Research Needs and Opportunities
Maintaining the Momentum

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The debate about health care reform has included little substantive discussion of the role of biomedical research, yet the future of health care in the United States vitally depends on a robust research effort. It is only through research that we will ever truly be able to achieve one of the principal objectives of health care reform: namely, to control the growth of health care costs. Research will allow us to supplant existing high-cost treatments (once described by Lewis Thomas as “half-way technologies”—the iron lung being a classic example) with true high-technology interventions, such as vaccines, that invariably lower treatment costs. Research studies, such as the Cardiac Arrhythmia Suppression Trial supported by the National Heart, Lung, and Blood Institute (NHLBI), will allow us to reject costly treatments that are either without therapeutic value or even harmful. Research will also allow us to reduce the indirect costs of illness—those that represent the burden of morbidity and premature mortality.

The federal government and, in particular, the National Institutes of Health (NIH) have long played a significant part in promoting health-related research in this country, and the American public, speaking through its representatives in Congress, has supported the endeavor with generosity and enthusiasm. Most of the funding and many of the successes of the scientific effort have been driven by public perceptions of research needs, which range from widespread threats to the nation’s health, such as polio and AIDS, to rare diseases that affect relatively few people, such as the homozygous form of familial hypercholesterolemia. Yet, science is frequently unable to respond directly to those needs. As you well know, despite the best efforts of the NHLBI, the American Heart Association, and many others, cardiovascular diseases remain the leading cause of death in the United States.

What science can always do, however, is to respond to research opportunities. Indeed, many of our greatest successes in biomedical research have been achieved because cutting-edge discoveries and advanced technologies created new scientific opportunities that, in turn, led to promising new directions for exploration. And those directions ultimately led to discoveries with immediate application to publicly identified research needs. This is the reality of biomedical science—research needs are often most effectively addressed not by targeting them directly, but rather by focusing research efforts on the opportunities science presents. Consider a few such examples.

Resolution of the structure of DNA by James Watson and Francis Crick in 1953 began a path of opportunity that Herbert Boyer and Stanley Cohen exploited 20 years later when they performed the first successful recombinant DNA experiment. As with all major research advances, it was not a linear path, and many other steps were necessary along the way. One of the last, and certainly one of the most important, was discovery of restriction enzymes. Although this may have appeared, at least from some perspectives, to be merely another interesting scientific observation, it made the Boyer-Cohen experiment possible. That experiment, in turn, made possible bacterial production of human insulin 5 years later and commercial production and marketing of human insulin 4 years after that. It also made possible a number of other recombinant products, including human growth hormone and recombinant tissue plasminogen activator (TPA), each of which has found clinical application in addressing perceived public needs—needs that, on the surface, suggested no relation to manipulation of DNA.

The evolution of thrombolytic therapy using TPA presents a similar story. Undoubtedly, the presence in tissue of a protein that catalyzes conversion of plasminogen into plasmin was interesting when it was first observed in 1947, and so too was production of TPA by melanoma cells when it was first reported in 1980. Both discoveries were essential before TPA could even be considered as a potential therapeutic option for intervention in heart attacks, but neither was achieved as an immediate consequence of an existing research need. However, when the complementary DNA for TPA was cloned and expressed in bacteria in 1983, a scientific opportunity was created. The NHLBI focused attention on that opportunity by including TPA in phase I of the Thrombolysis in Myocardial Infarction trial. TPA was found to be so much more effective than streptokinase in establishing reperfusion in obstructed coronary arteries that the trial was concluded prematurely. Today, with TPA well established as an important therapeutic option for intervention in acute myocardial infarction, attention is now focused on how to ensure that thrombolytic therapy is administered as rapidly as possible. Toward that end, the NHLBI supported a randomized trial in Seattle that showed that thrombolytic therapy could be safely administered by emergency medical personnel.

Another clear example of the way in which pursuit of research opportunities has provided a basis for solving...
clinical problems is the saga of the treatment of homozygous familial hypercholesterolemia. This most recent success in genetic therapy had its origin in 1973, when Michael Brown and Joseph Goldstein began publishing their work on the cellular synthesis of cholesterol and cellular receptors for low-density lipoprotein (LDL) and their relation to serum cholesterol levels and atherosclerosis. This work, which won the Nobel Prize in 1985, offered great insight into the feedback regulation relation between the level of serum LDL and the cellular synthesis of cholesterol and uptake of LDL. The findings led not only to the liver transplantation therapy for homozygous familial hypercholesterolemia but also to improved agents for regulating serum cholesterol among individuals with seriously elevated circulating serum cholesterol, including those individuals with heterozygous familial hypercholesterolemia. The 1987 licensing of the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitor mevinolin for the treatment of hypercholesterolemia was a direct result of the Brown-Goldstein work.

These few examples underscore the importance of taking a long-term perspective when investing in research. Such a perspective necessarily includes nurturing succeeding generations of talented young scientists capable of sustaining the enterprise. In that regard, a recent study by the National Research Council may be cause for alarm. The study indicated that the number of young scientists—researchers under 36 years of age—seeking individual investigator grants from the NIH decreased 54% between 1985 and 1993. Although a number of possible explanations for this trend have been put forward, it is reasonable to assume that the difficulties of securing competitive funding for research have discouraged young people from setting their sights on a research career.

We sincerely hope that the scientific community will join us in an effort to reverse this unfortunate trend. We must send the message that there will always be room in the research enterprise for bright, well-trained, curious, enthusiastic, committed young people. We must serve as role models who illustrate the rich rewards that come from contributing to scientific knowledge and human welfare through research. We must take every opportunity to nurture the dreams of our young people and eliminate obstacles to their fulfillment.

Here at the NHLBI, we have struggled to achieve a balanced response to both publicly defined research needs and scientifically created opportunities and to build a program that will serve us well not only today, but also 5 years, 10 years, and 20 years from now.
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