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SPECIAL ARTICLE

BIOMEDICAL RESEARCH IN THE 1980s

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THE new administration could be the most fiscally constrained in half a century, and yet it must endeavor to provide full support to a revolution. That is the best word to describe the present state of the biologic sciences. Their economic foundation, however, has rarely been more precarious.

Never has there been a comparable period of growth in the knowledge of living things. The current revolution in the life sciences is not a simple, linear projection of the growth curve in knowledge for the past century. A striking perturbation of that growth has occurred, amounting to a geometric progression of available information. Achievements of research in chemistry, physics, and many allied disciplines during this same period have led to new technologies contributing to a flood of discovery in biochemistry, physiology, and medicine. Our ignorance is still vast, but we are on the threshold of some unusual transformations in health practices, agriculture, and industry.

The major reason for all these events is the commitment of serious public support for research in the natural sciences. In the United States this commitment did not occur until a little over 30 years ago. Our example proved infectious to other affluent, developed countries, some of which had to reconstruct their science base after a devastating war.

Since 1950, approximately \$75 billion from private and public funds has been expended for research and development in health care in the United States. This investment represented 0.06 per cent of the gross national product in 1950 and 0.33 per cent in 1974; it has remained at about 0.31 per cent in the past few years. The contributors and participants have been in industry as well as the nonprofit sector. About 60 per cent of the total funds and an estimated 90 per cent of the basic research has been supported from the federal budget.

Over these three decades an unprecedented system of inquiry has grown up. It involves private and federal laboratories and nearly all universities. These institutions have adapted their structure and organization to incorporate greatly expanded scientific investigation as an essential part of the teaching function, to maintain the necessary replenishment of trained researchers, and to cope with the vast increase in the flow of information, synthesizing it into

knowledge and encouraging its diffusion and practical application.

Such scientific endeavor is of necessity largely an instrument of the state. Increasingly, weaknesses in the economies of America and the rest of the world have jeopardized the ability of governments to sustain the biologic revolution. We have the responsibility to alert the governors of our societies that one of our greatest intellectual adventures — one ultimately crucial to our survival — needs careful stewardship so that it will not wind down irreversibly.

STEP BACK 100 YEARS

For purposes of perspective, let us go back about 100 years. Pasteur had dispelled the myth of spontaneous generation of living things. Koch had risen among a generation of great pathologists and chemists in his country to set the rules for proving that an organism causes a particular disease. Modern physiology was under way with Claude Bernard. Laboratory experiments were beginning to shake up medical epistemology. The action was mainly confined to Britain and the European universities.

In America at the turn of the century, John D. Rockefeller's advisor picked up Osler's latest medical textbook. The art of descriptive medicine seemed to be high, but the impotence of the healing arts was unconcealed. He encouraged his patron to create the first medical-research institute in America in 1901. Simon Flexner, whose patron was Carnegie, soon determined how to force a marriage of medicine to science. Over 70 nonacademic proprietary medical schools were thus forcibly closed between 1910 and 1925. Rockefeller's funds also created clinical-science units, with a full-time physician-investigator in charge, at Johns Hopkins and then in London.

Then came the World Wars. The medical corps of the Allies and the Central Powers attended the victims of World War I with arsenicals and carbolic acid. They entered World War II with German sulfa and finished with British penicillin. At the end of this war, America emerged with its industries intact and in possession of nuclear power. Its government was persuaded to make a fateful investment: public support of scientific research in university and federal laboratories.

There was a special desire on the part of the Congress to have just one more war, this time against disease. A tiny federal agency, the National Institutes of Health (NIH), was given trusteeship for federal funds devoted to increasing knowledge of human biology and medicine. The growth of the NIH was prodigious.

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Its resources and its example of public support of science flowed to Britain, Europe, and Asia to revive the activities of older partners in a scientific universe in the process of rapid expansion.

THE GROWTH SPURT BEGINS

Let us take 1950 as a reference year. The pump oxygenator was used for the first time. A remarkable epoch in cardiology commenced, with diagnostics and surgery competing and combining to achieve mastery of the heart — one of the inviolate organs since ancient times. An artificial kidney was spinning in Boston. The recently available shipments of radioisotopes from Oak Ridge were setting in motion innumerable raids into the previously inaccessible interiors of intact organisms. Metabolic maps that once had taken a lifetime to trace were rapidly composed and disseminated.

Molecular biology was in its infancy, although evidence of the immortal secret of DNA had been unearthed in the 1940s. There was some rereading of the forgotten Croonian Lectures of Sir Archibald Garrod (1908). By mid-century the term "inborn errors of metabolism" could be rephrased to become "one mutant gene — one defective enzyme."

MOLECULAR DISEASE

The 1950s began with a revolutionary restatement of the hypothesis epitomized as "molecular disease." About 100 metabolic diseases were recognized to be of genetic origin. One of the first identifications of a specific enzyme deficiency was Gerty Cori's demonstration in 1952 that deficient glucose-6-phosphatase activity was an underlying factor in von Gierke's glycogen-storage disease. It had taken 50 years from the first case report to elucidate the cause.

By the end of the 1950s, a dozen such enzyme deficiencies had been clarified. Two of the four diseases that had been considered 40 years earlier in Garrod's classic writings were among them: alcaptonuria, reported at least 100 years before, and albinism, which had been described by Pliny.

The precise error in structure of the chain of amino acids dictated by a mutant gene was first exposed in this period. The sometimes fatal association of sickle cells with anemia had first been reported by a Chicago physician in 1910. New methods for separating globins by electrophoresis led to the hypothesis that a single amino acid substitution in hemoglobin S was involved (1949). Within a few years, the switch of one valine for a glutamic acid residue in a chain of 280 amino acids was uncovered (1956). This profound demonstration of how human misery can spring from so tiny a base marked an epochal expansion in the scale of our self-comprehension.

The list of genetic disorders in which the defective gene product is known grew from 15 in 1960 to over 1000 in 1980, and today we can identify the chromosomal location of more than 35 such mutant human

genes. It has been predicted that the entire human genome (more than 100,000 genes) may be mapped before the 21st century.

In the past two decades whole collections of pathologic processes have been lifted out of obscurity, with an accompanying illumination in physiology. An example was the conversion of the numerous and mysterious diseases of mucopolysaccharide and sphingolipid storage to specific acid-hydrolase deficiencies in the period from 1965 to 1975. Simultaneously, the normal scavenger system located in reticuloendothelial lysosomes suddenly emerged, complete with a catalog of the loci of potential malfunctions.

A timely mastery of the art of growing human cells in tissue culture permitted detection of abnormalities in the fetus and recognition of carrier states in potential parents. Enzyme defects can now be demonstrated in cultured skin fibroblasts for over 100 inborn errors of metabolism and in cultured lymphoblastoid cells for at least 25. Not one such enzymatic error could be so identified in 1960.

There has also arisen over the past 25 years a concept of genetic polymorphism that is invaluable for the understanding of protein differences in normal persons. Someday not too far off, all the proteins in the blood or organs will be identified and measured. This concept of allelism will greatly enhance our ability to determine hereditary variations in diseases and in individual adaptability to stress.

The structure of DNA (1953), the replication of genetic messages, the major features of their transcription and translation (by the mid-1960s), and the revelation of the genetic code all represent leaps in understanding that cannot be fully described here. The same fleeting mention must be made of the molecular vision acquired by science through numerous new tools. Now we can not only see organelles and cell surfaces but also comprehend the baroque beauty of multiple overlapping controls on enzyme activity and the demography of receptors and agonists that regulate a seemingly infinite number of metabolic processes.

Certainly, one should emphasize the applications of such research that have affected the lives of millions over these same 30 years — achievements such as hormonal contraception; eradication of smallpox by vaccination; control of polio, rubella and Rh disease by immunization; and the remarkable changes in mortality from cardiovascular disease.

GENETIC RECOMBINATION

In the early 1970s, the techniques for combining genes seemed the most exciting and provocative addition to the "new biology." We added to our bag of molecular images such desiderata as "sticky ends," circular plasmids, nose cones of insertable viral vectors, and a parade of imaginary genetic chimeras. At the time, some of us also had to cope with more tangible phenomena such as protests, guidelines for ex-

perimentation, and statements on environmental impact. As genetic recombination moved from a highly speculative curiosity to the basis of a new industry, we took lessons in public governance of science that will surely stand us in good stead in the 1980s.

In the years of exploration preceding emergence of this startling technology, the public also amortized costs of research and development that no industrial conglomerate could have programmed or underwritten. These new means for producing valuable biological materials promise great economic return. The costs of development, however, have already been repaid in fundamental information about gene structure and control that only the pure proteins or polynucleotides produced by the unicellular factories could provide.

Methods of genetic recombination and techniques for rapid determination of the sequential structure of genes resulted in Nobel Prizes in 1979 and 1980. Few discoveries have been so promptly rewarded, and few have projected us so fast into the future. Yet the 1980 Nobel Prizes also recognized spectacular achievement in quite another sector of biology.

MONOCLONAL IMMORTALITY

The 1980 Nobel Prize in Physiology or Medicine was awarded for the discovery of the major histocompatibility complex (MHC).

The MHC is far from being completely understood. It appears to be a "super-gene," of which a well-explored region is the major regulator of the immune response to foreign substances or antigens. It controls the interactions of different classes of lymphocytes with one another and with scavenger cells, and it regulates the interaction of these cells with antigens. The rapidly unfolding story of the immune system boggles the mind. In it lie the bases for resistance to infections and for rejection of grafts. Doubtless, immunology holds secrets of the cause of cancer and resistance to it. Disorders, such as multiple sclerosis, juvenile diabetes mellitus, systemic lupus erythematosus, and other rheumatic conditions are also mysteriously associated with certain recognition antigens on the surface of cells — antigens located under the directions of the super-gene MHC.

The growth phases in our knowledge of immunology have followed the time phases of disciplines already mentioned, although the affinity of an antibody for an antigen has long been one of the most important tools for sensitive, highly specific identification and quantification of substances. In the past dozen years, Nobel Prizes have been awarded for the development of radioimmunoassays and for the elucidation of the complex structure of antibodies. Remarkable progress has recently been made in differentiation of the roles of lymphocytes.

Multiple B-lymphocyte clones respond to introduction of an immunizing agent in the body by producing antibodies directed against the antigens. Each responding lymphocyte clone produces identical anti-

bodies to one of the antigenic determinants. The result is a mix of closely similar antibodies that hunt down the antigens and selectively bind to them. Other T lymphocytes, communicating through chemical messages, either induce the B cells to respond to antigens or keep them from doing so. Some T lymphocytes become "killer cells" capable of destroying other cells.

Immunology has not only gone molecular; in the development of the hybridoma, it has perhaps discovered perpetual motion. Five years ago a procedure was described that consists of fusing in culture a myeloma cell (a plasma cell that has been malignantly transformed into an uncontrollable immunoglobulin secretor) with single lymphocytes immunized to produce specific antibody. The resulting hybridoma thus confers the immortality of the myeloma cell on the secreting lymphocyte. Under appropriate conditions, these fused cells yield clones of lymphocytes that emit monoclonal antibodies. The secretors can be maintained permanently in culture, each producing large amounts of antibody to a single antigenic determinant.

The myeloma cell, or "permissive horse," when provided with the desired template, becomes a remarkable mammalian cell-cloning vehicle. It is comparable to a host bacterium, such as *Escherichia coli* K12, as used in recombinant technology, into which has been inserted the appropriate genetic messages for continuous production of a foreign protein or polynucleotide. If one imagines a combination of the bacteria to produce genetic programs for antibodies and the hybridomas to make the products, a library containing the 10 million or so potential human antibodies is within grasp — an incomparable collection of tools if some means can be devised to make them readily accessible.

NEW MEDICAL MAGIC

The exquisite specificity of antibodies, which lies in the vast number of structural permutations that are programmable in the "hypervariability" portion of the antibody molecules, provides the capability for targeting messages to a single cell in the body. There are some researchers who contemplate making an antibody with an affinity for certain cancer cells and conjugating it with a drug — say, a molecule of ricin, a castor-bean poison so powerful that one molecule can kill a cell. Others are busy purifying human killer T lymphocytes directed to recognize only specific metastatic tumor cells. Unleashed into the circulation, the killer cells are expected to seek out their targets and to devour them selectively.

Recombinant-DNA technology is ideally adapted to producing large amounts of pure antigens-for use in vaccines. The days of sensitizing protein impurities in commercial vaccines may be gone. Doors are also opening that lead to vaccine control of some protozoan infections, perhaps including malaria, the

world's greatest killer, or Chagas' disease, the scourge of Latin America. The new technology may have inestimable value in providing antigens or antibodies to use against these age-old enemies.

Let us pass over other opportunities for obtaining new knowledge — interferons and how they thwart viral infections or the study of cell transformation in the malignant process — and give one more example of the revolution.

Modern electronics has put us in awe of the numerous transistors connected in a single chip so that an almost infinite number of computer programs can be accommodated. The microcircuitry of the brain and its programming to achieve the very-large-scale integration of higher neurologic function is much more complex and romantic.

Over a period of 30 years, separate discoveries have coalesced to reveal the structure of the brain. Molecular visions of the chemical anatomy and bioelectric integration of the circuitry of the nervous system are now emerging. It is no longer news that the discharge of the neurons is both initiated by and productive of chemical neurotransmitters. The recent elucidation of how numerous kinds of neurotransmitters play upon specific receptors around the body of the neuron to regulate its electrical activity is indeed news, if one has not been keeping close tabs on developments.

Different classes of neurotransmitters — those derived from norepinephrine (such as dopamine), amino acids (such as gamma-aminobutyric acid), or polypeptides (such as the endorphins) — have been identified with great specificity, and their structures have been described in detail. The regulation of the sensitivity of their receptors is becoming clearer, as are the mechanisms by which each finally acts on the neuron to regulate its electrical potential. The firing of each nerve — an impulse releasing neurotransmitter at the next nerve synapse — is governed by multiple influences.

With this greater fundamental knowledge has come a comparable growth in concepts of nervous-system dysfunction and its treatment through safe and reasonable methods. The effect of lithium, which was serendipitously discovered in 1949, and of other tranquilizers, such as the benzodiazepines introduced in 1960, have markedly changed the management of mental disturbance. The mechanisms of action of these powerful drugs are now known in considerable detail. It will not be too long before the affective disorders, with their curious rhythms and awful intensity, can be better controlled through knowledge based on this kind of molecular dissection. Other mental disorders, especially those with genetically determined components, will similarly come within the reach of the therapist.

As these examples illustrate, the limits to our conquest of the mysteries about us have been radically displaced. Little of the unknown in the physical realm seems to be ultimately unconquerable if the inquiry is sustained.

DARKENING SKIES

However, there are unmistakable threats to the size and vigor of scientific inquiry today. Monetary inflation, decreased growth of industrial productivity, and critical shortages in energy are seriously and continuously undermining the affluence of all the developed countries in which scientific research has thrived.

The situation might be viewed in the context of the activities of the National Institutes of Health. The NIH began in 1887 as a modest public-health laboratory on Staten Island, N.Y. In 1937 it was relocated in Bethesda, Md., with a newly created National Cancer Institute.

In 1948 enthusiasm for peacetime continuation of federal support for health research resulted in the formation of additional institutes. The National Heart Institute, the National Dental Institute, and the National Institute of Mental Health were established next. (The National Institute of Mental Health left the NIH in 1967 and is now part of the Alcohol, Drug Abuse, and Mental Health Administration. Its intramural research activities remain on the NIH campus in Bethesda. Data presented here do not include the resources of the Alcohol, Drug Abuse, and Mental Health Administration.) Eight other institutes were later established, and the aggregate NIH was on its way to becoming the single largest supporter and conductor of research in medicine and the life sciences that the world has seen — or, conceivably, may ever see again, depending on the fortunes of the American economy in the years ahead.

The annual NIH budget grew almost exponentially, expanding 13-fold between 1956 and 1966 (Fig. 1). Even after the dramatic rate of growth had declined, the separate appropriations for some institutes continued to increase. Obligations for all institutes totaled \$3.2 billion in fiscal year 1979. It is possible that this sum may have been a high-water mark in purchasing power. In constant (1969) dollars, it was equivalent to \$1.62 billion — a 49 per cent increase

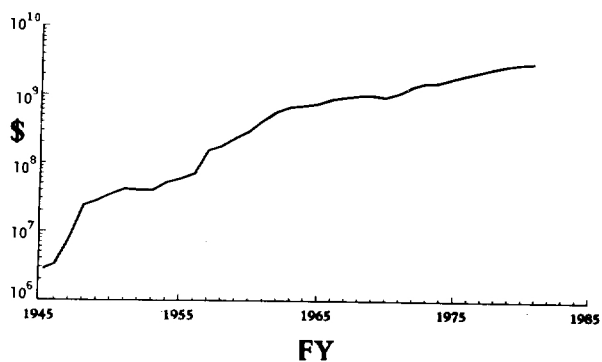


Figure 1. Congressional Appropriations for the National Institutes of Health, Fiscal Years 1945 through 1981.

Aggregate appropriations rose from a total of under \$2 million in 1945 to \$3,616 million for 1981. As shown on this semi-log scale, the rate of increase was steepest in the early years. (In 1957 the program doubled.)

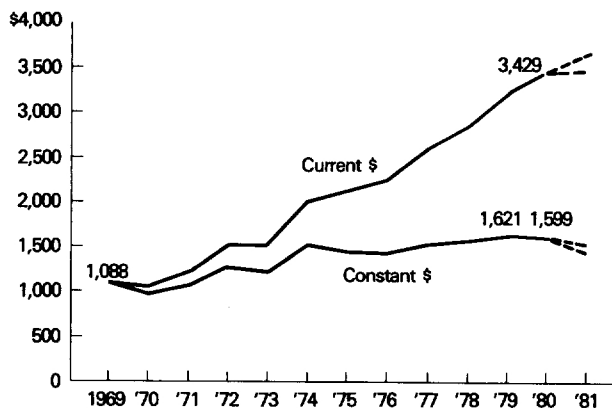


Figure 2. Obligations of the NIH in Current and Constant (1969) Dollars.

Obligated funds for the aggregate of NIH programs are shown for fiscal years 1969 through 1980, with alternate projections for fiscal 1981. In terms of constant dollars, the high point is 1979. Even the higher projection for 1981 (which has proved to be accurate) represents a decline in the purchasing power of 5.5 per cent, according to a price index for biomedical research and development.

over 1969 (Fig. 2). Since 1979, however, the tide has turned. The Congress, engaged in a struggle to set budget ceilings for itself, never passed an appropriation for the Department of Health and Human Services (DHHS) for fiscal year 1980, and the stopgap "continuing resolution" included \$1.6 billion (1969 dollars) for the NIH.

One could easily fail to understand the competition for funds for research if one sees that the NIH budget represents only a small fraction (less than 2 per cent) of the huge budget of DHHS (\$195 billion in 1980). Yet all but \$11 billion of the departmental budget consists of fixed entitlements for health and welfare. The budget of NIH was one third of the residual — "controllable" — fraction!

The 96th Congress also failed to pass an appropriation for fiscal year 1981. On its final day it approved a continuing resolution through June 1981, which brought the NIH budget to a projected annual figure of \$3.6 billion, or \$1.53 billion in 1969 dollars. This amount represents a decrease of approximately 5 per cent in purchasing power from the 1979 level. President Carter, in his budget message of January 15, 1981, proposed a rescission of \$50 million from the continuing resolution level. His proposal for NIH for 1982 was \$3.85 billion (an estimated \$1.49 billion in 1969 dollars).

The distribution of NIH support can be plotted on numerous axes. In one projection it is spread over categorical regions (related to organ systems and other diseases) and nonclinical disciplines that provide tools to help to reduce problems of biology and behavior to the more manageable molecular terms. These elements of the NIH are known as the BIDs (bureaus, institutes, and divisions), and 14 of them have separate appropriations individually defended in

Congressional hearings. This projection of activities (Fig. 3) thus reflects the one preferred by the Congress in its oversight of health research.

One of the most useful ways to examine the aggregate of NIH activities is to distribute them serially from a less differentiated "science base" through the stages by which discoveries proceed to practical applications (Fig. 4). This examination includes clinical trials, the transfer of useful inventions into practice, and some continued sorting through the doctor's bag to help decide what should be discarded. It is axiomatic that research activities must also include the training of scientists. I believe that the amount of training now subsidized is the minimum desirable fraction of federal support for health research.

COMMUNAL RESOURCES

Today's international biomedical-research system has a high dependence on certain resources and services, some of them maintained through co-funding or other cooperative means on an international basis. The National Library of Medicine in Bethesda is the world's principal curator for biomedical-research information. Nearly every country uses and contributes to its programs for data collection and retrieval. The demands for data management are rising rapidly, and new technical gains introduce marked jumps in need. For example, the accelerated ability to determine the structure of polynucleotides (including genes, messenger RNA, and viruses) is producing a stream of data that must be stored and made accessible so that its rich content of new knowledge can be efficiently used.

Biomedical science, represented by institutions supported by the NIH and the National Science Foundation in the United States and by the medical-research councils and similar organizations abroad, is also the curator of other kinds of living information. A huge inventory of organisms and other cell lines represents a priceless and irreplaceable chain. It grows daily, and so does the task and the cost of maintaining access to its components.

The NIH maintains a total of about 1200 beds for clinical investigation. Five hundred are at the Clinical Center in Bethesda, and the rest are grant supported. As hospital costs rise and constraints on use of facilities become more severe, much clinical investigation can only be conducted in units specially set aside for it. As clinical care and medical research increasingly involve ambulatory and often normal subjects, facilities for handling observations of these populations will become more and more important in the 1980s.

The NIH runs seven large primate centers. These centers are important not only for the research they do but also for breeding to replenish the dwindling world supply of valuable research animals. The installation and maintenance of large equipment such as scanning electron microscopes, electron probes, mass spectrometers, and many specialized data-manage-

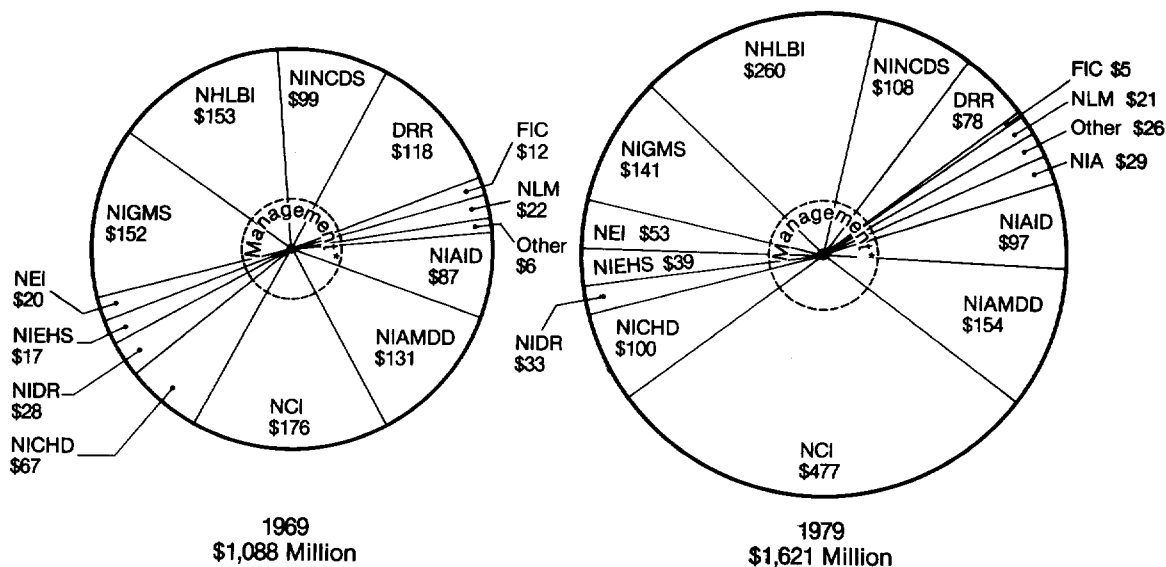


Figure 3. Obligations of the NIH by Program, 1969 and 1979, in Constant (1969) Dollars.

The institutes and research divisions of NIH accounted for \$3,185 million in 1979, which represents \$1,621 million in 1969 purchasing power.

The National Cancer Institute (NCI) shows a 171 per cent increase in constant dollars, while the Division of Research Resources (DRR, which contains the biomedical research support grants program) and the National Institute of General Medical Sciences (NIGMS, which contains a high proportion of NIH training programs) declined by 34 and 7 per cent, respectively. NIAID denotes National Institute of Allergy and Infectious Diseases; NIAMDD Arthritis, Metabolism, and Digestive Diseases; NICHD Child Health and Human Development; NIDR Dental Research; NIEHS Environmental Health Sciences; NEI Eye; NHLBI Heart, Lung, and Blood; NINCDs Neurological and Communicative Disorders and Stroke; FIC Fogarty International Center; NLM National Library of Medicine; and NIA National Institute on Aging.

*The costs of the Office of the Director and buildings and facilities are included here as costs of management.

ment systems are other examples of communal resources to be accommodated in each year's budget.

INVESTIGATOR-INITIATED RESEARCH

The most important scientific discoveries are made by investigators pursuing their own ideas. In competition for support, they are willing to set forth their hypotheses and the methods that they would use to test them. Once support is committed, it should be guaranteed for a reasonable period, and the scientists should be given latitude to adapt their methods to overcome unexpected barriers. In support of research by NIH, evaluation is both prospective and retrospective, and the whole enterprise is kept accountable by peer recognition and review. Under the prevailing strict and uncompromising arrangements, one must produce to stay in the system.

Most of the research that NIH supports is maintained through grants. A grant of the means to pursue new knowledge is different from a procurement contract, under which some kinds of scientific research and development are conducted. Among grants there are many distinctions. The largest share of NIH-sponsored, investigator-initiated research is supported by the "research-project grants" shown in Figure 4. A little over 16,000 such grants are in effect at any one time. The project grant is a commitment to support one or more scientists for a period of time, which now averages 3.5 years. In each fiscal year these continuing commitments are met first, and appli-

cants for renewal of their expiring grants join those submitting new proposals in competing for the remaining project-grant funds.

Since the total number of grants in the portfolio of a given institute reflects several cumulative years of

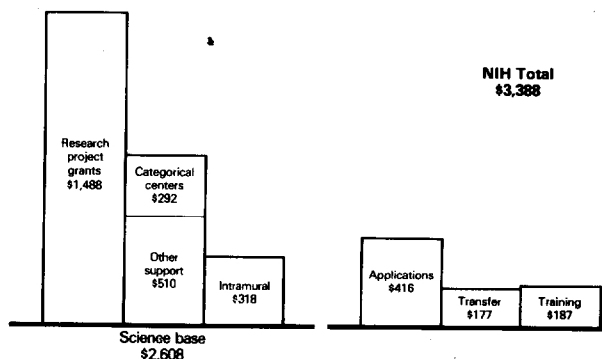


Figure 4. Distribution of NIH Funds, Fiscal Year 1980. Congressional appropriations totaled \$3,388 million (1980 column of 1981 President's budget). It is useful to distribute the research budget in terms of "SATT" — science base, applications, technology transfer, and training. The science base is further divided into investigator-initiated project grants, categorical research centers and other support, including research resources, and the intramural program, mainly at Bethesda. Research-project grants to scientists in non-federal laboratories and clinics constitute 44 per cent of NIH funds. Such grants include traditional research grants and program project grants.

funding, the "new and competing" awards made each year are subject to considerable change. The 1975 level (4600) fell in 1976 to 3460, rose in 1978 to 5200 and again in 1979 to 5900, and was fixed at 4800 in 1980.

Another source of instability is inflation, which has recently outrun budget projections. The average annual cost of a project grant was \$88,000 in fiscal 1979, \$99,000 in 1980, and an estimated \$108,000 for 1981. The total number of new and competing awards that are fundable is also affected by rises in indirect costs — the administrative and overhead costs of sustaining the research enterprise — that the scientist's institution can recover from the federal government. These rises now average more than 27 per cent of the cost of the grant.

The resources available for competing awards are affected by the many interests that must be accommodated by the institutes in preparing the federal budget and arriving at congressional appropriations. The 96th Congress, for example, debated budget levels (Fig. 2) that represented capacities to fund competing grants in fiscal 1981 in numbers varying from 3800 to 5000. These two projected numbers of grants represent an alarming difference. At the level of 3800 awards, an average of only one in four approved competing grant proposals would be fundable. The immediate effect would be to deprive over 1000 productive scientists competing for renewal during the year of the drop.

STRIVING FOR STABILITY

Such prospects have led us to search over the past five years for ways to seek stabilization and to set priorities in anticipation of austerity. The share of NIH research dollars for investigator-initiated research through research-project grants has been preferentially protected, whereas the shares going to clinical trials, developmental work under contract, categorical research centers, communal resources, control programs, and other forms of scientific endeavor have declined. An initiative for stabilization of the funding of project grants has had the endorsement of most of the health-research community. In the 1980 budget, the Administration agreed to request funds for approximately 5000 competing grants, and Congress appropriated that amount. Although President Carter twice found it necessary to reduce his 1981 budget, the 5000 grants survived both reductions. Congress ultimately included funds for the 5000 in the continuing resolution for fiscal 1981.

The willingness of the executive and legislative branches to support the principle of stabilization through these recent difficult years is a dramatic gesture toward continued public support of the biologic revolution.

RECRUITMENT TO SCIENCE

In the long term, the most devastating of the effects of financial instability is the discouragement of the

young from entering scientific research. It is a profession with a "high metabolic rate." The best NIH figures suggest a loss of up to 10 per cent of the scientists whom we support each year. In the United States, this loss can mean something on the order of 2000 principal investigators. There is inadequate information to explain this turnover. Some of it is due to loss of scientists to teaching, administration, or industry, and some of it to failure to compete successfully for renewed support. Whatever the reason for this turnover, a continuing tide of young people moving into research is crucial to the vitality of science. Their hands perform much of the research. Their enthusiastic curiosity is the oxygen required to keep the flame bright.

The federal government now supports some of the training of more than 50 per cent of the workers who are awarded NIH research grants. Training awards were introduced early (1938) as part of the NIH research program. For about 20 years, NIH grants and fellowships had perhaps the greatest influence of all federal programs on the organization and curriculum of the academic medical centers. They also provided the bulk of the American scientists who helped create the revolution in biology. The numbers of trainees maintained by the NIH on training grants and fellowships today is about half the number supported in 1965.

THE DWINDLING BEDSIDE CONNECTION

A disturbing feature has been added to the problems of replacement of scientists in the existing system of inquiry; it confronts biomedical research not only in America but in the rest of the world as well. Physicians and dentists are losing interest in being clinical investigators. The number of physicians seeking postdoctoral research training is declining, according to all available indexes (Fig. 5). The reasons for this decline are complex and include the indebt-

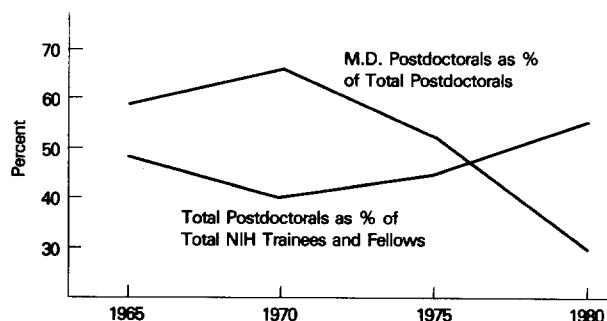


Figure 5. Percentages of Postdoctoral Trainees and Fellows and of Physician Postdoctoral Researchers, NIH, 1965 through 1980.

The total number of NIH trainees and fellows declined from 18,945 in 1965 to an estimated 10,284 in 1980. Over this period, total postdoctoral trainees, although declining in number, rose as a per cent of all trainees (48 to 55 per cent). Physician postdoctoral researchers, however, declined in both number and per cent (59 to 30 per cent) of all postdoctoral researchers.

edness amassed by many physicians in qualifying for their medical degrees, the higher percentage of graduates who are married, the economic disadvantages of academic employment, the contemporary interest in primary care, and the ascendance of life styles that are incompatible with spending weekends in the laboratory.

Another important reason is the changing demands made by science itself. The pace of advance is now so fast, and the shifts in required technology so frequent, that to be a first-rate scientist in addition to being a well-qualified medical specialist requires painful straddling of divergent ambitions. Students in the upper reaches of medical-school classes generally will not compromise with excellence in whatever they do. Therefore, in the 1980s the ranks of medical research will be increasingly filled by scientists who are not medically trained. We will need better training for nonmedical doctorates of a sort that will broaden perspectives in human biology and provide greater access and interest in paraclinical research.

PUBLIC RESEARCH AND PRIVATE PROFIT

The profits of the Industrial Revolution have made possible the biologic one. Conversely, technologic exploitation of discoveries from biomedical research has repaid part of that debt by revitalizing industries.

Thanks to biomedical research on proteolytic enzymes, proteins no longer precipitate in beer. My sources thus credit to such research the development of the canned and bottled-beer industry. Similarly, basic enzyme research has contributed technology to the billion-dollar laundry-detergent business. From studies on the preservation of biologic materials has come lyophilization, or freeze-drying — now a major procedure in the preparation of instant coffee and other food products. Structural studies of complex carbohydrates have led to the manufacture of bonded starches resistant to amylase, and these compounds are the most important stabilizers now employed in the food industry to extend the shelf life of food products. Even the drive to microminiaturization within the electronics industry is profitably exploiting our fundamental knowledge about lipid membranes.

If much of this profit-taking from adaptations of research far removed from the biomedical starting point has been obscure, the recent emergence of many professors of biochemistry as corporate executives has not escaped notice. The rush of investment capital into recombinant-DNA technology and the isolation or production of interferons, which are likely to be followed soon by commercialization of antibody production, represents a new wave of industrial exploitation of the more recent discoveries in biology. Much of the intensity is derived from a recent Supreme Court decision that new forms of life are patentable.

Celebration of this success should be tempered by concern for three unpleasant side effects that it will bring to biomedical research in the 1980s. Perhaps the

most superficial of these effects will be a tendency to forget that much of the basic research on which profitable development depends cannot be supported by industry or any other private sources. It is therefore alarming to hear sanguine expressions of confidence that private patrons would come forth to support all worthwhile scientific research if the federal government withdrew. One is reminded of the dismal failure of the National Research Fund, which was established in 1926 to channel industrial funds into basic research. A goal of \$20 million over a 10-year period was set, but less than 2 per cent of that amount was received by 1930. Four years later, \$356,402 was returned to the contributors.

A second source of unhappiness may be the unmet need for clinical investigators. This shortage has a bearing on the recent flood of private capital into biotechnology. It is obvious that assessment of safety and efficacy will be an essential step before profits can be realized from interferons, specific antibodies, or other biologic agents prepared in new ways. No industrial combine can or should undertake all the clinical trials that will be required. Moreover, potential conflicts of interest will make it necessary for many clinical experiments to be publicly supported.

In the long view, the ability of the academic wing of the scientific community to deal with the increased temptations of profit will be a severe test of biomedical research in the 1980s. The recent decision by Harvard University not to exploit recombinant technology for profit was important, for although Harvard is the university most able financially to forgo such investment, it would also have been the institution most widely imitated if it had so invested. One is always being reminded that chemists or scientist-engineers have managed to survive in ventures that have become excessively proprietary, but has their science maintained its excitement and pace with greater commercialization? *

We have only just learned how unlimited freedom of communication — making possible the most rapid and complete synthesis of experiences into wisdom — has allowed us to pass through the period of anxiety over recombinant-DNA technology without any evident harm to science or the world. Secrecy in science is anathema. Biology, as the science of life itself, is under special ethical constraints to remain as free as possible, and thus open and preeminently humane.

THE ZERO-SUM BALANCE

Biomedical research in the 1980s will require as much creativity in adapting to austerity as was evident in the period of maximum growth. When reallocation of resources becomes a zero-sum game, some of the rules need to be modified. All players must suppress narrow interests to the degree necessary to maintain the whole of the enterprise in balance with

respect to several key equilibriums: selective growth in areas in which scientific opportunity is hottest and persistent activity in colder areas in which need of knowledge is still great; highly categorical programming and the provision of communal resources with broader institutional support; the need for continuing quality control by competitive review and the longer-term investments merited by scientists of proved productivity; and a full continuum of activities from the most fundamental to the most practical ends of biomedical research.

The allocations of NIH resources shown in Figures 3 and 4 do not necessarily represent a perfect harmony of the balances just described. The categorical distributions (Fig. 3) shown for 1969 and 1979 reflect the play of scientific, social, and political factors. Because each institute supports fairly broad basic research as well as its categorical activities, adjustment to the ever asymmetrical nature of scientific opportunity is better than a superficial view of the situation might suggest.

Nevertheless, the distribution of resources needs to be frequently and systematically tuned. There is a requirement for a continuing technical and collegial process for setting (or at least recommending) priorities for allocations within the vast area covered by all the institutes. The Administration and the Congress clearly have final powers and responsibilities for these determinations. Their task can be aided by analyses emphasizing aggregate distributions of activities, represented in Figure 4. They have recently adopted such a global view in endorsing and supporting the move toward the stabilization of one portion of the resource allocation — the annual number of competing research-project awards. The next steps involve similar attention to the other essential elements of research support and the balance among them. For some of these elements, we have already reached the limit of sacrifice for maintaining the ability to award project grants.

Necessary economies in public spending for research in the 1980s may also create some especially difficult challenges for educational institutions. We have come to think of teaching hospitals as different from the ordinary kind. Now we hear talk of "research universities." Few of us were alive when the healing arts were learned in places that had no laboratories beyond the abattoir, no libraries but a shelf of old texts and proprietary pamphlets, and no bridges to connect the questions raised by illness to the answers lying in research. The health sciences have led the healing arts out of dark empiricism, and there must be no retreat.

The same is true for the university's need for an intimacy between scientific inquiry and teaching. Again, the highly categorical project orientation of the NIH places the universities in jeopardy when teacher-researchers in the faculty lose their grants.

If the biologic revolution, now so well launched, is to be sustained through the 1980s and beyond, a *sine qua non* is increased attention to the government-university interaction in science. From the beginning, there has been a partnership of mutual need and support. Yet strains and misunderstandings abound and add to the problem of shrinking resources. In the 1980s, the NIH, the layers of government above it, and the members of the academic-science community must consult and work together to keep the partnership whole. Three aims in particular warrant careful examination: ensuring continued strength in the research capacity of the academic partners; attaining reasonable accountability in the use of public funds for science, without an excessive burden of accounting; and establishing basic concepts of cost sharing between the government and the university.

A sound partnership will temper the effects of economic stresses on the realization of the unparalleled opportunity in the health sciences.