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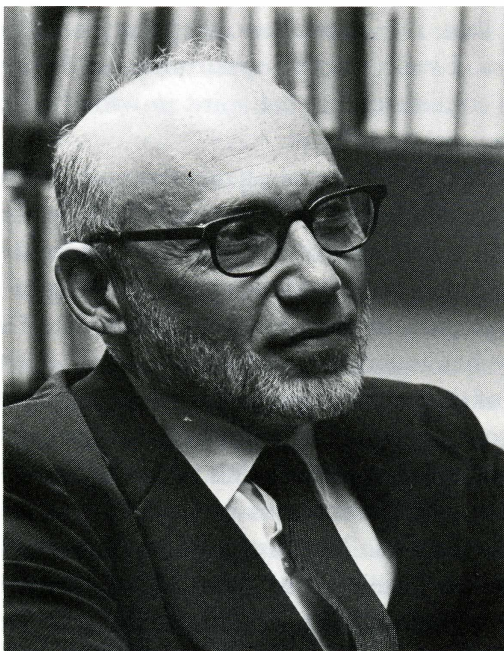
1978-1979 Report of the President

The Rockefeller University

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REPORT OF THE PRESIDENT
1978 - 1979



Joshua Lederberg
President

Because it is my first annual report as president, this writing is a panoramic personal reflection of my views of The Rockefeller University. This first year has remarkably confirmed my optimistic expectations about the University. My greatest surprise was to have experienced so few surprises about the kind of place it is and the kind of people who work here.

Three years ago, The Rockefeller University—founded in 1901 as The Rockefeller Institute for Medical Research—observed its 75th anniversary. A theme of the celebration was the continuity of the tradition and achievement which marked the transition from Institute to University. As I noted in my inaugural remarks last October, the record of that anniversary reflects the success of the transition and also dramatizes the opportunities that drew me here: to conserve and enhance the most vital tradition of biomedical research to be found anywhere today.

In keeping with the vitality of this tradition, many of the things I write will not now, nor in the future, appear as radical innovations.

It is my hope that, if events allow, they may bear repeating several years from now. I welcome the opportunity to define, in the light of contemporary circumstances, the spirit in which I approach my new responsibilities.

The substantial scope, simple structure, and coherent goals of this University offer a unique challenge to scientific leadership. Certainly today we have a broader conception than existed in 1901 of the scientific foundation needed for an understanding of human biology. Thanks, in large part, to the inspiration of the late Detlev W. Bronk, the University has incorporated the behavioral sciences and broadened the base of the physical sciences on this campus. It was President Bronk who brought Carl Pfaffmann here to develop the University's strong program of behavioral studies. Dr. Pfaffman, who retired this year as vice president, continues to head one of our physiological psychology laboratories. The distinction of our physics and mathematics faculties and their positions at the international forefront in their disciplines have added a stimulating new dimension to the intellectual life of this scientific community. But the scientific programs of the University, for all the diversity of fundamental and clinical research carried out in its 60 independent laboratories, remain firmly based on the biomedical sciences and sharply tuned to the protection and improvement of the health of the human species.

In leading institutions that have multiple concerns and aims, as is typical of many larger universities, presidents are preoccupied with negotiating compromises between disparate sets of values. This is a leadership challenge of a rather different kind and implies a strong political role. But here basic political questions are, in a sense, already settled: first by the University's coherence of goals, and second by its fundamental structure.

Our University is unusual in not being divided into schools with competing interests and distinctive concerns such as law, medicine, or engineering. We have no division of undergraduate studies competing for attention and resources for other purposes. Nor do we have academic departments which carve out sovereign intellectual territories. Instead, we are organized simply into individual laboratories, each led by a senior investigator. The work of the laboratory is, of course, shared by a varying number of junior faculty, postdoctoral

fellows, graduate students, and technicians.

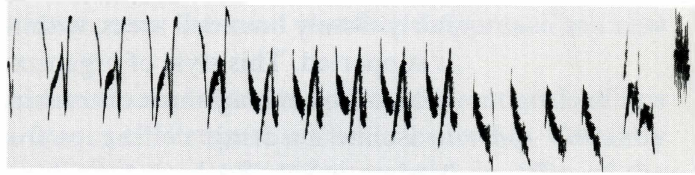
The usual departmental structure aggregates specialists within fairly closely bounded areas, within which intensive conceptual effort is supported. This style of organizational structure may be indispensable for the management of teaching or service functions. Yet it tends to isolate academic colleagues from those in other disciplines and hinders novel and boundary lines of research. These are very real obstacles to certain kinds of innovation.

Our University could have had departments of physiology or biochemistry or pharmacology or pathology. But the conscious renunciation of this pattern of organization, from the initial founding, has fostered innovative interdisciplinary research. (The continuous momentum of the scientific and educational work of the University during the past year is described in the publication *Scientific and Educational Programs*.) Some of the brief sketches of current research accompanying this report illustrate the quality of such interaction, which can start with a conversation in the cafeteria, a short stroll from one building to another on our compact 15-acre campus, or in the mind of a clinical researcher sensitized by continued laboratory contact to think "chemically" about a medical problem. It is no accident that it is possible here for an organic chemist or a pharmacologist with a Ph.D. to be involved in clinical investigation of the highest quality. It is equally easy for a behavioral scientist to collaborate with a biochemist or a physiologist in uncovering the mechanisms underlying behavioral data gathered in field studies.

In addition, the University offers an opportunity for undistracted research, which is appealing to scientists who, at some institutions, might have to spend considerable time doing other things, useful and important but not directly related to their research.

A Collegial Structure

A simile for this organization is that the president here functions like the head of a single academic department with a regular faculty of 200 scientists. Now, whether 60 laboratories can report to one individual, and sustain an acceptable degree of managerial effectiveness, raises questions that a beginning student of management will anticipate. Yet this simple structure has, over the decades, stimulated a



Male Chaffinch and sound spectrogram of complete song.

Bird song, one of the most common and delightful natural sounds on earth, is a biologically important, complex form of reproductive behavior used by the avian male to attract and keep a mate and to defend the territory where he lives, mates, and nests. Peter Marler, head of the University's Field Research Center at Millbrook, N. Y., has found many parallels between bird song and human language. For one thing, probably all the Oscines — songbirds, such as canaries, sparrows, robins, and finches — learn to sing the way humans learn to speak by listening to and imitating others of their species. Birds and human beings are the only creatures known to learn the sounds they use to exchange information.

For almost a decade, Fernando Nottebohm, a colleague of Dr. Marler's, has collaborated with members of several Uni-

versity laboratories in interdisciplinary studies of songbird behavior, ranging across anatomy, neurophysiology, and biochemistry. Significant clues have emerged on how the brains of songbirds approach the task of vocal learning.

Bird song is produced by the syrinx, a structure deep within the chest where the two bronchial tubes from the lungs join the trachea, or windpipe. In Oscines, the syrinx has two sound sources, the internal tympaniform membranes, which form part of the medial wall of each bronchus. Air rushes through the bronchi and past the tympanic membranes, which vibrate rapidly to produce sound. Pitch and loudness are modulated by the syringeal muscles, which set membrane tension and control airflow. Each half of the syrinx is innervated by a branch of the hypoglossal nerve.

When Dr. Nottebohm began his research, virtually nothing was known about the neural pathways involved in song pro-

duction. Using behavioral studies and anatomical techniques, he and neuroanatomist Christiana Leonard traced central nervous pathways that control song in the canary. They described discrete vocal control areas in the brain where nerve pathways related to song production interface with centers for processing auditory information. A totally unexpected, but highly significant, finding was that in songbirds, as in humans, the left hemisphere of the brain dominates vocal behavior. This was the first reported non-human example of hemispheric asymmetry, the concentration of a specific function on one side of the brain.

Another important discovery, by Dr. Nottebohm and Arthur P. Arnold, was that brain vocal control areas in male songbirds are several times larger than in females. This so-called sexual dimorphism seems to be related to differences in behavior: male birds learn songs by imitation and sing profusely; females sing little, if at all. When reported in 1976, this was the first description of such a gross sexual difference in a vertebrate brain.

There is a wide body of evidence that in both humans and animals sexual behavior is heavily influenced by steroid hormones secreted by the gonads. They stimulate such behavior by acting on nerve cells in the brain. For instance, testosterone, a male sex hormone, determines the amount of singing done by canaries and zebra finches. During the breeding season, normal males sing a lot. Castrated males sing very little, but this can be corrected by administering testosterone. Using radioactively tagged hormones, Dr. Arnold,

with the help of Dr. Donald Pfaff and as part of his thesis work in the Nottebohm laboratory, discovered that some vocal control stations in the songbird brain concentrate testosterone in their cells. In particular, the motoneurons which innervate the syringeal muscles also are hormone-sensitive "target" cells.

Several years ago, Dr. Nottebohm joined forces with Bruce McEwen's group to see whether the anatomical and physiological findings on bird song could be related more directly to biochemical effects on behavior. Dr. McEwen's laboratory group is seeking to learn how hormones interact biochemically with nerve tissue to activate behavior.

Doctors Nottebohm and Ivan Lieberburg established by test-tube experiments that syringeal muscle also has testosterone-sensitive cells. This suggests a direct hormonal influence on song-control muscles. Experiments done with Doctors Victoria N. Luine and Cheryl Harding indicate that testosterone is necessary for maintaining the levels of an enzyme in the syringeal muscle that is important in neuromuscular transmission. Clearly, the effects of sex hormones on bird song occur at multiple levels, from the brain to the very muscles that modulate song.

Dr. Nottebohm believes that the study of phenomena as disparate as hemispheric dominance, sexual dimorphism, and hormonal regulation of behavior is leading him to the more difficult and fascinating question of how learning affects brain pathways. He is confident that the avian brain, evolved to master song-learning, will also yield insights into this question.

remarkable record of scientific achievement. Mainly because, at the heart of it, is this truly collegial concept—to provide maximum incentive for the carefully selected and highly gifted individuals gathered here to relate to their fellow scientists across many different specialties of knowledge and styles of critical thinking. Whether there is any sense to having an institution of this kind at all depends on the extent to which “colleague-iality” is protected, fostered, and encouraged. This concept bears directly on our style of recruitment, on career advancement plans, on the identification of areas selected for emphasis in research, and on almost every other aspect of day-to-day life at the University.

On a very personal level, I might describe myself as in a state of transitional reconstruction—after a leap from the laboratory bench to the board room—and wondering how to apply experience in scientific scholarship to organizational leadership. However, I have been confirmed in the belief that the inherent structure of The Rockefeller University lends itself to a president who has personally experienced the stresses, tedium, and thrills of the scientific pursuit. Exciting about this environment is the responsibility that it places on the president to fit into a collegial framework, to be sufficiently informed or educable to enter into critical judgments about the wide diversity of research in progress, to help bring people together from different parts of the network, and to participate in the critical dialogue that is the substance of scientific progress. Most of the people at the University work in areas that are familiar to me and that I care deeply about. This heightens my sense of the unparalleled opportunity offered here for intellectual adventure and human service.

Scientific research is one of the most enthralling pursuits that can occupy the human mind, and those of us who can dedicate our lifework to it are privileged indeed. But the private excitement of discovery should not obscure the enormous public stakes of the enterprise. What we learn today about the structure of DNA and of cells and how these are knit together in a functioning organism will be indispensable tomorrow for what is indeed a war against pain, disease, and death.

Scientific Direction

Manifestly, I have not returned to Manhattan to chart major changes in institutional trajectory. Rather, I would aver that the University can best perform its social function by consolidating its scientific interests to hew more closely to the course implied in its original name. This orientation is consistent with the goals and priorities articulated by the preceding administration with our faculty and the University Board of Trustees. Nonetheless, constant reexamination of goals, priorities, and performance is an obligation of any institution in the present climate of skepticism and inquiry about our entire social fabric.

Our motto, *pro bono humani generis*, has its most direct application in the discovery of health-saving, death-combating knowledge. Its most obvious exemplification is in clinical research applied to the development of drugs and vaccines. But these publicly acclaimed advances are not the products of a static, stereotyped system of preplanned discovery and invention. They are the fruits of a multi-dimensional, dynamically changing structure—the complex tissue of health science and technology. Health progress must be informed by scientific insights from an unpredictable variety of fields, and then sometimes it leaps forward by purely empirical discovery. The basic sciences have their own dynamics and are often energized by new puzzles from the world of practice.

I am often asked whether the renewed consolidation of our institutional identity with health research means that every professor should make an immediate contribution to health applications. “No,” I must reply, “that would soon be self-defeating.” But we must design and maintain an institutional structure that as a whole will make the most effective contribution to both the underlying basic sciences and their applied fruits. Each new appointment should be scrutinized for its contribution to our collegial effort. In bringing a person here, we should ask whether there is an advantage to the institution’s entire program that would socially justify the stresses and costs of moving people from place to place. The excellence of a scientific work viewed in isolation is thus an important, but not an exclusive, criterion.

As I have already noted, most of the nation's larger, more complex institutions—in order to reconcile the conflicting demands of their established constituencies—find it difficult or impossible to identify their fundamental goals and to design evolutionary structural changes that will make them functionally most effective in meeting their own aspirations. The Rockefeller University is a uniquely modern institution, in that it was thoughtfully and consciously designed at its inception and redesigned, with equal care, at several historic transition points. It is true that in adopting the title *University*, the institution ran some risk of simply inheriting a trunkful of traditions rooted in the history of academic life generally, not all of which are pertinent to its own goals and capabilities. But an advantage deriving from the change is that our students and faculty have better access to the mainstreams of career opportunities and, in turn, we can more readily recruit from external sources. Since 1901, partly because of the inspiration supplied by the success of The Rockefeller Institute, biomedical research has grown enormously, and we cannot afford to be isolated from the extensive efforts being made at many other kinds of institutions throughout the world.

From time to time, the question has been posed, quite correctly: In the light of the overall growth of research capability, what now is the special role of The Rockefeller University? The manifest answer is, as it has always been, the standard of excellence set by its faculty and students. To continue to meet that standard requires a flow of public and private resources that entails unremitting struggle to sustain. To justify that flow requires a vision of inspiration and organization, a design to meet the goal of the advancement of science for health.

The main elements of scientific direction are, on the one hand, the identification of research opportunities and of the superlative individual competence needed to exploit them. On the other hand, there are the institutional responsibilities for nurturing that competence, both materially and morally, and for facilitating the mutual criticism, communication, and collaboration that make an institution more than a “boarding house of scholars.” With respect to both of these elements, I repeat that our present institutional structure offers a unique opportunity for leadership. We are less encumbered than any comparable

organization in the capacity for self-management and adaptive change, after thoughtful consideration, to improve the efficiency and efficacy of scientific research. Since the beginning of the century, the fruit has been a continuing harvest of the most consequential and highly regarded discoveries, impressive in absolute terms, and surely preeminent in the yield per dollar invested.

At the present time, the flow of federal funds for the support of research is essentially at a plateau, but an enormous one—so large as to have discouraged the private sector from sharing in the support of

Messenger ribonucleic acid (mRNA) is the information carrier that transmits the messages encoded in the cell's genetic data bank, deoxyribonucleic acid (DNA). The messages instruct the cell's machinery to make — in the amount needed, when needed — the proteins basic to all life processes. But how is a particular message, stored in one of the thousands of genes which constitute an organism's master code, "expressed" precisely when required? What switches genes on and off?

Scientists have made great progress in understanding the mechanism of gene expression in bacteria. The DNA in a bacterial cell (prokaryote) is not bound within a nuclear membrane, as is the DNA in the eukaryotic ("true nucleus") cells of humans and other higher organisms. In bacteria, the transcription of a genetic message into a molecule of RNA, followed by conversion into a protein, is a direct process. The primary RNA transcript, or copy, is the messenger RNA. As soon as the new RNA molecule begins to be transcribed, it is engaged by cell organelles called ribosomes, which then begin to make protein.

Not so, scientists have found, when it

comes to gene expression in the larger and more complex eukaryotic cell. Only recently have molecular biologists begun to identify the steps in the intricate process by which eukaryotes make messenger RNA, a key event in normal and abnormal cell growth.

Years ago it was found that DNA in eukaryotic cells produces RNA molecules substantially larger than messenger RNA. James E. Darnell, Jr., a Vincent Astor Professor at the University, and his associates have spent more than 15 years deciphering the meaning of these large nuclear RNA molecules. Their experiments have provided much of the evidence for the surprising conclusion that the large RNA molecules in the cell nucleus are the precursors of smaller messenger RNA molecules in the cell cytoplasm. The primary RNA transcript of the DNA code in the nucleus of the eukaryotic cell is not used directly as mRNA. Instead, the long, ribbon-like precursor molecules are cut — by enzymes — into smaller pieces that undergo certain chemical modifications. Then, as shown in the diagram, some of these RNA segments are spliced together to form messenger

experimental laboratory research. Ever-increasing bureaucratic harassments aside, it is true that federal funds can be obtained for a wide variety of specialized projects. But this government support is primarily for categorical disease-related research. What is often neglected in federal funding is the need for continuity in long-range research programs and their meaningful integration into an institutional effort.

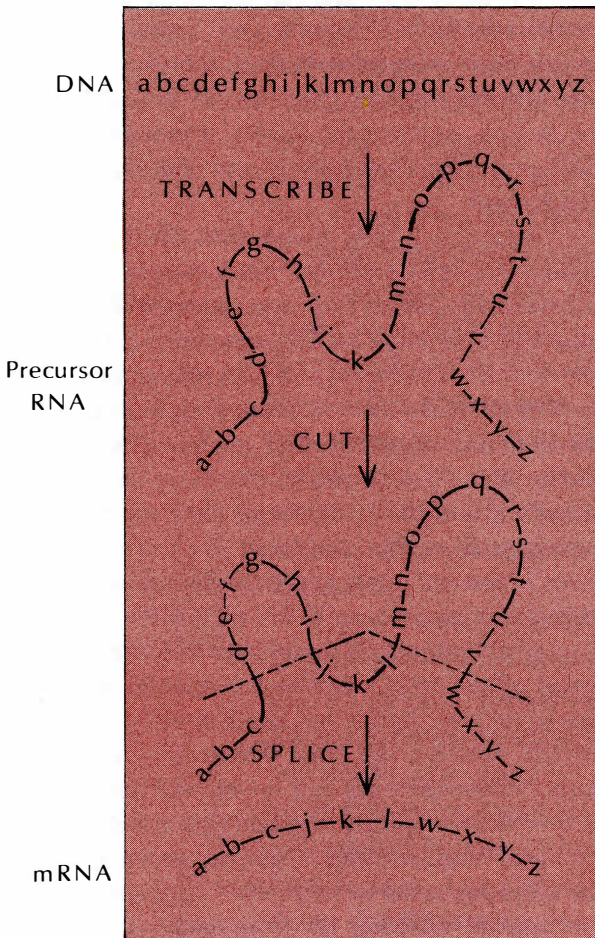
RNA, which directs protein production in the cytoplasm.

This new understanding of mRNA formation in eukaryotes makes it possible to

define in biochemical terms how and at what level gene expression is regulated in humans and animals. Beyond that lies one of the prime goals of biological science today — the regulation of cancer cells.

The differences between messenger-RNA formation in prokaryotes and in eukaryotes also has profound implications for the study of evolutionary biology. It has been assumed by many that eukaryotes evolved from prokaryotes. But the findings of Dr. Darnell and others strongly indicate that a simple sequential evolution of eukaryotes from organisms like today's bacteria did not occur. If this is true, Dr. Darnell suggests, "then it seems not only possible but logical that the basic rules of genome organization might also differ between present-day prokaryotes and eukaryotes." (The genome is the complete set of hereditary factors encoded in the cell's DNA.)

All of this may have an important bearing on future research. Dr. Darnell concludes, "If the molecular basis of eukaryotic gene regulation is to be explained in relation to developmental biology or cancer biology or endocrinology or many other topics, it is at least possible that we cannot rely on bacterial models but must again solve the molecular control mechanisms of eukaryotic genes."



This is compounded by the innumerable, subtle counter-incentives that constantly chip away at that integration. Private support is thus both indispensable and a means of leverage. By assuring the continuity and the integration essential to productive research, such support can assure the most creative utilization of the federal monies that constitute almost half of our operating budget. This ratio is appropriate; there would be great perils if it were to increase substantially.

In the years ahead, it will be one of my central responsibilities to reexamine the roots of scientific creativity. I have no easy prescription for fostering such creativity. In my own experience, however, nothing equals the confrontation of an eager, trained curiosity with the established doctrines and with the new findings of other disciplines. In such fresh encounters, new questions arise. The traditions and structures of our University offer unexcelled examples and new opportunities for this kind of discourse; but there is still much to do to bring this approach to its fulfillment. We may even have lost ground in recent years because of the expansion of the campus and the disappearance of the venerable Welch Hall dining room, which furnished such a congenial setting for interdisciplinary exchanges. To find a creative functional heir to that tradition is one of my immediate preoccupations.

Contemporary Challenges in Health Research

In 1901, bacterial infections—the great plagues—were the most serious challenges to health. Following on the work of Pasteur and Koch, the Institute was an important encampment of “The Microbe Hunters,” so called by Paul de Kruif in a book that inspired a generation of medical scientists (including myself). Developments in sanitation, vaccines, antibiotics, and nutrition have given our people the most startling improvement in public health experienced in history, and those diseases no longer top our list of concerns. But these same successes have raised public expectation to a level almost impossible to satisfy in other fields, although the development of vaccines for the important killer viruses has been a major accomplishment of the last 25 years.

Today, our public health concerns number heart disease, psychiatric disease, and cancer as the chief causes of severe disability and

death, and other virus infections and degenerative diseases, such as arthritis, as grave hindrances to a happy life expectancy and productive employment. The hunting of microbes was a relatively easy task—the villain was a well-definable alien species. We had but to track and kill it, or at least check its spread. For today's major health threats, the problem is lodged within our own bodies. We face the subtle challenge both of achieving a deeper understanding of the human organism, far more complex than any bacterium, and of refining the very process of research involving human beings to change our own physiology in order to improve our health. Of course, we generate many health problems through our individual life styles. The issues of diet, exercise, smoking, and alcoholism are too familiar to bear repetition. Even so, we do not properly understand the mechanisms or precise efficacy of changes of life style as they affect health, and the very accomplishment of more hygienic styles of living is a challenge to the behavioral sciences.

There is no lack of challenge to physiology, either. We really do not understand at all the perceived gratification that leads people to smoke, and we may well be on the wrong track in popular myths about the drives in alcoholism. Studies of the mechanism of action of opiates on the brain have just recently excited an explosion of discovery of previously unsuspected natural drugs in the brain, such as the endorphins, that may also be the key to many other psychiatric problems. The abysmal failure of most attempts to alter bad habits of excessive eating, drinking, and smoking tells us that to have a real impact on public health via "life style" will take a far more sophisticated insight into human behavior than moralizing about what is bad for you.

Prevention of disease is surely our primary objective for today's most serious health problems, simply because it is so difficult to effect useful remediation of the human body once its parts have begun to fail. Many specific environmental influences are now suspect in heart disease and cancer, and a clearer delineation of the hazards to avoid and of the specific dietary intake to encourage will add a badly needed precision and efficacy to life-style admonitions. As I will discuss in more detail further on, we also need more precise attention to risk-assessment of chemical hazards in the environment to provide credible direction to overarching policy choices in environmental

regulation, which otherwise may paralyze the national economy. In all likelihood, basic research will be even more cogent for these questions than for the design of new means of diagnosis and treatment of existing disease.

Besides the specific mechanisms of arterial disease or cancer, the more general condition of aging points to the most fundamental biological questions—why, for instance, are the life-spans of man and mouse so different?—that touch upon the gravest aspects of the human condition. To pursue these questions will require intense and sophisticated interweaving of basic and clinical pursuits.

Research Priorities

At this University, it is important that we maintain ourselves at the forefront of basic research in molecular and cell biology: those fundamental areas of chemistry that are most closely connected with understanding the structure and function of cells and the higher levels of organization of molecules into cells, tissues, organs, and organisms. We must also continue to explore the connections between behavior—animal and human—and the knowledge gained from studies at the molecular and cellular level. It is a short step from this kind of science to practice. We are becoming increasingly aware, for example, that such basic biological mechanisms as communication between cells and hormonal function must be better understood before we can deal effectively with the crushing practical problems associated with global human reproduction.

The University has a very strong record of significant contributions to the field of parasitology, particularly in the understanding of malaria and other major tropical diseases. (Some of this research is reviewed on page 15.) Parasitic infections constitute the greatest health problems in vast areas of the world. To sustain the strong research base we have for meeting this challenge and to energize it with the insights of molecular biology are concerns central to the University's mission.

Tremendous opportunities have arisen in the last several years for work that has a base in molecular biology on one side, involves behavioral science on another, and can contribute directly to solving the urgent problems of psychiatric illness. The University must follow

up on these opportunities and recruit people who respond to the potentialities of such broadly based research.

The reciprocal dependence of health research and clinical management of disease is mirrored in the techno-political problems we face in sustaining a healthy environment for our species. An expanding industrial society today inevitably spews out an unprecedented volume and variety of new substances to which we are exposed in air, water, foods, drugs, at the work place, and at home. Each such product, whether a natural compound like nitrate or a synthetic innovation like saccharin, poses an intricate scientific problem. What are the laboratory tests that will enable us to predict the toxicity to man of a given substance? And such knowledge would still be far from providing the framework for deciding how much of a given toxic exposure is an acceptable trade-off for an economic and social benefit. We have only a handful of people who are even able to communicate intelligently in the languages—scientific, technical, economic, political—used on each side of the discourse. There has been a grave failure in our educational institutions in that they have not grappled with how to educate more people to cope properly with these kinds of issues.

The Rockefeller University would certainly be an ideal setting in which to institutionalize the discipline of comparative toxicology, which is the scientific approach to these problems. That is, how can we use laboratory data on other species and field observations on sample populations to predict and assess risks to a wider consuming public? Such studies call upon all that we know of human genetics and evolution, particularly with respect to comparative biochemistry and physiology. They will require the use of the most sophisticated techniques of analytical chemistry and studies of the metabolism of particular substances in man.

The articulation of this new science with policy may demand more far-reaching steps. In the end, political decisions will have to be made involving participatory processes that are beyond the special ken of the University. Nevertheless, we still have an important responsibility to voice the consequences of alternative policy choices, applying the best technique of rational analysis that we can muster. The viability of an industrial economy, as well as our personal security as individ-

uals exposed to environmental threats, is at peril in these public policy choices.

In approaching the trade-offs to toxicity—which are inexorable because the very act of breathing pollutes the environment—we need new institutions where the academy can work more closely with government, with private foundations, and with industry. Exploring the most useful forms of such collaborations, particularly to exploit the existing resources and respond to the needs of the metropolis, has been an urgent and ongoing preoccupation for me.

The Outlook for Clinical Research

Before leaving the topic of research priorities, I would like to comment on our Clinical Research Center, The Rockefeller University Hospital. Since its creation in 1910, the Hospital has been an integral part of this institution. The recent competitive renewal of the major clinical research grant from the federal government attested to the great national importance of the Hospital's programs, which span a wide

Three years ago, William Trager, head of the University's parasitology laboratory, and James B. Jensen announced the first continuous cultivation in a test tube of *Plasmodium falciparum*, the parasite of human malaria. This achievement—which freed malaria research from its dependence on limited samples from human infections or on the availability of owl monkeys, the only suitable laboratory hosts—eliminated a major obstacle to scientists seeking a vaccine against the disease that claims more victims and lives around the world than any other.

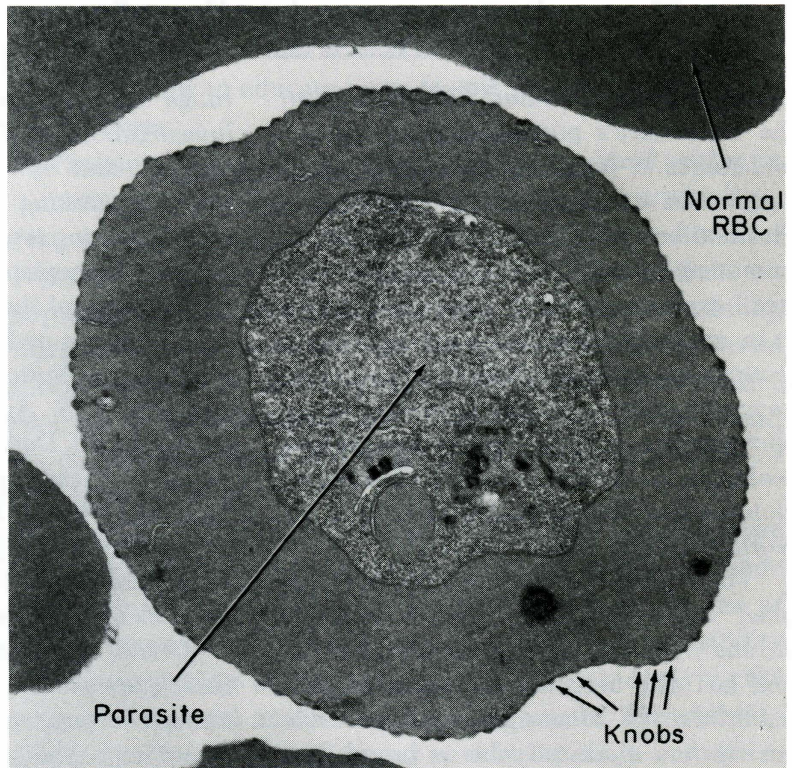
The culture method has now been applied successfully to several parasite strains from different geographical areas and has also been used for tests of anti-malarial drugs. Most significantly, the discovery has made possible a broad new

range of biochemical and immunological investigations by Dr. Trager and his colleagues, and by investigators elsewhere who are working against the background of an alarming resurgence of malaria, particularly in tropical and subtropical areas. A good deal of this research is funded by such agencies as the World Health Organization, the National Institutes of Health, and the U. S. Agency for International Development. Doctors Trager, Jensen, and Robert T. Reese have devoted considerable time and effort to helping other laboratories — particularly in Asia, Africa, and Latin America — to initiate and maintain cultures of *P. falciparum*.

One of the most promising lines of research opened by the availability of continuous culture techniques is related to the protrusions that develop on the outer

array of research efforts in the study of human diseases. More than 30 well-defined disorders, largely chronic and degenerative in nature, are under investigation. Overall, they represent a major portion of the disabling and lethal afflictions to which human beings are subject and for which we have yet to find wholly satisfactory means of prevention and treatment. Working with the senior faculty, administration, and trustees, the Hospital's physician-in-chief, Dr. Attallah Kappas, bears principal responsibility for appraising opportunities for new research initiatives that will enhance the strengths of this superb facility.

We are facing some redefinition of what constitutes clinical research these days. There was a time when the observation of disease at the bedside was, by itself, a very important part of medical progress. The clinical scientist still relies on direct contact with individual



patients, but more and more of the studies central to clinical research are done on tissue and fluid samples. This requires seeing patients for short intervals, rather than being directly engaged with them over a very long period of time. Such an approach has important practical implications for our Clinical Research Center that we are just beginning to explore in detail.

The Hospital has always been noted for a broad range of laboratory research that has complemented direct work with patients. Today, more than ever, we are seeing the Hospital as a base for research projects—involving human subjects—a very large measure of which is not done in an immediate clinical context. You might describe the Hospital as the summit of an iceberg of research that reaches deep into basic science. For example, in research on diabetes and other diseases, the investigators obtain samples from patients and carry out

membranes of red blood cells (erythrocytes) infected with the human malaria parasite. These “knobs” (visible in electron micrographs, like the one shown here, as inverted, cuplike plaques just beneath the membranes) occur only in erythrocytes harboring older parasites and are the portions of the infected cells that adhere to the endothelial cells of the capillaries imbedded in the heart and other organs, where the disease takes hold. By chemical and immunological studies, Dr. Araxie Kilejian showed that the material in the knobs is antigenically distinct from normal red-cell membranes and is clearly of parasitic origin. Susan G. Langreth and Dr. Reese then discovered that owl monkeys made immune to falciparum malaria produce antibodies to the knobs. Most recently, Dr. Langreth has made the intriguing discovery that each of three different

strains of the human parasite that had been in continuous culture between one and two years developed variants that do not form knobs in the erythrocytes they infect. This was the first report of a change in *P. falciparum* after extended test-tube culture.

Work is now in progress to determine the relative disease-producing potential (pathogenicity) of “knobless” and “knobby” lines of the human malaria parasite. Does knoblessness reflect a change in the pathogenicity of the parasite, which can be tested in experimental animals? Do other changes as yet undetected occur in the parasites after extended cultivation? The investigators do not yet have the answers. However, they do know that the answers will be especially relevant to research on possible malarial vaccines and to drug screening and chemotherapy.

some protracted observations of individual patients, but spend most of their time in the laboratory testing biochemical approaches to the treatment of disease. This is, in part, a result of new developments in scientific technique. If you can maintain human cells in the test tube, you can test the effects of chemicals on these cultures, rather than within a patient.

Since we need a certain minimum scale of activity for efficient operation of the Hospital, we are also actively engaging the interests of neighboring institutions in clinically related studies. We are happily situated in a neighborhood of medical institutions—The New York Hospital and Cornell University Medical College, the Sloan-Kettering Institute for Cancer Research and Memorial Hospital for Cancer and Allied Diseases—and have numerous possibilities for matching our own intellectual style and skills in research to the diverse problems and resources of our neighbors. This framework of cooperation means our investigators can undertake collaborative work at these larger hospitals with their highly advanced technology for patient care. In return, their staffs will have access to the different technical resources of our Clinical Research Center and to the, in some respects, more efficient and closer surveillance of patients it makes possible. This growing collaborative effort is of particular value in guiding the research and education of some of our younger scientists who hold clinical research fellowships. It gives them a much wider variety of experience than they would encounter within our Hospital alone. In like fashion, our proximity to the Payne Whitney Psychiatric Clinic at The New York Hospital has given us the opportunity to explore a range of options that will further research on the biochemical aspects of schizophrenia, depression, and other psychiatric disturbances.

Postdoctoral Training

This brings me to the University's traditional educational role—the support and preparation of gifted young people for scientific careers. From the very beginning, this institution has functioned as a focal point for individuals from all over the world who are seeking to deepen their experience in research by working side by side with senior colleagues who are recognized leaders in their fields. Thousands of gifted investigators have passed through our laboratories and have

moved on to important research posts in other institutions. Many of them return from time to time to share with former colleagues the fruits of their own investigations or to carry out some collaborative project in one of our laboratories. The impact of this continuing venture in postdoctoral education on the quality of biomedical science in this country is one of the University's major distinctions. It is a fulfillment of the hopes expressed at its founding, at a time when aspiring scientists had to seek their training in institutions abroad.

Everything I have said about the structure and style of the University with regard to research applies to its educational activity. The younger scientist taking his first step in a research career is received as a colleague in every sense of the word, and is free to move beyond his own laboratory to seek whatever advice or guidance he needs in building his own base of knowledge and research expertise.

Graduate Study Program

This is, to a large extent, equally true of our graduate program. A memorable experience that capped my first year in office was participating on June 6, 1979, in the awarding of the Ph.D. degree to 28 graduates. This was the University's 21st Convocation and the 25th anniversary of its assuming the status of a graduate university.

Having recently attended convocations with audiences in the tens of thousands, I was impressed by the focus on individual talent and performance that dominated our modest ceremony. We were able to present each candidate and review very personally his or her accomplishments and high promise. There is no doubt that these people will be the leaders of medical science, and that each one has the chance to reshape the way in which we view the world and how we adapt to live in it. Nothing could better exemplify the special quality of this institution.

Operationally, the graduate program takes advantage of the existing edifice of the research institute. The students enter a flexible tutorial program that encourages initiative on their part and places a heavy emphasis on research experience, which the University is so uniquely structured to provide.

All of us—and Dean James G. Hirsch and his associates in particular—put a great deal of time and expense into student selec-

tion. By bringing applicants to the campus, we can see them as individuals and evaluate their maturity and creativity. The very low dropout rate (about 5 percent) justifies the effort. In a closely knit campus community with a strong sense of common goals, the impact of 100 brilliant young people from all over the world is provocative in the highest sense, both intellectually and socially.

After just a quarter of a century, the University is justified in viewing its educational "experiment" as successful in its objective of producing leaders in science. This is indicated by the outstanding recognition given to it by scientists and educators throughout the world, as well as by the results of independent national evaluations of the quality of doctoral graduates in the biomedical sciences, all of which place the University's alumni at the top.

Equally impressive are the accomplishments of our alumni. Of

The skin is the largest organ of the human body, accounting for three to five percent of its total weight. Because this cutaneous tissue is a remarkably resistant and tough, yet pliable, membrane, we tend to view it primarily as a passive barrier that blocks harmful materials from entering the body and prevents essential body substances from escaping. But increasing concern about the possible toxic effects on human beings of many chemicals in the environment has focused increased scientific research on structures, like the skin, that function at the interface of the body and the world around it.

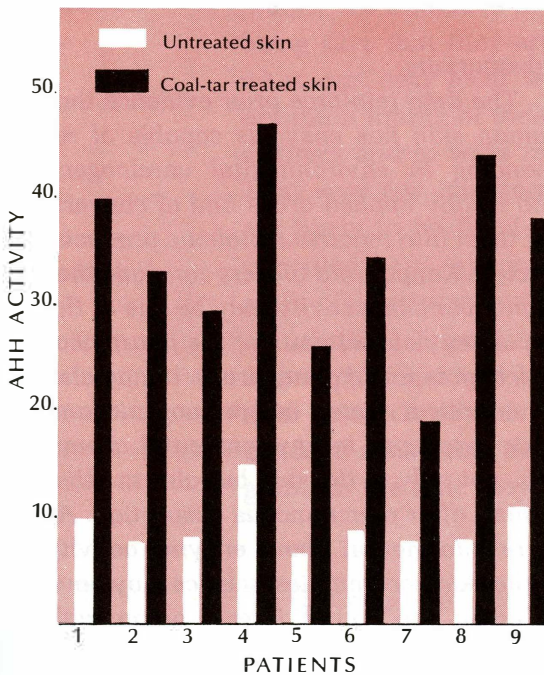
One of the scientists contributing to this research is Attallah Kappas, physician-in-chief of The Rockefeller University Hospital and head of the metabolism-pharmacology laboratory. A major interest of the laboratory is environmental biomedicine, particularly clinical studies of

human disorders caused by drugs and environmental chemicals. Research by Dr. Kappas and David Bickers, formerly a Rockefeller University Scholar in Clinical Sciences and presently chairman of the Department of Dermatology at the Case Western University School of Medicine, on coal-tar products and cutaneous tissue suggests the import of recent findings on the role of the skin.

Coal tar, a by-product of the gasification and distillation of coal, is widely used in the treatment of dermatologic diseases, particularly such chronic skin disorders as eczematous dermatitis and psoriasis. Coal tar contains a number of chemicals called polycyclic aromatic hydrocarbons, including 3, 4-benzo [a]pyrene (BP). BP is a precursor of several potent chemical carcinogens found in the environment; it is known to evoke tumors in the skin of experimental animals and, perhaps, also of humans.

325 graduates surveyed in the summer of 1978, 76 (23 percent) had reached the rank of full professor or the equivalent, 85 (26 percent) were associate professors, and another 26 percent had become assistant professors. About 95 percent of all graduates were engaged in full-time research and teaching. Two graduates have won the Nobel Prize. In reading these figures, one should bear in mind that our alumni are, on the average, only a decade beyond completion of their graduate work.

I strongly agree with the well-established policies of our graduate program—that it should continue to operate according to the principles and scale that have governed it from the start. Our most pressing needs for educational innovation relate to the integration of scientific and medical interests. Our current response to this concern is the joint M.D./Ph.D. program with Cornell University Medical



Coal-tar solution was applied to the skin and 24 hours later the site was biopsied. Skin homogenate was prepared and AHH activity determined.

Studies in experimental animals suggest that aryl hydrocarbon hydroxylase (AHH), an enzyme present in skin, plays an important role in metabolizing (chemically transforming) polycyclic hydrocarbons like BP into intermediate substances that may directly trigger cancer. Dr. Kappas and his colleagues had demonstrated earlier that AHH is present in the skin of newborn human beings, and that enzymatic activity is considerably increased by the process of enzymatic induction when cutaneous tissue is incubated in cultures with a polycyclic hydrocarbon, such as benzantracene. With all this as a background, Doctors Kappas and Bickers thought it important to assess the AHH induction effect of coal tar on patients undergoing treatment for chronic skin disorders, for which this widely used drug is employed.

Their studies showed, for the first time, that the application of a coal-tar prepara-

College, launched in 1972. This program is designed for a small group of candidates who are strongly motivated toward a research career in the basic or clinical biomedical sciences. The first Ph.D. degree in this program was awarded in 1977, so a definitive evaluation is still some time off, but the sheer quality of our registrants is a guarantee of success. One objective indication is that this program was one of the very few to get a renewal from the National Institutes of Health with substantially full funding of our request. This gives us the time to undertake a critical examination of the basic educational goals of the effort and to seek approaches that will assure the maximum return from the substantial investment of time and other resources.

Responsibilities to Young Scientists

The University seeks to provide a special place for the early development of careers in science with the expectation that the people

tion to the skin of patients with dermatologic diseases induced AHH activity in cutaneous tissue. This activity was from two to five times greater than the enzyme activity in untreated areas of the skin of the same individuals. Of the several coal-tar constituents available for testing, BP had the most potent effect. In related test-tube experiments, the investigators found that enhancement of AHH activity also took place when human skin was incubated with coal-tar solutions.

A third set of studies showed that use of coal tar on the skin of experimental animals causes induction of cutaneous AHH and, after absorption through the skin, also of AHH in the liver. Recent studies in humans confirm that when coal tar is applied to the skin, liver metabolism of drugs and other chemicals is altered

substantially.

The data reinforce prior evidence that human skin has enzymes capable of responding to environmental carcinogens and locally applied drugs and of converting them into reactive metabolic products. Doctors Kappas and Bickers conclude that such metabolic activity may be one of the important determinants of the pharmacological potency of many drugs. It may also be a critical factor in carcinogenic and toxic responses to environmental chemicals, not only in the skin but also in other tissues, after percutaneous absorption. As more information about enzyme activity in the skin accumulates, science may have to credit the body's largest organ with being a far more active part of its metabolic machinery than traditional views suggest.

whom we have recruited will find important research positions, not just jobs, elsewhere. But there have been many changes in the environment for science. We no longer live in an era where infinite growth is the implicit agenda. Problems with the overall level of science funding in this country, and the fact that only a small fraction of approved grant applications is actually funded, are very discouraging and tend to push people to aim for only safe targets. In fact, the academic market for most doctoral graduates has shrunk, as have the resources available for their training. This, in turn, reduces the mobility from one center to another that is so important for the vitality of science.

Having undertaken the responsibility of a productive and transforming role in dealing with scientific talent, we have to think very carefully about the careers of our people. At one level there is the eternal issue of quality control, to insure that the people we recruit warrant the investment entailed in simply having them here, and that they will make the most effective contribution to our research programs. We also have to be careful about justice to them, primarily in being sure that they are fully aware of what the world is like, and what our own local world is like. We must plan with them the optimum timing of their entry and, for most of them, their departure at times and in ways most appropriate to their career development. That very few long-term positions become available and that these are likely to be filled on the basis of a national search has always prevailed here, whereas at many other institutions it has become a reality fairly recently. What we owe our young fellows and faculty is an adequate opportunity to prove themselves and to develop their own capabilities and intellects to the point at which they can further their research objectives. Wherever appropriate, we foster independence to assure that their work is fundable by indispensable research grants at the time they move to other positions.

Material Resources

To this point, my report has focused on the importance of our work and the task of communicating and shaping that work to the best interests of the human purposes we ultimately serve. But there is a complementary task—a material one—of matching our plans and

operations to a realistic model of the resources available.

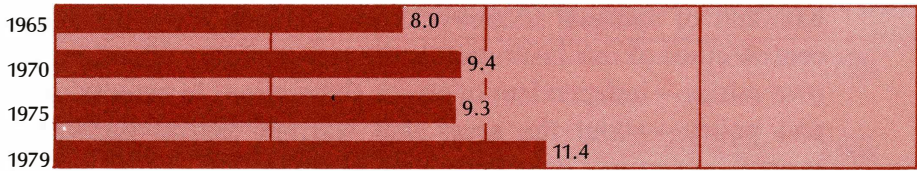
The concept of collegial effort, *pro bono humani generis*, was basic to the motivation of the Institute's founder. In 1901, John D. Rockefeller, Sr. provided the financial base, which, with subsequent additions from other family sources, enabled it to operate entirely from endowment income until the 1950s. By the early 1970s, however, it became evident that the scope of the work of the University and its importance to society had grown beyond the point where it was either practical financially or appropriate in principle to depend on a limited base of private support. If the University is to continue in the forefront of the life sciences and as a major contributor to the improvement of the human condition, then it has the obligation to develop future support from an entirely new constituency of private donors. We can best earn the confidence of these prospective supporters by adhering to the core principles of this coherent research community.

One other observation is pertinent in this connection. A glance at Chart 1, showing the sources of University income, reveals a steady increase in government grants since it was decided to seek outside funding. Such support is absolutely indispensable and, in fact, government grants account for almost half of our annual operating budget. However, as I noted earlier, it is predictable but lamentable that this level of federal involvement inescapably comes to be associated with a frustrating degree of centralized management by the government. Much of this funding is aimed at the "purchase" of specified research results, neatly packaged in "projects." At its inception, the federal support of biomedical research, administered primarily through the National Institutes of Health, reflected ideals similar to the University's and admirably supported major innovations and discoveries. But the project grant system is now run in ways that, however well-intended, sometimes threaten to disintegrate institutions, to discourage the confluence of creative ideas, and to erect serious obstacles to the collaboration of basic scientists in a wide variety of clinical applications.

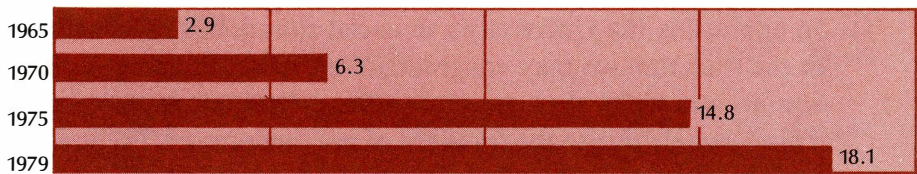
In the long-term planning for the University's financial future, we cannot forget that one of the most important functions of a privately endowed institution is to offer an effective counter-example to the

REVENUE SOURCES

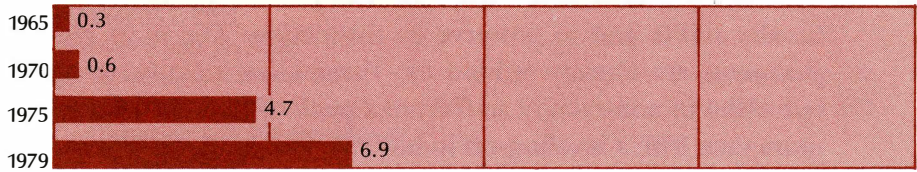
INVESTMENT INCOME



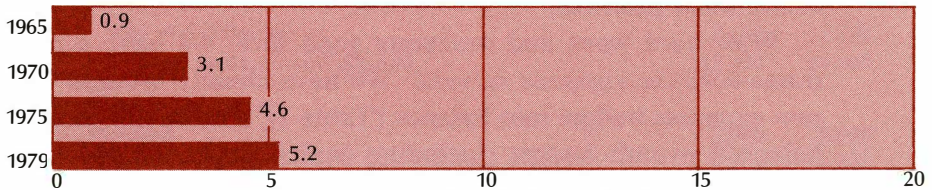
GOVERNMENT GRANTS



PRIVATE GIFTS AND GRANTS

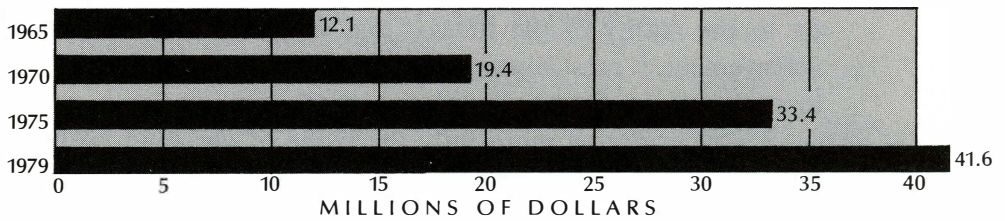


OTHER REVENUES



MILLIONS OF DOLLARS

TOTAL ALL REVENUE SOURCES



MILLIONS OF DOLLARS

CHART 1

services-rendered approach to research support. We have in mind the investment of *venture capital* in the identification of creative individuals and of collegial frameworks for reaching the same ends. The central ethos of this institution is the responsibility of making up our own minds—independent of erratic fluctuations in external attitudes and policy—about the areas that warrant careful nurturing and support, sometimes over fairly long periods.

A Financial Projection

In appraising the University's financial situation, I must affirm right at the start that we may congratulate ourselves in being far closer to equilibrium today than are most other private academic institutions. This is largely due to the foresight of my predecessor, Frederick Seitz, and the University Board of Trustees in husbanding the University's resources so carefully and launching the first fund-raising effort in our history. There has been a decade of effort to make the University fiscally stable and to preserve its distinction. The most painful adjustments are already behind us. These have included a significant reduction in non-faculty staff from a peak of 1,033 in 1971 to slightly more than 890; a leveling-off in both tenured and non-tenured faculty at about 450 after an almost threefold growth since 1955; a concerted effort to hold down costs; and an ongoing process of reexamining institutional priorities.

With hard work and moderate good luck, we have a planning framework for vigorous survival. We have already brought our current expenses budget into balance (Table 1), and we are projecting a balanced overall budget (including capital expenses) within a few years. But, as Chairman of the Board Patrick E. Haggerty has stressed, this projection is based on the "conviction that fund-raising from diverse private and public sources must be an intensive continuing effort open to periodic adjustment of goals. The University has faced up to the reality of the times—that to maintain its high level of achievement, it must sustain indefinitely the effort of the past decade to attain greater financial independence."

Before exploring more fully the scope of our fund-raising commitment, I think it is necessary to answer a question that may be prompted by the picture I have presented of an institution that is

consolidating its goals and stabilizing its growth in size and numbers. “Why do you need more money if your policy is to hold to the present size of the University?” There are two answers to this question: one to be found in an analysis of where our money goes and the other in a statement of our basic endowment needs.

Where the Money Goes

A glance at Chart 2 shows that 65 percent of our current expense dollars are direct expenditures for our research and education programs. That is as it should be, because we are really talking about the support of first-class scientific work by people of the highest caliber. The fact is that a certain amount of renovative growth has to be built into such a community to sustain vitality. Even though we do not plan to increase the number of full professors, an inherent growth of “technicality” at this University is related to the complexity of the equipment we use and the sophistication of the work we do. This is not numerical growth, but it is definitely a cost growth. Similarly, in an institution where there is a constant coming and going of investigators, particularly at the non-tenured rank, we need the resources to regenerate the system constantly, even though, over the course of time, there are no major fluctuations in the overall scientific population.

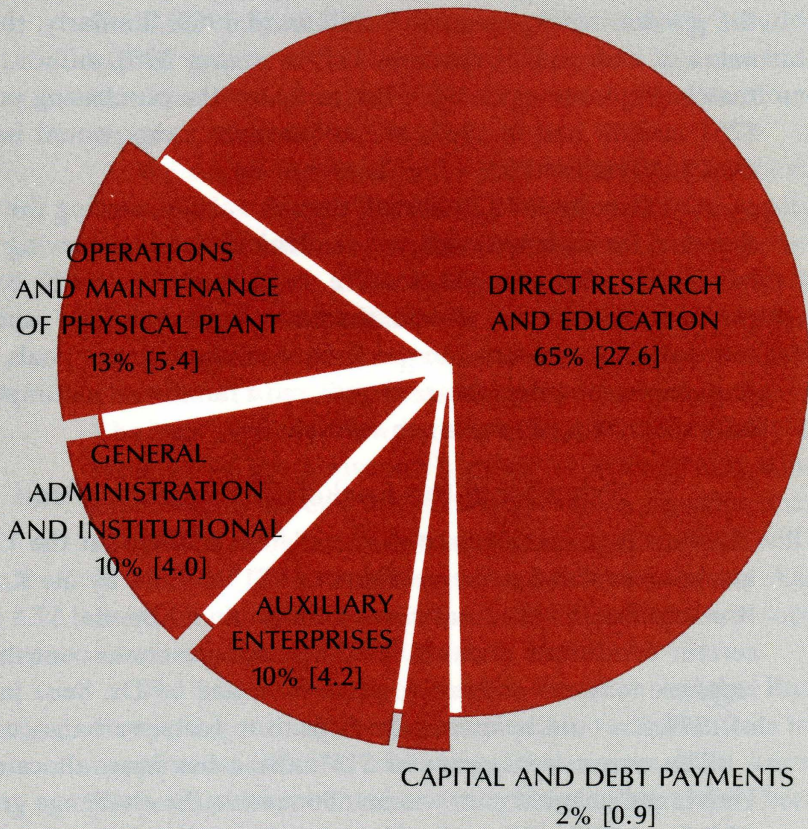
A related figure in Chart 2 is the 13 percent that the University expends for the operation and maintenance of its physical plant. Over half of this amount is spent for energy. It is inherent in an institution such as ours to be energy-intensive for the operation of instruments, to keep laboratories working around the clock. Controlled environments, which require high usage of energy, are mandated by government regulations, as well as necessary for stable results in experiments with animals. With the onset of the fuel crisis, the impact of energy costs has been increasingly aggravated and, even as I write, threatens to upset budget balances.

Strengthening Endowment

The energy problem is also involved in the second answer to our question about financial needs—we need additional resources to repair the depredations of our endowment. These stem from all the fiscal and economic blows we share with other non-profit institutions

EXPENDITURE CATEGORIES

YEAR ENDED JUNE 30, 1979 [Millions of Dollars]



EXPENDITURES:

CURRENT	41.2
CAPITAL AND DEBT PAYMENTS	.9
TOTAL FOR CHART	42.1

CHART 2

and that are built into the American economy, inflation above all. For example, there was a small, absolute rise in endowment income from \$8.9 million in 1969 to \$11.4 million in 1979. However, this seeming improvement quickly fades if we consider that the income would have had to be on the order of \$15 million in 1979 to match the purchasing power of \$8.9 million in 1969. Similarly, the market value of endowment funds in 1979 was over \$201 million, approximately the same as in 1969. But to match the purchasing power that \$201 million had in 1969, our endowment today would have to be over \$350 million.

As I have already indicated, though not discounting the very real threat of the unforeseeable, we can look ahead to achieving financial balance in the near future. We have made carefully considered projections, and we update them on both quarterly and annual schedules to measure our performance against our goals. But the projections for a decade are sensitive to a number of assumptions that only the march of events can validate.

Grant from the Rockefeller Brothers Fund

The best financial news of this academic year is that the University has been awarded a five-year grant of \$15 million by the Rockefeller Brothers Fund, with future provision for an additional \$7.5 million if certain conditions are met. Without this generous contribution, in response to a comprehensive plan submitted by Dr. Seitz in October of 1977, it would be extremely difficult to foresee a balanced budget.

The unrestricted grant of \$15 million has been allocated to the University's capital endowment. To receive the challenge grant of an additional \$7.5 million, the University must satisfy two conditions by December 31, 1986. The first is that the institution raise \$10 million in new endowment in addition to the RBF basic award of \$15 million. The second is that we match the additional \$7.5 million fund, dollar for dollar, by contributions to endowment from other private sources.

The RBF has also stipulated that funds, estimated at about \$500,000 annually, will be available to the University, Memorial Sloan-Kettering Cancer Center, and The New York Hospital-Cornell Medical Center for joint or cooperative projects initiated between this year and the end of 1983. I believe this is a highly constructive

mechanism for financing a number of worthwhile interinstitutional ventures, and a joint steering committee is working hard on tangible proposals.

In fulfilling its special responsibilities to one of the organizations that historically has been of strong interest to the Rockefeller family, the RBF indicated that it contemplates making no additional large capital grants to the University. This does not preclude the future consideration of project requests in the light of the Fund's evolving program interests.

We are all indebted to the RBF for this inspirational demonstration of faith in the future of The Rockefeller University as a major source of scientific innovation and medical progress. As magnificent as the grant is, we know it does not solve all our financial problems. However, the RBF award will serve as the cornerstone of a new and intensive plan, which responds to the challenge and calls for raising a total of \$150 million from private sources within the next ten years. The new plan—shown here in summary form (Table 2)—incorporates all of the University's prime objectives, and aims to achieve them before the end of the next decade. A significant component of this plan is the University Associates Program, which will be instituted in 1979–80. This replaces and expands the current Annual Giving Program. It will broaden the base of constituency support for our annual operating expenditures.

The task before us is not to be taken lightly. But we have a compelling message and a sound plan to communicate to prospective supporters, and the confidence that comes from knowing we are proposing investment in an enterprise that has always been productive of public good.

An Afternoon to Remember

This has been a hectic year, a rewarding year, a full year. Even in so short a time I have many rich memories of this unusual community of which my family and I are now enthusiastic citizens. And we are deeply impressed by the spirit of cooperation and the individual concern shown by all members of the staff, whatever their area of responsibility.

In closing this report, I would like to look back on one event that

TABLE 2
THE ROCKEFELLER UNIVERSITY
10-YEAR DEVELOPMENT PROGRAM

ENDOWMENT	<u>Millions</u>
For People	
20 Professorships	25
10 University Fellowships	8
10 Clinical Fellowships	8
20 Postdoctoral Fellowships	10
50 Doctoral Fellowships	<u>20</u>
Total for Endowment	71
 OPERATING SUPPORT AND CAPITAL PROJECTS	
For Fundamental Investigations, Including:	35
cell biology	
the neurosciences	
parasitology	
reproductive biology	
immunology	
toxicology	
For Clinical Studies, Including:	20
metabolic/genetic diseases	
immunological diseases	
biochemical psychiatry	
cancer	
environmental medicine	
pharmacology	
For Essential Facilities	
Information/Computing Center	5
Modernization and Renovation of	
Laboratories and Hospital	10
For General Operating Support*	<u>9</u>
Total for Operating Support and Capital Projects	<u>79</u>
Grand Total	<u>\$150</u>

* Includes University Associates Program

had deep personal meaning for me, both as a scientist and a “freshman” president. On the afternoon of February 2, 1979, a seminar was held in Caspary Auditorium that drew a large audience from the campus, as well as scientists from a number of other institutions. The occasion was the 35th anniversary of the publication in *The Journal of Experimental Medicine* for February 1, 1944, of a paper by Oswald T. Avery, Colin M. MacLeod, and Maclyn McCarty on the chemical composition of the “pneumococcus transforming factor.” The transforming factor, of course, was DNA, and the paper encapsulated perhaps the most revolutionary biological discovery of this century—that DNA is the basis of heredity in all organisms.

Dr. Avery retired from The Rockefeller Institute for Medical Research in 1948 and died on February 20, 1955, in Nashville, Tennessee. Colin MacLeod served on the staff of The Rockefeller Institute from 1934 to 1941, then became a professor at New York University Medical School. He died on February 12, 1972, in London. Maclyn McCarty is now a John D. Rockefeller Jr. Professor at The Rockefeller University, having also served as vice president from 1965 to 1978 and as physician-in-chief of The Rockefeller Hospital from 1960 to 1974. In fact, that February seminar was equally a celebration in his honor.

Participating in the warm and spirited exchange of reminiscences that enlivened the gathering, I felt again the excitement with which—as a new graduate of Columbia College venturing into research—I first read that now-historic paper and sensed its unlimited implications. It was the initiating impulse to my own scientific career. How gratifying then, 35 years later, to be among my peers in this community, with the opportunity to help sustain a tradition and a style of biomedical research that have no match.

GIFTS AND GRANTS

On behalf of our faculty, graduate fellows, and trustees, I would like to express our warmest thanks to the following donors who have contributed to the University during the nine fiscal years since the first comprehensive effort in our history to broaden our base of private support was launched.

The first list includes those donors whose assistance is helping to fulfill the goals of the University's overall Development Program. Since its inception in 1971, the Program's goals have emphasized additional endowment and long-term operating support for basic research

in selected life sciences, for the clinical programs of our Hospital, for professorships, and for predoctoral and postdoctoral fellowships. Several major donors also have aided the construction of our new Laboratory Animal Research Center, a high-priority objective for which the remaining funds are still being sought.

The second list recognizes contributors who have provided funds for general operating expenses, as well as for ongoing research and special University-wide projects.

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