1982

INTRAMURAL SCIENCE AT THE NIH

Introduction

Periodically the National Institutes of Health prepares a formal document describing the intramural program on its campus in response to questions about the reasons for the existence of such a program, the size of the program, or the quality of science done therein. The last comprehensive report was prepared by DeWitt Stetten, Jr., in 1976. The year 1982 may well be an appropriate time to fashion another report since these last six years have seen the substantial beginnings of a biological revolution. Hence, it should be possible to evaluate the role of intramural science at the National Institutes of Health in this enormous transformation in basic understanding of biological processes and their control. In this paper we will briefly touch upon the history of the National Institutes of Health, then we will analyze the rationale for the existence of specific Federal research done within the walls of the National Institutes of Health by employees of the Federal Government, and in the final section we will detail how the quality of the science done at NIH is evaluated and, insofar as possible, give some statistics on the quality of the science being done at the NIH over the last ten or twenty years.

Historically, the National Institutes of Health began as a laboratory of the Marine Hospital Service in Staten Island, New

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York, which was set up in order to meet some of the responsibilities of that hospital. This laboratory was called the Hygienic Laboratory, and in 1891 it was moved to Washington, D.C. In 1912, the name of the Public Health and Marine Hospital Service was changed to Public Health Service, and in 1930 the Hygienic Laboratory was renamed the National Institute of Health. By 1938 the NIH had moved to the campus in Bethesda, Maryland, a substantial part of which was donated by private citizens to the United States Government for the express purpose of its use to house a research laboratory of the Federal Government. By 1938 the achievements of the then recently named National Institute of Health were not inconsiderable. Joseph Goldberger, an early Public Health Service officer, had established the dietary cause of pellagra and the requirements of the specific nutrient to prevent it. Only his unfortunate early death prevented his identification of the vitamin itself. In the laboratory, Claude Hudson was already world famous for his work on sugar chemistry. This fundamental work which appeared to have no application to medicine was important in providing compounds and reactions which are involved in an important route for glucose metabolism (sedoheptulose in the hexose monophosphate shunt). The Laboratory of Toxicology had developed important investigations into the toxicology of numerous foreign substances and was already interesting itself in radiation. The Cancer Institute was established as a specific institute in 1937, and owing to its legislative authority in 1938 and 1939 awarded the first research grants and fellowships.

The research grant operation of the National Institutes of Health remained small throughout the second world war until 1946 when a specific office to administer grants was transferred to the Public Health Service from the wartime Office of Scientific Research and Development, and the next year the Division of Research Grants was established. By 1948 the leadership at the National Institutes of Health recognized that it was difficult to study human disease without access to some type of research hospital. Therefore, the hospital now known as the Clinical Center, on the grounds of the NIH, was conceived. It was begun in about 1950 and was opened for its first patients in 1953. At this time (1953), almost 30 percent of the total budget of the NIH was spent on its campus in Bethesda, and about 70 percent of its appropriated funds were spent for research grants and training. Figure 1 gives the apportionment of the total NIH budget spent intramurally and extramurally since this time. It is clear that the great rate of growth of the NIH during the 1960s was largely concentrated in grants-in-aid for the support of research done largely in universities. It is important to note that many of the mechanisms and techniques for awarding grants and subsidizing training were developed by the leaders of the intramural program at the NIH. For example, the introduction of peer review in the evaluation of applications for grants-in-aid of research, the establishment of general clinical research centers, and the establishment of research career development awards were all conceived by intramural scientists at the NIH in order to utilize effectively appropriated funds in universities and research institutes throughout the country.

The Rationale for Intramural Science at the NIH

Perhaps the most basic question to be answered is whether the Federal Government should assume the responsibility for support of basic biomedical research. The answer in all Administrations for the last 40 years has been "yes." This positive answer has been reinforced in the latest State of the Union address by President Reagan. The reason for this unanimous agreement is that there are no other reliable sources of significant support for basic biomedical research. Industry can support directed, relatively short-term projects but it is altogether too risky for even large companies to support basic research when they cannot be sure that the results of that research will be useful in their own companies' products in the course of the next five years. They may suspect that the most important and most basic of the research is liable to have wide applicability, but it may be ten to thirty years after it has been done and it may benefit other companies. The importance of basic research in the development of important new diagnostic or therapeutic procedures has been investigated by Julius Comroe, who has, for example, traced the origin of open heart surgery which so dramatically changed the lives of so many people with congenital and acquired heart disease. Dr. Comroe has found that the roots went back many decades and encompassed a variety of seemingly almost random basic science studies in cardiac physiology, in oxygen transfer, and in membrane permeability: a variety of fields which seemed at the time not to be related at all to cardiology or to surgery. Given that the funding of basic biomedical research is the responsibility of the Federal Government, there are still questions that remain. Where should the research be done? Most governments have established federal research institutes. One example is the Kaiser Wilhelm Institutes in Germany, known since the second world war as the Max Planck Institutes. In England, the Medical Research Council has supported its own units in addition to a major medical research unit at Mill Hill. In France, the CNRS has its own governmentally financed government employees doing research at a variety of both university and non-university settings throughout the country. This was the case as we saw earlier with the United States Government; namely, the National Institutes of Health began as an exclusively governmental research institution which only later took upon itself the responsibility of providing a mechanism for the channeling of Federal funds to research institutes and universities throughout the country. Although the history of the various legislative acts which gradually created the NIH are somewhat clouded by time, it seems likely that one reason for its creation is that the Federal Government frequently needs competent and unbiased scientific advice. Many times it turns to the National Academy of Sciences for studies and advice. Scientists at the NIH, however, represent a significant additional resource for advice needed by the Government. Intramural NIH scientists are a particularly good source of genuinely disinterested advice. Why? Because they:

1) cannot have any ties with industry;
2) do not engage in private practice (if they are physicians);
3) are not recipients of grants or contracts;
4) as employees of the Federal Government, have loyalty only to it.

Hence, we conclude that one reason the NIH was established by the Federal Government was to have an independent, unbiased science base in the Government itself.

The point is made from time to time that scientists in the intramural program at the National Institutes of Health should, by and large, be doing research which cannot be done elsewhere, or which can be done at the NIH a great deal more easily than in universities and research institutes throughout the country. It is not entirely clear what the nature of this research is that could uniquely be done at the National Institutes of Health. There are, however, several possibilities:

First, research which requires unusually expensive equipment. This does not seem like a reasonable position to take because there is no *a priori* rationale for the intramural NIH to have more expensive equipment than any large research institute or university in this country. Another aspect of this, however, is that perhaps the NIH should be involved in long-term research and development efforts. An example of this might be the development of the positron emission tomography (PET) instrumentation. In point of fact, this was developed largely in England. Intramural scientists at the NIH only recently have developed a considerably more sensitive modification of the PET scanner, but other modifications are being introduced, largely by industry. Previous experience, in which the NIH attempted to build special probes for nuclear magnetic resonance that could look at atoms other than hydrogen, showed that the NIH spent a considerable amount of time and money and did develop a useful probe. Industry, however, had a probe ready to sell about the same time NIH completed its probe. This is clearly a difficult area to evaluate. Experience suggests that major new biomedical research instruments such as spectrophotometers, developed in the '40s, scintillation counters and NMR instrumentation, developed in the '50s, and the CAT scanners (computerized axial tomography), developed in the '70s have all been developed by industry. In most instances the ideas for these instruments and occasionally a prototype will be developed in a university, but industry is in a far better position to mobilize the engineers required to develop reliable, efficient, and inexpensive machines which can be produced in large enough quantity to satisfy the demands of the scientific community. Hence, in general, it does not appear that the NIH should intramurally do research requiring particularly expensive equipment or involving the development of expensive new equipment.

A second possibility is that intramural scientists at NIH should engage in expensive projects such as the study of patients with unusual diseases who would require hospitalization as well as travel and who might have to be recruited nationwide or worldwide. An example of this would be research in Xeroderma Pigmentosa, in which patients have a defect in enzymatic mechanisms for repairing DNA. Indeed, there is a major program under way at the National Institutes of Health in just this disease, but there are other programs in university hospitals throughout the country also investigating this same disease. Furthermore, the General Clinical Research Centers program provides hospitalization for just this kind of patient. So it would appear that, although the NIH might be in some instances better suited to recruit patients with unusual diseases of great biological importance, nonetheless this same work can go on--and, indeed, does go on--in university and research institutes throughout the country.

A third possibility is that the NIH should undertake clinical research requiring large numbers of patients. Actually, in the average university hospital, in major clinics, or in major health plans, large numbers of patients with specific diseases are generally available in the normal function of the hospital or clinic. It is therefore much more economical for a large clinic, a large university hospital, or a large health plan to investigate a new treatment or evaluate the efficacy of a new diagnostic procedure in a large number of selected patients which require diagnosis and treatment in any event. If this were done at the National Institutes of Health, the entire cost of research and the provision of medical care would of necessity come from research funds. This argument seems to suggest that at least there is one thing the NIH intramural program probably should not do and that is to undertake large clinical studies.

Finally, fourth, there is the possibility that a unique role for NIH intramural scientists is in interdisciplinary research, particularly that in which there is a mixture of clinical and rather fundamental science. This obviously can be done anywhere good clinical investigators and first rate basic scientists coexist. However, many medical schools are separated geographically from the parent university. It is somewhat difficult to collaborate effectively when the individuals involved have their laboratories even several miles apart, and certainly much more difficult when their laboratories are 10 or 100 miles apart. At the NIH, there is a rather compact aggregation of essentially all the basic sciences and the clinical investigators. It is clearly considerably easier for collaboration to develop when the scientists involved work within a few hundred yards or a few hundred feet of one another. So this would appear to be an area where the NIH, because of its concentration of both clinical investigators and basic scientists spanning the entire gamut of science from mathematics to physical chemistry to biology, might more effectively do collaborative interdisciplinary research. There are obviously many exceptions to this because there are some medical schools on the university campus, and many examples of superb interdisciplinary work done in research institutes and universities throughout the country. Furthermore, the quality of the research in any event depends somewhat less on the proximity of the researchers than on the quality of the scientists.

What can we conclude from the above discussion? One conclusion seems evident: University hospitals and large clinics are far better places in which to perform extensive clinical trials than is intramural NIH. Second, most biomedical research can be done in any university, hospital, or research institute. The quality of the work done depends largely on the quality of the researchers. Finally, the NIH appears to be a somewhat better place for interdisciplinary research than the average university or university hospital or clinic, but there are certainly many exceptions to this. Hence, it would not appear that there is any general, cogent argument that can be developed to suggest that there is a certain type of research which intramural scientists at the NIH should do, and there is another large type of research which the intramural scientists at the NIH should not do. Scientists at NIH must do good research and their research should be judged and supported on the basis of its quality. Particular effort should be continued to encourage interdisciplinary research at intramural NIH because of its scientific breadth and concentration.

Sometimes questions are raised about the size of the intramural program at the NIH. In 1965, for example, there was an extensive report to the President on "Biomedical Science and Its Administration: A Study of the National Institutes of Health," popularly known as the Wooldridge Report. In this very comprehensive study we find among others the following: "We have been unable to find any analysis leading to the conclusion that the present 10,000-man* level of intramural activities at NIH is more nearly optimum when related to the entire national picture of health research than would be, say, a 5,000-man or a 20,000-man level." This suggests that there must exist a logic which will force a conclusion that the intramural program at the NIH should be of a given size, perhaps as a proportion of the total Federal budget for biomedical research or perhaps in absolute terms, such as the number of employees engaged in research. It would seem clear that if there is indeed a logic to force such a conclusion with respect to intramural research at NIH, then there should be a similar logic that would force a similar decision with respect to the size of, for example, Harvard University, the Rockefeller University, or indeed any or all organizations performing biomedical research. Obviously the logic must consist of some kind of analytical paradigm which includes parameters and functions and constants so that such an analysis can be properly carried out. _A priori_ it seems somewhat unlikely that any of the actors in this drama would be able to agree on any of the functions employed, much less any that would have any specific relationship to their own institution. Furthermore, such a program would appear to require as large an investment in analysis of

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*There appears to have been some confusion in the Committee about the size of NIH. At that time, of the 10,000 employees of the NIH about 1,500 ran the hospital and around 3,500 scientists and support personnel actually did intramural science. The remainder of the employees managed the extramural programs.

where research should be performed as the investment in the actual pursuit of such research. There are, however, some practical points to be considered. It may be difficult for a small research group to probe deeply into many of the implications of its discoveries. This would occur when the isolation of some natural product is attempted and the group does not include organic chemists and modern analytical equipment such as mass spectrometers, high pressure liquid chromatography, and NMR equipment. It could be a problem when the cardiologist is interested in new radioactive isotope imaging techniques but does not have access to a modern computer and skilled programmers. Hence there is a considerable advantage in having any research group enmeshed in a large scientific enterprise in which the gamut of science from mathematics, physics, chemical physics, chemistry, molecular biology, physiology, and clinical investigations is well represented. It seems, therefore, that in a general sense a research group is more likely to be most productive when it is a part of a large scientific enterprise. Short of these general considerations it seems from the above analysis highly unlikely that there is going to be any logic which will force a conclusion to give in absolute numbers the optimal size of any institution.

Another important historical precedent which deserves consideration is the peculiar type of pluralistic support of societal institutions which was developed in the United States in the very early days of the Republic. For 200 years, for example, higher education in the United States has been supported by many different mechanisms. Some of the earliest colleges and universities were formed by religious groups which were also interested in education. There were other private colleges of a non-religious or nonsectarian nature. Cities themselves, particularly the great cities of the country such as New York, set up their own university system. A post-World War II phenomenon has been the community colleges, such as Montgomery College. State universities have been important for well over 100 years, and in the land-grant institutions a special Federal contribution to the State school has been an important component. This pluralistic attitude and utilization of many different modes of pursuing the same goal has resulted in a richness in the educational experience in the United States and opportunity to experiment and to change that most governments throughout the world envy. It is interesting to note that from a primitive and backward condition with almost no tradition of scholarship (the first Ph.D. being awarded in the 1860s by Yale), higher education in the United States has developed into a vast system of educational enterprises which in 1980 graduated almost 30,000 people with the Ph.D. This remarkable ability of the United States educational system to go from being insignificant academically in the mid-1800s to the major academic and scholarly forum in the entire world by the mid-20th century derived in no small part from the diverse sources of support which institutions of education and learning enjoyed and from the possibility of multiple, different, and decentralized approaches which could be used. There is a similar but considerably shorter history of the pluralistic support of biomedical research. In addition to research conducted at colleges and universities which enjoyed support from the different sources enumerated above, there have been free-standing research institutes, some the result of private charities such as the Rockefeller Institute, the Wistar Institute, or the Sloan-Kettering Institute. Extensive industrial laboratories, where, in addition to more applied research, a certain amount of fundamental research is pursued (the Roche Institute of Molecular Biology, the Merck Institute), have been on the scene for many years. Research, however, has changed in the 20th century, and particularly since the second world war. It has changed in a quantitative way, even more dramatically than the educational enterprise has changed. As in nuclear physics or astronomy where massive and expensive machines require Federal support, so do the small but expensive and numerous apparatuses which biomedical researchers need also require Federal support. There is good reason to think that the pluralistic approach utilized in the United States has been one of the reasons for the great success of biomedical research enterprise in this country. Given this, it would seem rash arbitrarily to abolish any part of the current research enterprise or attempt by fiat to rearrange the various subdivisions of the institutions which perform the research.

To summarize, the argument that intramural research at the National Institutes of Health should be set at a predetermined level of support fails because (1) no logic exists to determine such a level, and (2) a pluralistic approach toward solving societal problems has been a unique contribution of the Federal Government for 200 years and it has met with great success. It would seem unwise without a preponderance of evidence suggesting otherwise to change this philosophy at this time.

The Quality of Scientific Research Done by Intramural Scientists at the National Institutes of Health and How It is Appraised

Even if we accept the argument that it is not possible to assign a particular appropriate size to the research enterprise done intramurally at the NIH, and even if we accept on general grounds that it is important to maintain an intramural operation at the NIH, we still face an important question: Is the research done at the NIH intramurally of first quality? If the research is not of first quality, irrespective of how the previous questions are answered, the research should be curtailed drastically. Just as funding goes to research projects which seem most meritorious in univerities and research institutes, so should intramural funding go only to research projects of high quality.

Let us look at some statistical analyses that have been done using citation indices. This is possible with the new computerization of biomedical research articles both as to the authors of the articles and authors of articles which are referred to in each publication. As a general rule of thumb, the more frequently an article is referred to, the more important it is, and hence the more important the work that the individuals who published the paper in fact did. In 1975, Computer Horizons studied the total annual production of papers in biomedical research journals during 1973. Table 2 shows that the University of California heads the list in terms of the total number of papers published; this reflects the aggregation of all the campuses of the University of California. The NIH comes second, followed by Harvard. It is also possible to calculate the average publication weight (Table 2). This is a measure weighted by the influence of the referencing journal and normalized to the size of the cited journal. The higher the score for publication weight, the more important the publications appear to be. Harvard leads in this with a calculated score of 31.2, the NIH intramural program is second with 29.8.

Another way of evaluating the quality of scientists in an institution is to examine the journals in which they publish. On the basis of which journals are most cited by authors, one can establish an "influence" factor associated with each journal. Table 3 gives some indication of where scientists at the NIH published. To get some idea of the absolute value of these numbers we need another kind of denominator. This is supplied by the ratio of NIH publications to total U.S. publications in these various journal sets compared to the fraction of members of the Federation of American Societies for Experimental Biology who work at the NIH. It can be seen that intramural NIH scientists tended to publish a disproportionately large number of papers in the more influential journals.

Somewhat later, Eugene Garfield in Current Contents reviewed the 300 most-cited authors from 1961 to 1976. This included all the names on the paper, which is an important consideration because not infrequently the head of a laboratory has his name appear last, and the first author will be the postdoctoral fellow working with him. The basis for this compilation of the 300 most cited authors was over 10 million author entries in the Science Citation Index data base matched against approximately 32 million citations in the citation index. Some 31 individuals on the 300 most cited lists were working in the intramural part of the National Institutes of Health at the time this information was published in 1978. This, then, means that slightly over 10 percent of the most cited authors covering the entire world worked in the intramural program of the NIH. Approximately 1 million scientists were working during this period of time according to Garfield, and so this in a very crude way could be used as a denominator. The numerator for intramural NIH would be approximately 1,500 scientists who were, on the average, working at the NIH during the years 1961-1976. Hence, approximately 0.15 percent of the working scientists contributed something over 10 percent of the most quoted papers. Garfield has updated this in 1981 to include the 1,000 most quoted authors over the same span of years. In the list of the 1,000 most quoted authors, including scientists throughout the world and including fields of science in which there is no representation at the NIH, such as geology, geophysics, botany, astronomy and physics, we find the names of 86 scientists working at the NIH (a few retired at present). Hence, 8.6 percent of the 1,000 most quoted authors in any field of science worked in the intramural NIH program. A crude way to estimate the significance of this number is to calculate that fraction of the total research funding in the U.S. and throughout the world represented by the funding provided to intramural NIH. During the period in question, approximately 10 percent of the NIH budget supported the intramural program at the National Institutes of Health. In addition, during the same period of time approximately 40 percent of the entire United States expenditure for basic biomedical research was provided by the National Institutes of Health. As a rather crude approximation, the United States spent about half of the total world expenditure for biomedical research. Putting these all together, it can be seen that intramural scientists received approximately 2 percent of the total funding for biomedical research throughout the period 1961 to 1976. However, during this same period of time they represented 8.6 percent of the most quoted authors in the world.

Another way of looking at the quality of science in the United States is to consider membership in learned societies. The National Academy of Sciences of the United States is probably the organization that is most prestigious in this regard. At the present time there are 34 scientists from the National Institutes of Health who are members of the National Academy of Sciences, which has a total membership of about 1,200, of whom, however, only 663 are in chemical and biological sciences represented at the NIH. Hence about 5 percent of the scientists in the National Academy of Sciences and the appropriate sections are on the staff of the NIH. Nobel prizes are generally considered to be the ultimate form of recognition, particularly for scientists in the biomedical fields, since Nobel prizes are available in physiology and medicine as well as in chemistry. Intramural scientists at the NIH have won four Nobel prizes in the last 15 years.

All of these objective criteria, which attempt to evaluate the quality of science in a given institution or as practiced by any individual, seem to suggest that intramural scientists at the NIH are at the top in this country and in the world in terms of the quality of the science.

In addition to evaluating the scientific achievements of the people working in the intramural program at the NIH, it is important to ask what has been the influence of the intramural NIH in the training of biomedical researchers. There are numerous anecdotes supporting the belief that a large fraction of the professors of medicine, biochemistry, and microbiology had a period of training at the NIH, but these are more or less convincing. The National Academy of Sciences in October 1981 published "The NIH Intramural Program Evaluation on the Status of Medical School and Clinical Research Manpower." In Table 3, graduates of the Medical Scientist Training Program, sponsored by the National Institute of General Medical Sciences, in which medical students work simultaneously toward an M.D. and a Ph.D., are compared with NIH Research Associates, NIH Clinical Associates, and Extramural

Postdoctoral Trainees of the NIH. These were graduates through 1973 who were in training between 1963 and 1975, and who had been matched in terms of their qualifications by their MCAT scores and by the quality of the undergraduate schools they attended.* As can be seen in Table 3, the NIH Research Associates do somewhat better in the fraction of those that could be followed who are presently in research or teaching. The number of publications again appears to be approximately the same although the somewhat larger number of individuals who could be followed in the MSTP program appeared to have substantially more publications than the NIH research associates. These data suggest that the NIH Associates have done reasonably well by comparison with training programs in universities throughout the country.

Finally, we must ask: How does intramural NIH review the work of its scientists? First of all it is important to understand the structure of intramural NIH. There are 10 Institutes, each one with a Scientific Director and a variety of laboratories or branches under which are sections. There is a constant review of progress of each scientist by the section chief, laboratory chief, and by the Scientific Director. This occurs on a day to day, week to week, or month to month basis, depending on who is

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*A matching technique such as this may produce anomalous results. Consider Institution A with an international reputation which picks only the best students. Institution B is not nearly as prestigious so attracts less able students. However, if the graduates of programs from Institutions A and B are matched, the ensuing process compares the careers of the lowest 10 percent of the graduates of A with the top 10 percent of B. Such flaws in design should be borne in mind in evaluating the results of this study.

involved. The Scientific Directors as a body meet twice a month to consider general problems of intramural science at the NIH and to act on all promotions. The promotion receiving the most attention is the promotion to "tenure." The NIH has managed to achieve a program unique in Government called the Staff Fellowship Program, which permits scientists to work at the NIH for up to seven years before being awarded a tenured position. Decisions require at least three levels of review, and outside letters are solicited not only by the Institute involved but by the Deputy Director for Science. After all of these have been acquired and the candidate has passed preliminary review bodies, he is presented to the Scientific Directors in their committee meeting. In addition, once a year each Scientific Director presents to the assembled Scientific Directors his entire intramural Institute program, individual by individual, outlining what changes he thinks will occur in the succeeding year in the division of space and resources among the laboratories, and signaling the scientists he expects to come up for promotion and indicating those scientists whose work is not of acceptable quality.

Outside review is provided by Boards of Scientific Counselors. These were established on an informal basis in the late 1950s and consist of distinguished scientists from outside the NIH. They are usually comprised of six to eight scientists for each Institute. They meet two times per year for 2-3 days, and special ad hoc reviewers may be invited to assist in the evaluations conducted at these meetings. Every tenured intramural scientist presents every three to four years to this group, very much as though it were somewhat of a detailed site visit. The scientist prepares a curriculum vitae and bibliography, lists the amount of support that he receives, and describes in narrative form recent results that he has acquired and his plans for future work. The Chairman of the Board of Scientific Counselors, who is outside the National Institutes of Health, prepares minutes and these are circulated for discussion to the Board of Scientific Directors. This provides to the other Scientific Directors and to the Deputy Director for Science an overview of each laboratory in the entire intramural program. In some Institutes, the Board of Scientific Counselors has the major voice with respect to tenure decisions. An important aspect of the review process is the fact that the NIH has gradually over the last two decades moved from a largely tenured staff to one in which tenured scientists represent approximately 30-40 percent of the scientific work force. Postdoctoral scientists represent 60-70 percent of the scientists on the campus. This permits more rapid changes in the allocation of resources, and it permits each Scientific Diector to review a large number of postdoctoral fellows who come and go and to offer tenure to the very best. The NIH is currently in the midst of a review of the functions of the Scientific Counselors and the mechanics of how they are utilized by each Scientific Director, and we expect sometime this fall to be able to make a more thorough evaluation of the role of Scientific Counselors in the management of intramural NIH and possibly to increase their influence and effectiveness.

It is not easy to answer another question posed in the Introduction: Have NIH intramural scientists contributed to the dramatic advances in molecular biology and recombinant DNA technologies of the last decade? Some accounting, however, can be made. We begin almost 20 years ago when Nirenberg deciphered the exact wording of the genetic code. Over a decade ago Gellert discovered the enzyme DNA ligase. This enzyme which can close covalently double stranded DNA is an absolute requirement for all the plasmid constructions used in DNA recombinant work. Huebner and Rowe early on hypothesized the existence of the now well-known onc genes. These are normal cellular genes which, if turned on by viruses or portions of viruses, can cause malignant transformations of cells. Scolnick and Vande Woude have pursued and verified this hypothesis using two different viruses. Aaronson and his group have also worked out some aspects of this problem. Khoury has been in the forefront of work on the SV40 virus and its use as a vector for gene transfer. Gallo has identified a human tumor virus involved in a certain type of leukemia. Leder was one of the first to show the presence of introns in cellular genes and contributed mightily to our understanding of the genetic rearrangements that occur when an uncommitted plasma cell begins to produce antibody. Todaro has shown that tumors secrete a growth factor and has identified some of them. Pastan and de Crombrugghe were the first to determine the structure of the extraordinary collagen gene. Felsenfeld and Simpson have shown the structure of chromatin and begun to give us a picture of how gene activity might be controlled. In the similarly exploding field of immunology, Potter showed how to produce at will specific immunoglobulin producing tumors. Davies used these with X-ray crystallographic techniques to give the first exact three dimensional picture of an antibody. Paul, Fauci, and Metzger further contributed to our knowledge of the immune response.

Even this cursory and incomplete description of recent work shows that scientists in the intramural NIH have played a major role in the biological revolution of the last decade.

CONCLUSION

It is not possible to calculate analytically what proportion of Federal funding should go to any particular institution, be it a private university, a research institute, or a Federal laboratory. It is possible, retrospectively and with certain caveats, to evaluate the scientific productivity of any institution. By all the methods that we have been able to discover which have investigated the quality of science produced by intramural scientists in comparison with the quality of science produced by scientists at the leadings institutions throughout this country and abroad, it appears that the intramural program at the NIH is at or near the top in quality. Given the above, it would seem unwise to arbitrarily change or to reassign the proportion of the Federal Government budget for biomedical research which is allocated to any particular institution.

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Table 1

NIH Budget
(Dollars in Millions)

Time	Total NIH Budget	Percent Intramural
1955	$ 66.7	28.6
1960	329.2	12.6
1965	773.1	9.8
1970	1,057.8	10.7
1975	2,108.9	10.1
1980	3,428.8	11.0

Table 2

Publication Counts*

Institution	Number of Publications (1973)	Average Publication Weight
Universities**	28,284	22.6
Hospitals	2,131	19.4
Other	3,114	26.4
University of California (All Campuses)	2,951	22.0
NIH	1,535	29.8
Harvard University (Boston)	1,046	31.2
Johns Hopkins University	771	24.9
State University of New York	770	20.4
University of Pennsylvania	693	24.8
Columbia University	673	24.8
University of Wisconsin	671	28.2
Yale University	667	27.3

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*For 500 biomedical journals

**Refers to all institutions among the 24 largest NIH grantee institutions

Table 3

NIH Biomedical Publications in Special Journal Sets

	NIH Intramural	All U.S.	NIH Intramural/ All U.S.
12 Biomedical Review Journals	12.5	166.9	7.49%
20 Biomedical Journals with Highest Influence Weight	271.9	4,703.3	5.78%
20 Biomedical Journals with Highest Total Influence	380.4	8,779.5	4.33%
20 Biomedical Journals with Highest Influence/ Publication	272.6	5,324.3	5.12%
20 Journal Set	436.2	7,927.0	5.50%
35 Journal Set	524.8	10,774.3	4.87%
Variable (full) (∼1000) Journal Set	1,558.4	45,374.0	3.43%

NIH members/total FASEB membership = 3.22%

Table 4

Status of M.D. Trainees

	Now in Research or Teaching	Publications (# Individuals)
MSTP	94%	995 (50)
NIH Research Associates	95%	716 (46)
NIH Clinical Associates	86%	673 (51)
Extramural Postdocs	83%	408 (45)

Graduates through 1973 (training 1963-1975)