1981

1980-1981 Report of the President

The Rockefeller University

Report of the President, 1980 & 1981

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The Rockefeller University

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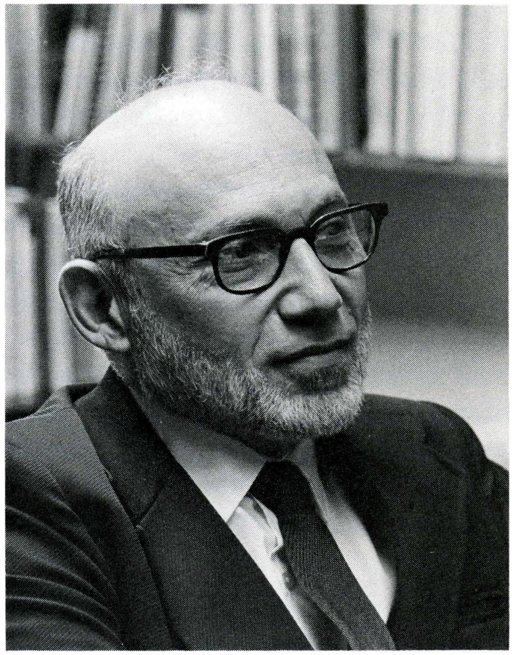


Joshua Lederberg, *President*

JUST two years ago, I presented my first report as president of The Rockefeller University. There, I portrayed the distinctive challenges to the University as seen by an enthusiastic new recruit. With undiminished enthusiasm, I can now bring to my second report a better-informed appreciation of the practical tasks of leadership. This periodic stock-taking of our progress is also a reaffirmation of our mission: to seek new knowledge as the most fruitful way of achieving public benefit, as well as to sustain the traditions of a major scientific institution.

The prospects for basic advances and practical "payoffs" from the life sciences have never been brighter. At the same time, many forces in the social, economic, and political environment are pressing on the world of research. Tremors in the global and national economy erode the institution's reserves and the indispensable nourishment of basic science from federal funds. The very advances of biological research in recent decades have evoked both peril and

promise in the public mind. Clear understanding of the linkage between basic discovery and applied benefits demands much more analysis and less passion.

I had the privilege and joy of working at the research bench for more than 30 years before assuming the administrative tasks of leading a great institution and explaining it to those from whom we seek support. On the basis of that experience, I honor these challenges as a personal and institutional opportunity to respond with confidence and credit. This report will stress the issues raised by the very complex external environment in which science today must play its part. In that environment, our own institution has a special role. In order to succeed in it, we must respond to society's expectations of science and technology and must articulate our mission in the system of scientific discovery, technological design, and public dissemination of their fruits.

Rockefeller University: Then and Now

This University was founded, as The Rockefeller Institute for Medical Research, some 80 years ago. It was designed to launch the scientific investigation of medical problems in this country and to match the heroic accomplishments of European medical science, symbolized by such "Microbe Hunters" as Louis Pasteur and Robert Koch. Here, too, infectious diseases took the center stage; but the Institute's first director, Simon Flexner, also emphasized the most fundamental research in biological and chemical science. From its beginnings, The Rockefeller has always encouraged a balanced convergence of clinical investigation and basic scientific activity. Many scientific advances had their roots in the wards and laboratories of The Rockefeller University Hospital. In turn, many clinical insights have been inspired by basic findings in biology and chemistry. Nevertheless, many medical institutions are experiencing the growing divergence—even alienation—of these two streams of investigation, a trend we work to forfend.

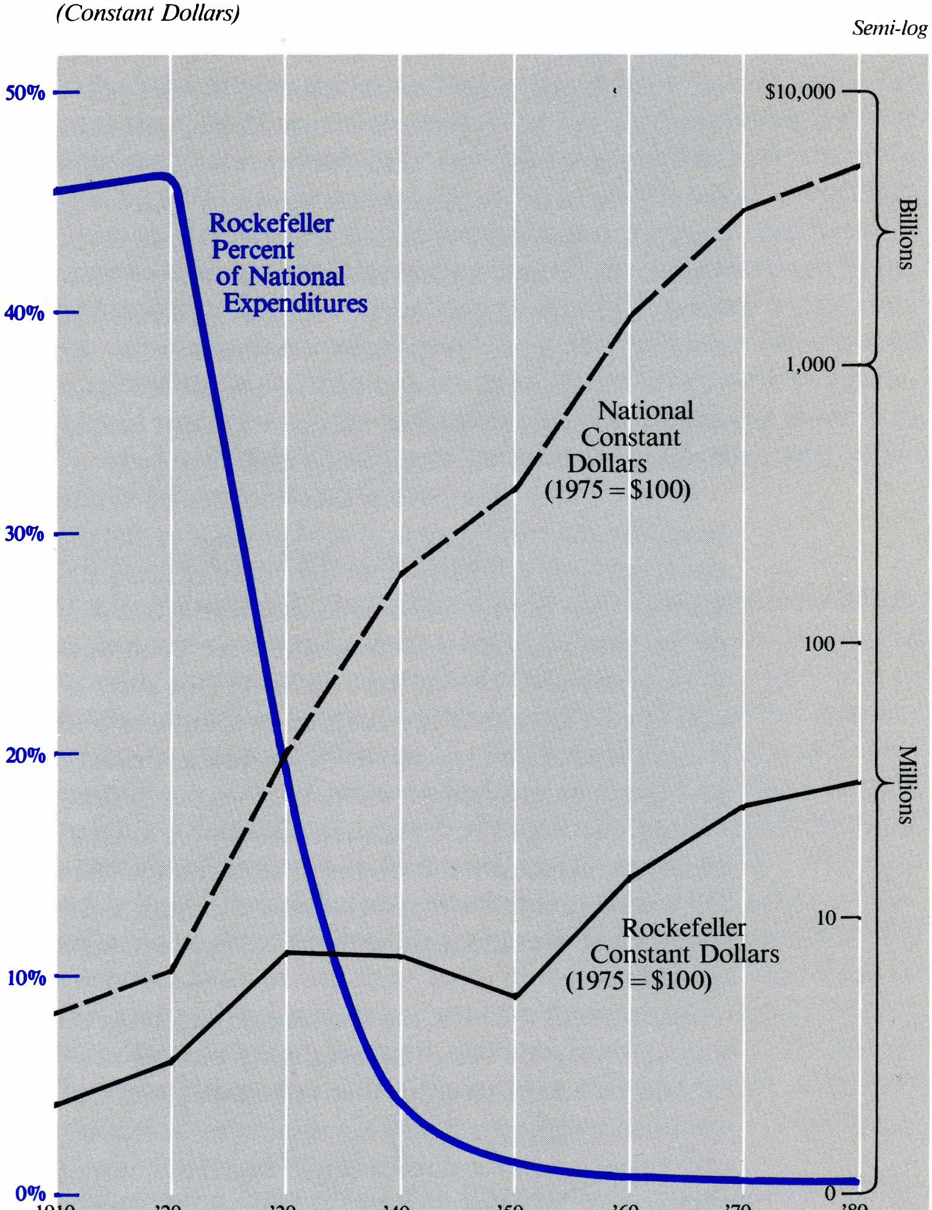
During the early years, The Rockefeller, thanks entirely to the generosity of a single private donor, enjoyed a remarkable share—initially almost half—of the total investment in medical research in the United States. The Institute soon achieved preeminence in the

scientific life of the country and furnished a model for the creation of similar research centers. That tradition of leadership is today a unique asset and responsibility, but the national investment in biomedical research and its allocation have, of course, changed dramatically. In 80 years, as measured by annual budgets in "constant dollars," the University has grown by a factor of about 15, but medical research nationally has grown by a factor of 1,000 (Chart 1, page 4). Most of the national increase and three-fourths of our University's were made possible by the commitment of federal funds, through the National Institutes of Health. Having been thus emulated on a very large scale, we now account for barely one percent of the national expenditure in biomedical research. Our special impact is now expressed by the quality of our people and our distinctive organization and traditions, rather than by gross level of effort.

It in no way diminishes the Rockefeller family's role, in the founding and early growth of the University, that their personal generosity cannot alone shoulder the vastly expanded costs of a mature institution. The scope and expenses (some $55 million in 1980-81) of this university of science would have been unimaginable when the first few laboratories were opened in the early 1900s. The largest part of this growth is represented by numbers of laboratories, the wealth of scientific specialties that give the University a formidable profile in almost every pertinent area—from molecular and cell biology to behavior and clinical investigation. A related investment that has borne valuable fruit was the introduction in 1954 of the graduate fellows program, the formal scientific training leading to the Ph.D. degree that was associated with the change of name from Institute to University.

For much of the '70s, the University, like many other institutions, was seriously buffeted by escalating energy costs, general price inflation, and the slowdown of federal support. Substantial deficits enforced a tighter rein on expenditures, a realistic adjustment of self-image, and a reexamination of its central purposes. The conclusion was to focus on our institution's traditional success in a balanced program centered on biomedical research, like that inspired by Flexner. This would necessarily be extended to include studies of the behavior of the entire organism and to draw on special insights

Chart 1. Expenditures for Biomedical Research
(Constant Dollars)



In 80 years, Rockefeller University expenditures on biomedical research have grown fifteenfold, total national expenditure a thousandfold. The University now accounts for one percent of national investment in biomedical research.

from the mathematical and physical sciences. Unlike many larger institutions, however, we are not hostage to large-scale fixed obligations for undergraduate education or general medical services. Hence, we can continue to work within a simple administrative structure—with individual laboratories reporting directly to the president—that avoids the politics and overhead of potentially divisive departments and separate specialty schools.

The University's successful discipline in a time of economic insecurity has helped us to inspire the support of many private donors, reached by a general fund-raising effort organized barely ten years ago. With their help, the University has been able to balance its fiscal accounts and to make a realistic projection of future needs and resources. The model envisions that the University will continue to maintain its present scope and mix of programs, with 55 or 60 laboratory groups. A dynamic equilibrium will be achieved by balancing retirements of laboratory heads with new tenured appointments and promotions. Each such opportunity will be the occasion for a fresh examination of the University's needs and priorities. It will also be a time to allow for the continuing professional advancement of our most talented younger faculty. Within the limits of a balanced size, our system thus provides for evolutionary changes to meet new scientific opportunities, unencumbered by squatters' rights of existing specialties and departments.

This might appear to be an unglamorous model for the future, building as it does on our past traditions. To the contrary, we should be reassured that The Rockefeller has exhibited extraordinary breadth and strength in its established disciplines. With a few exceptions, these evolutionary accommodations provide ample openings for fresh insights and new technical approaches. Our present size encourages a quality of collegial communication that would be diluted by rapid growth, even if this were permitted by available fiscal resources.

Biomedical Research Today

In many ways, The Rockefeller University is a microcosm of the national effort in medical research. Economic strictures in federal funding for basic science have been less a general cutback than an

end to growth in available resources. This has already collided with a hard-won fruition of maturing and capable scientists who have enormous potential for making contributions to scientific and medical knowledge.

This disparity between shrinking funds and burgeoning talent and scientific opportunity has intensified the competition for established resources and positions. It has eroded the stability of support for research programs. It aggravates the anxieties of investigators about their opportunity to continue research. It tends to immobilize them in location and in scientific interests. It impels them to spend enormous amounts of time and emotional and intellectual energy in entrepreneurial ("grantsmanship") activities at the expense of their central passion and responsibility. By maintaining a stable setting for a faculty of excellence, The Rockefeller University makes an extraordinary contribution in substance and by example. The ebb and flow of government support and the rigidities it imposes (in the name of accountability) are a major source of the pressures. Hence, it is the University's autonomy as a privately supported institution, that bridges the financial gaps and crevices left by spasmodic public funding. Not for many years has it been possible for any institution to match from other sources the federal support it received for the major portion of its research expenses. However, even modest general funding for this bridging of contingencies greatly amplifies the efficacy of government funding.

The University has a most successful tradition of supporting and developing creative leaders in research. Hence, programmatic orientation tuned to trends in research support takes second place to sustaining an effective style of research career. We aim to furnish first-class investigators the freedom to set their own directions and determine their own research objectives. For the University to continue to do so will require extraordinary effort in the face of global economic difficulties and their impact on government, corporate, and individual philanthropic investment in science. The commitments made by the University to its faculty and major programs span decades. The funds to meet them must be anticipated and provided for over a much longer period than their sources can be accurately foreseen. The most reliable long-term source of funds—the real in-

come from endowment—covers scarcely a fourth of our operating budget. However, this is the margin that enables us to underwrite our plans against the uncertainties of year-to-year support.

No single measure of inflation assures an authentic picture of the institution's financial standing in a single year. For example, the recent high interest rates resulted in a temporary rise in our revenues. On the other hand, many of our future expenses will, no doubt, increase in the same measure, but will not all be reflected in a single annual statement. In addition, the University is just now catching up with many long-delayed maintenance tasks and laboratory renovations. However, our ten-year projections—premised on sustained effort in our development program—show a continued equilibrium of income and expenditures. These forecasts are the most realistic tools for long-range planning. Table 1 on page 8, prepared by David J. Lyons, the University's vice president and controller, is another effort to review the stability of our endowment reserve through the turbulence of the last decade. The outcome is, of course, highly sensitive to conflicting measures of real costs of research, but it does provide reassurance that the University can manage its affairs successfully even through such storms.

Sustaining Public Confidence

Despite the leveling off in federal funding, biomedical research still enjoys a privileged place in the expectations of the public. The NIH and similar programs were almost the only ones, besides national defense, to escape crippling wounds in the 1982 federal budget. Continual strictures in federal expenditures have, however, made deep inroads in the integrity of many programs in research and graduate training.

We have a special opportunity and obligation to sustain public confidence, and the University's concern for critical scrutiny of our research converges with that of the larger society. This is directly related to the ongoing renewal of our faculty. The premise of our system of career appointments is the most stringent selection of those who receive them. In exchange for that stringency, the University gives those appointed the widest encouragement and the support they deserve as leaders in the difficult paths of scientific discovery.

That so much responsibility is delegated to the laboratory heads is precisely why these choices must be so closely scrutinized. The first criterion is, of course, the investigative excellence of the candidate. Then we may optimize our choices with respect to the fit of a candidate to the institution's primary mission as a biomedical research center and a community of scholars, and to other dimensions of campus life.

No one can accuse this institution of making its choices on the basis of parochial relevance. Historically, the University's most distinctive characteristic has been the conviction that our explorations need but go deep enough for discovery to relate to profound human benefit. Nonetheless, we must recognize that outside forces often demand short-term yields that are simply unachievable: least of all by insistence on "targeted" research. The NIH budget is, in fact, the largest federal commitment to basic science: a preponderance that is socially justified by benefits to public health that derive from the most fundamental knowledge of living systems. This is not a universally recognized linkage. For one thing, the partial successes of semi-empirical medicine with vaccines, antibiotics, and psychotropic medications have obscured how incredibly crude our insight is about how and why these interventions work—how far medical scientists are from the kind of understanding that unites the physicist and the integrated-circuit design engineer. It is not lack of ingenuity or diligence; it is the inherent complexity of living organisms—above all the human—that frustrates our moving medical care and preventive health into the realm of design enginering. To meet such an ambitious goal entails still more basic research, on a scale that would remain a small percentage of expenditures on health care. Despite many isolated improvements, the overall limits to our success in dealing with cancer, even during the last decade, illustrate the shortfall in our needs for basic biomedical knowledge.

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

tion of health technology is not in the hands of scientists, but is the preserve of two other communities—the medical practitioners and the pharmaceutical industry. These two groups are closely coupled to a health economy with very large revenues. Basic research is not. Considering the attendant pressures so evident on the public scene today, it would be a mixed blessing if basic research were so coupled. The research laboratory is not well organized to get "results" in a sphere that depends more on market analysis than it does on scientific understanding.

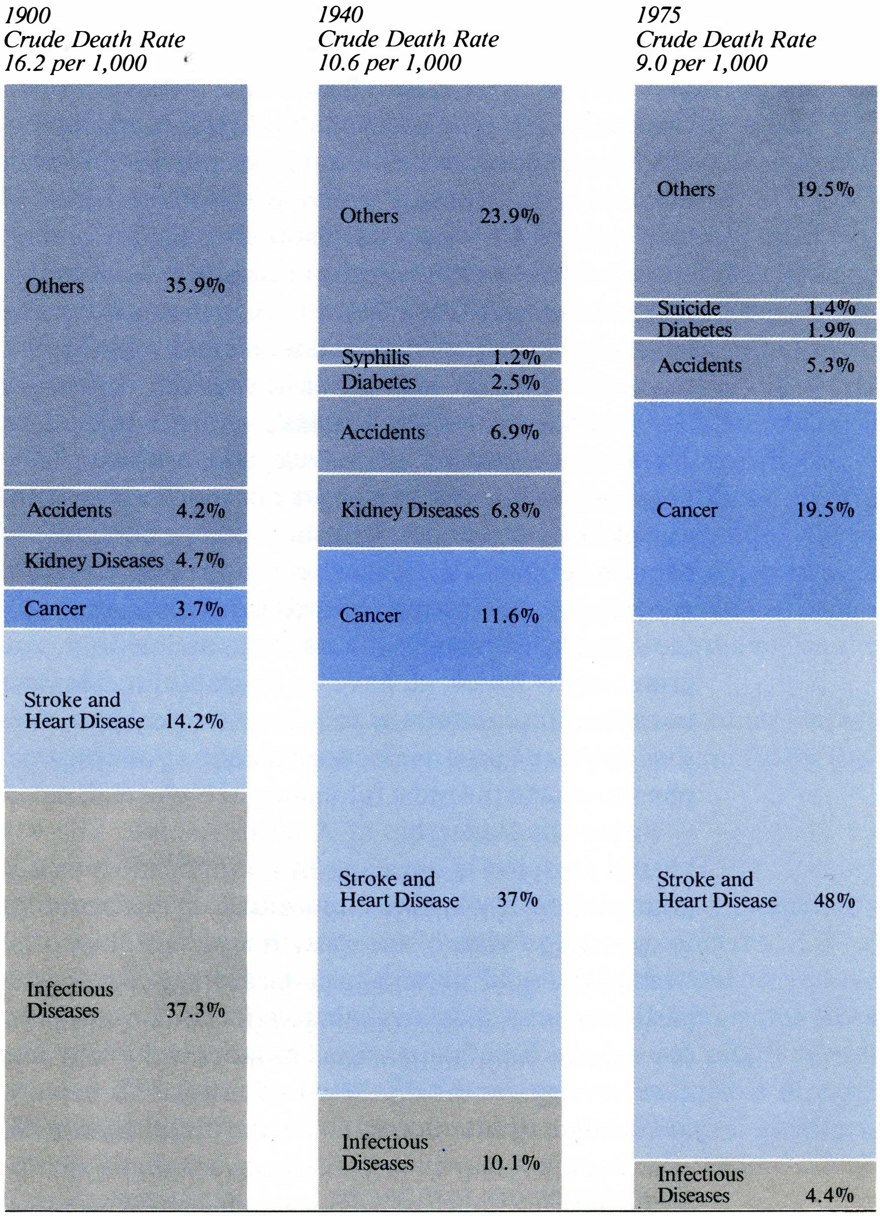
Equally unfortunate is the quarrel between some advocates of public policies for preventive health and of rational medicine. There is no controversy that disease-prevention is vastly preferable to the most sophisticated of cures. It is also true that important improvement to personal health is achievable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

We may recall that, in the last century, cholera was believed to be a visitation for sin; many still place sexually transmitted diseases in that category today. Whatever the merits of these views as moral philosophy, they have been far less productive of material health advances than an understanding of the biology of the causative organisms and development of specific measures against them (Chart 2).

A Question of Balance

Yet it is uncertain whether scientists have been able to articulate a sufficiently persuasive response to the taxpayers' expectations. Both in rhetoric and in policy, we face a delicate task of balance for our own institution, to maintain its distinctive genius, and to fulfill the

Chart 2. Major Causes of Death in the United States 1900-1975



Causes of death: In these crude death rates, the largest factor in the shift is the "conquest" of infectious disease and the resultant rising age level, as shown by the increase in cancer and heart disease.

mandate of our motto: *pro bono humani generis.* Of course we should eschew applied research tasks to which we are ill-suited. However, there is no contradiction between hewing to our pursuit of basic knowledge and educating ourselves about the realities of disease as a rich source of puzzles of biological behavior that stimulate our theoretical imagination. Nor should this mandate for a well-knit institution be confused with intrusive and unrealistic demands on individual investigators. We may again look to Simon Flexner's initial conception of a balanced institution encompassing an unbroken spectrum of basic to clinical investigation, from the laboratory to the research-hospital ward. Many universities and medical schools have jeopardized that balance, and weakened support for and useful intercommunication with the basic sciences, by assuming the obligations of large teaching hospitals and the related heavy and self-aggravating burdens of service and practice. This development deepens the imperative that we sustain The Rockefeller University as a place where clinical investigation can be significantly represented without swallowing up the entire research effort. That clinical component, embracing research on distinctive problems of human biology and pathology, makes it impossible to put out of mind the grievous ills which we have an obligation to alleviate. It also alerts our scientific community to pathobiological processes, information that time and again has opened our eyes to previously ignored phenomena of the most fundamental biological importance.

Under the leadership of Attallah Kappas, The Rockefeller University Hospital is engaging in a significant renascence of its programs. Notable are major new efforts in endocrinology and dermatology. The focus of interest in endocrinology in the laboratory headed by Jack Fishman is on the biology of steroid hormones with particular emphasis on their role in human physiology and pathophysiology. The laboratory of cutaneous biology and investigative dermatology, under D. Martin Carter, will explore fundamental mechanisms that are operative in the disabling skin diseases.

Complementary Institutions

In the University's continuing effort to maintain an optimum balance in its research efforts, we have a considerable advantage in the

close proximity of two major patient-intensive hospitals—Memorial Sloan-Kettering Cancer Center and The New York Hospital-Cornell Medical Center. The development of a dermatology program at our hospital was made possible by opportunities for research collaboration with New York Hospital-Cornell. Similar collaborations are under discussion with the Population Council's Biomedical Research Division, whose laboratories are situated on our campus, and with Memorial Sloan-Kettering.

It is in clinical research that our strengths and interests most evidently complement those of our neighbors. We are also seeking every other means to further the maximum good from our collective human and physical resources. The three institutions at the intersection of York Avenue and East 68th Street are—by world standards—a formidable concentration of medical interests, services, and science. Increased communication and collaboration within this complex will go far to ensure that our scientific efforts are informed by human health needs. In turn, no opportunities will be overlooked to go from research advances to practical application at the earliest occasion. In addition, choices of programs to be further emphasized can be made in the light of existing strengths within the complex.

The metropolis has a rich academic culture at many other places, as well, and as a specialized center we are particularly grateful for that environment.

Public Health Problems

If there is a significant weakness or imbalance in the complementary efforts of the three institutions to address human concerns, it is related to certain widespread problems of public health and preventive medicine. This imbalance is national, even global, and stems from the relative poverty of funding available for research programs not related directly to an existing and potentially remediable disease. Especially impoverished is work on the parasitic scourges, which primarily attack the populations of developing countries, locked in a vicious cycle of ill health and low economic productivity.

In the latter category, we are continuing our traditional support of work in parasitology with a particular view to unifying it with modern

developments in molecular and cell biology. These will have most exciting, as well as useful, applications for such tropical diseases as malaria, trypanosomiasis, schistosomiasis, leishmaniasis, and filariasis—scourges happily almost unknown in this and other of the more developed countries, and for that reason grossly neglected. It is with particular gratification that we can announce the recent appointment of George Cross, a molecular parasitologist, who will come here from England. We will also be working closely with The Rockefeller Foundation's global network on the "Great Neglected Diseases," for example in the organization of summer laboratory courses at the Woods Hole Marine Biological Laboratory.

In the category of protective health problems not directly related to disease, a vitally important research need is an effort to put environmental toxicology on a scientific base. The last decade has seen a dramatic awakening of public concern over the injurious effects of certain substances. This is a long-overdue reaction to neglect and ignorance of the power of an industrial society to pollute even the global environment. It has been accompanied, however, by stringent regulatory controls that threaten to hinder industrial development at a time when our economy is already under heavy pressure. These costs may be unavoidable in the light of potential hazards to public health, but in the present state of our knowledge they are too often inflicted on the basis of alarm rather than proven assessment of hazard. This unproductive impasse cannot be a stable basis for national policy, and any improvement must be based on sharper tools for predicting the actual hazards to human health from exposures to substances for which some alarm has been elicited from limited laboratory findings. That the Congress has singled out saccharine for exemption from the prevalent standards of food-additive regulation illustrates the arbitrariness of judgment that now prevails.

Toxicology, as an academic discipline, has suffered sharply from being too tightly coupled with routine regulatory test demands. In fact, as a scientific challenge, toxicology is intimately connected with the most intricate issues in molecular and cell biology. Many of the most basic discoveries in metabolism and in neurobiology stem from the investigation of toxic effects of particular substances. With the gratifying endowment of The R. Gwin-Follis-Chevron Chair by

the Standard Oil Company of California, we are in the position to seek the leadership for a major program in comparative toxicology.

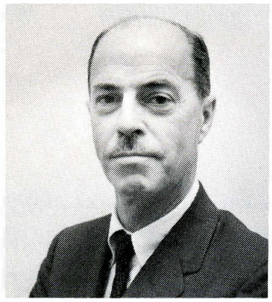
The Basic Sciences

The areas of clinical and public-health science just surveyed have, of course, the most immediate relationships to the practical problems that are the justification for public investment in The Rockefeller University. In danger of being overlooked is the intricate connection between these public fruits and the basic scientific work that fully defines our mission. Historically, the University has made innumerable and invaluable contributions to public health. These include the development of vaccines, the transfusion and preservation of blood, the monitoring of body metabolism in pathological states, research underlying organ transplantation, and a host of other therapeutic techniques. Such advances are indispensable to the really important triumphs of medicine, but only the most sophisticated of observers could know the distant origins of such triumphs in the laboratories of the biochemist, molecular biologist, or biophysicist. The basic contributions are overshadowed by the communities of other technologists and practitioners, who interface much more directly with the public.

A notable example is the discovery of the biological significance of DNA, brought to light in 1944 by Oswald Avery, Colin MacLeod, and Maclyn McCarty (page 16). The historical links between that momentous discovery and the current technological breakthroughs in recombinant DNA methods and genetic engineering are unambiguous and well known within the scientific field. However, it would be hard to find a mention of them in the prospectuses for new industries spawned by DNA science; nor is there any direct way that the University can be rewarded, precisely because this was such a fundamental discovery. Could the interval of more than 35 years between discovery and invention have been shorter? Probably not, in view of the extensive superstructure that had to be built on the initial finding.

When it comes to medical applications, I have sometimes asked, during the past decade, whether DNA science has yet made a contribution to medical practice to match the revolution it had brought

Oswald T. Avery



Colin M. MacLeod

Maclyn McCarty

STUDIES ON THE CHEMICAL NATURE OF THE SUBSTANCE INDUCING TRANSFORMATION OF PNEUMOCOCCAL TYPES

Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III

By OSWALD T. AVERY, M.D., COLIN M. MacLEOD, M.D., and MACLYN McCARTY,* M.D.

(*From the Hospital of The Rockefeller Institute for Medical Research*)

Plate 1

(Received for publication, November 1, 1943)

Biologists have long attempted by chemical means to induce in higher organisms predictable and specific changes which thereafter could be transmitted in series as hereditary characters. Among microörganisms the most striking example of inheritable and specific alterations in cell structure and function that can be experimentally induced and are reproducible under well defined and adequately controlled conditions is the transformation of specific types of Pneumococcus. This phenomenon was first described by Griffith (1) who succeeded in transforming an attenuated and non-encapsulated (R) variant derived from one specific type into fully encapsulated and virulent (S) cells of a heterologous specific type. A typical instance will suffice to illustrate the techniques originally used and serve to indicate the wide variety of transformations that are possible within the limits of this bacterial species.

Griffith found that mice injected subcutaneously with a small amount of a living R culture derived from Pneumococcus Type II together with a large inoculum of heat-killed Type III (S) cells frequently succumbed to infection, and that the heart's blood of these animals yielded Type III pneumococci in pure culture. The fact that the R strain was avirulent and incapable by itself of causing fatal bacteremia and the additional fact that the heated suspension of Type III cells contained no viable organisms brought convincing evidence that the R forms growing under these conditions had newly acquired the capsular structure and biological specificity of Type III pneumococci.

The original observations of Griffith were later confirmed by Neufeld and Levinthal (2), and by Baurhenn (3) abroad, and by Dawson (4) in this laboratory. Subsequently Dawson and Sia (5) succeeded in inducing transformation *in vitro*. This they accomplished by growing R cells in a fluid medium containing anti-R serum and heat-killed encapsulated S cells. They showed that in the test tube as in the animal body transformation can be selectively induced, depending on the type specificity of the S cells used in the reaction system. Later, Alloway (6) was able to cause

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* Work done in part as Fellow in the Medical Sciences of the National Research Council.

Opening page of the DNA paper, published in 1944 in *The Journal of Experimental Medicine*

about in biological research. To pursue this question, we should review the development of biomedical research of the past century.

About a hundred years ago, the germ theory of disease was the principal foundation of modern scientific medicine. Antisepsis saved innumerable lives in childbirth and in surgery. Elementary hygiene and protection of food and water supplies from contamination saved even more. As bacteria were grown in pure culture and identified as specific agents of disease, vaccines could be developed. The aspects of applied medical microbiology concerned with bacteria reached their zenith in the 1950s with the wonder-drug antibiotics, which have totally reversed the odds in the battle between afflicted patients and many infectious invaders. The development of polio vaccines soon after was a similar culmination, in the public's awareness, of the application of basic findings in virology to the conquest of infectious diseases.

The human benefits from scientifically informed attack on the problems of infectious disease are incalculable. Lamentably, we have not seen the last of threats to health from microbes and viruses. Antibiotic-resistant pathogens evolve in the most troublesome way, and may yet provoke major epidemics difficult to control. Vaccines for pneumonia, having been preempted almost 40 years ago by sulfa drugs and antibiotics, have been dusted off the shelves and are reemerging as a delayed fruit of the Rockefeller Institute's research. Most virus infections still defy systematic treatment: only with a clear understanding of the genetic structure and evolutionary potential of the influenza virus, and of its protein structure, can we develop fully effective prevention for this debilitating disease, which may affect tens of millions of people in an epidemic year.

This extraordinary success of medical science between 1880 and 1950 was the main inspiration for vigorous national support of research modeled largely on The Rockefeller Institute: the federally funded programs of the National Institutes of Health. However, with these same dramatic successes against infections, our priority health problems have shifted to heart disease, cancer, and psychiatric illness. The inherent intricacy of these problems, which are rooted deeply in the molecular and cellular structure of the human organism, outreaches the existing base of applicable scientific

knowledge. This ignorance has frustrated the building of a theoretical program for the control of these killers comparable with the advances in the golden age of bacteriology to which Rockefeller scientists made such historic contributions.

This frustration is partly obscured by a number of valuable piecemeal advances in all of these fields, by the proliferation of high-technology diagnostic machines, and by the development of scientifically trained, sophisticated specialties to make these accessible to patients. This technological revolution has also carried a heavy price tag, and some political pressure for cost-reduction that would better be directed to benefit-improvement. The training of these specialists has been the main contribution of academic medical institutions to today's "half-way technology" in medical care. Most of the important new drugs of the past 30 years have been discovered through empirical, not rational, procedures and in industrial, not academic, laboratories. Empirical as they are, these discoveries also depended on an infrastructure of scientific knowledge to calibrate how drugs like aspirin, chlorpromazine, or thiazides can best be employed. Equally important, a host of spurious remedies would be firmly planted in our medicine cabinets without the certification of efficacy and safety that must be informed by the most rigorous scientific judgment.

This perspective on recent medical science is a controversial one. It deviates from the optimistic forecasts of the 1950s and from the "crusade against cancer" of the '70s that seemed to promise an early solution to these pervasive health problems. Many believe in a more rational reductionist approach to medicine that would be firmly based on rigorous scientific knowledge, and would give academic laboratories greater credit for practical health advances. In fact, I firmly espouse that view; my critical reflections have to do with the time-scale of these expectations, and with an authentic reading of the actual history of the last 30 years. My greatest fear is that scientific insight is dissynchronized with public understanding. Instead of sensing the remarkable opportunities through which science can contribute to society—opportunities that, historically, occur in cycles—the public may become disillusioned; the result could be retrenchment of research support.

The current cycle is impelled by the most fundamental of biological sciences, the study of DNA and proteins. It can now be estimated that the human body contains some 100,000 different and distinct categories of proteins. As organisms, we are a hundred—or a thousandfold more complex than the microbes we target in warding off infectious disease. Today, we have some skimpy knowledge of perhaps 1,000 of those human proteins: we have scratched the surface to a depth of one percent! Almost everything we attempt in rational medicine is connected with the structure and behavior of proteins. We stumble in a dark cave, guided more by intuition and trial-and-error than by a readable topographic map. Our hopes for radical interventions to prevent or reverse such complex processes as cancer or aging can scarcely outpace that knowledge.

Until about ten years ago, our methods enabled only crude guesses at these orders of complexity. Today, news of DNA pervades the stock market. It may be woefully ill-informed in detail, but it has accurately mirrored the confidence and energy of investigators who are rapidly developing these new biological tools at an escalating pace. No prophecy can be safe: but all of the crucial disease threats to human life now fall within the reach of fundamental molecular and cellular investigation. Just this scientific base remains the main core of The Rockefeller University's programs. If we can sustain our courage, critical candor about the historic stages of development of medical science, and public confidence, we can indeed complete a new cycle of health benefit to match that of the heroic conquest of bacterial infection. To underestimate either the hurdles or the fruits will vitiate our effort.

The Spectrum of Science

The breadth of the University's commitment to fundamental biology defies compact summary. It can be found in the reports of the majority of our laboratory groups. Their work ranges from the ultrastructure and biophysics of cell membranes to the neuronal basis of bird song. This institution has been designed to be of such a size and scope that it can just encompass almost every important field of biological investigation, and is structured so as to facilitate communication among its specialists.

A few words, then, about several movements for change within this well-established setting. The neurosciences have been an important tradition at Rockefeller University. For example, its second director, Herbert Gasser, was a pioneering neurophysiologist who introduced the oscilloscope into that line of research. For the last 20 years, a fertile intersection of neurophysiological research with the integrative outlook of the behavioral scientist has been the contribution of Carl Pfaffmann and the group he helped to develop at the University. Recent and imminent retirements now impel a special emphasis on renewal in this general field, and we have been marvelously assisted by the benefactions of the Astor Foundation. In my next report, I hope to announce several recruitments.

We can already take pleasure in the move now underway to our campus of the Neurosciences Research Program (NRP), formerly at Boston, Massachusetts, and presently directed by Vernon B. Mountcastle of The Johns Hopkins University. The NRP is sponsored by the Neurosciences Research Foundation under the chairmanship of William T. Golden, a member of The Rockefeller University Council. One of the major activities of NRP at The Rockefeller University is a new Neurosciences Institute; Gerald M. Edelman of our faculty, who serves as scientific chairman of NRP, will be its director. Working with Dr. Edelman, a scientific advisory committee directed by W. Maxwell Cowan of the Salk Institute will extend invitations to brain scientists the world over who wish to use the facilities of the Institute. Visits by these scientists will enrich communications here and elsewhere and help us to understand the challenging problem of the basis of higher brain function.

Similarly, the University recently reaffirmed its longstanding interest in the lessons to be learned from the botanical world. In the new laboratory of Nam-Hai Chua, DNA methodology has been applied to study fundamental aspects of protein synthesis that are important to the efficiency of plant photosynthesis. This research could have an important bearing on the improvement of the productivity of major crop plants and testifies to the continued vigor of a university tradition pioneered by Louis O. Kunkel, Wendell Stanley, and Armin Braun.

Advances in molecular biology have gone so far that one possibly

overenthusiastic commentator has bewailed the looming lack of unsolved scientific problems. That may be for the next millenium; meanwhile the translation of genetic blueprints into the fabric of the organism, i.e., the problem of development, is one of our most urgent and exciting challenges. We are gratified at the further rejuvenation of our research programs in this field through the recruitment of Robert Roeder, a world-esteemed colleague who may well be said to substantiate the traditions established at our founding by Jacques Loeb.

Some of the proudest accomplishments in the University's history have concerned the structure of enzymes—their chemistry as protein chains of amino acids, and how their shape endows their near-miraculous role in metabolism. These structures are the working machinery of the cell, the material product of the DNA genetic blueprints. To sustain our leadership in this field, we are gratified that another world-eminent figure, Emil Thomas Kaiser, will shortly be joining us. His research to date has been notable in its application of rigorous physico-chemical measurement and construction to fundamental and to practically important biological problems.

Physical, Mathematical, and Computer Sciences

Mathematical reasoning is the ultimate tool of rational human discourse. We cannot truly claim theoretical understanding of a natural phenomenon until we apprise it well enough to express our models in mathematical notation. Then, and not before, they are amenable to formal verification and search for inconsistencies and further implications. To a large degree, physics and chemistry have been unified through this process. By allowing us to approach rigorous calculations of the shapes and attractive forces of organic molecules, these studies have already helped to place molecular biology and pharmacology on a more sturdy theoretical basis. Mathematical calculations are also beginning to help us manage the complexity of the nervous system: How else could the human brain hope to understand its own complexity? Finally mathematical statistics is an indispensable underpinning for testing hypotheses in experimental biology and medicine, and especially for studies in population biology and epidemiology.

Nevertheless, much of contemporary biological research is beyond the reach of mathematical theory: the rules do not lend themselves to precise expression with existing algebras and in the present state of our knowledge. Rapid advances in molecular biology are beginning to allow us to treat living phenomena with greater rigor, and there is then some hope of the feasibility of a more mathematical theory for biology that should help knit together the various branches of study, both within biology and in its relationships to physics and chemistry.

It is not easy to prescribe how to reach such a goal, but The Rockefeller University with its capability for interdisciplinary study has a special responsibility. We are in the course of an analytical study of the place of mathematics here, whose outcome cannot be anticipated, especially as limited resources will oblige us to select only the most persuasive of a group of desirable options. The issues to be considered must include: a) What is the current status of mathematical biology, and who are its most effective exponents? b) How can we best expand our efforts in the physical sciences, most effectively to bridge the gap between the small, superb group in high-energy physics and the main body of research that deals with molecular rather than subatomic phenomena? c) How to take advantage of the explosive developments in computer science and technology? And all of these in a fashion that engenders an organically effective, overall program here.

The Rockefeller University has been among the pioneers in biomedical electronic instrumentation; it is then ironic that it should have been relatively tardy in the applications of general-purpose computer technology and information science. This can be understood in light of the extensive framework of engineering and other technological capabilities that are centered outside the biomedical sciences, and can only be found at the largest general university centers like Stanford and MIT. We cannot indefinitely ignore these developments, especially as the costs of computing hardware, and general access to computing centers through digital telecommunications, bring these capabilities within our reach. Besides the well-established role of computers in mathematical calculation, the linkage of computers with communications can greatly advance library

information services, administrative management, personal scientific interactions, and the individual's own extended memory. In a word, this technology is indispensable for the kind of institution we describe ourselves to be.

To date, we have taken only the first steps in establishing a sophisticated computer network, with the installation of modest-sized DEC (PDP-11/70 and VAX-11/780) machines and a campus network through our telephone lines. This offers document-processing as well as mathematical-calculating services, and during the next decade should become the most robust medium of personal communication, as well as information-storage and -retrieval on the campus. This document, for example, is one of the first of our university publications to be fully drafted, edited, and prepared for print on our system. We are most grateful to Bell Laboratories, Inc., for their assistance in mounting the UNIX™ operating system, which has been designed to meet a similar range of needs.

Relations with Industry

We are entering an era when the industrial sector is bound to be more important in university policy for many converging reasons. The leveling of federal support is only the most superficial of these. Perhaps the most important is the national need for the revitalization of our economy through technology, and of individual productivity through the enhancement of human skills. Industrial funding is now indispensable for not-for-profit institutions. In addition, new forms of tangible cooperation, through the convergence of complementary skills and backgrounds, can offer many other advantages. Yet, there is an undeniable and intrinsic source of conflict, namely between the proprietary interest of a single firm and the public responsibilities of the institution. However, this conflict can be managed and contained to achieve many countervailing benefits. The University should not forget or confuse its distinctive role as a fount of fundamental knowledge. Nevertheless, it can be a clearly identified partner with sponsors, if mutual interests serve practical purposes. But it must not become a captive of particular interests, lest it fail its public responsibilities and antagonize other potential partners.

These are not easy issues to resolve, and relations with industry will continue to demand the most careful deliberation and maximum understanding among faculty, president, and trustees. Fortunately, the organization of this University into distinct laboratories enhances our flexibility in dealing with industrial sponsors. Each laboratory is a unit large enough to be important in its field of research, yet small enough for agreements to be negotiated responsibly; as a result, the funds involved in a given transaction with any one laboratory will not be thought to distort the institution's overall priorities. The University's role is to be a responsible agent, to protect the faculty against undue intrusion on academic prerogatives and freedom, to ensure that external agreements do not abuse other elements of the University, and to negotiate in ways that do fairly reward the institution. Above all, we have the *pro bono* responsibility of helping to accelerate useful applications of scientific advances.

Life on Campus

The daily stresses that affect the life of science are ameliorated at The Rockefeller University by the spirit of the campus community. The tranquil beauty of the campus, especially in contrast to the stridency of the city, is an irreplaceable asset.

These surroundings are the setting for another unmatched asset—a staff with a truly impressive range of skills and talents and a rare level of dedication. Probably only those in this research community can ever know how much the University's success rests on the skills of the entire staff—office workers and instrument-makers, nurses and gardeners and technicians, engineers and cleaners. Their competence and pride, and in many cases their ingenuity and even heroism in the services they provide, have been extraordinary over the years.

Perhaps the most intangible of our attributes is the quality of communication within our group of scholars. The Rockefeller University was designed for interdisciplinary efforts, and for the intellectual revolution that can attend them. This kind of effort does not come naturally. In various ways it flies in the face of many structural obstacles in contemporary institutions. Witness just the fragmentation of federal support via splintered project grants. When the University

was much smaller and more tightly directed, it was far easier to sustain a coordination of mutual interest. Our laboratory heads, who number fewer than 60, can more readily sustain an institutional orientation. Our junior faculty and fellows number some 500, and their responsibilities to an individual laboratory may add to the difficulty of relating to the overall community. A number of devices are in play to help provide a reasonable balance of focus and perspective for the professional activities of this group. For example, a weekly colloquium is a long-standing, traditional forum for the entire University. Nevertheless, so much of our energy during the past decade has been consumed by fiscal crises that we should now seek further measures to help us function as an intellectual community, with the utmost cross-stimulation and criticism. The overall size of an institution may be an intrinsic obstacle to that easy intimacy of minds, but this is a task that must engage all of the wisdom of the campus. As we succeed, our campus community will continue to stand as a model for collegiality of scholarship.

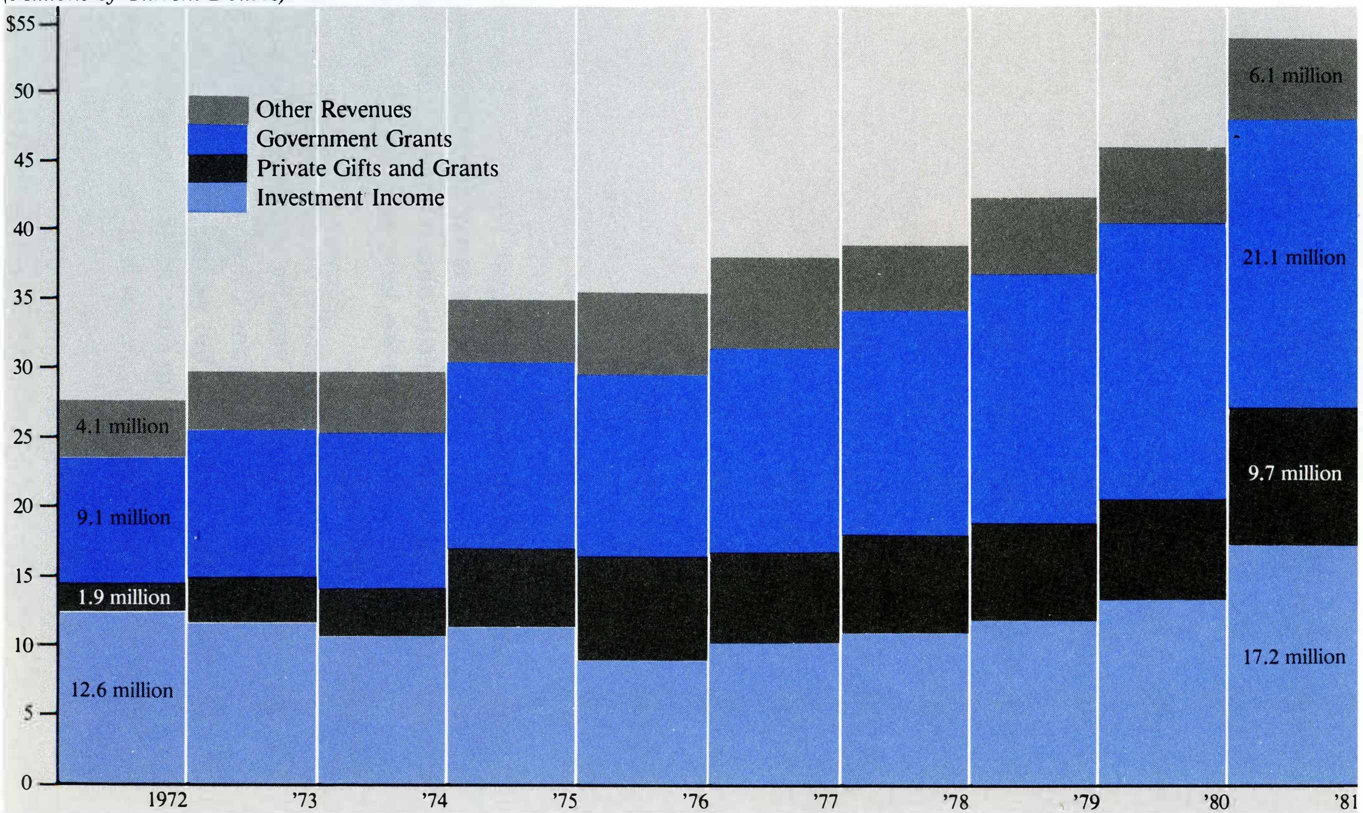
Financial Trends

Financial operations for the year ended June 30, 1981, showed improvement from the previous year and, for the second consecutive year, revenues exceeded expenditures. Table 2 summarizes revenues and expenditures, including capital budget operations, for the last three fiscal years.

The amounts in Table 2 do not include the approximately $26,550,000 in net additions to endowment and similar funds during the three-year period. These funds provide additional investment income (see line 3, Table 2) which helps to offset the decline in purchasing power of the current investment income.

Chart 3, page 27, shows the trend in revenues for the last ten years. There are three basic sources of revenues: investment income, private gifts and grants, and government grants. The "other revenues" are primarily associated with the self-balancing operations of housing, food service, and The Rockefeller University Press. Development efforts were first begun in 1972; the subsequent growth in private gifts and grants and the increased investment income from additions to endowment funds have provided

Chart 3. Revenue Sources
(Millions of Current Dollars)



the opportunity to manage the large increase in governmental funds without losing flexibility or control of institutional priorities.

Chart 4 shows the different components of revenues and expenditures with the related percentages for the fiscal year ended June 30, 1981.

The market value of endowment investments at June 30, 1981, was approximately $270 million. Independent analyses of our portfolio by Merrill Lynch over an extended period of time show that our professional management has produced exceptionally good results when compared with other funds with similar objectives.

Financial Outlook

The greatest threat to our financial operations at the present time is the uncertainty about the level of governmental funding which provided more than $21 million in fiscal 1981. The University currently has in excess of 250 active federal grants, and nearly every one of our laboratories will be affected by federal budget cuts.

Provision for capital expenditures in the years ahead is an urgent concern. A continuing need is to obtain more sophisticated equipment, to modernize support functions, and to comply with regulatory requirements that affect the operations of research laboratories. Beginning in 1982, we will modernize older buildings as we start several major new laboratories. The "start-up" costs of launching a new laboratory are significant. We also will soon have to reckon with the very large financial burden of additional housing for our faculty. It is almost impossible to obtain governmental funds for these capital expenditures, so we look primarily to private donors for our essential needs.

The University operates on a ten-year financial plan that is updated three times each year for review by the Board of Trustees. The most recent projections show that we should again operate in the black in fiscal 1982, but we are projecting a deficit in fiscal 1983 because of the start-up costs of new laboratories. In effect, we will be using most of the reserves built up in our operating budgets during the last two years. Projections for the balance of the ten-year period reflect an intent to maintain our programs at roughly the present level and to conduct financial operations at break-even.

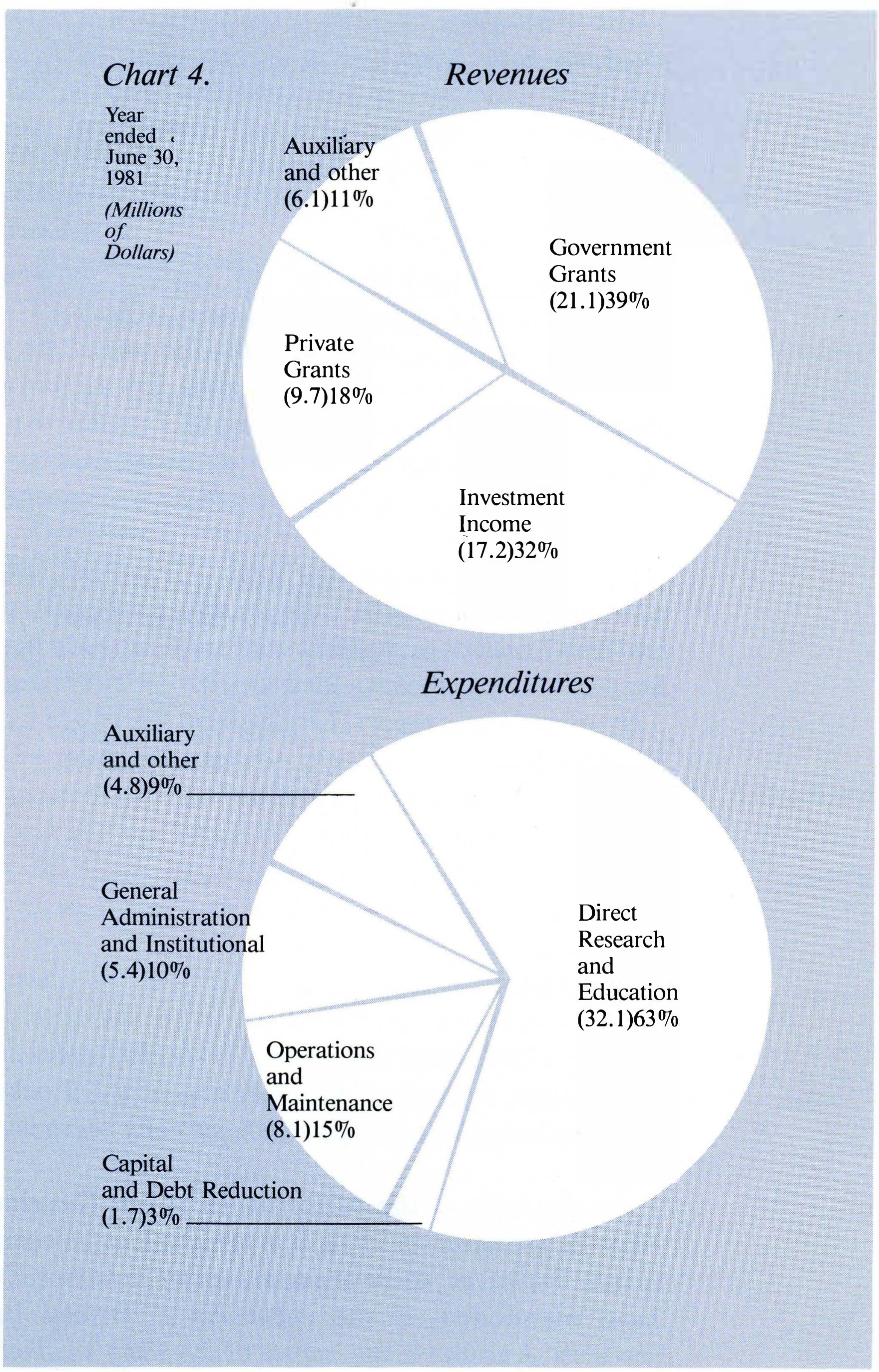


Chart 4.
Year ended June 30, 1981
(Millions of Dollars)
Revenues
Auxiliary and other (6.1)11%
Government Grants (21.1)39%
Private Grants (9.7)18%
Investment Income (17.2)32%
Expenditures
Auxiliary and other (4.8)9%
General Administration and Institutional (5.4)10%
Direct Research and Education (32.1)63%
Operations and Maintenance (8.1)15%
Capital and Debt Reduction (1.7)3%

The attainment of these projections will certainly require great effort and some good luck in the face of probable levels of inflation and likely reductions in governmental funding. But I am confident that the quality of our work will continue to attract the support necessary to perform our mission.

Development Program

The detailed objectives for the current ten-year, $150-million Development Program, which began in July 1978, are shown in Table 3. Progress by June 30, 1981, the end of the third year of the program, was $67.7 million, including $59 million in new gifts and pledges received since July 1978 and $8.7 million in payments on earlier pledges. This represents 45% of the ten-year goal. Not included in the total is an additional $11.9 million in trust and estate commitments.

Nearly half of the ten-year total, $71 million, is being sought for additions to endowment. I am therefore especially pleased to report that $40.1 million of that $71 million has already been pledged. This has provided significant added security for our financial outlook.

In my previous report, I announced the award by the Rockefeller Brothers Fund of a five-year, unrestricted grant of $15 million with provision for an additional $7.5-million challenge grant if two conditions were met by December 31, 1986: that the University raise $25 million in new endowment and that we match the $7.5 million RBF challenge grant by additional contributions to endowment from gifts or other sources.

I am pleased to report that by June 30, 1981, we had met and exceeded the above conditions five years ahead of the deadline (including allocation of the original $15-million grant to endowment). Subsequent discussion with officials of the Rockefeller Brothers Fund indicates that we may anticipate early payment of the challenge grant.

On the basis of the performance of our Development Program since its inception in 1972, it is tempting to be optimistic about the future. However, there are some major concerns. One of them, as I have mentioned, is the reduction in federal funding of basic research. Another is the impact of the 1981 Tax Reform Act, which

Table 3. The Rockefeller University Ten-Year Development Program, July 1978 to June 1988

		Amount
ENDOWMENT		
20 Endowed Professorships:		$ 25,000,000
Fellowships:		
10 University Fellowships	$ 8,000,000	
10 Clinical Fellowships	8,000,000	
20 Postdoctoral Fellowships	10,000,000	
50 Doctoral Fellowships	20,000,000	46,000,000
Total for Endowment		$ 71,000,000
PROGRAM SUPPORT AND CAPITAL PROJECTS		
Restricted Program Support		
Fundamental investigations, including molecular and cell biology, the neurosciences, parasitology, reproductive biology, immunology, toxicology	$35,000,000	
Clinical studies, including metabolic/genetic disorders, immunological diseases, cancer, environmental medicine, pharmacology	20,000,000	$ 55,000,000
Unrestricted Program Support		
For use at the discretion of the President and Trustees		9,000,000
Facilities		
Modernization and renovation of laboratories, hospital, and essential support services		15,000,000
Total for Program Support and Capital Projects		$ 79,000,000
Grand Total		$150,000,000

is not known at this time and will not be for many months. Nevertheless, it is the most far-reaching tax legislation in many years, and the uncertainty about its eventual impact on philanthropy is cause for careful attention and concern. Increased cost of housing in New York City, the need to modernize older laboratories, continuing inflation, and the signs of national economic downturn are further causes for concern.

On the positive side, our development efforts, begun so carefully by my predecessor Frederick Seitz a decade ago with almost no previous history of institutional donors, this year reached an annual level of $15 million in new gifts and pledges, with a momentum suggesting further growth. Most important, the demonstrable excellence of basic research and teaching at The Rockefeller University marks it as one of the best opportunities for philanthropic "investment."

The ultimate success of the Development Program rests on our ability to identify, involve, and communicate with an expanding constituency of individuals, corporations, and foundations. To accomplish this, we are enlarging our programs of campus visits by individuals and groups who can speak for the University and contribute to its financial well-being. This progress is augmented by a continuing series of regional meetings and an increasing variety of University publications. In summary, I am optimistic of achieving our $150-million goal in good time for the 1988 target.

Finally, my sincere thanks, on behalf of the trustees and the campus community, to all of our donors, and to the volunteers who conduct our programs. Without this material manifestation of widely based, public-spirited support from private individuals and organizations, we could not hope to meet our obligations to the welfare of humankind.

Gifts and Grants

The University's Development Program seeks $150 million by the end of 1988. The goals emphasize additional endowment and long-term operating support for basic research in the life sciences, clinical programs of our hospital, endowed professorships, predoctoral and postdoctoral fellowships, and the renovation of research facilities.

The following pages include two lists of donors for the current two-year period. List I represents individuals, foundations, corporations, and bequest gifts contributing to general goals. List II comprises governmental and private sponsors of special projects.

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