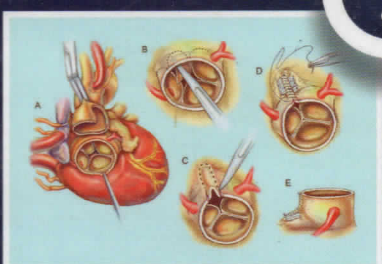
PEDIATRIC CARDIAC SURGERY

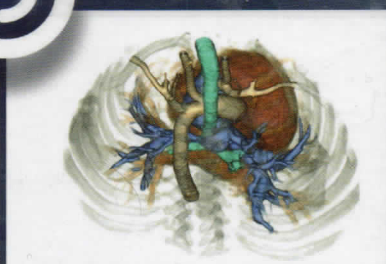
FIFTH EDITION

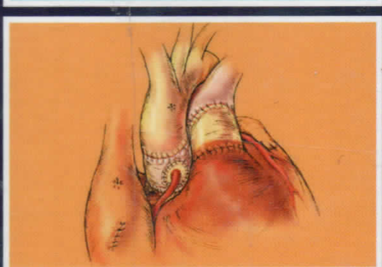
EDITED BY

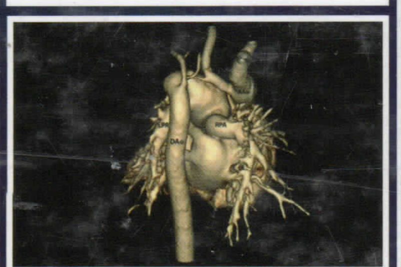
CONSTANTINE MAVROUDIS

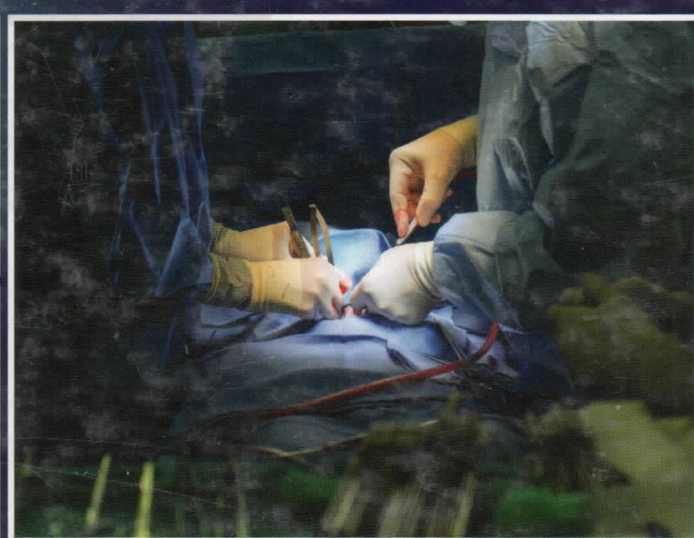
CARL L. BACKER











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CHAPTER 1

Development of the Heart and Great Vessels

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Major advances in molecular genetics, establishment of appropriate animal models, and improvements in analytical techniques have contributed to a greater understanding of cardiac development. Modern cardiac embryology now combines molecular and cellular biologic techniques with traditional embryologic morphologic approaches across multiple model systems. A significant proportion of our understanding continues to be derived from nonhuman experimental models, supplemented by observations imputed from the congenitally malformed human heart [1]. In early studies, avian embryos were the favored experimental model because of the ease with which they could be observed and manipulated. Due to the strength of genetic and molecular investigative tools, the mouse has now become the preferred model for studying cardiac development. Table 1.1 provides a simplified comparison of developmental staging in human, mouse, and chicken embryos [2–8]. Understanding cardiac development not only has implications for classifying and managing congenital heart disease, but also provides a platform for the development of novel management approaches, in both children and adults.

With a goal of simplifying the description of complex developmental structures, in this chapter we have made efforts to harmonize nomenclature using descriptive terms that relate as much as possible to human development. Thus, "anterior-posterior axis" is replaced by "dorsal–ventral axis" or "cranial–caudal." "Anterior" is often replaced by "ventral" or "cranial." "Posterior" is frequently replaced by "dorsal" or "caudal." "Conus" is replaced by "proximal outflow tract," and "truncus" is replaced by distal outflow tract. The "dorsal mesocardial protrusion" is referred to as the "vestibular spine."

Origin of Cardiac Precursor Cells

All cells destined to become part of the heart derive from populations of undifferentiated precursors. These precursor cells are influenced by external signals and guided to their final developmental state. In humans, during the second week following fertilization, the blastocyst has partially embedded into the uterine endometrium. At this stage, the inner cell mass, or embryoblast, differentiates into two distinct layers of cells: a larger columnar epiblast layer and the smaller cuboidal hypoblast layer. The third week of development is characterized by the next critical embryonic process, termed gastrulation. A primitive streak is formed in the epiblast layer, following which some epiblast cells invaginate under and displace the hypoblast. Subsequent widespread cell migration into, and reorganization within, the blastocele cavity results in the formation of three germ layers: the ectoderm, mesoderm, and endoderm. This sets the stage for the determination of the future body plan of the embryo (Figure 1.1) [3,9].

Migrating epiblast cells, which have now formed the mesoderm of the embryo, gradually travel cephalad. During this migration, they join the lateral plate mesoderm at the level of the primitive node. The lateral plate mesoderm then divides 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]. To date, however, no single gene has been identified whose ablation leads to a specific failure of all myocardial

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