As the revolution in genetics and molecular biology continues into the first decades of the new millennium, it is appropriate to examine the tools that a physician might need to make appropriate use of the information that she or he will have at her or his disposal.

I was both honoured and humbled when Dr. Sweeney approached me to talk about the implications of the new genetics for medical education. I thought about the classic text on inherited metabolic disease, which originally dealt with a limited number of rare disorders but which has now expanded into a veritable textbook of medicine. In preparing this talk, I have relied heavily on the thinking of Barton Childs, professor emeritus of pediatrics at Johns Hopkins University and a philosopher of medicine, who has contributed greatly to our understanding of the proper place of medical genetics in modern medicine. His chapter, entitled “A logic of disease,” should be obligatory reading for all physicians.

In his chapter, Childs cites the well-known seminal work of Garrod:

It might be claimed that what used to be spoken of as a diathesis is nothing else but chemical individuality. But our chemical individualities are due to our chemical merits as well as our chemical shortcomings; and it is more nearly true to say that the factors which confer upon us our predispositions to and immunities from the various mishaps which are spoken of as diseases, are inherent in our very chemical structure: and even in the molecular groupings which confer upon us our individualities, and which went to the making of the chromosomes from which we sprang.

In his chapter, Childs contrasts the Oslerian view of medicine — in which illness is viewed in terms of a broken machine — with a Garrodian view — in which medicine must be viewed against the background of individual variation and evolution. Whereas Osler focuses his attention on the specific disease, Garrod puts his focus on the individual patient. The Oslerian model focuses on the “classic case,” as if a disease were the same in every person. This approach fails to take into consideration that “no two diseases are the same because of individual differences in predisposition and susceptibility, exposure and experience.”

To give concrete clinical examples from my own practice: Why is it that, in the same family, a 70-year-old woman with a BRCA1 mutation has never had breast cancer, whereas her daughter, who has the same mutation, had breast cancer in her 30s?

Why does an individual with elevated levels of phenylalanine in adulthood not get screened at birth and grow up to have normal intelligence? Why does she next come to medical attention when she gives birth to microcephalic and developmentally delayed children because of her own high levels of phenylalanine during pregnancy?

Childs champions the view that, whereas Osler was considered the prototypic physician for the 20th century, it is Garrod who will be seen as fulfilling that role for the 21st, because Garrod has provided the better model for a correct understanding of the concepts of health and disease.

It is clear that evolution is the process that drives biology and that, in order to understand human biol-
ogy, one must understand evolution. Childs puts forward the concept of “congruence.” He states that, since evolution occurs by a process of descent with modification, the fate of individuals and their genes depends on their ability to adapt to the environments that they meet.

Through selection a species perfects its adaptation, so it is the molecular mechanisms by which this adaptive success is attained that occupy the minds of biological scientists. ... So biology, including genetics which is its foundation, is the study of ‘congruence’ and it is in the framework of selection and evolution that the rules for the organization and behavior of living organisms are elaborated.\footnote{1}

“The attainment of congruence for the species requires a stock of variation from which to choose,” Childs elaborates. Some of this variation results in dissonance rather than harmony, and therefore Childs states that disease is a consequence of incongruence with some aspect of the environment, internal or external, that is expressed in difficulty carrying out daily life, or as a threat to life or reproduction that may lead to residual handicap. It is an expression in microcosm of processes that in macrocosm account for evolution.

It is evident that evolution is a process that takes place over very long periods of time and that it is not possible to attribute changes that occur over short periods of time to evolution. But it is possible to use this model as a framework that translates the processes of evolution to the level of the individual.

It is the mechanisms of mutation and selection, mediated through reproduction, that are the background for the understanding of human variation. It is the study of human variation between individuals, families and cultural groups that forms the basis of genetics. Genetics attempt to answer the question, “Why does this individual have this disease now?” It attempts to unravel the mystery as to why, when different individuals are exposed to the same environmental agent — be it a pathogen, a carcinogen, or a therapeutic drug — they respond as individuals and not as a group.

The challenge is to translate fundamental principles that allow us to understand disease to practical applications that allow us to treat patients and communities better.

In his chapter, Childs gives a brilliant summary of how using the genetic model changes the framework for a discussion of the rationale of medicine:

Representing disease as a consequence of incongruence gives it a biological as well as a social definition, and if it is biological and deriving from an evolutionary context, the rules that provide a logic of life, must also provide a logic of disease, a set of principles that at the same time accommodate all diseases and the qualities that distinguish them. The basis for this logic is, on the one hand, our human-ness, which will determine which diseases are possible and which not, and on the other hand, our individuality, which must determine who experiences them and to what degree. The concept of disease as an outcome of incongruence is the antithesis of that of the broken machine. If congruence represents a favorable ecological relationship which disease disrupts, then the doctor, who must be no less ardent in interventions to repair the dislocation, must see as his primary concern that of conservation. Accordingly, this concept is far more tolerant of prevention than the concept of the engineer. Indeed, the role of conservator flows naturally from the principle of a favorable ecological balance. When the primary job of the doctor is perceived as treating disease, then prevention must accept a secondary position. But when the necessity to fix something broken is perceived to be due to failure of that which is believed to be the primary aim of medicine, then adaptation and prevention rise to preeminence. \[italics added\]\footnote{1}

Indeed, Childs does not advocate change in curriculum, but rather a change in ideas, a different point of view, a change in how people think.\footnote{3}

The revolution in genetics and the revolution in information technology are coming together at a pace that will make the rational application of genetic thinking possible. The goals are pretty clear. Apart from the purely mechanistic aspect of the fact that the Human Genome Project has already led to, and will continue to lead to, the identification of novel genes and proteins, the next giant step will be the determination of the extent of variation between individuals.

The challenge is great, because increased knowledge does not immediately translate to better treatments. It took many years before an understanding of the structure of sickle hemoglobin led to improved therapy. The study of individual variation at multiple genetic loci is even more complex, but the technologies are developing so rapidly that the question is not whether applications will be applicable at the bedside, but when and how.

In the area of infections, genes have been isolated that confer resistance to tuberculosis in mice. In the
area of pharmacogenetics, genes that affect therapeutic responses and toxicity are known. One of the exciting areas of pharmacogenomics is the identification of polymorphisms of genes within a single metabolic pathway to determine individual response. The hope is that we will recognize not only patients who may have toxic reactions to drugs, but also drugs that, although they are ineffective in some patients, may have a high therapeutic index in others.

This type of thinking will never be imported into everyday clinical practice unless and until the technology makes it simple and cost-effective. But I put to you that the same was true earlier this century when physiologic and biochemical measurements were being introduced. How can we teach physicians to think in terms of individual variation if they do not have even a basic understanding of the biological processes?

My concern about centering the teaching of medical students entirely around specific patients relates to the prospect that they may never grasp the significance of human variation. Anyone with even a superficial interest in genetics or development can only marvel at the insights into human disease that have resulted from the study of other (not necessarily) lower organisms. Insights into cancer have come from an understanding of replication repair in yeast. Understanding of human malformation has come from the study of *Drosophila* and mice. With the drive toward producing humanistic, “well-rounded” medical students, we run the risk of having physicians who are unable to understand the implications of comparative biology at the very time when their applications to medicine are greatest. Or, in the words of Childs:

It is time for formal action to incorporate into medical education the new ideas generated by a penetrating understanding not only of the structure of genes, but of their origin in evolution and the function of their products in human homeostasis and disease … to organize our thinking to give students the intellectual equipment to adapt to the diversity of changes that are upon us.

All of these advances are occurring when superstition and anti-science are becoming more and more pervasive in society. The physicians of the future must be in a strong intellectual position to understand the arguments in the community and act as interpreter for their patients.

This only can be done if the physicians can understand the argument.

I will close by quoting from the consensus recommendations of a conference entitled “The implications of new genetics for health professional education,” sponsored by the Josiah Macy Jr. Foundation in October 1998, and at which Childs was the keynote speaker.

The explosive growth of knowledge about human genetics and its powerful implications for the treatment and prevention of disease demands the transformation of medical education. A genetics point of view is not something to be added to an already crowded curriculum, but a new way to think about illness and to interact with patients that must be incorporated into all teaching. It has the potential to individualize care in a way never before possible. Physicians who bring a genetic perspective to clinical practice will be able to custom design programs of prevention and treatment that consider the health status of each patient as a unique outcome of the interactions between genes, development and environment, with roots in the past and potent implications for possible futures. These goals will not be achieved until medical schools use the new genetic knowledge to refocus medical education so that physicians in all specialties view their work though the new genetic/developmental/environmental lens.

References