"The Beginning of Health Is to Know the Disease"

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SYNOPSIS

There is public impatience over the pace of medical progress. Some say prevention and health have not been well served by the research community. Rather than devising extended investigations, scientists should apply now what we know now. Activists argue that, although research on a better understanding of disease must continue, a companion effort to develop strategies for health promotion and disease prevention should exist. The national effort should emphasize "health" and not "disease," as the names of the various NIH Institutes would imply.

I disagree with that proposed direction of prevention research. It is not possible to divorce research on health from research on disease. Are the secrets of nature open to us through mere observation? Does not research require the perturbation of a system in order to make valid observations on the nature of that system? This, after all, is the nature of the scientific method.

Disease is, itself, a perturbation of the state of health and it is through our research on disease that we learn how to prevent it. I believe that the National Institutes of Health does devote equal time to the study of health. For it is my thesis that by studying disease we have, in fact, given our total time to the study of health. "The beginning of health is to know the disease."

THERE IS IMPATIENCE IN THE AIR these days over the pace of medical progress. Alarmed by the escalating costs of medical care, disappointed by stalemates in the wars on cancer, heart disease, and genital herpes, public officials as well as the medical profession are casting about for a source of new solutions to prevent disease and promote health. Some say that prevention and health have not been well served by the research community. A perception lingers that medical investigators are preoccupied with arcane busywork, and that those of us who manage the research enterprise recite the catechism of prevention but are closet scientists at heart—scientists who dwell in the dark and finger the molecular rosary of *E. coli*.

'It is not possible to divorce research on health from research on disease, as if the latter contributed in no way to the former. Quite the contrary.'

In the last several years the Public Health Service, including the National Institutes of Health (NIH), has issued several reports that address the issue of prevention. Desirable health goals for the year 1990, for example, are outlined in "Healthy People" (*1*). Another publication, "Promoting Health/Preventing Disease" (*2*), sets national objectives that include a lower infant mortality rate and increased immunization among the young.

Threaded through each of these reports is the notion that the time has come—indeed, the time is past due—to apply what we know now to prevent disease. "Healthy People" tells us, for example:

Within the practical grasp of most Americans are simple measures to enhance the prospects of good health:

- elimination of cigarette smoking;
- reduction of alcohol misuse;
- moderate dietary changes to reduce intake of excess calories, fat, salt and sugar;
- moderate exercise;
- periodic screening for major disorders such as high blood pressure and certain cancers; and
- adherence to speed laws and use of seat belts.

Widespread adoption of these practices, the publication says, could go far to improve the health of our citizens (*1*). One recent epidemiologic study suggests that modification of lifestyle in ways that take these measures into consideration can extend one's lifespan an average of 11 years, when compared with persons who did not follow these precautions.

Health Research or Disease Research?

Activists urge that research not be used as a substitute for getting something done, and they scold those who seek solutions to complex problems through extended investigations. Those articulate and vigorous spokesmen for the direct approach of preventing disease urge that, despite our current medical ignorance and inadequacies, we need to apply what we know now. Although research on a better understanding of disease must continue, they argue that it should be a companion effort to developing strategies for health promotion and disease prevention.

Others have gone even further, preparing legislative proposals. They propose a new institute for health preservation within the NIH. Some feel that although the title "NIH" implies a focus on health, the separate institutes emphasize diseases instead. There is, they feel, considerable merit in giving the concept of health and prevention equal time and visibility.

I agree with the importance of prevention. I know what prevention is all about. I am not just an armchair theorist, having been in the battle to prevent rheumatic fever. But I disagree with the proposed direction of that future prevention research. My disagreement arises from the emphasis on health research rather than on disease research. To my mind, this puts the cart before the horse. It is not possible to divorce research on health from research on disease, as if the latter contributed in no way to the former. Quite the contrary. I suspect the major way, perhaps the only way, to study health is to study disease. And so the title of these remarks, "The Beginning of Health Is to Know the Disease."

Some misunderstand the mission of the NIH, believing that the primary focus of the NIH is disease. That is not the case. Health *is* the mission of the NIH. And that is *why,* if my thesis is correct, we conduct research on disease. Through our research on disease we learn how to prevent it. We learn what health (the absence of disease) is and how to maintain it.

There are, then, two issues at hand: First, knowledge about health through research on disease; and second, the health mission of the NIH.

Let me ask this question: Could we define health if there were no disease? Or to put the biological question in broader and more theoretical terms: Can we study natural phenomena without perturbing the system? Are the secrets of nature open to us through mere observation? Does not research require the perturbation of a system in order to make observations on the nature of that system? This, after all, is the nature of the scientific method.

Disease, of course, is a perturbation of the state of health, and that is implied in the title of these remarks: "The Beginning of Health is to Know the Disease." This is not my phrase. It is borrowed from a passage in "Don Quixote" by Miguel Cervantes. But this phrase does express the essence of what I am trying to say.

The Lesson of Rocque Guinart's Labyrinth

Let me digress to give the background of this quotation. In his travels about Spain with his squire, Sancho Panza, Don Quixote lashed out at things he perceived as evil, performing chivalrous but often ridiculous acts; the old knight saw beauty in an otherwise ugly world. On the way to Barcelona, the two met a band of robbers led by the infamous Rocque Guinart, a kind of Spanish Robin Hood who becomes a foil for the more spiritual Don Quixote.

Guinart, like most men, wrestles with his evilness, describing himself as one who is, in truth, inclined to be merciful rather than stern. He is a symbol of man's struggle to overcome the stigma of original sin. Guinart has been plagued with more than his share of sins, one sin leading rapidly to another and another until, as he laments, "it's a bewildering labyrinth." He becomes ill and sick of heart in that labyrinth. Not a bad phrase, really, to describe illness as a labyrinth. "But there's hope," Don Quixote tells Guinart. Reminding the bandit that "the beginning of health is to know the disease," he explains how health can indeed be restored if one realizes he is ill and knows the source of the illness.

Cervantes' phrase "the beginning of health is to know the disease" is a condensate of my thesis: we can decipher the book of health through a lexicon of disease.

There are numerous examples to illustrate that research on disease is, in reality, research on health. Notable examples include research on those diseases

that have been called "experiments of nature." I have never been certain that nature performs experiments. I rather doubt it. I prefer to call such diseases "accidents of nature." I suspect nature is a benign force, and when misery occurs it is due to an accident and not to some deliberate manipulation.

The Lessons of Sir Archibald Garrod

Among the more important accidents of nature are metabolic errors. In 1902, Sir Archibald Garrod, an English physician, published the first of a series of papers on what he called rare maladies. With precise and clear logic he coined the phrase "inborn errors of metabolism." His work led to the view that a disease of this sort was due to the absence of a specific enzyme caused by an alternation of a controlling gene (*3*).

Garrod made a prediction which turned out to be correct. He predicted that "among the complex metabolic processes of which the human body is the seat, there is room for an almost countless variety of such metabolic sports." Such diseases, or metabolic sports as Garrod called them, are now commonplace and come in every shape and size, so to speak. A lengthy list of these illnesses in the latest edition of the "Cecil Textbook of Medicine" covers two tightly printed pages.

Subsequent work has fully substantiated Garrod's belief that a disease of this sort is caused by a block in a metabolic pathway occurring because of an inherited deficiency of a specific enzyme. But there is another aspect of Garrod's work that bears on my thesis. Through research on these accidents of nature, Garrod came to important conclusions concerning the normal physiological processes of the healthy state.

Garrod's research cleared out a vast amount of confusion in the genetic underbrush, and he arrived at a sweeping concept concerning the normal genetic events that govern the destiny of all living things. For example, the one gene, one enzyme hypothesis had its roots in his observations, and this happened long before the notion was proposed by George Beadle and Edward Tatum as a consequence of their experimental work on *Neurospora.* Thus from Garrod's work on disease, we learned a fundamental and underlying principle of genetics. Indeed, "the beginning of health is to know the disease."

Another group of diseases whose study has paved a high road to health are those caused by vitamin deficiency. I suspect we would still be in the dark about the nutritional requirements for niacin and vitamins C and D if it were not for the occurrence of pellagra, scurvy, and rickets. Nearly lost to memory is the monumental research that identified the dietary defects that cause these diseases. Surely they were living experiments and, through them, we came to understand the role of vitamins in normal metabolism. "The beginning of health is to know the disease."

All of this talk about acquiring knowledge of health through research on disease must seem a commonplace; self-evident because it is so obviously central to the nature of scientific investigation. Previously I put the scientific question more broadly: Can we study natural phenomena without perturbing the system under observation? Does not the scientific method require this perturbation before we can draw conclusions about the system?

The Uses of Perturbation in Research

We are so familiar with this experimental approach that it becomes subconscious habit in the laboratory. The procedure is to control all the known variables and begin a series of experiments, altering each variable one by one: raise the temperature, lower the temperature, raise the pH, lower the pH, add an enzyme, or add an enzyme inhibitor. When we run out of imagination, we throw in a pinch of cyclic AMP (adenosine monophosphate)! After all such pertubations of the experimental system have been performed, knowledge of the processes of the healthy state emerges; the Krebs cycle, for example, or DNA replication, or transcription, translation, or protein synthesis.

Some may feel I have been too sweeping in my generalizations about the nature of scientific inquiry. Surely, there is still a case for observing the affairs of nature in the normal state, even in the health sciences. Can we not just observe healthy people, or at least people who seem healthy, and arrive at scientific conclusions? A fair proposal. Indeed, in the past, the research of the naturalist or the astronomer rested in large part on observations that do not perturb the system under investigation.

Darwin's monumental and sweeping conclusions concerning evolution, for example, were based on detailed observations of the living world around us. And for the most part, a healthy world is what he scrutinized. Darwin reached his revolutionary conclusions without perturbing the system. No natural process was deliberately altered to gain information. The same might be said of Galileo. His heretical notions concerning the movement of the heavenly

bodies were drawn from his passive observations of the universe, distilled through the logic of his powerful mind and fertile imagination.

But certainly in biology and medicine—I am unequipped to speak for physics—there are limits to the effectiveness of this passive approach to experimental observations. No matter how hard 19th century naturalists tried, they could not decipher the biological processes that engineered evolutionary events. Only the experiments of Mendel, and all that has followed in these decades of molecular biology, have allowed us to comprehend the genetic events that bring about the alterations of a species. In a sense, of course, these mutations are diseases. And yet from such genetic alterations, we have deciphered the forces that drive the evolutionary progression. "The beginning of health is to know the disease."

Misunderstanding NIH's Mission

The second issue about which I believe there exists a misunderstanding concerns the mission of the NIH and a need for equal time and visibility for health and prevention research—implied, of course, is equal time to that devoted to the study of disease. It is my thesis that by studying disease we have, in fact, given our total time to the study of health.

We at the NIH are deeply committed to the prevention of disease. Indeed the mission statement of the NIH stresses both health and prevention of disease as major goals and objectives. "The mission of NIH is to improve the health of the nation by increasing our understanding of the processes underlying human health and by acquiring new knowledge to help prevent, detect, diagnose, and treat disease."

In the National Institute of Allergy and Infectious Diseases a specific prevention effort is the accelerated development of new vaccines. Nothing could be more timely. The biological revolution on our doorstep is offering new opportunities to develop those vaccines through the use of monoclonal antibodies, recombinant DNA technology, and sophisticated synthetic biochemical techniques. Viruses are being altered in previously inconceivable ways to convert them into more potent vaccines. Isolated antigens are being extracted and purified by new and novel biochemical methods; greater refinements include the chemical synthesis of the peptide determinants of microbial antigens and stitching such synthetic compounds onto carrier molecules. Our increasing understanding of the immune system and the role of adjuvants offers a new opportunity and a new day for the development of vaccines.

In the public dialog on prevention and prevention research:

- There will be general agreement that research on vaccines is prevention research;
- There will be general agreement that prevention research includes the identification of risk factors that may predispose a person to heart disease and cancer, for example;
- And there will be general agreement that health promotion research includes efforts to determine the effect of changes in lifestyle to diminish those risk factors and behavior patterns that adversely influence health.

But is that all there is to prevention research? I believe not and I believe that, on this subject, we need much more public debate.

If my thesis is correct—that the beginning of health is to know the disease—then the knowledge about disease generated by the NIH is germane to disease prevention. It is not enough to approach disease prevention or health promotion in a way that avoids the study of disease. Although there are instances where the disease can be prevented before the etiology is totally understood, we are barred from erecting barriers of prevention for most of the diseases that still plague us because of our ignorance of their etiology and pathogenesis. Great strides have been made in the biomedical sciences, and yet our ignorance remains so broad that, for many illnesses, we could not begin to guess what the possible risk factors may be or which health promotion approaches might be reasonable.

Who has any clear idea how to prevent rheumatoid arthritis, lupus erythematosus, diabetes, pemphigus, psoriasis, acne, amyotrophic lateral sclerosis, multiple sclerosis, cystic fibrosis, Alzheimer's disease, asthma, allergies, or the common cold for that matter? And I haven't even mentioned heart disease and cancer or the tropical diseases that still elude us. And now we have acquired immune deficiency syndrome (AIDS)—a new disease, it would appear, although that is still an uncertain conclusion. There is no other way out of the labyrinth. "The beginning of health is to know the disease."

Need for Public Debate on Research Policy

I said earlier that we need more public debate on these issues: debate about the strategies and policies that influence biomedical research, including research on prevention and health promotion. On these

matters, I would like to quote the remarks of Dr. Joshua Lederberg, president of the Rockefeller University. From his 1982 report to the university (*4*):

. . . we must recognize that outside forces often demand short-term yields that are simply unachievable: least of all by insistence on "targeted" research. The NIH budget is, in fact, the largest federal commitment to basic [health] science: a preponderance that is socially justified by benefits to public health that derive from the most fundamental knowledge of living systems. This is not a universally recognized linkage. For one thing, the partial successes of semi-empirical medicine with vaccines, antibiotics, and psychotropic medications have obscured how incredibly crude our insight is about how and why these interventions work—how far medical scientists are from the kind of understanding that unites the physicist and the integrated-circuit design engineer. It is not lack of ingenuity or diligence; it is the inherent complexity of living organisms—above all the human—that frustrates our moving medical care and preventive health into the realm of design engineering. To meet such an ambitious goal entails still more basic research, on a scale that would remain a small percentage of expenditures on health care. Despite many isolated improvements, the overall limits to our success in dealing with cancer, even during the last decade, illustrate the shortfall in our needs for basic biomedical knowledge.

In any event, there remains a needless and damaging alienation between the adherents of this view and those who seek to accelerate application of the advances we have made. The alienation arises, in part, from the understandable anxiety of basic scientists about the seeming social ambivalence regarding the support of their efforts. . . .

Equally unfortunate is the quarrel between some advocates of public policies for preventive health and of rational medicine. There is no controversy that disease-prevention is vastly preferable to the most sophisticated of cures. It is also true that important improvement to personal health is achievable by commonsense attention to lifestyle (e.g., diet, smoking, use of alcohol and other drugs, exercise, and sleep). While we have long since set aside prohibition as an answer to alcohol abuse, there remains a widely held attitude that disease is the penalty of sinful life. The fact remains that many heart-disease victims are not obviously stigmatized by their lifestyle, and that the health penalties of aging will be with us regardless of personal hygiene.

Lederberg continues, saying this about areas of research that some basic scientists either misunderstand or view as controversial (*4*):

The delineation of the most important and useful elements of personal behavior and of environmental protection is a cogent challenge to the most sophisticated biomedical research. So also are the factors that entrain people into behaviors they well know to be self-destructive. [italics added]

Lederberg has spoken of an alienation between those who hold views at the opposite ends of the health research spectrum. But just as the colors of the visual spectrum merge at the margins, so do these differences of opinion. Surely, it should be possible to end the alienation between these opposite views on health research and arrive at a common ground. This outcome will require debate on the policy issues. It will require debate on the nature and scope of health research supported by the National Institutes of Health. There is no other way out of the labyrinth.

A year ago I concluded a talk on public policy in preventive medicine with the following remarks. It seems appropriate to repeat them (*5*).

Intense demands will be placed on the health dollar in the 1980's and well-planned research strategies are needed to control medical costs through prevention of disease and promotion of health. At the same time, we cannot neglect vigorous research that will allow broader and more effective prevention and treatment in the future. We are making withdrawals from the bank of past discoveries. To prevent liquidation of these assets, we must replenish our research reserves. There is no other fiduciary. There is no other way to insure the prosperity of the future. Prevention for the future is too serious a matter to be left to the guesswork of the past.

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