

# GENETICS AND MOLECULAR BIOLOGY: from a monastery garden to rebuilding the heart

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*The advent of molecular cardiology stems from advances in knowledge of genetics spanning over 400 years. The seeds of what was to grow into a forest of knowledge were planted by Harvey, Leeuwenhoek, and Virchow. Mighty trunks arose from the works of Darwin, Galton, and Gregor Mendel (pea breeding experiments). Branches started shooting out with experiments on the fruit fly (Drosophila) and the works of Morgan, Garrod, Fisher, Haldane, and Penrose. After that, discoveries simply bloomed, culminating in human molecular genetics, the human genome projects, and the beginnings of the postgenomic era in which we are just starting to find out how the whole thing works. In this forest, molecular cardiology is but one tree, yet one that holds enormous promise for the future.*

*If I have seen further  
it is by standing on the  
shoulders of giants*

Sir Isaac Newton (1642-1727)

Although Isaac Newton's modest statement in a letter to Robert Hooke has been reinterpreted by modern historians as a veiled insult to his colleague, it is certainly pertinent to the difficult task of trying to trace the origins of the applications of genetics and developmental biology to modern cardiology. Indeed, the arboreal metaphor requested by the Editor is almost impossible to sustain, given the enormous forest of multidisciplinary knowledge that has formed the basis for our current understanding, limited as it is, of the function of our genomes in health and disease. But after all, Ramon Llull, the "enlightened doctor" whose *Arbor Scientiae*, across the centuries, is providing the framework for this issue of *Dialogues*, devised not one, but *sixteen* "trees of knowledge," as I discovered when perusing his biography. Well did he realize that knowledge was a forest, and so, after all, I feel quite comfortable writing this review under the Magister's benevolent gaze.

## THE EARLY SEEDS

In his investigation of the origins of classical genetics, Carlson<sup>1</sup> describes some of the seeds that led to this

field becoming an interdisciplinary science at the beginning of the 20th century. Starting in 1651 with William Harvey's identification of the egg as the basis of life, "ex ova omnia," he describes Robert Hooke's account (in his book *Micrographia*) of how cork is composed of trillions of cells, and Antoni van Leeuwenhoek's descriptions of spermatozoa in his semen. Later, these discoveries were to lead Mathias Schleiden and Theodor Schwann to develop cell theory and Rudolf Virchow to propose that all cells arise from pre-existing cells. However, during the 17th and 18th centuries, views on the mechanisms of embryological development were incompatible with any logical theory of heredity.<sup>2</sup>

## THE TRUNKS: THE BIRTH OF GENETICS IN THE 19TH CENTURY

Three unrelated events in the middle of the 19th century, two of them in the same year, together with an increasing understanding of the properties of cells, were to revolutionize biology in general and the understanding of genetics in particular: on November 4th, 1859, the first edition of Charles Darwin's *The Origin of Species* was published; on February 8th and March 8th, 1865, the Moravian monk Gregor Mendel (*Figure 1*) presented his studies entitled *Experiments in Plant Hybridization* to the Natural Science Soci-

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ety in Brunn, now Brno, Moravia, and subsequently published them in the Society's proceedings; and in the same year an Englishman, Francis Galton, published two short papers entitled *Hereditary, Talent, and Character*. These events laid the ground for the understanding of how species have developed, the genetic mechanisms involved, and the practical applications of the science of hereditary for the study of human characteristics, and, later, inherited diseases. However, if we have to identify a "founder" tree, it must surely be Gregor Mendel.

Mendel spent most of his working life in the Augustinian Monastery in Brunn, combining religious duties with a passionate interest in science (Figure 2). Although sometimes depicted as a lonely monk whose hobby happened to be breeding flowers, he was in fact part of a lively scientific community in which animal and plant breeding, because of their commercial importance, were



**Figure 1.** Gregor Mendel (1822-1884).

Reproduced from: Weatherall, 1995.<sup>3</sup>  
Courtesy of Wellcome Institute for the History of Medicine, London.

selected peas for his experiments. As the result of studies carried out on some 28 000 plants between 1854 and 1863 he was able to formulate the way in which units of heredity, later called genes, are passed from generation to generation according to two simple mathematical laws. First, genes segregate; mem-

genes move to gametes independently of each other. Or, to put it in a nutshell, alleles segregate; non-alleles assort.

Mendel's work was largely forgotten until it was rediscovered independently by several workers at the beginning of the 20th century. At first, it was the subject of great controversy, but thanks to strong protagonists, notably the English biologist William Bateson, it gradually came to be accepted. The word gene seems to have been first coined by a Danish botanist, Wilhelm Johannsen, in 1911. Apparently, he did not like the term unit character, which was becoming popular, and suggested instead the word gene, a shortening of pangenes which had been derived from Darwin's theory of pangenesis.<sup>1</sup> During the latter part of the 19th century, chromosomes were identified and it was suggested that they might be vehicles for genetic transmission.

Hence the scene was set for the development of the classical era of genetics, the exploration of Darwinian evolution and the understanding of the genetic basis for how it had come about, and the early beginnings of human genetics and its applications.

### THE BRANCHES: CLASSICAL GENETICS AND THE BEGINNINGS OF HUMAN BIOCHEMICAL GENETICS

The period from the turn of the century up to the end of World War II was an extremely productive time for the development of genetics in general, and human genetics in particular. Although there are many branches, those that seem most relevant to the development of molecular cardiology are the breeding experiments with the fruit fly, *Droso-*



**Figure 2.** The Augustinian Monastery in Brno today. This is the actual site where Mendel carried out his famous plant breeding experiments. A statue in his honor can be seen in the distance on the left hand side of the picture. Courtesy of the author. All rights reserved.

of major interest. He was stimulated to carry out his famous breeding experiments by observations on ornamental plants, for which he tried to breed new color variants by artificial insemination. In the end he

members of the same pair of genes, alleles, are never present in the same gamete, but always separate and are transmitted in different gametes. Second, genes assort independently; members of different pairs of

*phila*, by Thomas Hunt Morgan, the first application of statistical methods to study the behavior of genes in populations, begun by Francis Galton in the late 19th century, and continued by Karl Pearson, Ronald Fisher, and “JBS” Haldane (always known as “JBS” to distinguish him from his famous father, “JB”) in England, and Sewall Wright in the United States, and the first description of inborn errors of metabolism by Archibald Garrod in England. The story of the development of genetics during this period is covered by Carlson<sup>1</sup> and the early development of human and clinical genetics is described by Weatherall.<sup>3</sup>

The early studies of the *Drosophila* group worked out the true significance of sexual reproduction and meiosis. Although Mendel's laws had dealt with the inheritance of a particular gene, Morgan's group and Bateson in England pointed out that if two genes are on the same chromosome, and especially if they are close together, they will tend to be inherited together; the genes are then said to be linked. When the parental chromosomes become closely opposed at meiosis, crossing over of genes may occur so that the two characters determined by them will part in some of the offspring. These observations were the basis of the first maps of genes on chromosomes. Furthermore, Hermann Muller established that genes can change their structure—that is, undergo mutation—a process that can be speeded up under certain conditions, exposure of cells to radiation for example.

The first serious efforts to measure inheritability in human populations were made by Francis Galton, an English polymath who was born in the same year as Mendel. Having been left a large inheritance on the death of his father, which freed him

from any need to earn a living, he spent his life traveling and making numerous important contributions to exploration and to the biological sciences. He became fascinated by how talent appears to run in families, particularly those of Lord Chancellors, and he was interested from the beginning in attempting to im-



**Figure 3.** Sir Archibald Garrod (1857-1936), at the time of his retirement as Regius Professor of Medicine at Oxford in 1927.

Reproduced from reference 3: Weatherall DJ. Science and The Quiet Art. The Role of Research in Modern Medicine. New York, NY: Oxford University Press; 1995. Copyright © 1995, Oxford University Press. The original figure was reproduced by the kind permission of Dr. A.G. Bearn, Rockefeller University.

prove the human species by selective breeding. In this sense he was undoubtedly the father of the eugenics movement, which did so much damage to the name of genetics, particularly in World War II. His early studies were summarized in 1869 in his book, *Hereditary Genius*, a second edition of which was published in 1892. Although much of his thinking about genetics was confused because, unlike Mendel, he was most interested in traits that did not follow simple patterns of inheritance, he was, nonetheless, the initiator of quantitative human genetics at the turn of the century; those who followed him, Karl Pearson, Ronald Fisher and “JBS” Hal-

dane, were later to lay the foundations of human population genetics. However, the main branch that was to establish genetics as an important part of clinical medicine stemmed from the work of the English physician Archibald Garrod (*Figure 3*), and led to the beginnings of an understanding of the biochemical basis of human genetic disease and, in the longer term, of how genes function.<sup>4</sup> In June 1908, he delivered a series of lectures at the Royal College of Physicians, London, to be published in *The Lancet* later the same year. This work was extended and formed the basis for his famous book *Inborn Errors of Metabolism*, which described several rare diseases that, Garrod realized, with some promptings from William Bateson, were due to inherited defects in the body's chemical pathways.

Garrod's work, like that of Mendel, was ignored for many years. Its true value became apparent only after advances in biochemistry led to recognition of the importance of the genetic regulation of metabolic pathways. Indeed, it was not until the early 1940s that the elegant studies by the American scientists George Beadle and Edward Tatum on the bread mold *Neurospora* demonstrated that the primary action of a gene is to direct the production of a specific protein. In a lecture delivered in Stockholm in 1958 on the occasion of the award of the Nobel Prize to Beadle and Tatum, and in a generous tribute to the work of Garrod, the prize winners said, “In this long and roundabout way, first in *Drosophila* and now in *Neurospora*, we have rediscovered what Garrod had seen so clearly many years before.”<sup>4</sup>

Genetics flourished in England during the first half of the 20th century. The work of Fisher, Haldane, and later Lionel Penrose established the



scientific basis for studies of human genetics. It placed human pedigree analysis on a firm statistical basis, established the first genetic linkages in man, and laid the foundation for the study of genetic disease. However, it had virtually no impact on the medical profession; it was not until the 1950s that medical genetics started to flourish as a separate discipline in the USA.

### THE FOREST: MOLECULAR GENETICS, GENOMICS, MEDICAL GENETICS, AND MOLECULAR MEDICINE

Rapid developments in physics and chemistry in the second part of the 19th century were to lead to an understanding of atoms and subatomic particles and, ultimately, to a detailed knowledge of the way in which large molecules such as proteins, the basis of all living things, are put together and function. In 1943, a remarkable series of lectures was given by Erwin Schrödinger, entitled *What is Life?* In these lectures, which were later published as a book that was reprinted many times,<sup>5</sup> Schrödinger echoed Claude Bernard when he offered a novel view of living things that was based on the laws of physics. A new type of biology was evolving that was to come under the influence of physicists and chemists as well as geneticists.

In March 1953, Fred Sanger and his colleagues in Cambridge published the amino acid sequence of insulin, work that established that proteins consist of chains of amino acids that are always in the same order. Hence, it followed that an informational system must exist to ensure that this happens. The central questions were, therefore, how is this information stored and passed from generation to generation, and what kind of complex cellular machinery

is needed to convert a piece of coded information into a string of amino acids, and, more importantly, to put them in the right order every time.

The first hint that DNA, discovered by Freidrich Miescher in the mid-19th century, is the informational molecule came from the work of an English bacteriologist, Fred Griffith, who discovered that whatever causes virulence could be transferred between different strains of bacteria. The transforming factor was identified as DNA in a series of beautifully executed experiments by Oswald Avery, Colin MacLeod, and Maclyn McCarty, in the USA. The story of the extraordinary years that followed, during which the work of Avery and his colleagues was finally accepted and the structure of DNA was established by James Watson and Francis Crick (1953), has been told on many occasions. Over the next few years, the genetic code was deciphered, the cellular machinery whereby its information can be transferred from the nucleus to the cytoplasm by messenger RNA was determined, and the way in which the latter can act as a template for protein synthesis, was fully worked out.<sup>6</sup>

Undoubtedly, the years that followed Watson and Crick's seminal discovery were among the most exciting in the history of human biology. It was a period of the coming together of the remarkable discoveries in phage and microbial genetics with new technology for cloning and sequencing genes, and for starting to understand how they are regulated.

At the same time there was a much quieter and generally unsung revolution starting in the medical sciences. As mentioned earlier, up to the end of the World War II, genetics had virtually no impact on clinical medicine. Things changed quite

dramatically during the 1950s and, whereas the early development of human genetics took place largely in the UK, the major developments in clinical genetics occurred in the USA. During the late 1950s, several departments of medical genetics were established, sometimes by those who had come to genetics almost by chance. For example, Victor McKusick at Johns Hopkins Hospital trained in cardiology and for some years led a schizophrenic existence between the arcane world of spectral phonocardiography and the study of the inherited disorders of connective tissue. It was undoubtedly his work on the latter conditions that led to the realization that medical genetics was here to stay; in 1957, he was invited by the Chairman of Medicine at Hopkins to develop a Division of Medical Genetics. At about the same time, Arno Motulsky established a similar department in Seattle; others rapidly followed.

By the late 1950s, remarkable progress had been made in clinical genetics. Many single-gene disorders had been defined at the protein level, a large number of syndromes associated with abnormalities in the number or structure of chromosomes had been delineated,<sup>7</sup> and by twin studies and other indirect approaches some indication of the complex heritability of common diseases that did not follow a Mendelian pattern of inheritance had been characterized. But what was going on in the cell nucleus at the level of the genes themselves still remained a mystery, a situation that was soon to change dramatically.

The story of how clinical genetics moved into the molecular era provides yet another string of branches. A seminal event, and one which occurred in the distinctly nonarbo-real environment of a train journey,

was a conversation between Linus Pauling and William Castle on an overnight journey between Denver and Chicago in 1945. Castle told Pauling that he and his colleagues had noticed that the red blood cells of patients with sickle cell anemia have an unusual appearance when viewed under polarized light. As

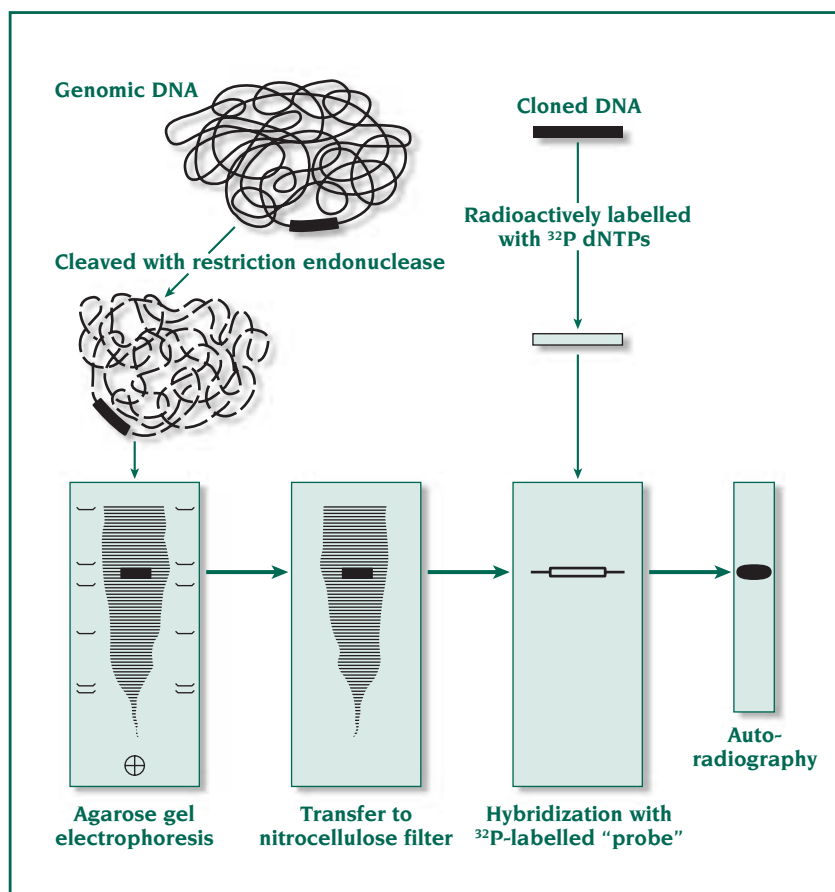
Pauling and his colleagues coined the term “molecular disease” to describe sickle cell anemia.<sup>8</sup>

These findings were confirmed in 1956, when Vernon Ingram, a young protein chemist working in Cambridge observed that sickle cell hemoglobin differs from normal

The story of how scientists of diverse disciplines and backgrounds descended on the hemoglobin field in the late 1950s has been recounted recently.<sup>9</sup> As a result, the genetics of hemoglobin and its disorders became extremely well characterized and was ready-made for the application of the technology of molecular biology which became available in the period after 1970. First, by molecular hybridization or Southern blotting (Figure 4),<sup>10</sup> and later by cloning and sequencing of globin genes both in health and disease, a remarkable picture emerged of the molecular pathology of a group of common genetic diseases.

These early successes in human molecular genetics resulted from research in which the abnormal gene product was known and therefore in which it was possible to devise gene probes to study the gene in question. At first, it was difficult to imagine how it would be possible to define the molecular pathology for diseases about which nothing was known of the abnormal gene product.

The discovery of restriction enzymes, enzymes that cut DNA at predictable base sequences, and the finding that there is remarkable individual diversity with regard to the base-structure of the genome, led to the concept of using restriction-enzyme polymorphisms as potential linkage sites throughout the human genome. In studies of this kind, families were examined both for the presence of a particular restriction enzyme marker and for the disease or other trait that was being studied. If the disease and marker were on different chromosomes they would be found together as often as they were apart in different generations. On the other hand, if they were close together, independent assortment of this kind would not occur. After

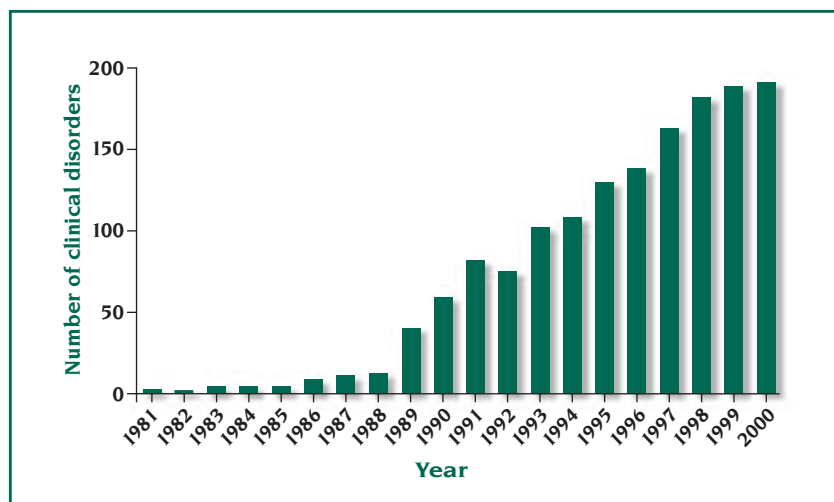


**Figure 4.** Southern blotting, named after Edwin Southern, its inventor.<sup>10</sup> This major technical advance made it possible to analyze the structure of human genes for the first time in the late 1970s. DNA is digested with a restriction enzyme, the fragments separated by size by gel electrophoresis, the fragments “blotted” onto nitrocellulose filters, and identified with radioactive gene probes and autoradiography.

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a protein chemist, Pauling was intrigued by this observation and realized that the changes that Castle had noted might mean that the defect in sickle cell disease is within the hemoglobin molecule. This turned out to be the case; in 1949,

hemoglobin by a single amino acid substitution, valine for glutamic acid in one of the pair of peptide chains of globin, thus moving the story of gene action from Beadle and Tatum’s “one gene–one enzyme” to “one gene–one peptide chain.”



**Figure 5.** The remarkable increase in the discovery of the genes for Mendelian disorders following the development of positional cloning.

Figure prepared for the author by Dr V. A. McKusick. With kind permission.

establishing a linkage of this type, and by some ingenious genetic engineering, given the rather picturesque name of chromosome walking, it became possible to move from the marker towards the gene of interest. This unlikely activity, originally called reverse genetics, but later rechristened positional cloning, became one of the most important developments in molecular medicine.<sup>11</sup> Its early successes included the discovery of the genes for muscular dystrophy and cystic fibrosis. Many other genes for the monogenic diseases were found in this way subsequently (*Figure 5*).<sup>4</sup> Furthermore, it became clear that each of us is unique with respect to the structure of our DNA, a finding that led to the development of "DNA fingerprinting" (*Figure 6*).

With increasing knowledge about the location of genes on different chromosomes, it is not surprising that, with the development of increasingly rapid automated gene sequencing techniques, thoughts turned to the long-held dream of clinical geneticists that it might be possible to determine the complete sequence and, ultimately, a detailed

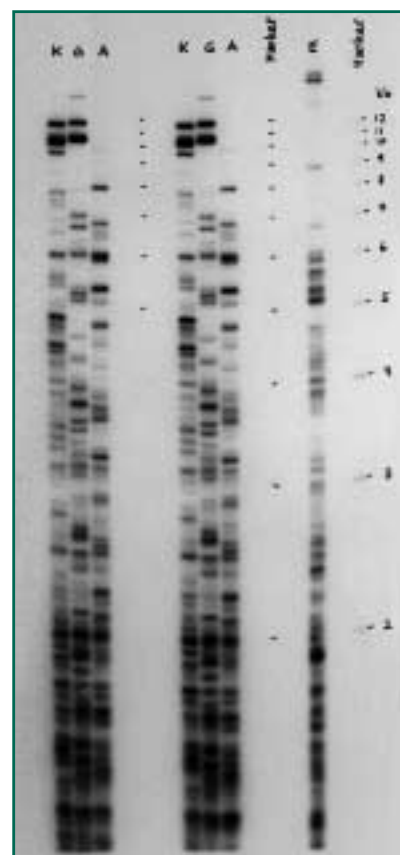
map of the human genome. The first part of this remarkable achievement was completed in both private and public sectors in 2001.<sup>12,13</sup>

### CARDIOLOGY IN THE MOLECULAR ERA

How has cardiology fared during this period of remarkable technological advance? Can we begin to talk about a new field of "molecular cardiology?"

The most impressive progress so far has been made in the elucidation of the molecular basis for Mendelian disorders that involve the cardiovascular system. Here, there is no difficulty in defining the seminal branch. The elegant series of experiments by Michael Brown and Joseph Goldstein<sup>14</sup> on familial hy-

percholesterolemia were undoubtedly one of the most impressive examples of the application of modern cell and molecular biology to the study of human disease. The seeds had been sown by the recognition that this condition is characterized by a selective increase in the plasma level of one lipoprotein, designated low-density lipoprotein (LDL). Using cultured fibroblasts from homozygotes, Brown and Goldstein discovered the cell-surface LDL receptor and showed that familial hypercholesterolemia is caused by mutations in the genes specifying this protein. Later it was possible to purify the receptor protein, clone its cDNA and, by 1985, to isolate and characterize the particular gene involved. An analysis of the molecular pathology has disclosed that there are over 400 different mutant alleles responsible for



**Figure 6.** DNA fingerprinting. After digestion with appropriate restriction enzymes and separation of the fragments by size, gene probes are used that identify particularly variable regions of DNA. The duplicate tracts on the left show the remarkable reproducibility of these patterns; a test case from a different individual is shown on the right.

Figure prepared by Professor Alec Jeffreys, the inventor of this technique. With kind permission.

this condition, which can be classified into various subgroups depending on their effect on its complex functions, including recycling of the receptor. A great deal of progress has also been made in the analysis of other disorders of lipid metabolism, which have important implications for cardiovascular disease, particularly disorders of synthesis and secretion of lipoproteins, including the B apolipoproteins.<sup>15</sup> As well as their intrinsic value in determining the molecular basis of important monogenic diseases, these studies are continuing to provide valuable insights into the pathogenesis of atheroma and, in particular, approaches to its management.

Studies of the molecular genetics of other Mendelian disorders, including hypertrophic and dilated cardiomyopathy, and arrhythmias such as the long QT syndrome, are providing extremely valuable information about the molecular pathogenesis and biochemistry of cardiac failure.<sup>16,17</sup> Mutations of a variety of different genes have been implicated as the cause of familial cardiomyopathies (see, eg, reference 18), work that has also benefited from the use of animal models such as transgenic or knockout mice. Again, as well as their intrinsic interest, they have provided invaluable insights into some of the fundamental mechanisms of cardiac dysfunction. The rare Mendelian forms of hypertension or hypotension all appear to involve the renal pressure natriuresis mechanism that is implicated in essential hypertension; in a few cases the molecular defect has been defined. Similarly, considerable information has been obtained from studies of the molecular pathology of disorders like Duchenne muscular dystrophy and related conditions in which the heart may be involved. And there has been some progress towards a

better understanding of the genesis of congenital heart disease that is associated with complex syndromes related to specific chromosomal abnormalities.

In short, an analysis of Mendelian disorders involving the cardiovascular system at the molecular level has provided some valuable insights into both their pathogenesis, but also into disease mechanisms that may be active in the more common, multigenic forms of these conditions.

### THE FUTURE

As we have progressed down the multiple trees, stems, and branches of the enormous forest of modern molecular genetics, it has become apparent that no medical discipline is an island and that we are entering a period of integrative biology in which extremely talented branches are generating what used to be viewed as individual trees. What is the future of cardiology in the post-genome era?

It has already been possible to produce databases that contain an annotated compendium of over 25 000 distinct cardiovascular-expressed genes.<sup>16</sup> It appears that in many cases these genes form nonrandom clusters at particular chromosomal sites. Genetic linkage strategy has already been used to identify chromosomal loci linked to heart failure in mouse models. More recently, it has been possible, with the advent of microarray technology, to analyze many of the 25 000 or more genes that may be expressed in complex multifactorial conditions such as the failing heart. It seems likely that approaches of this kind will provide valuable information about the molecular pathophysiology of heart failure and other cardiovascular diseases and may, in the long term, offer new targets for therapy.

Much has also been made of the possibility of defining the genes involved in multigenic disorders like coronary artery disease, hypertension, diabetes, and other common killers of middle and old age. Since the genome is now plastered with linkage markers and single nucleotide polymorphisms (SNIPs), approaches using very large populations that have been carefully genotyped, combined with extensive linkage studies, may unveil some of the players in these complex diseases, that often reflect a variable degree of heritability combined with a large environmental component. While these approaches may bear fruit, at the moment they must be viewed with extreme caution, given the multiplicity of genes involved, the relatively low degree of heritability, and the extreme difficulty of defining human genotypes.

Another hope for postgenomic medicine is the individualization of therapy based on varying genetic response to therapeutic agents, a field that has attracted the formidable names of pharmacogenetics and pharmacogenomics.<sup>19,20</sup> Of course, well-defined polymorphisms in the handling of drugs used in the treatment of cardiovascular disease, notably warfarin, have been known for many years and yet this knowledge is only now being applied in clinical practice. There is little doubt that polymorphisms of drug metabolism will be discovered more rapidly in the future, but whether this information becomes part of day-to-day clinical practice will depend on their frequency, the magnitude of their metabolic effects, the cost-effectiveness of testing for them, and the feasibility of carrying out these tests in a general hospital setting; much work is required before the era of personalized medicine is reached. In the long term, it may also be possible to identify individuals at partic-



ularly high risk for common cardiovascular diseases at a stage early enough so that, by environmental or other means, it may be feasible to reduce the likelihood of contracting the disease; this approach will require the development of a new specialty, genetic epidemiology.

At the moment it is impossible to anticipate how long all this will take, let alone how it will eventually affect day-to-day medical care. But one thing is sure: given the enormous biological complexity of sick people, genomic medicine, although it undoubtedly has enormous promise for the future, will not alter our clinical practice overnight.

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