Western civilization had two great epochs—the sixth century B.C. and the 18th century. The 21st century is likely to be the third great epoch. Although cardiology has advanced more in the last 50 years than in the previous 2,000, it is likely to advance more in the next two or three decades than in the previous 2,000 years, including those 50 golden years. The engines of ingenuity to provide the thrust for the 21st century will come from molecular genetics and the application of recombinant deoxyribonucleic acid (DNA) techniques. Identification of all human genes (50,000 to 100,000) in the next two to three years will help link thousands of etiologies and risk factors with their respective diseases, which represents a new paradigm in medicine. This is illustrated by the implications to be drawn from familial hypertrophic cardiomyopathy and the 50 new genes already identified to be responsible for cardiac disease. The hope for prevention and treatment of human disease is unprecedented. Twenty diseases account for 80% of the deaths in the Western world and are due to 100 to 200 genes, all of which will be available in a couple of years. The Phoenician alphabet (inclusive of the Greek vowels) of 26 letters launched two millenniums of Western civilization, whereas the DNA alphabet of only four letters will launch and dominate the next millennium. (J Am Coll Cardiol 2000;36:661–7) © 2000 by the American College of Cardiology

Western civilization is noted for two great epochs—namely, the 6th century B.C. and the 18th century A.D. 4859 (1). The high level of conceptual thinking of the Greeks in the 6th century B.C. led to the birth of Western philosophy and democracy from which evolved the foundations of Western civilization. The widespread use of the phonetic alphabet is arguably a major factor that contributed to the success of the 6th century B.C. The alphabet (defined as one with <30 symbols), claimed to be developed by the Semites (Phoenician), had no vowels. There were written languages before—namely, hieroglyphics (Egyptians), cuneiform (Sumerians) and Chinese characters—but these were all pictorial and emphasized concrete thinking. The alphabet, with its symbols, was simple and stimulated abstract thinking. The addition of the vowels, probably between the 9th and the 6th century B.C. by the Greeks, is thought to have significantly facilitated the translation from the spoken to the written world. It is well recognized that translating the spoken word into the written word of Indo–European languages is very difficult without vowels (2). The 18th century brought the Industrial Revolution, a uniquely Western contribution, which started us on the road to modern technology and has continued at an accelerating rate. From the 15th to the 18th centuries, European explorers took Western civilization to all corners of the Earth, as remarked by Captain Cook, on reaching Australia in 1770 (3): “Not only have I traveled farther than any man has traveled, but I have traveled as far as man can travel.” There is little doubt that the 6th century B.C. molded our society for the next two millenniums, and the Industrial Revolution of the 18th century continues to improve the living conditions of all mankind. A comparable timeline for the history of medicine starts in Greece on the island of Cos with Hypocrates, the founder of modern medicine. The Greeks pursued medicine with great intensity, but throughout the Dark Ages and the Christian and Islamic religious eras, when medicine experienced some significant advances, for the most part, science was stifled. Evolution of reason and scientific thought after the Renaissance restored a progressive approach to science and medicine. Nevertheless, just over 60 years ago (1931), Paul Dudley White boldly stated there was no effective treatment for valvular disease, coronary artery disease, hypertension or syphilis (4). In the 1940s, sulfonamides and penicillin were introduced, followed by an explosion that ushered in the modern era of cardiology. Cardiology has without doubt advanced more in the last 50 years than in the previous 2,000 years. Today, the heart is just another work place we invade with a variety of tools such as the coronary catheter, the angioplasty catheter, bypass grafts, pacemakers and a host of others. Their application, along with preventive medicine, in the past 30 years has resulted in an astounding 60% reduction in the death rate from heart disease (5). It is reasonable to assume the 21st century will be the third great epoch for our civilization, and it is likely to be evident in the next 20 to 30 years, as I believe cardiology will advance more in the next two to three decades than it has in the previous 2,000 years, including
that great golden age of the last 50 years. The engines of ingenuity to provide the thrust for the 21st century will come from molecular genetics and the application of recombinant deoxyribonucleic acid (DNA) techniques.

In the 20th century, man has mapped the earth, its oceans and explored its inner composition. We have experienced the excitement of the gold rushes and the oil gushes and characterized Earth's precious gems and metals. We have seen the development of the physicist's table of elements that in turn led to many exciting innovations. The 21st century will be ushered in by the new science of molecular biology, based on the fundamental units of mankind that are responsible for passing on all of the inheritable characteristics—DNA. For the first time, the biologist and the physician will march together with their complete table of elements, and it will not be a list of inorganic components but rather the 50,000 to 100,000 genes responsible for one human. Knowing the genes and their functions will have universal appeal and invoke interest from all phases of medicine, science, philosophy, ethics, the arts and government—it will be as Francis Collins has stated, a "code for the book of life" (6). The DNA code uses four letters: A (adenine), G (guanine), C (cytosine) and T (thymine). These letters are strung together into distinct units referred to as genes, which give rise to a unique protein destined for a distinct morphologic location and function within the human body. These proteins are responsible for every action that a human being performs. Thus, most of what we do and how we do it is strongly influenced by the sequence of these four letters. The Phoenecian alphabet (inclusive of the Greek vowels) of 26 letters launched more than two millennia of Western civilization, whereas the DNA alphabet of only four letters will launch and dominate this millennium. Although progress will continue on the inner structure of the Earth and great strides are likely to be made in exploring our galaxy, the hallmark of the 21st century will be the exploration of the inner workings of a human being. To use a phrase from the old millennium: “Your genes will be up in your face.”

The human genome, contained in 23 chromosomes, consists of three billion bases with an estimated 50,000 to 100,000 genes. The genes (made of exons) make up about 3% of the DNA, and the in-between sequences (introns) have an unknown role so far. The Human Genome Project, initiated in 1990 (7), was to sequence all of the DNA, including the genes, by the year 2005. Commercial efforts announced that all of the human genes would be sequenced by the year 2001 (8,9). The Human Genome Project has also been progressing more rapidly than expected. It was predicted that half of the human genome would be completed by the year 2001 and the remainder by 2003 (10). More recently, with the boost in funding for the three major U.S. players (Baylor College of Medicine, Washington University and The Whitehead Foundation), it is predicted that a rough draft of 90% of the human genome will be available by March 2000 (11).

The new paradigm for cardiology and medicine—etiologic and individualized treatment. Despite our knowledge of diagnosis and treatment, we seldom know the etiology or the specific molecular defect responsible for disease, and thus our therapies are not as specifically targeted as one would desire. In the next couple of years, regardless of when the Human Genome Project is completed, there will be at least 30,000 genes available, and thus we will have thousands of etiologies and specific molecular defects to be linked with their respective disease. This will represent an entirely new paradigm in the field of medicine. Similarly, in the field of preventive medicine, there will be thousands of genetic risk factors that will need to be matched with diseases for which they are predisposed. We, as physicians, are taught to treat the crisis, and until the 1990s, physicians who saw and treated a high percentage of normal individuals were considered perhaps to be nondiscriminatory in applying the art of medicine. Prevention will be the key to future successes, and the unraveling of human genes will catapult prevention as a major initiative for the 21st century. In the management of coronary artery disease, individuals will be identified in their teens so that treatment and prevention appropriate for their medical risk profile and life style can be properly individualized. Treating coronary artery disease after the crisis of myocardial infarction, when a part of the myocardium has already been lost to scar, will be seen in the 21st century as negligent and a missed opportunity. It is evident from present day knowledge that primary prevention of atherosclerosis is far more effective than treating acute myocardial infarction. The massive array of specific etiologies and risk factors will be truly staggering, and it is for this reason that all of us as physicians must at least become acquainted with the new terminology. The area of pharmacogenomics (12), although now only in its infancy, will rapidly evolve in the next 10 years.

Individuation of therapy, the antithesis of health maintenance organizations and managed care, will be the norm. Angiotensin-converting enzyme (ACE) inhibitors may be more effective than angiotensin one (AT-1) receptor blockade for the hypertensive patient who has expressed a vulnerable polymorphism in the ACE, whereas the latter might be more appropriate for those with an expressed vulnerable polymorphism in the AT-1 receptor. Because the genes present in the DNA of a white blood cell are identical to the genes in the cell of any other organ (brain, heart, etc.), these
genetic etiologies and risk factors responsible for diseases can be detected from analysis of a single blood sample (13). The development of DNA as a computerized chip will make it possible to screen for thousands of mutations within a few hours. It was realized very early in the genetic revolution that there would have to be a new science (bioinformatics) to store and retrieve such massive information. A computerized network of gene banks was established in London, Washington and Tokyo and made available to PC users throughout the world. The GenBank has stored over two billion bases of DNA from 39,000 species (6) and 1,000 genes with 20,000 mutations known to cause human disease (4). The establishment of computer terminals at nursing stations throughout hospitals will provide access to the computerized gene data bases so that genetic information is immediately accessible to the clinician and paramedical personnel.

Progress in cardiovascular genetics. Until recently, it was possible to identify only genes responsible for disease if one knew the specific protein, whereas today, using a technique of genetic linkage analysis to map the chromosomal location of the gene and positional cloning, one can identify the gene without knowing the molecular nature of the defect or the responsible protein (15). The ultimate goal of the Human Genome Project was to sequence the human genome; however, other important objectives were completed along the way. A genetic map was developed with over 6,000 chromosomal markers placed throughout the human genome at intervals of less than one million bases. This revolutionized the mapping of the chromosomal location (locus) of disease-related genes. The success of genetic linkage analysis is directly proportional to the quantity and quality of the markers available to map the chromosomal location of a gene. The development of the genetic map made it possible in a three-generation family to map a locus in months to weeks as opposed to several years. The other objective was the tagging of unique expressed sequences (EST) with the hope that each tag would represent a distinct gene. A map of over 40,000 ESTs has been developed, which, in conjunction with the list of genes already mapped, has rapidly accelerated identification of genes responsible for disease (16). The first primary cardiomyopathy to succumb to genetic linkage analysis was familial hypertrophic cardiomyopathy (FHCIM) (17), and beta-myosin heavy chain (beta-MHC) was shown to be the responsible gene (18). In 10 years, there has been an avalanche of genes associated with a variety of diseases of the heart. Over 50 genes known to cause heart disease have been mapped to their chromosomal location (19). Eight genes responsible for HCM have been identified with over 100 mutations. Although nine loci have been identified (mapped) as responsible for familial dilated cardiomyopathy (FDCM), only two genes have been identified—actin (20) and desmin (21). Four loci (22) have been identified as responsible for cardiomyopathies of the right ventricle—namely, arrhythmogenic right ventricular dysplasia (ARVD). Several genes have been identified in the mitochondrial DNA to be responsible for cardiomyopathies (23). Genes have also been identified as responsible for ventricular arrhythmias, supraventricular arrhythmias, conduction disorders, anatomic defects (septal, aortic) and neuromuscular disorders affecting the heart (see review in [19]). In addition, several genes that cause lipid disorders, hypertension and various vascularopathies have been identified. Many other genes present in the invertebrate and vertebrate heart have been identified and shown to play a major role in the development of the heart, which will accelerate the finding of their analogues in the human heart (24). The genetics of cardiac development is progressing in simpler organisms such as the zebra fish and the chicken embryo and from genes identified as responsible for inherited cardiac developmental defects. These pathways of investigation will merge and accelerate the identification of genes responsible for early cardiac development, while at the same time they will provide fundamental insight into understanding the cardiac growth response.

Familial hypertrophic cardiomyopathy as an illustrative example of genetics for the 21st century. Familial HCM, an autosomal-dominant disease, is the most common cause of sudden death in the young, particularly in the athlete. Familial HCM is more common than realized, occurring with an incidence of one in 1,000 in the population. It is associated with cardiac myocyte and filament disarray, hypertrophy and increased fibrous tissue (25). This is a disease that represents a paradigm of the hypertrophic response of the heart to injury. The heart adapts to injury, whether physiologic or pathologic (e.g., pressure or volume overload), through one of two growth responses—namely, hypertrophy or dilation, or both (26). Familial HCM represents the hypertrophic response, whereas FDCM represents a paradigm of the dilated form. It remains to be determined whether cardiac dilation is a growth response. It has been postulated that it is a normal growth response in which the sarcomeres are added in sequence as opposed to in parallel (in hypertrophy); however, it could represent an impaired growth response (27). In athletes, the response consists of hypertrophy and dilation and returns to normal with cessation of exercise, suggesting that both responses are normal. However, it has not been shown morphologically that sarcomeres are formed in parallel in athletes. The hypertrophy of FHCM, although eccentric in 80%, often becomes concentric but is almost exclusively in the left ventricle, with <5% involving the right ventricle. The first gene identified to be responsible for FHCM was beta-MHC at 14q1 (17). Since that time, there have been six other genes identified—troponin T, tropomyosin C, troponin I, myosin-binding protein C and the two myosin light chains (28). Although there are other genes to be identified, experience with genotyping new families with FHCM suggests that most of them are due to one of the known genes. On the basis of our data base of over 3,000 individuals with FHCM, the beta-MHC gene accounts for >50%
of the patients, and myosin-binding protein C together with troponin T accounts for another 30%; the results published by Seidman et al. (29) are similar. Thus, it is likely the seven known genes are responsible for 80% to 90% of FHCM. It is important to emphasize that essentially all of the cases of HCM (excluding those with known acquired causes) have a genetic basis, but some are sporadic rather than familial. Of course, once a sporadic de novo mutation occurs, it is highly likely to become familial in the next generation, although mutations with very low penetrance may not be expressed in all generations. There are over 100 mutations now identified in the seven genes responsible for FHCM, and most are due to a single base substitution that results in the substitution of one of the amino acids; however, a few are due to small deletions or insertions.

From genotype–phenotype correlations, it is rare to observe any clinical, electrocardiographic, or echocardiographic features of FHCM before puberty (30–33). Rare cases have been observed before puberty, but they probably are homozygous from both parents having the disease. The lack of disease before puberty provides an important time window for prevention when such therapy becomes available. After puberty, the age of onset is highly variable, and, as stated previously, in HCM due to the myosin-binding protein C gene, onset may not occur until the fifth or sixth decade of life. Second, the presence or absence of clinical features, even within the same family, is highly variable. Third, the incidence of sudden death is highly variable and does not correlate with the presence or severity of any of the clinical features. In patients with FHCM due to troponin T mutations, there is very little cardiac hypertrophy but a high incidence of sudden death (34). In patients with FHCM due to mutations in the beta-MHC gene, there is consistently hypertrophy, but the incidence and frequency of sudden death are highly variable. Last, several studies by several investigators have shown a strong correlation between the incidence of sudden death and the type of mutation (35,36). This is illustrated in Figure 1, which shows that patients with the Arg403→Gln mutation have an average life span of 28 years as compared with an average life span into the 60s with the Glu930→Lys mutation.

In summary, only the mutations correlate with the incidence of sudden death. On the basis of the observation of a large number of families, we have observed that Arg403→Gln, Arg453→Crs, Arg719→Trp predict an average life span of 28 years, whereas the mutation Glu930→Lys, Arg→249-Gln has a life span of 43 years, and Leu908→Val, Val606→Met, Cly256→Glu of 62 years. It should be emphasized that while certain mutations appear to be predictive, other factors are very important—namely, interactions with other genes and environmental stimuli. These factors hopefully will be elucidated and shown to explain the variation that occurs in the phenotype of this disease, even within the same family with the same mutation. The importance of environment on expression of the mutant gene is amply illustrated by FHCM, in which the disease is seldom seen in the right ventricle despite the mutant gene’s presence in equal abundance in the right and left ventricles. This is similarly illustrated in ARVD, in which the disease is present primarily in the right ventricle. Gene-to-gene interaction is emphasized by the observation that FHCM mutations occurring in individuals with the DD allele of the ACE genes have more extensive hypertrophy and a higher incidence of sudden death. Because the genes present in the DNA of a white cell are identical to those in the heart or brain, a blood sample provides immediate access to all genes (39). Thus, a new era will dawn with the ability to genotype for all diseases; a specific diagnosis can be made using a single blood sample, enabling a rational basis for their prevention and treatment. It is awesome and scary to realize that a single blood sample will provide the specific etiology of thousands of diseases. In the near future, as we learn more about factors that affect gene penetrance and expression, genotyping will provide not only a more specific diagnosis, but also a basis to risk, stratify, and select more appropriate individual therapy.

Genetic surprises. As more and more genes become available, it is highly likely that many defects not previously considered to have a familial origin or disposition will be shown to have a genetic component. One example of this is
atrial fibrillation (AF), which hitherto was regarded as an acquired disease. In 1996, we identified a family with early onset of AF and mapped the genetic defect to chromosome 10q22 (40). The disease is inherited as autosomal dominant and is probably far more prevalent than expected, since over 100 families have been identified and loci heterogeneity has been demonstrated (41). In Italy, ARVD is a disease that is the most common cause of sudden death in the young. It initiates in the right ventricle and only much later in life does there appear to be left ventricular involvement. Does this mean there is a chamber-specific gene? Or does it mean that a stimulus specific for the right ventricle interacts to develop this phenotype? It is more likely the latter because other cardiomyopathies that develop in the left ventricle seldom involve the right ventricle, even though the defective gene is equally abundant in the right ventricle. Three loci have been mapped responsible for ARVD (42–44) in families from the Veneto region in Italy and in another family in Greece (44). In 1998 (22), a gene was mapped to chromosome 3p23, responsible for ARVD in a family from North America, and a second locus to 10p12 (45). It now appears that ARVD may account for up to 15% of sudden deaths in the young in North America (46).

Genetic animal models and inherited human disease—the hope for functional genomics and improved therapy.

The excitement and challenge for the next few decades will be in determining the function of the genes. At present, we have the ability to identify about 2,000 proteins, so we are missing only 48,000 to 98,000. In a symposium held in Cold Spring Harbor, we estimated that if 15 mouse clinics were missing only 48,000 to 98,000. In a symposium held in Cold Spring Harbor, we estimated that if 15 mouse clinics were identified at the end of 1998 (55). This is the first human genome, several small genomes of single cells are also being sequenced. The first genome to be completely sequenced, and all of its genes identified, was Haemophilus influenza in 1995 with 1.4 million bases. Since 1995, over 40 single-cell organisms have been sequenced, including the large organism Saccharomyces cerevisiae with a genome of 12 million bases. This paved the way for the development of novel antibiotics targeted to specific genes. However, the most significant development occurred at the end of 1998 with the sequence of C. elegans (55). This is the first multicellular organism for which the genome has been sequenced; it has 97 million base pairs and 19,000 genes, one-fifth the number of human genes. Furthermore, a significant percentage of the genes identified are identical to those of human genes. In C. elegans, all 959 cells that make up this tiny worm have been recognized, and because of its transparent skin, it is possible to observe the development of this organism and determine the function of each gene and its morphologic phenotype (56). Although humans may have up to 100,000 genes, it is highly likely that many of the physicians investigators are facing.
these genes belong to families with common consensus motifs that share a specific similar function. An example of this would be kinases, which transfer high energy phosphate from one molecule to the other, a common process throughout the body. There are over 3,000 genes that encode kinases, but all of those have in common a sequence motif and the function of transferring high energy phosphate. The development of the gene bank of different genes from different species now makes it possible to travel back about one billion years in time. This will help tremendously in determining the function of genes. A DNA sequence of unknown function can be aligned to a DNA sequence in the gene bank from other species. If the function of the sequence is known in another species, a similar function will most likely prevail in humans. It will also play a large role in understanding evolution, this time at the molecular level—namely, the gene that has been altered—rather than studying the evolutionary change expressed through the phenotype.

A look into the future. The Human Genome Project has been compared to that of the Apollo or the Manhattan Project. The impact of the Human Genome Project, in my opinion, is likely to be far greater than that of either the Apollo or the Manhattan Project. The technology to genotype thousands of mutations through use of technology such as the DNA chip or mass spectrometry is progressing rapidly and promises to have an assay turnaround time of hours. This will make available all of the human genes and their variants. Development of this technology and the completion of the human genome will provide clinical access to thousands of genetic risk factors and specific etiologies. Genotyping for gene variation will provide a new era for selecting appropriate drugs (pharmacogenetics). For example, a hypertensive individual with the DD form of the ACE gene would more likely respond to an ACE inhibitor, whereas someone with a gene variant causing increased catecholamines would more likely respond to a beta-blocker. The elucidation of the pathogenesis of disease in genetic animal models provides specific molecular targets for drug development. The target is not just the defective molecule inducing the disease, but also the additional targets upstream and downstream from this molecule, which comprise the pathway of signaling proteins and other necessary substrates. An example may be the work of Brown et al. (57) on elucidating the cholesterol receptor in familial hypercholesterolemia. This disease is responsible for perhaps <1% of heart disease, but today drugs inhibiting the cholesterol synthetic pathway are also first-line treatment for acquired forms of the disease. Similarly, unraveling the molecular defect for familial AF should elucidate a pathway essential to normal conduction and is involved with acquired forms of AF. Although the human body has hundreds of trillions of cells, there are only about 200 different cells that have a unique function. The recent research on pleuripotent stem cells has laid the groundwork for stimulating these cells to develop into the cell or organ of choice. It is well established that myoD stimulates a fibroblast to convert into a skeletal muscle myocyte. The National Heart, Lung, and Blood Institute of the National Institutes of Health (Bethesda, Maryland) has proposed a new goal under the term “restorative biology” to grow human organs (heart, lung and brain) over the next 10 years. Gene therapy for solid organs has not yet been effective, but the ease of ex vivo gene uptake into organs such as veins for bypass grafts or the explanted heart for transplantation into the donor makes this a likely success in the near future. We now know that 20 diseases account for 80% of the deaths in the Western world, and it is reasonable to assume that only about 100 to 200 genes are involved in these diseases. All of those genes will be available in a couple of years, and the implications of genetic screening for prevention or of new therapies resulting from targeted development are enlightening and staggering. The implications of the human genome for the prevention and treatment of disease are greater than we can imagine. It was once postulated that our genes would all be on a CD-ROM and available during an interview, such as for employment by the year 2030; this is now possible by 2008. There could be some casualties, as occur with any revolution, and thus bioethical considerations must proceed along with the scientific discoveries (58). Despite the concerns, the proper application of these techniques should affect a marked reduction in human suffering from disease, and it has been predicted that human life span will be prolonged by at least 50% in the next millennium.

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