From the Double Helix to Genomic Medicine

The monumental contribution of Watson and Crick—proposing the structure of DNA—is being celebrated this spring on the 50th anniversary of their classic publication in *Nature* (1). Expressed simply, clearly, and logically, their analysis was a signal event in the history of science. In the five decades that have followed, a series of truly remarkable discoveries have occurred throughout all of science based on the implications of their conclusions. While it is very difficult to quantify the effect of this progress on clinical medicine today or what it might be in the future, several observations may provide a perspective for the busy clinician.

First, it is important to emphasize that the living cell or, indeed, the complex human organism, is not constrained by our definitions of disciplines. It is not chemistry, biology, genetics, genomics, proteomics, computer sciences, or, indeed, bioinformatics that the cell has to choose among to conduct its life processes. Rather, it is a wondrous integration of all disciplines, known and perhaps unknown, that is used by the cell, tissue, organ, or even ourselves. The accretive and interdisciplinary nature of scientific progress has brought us to a highly sophisticated understanding of both normal and aberrant processes in the human organism.

Second, the impact of scientific progress, as it may be applied to clinical medicine, may not always be fully appreciated if one is looking only for that "silver bullet" as evidence of progress. Two examples well illustrate how recent breakthroughs in DNA technologies have advanced the practice of medicine.

A first example is the development of polymerase chain reaction. This technology allows one to amplify by many-fold the sequences of DNA or messenger RNA for analysis, even from a single cell. The ultrasensitivity of this technique has allowed the definition of human variation, including mutations in specific genes in various genetic diseases, and the identification of DNA from vanishingly small samples, thereby serving an important role in our better understanding of evolution and even proving useful for forensic purposes. This type of evidence has not only helped convict many guilty persons of crimes but has also freed more than 120 innocent people from prison, some from death row, according to the Innocence Project. Finally, polymerase chain reaction has proven critical for the diagnosis and management of nongenetic diseases, such as AIDS.

A second example is the development of positional cloning. Positional cloning is the identification of a disease-causing gene by its position on the genome. Before the pioneering work of Collins, Lap-Chee Tsui, and colleagues, who used this approach to identify the causative genetic mutation leading to cystic fibrosis, the standard technique involved trying to identify some functional abnormality in the patient, seeking to find the underlying metabolic aberration and the enzyme responsible—and then tracing backwards to its corresponding gene. The inefficiency of this approach is apparent. For cystic fibrosis, as an example, hundreds of investigators, after decades of work, had failed to go much further than the observation that sweat chloride levels were elevated in these patients. There was no clear identification of an abnormal protein or enzyme, and, hence, the gene could not be identified. Positional cloning allowed the gene to be identified, an accomplishment that may have taken decades more at the rate of previous progress. Now that the human genome is sequenced, a search for a disease gene may take a matter of days to weeks, not years to decades, once the family information and biological material is available. Thus, we have witnessed impressive progress in the identification of more than 1000 disease-related mutated genes by the end of 2000, and the list is growing rapidly (2, 3). Each time a specific gene related to a human disease is identified, one then has an opportunity to understand the pathophysiology of the disease at the most fundamental level, develop highly specific laboratory tests to diagnose the disease and its variants, and design possible therapeutic approaches using chemical (traditional pharmaceutical approach), biological (recombinant technology), or genetic (gene therapy) modalities. This approach may be particularly helpful, for example, with some of the neuropsychiatric illnesses (such as schizophrenia and depression); in this area, research is progressing.

Finally, scientific progress may have unforeseen or unanticipated benefits. Again, several examples may suffice. The early concepts of gene therapy focused on replacing a gene that was defective in a specific well-defined genetic disease. However, it seems more likely, at this time, that this technology may actually be more helpful, at least initially, in several nongenetic diseases that are largely untreatable today. Major targets of gene therapy now moving toward phase III clinical trials include pancreatic cancer and sarcoma, in which tumor necrosis factor is directed into the cancer cells; end-stage coronary artery disease, in which vascular growth factors may be life-saving; and macular degeneration, in which loss of sight might be prevented. In each case, the appropriate therapeutic genes are inserted by using in vivo gene therapy with adenoviral vectors. Another example of an unexpected benefit from a form of gene therapy was the discovery that highly specific immunity could be induced by injecting into skeletal muscle free DNA that had been manipulated to carry a gene encoding a specific antigen. This important conceptual advance is discussed fully in the outstanding review by Srivastava and Liu in this issue (4). These forms of therapy, called in vivo gene therapy, do not lead to integration of the donor gene into the host DNA. Hence, insertional mutagenesis due to disruption of the host DNA, suspected as the cause of leukemia in the two patients with severe combined immunodeficiency disease who received a different form of gene therapy, called ex vivo gene therapy, would not occur.

Although the translation of advances in science to improved clinical care may seem painfully slow, difficult to define, and hard to appreciate, the economic effect is impressive. From 1970 to 1990, life expectancies increased by 6 years, valued by economists at $57 trillion (5). If only 10% of this gain was due to advances in medical research, the $240 billion per year return would be greater than a 6:1 return on the total research investment in the United States from all sources.

What we take for granted in the clinical literature today was considered basic science only a decade or two ago. And one can be confident that we are only at the beginning of reaping the benefits of the truly impressive scientific progress achieved over the past 50 years. As a nation, we must, however, support the continued funding of this research, both basic and clinical, as well as the training of physician-scientists, who are most critical to conducting the necessary translational research. Without this support, we will not fully realize the ultimate promise inherent in the discovery of Watson and Crick.

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