The Constant Presence of Death

Edward Golub

Few of us trained in science or business are aware that this is the first century in which death is associated with old age. Until the present century, people lived in "the constant presence of death," with mean life expectancies of only 30 years. Through all of that time, infant mortality was 25%, childhood mortality was 25%, and less than 2 % of the population was 65 years or older. Most early death came from infectious diseases like smallpox, tuberculosis, and undefined "fevers" that were endemic, but many who escaped or survived these daily threats were swept away by epidemic scourges like plague and cholera. Life was, in the words of Thomas Hobbes, "nasty, brutish, and short."

Throughout this *longue durée*, the conception and the treatment of disease remained that of the Greeks (Hippocrates, 500 BC and Galen, 200 AD). Health was conceived of as the "humors" in proper balance, and disease was the result of these humors being put out of balance by changes in diet, climate, and especially the "miasmas" and "mephitic vapors" that came from the ever-present dirt, decay, and odors of preindustrial life.

During this long period, our perception of ourselves and our place in the cosmos changed drastically, the growth of representative democracy changed how our lives are governed, commerce and invention changed the way we work, and arts and literature changed the way we think. Yet nothing changed the things that matter most to all people; the health and physical well-being of their children and themselves.

Science changed all this toward the end of the last century, but contrary to what we have been taught by books like *Microbe Hunters* or press coverage of the latest medical "breakthroughs," the most important contribution of science was not the drugs of modern medicine. As I argue in *The Limits of Medicine: How Science Shapes Our Hope for the Cure*, the most stunning achievement of science was how it changed the way we think about disease. It was only when science brought specificity to medicine that cures based on treating the causes of disease could be conceived of. It was this change that allowed us to look for therapies like penicillin, insulin, and vaccines.

Thinking in "Penicillin Mode"

Louis Pasteur's germ theory of disease brought this change about. Using a combination of chemical and biological scientific reasoning, he was able to convince the scientific world that specific diseases have specific causes. But this change in concept was not immediately responsible for the elimination of the "constant presence of death." In fact, it was the building of sewers, water purification, better housing, and better working conditions that reduced infant and childhood mortality by lowering the incidence of infectious diseases. With industrialization, labor was as important as the machinery in the mills, but the mean life expectancy of the average factory worker was only 25 years. It was good business to extend the working lives of laborers by cleaning up the environment in which they lived. The first public health laws were passed in England in the 1840s, fully twenty years before disease specificity came to medicine through the germ theory.

But while sanitation and industrialization made it possible for fewer people to become infected, they could do little for those unfortunate enough to get sick. With the realization that infectious diseases have specific causes, science gave us a conceptual framework in which to seek specific therapies for specific diseases.

During this century, when for the first time we were able to cure infectious diseases with antibiotics and vaccines, it became axiomatic to seek specific, "magic bullet" cures. This "penicillin mode" of thinking has come to dominate our thoughts about disease in general. Because of the practical power of this way of thinking, it is difficult for us to keep in mind that disease specificity is a relatively recent intellectual invention and not the result of the long, steady march of scientific progress. It is even harder for us to recognize that the penicillin mode may not be transposable to all other types of illness.

The Changing Nature of Disease

As a result of sanitation, vaccination, and antibiotics, mean life expectancy in this century has gone from 35 to almost 80 years. By the middle of the next, more than 25% of the population will be older than 65 years. This phenomenal change in demographics has resulted in a change in the kinds of disease we face—our aging (and aged) population suffers and dies from chronic, not infectious, illnesses. Cholera and tuberculosis have been replaced by cardiovascular diseases, Alzheimer's, autoimmune disorders, and cancer. Many caregivers of the aged have come to believe that the indignities of the slow but steady loss of memory, sight, hearing, and mobility are even greater problems than those we usually identify as "medical."

But while there is little disagreement with this

Edward Golub is a consultant in concept-based science education at E.S. Golub Associates, Solano Beach, CA 92075. (e-mail: egolub@esga.com). He is the author of The Limits of Medicine: How Science Shapes Our Hope for the Cure, *1994, Times Books, New York, $23.00.*

assessment of the changing nature of disease and therefore of the new "unmet medical needs" of Western society, we have not yet changed our penicillin mode of thinking in our approach to them. There is a pervasive notion among scientists, the press, public, and the biotech industry that we are entering the era of "genetic medicine," and that the diagnoses and therapies of these chronic diseases will come from the explosive understanding of biology that genetics has made possible. I think this is a short-sighted view, because for the most part these new diseases do not fit the specificity paradigm and the penicillin mode of thinking. It is becoming increasingly clear that most chronic diseases may not have single, identifiable causes and that many may have pathology that is the result of complex cascades of reactions. This means there will almost certainly not be single, magic bullet cures for the vast majority of the diseases that will afflict increasing numbers of patients.

The reason we turned to genetics is obvious: The gene is the ultimate object of specificity. It is only natural that we make the assumption that the future understanding of disease and cure will be based on this specificity. But the great irony is that genetics is showing us that the era of the biology of specificity may rapidly be drawing to a close and that we are entering the era of the "biology of complexity."

The Biology of Complexity

We are already aware of how complex biological systems are from our experience of side effects, as seen with such commonly used therapeutics as the corticosteroids. But if there is any doubt, even single-gene defect diseases like cystic fibrosis (CF) are proving to be more complex than had originally been suspected. The CF gene is really a chloride channel gene, and at least 350 different mutations in the gene have been found that can be associated with some form of CF. Because the disease is a double recessive and requires two mutated forms, there is an enormous number of combinations of mutations possible in a patient. We are seeing that different combinations of these mutations have different effects, ranging from fatal lung or pancreas disease, to only mild asthmatic symptoms, to sterility because of a malformed epididymis.

This is only a glimpse of the kind of complexity we can expect when we turn to diseases such as juvenile onset diabetes, in which we know multiple genes are involved in both susceptibility and pathogenesis.

Perhaps the greatest insights into the complexity of gene interactions in health and disease are coming from studies with gene knockout mice that show that the functions of genes *in vivo* are far more complex than *in vitro* reductionist experiments are able to capture.

A few examples will suffice to make this point:

- The myf-5 gene was thought to be crucial in muscle development, and it was predicted that when the gene was knocked out the mice would die *in utero* because of improperly formed muscles. These gene knockouts had almost normal muscle development, but they had no ribs!
- TGFa knockouts were also shown to have normal development but they had wavy hair and curly whiskers.
- Beta-2 microglobulin knockout mice have no class I MHC proteins or CD8+ T cells as predicted, but they have almost normal immunity; IL-2 and IL-10 knockouts have almost normal immune function, but they have inflamed bowel disease.

These surprises are opening whole new vistas of *in vivo* function. Much complexity is due no doubt to redundancy in biological systems, but much of it may be due to the fact that there are "emergent" systems in which the two gene products interact to form products and initiate events that are not found in our *in vitro*, reductionist systems. The challenge of the biology of the 21st century will be to devise quasi-reductionist experiments that are able to explore this complexity.

When Sir James Black, Nobel Laureate in Physiology or Medicine in 1988 for the discovery of both beta- and H2-blockers, was asked to give his views on the future of science, he replied that it would be "the progressive triumph of physiology over molecular biology." The only way we will be able to understand the biology of complexity is by merging molecular and structural biology with physiology. But given the first glimpses we have had of this complexity, we are going to have to be as creative in advancing the new physiology as we have been in advancing molecular genetics and structural studies.

Complexity, Aging, and Medicine's Changing Goals

It seems clear that we are entering a period when we will be constantly altering our views of normal function as more and more of the complexity in normal systems and chronic disease becomes revealed. It is unlikely that there will be many magic bullets for chronic diseases, so we will have to alter our ideas about the goals of medicine and the therapeutics we develop.

A significant number of treatments may have to be low-tech therapeutics for alleviating discomfort without removing underlying causes, but there will certainly be a place for well-conceived therapies based on insights gained from high-tech science. However, we must not fall into the trap of assuming that we should always use the technology that allowed us to understand a condition to treat that condition. The value of understanding how something works is that it frees us to devise clever ways of manipulating it. Neither science nor the biotechnology industry should be judged by the sophistication of its technology; it is the delivery of usable information and products to medicine that society will judge us on.

When life expectancy was only 35 years, the goal of medicine was to extend life. But as life expectancy approaches 80 years, more and more of our technology will have to be aimed at maintaining normal function and extending health. This is both a scientific and an industrial challenge: How we meet it will determine the confidence the public has in academic science and the biotech and pharmaceutical industries in the crucial years ahead. ///