Fifty years ago, cardiovascular genetics simply did not exist. Genetics was a nascent field of basic research, with little apparent relevance to cardiovascular science or any other medical subspecialty. Today, cardiovascular genetics is a discipline that fully integrates high-technology laboratory investigation and clinical medicine. From this hybrid have emerged discoveries that have precisely identified the cause of heretofore “idiopathic” disorders, provided fundamental insights into disease processes, and delineated subtypes in well-defined pathologies. Insights from these discoveries uproot traditional anatomic classifications of disease and integrate cell physiology and molecular biochemistry into the study of pathology. For researchers, practitioners, and patients alike, cardiovascular genetics is having a growing impact on the definition and diagnosis of disease, the explanation of prognosis, and the expansion of treatments.

While appreciating the progress that cardiovascular genetics has achieved, one must be mindful of antecedent and seminal discoveries in the broader field of genetics that enabled the birth and growth of the molecular era. By the mid 1900s, Mendel’s theory of inheritance was proven, the segregation and assortment of chromosomes during meiosis was recognized, the linear arrangement of genes on chromosomes was appreciated, and recombination frequency was accepted as an accurate assessment for the distances between genes. Even the potential for assigning genetic traits to specific chromosomes through the study of human inheritance was appreciated: familial transmission of color blindness and hemophilia was correctly interpreted to indicate genes encoded on the X chromosome.

Any review of the critical developments that fostered the birth of cardiovascular genetics must acknowledge the enormous contributions made by clinicians, patients, and families. For advances in genetics to become relevant to clinical cardiology, the heritable nature of cardiovascular disease needed to be recognized. This recognition was gained through case reports, descriptions of the familial aggregation of diseases, and epidemiological studies, which provided compelling evidence of a genetic component to many cardiac diseases. The significance of these contributions is perhaps best appreciated through the Mendelian Inheritance in Man website. This catalogue meticulously details 800 distinct inherited human phenotypes and classifies each as autosomal-dominant or -recessive, X-linked, or mitochondrial trait on the basis of clinical descriptions. More than a third of these entries have a cardiovascular component.

The pace of genetic research markedly accelerated after 1950; this can be attributed largely to progress in molecular biology, statistics, and computer science. The biochemical components of DNA were deduced, and bacterial (restriction) enzymes were discovered to cleave DNA, thus enabling cloning technologies and hybridization (Southern) blotting methodologies. The year 1977 heralded the development of DNA sequencing; this was followed soon after by the recognition of the considerable variation in nucleotide sequences (polymorphisms) in human genomes. The utility of polymorphism analyses for defining the chromosome location of genes in concert with statistical approaches (calculation of logarithm of odds ratios) firmly established the feasibility of molecular genetic approaches to define the chromosome location of genes, a first step in identifying disease-causing mutations.

The 1980s initiated a decade of genome cartography. Early maps were based on restriction fragment length polymorphisms (RFLPs) and, in 1987, the first genome-wide map was published. These early maps provided few landmarks in comparison with contemporary versions, as illustrated in Figure 1. The subsequent identification of variable nucleotide repeat sequences (di-, tri-, and tetra-nucleotide) and a definition of their extensive distribution throughout the genome led to the construction of detailed maps, which continue to underpin contemporary strategies for the chromosomal localization of genes. Concurrent developments of molecular technologies throughout the 1980s, such as the notable discovery of the polymerase chain reaction (PCR) for selective amplification of prescribed segments of DNA, enhanced the feasibility of genetic mapping strategies. Analyses of RFLPs required large amounts of DNA and repetitive Southern blots, and they provided limited polymorphic content; PCR-based analyses of di-, tri-, or tetra-nucleotide repeats were more efficient and informative.

Chromosome mapping formed the basis for a novel approach to finding genes that, when mutated, cause human disease. The previous discoveries of the genetic basis of diseases came from meticulous dissection of perturbed biochemical pathways or cell processes. Pinpointing the inciting flaw was laborious and often impossible. Studying the genetic basis of cardiovascular diseases compounded these chal-
Chromosome 1

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Figure 1. A comparison of a historical and a contemporary genetic map of chromosome 1. A, The identification of restriction fragment length polymorphisms (horizontal marks) in 1984 provided a primitive map of chromosome 1. B, A current map available through National Center for Biotechnology Information indicates that the largest human chromosome contains 286,000 kb. Data on the contigs assembled (left), genes mapped to chromosome 1 (center), and 4351 polymorphisms (right) are indicated.

Inborn Errors of Metabolism: Lesson Learned from Familial Hypercholesterolemia

In 1901, Sir Archibald Garrod studied a patient with black urine and suggested that genetic mutations can lead to a deficiency of a single enzyme in a metabolic pathway, thereby disrupting the normal metabolism of a product in the pathway. Garrod termed such disease processes an “inborn error of metabolism,” thus setting the stage for contemporary biochemical genetics with his observations in a patient with alkaptonuria. In 1972, Michael S. Brown and Joseph L. Goldstein applied the concept of inborn errors of metabolism...
to the study of the human genetic disease familial hypercholesterolemia (FH); they postulated that the genetic defect in FH resulted from a failure of end-product repression of cholesterol synthesis. Patients with FH have greatly elevated levels of cholesterol in their blood, leading to premature heart disease early in life. In the mid 1960s and early 1970s, it was shown that FH existed clinically in a severe, homozygous form and a less severe, heterozygous form.15

Because DNA sequencing and cloning techniques were not available at that time, Brown and Goldstein’s approach was to apply the techniques of cell culture to identify the genetic defect in FH. Initially, they used the dermal fibroblasts explanted from normal individuals to study 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase activity, the rate-limiting enzyme of cholesterol biosynthesis. When these fibroblasts were cultured in the presence of lipoproteins, HMG CoA reductase activity was low. When the lipoproteins were removed from the culture media, the activity of the enzyme rose by 50-fold over a 24-hour period. Further studies determined that of the 2 major cholesterol-carrying lipoproteins, low-density lipoprotein (LDL) and high-density lipoprotein, only the presence of LDL in the media could repress HMG CoA reductase activity. Both the fact that the repression of HMG CoA reductase was specific for LDL and the observation that very low concentrations of LDL could repress enzyme activity suggested that a high-affinity receptor was responsible for the enzyme repression.

The studies of fibroblasts from homozygous FH patients supported the observations of the mechanisms of LDL regulation of HMG CoA activity. The presence of LDL in the culture media did not repress HMG CoA reductase in FH cells; when grown in the presence of LDL, FH fibroblasts had reductase activities that were 50-fold higher than control fibroblasts. Interestingly, when FH cells were incubated with an emulsion of free cholesterol that can enter cells passively, HMG CoA reductase was repressed in both FH and control cells. These observations led Brown and Goldstein to hypothesize that the genetic defect in FH cells was in the high-affinity receptor responsible for repression of HMG CoA reductase by LDL. These investigators went on to demonstrate the existence of a high-affinity receptor for LDL in cultured fibroblasts. Furthermore, they showed that FH-homozygous cells lacked high-affinity receptors for LDL, providing biochemical evidence that the genetic defect causing FH was the lack of a high-affinity receptor for LDL.

Between 1972 and 1976, Brown and Goldstein completed work that was crucial to delineating the cellular metabolism of LDL and the feedback regulation of HMG CoA reductase; they also elucidated the defect in the high-affinity receptor for LDL in FH patients. Nine years later, in 1985, mutations in the LDL receptor gene were identified in FH patients, confirming that the genetic defect was indeed in the LDL receptor.17–21 This same year, the significance of this work was acknowledged by awarding the Nobel Prize in Medicine to Brown and Goldstein.

FH is an example of a single gene disorder that results in atherosclerosis and coronary artery disease, thereby contributing to the genetic basis of this common disease. Individuals heterozygous for LDL receptor mutations are common in the general population, with an estimated prevalence of 1 in 500. The risk for coronary artery disease in these heterozygotic individuals is significantly increased over that of the general population; the probability of a heterozygous male experiencing a myocardial infarction before the age of 60 is 75% versus 15% for the general population.

Subsequent studies have identified other loci influencing plasma lipid levels and increasing coronary artery disease risk, including apolipoprotein B-100, apolipoprotein E, li-
poprotein(a), lipoprotein lipase, apolipoprotein CII, cholesteryl ester transfer protein, apolipoprotein AI, lecithin-cholesterol acyl transferase, and microsomal triglyceride transfer protein. The contributions of these loci, as well as yet-to-be-identified loci, to coronary artery disease have expanded and will continue to expand our knowledge of the genetic basis of this common disease.

### Genetic Vascular Diseases: Heritable Disorders of Connective Tissue

In 1896, a renowned French pediatrician named Antoine Marfan described a young girl with unusual skeletal features, including long, thin extremities (dolichostenomelia) and long, spider-like fingers (arachnodactyly). Over the next 50 years, the cardiovascular and ocular manifestations associated with genetic vascular diseases continued to be studied. These diseases are now understood to be caused by mutations in a variety of genes.

**Figure 3.** Inherited disorders of the cardiovascular system located on ideograms of the human chromosomes. Chromosome bands are numbered and indicated by standard Giemsa patterns. ABCG6 indicates anthracycline resistance-associated protein; AF, familial atrial fibrillation; ARLK1, activin receptor–like kinase 1; ARVD, arrhythmogenic right ventricular dysplasia; AT, ataxia-telangiectasia; ATM, ataxia-telangiectasia mutated gene; AVSD, atrioventricular septal defect; βMHC, β-myosin heavy chain; CACNL1A4, calcium channel, L-type, alpha-1 polypeptide, isoform 4; CCM, cerebral cavernous malformations; COL3A1, collagen type alpha 1 gene; CVD, cardiac valvular dysplasia; DSG-C, δ-sarcoglycan; DCM, dilated cardiomyopathy; DCM & CD, dilated cardiomyopathy and conduction disease; DM, desmin myopathy; EDIV, Ehlers-Danlos type IV; EDVI, Ehlers-Danlos type VI; EvC, Ellis-van Creveld syndrome; FH, familial hypercholesterolemia; FHBL, familial hypercholesterolemia; FHM, familial hemiplegic migraine; FrA, Friedreich's ataxia; GLA, α-galactosidase; GNAI2, guanine nucleotide-binding protein, alpha-inhibiting activity polypeptide 2; HCM, hypertrophic cardiomyopathy; HERG, human ether-a-go-go related syndrome; HMD, hereditary multi-infarct dementia; HOS, Holt-Oram syndrome; HTNB, hypertension with brachydactyly; JAG1, jagged-1 gene; KCNE1, potassium channel, voltage-gated, Isk-related subfamily member 1; KVLQT1, potassium voltage-gated long QT syndrome 1 channel; LDLR, low-density lipoprotein receptor; LQT, long QT syndrome; MCR, mineralocorticoid receptor; MYBPC, myosin-binding protein C; MYL2, regulatory ventricular myosin light chain; MYL3, essential ventricular myosin light chain; NF1, neurofibromin; ORW, Osler-Rendu-Weber syndrome; PPH, familial primary pulmonary hypertension; PXE, pseudoxanthoma elasticum; SCN5A, sodium channel, voltage-gated, type V, alpha polypeptide; SVAS, supravalvular aortic stenosis; TAPVR, total anomalous pulmonary venous return; TBX5, T-box 5 transcription factor; TIE2, endothelial cell specific receptor tyrosine kinase; TNN13, cardiac tropinin I; VCFS, velocardiofacial syndrome; VHL, Von Hippel-Lindau syndrome; VT, ventricular tachycardia; WH, Wolf-Hirschorn syndrome; and WPW, Wolff-Parkinson-White syndrome.
such unusual skeletal features were recognized, along with the autosomal-dominant inheritance of the condition. The cardiovascular hallmarks of Marfan syndrome are a dilatation of the proximal aorta and aortic dissection associated with a degeneration of the elastic fibers in the tunica media of the aorta. Ocular lesions are localized to the lens in the form of congenital dislocations due to weakening of the suspensory ligament of the lens.

Marfan syndrome was the disease listed first in the catalog of heritable disorders of connective tissue described by Victor McKusick in the first edition of his book, *Heritable Disorders of Connective Tissue*, in 1956. In the fourth edition of this book, McKusick made the following prediction: “What the suspensory ligament of the lens has in common with the tunica media of the aorta is obscure. If this common factor were known, the basic defect of the Marfan syndrome might be understood.”278 McKusick’s speculation proved to be correct when, in 1991, it was determined that mutations in the FBN1 gene were the cause of Marfan syndrome.29–31 FBN1 encodes fibrillin-1, a major protein component of extracellular matrix structures called microfibrils, which either alone or in association with the elastin in elastic fibers provide critical biomechanical properties to a wide variety of tissues. FBN1 mutations cause a dominant-negative effect on microfibril formation through the production of mutant fibrillin-1 monomer on the background of a normal fibrillin-1 monomer from the nonmutant allele. Immunohistochemical studies and pulse-chase analyses have shown that dermal fibroblasts explanted from Marfan patients have a decrease in fibrillin-1–containing microfibrils in the extracellular matrix far below the 50% level predicted by a heterozygous FBN1 mutation.32–35

Although the vast majority of FBN1 mutations cause classic Marfan syndrome, they are also responsible for some familial forms of isolated thoracic aortic aneurysms, ectopia lentis, arachnodactyly, and disproportionate tall stature, along with the severe and rare congenital disorders termed neonatal Marfan syndrome and Shprintzen-Goldberg syndrome.36–40 FBN1 mutations can, therefore, cause a continuum of clinical phenotypes, which at one end present as severe congenital disorders, and at the other end, have features that merge with common traits found in the general population.

The role of type III collagen in maintaining the structural integrity of the arterial walls was recognized through the identification of mutations in the gene encoding the type III collagen polypeptides (COL3A1) in patients with Ehlers Danlos syndrome type IV, an autosomal-dominant condition. Although this condition is associated with thin, translucent, and fragile skin, the life-threatening complication of this condition is spontaneous rupture or dissections of the aorta or large- to medium-sized arteries in the second to third decade of life.41 Similar to FBN1 mutations, COL3A1 mutations exert a dominant-negative effect on the formation of type III collagen as a result of the multinumerization of the polypeptides encoded by COL3A1 into homotrimers of type III collagen.42

Supraventricular aortic stenosis (SVAS) is a vascular disorder that may occur as an isolated disease inherited in an autosomal-dominant fashion or as a part of a complex developmental disorder, Williams-Beuren syndrome.43–46 The typical vascular lesion in SVAS is an hourglass-shaped stenosis of the ascending aorta, which is associated with an increased volume of the medial layer with disorganization of the lamellar architecture of the media, irregular elastic fibers, and smooth muscle cell hypertrophy.47 In addition to the aorta, other major arteries, including the pulmonary, carotid, cerebral, renal, and coronary arteries, may also be stenotic in patients with SVAS.

Mutations in elastin, the major component of the elastic fiber system, cause SVAS. Surprisingly, these mutations lead to haploinsufficiency for the elastin gene, with decreased elastin production.48–51 Pathological studies of the aorta in SVAS and studies of mice with a targeted mutation of the elastin gene (ELN) suggest that elastin plays an unanticipated role in arterial morphogenesis by controlling the proliferation of smooth muscle cells and stabilizing arterial structure.52,53

**Linkage Heterogeneity: Unraveling Genetic Complexity**

Late in the 1950s, a report appeared in the medical literature that systematically detailed the clinical profiles of young patients with asymmetric hypertrophy of the heart.54 Throughout the subsequent 2 decades, thousands of patients were evaluated, and voluminous data were acquired on the pathophysiology of a disorder labeled idiopathic hypertrophic subaortic stenosis, asymmetric septal hypertrophy, hypertrophic obstructive cardiomyopathy or, in the vernacular, as IHSS, ASH and HOCM, respectively. Cardiac catheterization and, subsequently, echocardiography identified the hallmarks of the disease, which included hypertrophy, hyperdynamic systolic function, diastolic dysfunction and, in some, systolic anterior motion of the mitral valve and outflow tract obstruction.55,56 Diverse clinical outcomes were observed, ranging from severe cardiac symptoms and sudden death to minimal symptoms and excellent prognosis.57 Not surprisingly, these investigations prompted speculation about the causes of hypertrophic heart disease; suggestions were as diverse as heightened catecholamine sensitivity to congenital anomalies of intra-mural coronary arteries.57,58

Clinical studies clearly demonstrated familial prevalence in hypertrophic cardiomyopathy, and genetic transmission consistent with an autosomal-dominant trait was delineated. These data prompted genetic strategies to define the causal gene. In 1989, linkage analyses in one large kindred demonstrated that a gene responsible for familial hypertrophic cardiomyopathy was located on chromosome 14q2.59 This chromosomal location was the initial clue that suggested the cardiac myosin heavy chain genes might be mutated to cause this condition. Even before the β-cardiac myosin heavy chain gene encoded in this locus was established as the mutated gene at 14q causing familial hypertrophic cardiomyopathy, linkage studies in unrelated families demonstrated genetic heterogeneity.60 These genetic analyses demonstrated that this clinical disorder could also be caused by mutations in genes encoded on other chromosomes. Over a period of 5 years, hypertrophic cardiomyopathy disease loci were reported on chromosomes 1q, 11p, and 15q.61–63 Locus heterogeneity led to the hypothesis that genes mutated in hypertrophic cardiomyopathy might encode proteins of similar
function. This hypothesis was proven initially by the identification of the disease genes cardiac troponin T and atrypomyosin, and confirmed by the subsequent definition of disease-causing mutations in cardiac myosin binding protein-C, troponin I, cardiac actin, and the ventricular essential and regulatory myosin light chains. Hypertrophic cardiomyopathy was no longer an idiopathic pathology but a disease of sarcomere proteins.66

A second mysterious disorder, which consisted of congenital deaf mutism, prolongation of the QT interval, and sudden death, was also reported in the late 1950s.67 Shortly thereafter, Ward68 and Romano69 described a prolongation of the QT interval and a predisposition to torsades de pointes in individuals without hearing loss or other abnormalities. Reports of the electrocardiographic and electrophysiological features of this remarkable disease were followed by an increasing recognition of the considerable arrhythmia risk in such patients.70 Repolarization abnormalities that occurred in the absence of cardiac pathology induced arrhythmias, particularly in the setting of exercise or excitement. However, the spectrum of clinical manifestations and range of QT intervals made accurate diagnosis problematic. Related investigations into the mechanism for arrhythmias in animal models led to the suggestion that an imbalance in the sympathetic cardiac innervation accounted for this disease, and both β-adrenergic blockade and stellate ganglionectomy were considered therapeutic options.71,72

Genetic linkage studies again provided fundamental insights that ultimately led to etiological understandings of autosomal-dominant long-QT syndrome and autosomal-recessive Jervell-Lange-Nielsen syndrome. Over the past decade, 5 disease loci have been identified on chromosomes 3p, 4q, 11p, 21q, and 7q.73–77 Although genetic heterogeneity initially suggested considerable complexity in the molecular causes for this disorder, the identification of disease genes clarified this issue. Subunits for the voltage-gated potassium channels cause ST segment elevations and idiopathic ventricular tachycardia (Brugada syndrome81) or progressive atrioventricular block (Lev or Lenegre disease82). These observations indicate that clinically different cardiovascular disorders share molecular etiologies and, as a corollary, that selective biophysical and/or biochemical processes are perturbed by specific mutations. Elucidation of the signaling pathways triggered by particular gene defects is an area of active investigation.

Diverse Cardiac Malformations From Single Gene Defects

Epidemiological and pathological investigations of human congenital heart malformations have identified multiple teratogens, infectious agents, and factors in the maternal environment as important etiologies for some cardiac defects. However, in most cases, the cause of the disease remains unknown. In a posthumous publication, Dr Helen Taussig speculated that because “common cardiac malformations . . . occur in otherwise ‘normal’ individuals . . . these malformations must be genetic in origin . . . neither exposure to toxic substances nor the parents can be held accountable for the occurrence of (most) congenital abnormalities.”83 Recent molecular studies of congenital heart defects indicate the prophetic nature of her observations.

Clinical studies have recognized that occurrence of a congenital heart defect in a parent or preceding sibling is the greatest risk factor for developing a cardiac malformation. Epidemiological and family studies further demonstrate variations in the precise congenital defects exhibited by related, affected individuals. For example, the Baltimore-Washington Infant Heart Study demonstrated an increased incidence of tetralogy of Fallot, transposition of the great arteries, and truncus arteriosus in the family members of individuals with ventricular septal defects.84 These observations have been interpreted to indicate that some cardiac structures share developmental pathways. Such data also suggest that clinically distinct outcomes could arise from a single genetic defect, an observation that has hindered the recognition of the genetic basis of congenital heart disease. Recent identification of single gene mutations that cause multiple cardiac malformations support these hypotheses.

Compelling evidence for an essential role of genetics in human congenital heart disease comes from investigations of the etiologies for conotruncal malformations. Cyto genetic studies of DiGeorge syndrome (aplasia/hypoplasia of the thymus and parathyroid glands in association with conotruncal defects) indicate a visible or microdeletion of chromosome 22q11 in >90% of patients.85 Refined mapping of this disease interval has fostered the identification of many genes that are deleted in patients.86 Whether haploinsufficiency of
one or a few genes accounts for the pleiotropic findings in DiGeorge syndrome remains an open question.87

Human defects in laterality (heterotaxy) are associated with a wide spectrum of cardiac malformations. Recognition of the X-linked inheritance in some families led to the definition that a human gene for heterotaxy is encoded at Xq24.88 Positional cloning approaches defined mutations in zinc-finger of cerebellum (ZIC3), a transcription factor with homology to proteins involved in left-right axis formation. In women, ZIC3 mutations caused either mild or no consequences, whereas affected men had severe, complex heart malformations that frequently resulted in neonatal lethality.

Holt-Oram syndrome, a rare autosomal-dominant condition, is characterized by upper limb abnormalities and cardiac defects.89 Skeletal malformations vary from subtle defects in carpal bones and thumb anomalies (triphalangism or aplasia) to phocomelia. Most patients with Holt-Oram syndrome have congenital cardiac malformations that range from simple atrial and/or ventricular septal defects to multiple complex lesions. Conduction system disease and other anomalies, including anomalous pulmonary venous return, abnormal ventricular trabeculation, and right isomerism, are often present. Despite the considerable clinical diversity in Holt-Oram syndrome phenotypes, all patients have a mutation in the gene TBX5, which encodes a transcription factor that is essential for normal heart formation.90,91

There is also evidence that human gene mutations cause nonsyndromic congenital heart disease. Clinical reports have characterized familial cardiac malformations associated with conduction system defects.92 Although secundum atrial septal defects occurred frequently in these families, ventricular septal defects, tetralogy of Fallot, subvalvular aortic stenosis, pulmonary atresia, and redundant mitral valve leaflets with fenestrations were also observed. The relationship of these structural defects to slowly progressive conduction system disease was initially unclear. Sudden death in some family members occurred years after the surgical correction of congenital defects. Electrophysiological studies have localized abnormalities to the atrioventricular node.

Clinical evidence of autosomal-dominant transmission prompted genome-wide linkage analyses, and a disease gene for cardiac malformations and conduction system disease was mapped to chromosome 5q35. This genomic location identified the gene encoding the transcription factor Nkx2.5 as a candidate for human mutations; DNA sequencing affirmed this hypothesis.93,94 Developmental biologists had defined an essential role for Nkx2.5 in cardiac morphogenesis. These studies both extended this information to humans and indicated that this transcription factor must also be important for normal cardiac electrophysiology.

In addition to defining gene mutations as important etiologies for congenital heart disease, these examples suggest that mutationally altered transcription factors cause human cardiac malformations. Understanding why defects in these molecules can produce a wide array of clinical malformations will be essential for elucidating the biological function of these proteins throughout development. However, these examples indicate that insights into transcription factor biology gleaned from studies of lower vertebrate model systems will be relevant to the study of human cardiac pathologies. Given the significant incidence of cardiac malformations (5 to 8 per 1000 live births), the definition of the genetic basis for even a subset of these patients has the potential for insights into pathways that are critical for the extraordinarily complex process of cardiac development.95

The Next 50 Years

As the Human Genome Project moves toward completion, research efforts to identify genes related to cardiovascular diseases will move forward at a more rapid pace than ever before. The underlying genetic etiologies for not only monogenic cardiovascular disorders, but also for common disorders with complex polygenic inheritance will be determined. Mapping the genetic determinants for both rare, single-gene disorders and common disorders will provide further insight into the molecular pathogenesis of disease processes. This research will provide clinicians with such tangible benefits as genetic risk profiles for cardiovascular diseases and specific pharmacotherapy based on both the molecular pathology of the disease and the patient’s own genetic composition.

As the door to the human genome is opened, the challenge ahead is to determine the normal biological functions of these gene products in maintaining cardiovascular cellular homeostasis. Rational approaches to pharmacotherapy and gene therapy for congenital structural cardiovascular disorders, cardiomyopathies, cardiovascular malignancies, and complex traits such as hypertension and atherosclerosis can only be achieved by elucidating such basic genetic regulatory mechanisms. Moreover, it is likely that such novel therapeutic modalities will ultimately inform the future management of common sporadic nonfamilial cardiovascular diseases.

Such unprecedented advances in genetic knowledge are not without social and ethical implications. The new genetics raise problems of confidentiality, stigmatization, and insurability. Furthermore, genetic information providing “presymptomatic” diagnosis of diseases may lead to individuals altering their expectations and behavior based on the dangers encoded within their cells. Dealing with the complexity of these issues will be perhaps the greatest challenge facing clinicians in the future.

References


**KEY WORDS:** genetics ▪ cardiovascular diseases ▪ metabolism