Experimental Procedure

Hemoglobin S solution was purified as described elsewhere (*11*). A 2-percent solution was deoxygenated in a 50-milliliter round-bottomed flask with a cuvette attached at the bottom, similar to the flask described by Smith (*23*). The solution was alternately deoxygenated under reduced pressure (by an aspirator) and refilled with carbon dioxide (gas from Dry Ice placed in a stoppered suction flask) to pressure of 1 atmosphere. A recording spectrophotometer (Cary model 14) was used to determine the degree of deoxygenation. When completely deoxygenated, the contents of the flask exhibited a flow birefringence. The preparation of electron-microscopic grids was carried out inside a dry box with blocks of Dry Ice placed in it to maintain an anaerobic and anhydrous atmosphere. A small drop of Hb S solution (10^{-2} percent) was placed on each carbon-coated grid and then frozen, on a block of brass pre-cooled on Dry Ice; then the brass block, with grids, was placed in a desiccator and dried from the frozen state under reduced pressure.

Some of the grids were stained with potassium phosphotungstate (*p*H 7.2) for negative contrast or stained positively with uranyl acetate (2 percent), and some were shadowed by platinum vapor by means of a conventional technique. The grids were examined under an electron microscope (RCA EMU-3G).

In ten purified specimens of Hb S, each from a different donor, very small tubules were found in all instances. Micrographs yielding many details of the "microtubules" were obtained in certain uranyl acetate preparations where the supporting film had ruptured. In such preparations the electron beam was focused on an area adjacent to the small tubule under study, then the tubule was quickly moved into the field for photography.

For calibration, Indanthrene Olive TWP crystals (*24*) with molecular spacing of 24.9 angstroms, as determined by x-ray diffraction, were used.

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NEWS AND COMMENT

NIH: Demand Increases For Applications of Research

At the White House on 15 June, President Johnson discussed Medicare with influential medical and hospital leaders in a meeting that combined elements of a progress report and a pep rally. The President has taken a personal, almost paternal, interest in Medicare, and he and other federal officials were concerned over the possibility that a sizable number of hospitals in the South might be barred from participating in Medicare by failure to comply with civil rights legislation which applies to the program.

The meeting and the President's appeal for unstinting support were not surprising. What was unexpected was the President's announcement—obviously not an offhand remark—that he was calling a meeting of top officials in the health and medical research hierarchy of the administration to reason together on ways in which the results of federally supported biomedical research can be applied more widely, rapidly, and effectively.

These remarks received little notice in the press at the time, but they generated shock waves in the upper reaches of the federal health and medical research establishment.

Mentioned specifically by the President was the National Institutes of Health. NIH in Bethesda has a billion-plus annual budget, administers the largest complex of laboratories and clinics involved in health research in the world, and through its extramural programs now finances about 40 percent of national expenditure on biomedical research.

In his statement at the meeting the President made it clear that he expects NIH to do more applied or developmental research. What the President was driving at is clear in the following excerpt from the text of his remarks, released by the White House.

I am calling, very shortly, a meeting (I want to serve notice on Secretary Gardner publicly because I don't want to give him a chance to object privately) of the Director of the National Institutes of Health and the directors of the nine individual institutes as well as the Surgeon General of the Public Health Service. I

am asking them to come here to meet with me for the purpose of hearing what plans, if any, they have for reducing deaths and disabilities and for extending research in that direction. If we can hold such a meeting and follow it up with having meetings with other experts in the 50 States in these particular fields, then come back and meet three months later, we will be able to see what we can do.

We will go down their check list to see what specific efforts can be made to reduce deaths among the leading killers, especially arteriosclerosis of the heart and brain, and various forms of cancer—and to reduce disabilities such as arthritis and neurological diseases or illness.

Only since 1945 has death from tuberculosis ceased to be considered the will of God. Only since the early 50's and the development of the Salk vaccine has polio no longer struck terror in the heart of every mother, every parent, in this country.

A great deal of basic research has been done. I have been participating in the appropriations for years in this field. But I think the time has now come to zero in on the targets by trying to get our knowledge fully applied. There are hundreds of millions of dollars spent on laboratory research that may be made useful to human beings if large-scale trials on patients are initiated in programming areas. Now Presidents, in my judgment, need to show more interest in what the specific results of medical research are during their lifetime and during their administration. I am going to show an interest in the results.

I hope that meeting with the head of the NIH and the individual institute directors might energize—or make a contribution to, I guess, is a better way to put it —plans for specific results. That is, specific results in the decline in deaths and disabilities.

At present, a very small percentage of research money is spent on clinical research to necessitate new drugs and treatments on human beings. Until we do this, we won't have many new ways to reduce deaths and disabilities. But after I have heard plans which may not be specific today, I will then ask these men to return to give me more concrete proposals and recommendations that they have received from you and from their own knowledge. I would hope that for whatever time I have in the White House, about every six months we could come back and see what progress we were making. Because these men are now responsible for over a billion dollars of research and training money. I want them to be sure that they have the best defined programs and goals in this country.

To do what? To prolong the prime of life for all of our people. If we can hold two or three such meetings, I feel that with the deep sympathy, interest and leadership of the President, we will be able to get more results for the survival of our people than anyone else has ever done in the history of mankind.

The meeting with NIH officials alluded to by the President took place on 27 June. It did not result in the conversion of NIH into an agency for applied research and development. The meeting ran overtime, and there is little doubt that the President now knows more about what NIH is doing and what it thinks it can and should do in the future. On the other hand, NIH knows that the President is watching, and this will have its effect.

The act of calling in division-level officials as well as the top brass from the Department of Health, Education, and Welfare, the Public Health Service, and NIH was not out of character for the President. He has a voracious appetite for information, a prodigious memory and a long experience of dealing with the bureaucracy. And above all he likes to get results. What was unusual was that he clearly hadn't discussed the idea with HEW Secretary John Gardner.

This is especially odd because of the high value Johnson places on Gardner's work and the personal regard he has for the HEW secretary. Those familiar with health research politics, therefore, assume that impetus for the Presidential parenthesis came from outside the government.

There is precedent enough for this surmise because of the way in which policymaking in biomedical research differs from the making of science pol-

Excerpts from Ruina Report

The committee concludes that the most crucial single problem to be faced at NIH is the *scarcity of individuals in the biomedical area with the technical background, experience, and temperament needed to assume the responsibilities of program management.*

Correction of this managerial deficiency is so obviously the key issue in the future of directed biomedical research or development that it has overshadowed the committee's attempts to evaluate present or potential capabilities at NIH in other aspects of directed research programs.

The history of the cancer chemotherapy program at NCI illustrates repeatedly the fact that the managerial expertise required for successful direction of large-scale biomedical development is entirely different from that required for effective administration of the project grant apparatus.

Other Federal agencies which have entered into large programs of directed research or development (DOD, AEC, NASA) have experienced initial and continuing difficulties in obtaining adequate program managers. The absence at the present time of a sizeable pool of managerial talent outside of Government is not a problem unique to the biomedical field; and the inability of NIH to compete financially for the services of the few individuals who possess relevant managerial experience is not a handicap unique to NIH within the Government.

However, for NIH to meet the demands for managerial manpower now and in the future will be doubly difficult.

The difficulty arises, first, from the extreme reluctance of biomedical scientists to engage in administration or management of any type, much less the management of directed research on a full-time basis. Traditionally, the biomedical scientist has regarded his proper role in Government as that of advisor rather than responsible manager, and this tradition will not be altered easily. This concept of professionalism, a readiness to advise rather than to participate directly, assigns appreciably less importance to the managerial role, particularly when performed in the Government, than to academic research or private practice. The biomedical administrator or manager, at present, lacks status in the eyes of his peers.

Secondly, it is apparent to the committee that many excellent biomedical scientists, thoroughly familiar with the Study Section-Advisory Council mechanism for project grants, and completely oriented by the sense of participation of the extramural biomedical community in all aspects of the programs of the National Institutes of Health, have thus far failed to grasp the significant difference between the project grant and a contract program of directed research. Consequently, the feeling is widespread among university scientists that they can "help out" with contract programs and assure their success simply by offering advice of the sort that has sufficed in the project grant area.

icy in general. Where research in the physical and life sciences is concerned, the National Aeronautics and Space Administration, the Atomic Energy Commission, the Department of Defense, and the National Science Foundation adhere to a common pattern. General objectives and specific research projects are approved through machinery operated essentially by agency administrators working with advisers who are, for the most part, university scientists in appropriate fields (subject of course to the provision of funds by Congress).

Third Force

In the biomedical sciences a similar apparatus exists, but in addition to federal administrators and academic or industrial advisers a third force exists —the representatives of foundations, voluntary organizations, and influential private citizens interested in health problems.

Perhaps most effective in this group is Mrs. Mary Lasker, who, although she shuns personal publicity, is also probably the best known to those familiar with the development of federal biomedical research policy in the years of rapid expansion.

Mrs. Lasker is president of the Albert and Mary Lasker Foundation, which is dedicated to medical research with special emphasis on research and treatment of heart disease, cancer, and mental illness. She is a close family friend of the President and Mrs. Johnson, actively sharing, for example, Mrs. Johnson's interest in city beautification.

Mrs. Lasker also has an acute understanding of the political process as it affects medical research, and she is on excellent terms with Representative John Fogarty (D–R.I.) and Senator Lister Hill (D–Ala.), chairmen of the House and Senate appropriations subcommittees which have nurtured NIH to its present flourishing state. Her interests have made her allies in the medical profession, notably among eminent practitioners and clinical researchers, and a number of these men have given effective testimony over the years to the Hill and Fogarty subcommittees.

In general, she is recognized as having made a solid contribution to the growth of support of medical research in recent years. At the same time Mrs. Lasker and her allies are regarded by some biomedical researchers and administrators as representing the "layman's viewpoint" in expecting the rapid translation of research results into effective new medical treatment on a broad front. The discovery of antibiotics and of "cures" for tuberculosis and polio have created expectations of dramatic advances which cannot be achieved in some fields, say these critics, and voluntary organizations have sometimes overencouraged these expectations.

On the other hand, the layman does have a more intimate personal interest in a cure for cancer than he has in an advance in high-energy physics or polymer chemistry, and it is not surprising that the President himself, at least in his remarks of 15 June, was expressing the layman's view. The point is that scientific advice to the President has an added dimension in biomedical research.

There is here a real dilemma for NIH, which the President only partly expressed. The image of NIH has increasingly become that of a basic-research-supporting agency. To many biomedical research investigators, nothing could be finer. But the dangers could be considerable for NIH, which by law is responsible not only for basic research but also for the application of results. The conflict between the scientist's and the layman's viewpoints was well stated by Surgeon General William H. Stewart in April in a speech, titled "Research and Public Responsibility," in which he mentioned the lag of medicine in following research.

> How fast will medicine follow? Hopefully, it will follow faster than it is following today. The truth of the matter is that research is shaping the *best* of present-day medicine while leaving a good deal of the rest of it farther and farther behind. This is not, strictly speaking, a research problem. But it is a serious problem for the administrator of an enterprise whose interests involve both research and the application of its results.
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> Stated in slightly different terms, however, it becomes a problem for the scientist as well. To what extent is "the future of medicine" the concern of the researcher in biomedical science? Is the future of medicine the primary reason for his professional being? A secondary reason? Or should he be totally involved in the search for knowledge, with no strings attached and no holds barred?
>
> Most scientists would tend to give an affirmative answer to the last of these questions. So far as inner motivation is concerned, they are seekers after truth.
>
> On the other hand, most of the people who directly or indirectly furnish support to the biomedical scientist would be inclined to say that "the future of medicine" is what they are paying for.

NIH's history and organization make any rapid and major shifts of priorities to programs that are centrally planned. The NIH extramural program, which consists principally of research grants to individual investigators and construction funds to educational institutions, has grown at a much more rapid rate than the intramural program. The ratio now is roughly 10 to 1. Award of grants to individual investigators hinges on recommendations by study sections made up of expert advisers from outside government, who judge applications on merit. The NIH grant system came under fire in the early 1960's by Representative L. H. Fountain (D–N.C.), who criticized the agency for weaknesses in grant administration, and stiffer accounting procedures were instituted. The grant system itself, however, has generally found favor, as it did with the committee headed by physicist-industrialist Dean E. Wooldridge, which took an extensive look at NIH operations (*Science*, 25 March 1965).

The work done on research grants has been a chief glory of NIH. But since the interests of individual investigators determine what applications are submitted and the professional premium has been on "pure" research, NIH has had problems in fostering a balanced research program, and developmental work has suffered stepchild status.

As a consequence, major collaborative or developmental programs have had to be initiated and managed by NIH itself. Of these the cancer chemotherapy program is the biggest and the best known.

Research by Contract

Management of these large-scale programs of directed research has proved to be the Achilles heel of NIH. This aspect of NIH operations was the special focus of a study by a committee headed by Jack P. Ruina, who is returning to M.I.T. after a stint in Washington, most recently as president of the Institute for Defense Analyses. Like the Wooldridge Committee, the Ruina group found NIH generally admirable, but in its *Report of the Secretary's Advisory Committee on the Management of NIH Research Contracts and Grants** it severely criticized the management of contracts for applied and developmental research. An excerpt from the report's conclusions, printed on page 150 tells the story.

The Ruina study seems to have been

*Available from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402. 30 cents.

precipitated by discussion in Congress on whether individual research contracts, sometimes involving large-scale projects, should be reviewed and approved individually by the National Advisory Cancer Council, which advises the National Cancer Institute.

The question at issue was whether the authority of the council to review and approve research grants should be interpreted as extending to contracts as well.

Role of Councils

The advisory councils were established by the Public Health Act, and each of the seven national institutes of health has one attached to it. Members of the council are leaders in the fundamental or medical sciences and in public affairs. Appointment is by the Surgeon General with the approval of the Secretary of HEW. The appointments carry considerable prestige, and in recent years the White House has taken an interest in the choices.

The National Advisory Cancer Council has been an active one, and several members, including Mrs. Lasker, have felt that the council should act directly on approval of research contracts as it does in the case of grants.

Representative Fogarty initially took the same view, and his remarks on the floor of the House triggered formation of the Ruina committee by the HEW Secretary.

NIH and its parent agencies, PHS and HEW, have taken the view that the institutes, in awarding contracts for research, should follow standard government contracting procedures, which puts responsibility on agency staff members. The advisory councils would be limited to a role of general supervision and guidance.

Fogarty, after studying the law and discussing the matter at length with federal officials, appears to have changed his view. The issue appears not to have been settled within the council.

One practical problem affecting NIH capacities in contract management involves, not the professional prejudice cited in the excerpt from the report, but money. The salaries which NIH offers are lower than salaries for comparable jobs in universities and industry. The irony is that federal research grants in the biomedical sciences quite often provide the funds that make it possible for the universities to pay higher salaries. So NIH in a sense is running a race with itself and losing.

In general, NIH does not offer one special incentive which makes relatively low-paid jobs in agencies like NASA, AEC, and the Department of Defense attractive to some people. A man with technical-managerial talents can, for example, take a responsible job with NASA which in a few years will serve as a springboard into the executive suite of an aerospace company. Except for limited opportunities in the pharmaceutical industry, this is not the case for NIH. Careers and money are to be made in the universities and hospitals.

Prospects for special treatment for special job categories in NIH is dim. In government the Civil Service pattern prevails. NIH is part of the Public Health Service, and Congress would probably not stand for a realignment of the whole PHS pay structure which would put it out of line with other agencies.

One possibility is formation of one or more nonprofit corporations specializing in the management of larger projects in directed medical research. This has worked for the military services when they had "systems" problems, and it might work for NIH. Higher salaries could be paid, and the incompetent or merely competent administrator would not have the sanctuary of Civil Service status.

There are other impediments to the gearing up of applied research and developmental projects. Some medical problems which might yield to "targeted" programs, for instance, get insufficient attention. And the structure of medical education and research sometimes explains why. The national institutes tend to have constituencies in particular departments of medical schools, and therefore the institutes as a whole have developed a kind of academic structure. Some problems simply are of little interest to researchers and are therefore overlooked. NIH director James A. Shannon himself suggests that it may be necessary to give greater support to special-purpose institutes attached to medical schools and designed to tackle these problems of research oversight. Human reproduction, aging, toxicology and pharmacology, dental science, and even vaccine development have been suggested as areas offering promising prospects for intensified basic and applied research.

Some government officials feel research is now inhibited by patent policies and particularly by the view that when government funds in any proportion are involved in research, a government-take-all policy should prevail on patents. Critics of this viewpoint argue that such a policy makes it impossible to mesh federally supported research with the considerable industrial research effort in the biomedical field.

The argument that there are a lot of research results on the shelf which would provide ready applications in medicine if someone would only do the work gets scant support from federal science administrators. Big applied-research projects in medicine have been viewed skeptically because massive efforts can be wasted. And there is an obvious feeling that it is essential to keep the reins of control in the hands of "those who understand research." At the same time, the top men in the federal research establishment make no claim that everything that might have been done in the way of applied research has been done.

One problem is that the leveling off of funds has made it impossible to do everything. NIH has a special problem because it has been an education-supporting as well as research-supporting agency. It has seen a legion of investigators through graduate school and the postdoctoral years, and these people keep sending in grant applications. Academic careers depend on support of research, and it is clear that NIH feels an obligation to these researchers and realizes that good relations with the biomedical-research community depend on continued patronage.

NIH has entered an interesting and delicate period as a maturing agency. Shannon is retiring in 2 years. He has maintained extraordinarily good relations on two fronts—with Congress and the academic community. One observer put the problem for Shannon's successor when he asked, "How do you handle the transition from a one-man, charismatic operation?"

NIH is probably fortunate that in this period of transition Gardner is Secretary of HEW, Philip R. Lee is an assistant secretary for health and scientific affairs, Stewart is Surgeon General, and Shannon himself will be around. This is probably the strongest lineup that HEW-PHS-NIH has had, and these men do understand research.

Members of the biomedical research community, however, should grow accustomed to the idea that the spirit of the cost effectiveness analysis applies to them too.—JOHN WALSH