mesoderm, and smooth muscle of the proximal outflow tract arises from the second heart field. Neural crest cells are sensitive to both vitamin A and folic acid, and congenital heart disease involving abnormal remodeling of the aortic arch arteries has been associated with maternal deficiencies of these vitamins. Congenital heart disease involving the outflow tract can be associated with other defects of neural crest, such as cleft palate or craniofacial abnormalities.

Coronary artery formation requires yet another cell population that initiates extrinsic to the embryonic heart fields. Epicardial cells arise in the proepicardial organ, a derivative of the septum transversum, which also contributes to the fibrous portion of the diaphragm and to the liver. Proepicardial cells contribute to the smooth-muscle cells of the coronary arteries and are required for their proper patterning. Other cell types within the heart, including fibroblasts and potentially some myocardial and endocardial cells, also can arise from the proepicardium.

The cardiac conduction system, which functions both to generate and to propagate electrical impulses, develops primarily from multipotential cardiac precursors, which also give rise to cardiac muscle. The conduction system is composed of slow-conducting (proximal) components, such as the sinoatrial (SA) and atrioventricular (AV) nodes, as well as fast-conducting (distal) components, including the His bundle, bundle branches, and Purkinje fibers. The AV node primarily serves to delay the electrical impulse between atria and ventricles (manifesting decremental conduction), whereas the distal conduction system rapidly delivers the impulse throughout the ventricles. Significant recent attention has been focused on the embryologic origins of various components of the specialized conduction network. Precursors within the sinus venosus give rise to the SA node, whereas those within the AV canal mature into heterogeneous cell types that compose the AV node. Myocardial cells transdifferentiate into Purkinje fibers to form the distal conduction system. Fast and slow conducting cell types within the nodes and bundles are characterized by expression of distinct gap junction proteins, including connexins, and ion channels that characterize unique cell fates and electrical properties of the tissues. Developmental defects in conduction system morphogenesis and lineage determination can lead to various electrophysiologic disorders, including congenital heart block and preexcitation syndromes such as the Wolff-Parkinson-White syndrome (Chap. 276).

Studies of cardiac stem and progenitor cells suggest that progressive lineage restriction results in the gradual and stepwise determination of mature cell fates within the heart, with early precursors capable of adopting endothelial, smooth-muscle, or cardiac phenotypes, and subsequent further specialization into atrial, ventricular, and specialized conduction cell types.

REGENERATING CARDIAC TISSUE

Until very recently, adult mammalian myocardial cells were viewed as fully differentiated and without regenerative potential. Evidence currently supports the existence of limited regenerative potential of the mature heart. Considerable current effort is being devoted to evaluating the utility of various putative stem cell populations and regenerative approaches to enhance cardiac repair after injury. The success of such approaches would offer the exciting possibility of reconstructing an infarcted or failing ventricle (Chaps. 88 and 90e).