic genomes, and the promise of new paradigms and ontologies. Our readership from around the world has included numerous colleagues comprised of surgeons, cardiologists, intensivists, anesthesiologists, residents, students, perfusionists, and nurses. They have found the book to be well organized, easy to read, and to the point. We have preserved this format for the 4th Edition and added several chapters that have mirrored the directions and practice of pediatric and congenital heart surgery in the twenty-first century.

Several new chapters by new authors have highlighted the advances of congenital heart surgery. While this textbook emphasizes the pediatric nature of the specialty, it is clear that there are more adults with congenital heart disease living today than there are children with congenital heart disease. This is a testimony to the years of scientific and clinical research that have combined to improve the lot of these patients who now present with medical and surgical problems of their own. The new chapter on adult congenital heart disease reviews these very important issues and serves as an important contribution to the textbook. Several new and updated chapters, written by experts in their field, review advances that have been made in congenital heart surgery such as right ventricular to pulmonary artery conduits, arrhythmia surgery, double-outlet ventricles, and cardiac transplantation, among many others. In some cases, the same authors have updated their previous chapters. In others, new authors have been selected because of their demonstrated expertise.

The 4th Edition maintains its comprehensive coverage of the breadth of congenital heart surgery and related fields. Each chapter reviews the embryology, physical findings, diagnostic criteria, and therapeutic choices associated with each disease entity. State-of-the-art technology and the latest in surgical techniques are discussed.

As in previous editions of Pediatric Cardiac Surgery, the figures have predominantly been illustrated by Rachid Idriss. His drawing techniques are legendary not only because of his artistic talents, but more so for his ability to see an operation in his mind’s eye and demonstrate with a few lines the important parts of the relative anatomy and reparative operation. Sutures are clear, pledgets are well placed, and structures are anatomically correct. Hidden intracardiac anatomy is displayed by ghost techniques that transform the image into a three-dimensional living characterization of reality. His contribution to this 4th Edition cannot be overstated.

This textbook is reflective of the cooperation, expertise, and altruism that the contributing authors have so generously shared with the readership. Simply stated, these chapters are a delight to read. We are sure that the reader will have the same experience. All royalties from the sale of this book will be contributed to the Thoracic Surgery Foundation for Research and Education for the purpose of supporting congenital heart surgery initiatives. We are greatly indebted to the editorial staff at Wiley-Blackwell for their support, in particular, Kate Newell. Important editorial contributions were made by Patricia Heraty and, in particular, Melanie Gevitz who was so instrumental in organizing the successful efforts associated with the 2nd and 3rd Editions. In the Orlando Office, we found a jewel, Allison Siegel, who took on this project with an impressive zeal, expertise, and commitment that are rarely found anywhere.

The concluding paragraph in this Preface is quoted from the Preface of the 3rd Edition because it stands as a timeless dedication to our loved ones and family members who have shown their devotion, calmed the children, and explained our absences on countless occasions without rancor, excuses, or disappointment. It reads, "Finally, as with all surgeons and physicians, our accomplishments are
facilitated by the sacrifices made by our families. Every author who wrote a chapter for this textbook, no doubt, has loved ones who have contributed in one way or another to their creativity, stability, and industry. We thank each and every one of these wives, husbands, children, parents, and friends, including our own, which have had the patience, perseverance, and equanimity to stand by.”

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Introduction

Modern cardiac embryology combines molecular and cellular biologic techniques with traditional embryologic morphologic approaches during development. The limited descriptions of human cardiac development are necessarily supplemented by nonhuman models of cardiac development. Avian embryos have traditionally been favored experimental models because of the ease with which they can be observed and manipulated. More recently, the developing mouse has become the preferred model for studying cardiac development because of the strength of genetic and molecular investigative tools available in this species. Where possible, this chapter discusses how results in experimental animal models relate to human cardiac development. Table 1.1 provides a simplified comparison of two widely utilized developmental schemes for developmental staging in chick and mouse embryos [1–7]. The comparison of multiple species provides an important platform for understanding the development of the human heart and the pathogenesis of human disease.

Formation of Cardiac Precursors

All of the cells that will become part of the heart derive from populations of undifferentiated precursors that will be influenced by external signals into their final developmental pathways. In addition to the intellectual challenge of understanding how these acts of differentiation occur, intense activity in this field is also driven by the possibility of controlling cardiac tissue differentiation to replace diseased myocardium in the postnatal heart.

Repeated cell divisions of the fertilized egg form a cell mass that evolves into two distinct layers of cells. The epiblast layer is separated from a second layer of cells, called the hypoblast in the chick or the primitive endoderm in the mouse and human. The next critical stage of development is gastrulation where widespread cell migration into and reorganization within the blastocoelic cavity result in the formation of three germ layers (ectoderm, mesoderm, and endoderm) and the determination of the future body plan of the embryo (Figure 1.1) [7,8].

Gastrulation of precardiac cells is an early event in all species. In the human, gastrulation takes place at the beginning of the third week of development and angioblasts in the cardiogenic region are present shortly thereafter. At the time that precardiac cells gastrulate in chick embryos (Hamburger–Hamilton stage 3), the primitive streak is less than 1 mm in length; the portion of the streak through which the precardiac cells ingress extends as a relatively broad swath 0.125–0.75 mm from the anterior limit of the streak [9]. The most anteriorly gastrulating cells contribute to the most anterior portion of the primitive heart tube.

After cells have undergone gastrulation they enter the undifferentiated mesenchyme. Uncommitted precardiac cells enter the primitive streak only to become specified to their cell type or migratory pathways in the mesoderm after leaving the streak [9]. Subsequently, the precardiac cells will move laterally to join the lateral plate mesoderm at the level of Hensen’s node. The lateral plate mesoderm then splits into two layers, a splanchnic layer directly above the endoderm and a somatic layer directly below the ectoderm. The anterior endoderm provides signals to splanchnic mesodermal cells to enter the precardiac lineage. Fibroblast growth factors (FGFs)-1, -2, and -4 and bone morphogenetic protein 2 (BMP-2) are proteins that appear to be critical to this process [10]. However, to date no single gene has been identified whose ablation leads to a specific failure of all myocardial differentiation from precardiac mesoderm. This observation may argue the presence of either a considerable genetic redundancy in precardiac myocyte differentiation or an unsuspected diversity of
Table 1.1 Simplified comparison of developmental stages between human, mouse, and chicken embryos.

<table>
<thead>
<tr>
<th>Human</th>
<th>Mouse</th>
<th>Chicken</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnegie stage</td>
<td>Streeter horizon</td>
<td>Days gestation</td>
</tr>
<tr>
<td>9</td>
<td>IX</td>
<td>20</td>
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Precardiac myocyte lineages following independent genetic pathways.

Precardiac cells are found in an epithelial sheet at the cranial end of the splanchnic mesoderm and can be identified at this point by a variety of molecular markers such as the transcription factors NKX2-5, MEF2, HAND1, HAND2, GATA4, TBX5, and ISL1 [11–17]. The region of splanchnic mesoderm expressing precardiac markers is also known as the “heart-forming field” and is larger than the region that will actually contribute cells to the heart tube [18]. In rodent embryos, but not chick embryos, precardiac mesodermal cells exhibit spontaneous contractile activity, indicating a relatively advanced state of differentiation towards the cardiac myocyte lineage [19,20].

The precardiac mesodermal cell mass migrates as a single unit rather than as a collection of independent cells. The precardiac mesodermal sheets on each side of the embryo migrate together towards the midline cranial to the anterior intestinal portal. When the most cranial portions of the bilateral precardiac mesoderm masses meet in the midline, the total premyocardial cell population forms a horseshoe-shaped crescent called the first (primary) heart field. The cues that enable and promote movement of these cells are provided by a noncardiac tissue, the endoderm, as demonstrated by experimental removal of the endoderm and/or ectoderm. The extracellular matrix molecule fibronectin may be one of the important components of the endodermal surface to which the precardiac cells are responding [21].

Precursors of the endocardium follow similar migratory pathways as the precardiac cells, but there are important differences. Pre-endocardial cells and pre-endothelial cells are known as angioblasts. The endocardial angioblasts are first detectable in the splanchnic mesoderm. Mesodermal cells are induced to enter the angioblast lineage by signals such as transforming growth factor beta (TGFβ) 2–4 and vascular endothelial growth factor (VEGF) signaling from the endoderm [10]. Endocardial angioblasts migrate anteriorly and to the midline with the premyocardial cell mass, but they do so as individual cells.

### Formation of the Tube Heart

As the precardiac cell masses of the first heart field move steadily towards the midline, endocardial cells begin to
Development of the Heart and Great Vessels

Form a network of tiny channels that will coalesce into a complex endocardial network surrounded by a myocardial mantle [22]. If the mesodermal sheets are prevented from meeting in the midline as a consequence of genetic [15] or mechanical manipulation [23], dual heart tubes will be formed that undergo some degree of further independent development. However, in normal development, the endothelial network quickly transforms into a single endothelial channel within a single myocardial tube (Figure 1.2) [7].

The tube heart at the time of its formation is connected to the foregut along its dorsal surface throughout its length by a structure called the dorsal mesocardium [24]. As looping proceeds, the dorsal mesocardium degenerates until it remains connected only at the atrial and arterial poles of the heart. The disintegration of the central portion of the dorsal mesocardium is a key event for looping to proceed normally, while the arterial and venous attachments provide “anchors” for the looping heart tube. The mesenchymal portion of the dorsal mesocardium known as the dorsal menenchymal protrusion [25,26] protrudes into the atrium posteriorly and is a derivative of the second

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**Figure 1.1** Simplified schema of gastrulation, precardiac cell migration, and formation of the heart forming fields. **A,** Cells destined to become cardiac cells migrate from the epiblast into the primitive streak through a broad region caudal to the most anterior portion of the primitive streak. The direction of migration of the gastrulated cells, as indicated by the arrows, is away from the midline and anteriorly on each side. **B,** The embryo in cross-section at the level indicated by the dotted line in **A.** The precardiac mesoderm forms an epithelial sheet closely associated with the endoderm. The pre-endocardial cells are scattered throughout the same region and can be distinguished immunohistochemically from the general precardiac mesoderm. **C,** and **D,** The two lateral precardiac mesoderm populations (also known as heart forming fields) will migrate anteriorly before turning towards the midline (**C**). They will meet in the midline, as shown in **D,** at a location immediately anterior to the anterior intestinal portal.

**Figure 1.2** Formation of the tube heart is initiated by fusion of the bilateral precardiac mesoderm populations in the midline, resulting in formation of a myocardial tube surrounding an endothelial (endocardial) channel. The myocardial population of the cardiac tube at this stage consists of only the precursors of the future trabeculated portions of the left ventricle. Additional segments are added by ongoing migration of precardiac mesoderm into the tube heart.
significant new insights into the importance of this additional population of cells, called the second heart field, in the elongation and growth of the heart tube and in the formation of a mature four-chambered heart (Figure 1.3) [7]. Thus, these studies have demonstrated that the second heart field contributes at the arterial pole to the outflow tract and right ventricle and at the venous pole to parts of the atria and the dorsal mesenchymal protrusion.

The Tube Heart, Segments, and Segmental Identity

Traditionally, the heart tube has been regarded as containing the precursors of all of the cardiac segments. In reality, at the time the heartbeat is initiated the heart tube primarily consists of future left ventricular tissues [37,38]. Immunohistochemical, in situ hybridization, and cell fate tracing techniques have demonstrated that the outflow tract, the right ventricle [32], the AV junction segment [37], the atria [39], and the sinus venosus are added to the heart as looping proceeds. Indeed, these are the structures that are most important in the pathogenesis of the majority of forms of complex human congenital heart disease. Recent studies indicate that the outlet (truncal and conal) primordia [35,40] as well as the right ventricle and much of the
interventricular septum [35] and parts of the cardiac venous pole develop from the anterior/secondary heart field.

In prelooping and early looping stages the primitive heart tube consists of circumferential sheets of myocardial cells two to three layers thick surrounding an endothelial tube, these layers being separated by an acellular, extracellular matrix-rich space known as the cardiac jelly. As looping proceeds, the future segments can be distinguished morphologically by their position in the heart tube and by structural features, such as the striking accumulations of cardiac jelly in the AV canal and outflow segments. Segments can be distinguished physiologically by measurement of the differences in their velocity of muscular contraction and relaxation, their rates of spontaneous pacemaker activity, and the speed of electrical impulse conduction.

Segmental differentiation creates the physiological competence of the embryonic heart [41]. Unidirectional antegrade blood flow is maintained by organization of the tube heart into alternating regions of rapid and slow contractile properties [42]. The atrium has the fastest rate of spontaneous contractility and is the site of pacemaker activity. The wave of depolarization spreads from myocyte to myocyte from the atrium to the outflow tract, but the velocity of conduction is not uniform throughout the length of the heart tube. Atrial conduction is rapid, AV conduction is slow, ventricular conduction is rapid, and outlet conduction is slow. The zones of rapid conduction show rapid contraction—relaxation mechanical properties, while the slow zones of conduction demonstrate slow, sustained contractions. The result is a forceful contraction of the atria, followed by a sphincter-like contraction of the AV junction (prior to maturation of AV valves) that prevents the retrograde flow of blood during the forceful ventricular ejection phase. The cardiac cycle of the tube heart is completed by a sphincter-like contraction of the outflow tract (prior to maturation of the semilunar valves) to prevent retrograde blood flow from the aortic arches.

Genetic Determination of Cardiac Segmentation

In addition to functional differences, cardiac segments can also be distinguished by unique patterns of gene expression. However, despite the rapidly increasing number of markers that distinguish segments following heart tube formation, there has been less success in identifying segmental markers in the precardiac mesoderm. Data suggest that the final determination of lineage fate occurs in the precardiac mesoderm [9,31], but the timing and nature of the mechanisms are as yet poorly understood. Perhaps the best-studied determinants of the anterior–posterior axis in the gastrulating embryo are retinoids [43,44]. Retinoids are products of vitamin A metabolism, and manipulation of retinoid signaling pathways results in significant abnormalities in axial patterning in general and cardiac development in particular [45–49]. Abnormal development of atrial segments and systemic venous structures are observed in conditions of retinoid deficiency [50–52]. Excess retinoids create cardiac malformations, often involving the outflow tract [53,54], and result in ventricular expression of several genes that are normally largely restricted to the atria at these stages of normal development [55–57]. The spatial and temporal patterns of retinoid signaling in early cardiac development are highly correlated with the presence of retinaldehyde dehydrogenase 2 (RALDH2), a key enzyme in the retinol (vitamin A) to retinoic acid pathway [58–60]. Retinoid signaling pathways are clearly key mechanisms of segmental differentiation within the heart, but it is likely that other pathways yet to be determined are also involved.

Transgenic mice provide some of the most interesting data regarding differences between the genetic pathways regulating different regions of the heart. In these experiments, regulatory portions from one gene are used to drive the expression of a second gene whose product can readily be detected in the tissues. The DNA resulting from the combined portions of the two genes is injected into the male pronucleus of fertilized mouse eggs, and frequently the DNA is incorporated into the mouse nuclear DNA. The eggs are implanted in a female mouse and generally allowed to proceed through development until birth. The newborn animals bearing the new DNA (the “transgene”) can be identified by analysis of their DNA. If the transgene is present, the animal will be bred and its offspring analyzed for the pattern of expression of the transgene.

Use of this technology has demonstrated several features of segmental and regional gene expression in the heart [61]. The genetic elements that determine regional patterns of gene expression are modular, in that genes expressed widely in the heart often have discrete portions of their regulatory DNA responsible for subsets of the overall pattern. For instance, a transgene driven by a 10-kilobase (kb) segment of the Gata6 gene exhibits expression throughout the atria, AV junction, and left and right ventricles, excluding only the outflow tract; a smaller 2.3-kb fragment of the same gene drives expression only in the AV junction (Figure 1.4) [7,62]. The segmental and regional boundaries of gene expression determined by a specific genetic element may be variable during development, and transgenes expressed widely in the primitive tube heart can be restricted in their expression in the adult heart. Finally, the fact that some transgenes are differentially activated spatially and temporally in the heart is a striking confirmation of the nonequivalence of these tissues at the most basic level of gene regulation (Figure 1.4) [7].

Gene knockout experiments in mice also provide insight into the genetic regulatory networks critical to segmental differentiation. The requirement of the transcription factor HAND2 for normal development of the primitive right
The left ventricle moves inferior and anterior to the atrium, the right ventricle slightly anterior and to the right of the left ventricle. The bending of the heart tube is the first morphologic demonstration that the left and right sides of the embryo will not be morphologic mirror images, inextricably linking cardiac development to the correct establishment of the three body axes [68,69].

All vertebrate and most invertebrate body plans demonstrate fundamental asymmetries about the three body axes of anterior–posterior (A–P), dorsal–ventral (D–V), and left–right (L–R). At the molecular level, the axes are determined by asymmetric propagation of signaling events occurring very early in development. The process of L–R axis determination as it concerns heart development has been recently reviewed and broadly conceptualized as requiring three steps involving the initiation, elaboration, and interpretation of the sidedness signal [70,71]. The first step requires initiation of polarity along the A–P, D–V, and L–R axes. The initiating signals for these events are unknown in mammalian embryos. The second step is an elaboration and amplification of the initial L–R asymmetry through a variety of cellular signaling mechanisms. As is true in general for developmental processes, most of the molecules involved in elaborating the L–R signaling process in mice have easily recognized counterparts in birds. However, in a remarkable twist on that theme, some of the molecules required for left-sidedness in mice are determinants of right-sidedness in birds [72]. The molecules responsible for these processes in humans are poorly understood. The third step is the interpretation of the asymmetric signals elaborated in the second step by the cells and tissues of developing organs. The developmental fates of paired structures as to whether to form with mirror symmetries (such as the limbs), or as paired but unequal structures (such as the cardiac atria) is thus the result of both proper signal delivery to the organ primordia and proper reaction of the organ primordia to the signal.

As a measure of the complexity of the impact of genetic mechanisms on L–R axis determination on cardiac development, many genetic models of abnormal cardiac looping have now been described in mice [73]. Some are primarily models of abnormal directionality of looping, while others also show perturbation of the alignment of cardiac segments. Mouse models of globally randomized situs [74,75], situs inversus [76], situs defects affecting different embryonic organs to different degrees [77], and situs defects with preferential bilateral right- or left-sidedness have all been described [73]. Many of the genes implicated in the mouse models are candidate genes for heterotaxies in the human population [78].

The left and right atria have their molecular identities determined by L–R signaling mechanisms. Molecular distinctions between left and right atria are established early
after the atrial segment appears and are genetically dependent on L–R signaling mechanisms [79–81]. It is interesting to note, however, that there is often an increased incidence of transposition of the great arteries in mouse models of abnormal L–R axis determination [73], suggesting a possible element of L–R signaling in normal outflow development.

The mechanisms by which genetic signals result in regulated bending of the heart tube are unknown. Looping movements are intrinsic to the heart and will occur if the heart is isolated from the embryo, with or without beating [82,83]. The deformation of the straight heart tube into a looped structure likely results from some type of mechanical force [84]. However, the source of the required deforming force is not known. A simple explanation would be that myocytes replicate faster in the larger curvature of the loop and move slowly in the lesser curvature, and data suggesting a contribution of regional differences in growth have been presented [85,86]. However, cytochalasin B, an inhibitor of actin polymerization and therefore an inhibitor of cytoskeletal rearrangements, is also capable of either abolishing looping or reversing the direction of looping, according to whether it has been universally applied or selectively applied [87]. This suggests that the required asymmetric mechanical tension may be generated within the cells of the tube heart in response to as yet unknown regulatory signals.

**Looping, Convergence, and Septation – Key Landmarks**

Looping determines not only the sidedness of the heart but also the correct relationship of the segments of the heart to each other. Imaginary but useful divisions can be assigned to the morphogenetic steps leading from the more-or-less straight heart tube to the looped but still tubular heart, and from the looped heart to the heart poised for septation. Therefore, in this chapter, looping describes the initial period of growth, bending, and twisting of the heart tube. Looping begins and ends with the AV junction connected solely to the left ventricle and the outflow tract connected only to the right ventricle. The second phase of looping, sometimes called convergence, is the process of bringing the right atrial inflow over the right ventricle and the aortic outflow tract over the left ventricle, in the process aligning the outflow septal ridges for fusion with the primitive muscular septum and AV cushions. Ventricular septation is the process of closing the primary interventricular foramen while bringing the interventricular septum into continuity with the conus septum. Descriptions of these processes require recognition of a relatively small number of critical landmarks present in the embryonic heart during the looping and convergence stages of development (Figure 1.5) [7,88].

The looped heart has an inner curvature and an outer curvature. By nature of the tight angulation of the inner curvature the primitive atrial, AV, ventricular, and outflow segments are in close proximity for the remainder of cardiac development. As the region where the right ventricle acquires its inflow and the left ventricle acquires its outflow, the inner curvature of the heart is arguably the most critical, complex, and dynamic site in normal cardiac development.

On the lumenal surface of the heart, the fold in the heart at the inner curvature results in a small muscular ridge inside the heart between the AV junction and the outflow tract called the ventriculoinfundibular flange or ridge. Other key landmarks are the two major endocardial cushions of the AV junction and the two endocardial ridges of the outflow tract. The inferior endocardial cushion is attached to the dorsal AV myocardium and the superior endocardial cushion is attached to the ventral atrioventricular myocardium. As convergence proceeds, small right and left lateral AV endocardial cushions will become visible. The two outflow tract endocardial cushions form extended spiral ridges from the end of the truncus distally to the body of the right ventricle caudally. The endocardial cushion ridge ending in the anterior right ventricle is called the septal endocardial ridge. The endocardial ridge terminating posteriorly in the right ventricle is called the parietal endocardial ridge. The parietal endocardial ridge makes contact with the right lateral endocardial cushion, which itself will become continuous with the superior endocardial cushion. The septal endocardial ridge will make contact with the inferior endocardial cushion. As the endocardial cushions fuse during normal septation, they create, together with the mesenchymal cap of the primary atrial septum and the dorsal mesenchyme protrusion, the central AV mesenchymal complex extending from the AV junction to the distal extent of the myocardial outflow tract. At the most basic level the process of fusion of mesenchymal tissues can be thought of as a tissue zipper that septates the heart [26]. The reason that the endocardial cushion tissues of the conus septum cannot be found on inspection of the mature heart is that these mesenchymal structures are replaced by myocardium in the process known as myocardialization [89]. With respect to human congenital heart disease, this is a critical series of events, as disease phenotypes such as complex transposition, truncus arteriosus, and a number of tetralogy phenotypes all derive from aberrations of these normal developmental steps.

The left and right ventricular lumens are in continuity through the primary interventricular foramen. From the right ventricle, blood passes into the outflow tract of the heart. A myocardial cuff extends along the outflow tract to the junction with the aortic sac at the level of the pericardial reflection.
During convergence, the angle of the inner curvature of the heart becomes more acute. The right AV junction is formed by rightward expansion of the AV junction, while at the same time the major (or midline) AV endocardial cushions are approaching each other in the center of the lumen of the AV junction. The outflow endocardial ridges, although unfused, define distinct aortic and pulmonary channels. The aortic channel moves leftward and anterior of its original position. Because of the combined rightward expansion of the AV orifice and the leftward movement of the aortic outflow tract the acute angle of the inner curvature now defines the region where the AV junction and the outflow tract are in continuity. These same morphogenetic movements result in rotation of the outflow ridges to a plane that is closer to parallel to that of the growing muscular septum.

Endocardial Cushion Development and Myocardialization

When the tube heart initially forms, the myocardial and endocardial cell layers are separated by an acellular substance traditionally called “cardiac jelly” [90]. Cardiac jelly can be regarded as a basement membrane, as it lies between two juxtaposed epithelia (the myocardium and the endocardium) and contains traditional basement membrane proteins. The initial production and distribution of these molecules is largely controlled by factors produced by the associated AV myocardium [91,92]. Cardiac jelly condenses into opposing swellings at the outflow and AV regions of the early, looped heart. The resulting endocardial cushions function in combination with the specialized contractile properties of the AV junction and outflow tract myocardium to prevent reversal of blood flow [93]. The AV endocardial cushions also function as the substrate for the formation of the mesenchymal tissues of the crux of the heart, including the AV valves and central fibrous body [94]. Endocardial cushions of the embryonic outflow tract participate in the formation of the aorticopulmonary septum, semilunar valves, and conus septum [95]. During morphogenesis of the endocardial cushions, the mesenchymal cell population that populates the originally acellular cardiac jelly is derived from the endothelial cells of the heart [67,96] along with a population of epicardially
derived cells that also migrates into the AV cushions, but not the outflow tract cushions [97].

Endothelial invasion of the cardiac jelly results in a true transdifferentiation of cell phenotype, from a cell within a typical epithelium to an independently migratory, fibroblast-like mesenchymal cell [98–100]. This process has been compared to cellular changes during malignant transdifferentiation and is at least partially under the control of TGFβ-mediated signaling processes [101,102]. Only endocardium from the outflow tract and AV cushions are competent to undergo transformation, and only outflow tract and AV junction myocardium are able to induce transformation [101,103]. Not all the endocardial cells of the AV and conotruncal regions participate in these changes; as migration proceeds, residual endocardial cell populations undergo divisions to replenish their numbers. The mesenchymal cells also replicate actively to populate the cushions [99]. Recent data suggest that a similar process may result in an endothelial-to-mesenchymal transformation contributing to the neointima of atheromatous plaques [104].

Myocardialization is the process in which the mesenchyme of the endocardial cushions is replaced by myocardium [89]. All of the septal structures inside the heart – the interventricular septum, the atrial septum, and the conal septum – are created in part by fusion of nonmyocardial mesenchymal cushions. Myocardialization is responsible for the formation of the myocardial conus septum and the inlet and anterior outlet portions of the interventricular septum. In humans, the AV membranous septum is the only nonmyocardial septal structure derived from endocardial cushion tissue. The myocardialization of the conal cushions appears, based on Cre-lox cell fate studies, to primarily involve myocardial cell invasion of the cushion tissue. The mechanisms controlling this process are unclear [89,105,106].

### Atrial Septation

Atrial septation and connection of the common pulmonary vein to the left atrium are closely related events in the normal heart [81]. Recent investigations in mouse, chick, and human embryos highlight the importance of the dorsal mesocardium to these events. At the site where the dorsal mesocardium is in continuity with the atrium (approximately the level of the lung buds) there is a protrusion of mesenchymal tissue into the atrium. This tissue has been recognized for many years and by a variety of names, including “spina vestibuli,” “endocardial proliferation of the dorsal mesocardium,” “sinus venosus tissue,” and, most recently, the “dorsal mesenchymal protrusion” – the terminology adopted herein. Unlike other mesenchymal tissues in the AV junction, the dorsal mesenchymal protrusion is not derived from an epithelial-to-mesenchymal transformation, but rather is a derivative of the second heart field [25,26]. The dorsal mesenchymal protrusion extends into the atrial cavity and is contiguous with the mesenchymal cap on the leading edge of the septum primum. Together with the two major atrioventricular cushions, the dorsal mesenchymal protrusion and the cap eventually fuse to form the atrioventricular mesenchymal complex. This process is essential for normal atrioventricular septation (Figure 1.6) [7,81]. Recent papers strongly suggest that perturbation of the development of the dorsal mesenchymal protrusion might be one of the major mechanisms in the pathogenesis of atrioventricular septal defects.

Based on the expression of several molecular markers that distinguish between left and right atrial myocardium [81], the myocardial portion of the septum primum is derived from left atrial myocardium. Growth of the septum primum occurs by lengthening of its myocardial portion. As described above, the mesenchymal cap on the leading edge of the septum primum is mesenchymal, the cells being derived by endothelial-to-mesenchymal transformation similar to that seen in the endocardial cushions [67]. As growth of the septum primum proceeds, it brings the mesenchymal cap of the septum, as well as the dorsal mesenchymal protrusion into contact with the two major AV endocardial cushions (Figure 1.7) [25,26]. The primary interatrial foramen is closed by fusion of these mesenchymal tissues as they form the AV mesenchymal complex [26]. Knowledge of this process is critical towards understanding the pathogenesis of complete common AV canal, as well as understanding the tissue relationships relevant to its repair.

Before the closure of the primary interatrial foramen occurs, the foramen secundum appears in the body of the septum primum. In humans, this process is initiated by the appearance of small fenestrations that increase in number and size until they coalesce into a definitive foramen secundum [81].

The septum secundum forms as an infolding of the atrial roof in the intervalvar space between the left venous valve of the sinus venosus and the septum primum. The septum secundum also marks the site of boundary between left atrial and right atrial tissues. As a result, the left atrial myocardium of the septum secundum exhibits left atrial markers while the right atrial myocardial surface of the septum secundum exhibits right atrial markers [81].

### Interventricular Septation

As the primary interventricular foramen initially provides all of the inflow to the right ventricle and the entire outflow for the left ventricle, its correct closure is critical to normal cardiac development. Closure of the primary interventricular foramen is accomplished through coordinated growth of the muscular interventricular septum and fusion of
Figure 1.6 Sequence of events in atrial septation in human development. A, Heart at approximately 4.5 weeks of development. The leading edge of the septum primum is covered by a mesenchymal cap that is in continuity with the protrusion of the dorsal mesocardium into the atrial cavity. The superior and inferior atrioventricular cushions (sAVC and iAVC) are also in continuity with the mesenchymal cap. (DM, dorsal mesocardium; DMP, dorsal mesocardial protrusion.) B, Heart at -6 weeks development. The septum primum with its mesenchymal cap is approaching the fusing inferior atrioventricular cushion and superior atrioventricular cushion. Fenestrations (f) are appearing in the muscular septum primum (PS). C, At -6-7 weeks of development the fusion of the sAVC, iAVC, and cap of the septum primum is complete. The multiple fenestrations in the septum primum coalesce, forming the secondary foramen (sf). D, The secondary atrial septum (sAS) is created by infolding of myocardium at the junction of left and right atrial myocardium. Use of molecular markers distinguishing different populations of sinoatrial myocardial cells shows that the right-sided fold of the sAS and left venous valve (LVV) are derived from right atrial (RA) myocardium, while the left-sided fold of the sAS and primary atrial septum (pAS) are derived from left atrial (LA) myocardium. The right venous valve (RVV) is formed by infolding at the site of juncture of sinus venosus (SV) myocardium and RA myocardium, resulting in an RA molecular phenotype on the atrial surface and a SV molecular phenotype on the luminal surface. (CDM, endocardial cushion-derived mesenchyme; PuV, common pulmonary vein; OF, foramen ovale.) (After Wessels A, Anderson RH, Markwald RR, et al. (2000) Atrial development in the human heart: an immunohistochemical study with emphasis on the role of mesenchymal tissues. Anat Rec 259, 288–300 [81].)

eoccardial cushions in the AV junction and the outflow tract.

Growth of the muscular interventricular septum is closely associated with dynamic changes in patterning of the ventricular myocardium [107]. When the heart tube initially forms and early after looping, its myocardial layers are but a few cells thick. After looping, the ventricular chambers enlarge caudally in a pouch-like fashion. The pouches are located on the greater curvature of the looped heart and quickly develop a series of circumferential ridges on their internal surfaces (Figure 1.8) [7,107].

The myocytes of the primitive trabecular ridges differ from the subjacent compact myocardium in that the myocytes of the compact myocardium are actively proliferating, while the trabecular myocytes have withdrawn from the cell cycle and are not dividing [107]. The “germinal layer” of compact myocardium provides increases in the numbers of ventricular wall myocytes, but the initial major increases in myocardial mass occur through increase in the trabecular component of the myocardium [107]. The compact myocardium “feeds” cells into the ventricular junctions of the developing trabeculae; this is a relationship that persists throughout embryonic myocardial growth [107].

The primitive trabecular ridges become fenestrated and sheet-like as they expand. Trabeculae are believed to
Development of the Heart and Great Vessels

Produced by growth of the ventricular apices. Perhaps as a consequence, the interventricular groove is a more distinctive feature of mammalian hearts than avian hearts. The leading edge of the primitive muscular septum in humans is readily identified by the HNK1-Leu7 antibody that characterizes the primary ring (Figure 1.9) [7,111,112]. Use of this antibody in human embryos clearly demonstrates that the myocardial precursors of the right ventricle and right ventricular septum, including the inflow segment, are derived in their entirety from myocardial cell populations distal to the original primary interventricular foramen [113].

The primitive muscular interventricular septum is initially formed by a coalescence of trabeculae. In the mammalian heart, the primitive muscular septum appears to be the product of infolding of the compact myocardium produced by growth of the ventricular apices. Perhaps as a consequence, the interventricular groove is a more distinctive feature of mammalian hearts than avian hearts. The leading edge of the primitive muscular septum in humans is readily identified by the HNK1-Leu7 antibody that characterizes the primary ring (Figure 1.9) [7,111,112]. Use of this antibody in human embryos clearly demonstrates that the myocardial precursors of the right ventricle and right ventricular septum, including the inflow segment, are derived in their entirety from myocardial cell populations distal to the original primary interventricular foramen [113].

The primitive muscular interventricular septum is initially a crescent-shaped structure that extends at its posterior limit to the inferior endocardial cushion and at its anterior limit to the superior endocardial cushion. Part of the process of closure of the primary interventricular foramen consists of expansion of the superior and inferior endocardial cushions towards each other, where they will make contact and fuse at approximately 6 weeks’ gestation in the human. The mechanism of fusion of the endocardial cushions in spite of the continuous mechanical activity of the heart is not known, but certainly deserves respect.

assume several physiologic functions in the primitive heart. They enhance contractile function of the ventricles [108]. The surface area of the endocardium is greatly increased by the presence of trabeculae, which is believed to improve nutrient and gas exchange with the developing myocardium before the development of a true coronary vasculature [109]. The trabeculae have been asserted to be the conduction system equivalent to (and possibly precursors to) the distal bundle branches and Purkinje fibers in the developing heart [42]. Trabeculae also help to direct the flow of blood in the preseptated heart [110]. Thus, the infrequent, yet important echocardiographic finding of ventricular noncompaction bears important implications.

In the chick heart, the primitive muscular septum is initially formed by a coalescence of trabeculae. In the mammalian heart, the primitive muscular septum appears to be the product of infolding of the compact myocardium produced by growth of the ventricular apices. Perhaps as a consequence, the interventricular groove is a more distinctive feature of mammalian hearts than avian hearts. The leading edge of the primitive muscular septum in humans is readily identified by the HNK1-Leu7 antibody that characterizes the primary ring (Figure 1.9) [7,111,112]. Use of this antibody in human embryos clearly demonstrates that the myocardial precursors of the right ventricle and right ventricular septum, including the inflow segment, are derived in their entirety from myocardial cell populations distal to the original primary interventricular foramen [113].

The primitive muscular interventricular septum is initially a crescent-shaped structure that extends at its posterior limit to the inferior endocardial cushion and at its anterior limit to the superior endocardial cushion. Part of the process of closure of the primary interventricular foramen consists of expansion of the superior and inferior endocardial cushions towards each other, where they will make contact and fuse at approximately 6 weeks’ gestation in the human. The mechanism of fusion of the endocardial cushions in spite of the continuous mechanical activity of the heart is not known, but certainly deserves respect.

![Figure 1.7](image1.png) Three-dimensional reconstructions demonstrating the spatiotemporal relationships of the atrioventricular mesenchymal tissues during mouse heart development. Computer-generated three-dimensional reconstructions (AMIRA software) based on stained serial sections of mouse hearts A at embryonic day 11.5 and B at embryonic day 13. These panels show how the respective bodies of mesenchyme fuse with each other to accomplish atrioventricular septation. A, The mesenchymal tissues are viewed from above, while all other cardiac tissues are digitally removed to facilitate the study of the relationship of the mesenchymal components. At this stage, the individual mesenchymal components have not fused completely yet. The asterisks mark the groove within these tissues where the myocardial part of the septum primum is located (removed for reconstruction). B, The AV tissues are viewed as if one was standing in the right atrium. At this stage, all the mesenchymal tissues have fused. This panel demonstrates how the dorsal mesenchymal protrusion forms a wedge between the major AV cushions at the same time forming the base of the septum primum. At this stage the atrial cap cannot be distinguished any longer from the other endocardially derived mesenchymal tissues (for more detailed description see Snarr et al. [25,26].) (CAP, mesenchymal cap on the primary atrial septum; DMP, the dorsal mesenchymal protrusion; iAHC, inferior AV cushion; IIAHC, left lateral AV cushion; PAS, primary atrial septum [septum primum]; rIHC, right lateral AV cushion; sAHC, superior AV cushion.) (Reproduced with permission from Snarr et al. [26].)

![Figure 1.8](image2.png) Scanning electron micrograph of a section through the right and left ventricles of an embryonic chick heart. The pleat-like ridges characteristic of early myocardial trabeculum formation are easily appreciated. At this stage, the inner curvature of the heart separates the atrioventricular inflow from the right ventricle and the outflow tract from the left ventricle. (EC, endocardial cushion; IAS, interatrial septum; LA, left atrium; RA, right atrium; sAHC, superior atrioventricular cushion.) (Courtesy of David Sedmera.)
Further growth of the interventricular muscular septum results in fusion of the crest of the septum with the fused cushion. The boundaries between the original muscular septum and endocardial cushion-derived portions of the septum become obscured by myocardialization except for the membranous septum between the left ventricle and right atrium. Normal inlet septum development is primarily determined by interactions between the inferior endocardial cushion-derived tissue and the muscular ventricular septum, while the smooth anterior interventricular septum is derived from interactions between the superior endocardial cushion and the muscular septum. The membranous septum is the approximate site of final union between the muscular septum and the superior and inferior endocardial cushions [114].

**The Atrioventricular Junction Segment and Atrioventricular Valve Development**

The electrophysiologic and physiologic properties of the junctional myocardium between the primitive atria and ventricles are critical to the preseptated heart, as previously discussed. However, myocardial continuity between the AV junctional myocardium, the atrial myocardium, and the ventricular myocardium must be interrupted for the development of the fibrous crux of the heart and the correct
function of the conduction system. This is accomplished by formation of a layer of fibrous insulation called the annulus fibrosis that will completely interrupt myocardial continuity between the AV myocardium and the ventricular myocardium, with the exception of the penetrating bundle of His specialized myocardium. In the mature heart the remnants of AV junction myocardium become incorporated into the myocardium of the definitive atrium [94].

Fibrous interruption of AV myocardial continuity results from the fusion of mesenchymal cell populations of the AV endocardial cushions with a mesenchymal cell population found in the atrioventricular sulcus on the external surface of the looped heart. Atrioventricular sulcus mesenchyme cells are brought to the heart in the course of the epicardial cell migration (see Figure 1.3) [7], as discussed in greater detail later in this chapter in connection with coronary artery development. Morphologic studies suggest that the sulcus mesenchyme actively invaginates into the endocardial cushions [115]; the mechanisms driving mesenchymal invagination and the parting of the myocardial layer are unknown. Interruption of myocardial continuity begins at 52 to 60 days of gestation in the human heart and is normally “complete” by the fourth month of gestation [94]. Failure to form the insulating tissues of the AV junction may underlie clinical pre-excitation syndromes. Interestingly, isolated myocytes possibly representing remnants of the embryonic junctional myocardium, originally present between the sulcus mesenchyme and the endocardial cushion mesenchyme, have been identified bridging the fibrous insulation of normal neonatal hearts [116]. This location is different from that noted for parietal accessory atrioventricular bundles [117], which are described as sub-epicardial and, therefore, seem to represent a different myocardial path through the sulcus mesenchyme-derived fibrous tissue. No structures similar to parietal accessory AV connections are noted in the course of normal development. Thus, the possibility that these accessory connections develop postnatally should be considered. The relationship between pre-excitation pathways in general and normal morphologic events requires further investigation.

Atrioventricular valve development may be tied to the process of sulcus tissue ingrowth, as the hinge points of the definitive leaflets are normally found at the point of junction between the endocardial cushion tissues and the invaginating sulcus tissue. Atrioventricular valve leaflets are formed by separation of endocardial cushion tissue and myocardium from the ventricular walls in the poorly understood process of delamination [105,118,119]. Other events occurring at the same time that certainly influence normal valvar morphogenesis and may contribute to the delamination process include coarsening of the ventricular trabeculae, incorporation of trabeculae into the compact myocardium, and apical expansion of the ventricular cavity.

At the time of delamination, the atrial surfaces of the valve leaflets are composed of endocardial cushion tissue while the ventricular surfaces are primarily myocardial. The myocardial layer provides continuity with the evolving subvalvar tension apparatus. As leaflet morphogenesis proceeds, the myocardial component is eliminated by unknown processes. Initially, the ends of the AV leaflets are connected to the compact ventricular myocardium either directly or via trabecular outgrowths of the myocardium. As development proceeds, papillary muscles are derived by two mechanisms: from initially independent, pre-existing trabeculae coalescing together to form papillary muscles; and from delamination of myocardium into myocardial structures that join with trabeculae or form of themselves the papillary muscles. The mitral valve papillary muscles are derived from a single large trabecula that then separates into the two independent papillary supports [119]. Thus the surgically challenging group of patients with parachute mitral valve derivatives are likely due to deficiencies in this process. Tricuspid valve papillary muscles develop independently from each other and via different mechanisms; the anterior papillary muscle of the tricuspid derives from an early coalescence of trabeculae detectable at 6 weeks’ gestation, the septal leaflet papillary muscle is a product of delamination during the tenth to twelfth week of gestation, and the posterior papillary muscle complex is still a relatively indistinct structure at 12 weeks’ gestation [105]. Chordae are formed by progressive fenestration and fibrous differentiation of trabeculae and/or the initially solid individual valve leaflets; there is disagreement with respect to the derivation of chordae from myocardium or endocardial cushion tissue [105,107,118].

As previously noted, there are four endocardial cushions in the AV junction. The superior and inferior cushions are the most prominent endocardial cushion masses from their first appearance, but there are also important contributions from the lateral endocardial cushions, which are visible only after Carnegie Stage 17 (approximately 42 days) [94,118]. The left lateral cushion contributes to the posterior (mural) leaflet of the mitral valve. The right lateral cushion, which becomes continuous anteriorly with the septal endocardial cushion of the outflow tract, contributes to the formation of the anterior and inferior leaflets of the tricuspid valve.

Atrioventricular valve morphogenesis is one of the most prolonged aspects of human cardiac development. Recognizable elements of the tricuspid valve begin formation at 5–6 weeks’ gestation. The AV endocardial cushions are actively reconfiguring at this time, with fusion of the superior and right lateral AV endocardial cushions to each other. The conal cushions are also completing their fusion during this time. The fused outflow septum then expands apically to reach the inner curvature of the heart, anterior to the fusing superior and right lateral endocardial
cushions. In this position the fused outflow cushions will become adherent to the myocardium of the ventriculo-fundibular fold, establishing the anterior position of the conus septum with respect to the atrioventricular valvular structures, and also forming the crista supraventricularis [105]. Despite the overall advanced stage of cardiac morphogenesis at this point, the tricuspid valve leaflets are still very primitive in appearance and not freely mobile. The inferior leaflet is fully delaminated by the end of the eighth week of gestation, the anterior leaflet by the eleventh week, and the septal leaflet in the twelfth week. The commissure separating the anterior and septal leaflets is not complete until the septal leaflet is fully delaminated [105].

In development of the mitral valve, the inferior and superior AV cushions begin to fuse at roughly 5 weeks' gestation; even before fusion, the enlarged trabecular complex that will evolve into the two mitral papillary muscles can be seen connecting the superior and inferior cushions [118,119]. The left lateral cushion, the precursor to the posterior leaflet, is visible by the seventh week of gestation. At approximately this time initial delamination of the mitral valve structures becomes detectable and continues until the tenth week of development. Between the tenth and fourteenth weeks of development myocardial elements of the leaflets are eliminated, papillary muscles achieve their adult appearance, and chordae differentiate [118,119].

Development of the Conduction System

The sinoatrial node first becomes detectable at approximately 10.5 days in mouse development, roughly equivalent to Carnegie stage 14 (approximately 32 days) of human development, at the medial wall of the right common cardinal vein and extending cranially to the junction of the anterior and common cardinal veins. This corresponds to what will become the portion of the superior vena cava between the orifice of theazygous vein and the right atrium in the adult [120].

In the human embryo the AV node becomes detectable histologically at approximately Carnegie stage 15 (approximately 33 days) [121]. It is located in the posterior portion of the AV canal in the myocardium under the ventricular margin of the inferior endocardial cushion and is included in the primary ring [94]. The primitive AV node is in direct continuity with the AV and ventricular myocardium. From the earliest stages a cellular tract destined to become the bundle of His can be noted extending from the main mass of AV nodal tissue to the ventricular subendocardium. The AV sulcus mesenchyme will invaginate to make contact with the endocardial cushion mesenchyme inferiorly to the main mass of the developing AV node while encasing the future bundle of His in the fibrous insulating tissue at the crux of the heart [94].

The proximal bundle branches are detected in the human by antibodies to the primary ring antigen Gln2/HNK1/Leu7 (Figure 1.9) [7,111,112]. Differentiation of conduction tissue in the ventricles appears to occur by a process of recruitment of “working” myocardium into the conduction lineage and to be associated with withdrawal from the cell cycle [122,123]. Numerous observations support the contention that the trabeculae of the primitive heart are the initial conduction pathways connecting the proximal bundle branches with the ventricular free walls [124]. Subsets of trabeculae probably remain as elements of the conduction tissue in the mature heart.

The cellular morphology of Purkinje fibers is extremely variable between species [125]. In some species intramural Purkinje fibers are very difficult to distinguish by morphologic criteria. Molecular markers that unambiguously identify intramural Purkinje fibers across species are not known [124]. However, in all animals in which they have been studied, intramural Purkinje fibers are late-appearing structures in comparison to the central AV node–His bundle–bundle branch conduction tissues. In the developing sheep heart, where Purkinje fibers are easily distinguished by morphologic criteria from “working” ventricular myocytes, intramural Purkinje fibers are not seen until 60 days' gestation, while the AV node becomes visible as early as 27 days' gestation [126]. In this species, morphologic differentiation of the conduction tissue clearly progresses outward from the AV node.

Purkinje fibers in the chick embryo myocardium can be recognized by specific expression of the gap junction protein Cx42. Use of this marker shows that chick embryo Purkinje fibers are only detectable at day 10 of chicken development. In this model ventricular myocytes are recruited to differentiate into Purkinje cells only in the vicinity of developing coronary arteries [123]. Data suggest that endothelin signaling may be an important determinant of this process [127].

Morphogenesis of the Outflow Tract

Landmarks in the Outflow Tract

The morphologic terminology for the outflow tract used in this chapter follows that proposed by Pexieder [128]. The outflow tract is relatively short in the early phases of looping, after which it becomes elongated, with a distinct bend. The site of the bend is the primary external landmark dividing the truncus from the conus portions of the outflow tract: separate structures. The external landmarks for the entire region are the ventriculo-infundibular fold proximally and the aortic sac distally. The aortic sac–outflow junction is identified by flaring of the root of the aortic sac, the reflection of the pericardium, and the distal limit of the cardiac jelly and myocardium. The proximal end of the