SPECIAL REPORT

Contributions of Basic Research to Clinical Medicine*

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Whether we like it or not, all aspects of medicine are now being reexamined critically: the practice of medicine—because of the uncertain and unequal delivery of health care, and because of the tremendous increase in its cost; medical education—because some believe that medical schools are not producing enough doctors and are taking too long to train them, that newly-graduated physicians are academically oriented rather than practice oriented, and that medical students learn too much of medical science and not enough of medical art; medical research—because some think it occupies the time of physicians who otherwise would be in practice and because some believe that too much research is basic and undirected and too little is applied and directed.

I repeat, whether we like it or not, our activities, patterns and productivity are being reexamined—often by laymen, and recommendations for change are being made, also often by laymen.

Whether I like it or not, some medical students, some foundations, and some members of government have made specific suggestions for changes in medical research. Therefore, it is high time for physicians and medical scientists to look objectively at the present system to see how well it functions.

We all know that funds for medical research are shrinking. Let's look at some of the reasons:

The first restriction on support of medical research was budgetary, resulting from the costs of war in Vietnam and of Medicare at home. Even though the decrease in support of research was small in terms of dollars, the decrease came when costs of research were soaring by 10 to 15 percent a year so that $10,000 a year awarded in 1966 for five years will, in its fifth year (1971), buy $6,600 of research, only 66 percent of what it bought in 1966; and as the costs of Medicare go up and the government keeps its total budget for health the same, the dollars for research may be cut more and more.

The second restriction was a different one, a restriction on support of basic research. It seemed to begin with a conference in Oklahoma City in 1966 entitled: "Research in Service of Man." The title itself is unpleasant, in that it suggests that a significant amount of medical research is not in the service of man. The conference popularized a new set of terms: directed research, goal-directed research, targeted research, applied research, planned research, developmental research, mission-oriented research, strategy for the cure of disease, the payoff, payoff research.

The conference led to a new way of looking at medical research. The new way is essentially: "Most everything we need to know for the prevention and cure of disease is now known (as a result of handsome support of research for 20 years); all we must do now is apply it." As a result, many Institutes of the National Institutes of Health have shifted their programs to favor the support of clinical research and of training for clinical practice.

This led to the third restriction on support of basic research—the use of contracts instead of grants. When these contracts go to industry (instead of to universities and hospitals) two things happen: (1) the cost of research goes up (universities make no profit from their work and university salaries are usually lower than those in industry); and (2) since the government's total dollars for

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health stay the same, the number of dollars left over to support research in universities (and the educational process that is an inseparable part of research) goes down.

What I want to discuss is: Do we need basic science in the 1970's or 1980's? How much? Why?

There are several ways of examining the importance of basic research to medicine. First, we can start with a dramatic and highly publicized event in medicine and look backwards to see what had to precede it to bring it off. The most dramatic event of the century in medicine was transplantation of the human heart. The newspaper accounts and the television interviews dealt with the surgical procedures in the operating room, but the complete story should account for every step and procedure from the time that patient entered the hospital until he left; it should tell us what made each step and each procedure possible.

First came the diagnosis of heart disease in the patient and the evaluation of its severity. These involved the use of the stethoscope, the electrocardiogram, cardiac catheterization, x-rays and angiography and pulmonary function tests to determine if there was severe and irreversible damage to the lungs. Does Congress—do you—know how each of these diagnostic tests or instruments came into being? Was Roentgen, in discovering x-rays, looking for a way to study the heart? Was Einthoven, in discovering the string galvanometer, searching for a way to diagnose arrhythmias? Was Werner Forsmann, in performing the first cardiac catheterization, looking for a way to measure left ventricular end-diastolic pressure?

After diagnosis came the decision to perform transplantation. But this required, first of all, knowing that transplantation was technically possible as an acute surgical procedure in animals. It also involved knowing that the animal with a new heart (with no nerves connecting it to the brain) could live a reasonably normal life, that such an animal could regulate its cardiac output in relation to the needs of its body. So the basic studies on autoregulation of the heart that were done by Starling, and led to Starling's law of the heart, had to precede transplantation.

Long-term survival of the heart also required development of the science of immunology and knowledge of rejection by the body of foreign tissue. It required the technique of cross-matching of blood and tissue cells. It involved the development and use of immunosuppressive drugs.

Who was responsible for each advance in knowledge? How much was discovered largely by a mission-oriented scientist charged with the solution of a specific problem? How much by someone trying to understand how the body (or even the universe) works?

After the diagnosis and the decision to operate came the operation itself. This involved anesthesia. Now we must ask: How was anesthesia discovered? How was the particular anesthetic used in this operation discovered? After anesthesia came the operation. Who discovered aspergillus? Who discovered bacteria? Who discovered antibiotics? Since the thorax must be opened, we must inquire who discovered positive pressure ventilation?

Cardiopulmonary bypass was a necessity. Who developed it? Who helped him? Cardiopulmonary bypass required heparin. How was it discovered? Who invented polyethylene tubing? For what purpose? A transfusion was needed. Who discovered blood groups? Why? Who learned how to preserve blood? Where did we learn about the transmission of viral hepatitis, and how to prevent it?

Postoperatively, the cardiologist had to prevent or correct arrhythmias. What discovery gave us antiarrhythmic drugs? What led to the use of defibrillation? The artificial pacemaker? As a matter of fact, who discovered the natural pacemaker and the atrioventricular conduction system?

Such an analysis has not been done, but should be. It would be a study of the origins of a tremendous body of knowledge that had to precede a single therapeutic procedure to make it possible. Could it have been done on schedule by contracts?

A second way of looking at the role of basic science in the progress of clinical medicine is to look at each person involved in important advances. Since you are chest physicians, let us look at several men whose work led to the treatment of tuberculosis with streptomycin.

To the casual observer, a chest physician at the Mayo Clinic, H. Corwin Hinshaw, injected streptomycin into guinea pigs with tuberculosis, cured them, and then went on to cure patients with tuberculosis. The story sounds almost like William Withering's discovery of digitalis. But a little search shows that Hinshaw was a basic scientist before he became a physician. He received his A.B. in Idaho in 1923, his M.A. at the University of California in 1926 and his Ph.D. at the University of California in 1927. He then became Assistant Professor of Zoology at the University of California for a year. In 1928 he went to the University of Pennsylvania in the dual role of Instructor in Bacteriology and medical student. After receiving his M.D. there in 1933 he went to the Mayo Clinic, where he established a close relationship with another basic scientist, William Feldman, in the Pathology Department.
Hinshaw knew the meaning of the scientific method. He knew how to do painstaking and convincing experimental work. He knew how to develop a model (the guinea pig with experimental tuberculosis) for testing antituberculosis drugs. He knew how to use this model to get precise, quantitative data. When sulfapyridine came along, he was ready to test it. When promin came along, he was better able to test it. When streptomycin came along, he was even better able to test it. His experience and background permitted him to start and finish studies in animals and to start clinical investigation—all in a 12-month period.

Let's look at another man involved—Selman Waksman, Professor of Soil Biology in the Agricultural School at the Rutgers University. The mission of this school was primarily to improve agriculture, not to improve human health. Waksman was a student of microorganisms in soil. He noted that although countless billions of pathogenic organisms (including tubercle bacilli) were dumped into soil each year, no one could recover them by culturing the soil. The basic question was, "Where do they go?" Does something in soil destroy them? If so, is the something another organism? A specific soil organism?

In 1939 he began an intensive search into the mechanisms by which organisms in soil destroy each other. He isolated thousands of different bacteria from soil and isolated chemical substances from some of these. In 1943 he rediscovered Streptomycetes griseus and from it, he isolated a chemical substance, streptomycin.

This one story, the story of streptomycin, shows the complex nature of discovery and application. These may require the interaction of undirected basic research (in this case, the study of soil organisms), directed basic research (here, the study of experimental disease in animals), goal-directed applied research (here, the cure of tuberculosis in man) and goal-directed cooperative applied research (large-scale cooperative clinical studies in the United States and Great Britain led to the rapid evaluation of streptomycin in thousands of patients with a variety of infections).

The story of streptomycin also shows the "payoff" that occurred when a basic scientist, a clinical investigator and a physician were combined in one man (Hinshaw) and raises the question whether we need more or fewer physicians with a background in research. I agree fully that physicians should be compassionate and socially aware, but compassion and social awareness (without science) would not have cured tuberculosis.

In inquiring how much research should be undirected and how much should be aimed at specific disease targets, we must also look at the lag between basic discovery and clinical application and ask whether more directed applied research would lead to earlier application.

As an example, let us consider poliomyelitis vaccine. Viruses were discovered in 1881 (Pasteur). The virus of poliomyelitis was discovered in 1909 (Landsteiner). Poliomyelitis virus was successfully inactivated in 1953 and Salk vaccine was used first in 1955. Seventy-four years elapsed between the discovery of viruses and the use of polio vaccine. Why? Research in the United States (and elsewhere) was poorly supported until 1946 and very few men could afford a career in research, or even a year in research. Poliomyelitis vaccine was delayed 65 years largely because the science base was totally inadequate. So the question really is, What occurred in the last nine years—from 1946 to 1955? James Shannon determined what bodies of information had to be accumulated before anyone could develop the vaccine. The first requirement was a detailed study of the poliomyelitis virus. The second was knowledge of three antigenic types of poliomyelitis virus that led to paralytic poliomyelitis in monkeys. The third was a practical method of tissue culture; this was developed by Earle in 1949 for the study of cancer cells and was immediately transferred by Enders to the culture of polio virus. The fourth was a method for inactivating or attenuating the virus.

All of this, including application to man, was achieved in nine years. Why? Shannon believes that this achievement was, in large part, because the National Foundation for Poliomyelitis in 1946 decided on saturation support for the science of virology in general, with the hope that new knowledge would also apply to poliomyelitis virus. It did; it paid off in a big way. We will never know whether the same support granted only to scientists who worked only with poliomyelitis would have hastened or delayed the final answer.

Saturation or crash programs have great appeal for the people and for Congress. But there is a good time and a bad time for crash programs. Lots of money, buying lots of talent, at the right moment and for the right project, can greatly shorten the lag. Lots of money, at the wrong time, can waste lots of money, time and talent. Shannon points out that in 1953 the same National Foundation put all its money on a specific development project—the development of the Salk inactivated vaccine. Unfortunately, this goal-directed decision was made before all the basic research was done and it delayed by several years the testing and widespread use of...
Sabin’s attenuated polio vaccine. The decision to go all out for a specific crash program can be right or wrong. This 1946 decision (in retrospect) was right. The 1953 decision (in retrospect) was wrong.

We need to learn more about the chances of success with mission-oriented research. Perhaps we can learn from the drug industry how many chemicals must be studied over how many years at the cost of how many millions of dollars before a goal of a specific drug is reached—and how many of these drugs represent a major advance rather than a minor modification. We need to learn how to shorten even more the lag between basic discovery and clinical application. Maybe we should insist that basic scientists provide us not only with new data but also with speculation (labeled as such) on the possible uses of new knowledge; we should then see to it that the speculation reaches clinical investigators promptly.

Another way of examining the need for basic research has nothing to do with what has already been discovered, who discovered it and why; it is to identify and emphasize our areas of ignorance, how much we don’t know, how much there is to learn. This would tell us quickly whether we, as some believe, know all we need to know, whether we are simply not applying what we know. Let us look at a few areas of ignorance:

... We know how to recognize aging, but not how to prevent it.

... We can diagnose early or late cancer, but we do not know the basic mechanisms by which a cancer cell escapes from orderly regulation by the body.

... We know that 40,000 newborn babies die each year from respiratory distress syndrome. We don’t know what causes it or how to prevent it.

... We can, by use of modern physiologic diagnostic tests, detect emphysema in its earliest states. We do not know how to halt its progress to disability and death.

... We believe that there is some relationship between fats and atherosclerosis and between diabetes and atherosclerosis. We don’t know what to do about it.

... We know that peripheral nerves regenerate, but that spinal cord and brain do not. We don’t know why.

... We know nothing about the basic processes of learning, memory or reasoning, or about the greatest killers of all—prejudice, fear and hate.

In all of these areas of ignorance, there is little basic knowledge and there is little to apply.

In conclusion, it is time to reexamine the nature of discovery and then to determine the proper mix of completely undirected basic research, mission-oriented basic research, mission-oriented applied research and large-scale crash programs and to see that each receives the support it needs on a proper time scale. Important recommendations for change in magnitude and pattern may well result from such a reexamination, but until national goals and national priorities in medicine are defined and a careful study of the nature of discovery in medical research is completed, it seems prudent to maintain the present system in good health. Let us not put ourselves in the position of the militant students who want to destroy universities without having something better to offer.

REFERENCES
