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New Initiatives in Biological and Medical Science

The Rockefeller University

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Cover: Phagocytosis of a *Trypanosoma cruzi* parasite by a macrophage. Magnification ×4000.

New Initiatives at The Rockefeller University

In fulfillment of its mandate for excellence and cogency in research, The Rockefeller University has launched a set of new initiatives in fields of biochemistry and molecular biology, which encompass genetics, cell biology, and neurobiology.

These revolutionary frontiers for biological and medical science relate to problems of cancer, reproduction, food supply, brain science, mental disease, genetic abnormalities, and many degenerative disorders caused by agents ranging from viruses to parasites. The research undertaken will augment worldwide progress in agriculture, medicine, and public health.

Seven new research laboratories are being established in the brief period between 1981 and 1983. Appointment of the extraordinarily talented leaders of these new laboratories, along with their many gifted young colleagues, constitutes the most important surge of first-rank investigators onto the campus during the past 20 years. The opportunity for this surge stems in part from the retirement or death of some of the University's most notable figures. As always, new laboratories call for new levels of material commitment even at a time when the University as a whole is under a stringent discipline in its growth.

To supplement available private and public support, the University needs $35 million over the next two years to underwrite new initiatives in these fields. This funding would endow professorships, support part of the new and ongoing program for young investigators, and help meet the cost of urgent modernization of research facilities and equipment.

Molecular Biology–the New Frontier

To understand the emerging revolutionary opportunities in biology and medicine, which are central to the University's New Initiatives, it is important to grasp the overall perspectives of *molecular* biology. This modern science is organized around the principle that, in order to understand the complexities of living organisms, it is necessary to understand the very basic constituents–molecules–which form cells and, in turn, structure tissues and entire organisms. Investigations at the molecular level are aimed at the fundamental building blocks of life. These are, in themselves, complex biochemical structures.

Molecular biology emerged from the successful research by many laboratories in biochemistry and genetics in the late 1930s and 1940s. Perhaps the most notable landmark came from The Rockefeller Institute, with the discovery in 1944 by Avery, MacLeod, and McCarty that the chemical basis of heredity is DNA. The seminal quality of the molecular approach was deepened in 1953 with Watson and Crick's picture of the double-helix structure of DNA.

The double-helix DNA comprises two long thin chains twisted about each other in a regular manner, like a double spiral staircase. Each chain is built of smaller units (called nucleotides) that are cross-connected by a "lock-and-key" pairing of single units on each chain. The overall sequence of the units in a chain constitutes the genetic code.

The fundamental "words" of the genetic code were found to be groupings of three nucleotides. These "code words" pass their instructions first to so-called messenger RNA molecules and then to the key building blocks (amino acids) in the cell. They direct the amino acids to line up and combine in a particular sequence, forming specific proteins of the cell in a unique order. This specific sequencing is what makes, for example, the protein in our hair–coded by one gene–different from the protein in our red blood cells, coded by another gene.

Aware that the sequence of nucleotides is the code that determines

ultimately the character of genetic material, and by using procedures to move genes around, investigators discovered a new picture. This picture revealed more about the detailed structure of genes and the elements controlling their functions.

Later, when a way to synthesize proteins in the laboratory was discovered, the path to determining the genetic code was opened. Subsequently, the precise meanings of the "code words"—the triplets of nucleotides—were revealed. Although protein synthesis is complicated, the code was found to be universal. With only minor variations of "dialect," the same code appears in *all* living forms: microbial, plant, and animal. This fact has profound implications for understanding the interrelationship of living matter and the evolutionary history of life on our planet.

Large areas of research on cells were soon clarified by this intellectual revolution. Simple bacteria could be understood more readily; human cells (or "eukaryotic" cells, i.e., cells with nuclei) are far more difficult because cells in higher forms of life—including humans—have so much more DNA than bacteria. The power of genetic studies was still so limited in the early 1970s that further detailed analysis of DNA in higher forms seemed remote. It was at this juncture that critically needed techniques were developed.

Molecular biology and biochemistry are on the frontiers of exciting new horizons. For example, slight differences in DNA sequences (called DNA polymorphisms) can be used to analyze and map the human chromosome. Such maps will lead, in turn, to deeper knowledge of many diseases—from genetic disorders to cancer and aging.

These molecular, biochemical perspectives also will pave the way toward better understanding of the brain and nervous system, building the next stages of advanced agricultural production, and fathoming the causes of a broad array of diseases for which there is presently no effective approach to prevention or cure. Yet the accomplishment of this fundamental research—and the innovations that will be based upon it—will depend both on expansion of the tools in hand and on invention of new concepts and techniques.

Scientific Leadership for New Initiatives

In planning research initiatives and carefully selecting the leaders for new laboratories, the University has three goals. First, to sustain the University's mission of fundamental research. Second, to seize those research opportunities that relate directly to major unsolved human problems—fostering the applications that, over the next generation, will make a genuine difference to the world. Third, to advance our research leadership by adding a new generation of gifted scientists, replacing those who have retired recently or who will retire during the next decade.

Biochemical Genetics

One initiative is a new laboratory headed by Professor Robert G. Roeder, who was the James S. McDonnell Professor in Biochemical Genetics at Washington University School of Medicine in St. Louis.

His research activities are directed toward answering key questions about the molecular basis of processes such as (a) cell growth and proliferation (e.g., what are the mechanisms in the early development of the embryo?); (b) cell differentiation (e.g., what causes a liver cell to be different from a heart cell?); and (c) the infection and transformation of mammalian cells by DNA tumor virus (e.g., what are the controls in cells that relate to the mechanisms of cancer?).

The cellular and viral genes that affect these processes are controlled in part at the level of transcription (the first step in the readout of genetic information, from DNA to RNA). Dr. Roeder's work has focused largely on an analysis of the biochemical mechanisms that are involved in this process for individual genes.

Dr. Roeder's pioneering work in eukaryotic transcription (i.e., in cells with nuclei, as in human cells) began while he was a graduate student at the University of Washington. This work led to the first isola-

tion and characterization of the family of enzymes that directly copy genetic information from DNA. On the basis of such fundamental work on the eukaryotic transcription machinery, he was awarded the American Chemical Society's Eli Lilly Award in Biological Chemistry in 1977.

Dr. Roeder's studies complement and allow extension of work on gene structure and function already under way in many other laboratories at The Rockefeller University and elsewhere. For example, the ability to introduce specific mutations into genes (via recombinant DNA technology) has allowed the delineation of the DNA sequences that are important for expression and regulation. However, for most genes, such experiments do not readily allow the identification of the regulatory factors (presumably protein) that interact with and control these genes. The approaches in Dr. Roeder's laboratory allow direct identification of such factors and are necessary for fully understanding the mechanisms involved in gene control.

The power and elegance of this approach have been amply demonstrated for bacterial genes and appear to be equally promising for human genes. Ultimately, this line of research should clarify the reasons for developmental abnormalities and enhance the explanation of the causes of aging and cancer.

Organic Chemistry and Biochemistry

The initiative in organic chemistry and biochemistry is a new laboratory headed by Professor Emil Thomas Kaiser. Dr. Kaiser was at the University of Chicago as the Louis Block Professor in the Departments of Chemistry and Biochemistry. His research is focused on the actions of enzymes.

In future biomedical research, a major concern will be capitalizing on the extensive progress that has been made during the past 40 years in understanding the molecular architecture of enzymes—the catalysts that make it possible for us to do our daily tasks. The Rockefeller has a long tradition in this field; the coming years will see the fruits of past invest-

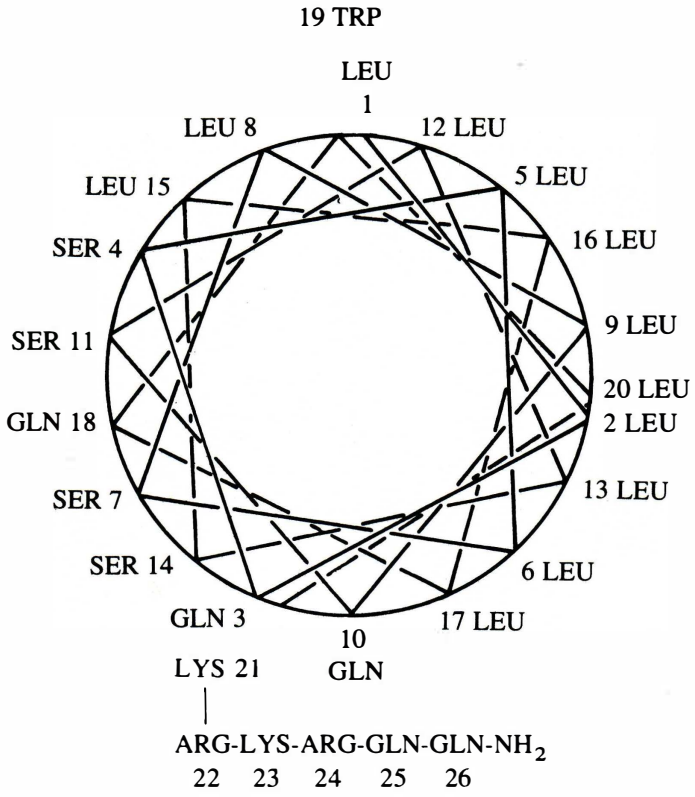
ment in such basic research. Significantly, Professor Kaiser came to the University with a distinguished record of accomplishment in this specific area.

He has applied his early training at Harvard in physico-organic chemistry to explaining the mechanisms by which enzymes selectively foster certain reactions in the body. For example, he has studied pancreatic enzymes, the enzymes concerned with blood pressure, and enzymes from the cardiac muscles and from the lung. The "active centers" of each of these molecules are being defined chemically, and methods of enhancing or reducing their biological "activities" are being developed. The work addresses the many difficult problems in understanding the relationships between the structure of a substance and the substance's function in the body.

Professor Kaiser has extended such studies to the formation of proteins with new catalytic functions. In these innovative experiments, he took an enzyme that facilitated the reaction of water with proteins and coupled it to an organic compound that gave the combination a catalytic activity toward materials that react with oxygen (such as those found in human cells). A new species of catalyst was made; he had achieved an artificial chemical hybrid. The preparation of new catalysts in this manner offers promise of application in industry as well as in biology and medicine.

Further, Dr. Kaiser has been exploring the synthesis, from elementary chemicals, of biologically active components. Proteins are polypeptides built from amino acid building blocks, and peptides now can be synthesized effectively by laboratory methods devised, in considerable part, by Bruce Merrifield at The Rockefeller University. Professor Kaiser is making ingenious use of these new synthetic approaches in the preparation of new peptides that, for instance, can inhibit enzymes, bind lipids (fats), prevent the formation of kidney stones, and prepare new hormonal agents.

These efforts illustrate the enormous opportunities for achieving, through organic chemistry and biochemistry, a fundamental under-

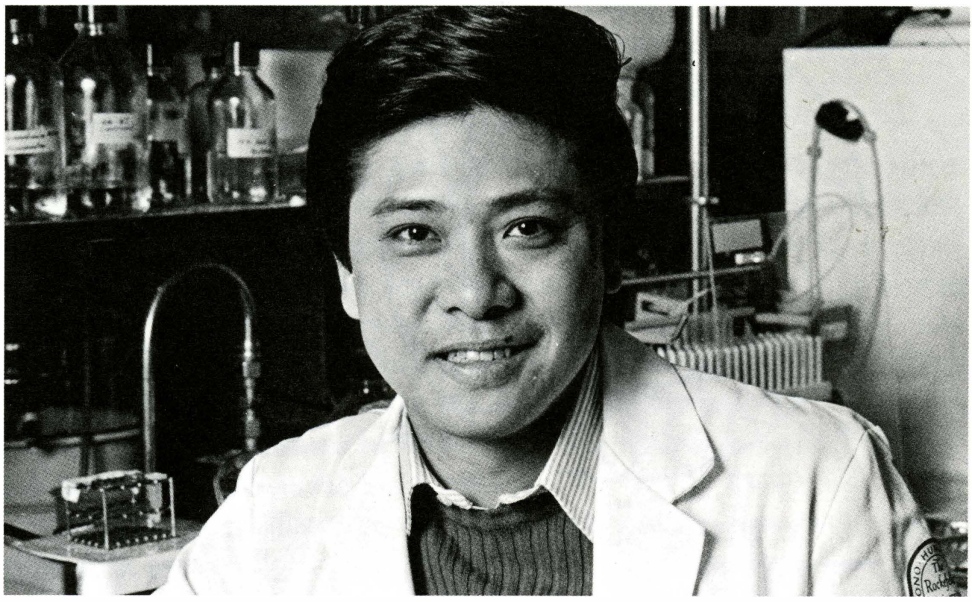


Axial projection of the α-helical region of the model peptide showing the relative location of the side chains with the segregation of hydrophobic and hydrophilic residues.

standing of intricate living systems. The University provides a stimulating context for Dr. Kaiser's efforts, working with both laboratory scientists in related fields and physicians whose patients have diseases that must be understood more fully in chemical terms.

Plant Molecular Biology

The study of plants has been seminal in the history of biology—both as a science and as a technology—from the traditional medicines derived from plants through Mendel's revolutionary work on genetics to the modern "green revolution." Numerous early and important discoveries



Nam-Hai Chua

at The Rockefeller Institute for Medical Research were based upon plant systems and extracts. The University intends to sustain its coherence as an institution devoted to the sciences-of-life by maintaining a vigorous program, in modern terms, in plant biology.

Nam-Hai Chua, born in Singapore and educated at Harvard, was promoted to full professor in July 1981 and organized a major new laboratory in plant molecular biology. Professor Chua is a cell and molecular biologist who has made contributions to the understanding of photosynthesis, chloroplast biogenesis, and plant gene structure and regulation. His special interest is the chloroplast, an organelle in the cells of green plants that is important to all life because of its role in photosynthesis. Energy from sunlight is trapped in the chloroplast and utilized in the manufacture of complex organic materials, particularly sugar, from simple inorganic substances.

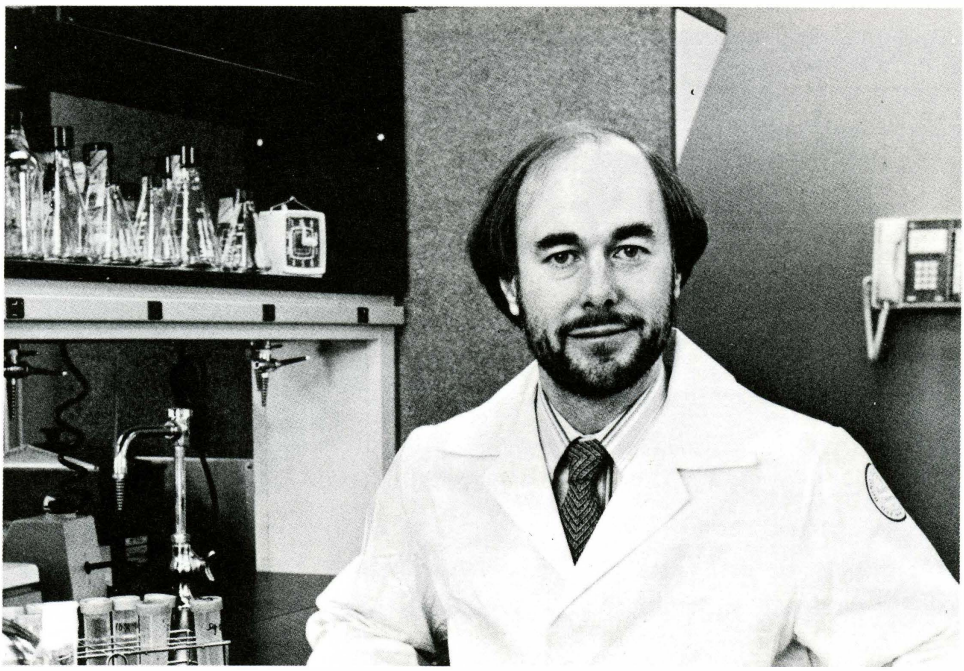
Dr. Chua has addressed himself to one of the long-standing puzzles in cell biology: how are needed proteins transported from their sites of synthesis elsewhere in the cell to subcellular organelles, such as chloroplasts, which have only a limited capacity to produce their own proteins?

His current interest is plant gene structure and regulation. He is investigating the mechanisms by which the gene that codes for the chloroplast enzyme (ribulose diphosphate carboxylase) is differentially regulated. This enzyme, found everywhere in green plants, is the most abundant protein on earth. It is used for carbon dioxide fixation, the key reaction in photosynthesis. It makes up 50% of the soluble protein in plants such as soybean, and is present to a lesser extent in other plants such as maize and sorghum, which are major food crops. Dr. Chua is attempting to identify the gene control regions for this enzyme, which would have substantial benefits for agriculture.

Molecular and Cellular Parasitology

Because parasitic diseases have not been a significant problem for citizens of the United States—except for travelers and our armed forces stationed abroad—research on these diseases has never received a high priority from public or private sponsors. Nonetheless, in global terms, parasitic illness and death are probably *the* leading health problem. Malaria alone kills a million children, infects about 200 million adults each year, and puts about 1.8 billion people at risk. Trypanosomiasis and schistosomiasis, among many others, also are critically important threats to human health and domesticated animals throughout developing countries.

Accordingly, the University has always devoted attention to this international problem—from pioneering work early in this century on cattle fever and hookworm, as well as on yellow fever and sleeping sickness, to the recent discovery by William Trager that may pave the way



George A. M. Cross

for a vaccine against malaria. Field work has been carried out internationally, from South America and the Caribbean to India and China, and throughout Europe and Africa.

George A. M. Cross, born in England and educated at Cambridge, came to the University from the Wellcome Research Laboratories (Kent), where he headed the Department of Immunochemistry, which is concerned with parasitic infections. Previously he was a member of the biochemical parasitology unit of the Medical Research Council at Cambridge. His new laboratory at The Rockefeller University will concentrate on molecular parasitology.

Dr. Cross's approach is to study parasitism as a disease process and to learn the underlying mechanisms of parasitism. These diseases go through specific sets of developmental changes during each life cycle. At

each stage, the parasite must express certain genes to facilitate its function. Decoding these special steps of parasitic action will allow the development of very specific agents for the most effective disruption of the disease process. Investigating the nature of stage-specific genes, the genetic structure and organization, and the expression of parasite-specific proteins—all should provide much greater insight into the use of chemical agents capable of lethal action on specific parasitic stages. It may also prove feasible to produce immunological agents capable of interrupting the parasite-host relationship and preventing infection.

This new line of research has recently been made possible by the rapid and revolutionary growth in research technology. To investigate the devastating human parasitic diseases at the cellular and subcellular levels, and now at the molecular level, requires analysis of parasite gene expression. Recombinant DNA technology, monoclonal antibodies, and other recent molecular biological advances are eminently suited to this work, and Dr. Cross has mastered these new techniques.

Biology of Skin Diseases

Skin, the largest organ of the body, has yet to be studied scientifically with the scope that it merits. Cancer, aging, disfiguring skin problems such as psoriasis and burns, and hazardous environmental pollutants that enter the body through the skin—these suggest the breadth of biological, medical, and occupational problems related to the skin. Yet dermatology rarely has received the attention of first-rank medical investigators. Accordingly, as the University considered biomedical fields that were ripe for attack in our Hospital, this area appeared promising. We concluded that there was an unusual opportunity for creative efforts on skin disease and identified a distinguished individual who could organize a sophisticated approach to research in this area.

David Martin Carter came to the University in the summer of 1981 from Yale University School of Medicine where he had been Professor of Dermatology. After graduating from Dartmouth, he earned an M.D. at

D. Martin Carter

Harvard and a Ph.D. in molecular biology at Yale (while serving as a Howard Hughes Medical Investigator). In a remarkable way, he combines the necessary laboratory expertise of biochemical analysis with the clinical experience required to investigate disabling and lethal skin afflictions.

During the past year he has recruited a group of young collaborators—all with a comparable mix of medical and scientific training. He has established strong links with our neighbors, the Memorial Sloan-Kettering and New York Hospitals, which have many patients in their dermatological services. The laboratory's studies of environmental impact on skin function deal primarily with damage resulting from exposure to chemicals, drugs, and radiation.

Chromosomes of peripheral blood lymphocytes, differentially stained to show sister chromatids. Exchanges between chromatids, promoted by DNA damage, are evident.

Dr. Carter's new initiatives—ranging from studies of damage to the DNA of skin cells to the treatment of various skin disorders—will help to build a firm foundation for this domain of medicine. The environment at Rockefeller University provides Dr. Carter and his colleagues with the opportunity to bridge the barriers that tend to separate laboratory investigations from studies of hospitalized and ambulatory patients with skin diseases.

Neurobiology

The neurosciences are one of the most dramatic and important frontiers for research in the coming decades. Understanding how the brain develops and functions, eliminating psychological (psychiatric) disorders, preventing and treating diseases of the brain and nervous system, and ascertaining the limits of brain function are the ambitious goals that, for the first time, are becoming feasible through the application of modern biological tools for research. The University has a long record of accomplishment in these fields and continues to assign a high priority to this general area.

Torsten Wiesel, M.D., comes to the University in early 1983 from the Harvard Medical School where he has been Robert Winthrop Professor and Chairman of the Department of Neurobiology. Co-recipient of the Nobel Prize in 1981, Dr. Wiesel and his colleagues have been pioneers in neurophysiology—carrying out pioneering studies of the cells in the brain that relate to vision.

Dr. Wiesel and his group of gifted young collaborators—including neuroanatomists, cell biologists, and biochemists—offer remarkable complementarity to our ongoing efforts in the neurosciences, from brain molecular biology to animal behavior. For example, Dr. Wiesel's current research includes "cutting edge" work on the study of methods of tissue culture that will permit analysis of single visual cells in isolation. Furthermore, the group exploits the entire range of modern instruments—from the electron microscope to computer graphics—in trying to reveal the elegant networks and ensembles that the brain uses to process information.

Neurochemistry

As Torsten Wiesel approaches the brain by examining in detail the processes of using visual information that comes from outside, the leader of another initiative approaches the functions of the brain by exploring the chemistry of its inner workings.

Paul Greengard comes to the University in mid-1983 from Yale University Medical School, where he has been Henry Bronson Professor of Pharmacology. He is one of the leading neurochemists in the world, and has attracted many talented students.

During the past decade, Dr. Greengard has made a series of discoveries about the biochemistry of the brain that have provided a conceptual framework for understanding the functioning of the nervous system in molecular terms. He demonstrated that certain pharmacological and clinical actions (both therapeutic and toxic) of several major classes of psychoactive drugs—including common antipsychotic, hallucinogenic, and antidepressant drugs—can be explained in terms of selective chemical actions. This work has provided a practical new approach to the development, by pharmaceutical companies, of drugs that act on the nervous system.

Greengard's work has had an impact on many branches of physiology, regulatory biology, and medicine. One of his results, formulated about 10 years ago, provides an explanation of how a single key compound can produce an enormous variety of biological effects. According to his widely accepted hypothesis, this chemical compound activates an enzyme present in the target tissues, and the specificity of the biological effects lies in the nature of the substrate for the enzyme in the target tissue. This approach is now being extended to focus on the mechanisms of action of environmental toxins—and of alcohol—on the brain.

The Financial Challenge for Scientific Opportunity

In formulating a program for New Initiatives, requiring $35 million in private support over two years, the University has three components in mind. First, $10.5 million would be used as endowment to establish professorships for these distinguished members of the faculty, the leaders of the new laboratories. Subject to consultation with donors, chairs may be named to honor individuals or organizations.

Second, $14.5 million would be directed toward the support of outstanding young investigators—ranging from advanced doctoral students through postdoctoral fellows and assistant professors. This fund would provide core support for research initiatives by young scientists at a time when federal grants for these purposes are declining. Salaries, benefits, and technical support will be allocated, at the discretion of the President, for research projects recommended by heads of laboratories.

Finally, $10 million would be directed to meeting the start-up costs of the seven new laboratories, including the modernization of research facilities, the purchase of scientific equipment, and data-handling systems required for the research. Such capital investments are indispensable for modern research, but the federal government is unlikely to provide any funding for these purposes.

An Investment in Talent. The need to endow and name professorships grows directly from the University's long-standing tradition and current fund-raising goals. The institution's policy is that all tenured members of the faculty (the heads of laboratories) are paid entirely from endowment income. Working full-time on a 12-month basis, these senior scientists are free from the concerns that most faculty members elsewhere face in seeking partial grant support for their own salaries. This has fostered greater independence and flexibility, resulting over the years in shifts of emphasis that might otherwise not have occurred and that have proved to be highly inventive.

To sustain this productive tradition against the pressure of rising costs, the University must supplement its endowment. Since 1971, one of the highest priority fund-raising objectives has been to add endowment for senior faculty, and a number of grants have been received for this purpose. During the next few years, with the renewal of several scientific fields on the campus, it will be even more important to assure the stability of support for our scientific leadership. Each chair requires $1.5 million to endow; the capital is invested and a portion of the annual income is used to preserve the purchasing power of the endowment.

The Laboratory and Technology of Science. Typically, a major new laboratory requires a substantial investment in start-up costs. Upgrading a laboratory—even space that has been used recently by active investigators—usually means extensive renovation to meet the special needs of the new group. Far from a routine "remodeling," the task is to design a research facility in a specialized fashion, meeting sophisticated standards for research. Changes also are mandated by governmental regulations on biological and chemical work in a safe environment. Typically, renovation costs are not less than $100 per net square foot, and a major laboratory usually requires about 6,000 net square feet of space. Therefore, the total cost of renovation for one laboratory is at least $600,000.

In addition, purchases of new and costly scientific equipment are often required. For example, major instruments (such as a nuclear magnetic resonance spectrometer or an electron microscope—each costing around $350,000) are crucial to the research effort. In many cases, particularly during the past decade, even distinguished investigators have been unable to purchase new instruments with federal funding. Computing and related data collection are also essential for nearly all research, and federal support for computers continues to be extremely scarce. New equipment for a laboratory usually requires not less than $500,000 and can be as much as $1,000,000.

Assuring Flexibility and Investigative Freedom. Although leading scientists continue to be able to attract government funding for their programs,

some "core support" for the laboratory must be provided to ensure the flexibility needed for exploratory studies. Such core financing may be used as a revolving fund to support parts of the salaries of postdoctoral fellows and younger faculty who are pursuing pilot studies, most of which lead, in time, to federal grants. Also, core support frequently covers the replacement of major parts for scientific instruments and other emergencies that simply cannot be budgeted or anticipated in either federal grants or the University's tight fiscal planning. Requirements for core support vary widely from lab to lab and from year to year. Usually, that support would be not less than $200,000 per year and might reach $350,000 per year for a large laboratory. Such a laboratory usually receives three times that level of funding from federal grants. Thus, private support permits great leverage in allowing new ideas to be pursued by providing start-up costs and by buffering shifts in availability of government funds.

Summary

The capital costs associated with the establishment of seven laboratories under the University's New Initiatives Program are as follows:

Professorships. Endow and name distinguished professorships for scientists who will lead new laboratories (seven at $1.5 million)	$10.5 million
Young Investigators and Fund for New Initiatives. Support flexible funding for young investigators and new projects; assist in core support of new laboratories for five years	$14.5 million
Research Equipment and Facilities. Partial support for purchase of scientific equipment and upgrading research facilities required to start new laboratories	$10 million
Total	$35 million

March 1983