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心血管疾病分子生物学

Molecular Basis of CARDIOVASCULAR DISEASE

A COMPANION TO BRAUNWALD'S HEART DISEASE

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Molecular Basis of Cardiovascular Disease

A Companion to BRAUNWALD'S HEART DISEASE

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Foreword

The very substantial advances in the diagnosis and management of patients with cardiovascular diseases represent one of the medical triumphs of the twentieth century. These great strides have been based on solid foundations of cardiovascular physiology and pharmacology and in many instances on the clinical applications of bioengineering. Notable examples include the development of a variety of accurate invasive and noninvasive diagnostic techniques and several classes of drugs that have profoundly beneficial effects on patients with cardiovascular disease, as well as open heart surgery, percutaneous catheter–based coronary revascularization, artificial cardiac valves, cardiac pacemakers, and internal cardioverter-defibrillators. These have prolonged and improved the quality of the lives of millions of individuals worldwide.

Despite these impressive advances, however, cardiovascular diseases still remain the most common fatal and disabling disorders in industrialized nations and are projected soon to be so on a worldwide basis. Clearly, bold new approaches to solving the problems posed by these conditions are needed. There is a growing consensus that just as the first wave of advances was based largely on the applications of physiology, pharmacology, and bioengineering, the next will exploit the new biologic sciences—molecular biology, genetics, and cell biology. Since most cardiovascular disorders now appear to have a molecular basis, appropriate preventive or therapeutic strategies will require an understanding of the molecular pathology.

Kenneth Chien and his distinguished associates—Jan Breslow, Jeffrey Leiden, Robert Rosenberg, and Christine Seidman—have enlisted a team of experts to produce *Molecular Basis of Cardiovascular Disease,* a superb book that provides an up-to-date picture of the impact that the new biology is likely to have on cardiovascular disease. In the first section they provide the background in molecular biology and genetics required to apply these sciences to the study of a variety of cardiovascular disorders. They then go on to demonstrate how the new molecular techniques can be applied to understanding disorders of cardiovascular structure, such as congenital heart disease and ventricular hypertrophy, and of cardiac function, such as heart failure and arrhythmias. The molecular bases of disorders of lipid metabolism and of coagulation, both of which may predispose to the development of chronic coronary atherosclerosis and its conversion to acute coronary syndromes, receive considerable attention.

Molecular Basis of Cardiovascular Disease is filled with important concepts and explanations that are clearly presented. This book should serve as an especially important resource not only to scientists and students in this rapidly growing field but also to clinical cardiologists who wish to understand the biologic principles underlying cardiovascular disease. It is a most fitting companion to *Heart Disease: A Textbook of Cardiovascular Medicine.*

EUGENE BRAUNWALD

Preface

It is now clear that abnormalities of molecular processes may be the basis of many cardiovascular diseases and that genetic influences play critical roles in the development of these abnormalities. . . .

EUGENE BRAUNWALD, M.D., 1997,
in *Heart Disease: A Textbook of Cardiovascular Medicine, 5th edition*

As noted above by the founding father of modern cardiovascular medicine, our field is now on the threshold of a molecular therapeutic era. Fundamental advances in our understanding of the molecular basis of heart disease are forming the foundation for novel diagnostic, prognostic, and therapeutic approaches to patients with heart disease. Over the past few years, a growing number of disease genes have been identified by applying genetic mapping techniques to inherited cardiovascular disorders, including long QT syndrome, hypertrophic cardiomyopathy, Marfan syndrome, familial dilated cardiomyopathy, inherited thrombotic disorders, congenital heart diseases, and genetic forms of hypertension (Liddle syndrome). The Human Genome Project, in combination with genetically engineered animal models of human heart disease, is identifying new targets for drug development. Breakthroughs in our understanding of the molecular mechanisms that drive the transition from cardiac hypertrophy to heart failure have also led to new therapeutic strategies for this common acquired form of heart disease. Second-generation thrombolytic agents are now being tested clinically, while the first-generation agents are finding new therapeutic indications in stroke and other vascular disorders. The discovery of new classes of cardiovascular receptors has also led to biologically targeted agents for hypertension and heart failure, such as endothelin receptor blockade. Therapeutic angiogenesis with defined growth factors for coronary artery disease has been proved to be efficacious in experimental models and is now being tested clinically. A new generation of intravenous and oral drugs have been developed that display improved selectivity and efficacy as platelet antagonists. Recombinant protein antibodies have also become effective drugs to blunt restenosis following coronary angioplasty. In addition, new anticoagulants are being developed that may offer improvements in bleeding side effects by targeting specific upstream points in the coagulation cascade. Finally, scientific and technological advances are forming the basis for new strategies for cardiovascular gene therapy in the next decade. In essence, the advent of gene-based technology is initiating a revolutionary new approach to heart disease by attacking the fundamental basis of the disease process itself; it promises to have a lasting impact on patient care.

Molecular Basis of Cardiovascular Disease (MCVD) is designed to highlight these advances in cardiovascular medicine for a wide general audience of cardiologists, clinical and research trainees, and basic scientists who are finding it increasingly necessary to keep abreast of cutting-edge clinical, technological, and scientific developments in this fast-moving area of medicine. Toward this end, each of the chapters is written by international authorities in their respective fields, including seven members of the prestigious National Academy of Sciences. Detailed figures and comprehensive tables are provided to allow technological advances to be readily grasped by practicing physicians. Finally, a glossary of over 500 separate terms in molecular genetics is included, providing an integrated reference source that will facilitate understanding of the chapters in *MCVD* and related articles that are listed in the detailed references.

The first section of *MCVD* provides a scientific foundation for the understanding of subsequent chapters that deal with specific aspects of cardiovascular disease. This section starts by highlighting general principles of molecular biology and providing prime examples of their application to cardiovascular problems. An overview of new technology that allows the generation of genetically engineered animal models of cardiovascular disease follows; this includes a discussion of the power of this approach to study disorders of lipoprotein metabolism and atherogenesis. The prospects for gene therapy–based approaches for cardiovascular disease and the potential applications of this cutting-edge technology for cardiovascular biology and medicine are illustrated in a manner that is accessible to both physicians and scientists. This section ends with an outline of modern genetic approaches to cardiovas-

cular disease and their implications for the practicing physician.

The second section of *MCVD* discusses molecular advances in our understanding of cardiovascular development and how these are forming a framework for understanding the mechanistic basis for various forms of congenital heart disease. Although a genetic basis for congenital heart disease phenotypes has been long suspected, there is now clear evidence of genetic factors that confer a risk for a defined subset of morphogenic defects. Prospects for understanding the molecular basis of hypoplastic left heart syndromes, via studies of a rare chromosomal deletional disorder, are also discussed. Of particular note is the review by Drs. McKusick and Dietz, which highlights major leaps in our understanding of genetically based forms of vascular disease, including the Marfan syndrome and supravalvular aortic stenosis.

Perhaps one of the prime examples of the power of utilizing molecular genetics to unravel heart disease is provided in Part III, which focuses on cardiac muscle and myopathies. An excellent overview is presented of our understanding of the structure and function of the muscle proteins that control cardiac contractile function. This forms the basis for understanding inherited cardiomyopathies that arise as a result of mutations in individual sarcomeric protein components. The specific types of gene mutations, the variety of disease genes, and the clinical implications for families that harbor these mutations are elegantly and clearly delineated. A series of studies have implicated mutations in mitochondrial DNA in a subset of patients with dilated cardiomyopathy and stroke; Dr. Douglas Wallace, a leader in this field, highlights this area, which has relevance to both cardiovascular disease and the biology of aging.

As noted in Part IV, our understanding of the electrophysiologic function of the heart has been a great beneficiary of molecular technology. A molecular definition of the channels that regulate the various phases of the cardiac action potential as well as the pathways that regulate conduction has been elucidated. A classic example of how this information on the fundamental nature of ion channels can lead to an in-depth understanding of the molecular basis of inherited cardiac arrhythmias is provided; it includes a discussion of the disease gene mutations that cause long QT syndromes and their importance for patient management. Although the vast majority of life-threatening arrhythmias occur in the setting of acquired diseases, a variety of new approaches are beginning to shed light on potential molecular targets for both supraventricular and ventricular arrhythmias.

Vascular biology and atherogenesis (Part V) have long been at the intersection between molecules and medicine. Drs. Gimbrone and Topper provide a beautiful overview of the biology of the vessel wall, which forms the basis for many of the subsequent advances in the field of vascular biology. These fundamental principles are beginning to offer insight into the atherogenic process itself, leading to a growing view of atherosclerosis as not only a disease of cholesterol metabolism but also an inflammatory process. The impact of recent discoveries in the signaling pathways that control cell growth and proliferation for vascular remodeling and coronary restenosis is integrated into the context of the clinical problem of coronary angioplasty. Finally, the exciting prospect of therapeutic angiogenesis with defined angiogenic factors for various forms of coronary and peripheral vascular disease as well as its scientific foundations is discussed in a chapter by Judah Folkman, the widely acknowledged pioneer in this field.

Part VI expands on the theme of coronary artery disease with a discussion from the Past President of the American Heart Association, Dr. Jan Breslow, and his colleague, Dr. Alan Tall, on the molecular basis of hyperlipidemias and other important risk factors as well as our current strategies for risk reduction. Inherited disorders of lipoprotein metabolism have formed the basis for our understanding of the mechanistic link between cholesterol regulation and atherogenesis and led to the development of a new wave of therapy that acts by modulating the low-density lipoprotein (LDL) receptor pathway. The importance of LDL oxidation for atherogenesis, a concept pioneered by Dr. Daniel Steinberg and his colleague Dr. Joseph Witztum, is elegantly discussed from the viewpoint of patient, clinician, and scientist. Finally, as there is clearly a risk factor conferred by diabetes for coronary artery disease, a penetrating review is provided of advances in the genetics of diabetes and the uncovering of new, genetically based risk factors for diabetes.

Part VII begins with a comprehensive overview of blood coagulation and its importance in cardiovascular disease. Subsequently, the importance of the fibrinolytic system and new approaches to thrombolytic therapy with second-generation thrombolytics and adjunctive therapy are discussed. Finally, the critical importance of platelet thrombosis and antiplatelet therapy in clinical cardiology is highlighted, along with new therapeutic agents for the treatment of platelet aggregation syndromes and related disorders.

MCVD would not have been possible without the guidance, vision, and steadfast support of Dr. Eugene Braunwald, who recognized at an early stage

the importance of molecular technology for a new generation of therapy in cardiovascular medicine. Our Managing Editor, Dr. Richard Zorab, and his team of coworkers served as able navigators for a crew of editors who now fully appreciate the challenges of a book of this scope. We are also particularly grateful for the assistance of Marion Sauter, who served as an editorial assistant for the book, and without whose diligence *MCVD* would have never come to fruition. Dr. Andrew Grace, a coauthor of the chapter Principles of Cardiovascular Molecular and Cellular Biology in the parent text, performed admirably in a supporting role as assistant editor. Finally, we thank Marisa and Elena Chien for their artwork included in the color insert.

Medicine, like art, often progresses via a series of distinct movements: Impressionism/Postimpressionism, invasive/noninvasive, surgical/interventional. By any measure, cardiovascular medicine is entering an era of molecular-based therapy. Molecular technology is having a major impact on cardiovascular medicine that is palpable to the community of clinical cardiologists. Our hope is that *MCVD* captures the excitement of this field and successfully bridges the diverse worlds of cardiovascular medicine and molecular science. Clearly, the foundation for the next generation of biologically targeted therapy rests on our ultimate understanding of complex cardiovascular diseases at the molecular level. As noted almost three centuries ago, the pathway toward effective treatment of disease often lies in unraveling the mechanistic basis of the disease process itself:

The same person who has a proper knowledge of the conditions which ensure perfect health will, whenever these are lacking, have an excellent understanding of the origin and nature of that failing—that is, of the disease. . . . He who has an absolutely clear insight into the immediate cause of an illness, must be considered preeminently capable of combating it.

Evidently the situation is the same in the case of a clock. If its hands show a deviation, even the layman is able to note the error; but nobody can put it right in an expert manner except he who, from his knowledge of the correct structure, discerns the defects of the parts and the ways and means of repairing them.

Hermanni Boerhaave
September 24, 1703

KENNETH R. CHIEN

NOTICE

Medicine is an ever-changing field. Standard safety precautions must be followed, but as new research and clinical experience broaden our knowledge, changes in treatment and drug therapy become necessary or appropriate. Readers are advised to check the product information currently provided by the manufacturer of each drug to be administered to verify the recommended dose, the method and duration of administration, and the contraindications. It is the responsibility of the treating physician, relying on experience and knowledge of the patient, to determine dosages and the best treatment for the patient. Neither the publisher nor the editor assumes any responsibility for any injury and/or damage to persons or property.

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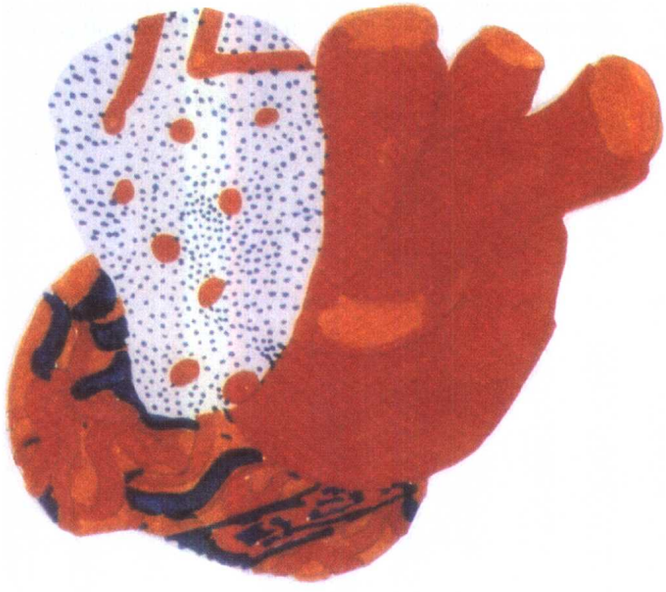
Heartwork One by Marisa Court Chien.



Heartwork Two by Elena Brooke Chien.

PLATE 1

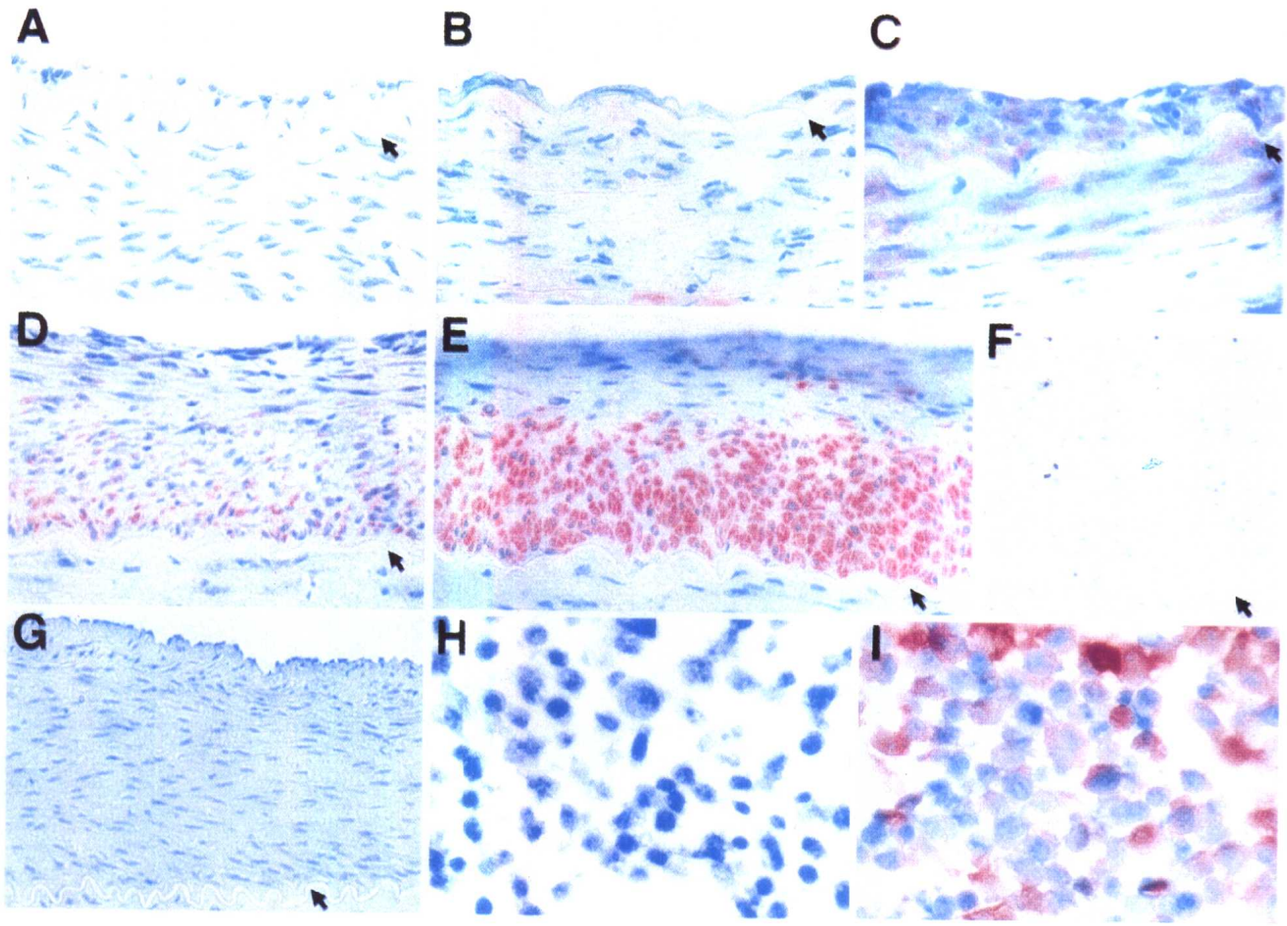


Figure 4–5 • Endogenous expression of p21 in normal and injured pig arteries. p21 is not detected in normal pig arteries *(A)* or immediately after balloon injury *(B)* when smooth muscle cells undergo replication. p21 is strongly expressed 21 days after injury *(D–E)* when cell proliferation is declining *(F)*. Sixty days after injury, when repair is complete, p21 is no longer detected *(G)*. (From Yang ZY, Simari RD, Perkins ND, et al: Role of the p21 cyclin-dependent kinase inhibitor in limiting intimal cell proliferation in response to arterial injury. Proc Natl Acad Sci USA 1996, 93:7905–7910.)

PLATE 2

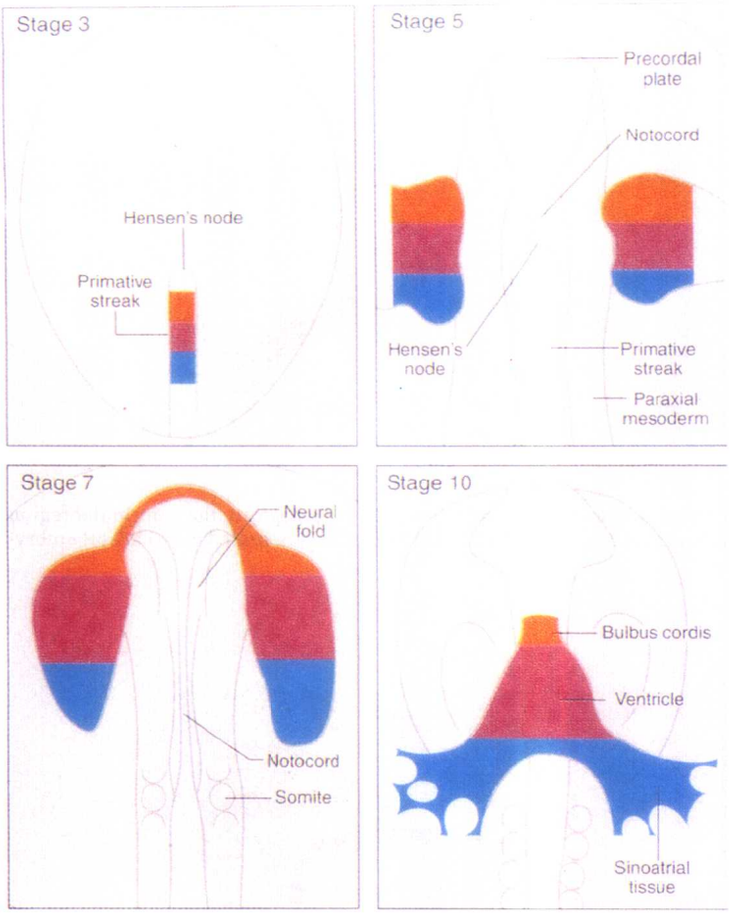


Figure 5–1 • Schematic of the location of heart precursors in the chick embryo, from a ventral view at the stages indicated. The patterns show the region of the heart to which precardiac cells will eventually contribute. The relative anterior-to-posterior position of precardiac cells in the primitive streak (HH stage 3) is retained in the heart field in the mesoderm (as shown in HH stages 5 and 7) and in the heart tube at HH stage 10.[14, 28, 187] There is no evidence for definitive borders of these lineages in the field. At stage 10, the anteriormost region is termed *bulbus cordis* (or *conotruncus*) and is the outflow region connected to the aortic sac. (Adapted from Fishman MC, Chien KR: Fashioning the vertebrate heart: Earliest embryonic decisions. Development 1997; 124:2099.)

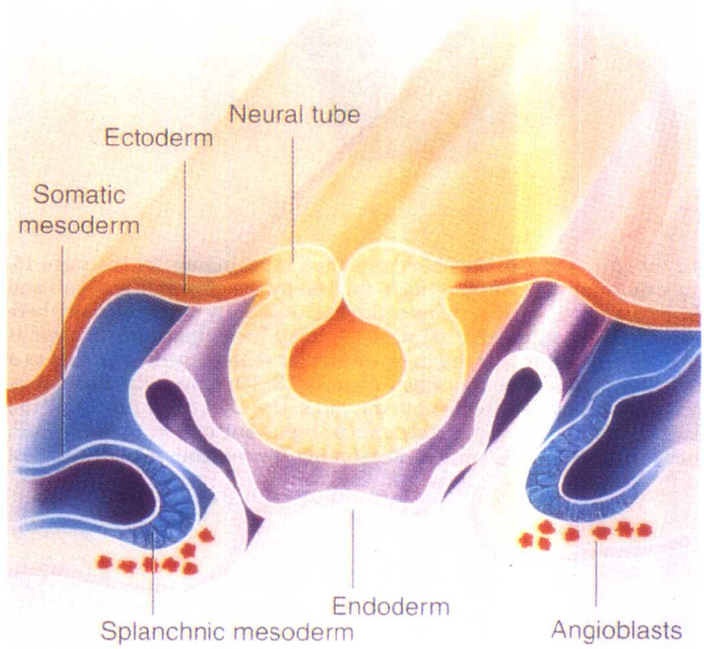


Figure 5–2 • Chick embryo at HH stage 8, viewed in cross section in the region of the precardiac mesoderm looking anteriorly. The embryo is folding ventrally, generating the foregut; the mesoderm has split into somatic and splanchnic layers, the latter containing the myocardial precursors. The endocardial angioblast precursors are between the splanchnic mesoderm and foregut. (Adapted from Fishman MC, Chien KR: Fashioning the vertebrate heart: Earliest embryonic decisions. Development 1997; 124:2099.)

PLATE 3

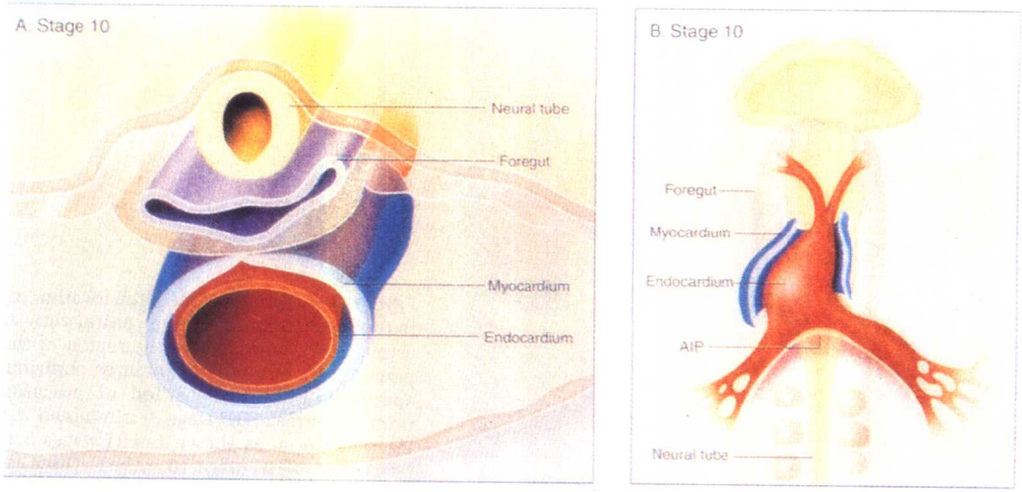


Figure 5–3 • Chick heart tube at HH stage 10, shown in cross section *(left)* and in ventral view *(right)*. By stage 10, the ventricular region of the tube is beginning to bend (loop) to the right. (Adapted from Fishman MC, Chien KR: Fashioning the vertebrate heart: Earliest embryonic decisions. Development 1997; 124:2099.)

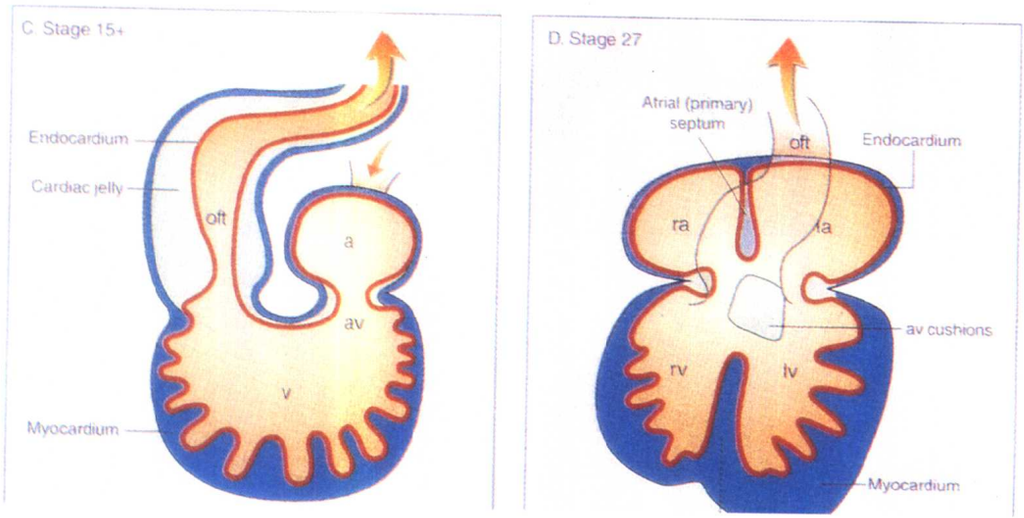


Figure 5–4 • Chick heart tube at HH stage 15+ *(left)* and HH stage 27 *(right)*, when, in the chick, septation is beginning. By HH stage 15, the two chambers, atrium and ventricle, are morphologically different; the ventricle is beginning to thicken by the growth of the wall and addition of trabeculae. The cardiac jelly separates the myocardium from endocardium and becomes thicker, especially in the regions where cushions and valves will form (i.e., the outflow tract and the atrioventricular junction). At HH stage 27, in air-breathing animals, there is division of the atrium and ventricle into right- and left-sided chambers by the growth of the interventricular septum, generated first as a coalescence of the trabeculae and by growth of the atrioventricular cushions. (Modified from Chan-Thomas PS, Thompson RP, Rober B, et al: Expression of homeobox genes *Msx-1 (Hox-7)* and *Msx-2 (Hox-8)* during cardiac development in the chick. Dev Dyn 1993; 197:203–216.) a, atrium; av, atrioventricular canal; la, left atrium; lv, left ventricle; oft, outflow tract; ra, right atrium; rv, right ventricle; v, ventricle; AIP, anterior intestinal portal; cushions shown in green). (Adapted from Fishman MC, Chien KR: Fashioning the vertebrate heart: Earliest embryonic decisions. Development 1997; 124:2099.)