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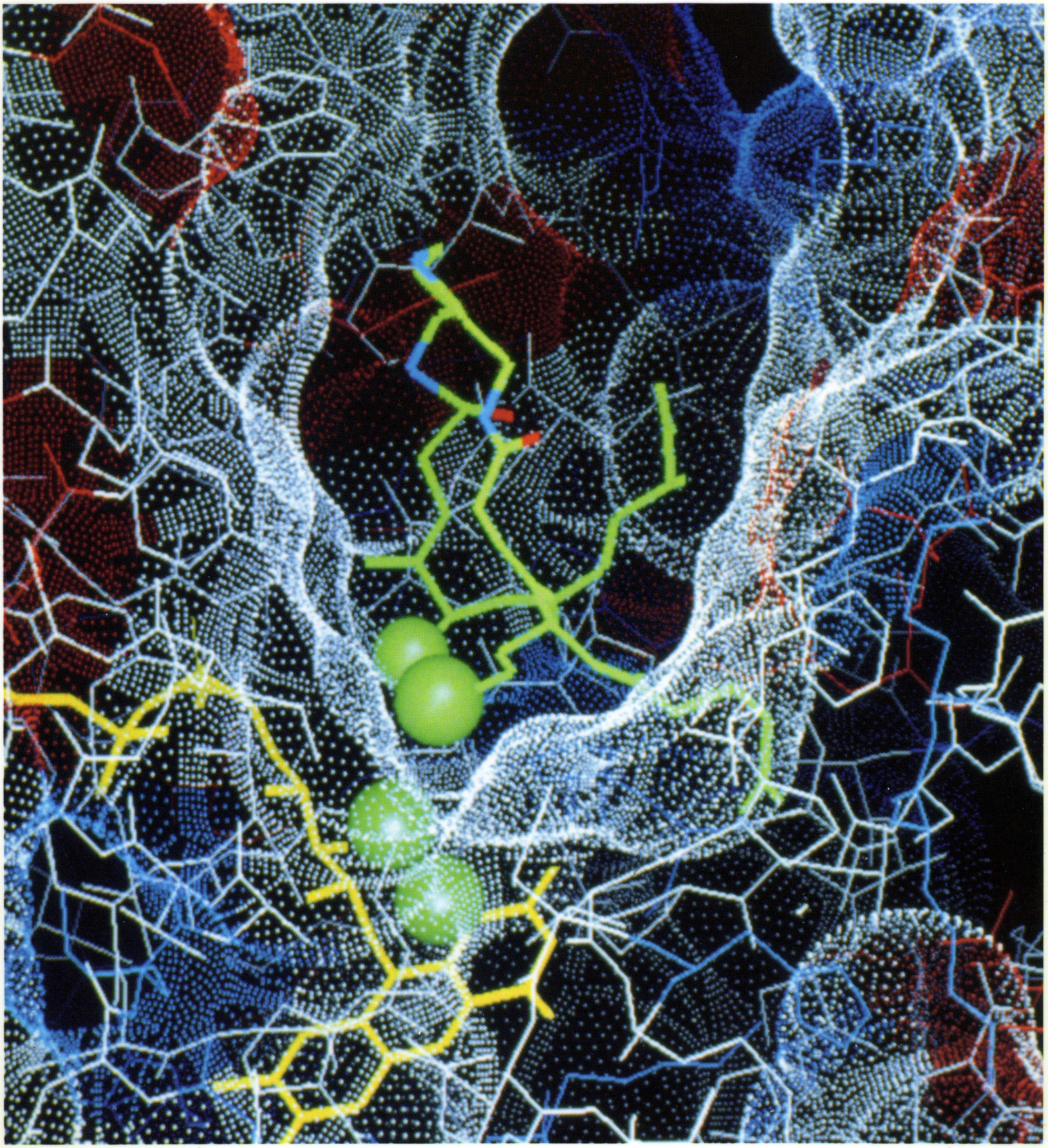
The Rockefeller University

Annual Report
Winter 1991
Vol. I, No. 4

SEARCH

THE ROCKEFELLER UNIVERSITY MAGAZINE



SEARCH

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***SEARCH* is published with the generous assistance of The Carl and Lily Pforzheimer Foundation.**

ON THE FRONT COVER
The active site of the parasite enzyme trypanothione reductase, a structure determined by X.-P. Kong, T.S.R. Krishna, and John Kuriyan, based on work done in collaboration with Anthony Cerami and the late Graeme Henderson. (See also photographs on page 17.)

ON THE BACK COVER
The university's new twelve-story laboratory research building, currently under construction, looms above the East River Drive on the southeast side of the campus. It is scheduled for completion in the summer of 1992.

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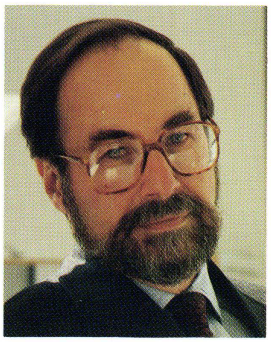
COMMENTARY

PERSPECTIVES ON A PRESIDENCY

David Baltimore
President, The Rockefeller University



Although we tend to think of communication as the transmission of a preformed story, often the process of communication creates the story. During the organization of material and formulation for publication, new insights may emerge. One can spend more than a year with an institution, as I have at Rockefeller, and still be impressed by new perspectives discovered by the writers for *SEARCH* as they filter through the diverse elements that make up the university.

One particular perspective that emerges from this issue of *SEARCH* is a shift in the focus of biomedical research during the last fifteen years. Rockefeller University was founded by perceptive research physicians who saw the opportunity to conquer infectious diseases by the application of then-new research techniques. Today, although our strength in infectious disease research continues that commitment, we are now focusing the bulk of our research energies on cellular disease: the ills that derive from changes inside our cells rather than from invasion by microorganisms. Cancer and heart disease are the most visible of these, but inherited diseases, immunologic malfunctions, neurologic problems, and anomalies of organismal development are others.

Actually, many of the reports here are written from the perspective of comprehending normal processes rather than pathologic ones — how the brain functions, rather than how it goes awry — but understanding the normal is essential for recognizing aberrance.

Another important insight in this issue is the key role of new technologies — a perspective from which much of modern biology could be approached. Often questions have been formulated for years before a new methodology opens the road to answers. This year's Nobel Prize, for instance, was given for a technique: the patch clamp method for analyzing the channels that regulate a cell's communication with the world outside itself. The existence and nature of such channels had been discussed for decades, but with a simple but powerful methodologic insight, a revolution of deep understanding was generated. It is often limitations of methodology that contain progress.

As the focus and methods of science change, so do the workings of its institutions. The challenges to the research enterprise are greater than I have ever seen because, in spite of the continued national desire for improved health, there is serious questioning of how much Federal resources should be put into research and how research should be made accountable to the public who pays for it.

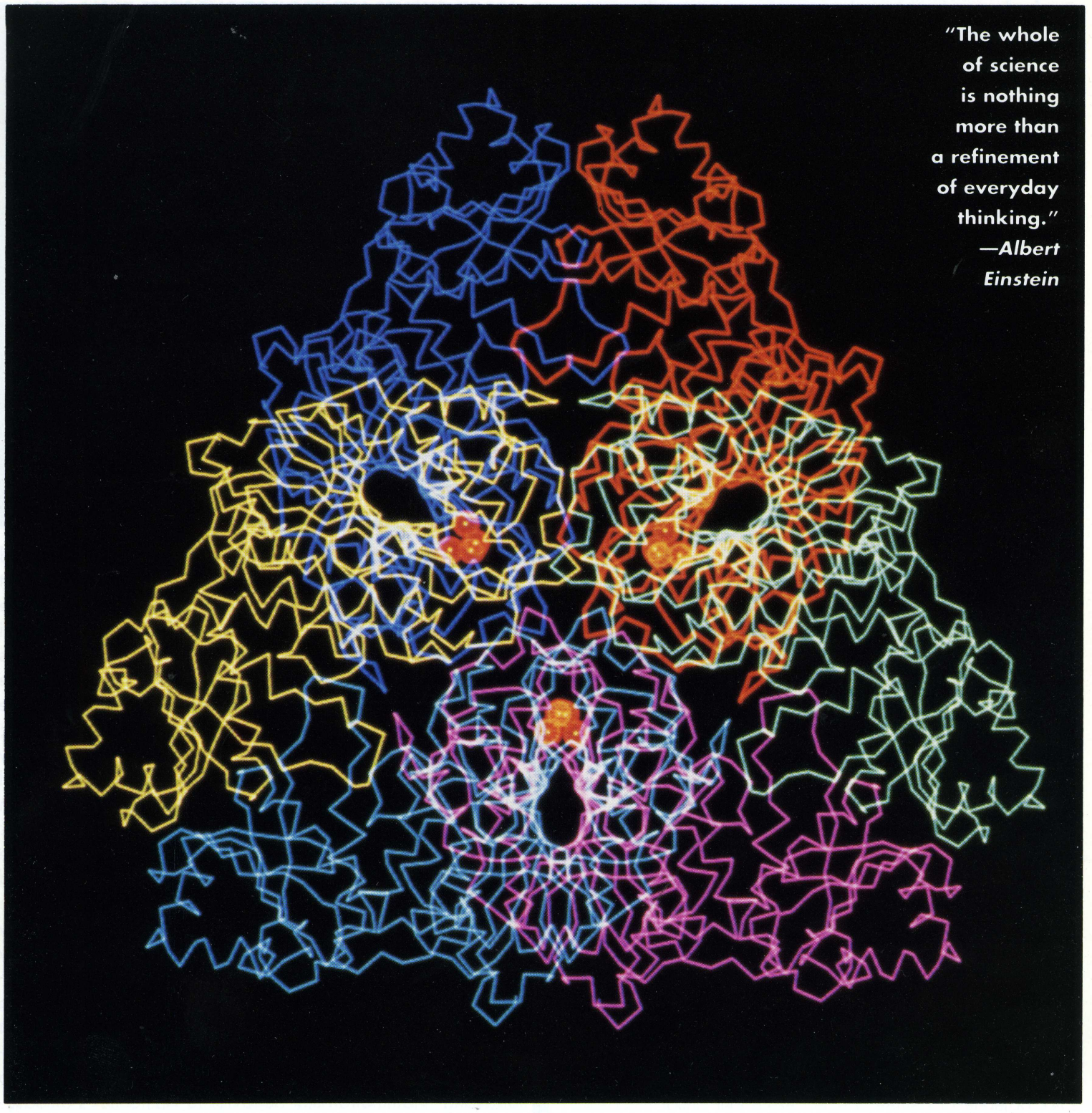
While those debates rage, progress continues at a dizzying pace. Policy makers could make a great contribution by clarifying the issues surrounding management and accountability of science. But they should not lose sight of where we are today: the only limitation on the rate at which we understand the diseases that afflict us is the quantity of resources applied to the questions and the freedom of scientists to deploy and redeploy those resources.

Closer to home, these changes have not left The Rockefeller University untouched. They have required adjustments, sometimes painful ones, in budget, personnel and governance. As difficult as facing these challenges has been, however, the progress we have made in the last year has been immensely rewarding. With most of the changes needed to strengthen the university now behind us, I believe we enter 1992 a robust institution, well-prepared to meet the challenges of doing biomedical research in contemporary America.

It is with great sadness, therefore, that I have decided to step down as president of the university, effective December 31, 1991. Although the transformations of Rockefeller that I had hoped to accomplish remain to be fully achieved, the *Cell* paper controversy — related to issues of external accountability alluded to above — has undermined my effectiveness to the point where I feel that new leadership can better carry the university forward.

EXPLORING NATURE'S MYSTERIES
AN OVERVIEW OF SCIENCE AT ROCKEFELLER

by Susan Blum, Geoffrey Montgomery, and Catherine Vanchieri



Computer-graphics representation of leucine aminopeptidase, a six-subunit enzyme that processes proteins in organisms ranging from bacteria to man. Structure determined by Stephen K. Burley and William N. Lipscomb.

The fundamental questions that intrigue scientists are the questions that fascinate us all. Glancing up at the nighttime sky, we wonder how our world and its neighbors are constituted. Cradling a newborn baby, we ask how such a perfectly formed bundle of complexity could arise from a single cell. Marveling at the beauty of a flower, we ponder how it feeds on sunlight. We learn, we think, we see, we feel—and, when we reflect, we wonder how our brains can coordinate such diverse and marvelous tasks. We may even wonder how we are able to wonder at all.

Everybody asks these questions; scientists at Rockefeller are attempting to answer them. They do so by refinement—by expanding the nature and scope of the questions, and pursuing them with a breadth of knowledge unimaginable to the merely curious.

Throughout the university, Rockefeller researchers are exploring nature's mysteries at every level—that of the organism, the cell, the molecule, the atom, and the subatomic particle. As they do so, they are not only refining "everyday thinking," but consistently redefining its limits, as well. What was revolutionary twenty, ten, or even five years ago is now everyday knowledge, serving as the springboard for tomorrow's investigations.

The description of research that follows gives only a glimpse of the fascinating and often revolutionary explorations occurring on campus. The subjects detailed in these pages are just a small sampling of the topics under investigation; even so, the work of every scientist engaged in those fields could not be represented. To tell the story of all the research at Rockefeller would be a story as vast as nature itself. But in the pages that follow, we invite you share the excitement of some of the questions answered—and some new questions raised—this year at Rockefeller.

THE BRAIN: COMPLEXITY UNPARALLELED

By the 1960s the treatment of cataracts was routine. Ophthalmologists removed the cloudy lens of the patient's eye, and replaced it with an artificial lens that allowed a clear image to be focused on the patient's retina. Yet the operation presented an enigma. A seventy-year-old woman blinded by a cataract could have her vision completely restored with an artificial lens; but a seven-year-old girl born with a cataract in one eye could remain blind or severely sight-impaired in the eye after the same operation. What was so different about the eyes of a child and an adult that the response to lens replacement could so radically diverge?

SUSAN BLUM is a science writer in The Rockefeller University Public Affairs Office. GEOFFREY MONTGOMERY has been a contributing editor at *Discover*, and is currently working on a book about vision and the brain. CATHERINE VANCHIERI is a science writer in The Rockefeller University Development Office.

APPOINTMENTS AND PROMOTIONS SINCE JULY 1, 1990

PROFESSORS: David Baltimore, Brian T. Chait, Vincent A. Fischetti, David C. Gadsby, Charles D. Gilbert.

ASSOCIATE PROFESSORS: *Alan Aderem, David J. E. Callaway, *Jeffrey Friedman, Richard A. Galbraith, Edward Gershey, Gilla Kaplan, Roger W. Rusack, *Elaine Tuomanen, *John Ding-E Young.

ASSISTANT PROFESSORS: Jesus A. Angulo, Giorgio Apollinari, Neal I. Azrolan, Kathleen A. Barker, *Stephen K. Burley, Helen M. Chao, Ambrose L. Cheung, Neile K. Edens, Samuel E. Gandy, Maureen N. Gannon, Robert B. Gibbs, Shelley L. Halpain, Michael D. Hayre, David C. Helfgott, Shiro Horiuchi, Frederick S. Jones III, Asaf Keller, John R. Kirn, James G. Krueger, Chau-Ching Liu, Philip L. Melese, Christopher V. Nicchitta, Constantine Pavlides, Anuradha Ray, Ann Robbins, *Thomas P. Sakmar, Hubert Schwabl, Robert L. Spencer, David S. Thaler, Gerald Thiel, Nancy G. Weiland, Lee M. Wetzler.

*Also appointed head of laboratory. All professors are heads of laboritories. Assistant Professor Arturo Alvarez-Buylla was named a head of laboratory as well.

The answer, discovered by scientists Torsten Wiesel and David H. Hubel in a series of seminal experiments in the 1960s, was that there was nothing different about the adult and child's eyes: the difference was almost certainly in their brains. Wiesel and Hubel found that the retinas of the two eyes project to alternating columns of cells in the mammalian brain's visual cortex; if vision to one eye is blocked at birth, these columns do not develop properly. The columns from the seeing eye crowd out columns from the blind eye; thus if lens replacement is not performed very early in life, the newly clear eye will have no place in the cerebral cortex to send its visual information. And because we see as much with our brains as with our eyes, the operated eye will contribute little or nothing to vision.

"We made the point that if you want to prevent the deterioration that occurs in the cortex," says Wiesel, a head of laboratory at Rockefeller, "you have to operate on the children very early." Such early surgery is now increasingly common; children who would once have been profoundly sight-impaired now see perfectly. And Wiesel's early research, for which he and Hubel received the Nobel Prize in Physiology or Medicine in 1981, provides a deep theme that threads through conversations with Rockefeller neurobiologists working on problems ranging from primate vision to birdsong, mammalian sex behavior to Alzheimer's disease. For all are asking a series of related questions. How is the brain, the most complex structure in the known universe, organized? How does this organization develop early in

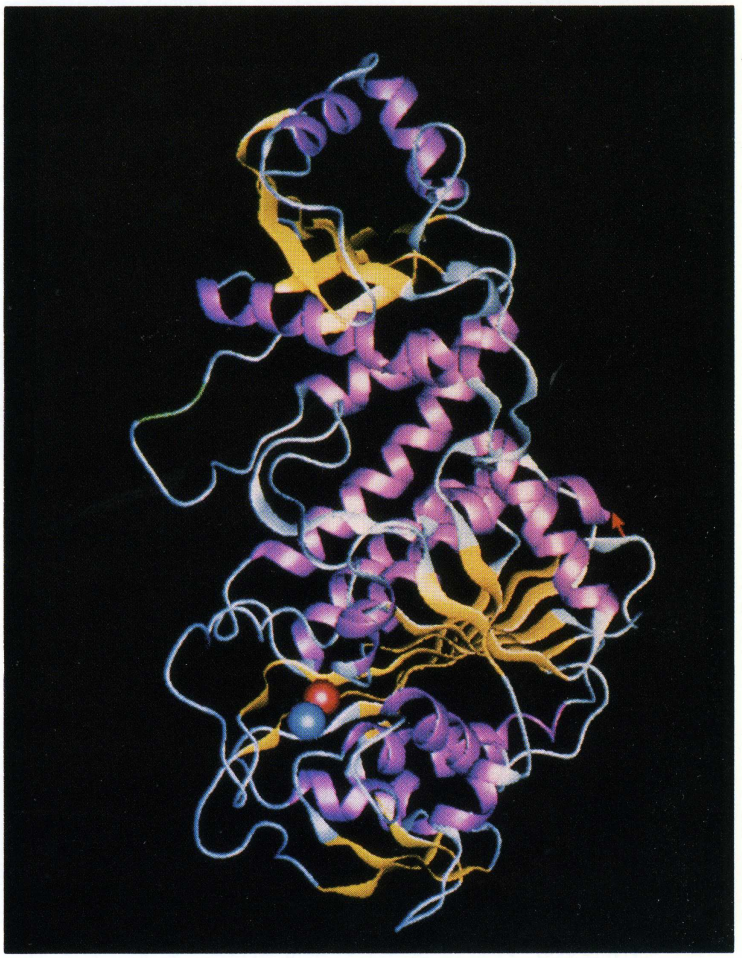
life? How is this organization regulated or changed during adulthood? And how might this knowledge be used to understand or treat brain diseases and disorders?

BLAZING NEW TRAILS

Wiesel, along with other Rockefeller scientists, continues to blaze new trails in understanding the visual cortex, which is today the best-understood part of the primate brain. Experience with stereoscopes and three-dimensional movies teaches us that the images reaching our two eyes are somehow combined to give the sensation of depth. The researchers have recently discovered where this combination occurs: specialized regions in the visual cortex in which information from the two eyes is compared in an astonishingly precise manner. Cells in this region fire a nerve impulse only when an object in space is at a specific depth, measured in terms of the "disparity" in the angles by which light from the object reaches the two eyes. For Wiesel, who has explored the visual cortex for over thirty years, the discovery comes as something of a revelation, bringing him closer to the long-sought goal of relating the objective behavior of brain cells to our human intuitions about how the visual world appears. "To have this category of cells that absolutely ignores anything if it isn't at the right disparity," he says, "comes, to my mind, very close to the sense of perception of depth."

Five years ago, Rockefeller researchers in the laboratory of Bruce Knight made the remarkable finding that the primate visual system, starting at the retina, processes light in different fashions along two parallel pathways, which have now been named the P and M streams. Cells along the two streams in the retina and in the thalamus respond, in general, to quite different aspects of the visual sense. P cells respond strongly to color and fine form; M cells hardly respond at all to color, but can sense very small differences in brightness contrast, and are highly adept at detecting light patterns that change quickly over time. According to recent studies in laboratories elsewhere, the two streams appear to play quite different roles in the pathologies of both glaucoma and dyslexia. Meanwhile, the Rockefeller researchers continue to test the detailed functions of cells in the two streams by analyzing their responses to complex, computer-generated light displays.

Charles Gilbert also uses complex visual stimuli to explore the properties of neuronal connections, called horizontal connections, which span the cortical surface and serve to integrate information across the field of vision. Step by scrupulous step over a period of fourteen years, Gilbert has analyzed both the anatomy and function of these horizontal connections, which, due to his pathbreaking studies, are now increasingly seen as a key to a host of perceptual processes. Recently Gilbert has shown that the horizontal connections may be crucial to aspects of the brain's recovery from injury as well. By making small laser lesions in the retinas of adult, anesthetized cats, Gilbert has found that areas of the cortex deprived of visual information from the lesioned site become reorganized to receive information from adjoining parts of the visual field. There is good evidence that this reorganization is mediated by the horizontal connections. "The idea that one can get this type of plasticity in adult cortex was quite surprising," says Gilbert, "but one could imagine that these effects might be involved in normal processes like learning and memory."



A subunit of leucine aminopeptidase, determined by Burley and Lipscomb. The red and blue spheres represent the two zinc ions that give the enzyme its biological function.

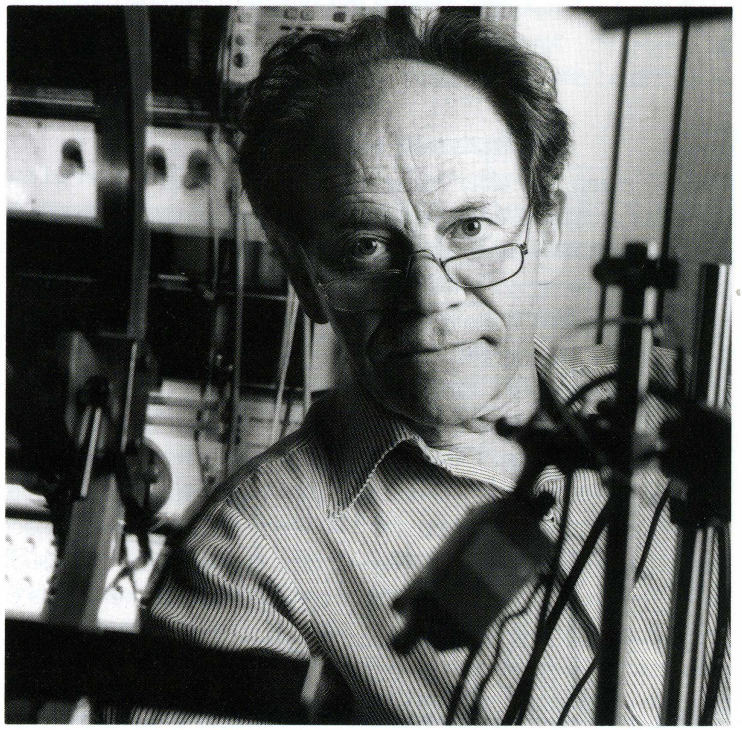
PLASTICITY PURSUED

Adult brain plasticity has also been a central theme of Rockefeller lab head Fernando Nottebohm's investigation of the neural basis of birdsong. After mapping the brain centers controlling song, Nottebohm found that these centers seemed to undergo large seasonal fluctuations in size. He and his colleagues then discovered that, astonishingly, bird brains continue to produce new neurons throughout adulthood—a process long thought to be

impossible in higher vertebrates. But Nottebohm and Rockefeller colleague Arturo Alvarez-Buylla have found that neurogenesis and the subsequent migration of newborn neurons in adult birds is remarkably similar to neurogenesis and migration in the developing brains of monkeys. This similarity gives them the hope that if the molecular factors controlling neurogenesis in birds are identified, these factors might someday be used to help reawaken neurogenesis in adult human brains damaged by age or disease. "We've looked at where these new neurons are born and how they migrate," says Nottebohm. "We know now that they become hooked up into existing circuits for song control." In the bird brain, adult neuronal birth is balanced by neuronal death. "You have a system that is constantly being torn down and rebuilt."

One long-standing puzzle has been that such radical renovations occur not only in canaries, which learn new mating songs each season, but in birds that sing the same tune all their lives. However, recent findings about neurons in the song control system may shed light on this puzzle. Cells all along the song control pathway do not merely produce song; they seem to perceive song as well. Even the muscles that vibrate a bird's version of a larynx respond when songs are played to the bird. "The hypothesis," says Nottebohm, "is that part of decoding the song signal may involve a motor rehearsing of what the bird has heard." A similar idea has been advanced regarding human language: that in order to perceive the syllables comprising a word, we internally sound out those syllables by rehearsing the vocal gestures required to produce them. In terms of birds, this perceptual process could place seasonal demands on memory space in the brain, demands met by neurogenesis. For even birds that do not learn to sing new songs must nevertheless learn to perceive novel songs in order to recognize newly arriving neighbors. "As a bird, if a new guy shows up singing, you tremble," says Nottebohm, "because he may be looking to take over your piece of real estate."

Mammals in search of mating opportunities must also integrate a variety of signals from the outside world, says Rockefeller scientist Donald Pfaff. Mammalian behavior is the research territory of Pfaff and his colleagues, who want to learn how an animal integrates internal signals, such as steroid hormones, with a variety of signals from the outside world. The scientists study the nerve cell mechanisms underlying emotional and instinctive behaviors: mating, aggression, eating, drinking, parenting, and responding to stress. Over a fifteen-year period, the group has identified the neuronal circuit that controls rat reproductive behavior, the first circuit ever to be determined for a mammalian behavior. Pfaff and his colleagues have discovered the neuronal command points in the hypothalamus that respond to the animal's hormonal state; moreover, they have tracked how changes in the DNA, the cell's genetic repository, account for the integration that must occur between environmental and hormonal signals if reproductive behavior is to occur. These changes are especially intriguing since males and females respond to steroid hormones—including sex hormones—in utterly different ways.



Torsten Wiesel, Vincent and Brooke Astor Professor and Head of Laboratory.

Recently, researchers in the Pfaff lab showed they could interfere with rat social behaviors important for reproduction by blocking the production of particular proteins. In addition, they have developed a powerful new analytic tool: a laboratory-altered viral particle that can act as a "Trojan horse" to sneak DNA sequences into specific parts of the living brain to study how they function.

THE BRAIN TRANSFORMED

Bruce McEwen's laboratory has found that a female rat's brain undergoes a remarkable transformation during her estrous cycle. "We've found that in the adult, neurons in at least two areas are plastic," says McEwen. The neurons sprout new dendritic connections right before ovulation begins—connections that quickly disappear when ovulation commences. The first area, the hypothalamus, is known to control mammalian sex behavior; the second, the hippocampus, is known to be essential to long-term memory formation in humans, and is involved in spatial learning tasks in rats. Members of the lab are now looking at the molecular events underlying these plastic changes by examining how genes for the basic building blocks of neuronal connections may be turned on and off by hormones such as estrogen.

The lab is also examining the flip side of hormones and neuronal

growth. In rats treated with high levels of adrenal steroids, a hormone released in response to stress, neuronal dendrites in the hippocampus will shrivel up, and the neurons will eventually die. It seems these hormones accelerate brain aging. In people afflicted by chronic stress, such as harried air traffic controllers or people struggling against poverty, it is known that high levels of adrenal steroids circulate continuously through the body. "These are the people you worry about," says McEwen, "because these are the conditions that can cause this kind of neural damage."

The dependence of both neuronal growth and deterioration on a shared regulatory process also emerges in two advances in the laboratory of Paul Greengard. "There are basic regulatory mechanisms that are used by cells to do what they have to do: to develop, to differentiate, to function, to die," Greengard says. "Protein phosphorylation regulates it all."

When Greengard first began to study protein phosphorylation in the late 1960s, his was one of only two labs in the world devoted to the problem. Now, there are thousands. Protein phosphorylation is the adding of a phosphate group to a protein such as an enzyme: this single addition can turn the enzyme on; subtraction of the phosphate can turn the enzyme off. This add-and-subtract mechanism is a powerful and universal way of modulating a cell's behavior—including cells in the nervous system. The most prominent phosphoproteins in the brain are the synapsins, which are localized at nerve connections and were discovered twenty years ago in the Greengard lab. Evidence acquired in recent years has demonstrated the synapsins' central role in regulating nerve signaling. In its dephosphorylated state, synapsin seems to act as a cage to hold back packets of neurotransmitters from exciting an adjacent cell; in its phosphorylated state this cage is broken, allowing the neurotransmitter's release.

This year, researchers in the Greengard lab showed that synapsins can also control the ability of neurons to form synapses in the first place. This discovery showed that inserting the gene for one kind of synapsin into a dish of neuronal cells induced a metamorphosis visible under the microscope. The cells, which normally make no synaptic connections with each other, now sprouted a plethora of them. The same machinery that regulates synaptic transmission thus seems to control synaptogenesis—one of the most fundamental processes of brain development.

CELL DEATH AND ALZHEIMER'S DISEASE

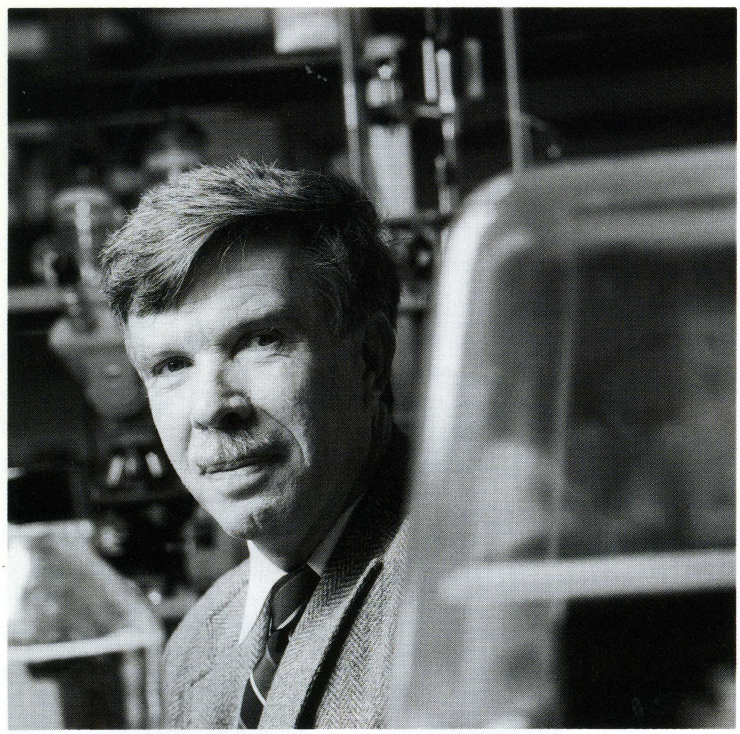
At the opposite end of the spectrum from synaptogenesis is the brain cell death associated with Alzheimer's disease. In the past two years a series of breakthroughs from labs across the world has greatly clarified the basic events underlying this terrible acceleration of normal brain-aging processes. The picture now emerging is this: A key cause of the disease is the deposition of toxic plaque,

Charles Gilbert, Professor and Head of Laboratory.

called amyloid, outside cells of the hippocampus and cortex. Amyloid forms when a normal brain protein, called APP, is improperly processed by enzymes.

The Greengard lab has discovered that APP processing is regulated by protein phosphorylation. The researchers have obtained evidence that, by artificially overstimulating this processing with phosphorylation regulators, small protein fragments containing amyloid may be generated. This result suggests that aberrant phosphorylation could be the cause of at least some forms of Alzheimer's—a finding that might eventually lead to neurochemical therapies based on the knowledge of phosphorylation amassed by the Greengard lab over two decades of intensive study. "Before, there was a lot of uncertainty about what was actually producing Alzheimer's disease," says Greengard. "But right now it's an extremely exciting time to be working in the field, because things are really moving."

Progress in neuroscience research over the last year may seem rapid, even sudden; but in fact it is only the breaking crest in a long wave of inquiry—a wave that will, in turn, crest again. Birds generate new neurons in adulthood; what are the molecular factors governing this neurogenesis? A universal molecular regulatory network controls synaptic signaling and development; might other mutant members of this network cause Alzheimer's? Regions of the visual cortex contain cells exquisitely sensitive to depth information; how do these cells help produce our perception of the colored,



Fernando Nottebohm, Professor, Head of Laboratory, and Director of the Center for Field Research in Ethology and Ecology.

moving, three-dimensional world around us? "I always like to do experiments that lead to another question," Wiesel says. "They answer one part of your problem, but at the same time they take you in even more deeply."

GENE TRANSCRIPTION: A KEY TO CELLULAR FATE AND IDENTITY

It is a wonder that never ceases to amaze: one single fertilized cell develops into a complex, multicellular organism—a plant, a mouse, a human being. Throughout the process of development, the first progenitor cell multiplies exponentially, faithfully bequeathing its full complement of genes to each of its descendants. As the multiplications proceed, each cell undergoes a programmed series of choices that ultimately leads it to become a fully differentiated cell, performing its own special function as, say, a cell in the liver, the brain, or the heart.

What distinguishes each descendant cell from its totipotent progenitor? What prompts each daughter cell through its adventure of development and then maintains its differentiated state? The key to the mystery is differential gene activity, for although each cell inherits the same complement of genes from the first fertilized cell, not every gene is turned on in each cell. In fact, the identity and fate of every cell, at every stage of its life, is determined by which of its genes are active.

Differential gene activity is the key to development and cellular differentiation because most genes code for proteins, and proteins give a cell its essential characteristics. They are the fibers that shore up a cell's structure, the enzymes that catalyze its biochemical reactions, the gatekeepers that determine which substances enter and leave. They are even the control switches for gene activation itself.

In a sense, a cell can be thought of as a protein factory and warehouse, where the current inventory depends on any number of factors including the processing of the product and its shelf life. But among all these determinants, probably the most important is the operational state of the genes, the machines that get the whole process of protein production going. For each gene, a fundamental question is this: Is it switched on or switched off?

A gene that is switched on is a gene that is *transcribed*. In transcription, the protein instructions encoded in the DNA are copied into a closely related molecular intermediary known as messenger RNA (mRNA). At a later stage, the mRNA effects the code's final translation by directing the assembly of linked sequences of amino acids into proteins.

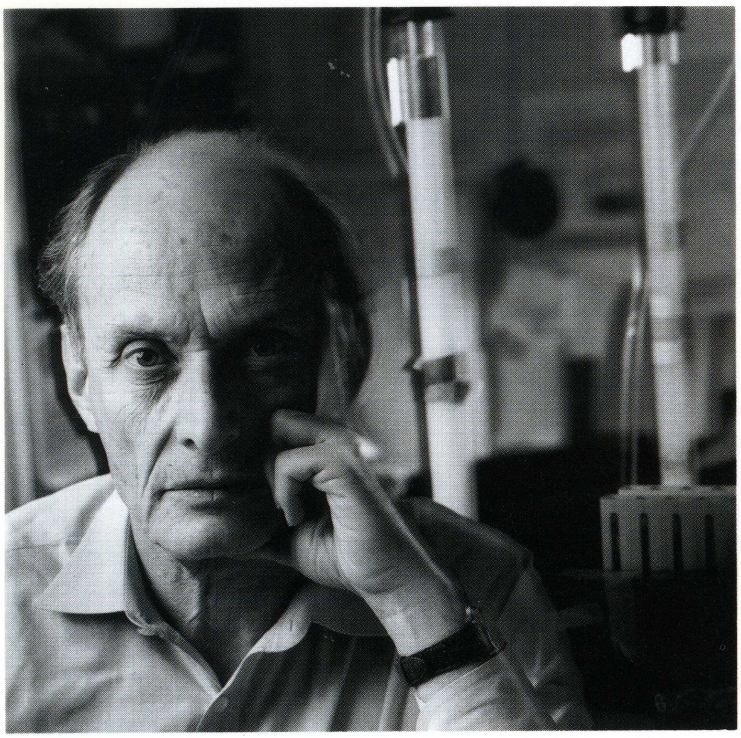
Since the 1960s, much has been known about transcription in procaryotes, single-celled microorganisms, such as bacteria, whose DNA is not sequestered in a nucleus. But for nucleated eucaryotic cells—the cells possessed by organisms ranging from yeasts to humans—knowledge about transcription has emerged only in the past decade or so.

THE BROAD PRINCIPLES

By now, the broadest general principles are well established. Eucaryotic genes have DNA regions that encode the instructions for making proteins, and noncoding regions necessary for the control of transcription. Proteins interact with the DNA control elements, with each other, or both to initiate transcription and affect its efficiency. These proteins include a *polymerase* (an enzyme that "reads" the DNA) and numerous *transcription factors*: general factors, present in all cells, which are required for transcription initiation; and regulatory factors, differentially distributed in different cell types, which communicate with the general factors to stimulate their function in a gene-specific way.

Described in such general terms, the process sounds simple. In fact, it is astoundingly complex and still poorly understood. In the past ten years, an avalanche of information has swept the field of research on transcriptional control. As it progresses, the terrain keeps changing. Many of the movers and shakers provoking the landslide are researchers at Rockefeller.

One of them is Robert Roeder, whose work partly focuses on the general transcription factors. These factors and the polymerase interact sequentially with a DNA control element to form an active



Paul Greengard, Professor and Head of Laboratory.

transcription complex that carries out the transcription process. Roeder was the first to identify the general factors for a number of different classes of genes, including class II genes—the ones that code for proteins in eucaryotic cells.

The general factor called TFIID is a key member of this group, since it is the first to bind to the DNA control element. This year members of the Roeder lab discovered that TFIID actually comprises a number of subcomponents specifically required for communication with the regulatory factors. Further elucidation of the relationships among these proteins should help unravel the mysteries of how transcription gets started.

Though essential, TFIID is far from the only general factor under study in the Roeder lab and elsewhere. Until recently, the known members of the "alphabet series" of general factors for class II genes ranged from TFIIA to TFIIG. This year, researchers in the Roeder lab found another factor, dubbed TFII-I. The discovery was remarkable for a number of reasons, among them the surprising new perspective it opens on the machinery of transcriptional initiation.

Scientists used to think that all members of the alphabet series of general transcription factors were required to form an active transcription complex. But the Roeder team has discovered that, in some cases, TFII-I can substitute for another general factor, TFIIA. "It now looks as if the general pathway isn't as fixed as as we thought it was," Roeder explains.

Another finding from the Roeder lab is also shaking up long-held beliefs about transcriptional control. Researchers in the lab have discovered a new class of transcription factors called cofactors. Neither fish nor fowl—that is, neither classical general factors nor classical regulatory ones—these new members of the transcription factor bestiary may turn out to hold important clues about how regulatory factors communicate with general ones.

New insights into the labyrinthine complexities of transcription have also emerged from the laboratory of David Baltimore. Scientists have long known that many transcription factors work in part by binding to DNA. But this year, researchers in the lab demonstrated that the mere fact of binding is not the whole story. Their experiments showed that a particular transcription factor binds to slightly different DNA control sites in different genes with exactly the same avidity, yet activates transcription only in some of them. "Clearly there is something subtle about the way the protein interacts with the DNA that we don't yet understand," Baltimore says.

GETTING SPECIFIC

Another mystery still intriguing scientists is how regulatory factors control specificity to ensure that transcription of a particular gene occurs only in the right type of cell and at the right time. Part of the emerging picture is that regulatory proteins act in combination to confer this spatial and temporal control.

In the lab of Nam-Hai Chua, for instance, scientists are trying to elucidate how plant genes respond to light, a potent signal with a dual function: helping control a plant's development and providing it with sustenance via photosynthesis. Previously researchers in the Chua lab discovered the DNA control element needed to confer light responsiveness on genes. This year they discovered a transcription factor, called GT-1, that binds to this element. Paradoxically, the scientists found, the transcription factor appears to bind to the DNA both in the light and in the dark. Moreover, it is found both in cells with high photosynthetic activity (such as leaves) and cells with virtually no photosynthetic activity (such as roots). Thus, the scientists believe, at least one other transcription factor must be working combinatorially with GT-1 to ensure that light-responsive genes are transcribed only where and when it is appropriate. They are now hunting for such additional factors.

Scientists in the lab of James Darnell, Jr., are also tracking down transcription factors that confer specificity in particular cell types. Their quarry is the mammalian liver, which makes an abundance of proteins produced only (or mainly) in that organ. Over the past year, researchers in the lab have discovered two new transcription factors, HNF-3 and HNF-4, that bring to four the number of factors so far known to help regulate liver-specific gene transcription. These factors work in combination with one another, although the

exact combinations differ from gene to gene.

Such discoveries provide important clues about transcriptional specificity but, researchers caution, many mysteries endure. For one thing, says Darnell, although the fact of combinatoriality is generally accepted, its mechanisms remain elusive. "The physiological rules are still not known, let alone the biochemical details," he reports.

There are other puzzles, too. For instance, though a particular transcription factor may help regulate the transcription of a specific gene (or genes) in a specific cell type, its distribution may not be limited to that cell type. The HNF-3 and HNF-4 factors discovered in the Darnell lab are a case in point. "If things operated in a simple and direct manner, these factors would be liver-specific, but they're not," reports Darnell. "All of them are found in cells other than liver cells."

This conundrum is also seen in the transcription factor called NF-κB, discovered in the Baltimore lab. First sighted as a factor that regulates transcription of a gene coding for a component of antibodies, NF-κB was initially believed to be present only in antibody-producing cells, the B lymphocytes. But researchers have since found that NFκB helps regulate gene transcription in every mammalian cell type tested; the particular genes transcribed vary from cell type to cell type.

FAMILY RELATIONSHIPS

Complicating the picture even further, many transcription factors are turning out to be members of larger families. For instance, all of the factors that determine liver specificity have close cousins; soon after discovering HNF-3 and HNF-4, the Darnell lab found relatives for each. Also this year, researchers in the Baltimore lab found that NF-κB's two subcomponents are closely related to one another and to a number of other proteins, as well.

An enhanced understanding of the family relationship among transcription factors may hold part of the key to the puzzle of transcriptional specificity. Like members of any family, related transcription factors can form alliances with one another. These alliances, called "dimers," join two proteins together to form a functional transcription factor; as in any family, the alliances can shift depending on changing circumstances. The more protein relatives there are in each factor family, the greater the number of possibilities for subtle control of transcriptional regulation, both within a particular cell type and among different types. For example, varying distributions of different family members in different cell types may help explain how factors can exist in more than one cell type, yet help confer specificity in each. Moreover, shifting dimer alliances within a cell may help confer precise control of the timing and extent of gene activation.

Cofactors are another exciting advance in the understanding of

Robert G. Roeder, Arnold and Mabel Beckman Professor and Head of Laboratory.

transcriptional specificity. In addition to finding one cofactor that works with every regulatory factor tested so far, researchers in the Roeder lab this year found a B cell type–specific cofactor called BAF that may help explain the longstanding puzzle of why antibody genes are transcribed only in B lymphocytes. Moreover, they speculate, cell-specific cofactors may be found in many other cell types, too.

As is usually the case in studies of transcription, one answer simply leads to another question, and the example of BAF brings up a major question, indeed—one to which any discussion of transcriptional control inevitably leads.

Like all other transcription factors, BAF is a protein. What regulates its transcription? The answer: another transcription factor, regulated in turn by another. "In a never-ending spiral, proteins that carry out specialized functions are regulated by other regulatory proteins," Darnell says.

A WALK THROUGH TIME

As scientists move through this hall of mirrors, they find themselves walking ever backwards through an organism's history, tracing in reverse the steps involved in development and tissue differentiation. Ultimately, the journey leads them back in time to the initial, totipotent cell, and then even farther back to the mother's contributions via the egg.

The fruit fly, *Drosophila*, is a good example. The earliest

developmental events in this tiny insect are regulated by mRNAs that preexist in the egg. Activated at fertilization, these mRNAs are translated into transcription factor proteins that transcribe the first set of genes belonging to the embryo itself. These genes, themselves transcription factors, in turn activate genes for additional transcription factors, and so it goes. The hierarchical cascade thus set in motion by the first, maternal genes results in a highly regulated interplay of transcription factors that first leads to an increasingly organized body plan and ultimately to organs composed of differentiated tissues.

Claude Desplan is studying how one of the fruit fly's maternal gene products, a transcription factor named bicoid, affects the transcription of *gap* genes, the first of the embryo's own genes to be activated. Even at this earliest stage of development, when the insect's rudimentary body plan is being laid down, gene transcription is highly regulated. A *gap* gene product called hunchback, for instance, is expressed only in a specific spatial pattern as a result of interactions with bicoid, with the protein products of other *gap* genes, and even with the hunchback protein itself.

This year, Desplan and his colleagues have deciphered the interactive rules determining hunchback's spatial distribution. A significant advance in itself, this work has also led the scientists to a striking conclusion. "The nature of the interactions makes us believe that before bicoid was 'invented' by nature for the special case of *Drosophila*, hunchback served an important role as a maternal gene," Desplan says. The implications of this theory are intriguing, for they might help explain the puzzle of development in organisms that do not share *Drosophila*'s special embryonic structure.

In its earliest stages, the *Drosophila* embryo develops as a syncitium, a mere bag of dividing nuclei with no intervening cellular membranes. This unusual structure allows the bicoid protein to regulate *gap* gene function simply by diffusing from one end of the embryo to the other, creating a protein gradient as it moves along. But the nuclei of most other organisms, including mammals, are isolated from one another in separate cells from the start of development, so regulatory gradients cannot arise from passive diffusion alone. Gradients of the hunchback protein are created by other means, so this protein offers a tantalizing glimpse into how maternal genes might be operating in mammals from mice to men.

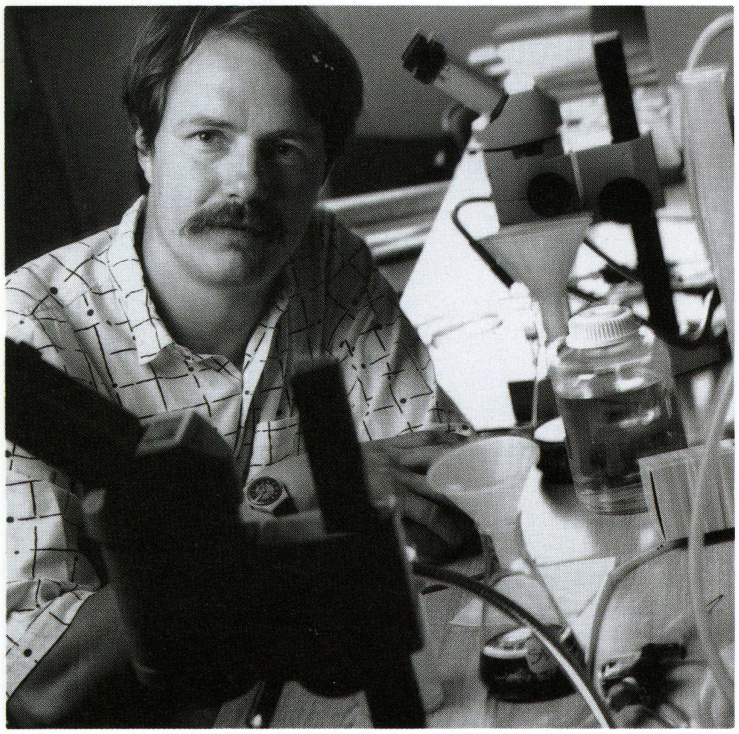
FROM FLY TO MAMMAL

The idea that discoveries about fruit flies might shed light on mammalian development is more than speculation. Time and again, in a way that first amazed scientists and now merely gratifies them, transcription factors are turning out to be remarkably similar among species.

Prime examples are the so-called "homeobox" factors, which play a crucial role in regulating many developmental events. First discovered in flies (and first confirmed as containing a DNA-binding region by Desplan and others), members of this transcription factor family have been found in species ranging from yeast to flies to rodents to humans—and even in plants. But similarities in developmentally important factors aren't found only in homeoproteins. In the Darnell lab, for instance, both the HNF-3 and HNF-4 factors involved in conferring liver cell–specific transcription have been found to be closely related to factors important for the development of organs in the fly's gut.

Nam-Hai Chua, Andrew W. Mellon Professor and Head of Laboratory.

Plants are also yielding insights into the process of development. This year, scientists in the lab of Nam-Hai Chua identified a gene, called P-DEF1, that codes for a transcription factor important in the control of petunia flower formation. P-DEF1 is a homeotic gene, one that helps determine an organ's identity. "With an altered homeotic gene, you don't get just nothing. You convert one something to something else," says Chua, pointing to the "Frankenstein flowers" in his lab's greenhouse as a prime example. Alterations in the production of this plant's P-DEF1 protein provoked the development of an extra whorl of petals, and of sepals that looked like petals. Pigmentation patterns were also abnormal, a fact that Chua says is not surprising. "The P-DEF1 gene is a master gene for petal development. It makes sense that it should help regulate many of the flower's characteristics."



Claude Desplan, Assistant Professor, Assistant Dean, and Head of Laboratory.

CONTROLLING THE MASTER GENE

Even master genes must be switched on, and in many cases the motive force behind development and tissue differentiation is probably a message from outside the cell. For instance, says Darnell, "there is cell–cell contact from day zero in the mammalian embryo, so the extracellular messages that help direct the changing composition of transcription factors have profound consequences for development from the very beginning." Similarly, he points out, once a cell has reached its fully differentiated state, signals coming from the cell's "outside world" help it maintain its differentiated identity and perform its specialized functions.

Cells receive these signals via extracellular messengers that latch on to receptors threaded through the cell's surface membrane. A cell has thousands of different kinds of receptors, each one a protein and each one specific for a particular molecular emissary.

As a model system for understanding how extracellular signals might affect the transcription of specific genes, researchers in the Darnell lab are studying how the messenger protein interferon-alpha induces gene transcription. This year, the researchers found that when interferon-alpha binds to its cell surface receptor, changes take place in proteins waiting just inside the cell's cytoplasm. These proteins, which together comprise a transcription factor, are normally found in an inactive state. But under the influence of interferon-alpha, they become activated, combine with one another, and move into the nucleus where they can interact with DNA to initiate transcription of a specific set of genes.

Furthermore, the researchers have found that three of the cytosolic proteins in this system belong to a new protein family never before described. They believe it may be possible that these proteins, and others yet to be discovered, belong to a hitherto-unknown class of proteins whose job is to signal that a specific cell surface receptor is occupied, and to ensure that a specific set of genes is subsequently transcribed. The scientists are currently exploring how the proteins interact with one another and whether they are, in fact, the harbingers of a new understanding of signaling mechanisms.

Darnell and his colleagues are just some of the Rockefeller researchers working to elucidate the process by which extracellular signals trigger gene transcription. For example, this year, researchers in the Chua lab discovered that the protein product of the P-DEF1 gene must be goaded by the addition of a phosphate group before it can do its job. Now, says Chua, the task is to keep moving higher on the signaling pathway, first to learn what prompts the phosphorylation, then to learn what prompts the prompter, and thus ever-upward to the initial signaling event itself. "A transcription factor can be considered to be a switch governing the final step in a signaling pathway," Chua says. "The major challenge for the future is to understand all the events that lead to the switch being flicked."

Scientists who study transcriptional regulation are not just intrigued by its complexities. They know that each new insight potentially deepens the understanding of disease. For instance, many viruses (such as the AIDS-causing HIV) do their dirty work by commandeering aspects of a cell's own transcription control system, and many cancers probably arise from transcription gone awry. By probing the mystery that turns one cell into a whole organism, researchers may ultimately learn how to keep that organism whole.

CANCER: CELLULAR CHAOS

The body of a multicellular creature is truly a body politic. Each cell in the organism must know its place, accept its role, and function in an orderly fashion for the benefit of the whole. If it revolts, the result can be chaos—and the name of the chaos is cancer.

Cancer cells may have many characteristics that distinguish them from orderly, cellular citizens. They multiply more or faster than they should. They become less differentiated and lose their ability to perform specialized functions. They encroach where they shouldn't, invading the bloodstream and seeding cancers throughout the body.

This disorder results from a breakdown in the communication

Brian T. Chait, Professor and Head of Laboratory

systems that regulate how a cell develops, grows, and divides. The problem may lie in the signals that tell the cell what to do, the receptors that pick up the signals, the messengers that relay the signals along, or the execution of the signals in the nucleus, their ultimate endpoint.

At each step in the signaling process, the crucial cellular players are proteins, and, says Rockefeller cancer researcher Hidesaburo Hanafusa, "at each step, there are possibilities for mistakes." For instance, the protein's structure may be changed in a way that makes it function improperly, or its normal function may be subverted simply because there is too much of the molecule.

Since genes carry the code for all proteins, as well as the instructions for regulating their production, the source of a cell's cancerous rebellion can ultimately be traced to abnormalities in the genes themselves. The fundamentally important knowledge that cancer is a disease of the genes is only about ten years old, but it has given researchers hope they might eventually conquer this scourge.

ONCOGENES AND PROTOONCOGENES

The first cancer genes to come under study were those whose normal function was to promote cell growth and division. When these genes go awry, scientists call them "oncogenes." Their normal, functional versions are dubbed "protooncogenes." About five years ago, a new class of cancer genes was discovered. These genes are the "antioncogenes"—genes whose normal function is to put a brake on cell growth. When these genes go haywire, cancer can also develop.

Rockefeller is the scene of vigorous research into the genes that cause cancer. Much of the research centers around genes involved in the complicated process of intracellular signaling controlled by phosphorylation. A complex, intertwined web of interactions, phosphorylation can be thought of as a relay race, in which a highly charged substance, phosphate, is passed among proteins by enzymes. The proteins' activities change as the phosphate is added to them.

In the great relay race of the cell, the first phosphorylated protein often goes on to phosphorylate a second, the second a third, and so on down the line to the nucleus itself. At each stage of the race, the amino acid protein subcomponent that gets the phosphate varies. It may be a tyrosine, or it may be one of two other amino acids known as serine or threonine. Enzymes that put phosphates on tyrosine are called tyrosine kinases; those that put phosphates on the other potential recipients are called serine/threonine kinases.

Hanafusa is a pioneer in the study of the oncogene called *src* which, like many other oncogenes, is a tyrosine kinase. He wants to understand where the src protein fits into the cell's signaling pathway. An especially intriguing challenge has been the attempt to find a protein that, once phosphorylated by src, phosphorylates another protein on serine or threonine. Such a protein is of crucial interest to researchers, because, as Hanafusa explains, "kinases involved in events toward the end of the signaling process, near the nucleus, are usually serine/threonine kinases."

FINDING THE TARGET

Until this year, the search for a serine/threonine kinase phosphorylated by src has been riddled with dashed hopes. But workers in the Hanafusa lab think the molecular target may now be in view. The scientists have found that src phosphorylates a serine/threonine kinase apparently related to a family of proteins, called cdc kinases, that play a central role in regulating the cell cycle. Much work remains in order to tease out the details regarding this protein, but the researchers are excited about their discovery's potential for helping explain how cell division might go awry in cancer.

In the complicated network of signaling through phosphorylation, another molecular player is also being explored. It is a region, called the SH2 domain, that is present in varying forms in many oncogenic protein kinases as well as in other proteins known or believed to be linked to oncogenes along the signaling pathway.

A protein's SH2 domain can bind to phosphorylated tyrosines on other proteins or, in a feat of molecular acrobatics, on the protein to which they themselves belong. Scientists believe that because

James E. Darnell, Jr., Vincent Astor Professor, Vice President for Academic Affairs, and Head of Laboratory.

they form links with so many different phosphorylated proteins, SH2 domains may serve as connectors that forge molecular assemblies along the signaling pathway. They want to understand how these protein/protein assemblies work in healthy cells, and how they might be functioning when a cell turns cancerous. Researchers in both the Hanafausa and the Baltimore labs are working on elucidating the structure and function of SH2 regions.

In the Hanafusa lab, work has focused on the domain in an oncogene called *crk*, an unusual gene whose protein product can cause cancer without having a "business end," such as a kinase, that might explain its activity. Collaborating with researchers in the Baltimore lab, the scientists have been assaying which tyrosine-phosphorylated proteins the crk SH2 domain binds to best in order to trace how it might be linking with other proteins in a process that turns a cell cancerous.

In the Baltimore lab, SH2 research focuses on the domain in the *abl* oncogene, a gene that causes chronic myelogenous leukemia. The researchers want to understand which structural and functional properties of the domain contribute to carcinogenesis. This year, they demonstrated that the capacity of abl's SH2 region to bind to phosphotyrosine is a crucial determinant of whether a cell becomes cancerous.

PROSPECTS FOR THERAPY

This demonstration points to possible strategies for cancer therapy at the molecular level, once the specific structure of SH2 regions and their binding sites are better delineated. With a well-defined binding site and a well-defined target, small molecular inhibitors might be designed to block the interactions that contribute to cancer.

Another exciting glimpse into future therapies comes from studies of phosphatases, enzymes whose function is just the opposite of kinases. While kinases put phosphate groups on amino acids, phosphatases take them off. Because these enzymes play a central role in the phosphorylation relay race, scientists have long speculated that they, too, might be important players in the origins of cancer. Until recently, technical problems hindered the exploration of this intriguing hypothesis, but recent advances have finally made such studies possible. This year in the Hanafusa lab, for instance, scientists have coaxed cells made cancerous by the *crk* oncogene to produce a phosphatase. The goal of these experiments is to see whether the phosphatase might allow the cell to revert back to a normal state. If this strategy proves fruitful, it will point toward an entirely new approach to the treatment of cancer at the molecular level.

In the end, all these cascades of phosphorylation and dephosphorylation—as well as other kinds of signaling processes—directly or indirectly affect events in the nucleus, where much of the mystery of cancer must lie. There, the genetic material, DNA, reproduces and otherwise readies itself for cell division. There, too, the genes embodying the coded instructions for proteins wait to be activated by the transcriptional machinery.

The nuclear events that lead to cancer are still an enigma. But this year, some important insights into possible connections between transcriptional events and cancer have emerged from the labs of Rockefeller researchers.

One discovery arose from the Baltimore lab's long-standing interest in the transcription factor NF-κB. (For more about NF-κB and transcription factors in general, see "Gene Transcription: A Key to Cellular Fate and Identity," page 8.) This factor, which helps activate genes in a vast array of cell types, is usually held in the cytoplasm in an inactive form by an inhibitory protein called IκB. IκB releases the NF-κB transcription factor in response to specific signals. This year, scientists in the lab discovered that an oncogene involved in human B cell cancers, called *bcl-3*, has properties very similar to those of the gene that codes for IκB. Because structural similarities often imply similarities in function, this discovery raises the intriguing possibility that the *bcl-3* gene represents a new type of *IκB* gene, and forges a tantalizing link between irregularities in transcription factor control and the development of cancer. Researchers also discovered this year that an oncogene called *rel*, which causes B cell cancer in birds, bears a close resemblance to the genes for both subcomponents of NF-κB, once again drawing connections between cancer and gene transcription somehow gone wrong.

GENE TRANSCRIPTION AND CANCER

The mechanisms by which genes regulating transcription may contribute to cancer are still unknown. But some fascinating insights have come from studies of transcription factors known to be important for cell differentiation.

By and large, a cell stops multiplying altogether, or multiplies only infrequently, once it is fully differentiated and engaged in performing its specialized function in the body politic. Cancer, which is characterized in part by unbridled cell growth, may thus sometimes arise because of a cell's failure to differentiate. This is why recent findings about helix-loop-helix (HLH) proteins hold hope for a better understanding of cancer.

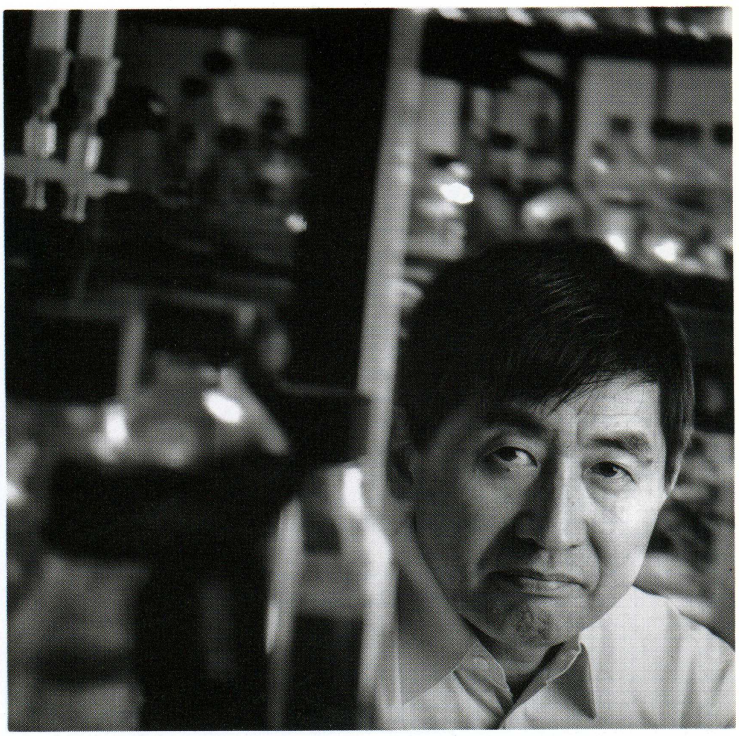
These proteins form a related family of transcription factors, many of which play crucial roles in tissue differentiation. The proteins' name refers to a configuration they share that lets them link up with one another in alliances called dimers. Shifting alliances among the various HLH proteins determine whether the transcription factor can activate transcription or is inhibited from doing so.

This year, workers in the Baltimore lab characterized the gene coding for a new variant of a class of HLH proteins called ID proteins. The job of ID proteins is to link up with certain HLH proteins critical for differentiation, and to keep them from functioning until the time is right. Should the genes for the ID protein be abnormal in some way, they might lead to abnormalities in the process of differentiation. Further understanding of these ID proteins may thus lead to a better idea of how differentiation is controlled, how it may go awry, and, by extension, how some cancers may get started.

Work in the Roeder lab on another HLH protein has also yielded exciting results with implications for the study of cancer. The lab's discovery this year of a transcription factor named TFII-I was surprising for what it revealed about the cell's general transcriptional machinery (see "Gene Transcription: A Key to Cellular Fate and Identity," page 8), but it was surpising for other reasons, as well.

The researchers found that TFII-I is an HLH protein and, as such, may be able to interact directly with HLH proteins important for cell differentiation. It may also be able to interact with the HLH protein products of *myc* oncogenes—genes of as-yet -unknown function that are implicated in a variety of cancers. The possibility of a functional link between the cell's basic transcriptional machinery and the important class of HLH transcription factors holds promise for exciting new research directions in cancer.

Cancer studies converge on the deepest mysteries of the cell: how signals are sent, how genes are activated, how an organism grows and develops. This convergence, at first glance so extraordinary, is actually just the reflection of the unity underlying cellular processes—a unity undreamed of only a few decades ago.

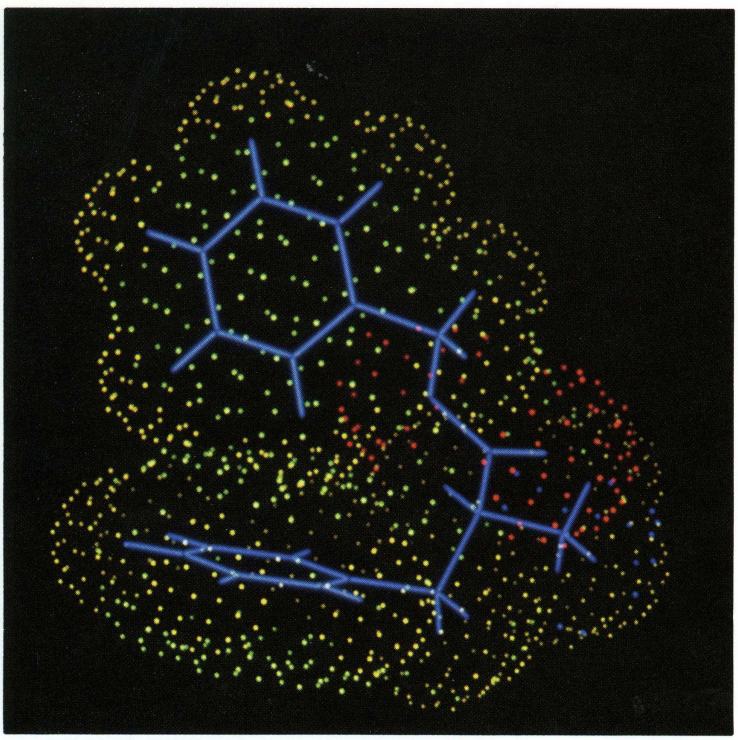


Hidesaburo Hanafusa, Leon Hess Professor and Head of Laboratory

MOLECULAR BIOLOGY: FORGING A COMMON APPROACH

On the seventh floor of The Rockefeller University Hospital, researchers in the laboratory of Jan Breslow are awaiting a very significant birthday—the day their first mouse will be born with a genetic change made possible only through the newest techniques of genetic engineering. It is an appropriate setting for the research team to await the results of their labors, for in the same building, one story down and about fifty years earlier, scientists performed the experiments that set the stage for the revolution that has transformed biological studies worldwide.

In 1944 Rockefeller researchers Oswald Avery, Maclyn McCarty, and Colin MacLeod reported the first experimental evidence that deoxyribonucleic acid, or DNA, is the repository of genetic information. From that seminal finding came a host of discoveries about DNA over the next thirty years. Scientists confirmed DNA's role as the substance of genes and elucidated its double-helical structure. They discovered how it copies itself before each cycle of cell division, and how the code embodied within it is translated into protein. They found the enzymes that act



Three-dimensional structure of a protein fragment containing two six-membered atomic rings. The colored dot surface represents the electron clouds surrounding the atomic nuclei. Structure determined by Burley and Andrew H.-J. Wang.

upon it to cut it, rejoin it, and convert it from one information-laden form to another.

By the early 1970s, scientists had enough conceptual and practical tools in their hands to start making recombinant DNA molecules never before seen in nature. The first experiments manipulated the genetic material of organisms such as viruses and bacteria. But as knowledge and techniques became increasingly more refined, it became possible to exploit the much larger genetic endowment of far more complicated organisms, such as plants, insects, and mammals.

Today, the theories and techniques of modern molecular biology have melded once-compartmentalized disciplines into a unified field of investigation. "Twenty years ago, immunologists talked immunology, neurobiologists talked neurobiology, and plant biologists talked botany," says David Baltimore. "Now, we're all talking the same language."

As it turns out, the apparent cacophony in biology's Tower of Babel was just a difference in dialects all along. For, says James Darnell, no matter what their specialty, "what every biologist does, in one way or another, is chase proteins"—be they proteins that direct development, shape a cell, receive or transmit a message, catalyze a reaction, stand guard against invaders, or perform any of the countless other functions that keep a cell healthy and useful to the organism.

BACK TO THE GENE

With the modern tools available to them, biologists can now chase those proteins back to their starting point, the gene. Segments of DNA can be isolated from their native cell, mutated in any way desired, yoked to DNA snippets from other organisms (or to snippets synthesized by machines), grown in vast quantities in yeast or bacterial "factories," and introduced into experimental hosts such as a single cell or an intact animal. This done, the scientists can assess the effect of these manipulations on a protein's function and, in a larger context, on the overall functioning of the cell or the organism.

All across Rockefeller, researchers are using these tools to study just about any biological question nature has to offer, for instance: how the cell cycle is regulated, how parasites wreak their havoc, how biological clocks mark their beats, how bacteria mutate their DNA to evade the onslaught of antibiotics, how the immune system functions, how brain cells communicate, how the cell maintains its structure and directs its internal dynamics, how genes are turned on, how cancer occurs.

Much of the research detailed in these pages would have been impossible without the new techniques. For example, scientists in the Greengard lab showed a synapsin's fundamental role in synapse formation by introducing extra copies of the gene that codes for the protein into a cell that does not normally form synapses. Similarly, researchers in the Hanafusa lab inserted a gene for a phosphatase enzyme into a cancerous cell to explore its possible effects. And researchers studying transcription routinely insert gene constructs into a variety of cells to see how fiddling with a DNA control element or altering the transcription factors available to it affects the process of gene activation.

TRANSGENIC CREATURES

While immensely informative, the study of engineered genes in cells in a culture dish can never elucidate the complexity of gene function in a living organism. That is why transgenic plants and animals—organisms carrying one or more or engineered genes—are such invaluable tools in modern biological research. With transgenic techniques, scientists can observe the effect of a gene, its mutation, or even its absence in a complex, multicellular system.

For instance, through transgenic manipulations, researchers in the lab of Nam-Hai Chua were able to induce petunia plants to make a higher-than-normal amount of the P-DEF1 protein and deduce its essential role in flower development. Claude Desplan and his colleagues also used transgenic strategies to learn how interacting transcription factors regulate early fruit fly development. So did the researchers in the lab of James Darnell, in their quest to track how certain liver-specific genes are activated only in a particular region of that organ.

The newest transgenic technique is making "gene knockouts," which let researchers see what happens to an organism when a gene is inactivated. Scientists in the Chua lab made petunias with knockouts of the *P-DEF1* gene by blocking it with anti-sense RNA—in essence, zip-locking the gene's mRNA intermediary and preventing the translation of information stored therein. These transgenic experiments helped confirm the gene's vital role in the formation of flowers. And, in the lab of Jan Breslow, researchers are using another technique, called "gene targeting," to knock out mouse genes involved in cholesterol metabolism in order to learn more about atherosclerosis and heart disease. This technique also allows researchers to replace one form of a gene with another. With the new gene knockout methodologies, the biologists' chest of transgenic tools is filled to the brim.

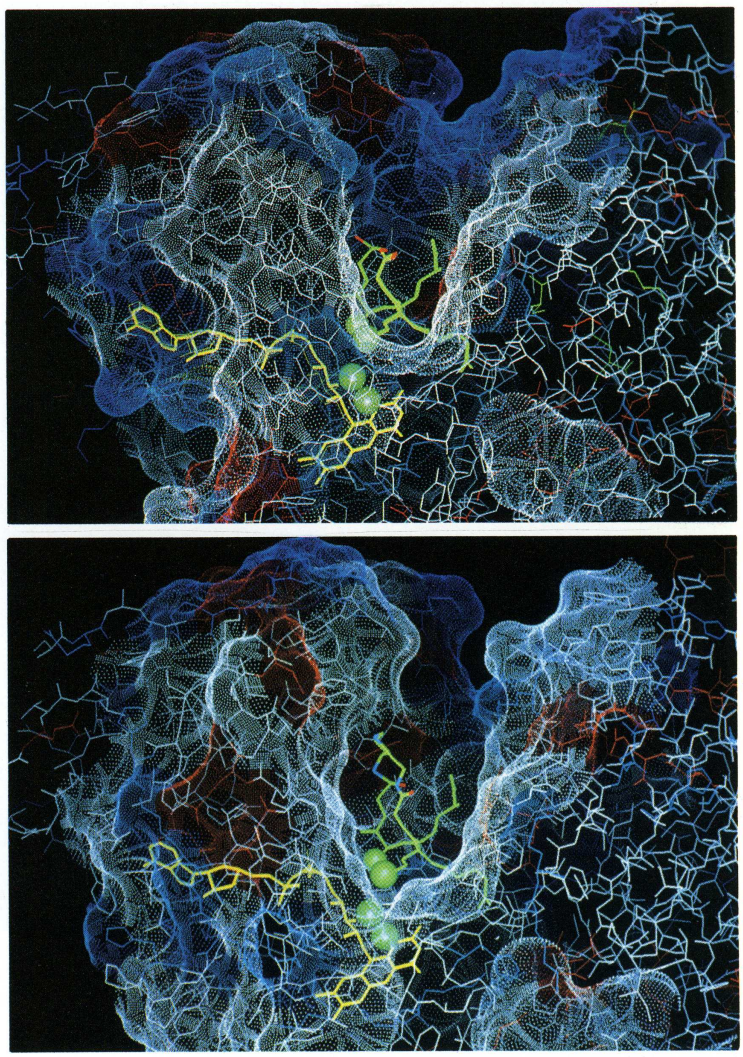
That the story of molecular biology's promise should come full circle at The Rockefeller University Hospital is poetic justice—and "scientific justice," too. The discoveries emerging out of labs worldwide are already finding their way to patients' bedsides in drugs designed and grown with genetic engineering techniques, and the prospect of gene therapy is closer than ever, with the first clinical trials already under way at the National Institutes of Health and elsewhere. Clearly, the new unified language of molecular biology has a lot to say for the benefit of humankind.

FORM AND FUNCTION: THE QUEST FOR MOLECULAR STRUCTURES

As scientists track down the seemingly endless assortment of molecules that play out the processes of life, some researchers are intensely curious about the physical nature of these molecules. What do they look like? How much do they weigh? How do their shapes change when they interact with one another? For enzymes, genes, transcription factors, and all the other biological molecules in a virus, a mouse, or a human being, form dictates function. A thorough knowledge of molecular structure is key to understanding biological activity—and knowing how and when to intervene.

X-ray crystallography is the best method for deciphering the three-dimensional structure of many large molecules, especially proteins. At Rockefeller, crystallographic studies are central to the research programs in two molecular biophysics laboratories headed separately by Stephen Burley and John Kuriyan. Last year, these research teams moved into new laboratory quarters, where they share state-of-the-art instrumentation that offers access to detailed views of the molecules of life.

In a sense, Kuriyan says, he and his fellow crystallographers are "photographers of the biological world." Their "cameras" consist of high-tech X-ray and computer systems, and their subjects are protein molecules that have been coaxed to come together into

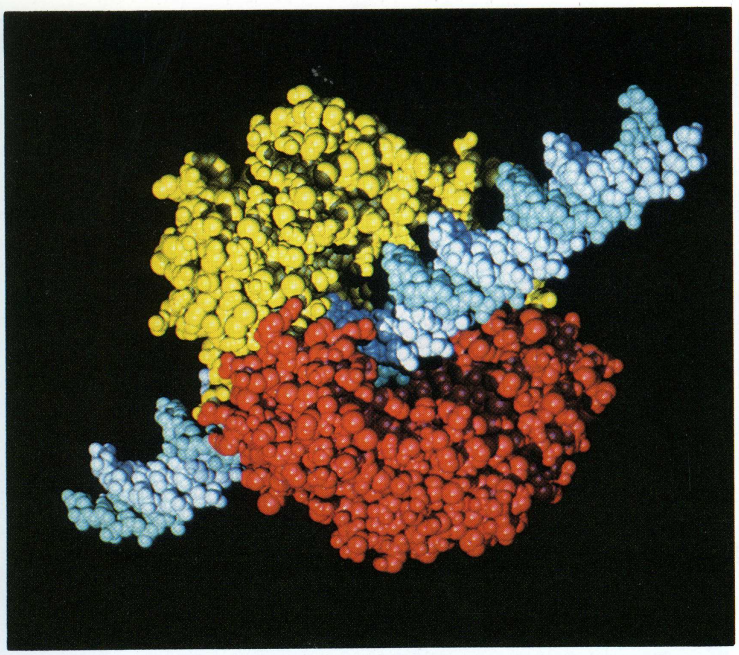


Two related enzymes that defend against the toxic effects of oxygen in humans (above, from Georg Schulz, Germany) *and trypanosome parasites* (below and cover, from Kuriyan's lab). *Idiosyncracies in the structure of the trypanosome enzyme may offer important clues for drug design.*

microscopic, jewel-like crystals. X-ray beams shot through a crystallized protein produce millions of telltale dots arranged in enigmatic, often beautiful patterns that offer important clues about molecular structure. An area detector, a new electronic version of X-ray film, records the diffracting X-rays; and mini-supercomputers speed the arduous process of interpreting their patterns and calculating the position of every atom in the protein. The same computers run special graphics programs that let researchers produce, analyze, and manipulate colorful representations of the molecules they study.

INNOVATIVE TECHNOLOGIES

The instrumentation of the crystallographer has evolved steadily over the past half century, so that a structure that once might have



taken years to determine can often now be solved in a matter of months. According to Kuriyan and Burley, though, it is the recent advances in molecular biology that have truly revolutionized crystallography.

The requisite first step in a crystallography experiment is to obtain large amounts of the purified molecule of interest, and until recently, crystallographers were limited to studying proteins that are naturally plentiful. Today, structural biologists like Kuriyan and Burley use recombinant DNA technology to mass-produce the protein product of virtually any known gene. The number of available research subjects is vastly increased.

Burley has chosen to tackle one of the central issues in biology today: how protein transcription factors recognize and bind with specific sequences of DNA to modulate genetic activity. By combining X-ray studies with a host of biophysical methods, Burley hopes to provide a direct look at the molecular mechanisms of transcription—how individual atoms of protein interact with individual atoms of DNA. One current focus is TFIID, the general transcription factor that was discovered in Robert Roeder's laboratory and recently crystallized by Burley's research team.

Kuriyan's interests have led him to study a range of molecules, including DNA-binding proteins, protooncogene products, and two enzymes whose structures he determined last year. One of these, trypanothione reductase, is found in trypanosomal parasites that afflict millions of people in developing nations. All organisms, from humans to bacteria, rely on a similar enzyme to defend against the toxic effects of oxygen, but through a "quirk of evolution," the trypanosomes' version is structurally different from all the rest—a fact first noted at Rockefeller. The precise information that Kuriyan has provided about this structural difference may point the way for other researchers to develop a compound that can destroy the activity of the reductase in the trypanosome, while leaving the human reductase untouched.

STUDYING MOLECULES IN SOLUTION

The technique known as nuclear magnetic resonance spectroscopy, or NMR, is also valuable for elucidating the relationship between molecular structure and function. Unlike X-rays, which are informative only about molecules that have been crystallized, the magnetic fields and high-frequency radio waves used in NMR can probe the atomic structure of molecules as they float in a solution. NMR systems use advanced computers and powerful magnets; the largest magnet at Rockefeller is about 200,000 times stronger than the earth's magnetic field.

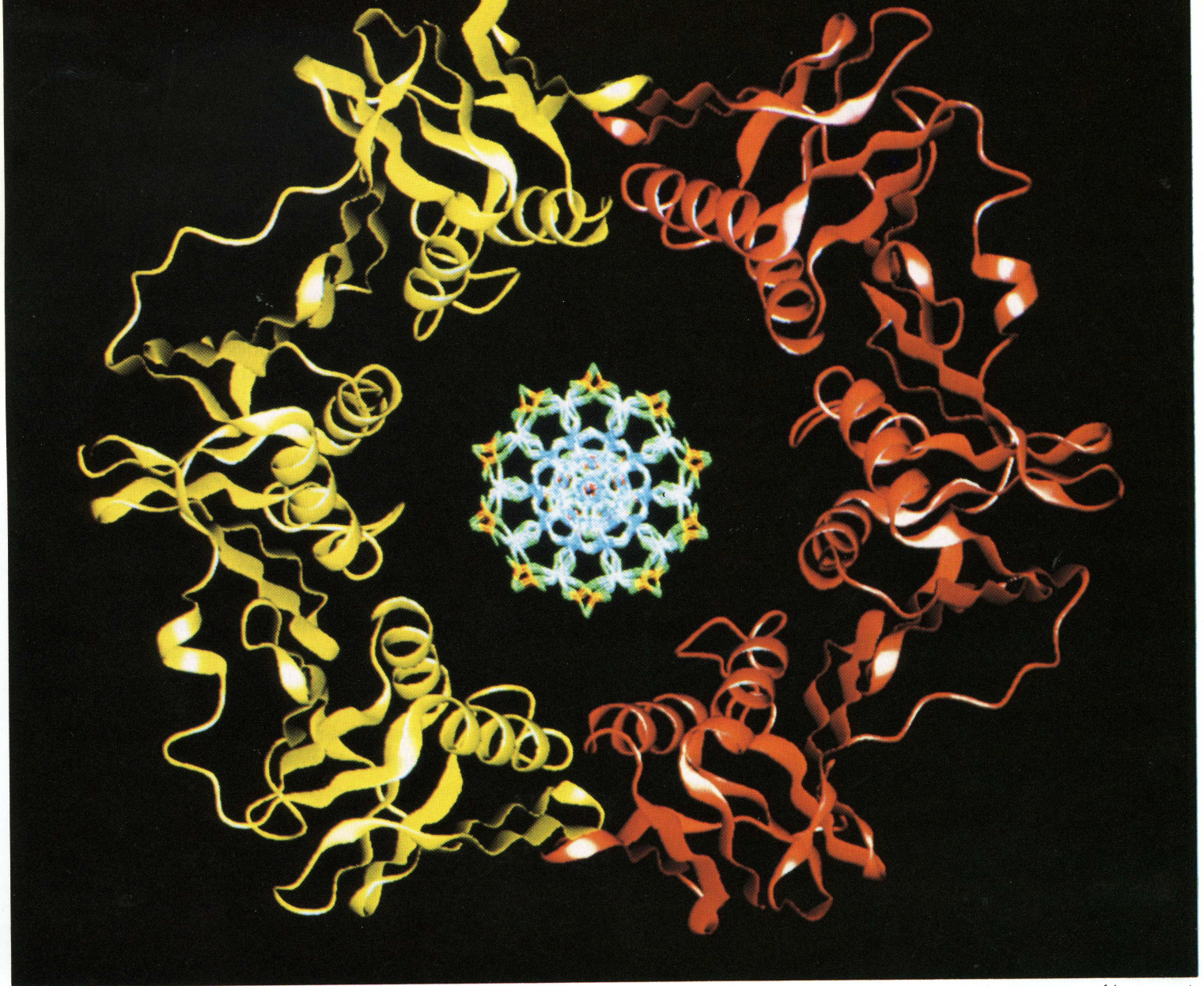
NMR is not yet readily applicable to the study of large proteins, but Rockefeller's David Cowburn says that the three-dimensional structures determined so far indicate that most large proteins consist of domains, or organized segments, that are small enough to be studied with current NMR technology. Cowburn suggests that "obtaining the structures of domains by NMR, and then finding out their higher level of organization by electron microscopy, could become an important approach to studying many larger proteins."

At present, he and his colleagues are taking this tack in a number of areas—including structural studies of protooncogene products, with a view toward understanding the roles these proteins play in health and disease. In addition, Cowburn's research team is developing new methods for using numerical analysis and what is called multidimensional NMR to extend the technology.

MOLECULAR SCALES

While NMR and X-ray crystallography can provide detailed information about the structure of molecules, instruments known as mass spectrometers are able to weigh them. The weight, or mass, of a molecule can be a key to learning about its identity and character. For many years, these devices were of limited use to biomedical researchers, though, because proteins and other large biomolecules are easily damaged when volatilized, or energized into the gaseous state—a prerequisite for study with a mass spectrometer.

In 1988, scientists in Germany developed a method for



An enzyme that replicates genes during bacterial cell division, polymerase III can glide along the DNA, hugging it tightly without getting stuck. The 3-D structure of the enzyme's DNA clamp is based on X-ray studies by X.-P. Kong and Kuriyan, with Rene Onrust and Michael O'Donnell (Cornell University and Howard Hughes Medical Institute). Shown are (above) *the skeletons of the enzyme and a stretch of DNA, and* (left) *all of the atoms in both molecules.*

volatilizing proteins without fragmenting them. Drawing on years of serious tinkering with mass spectrometry design, Brian Chait and his colleagues at Rockefeller have significantly refined this technique, known as matrix-assisted time-of-flight laser desorption mass spectrometry, and constructed a new instrument. Now available commercially, their spectrometer is finding its way into research laboratories around the world.

The new apparatus uses pulses of laser light to vaporize individual molecules out of a solid sample, conferring electric charge on them and sending them flying toward a detector. The weight of the molecules is proportional to the time it takes them to reach the detector—the longer the time-span, the heavier the molecule.

One remarkable feature of the new mass spectrometer is its ability to rapidly identify dozens of different proteins in a crude or impure mixture, even if the sample is extremely small. The instrument, which is especially useful for studying protein modifications, also provides information about abnormal genes by identifying their structurally defective protein products on the basis of discrepancies in molecular weight. In one recent study, Chait's research team joined with the laboratory of Jan Breslow to hunt for abnormal cholesterol-transporting proteins in blood samples from patients with inherited cholesterol metabolism disorders.

Chait notes that his group has conducted mass spectrometry studies of large biomolecules for more than ten years, but "only recently have they been relatively easy. Before it was a little bit heroic, sort of a miracle. Now it's becoming almost routine."

Turning the miraculous into the routine is a transformation common to researchers at Rockefeller. Yesterday's revolution evolves into today's accepted facts and tomorrow's new discoveries. The "refinement of everyday thinking" that Einstein described is the ongoing progress of science—a process no better illustrated than here at Rockefeller.

ANNUAL REPORT OF THE UNIVERSITY
FISCAL AND ACADEMIC YEAR JULY 1, 1990-JUNE 30, 1991

At the beginning of the year 1990-91, leadership of the university transferred from Joshua Lederberg to David Baltimore. On December 2, 1991, Dr. Baltimore resigned his presidency, effective December 31, 1991. Long-time faculty member Torsten Wiesel was elected to replace him while a search is conducted for a successor. James E. Darnell Jr., Vice President for Academic Affairs, also resigned, effective December 31, 1991.

During his tenure as President, Dr. Baltimore defined a vision for the continuing growth and development of the University that was the basis for a broad program of actions taken over the last year—actions that have reinvigorated the financial and academic posture of the university.

ADMINISTRATION, OPERATIONS, AND FINANCE

The most difficult challenge faced by the university in the past fiscal year—and an area of substantial achievement—has been the university's administrative and financial management.

Beginning in 1987-88, the university had incurred a series of significant and progressively larger budget deficits in its annual operations. Costs of operations, particularly overhead and support operations, continued to grow at an annual rate exceeding ten percent year-to-year. Staff was added to strengthen ongoing activities and to meet the needs for additional services. But income from all sources reached a plateau at 1986-87 levels, and larger and larger amounts of the university's endowment capital were expended to cover current costs. The overall deficit from capital as well as operating expenditures was $14 million in 1989-90; it rose in 1990-91 to a year-end level of $15.8 million.

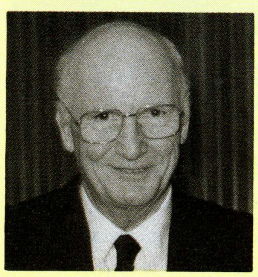
BUDGETS AND FINANCES

To address the difficult and deteriorating problem of university budget deficits, the administration concluded that prompt, strong measures—measures that would require considerable sacrifice by many in the university community—would be required to bring the university's expenses back into line with revenues. Even then, it would take several years to achieve financial balance in current accounts.

With support from the university's trustees, a number of actions were pursued to accomplish these financial objectives:

CHAIRMAN'S REPORT: A YEAR MARKED BY MANY CHANGES

Richard Furlaud
Chairman of the Board of Trustees



Change comes to all of us frequently. It never seems to come easily. A recent change experienced by The Rockefeller University was the resignation of President David Baltimore. The brevity of Dr. Baltimore's tenure should not overshadow his outstanding performance and the many positive changes which occurred under his leadership—changes designed to help meet significant challenges and strengthen The Rockefeller University's position as a preeminent scientific institution.

The changes were all carefully considered by a number of individuals in the university leadership—including trustees, Dr. Baltimore and his administration, and faculty members. They were intensely debated, but ultimately they were adopted because we firmly believe that they will serve the university well over the long term.

We have made great strides over the past year to improve the financial stability and security of the university. David Rockefeller provided an extraordinarily generous leadership gift, capping the most successful fund-raising period in the university's history. With more than $40 million raised since July 1990, we are ahead of schedule in achieving an ambitious goal of raising $250 million by the end of the decade.

Significantly, our fund-raising success reflects the fact that many new friends have come forward to support the university, as well as the generosity of long-time friends and donors. It results from the efforts of a large group of people, working together and individually, and is a particularly striking accomplishment in these hard economic times when most institutions are having difficulty raising funds.

Many trustees were involved in fund-raising under the leadership of Alex Forger. The Development Office staff did yeoman service and proved that hard work and persistence can achieve almost anything. And I must say that your president worked tirelessly and with enormous creativity to contribute to this effort.

But fund-raising is only half of what is necessary to ensure the long-term fiscal health of the university. The other side of the coin is controlling rising costs, and in this we are also making considerable progress. The administration and the faculty have successfully carried out their mandate from the Board of Trustees to reduce the university's operating deficit, which had been widening at an alarming pace. They have found the means to arrest the growth in expenses, stabilize services, and install systems that will help prevent excessive costs from recurring. This has not been the easiest of tasks. Hard decisions had to be made because the only way to make meaningful cost reductions was to attack the problem head-

• A strict but even-handed freeze on new hiring was established in offices providing administrative and research support services. Vacancies that occurred through attrition were filled selectively and with restraint.

• The Administration also took the difficult step of asking both faculty members and all non-faculty staff to accept a broad moratorium on salary and wage increases that would normally have been awarded for the year beginning July 1, 1991. Each member of the university community was asked, in effect, personally to bear a portion of the financial sacrifice that was required to assure the university's future. Exceptions to this freeze were granted, however, for younger faculty members at the outset of their scientific careers—assistant professors and postdoctoral fellows—on whom the university's future, and the progress of science, depend.

• Guidelines were developed that would, over several years, phase down support from the endowment for the university's research laboratories to more sustainable levels. Earlier commitments of support weighed too heavily upon the university's endowment.

• Steps were initiated to strengthen the two offices principally responsible for bringing resources into the university—the Offices of Development and Sponsored Research Programs. Each office now has effective new leadership for the years ahead.

• As a result of an ambitious and effective fund-raising program, private pledges of financial support for the university's research programs rose by twenty-three percent during 1990-91. Still, the university's trustees accepted the administration's recommendations for even more ambitious private fund-raising goals in 1991-92:

  • a doubling of private gifts and pledges to a new annual level of $23 million;

  • a twenty-five percent increase in cash gifts received to a new level of $16 million annually.

• With the trustees' concurrence, long-term tax-exempt debt at exceedingly low rates of interest was substituted for the $46 million previously withdrawn from the endowment to meet the university's share of the costs of a state-of-the-art biomedical research laboratory now being constructed at the southeast corner of the campus. The university's endowment has achieved superior investment performance over the long term, and the university needs an even larger and consistently growing endowment to support the growth of research programs now planned for the rest of the decade.

OBJECTIVES FOR 1991-92

With these initiatives in place, the administration set the following objectives for the year 1991-92:

• A reduction of thirty-seven percent in the budgetary deficit for current operations;

• A reduction of twelve percent in expenditures for overhead and research support, including fifty fewer budgeted staff positions in overhead offices and functions;

• The first measurable gains in three years—although still modest—in externally provided income/revenue for research and general operations.

STRENGTHENED MANAGAMENT TEAM

Another important achievement over the last year was the establishment of a strengthened management team.

As part of this process, many new people have been promoted on. Since by far the largest expense item is payroll costs, the only way to cut fixed costs meaningfully was to reduce payroll. Accordingly, increases to pay were suspended, except in the case of the most junior scientists. In addition, some employees have taken early retirement, and, unfortunately, a small number of layoffs has been necessary.

We have avoided, however, what is happening elsewhere throughout the country in these difficult times: massive layoffs and sharp reductions in programs. I am confident that we will continue to maintain and improve upon this healthy posture.

On the scientific front, the administration has worked closely with the Committee for Scientific Affairs of the Board of Trustees and with the faculty leadership to bring changes to the faculty structure. This will help assure that we will be able to build a cadre of junior scientists as well as to recruit some more senior colleagues to succeed those who will be retiring in the years to come.

All of us can be grateful to Dr. Baltimore for his role in laying the groundwork for the university's future success—and should continue to build on this groundwork as the university conducts an accelerated search for an equally outstanding administrator to lead us into the twenty-first century as the world's premier biomedical research institution.

from within, or brought in from outside, to give direction to key administrative offices and functions.

IMPROVEMENTS IN SERVICE

In addition, the administration moved to institute a series of faculty recommendations and other initiatives aimed at strengthening key university service functions.

Priority is being given to restructuring and integrating computing, telecommunications, and information services that are functionally overlapping but historically independent organizationally. The administration is also carefully adressing the planning issues that involve the interrelationships among faculty and research expansion and facilities, housing, and annual operating costs. At the same time, the university is continuously looking for ways to reduce and limit overhead costs without lowering the quality of services crucial for research.

FINANCIAL SUMMARY

EXPENDITURES

During the fiscal year ended June 30, 1991, total expenditures for current operations and capital project appropriations were $113.5 million, an increase of less than two percent over the previous year. The small growth in expenditures reflects significant cost reductions in nearly all areas of operations. In spite of the small increase in spending, several new research groups were launched, and $4.8 million was appropriated for capital projects, including renovations and other physical plant improvements.

REVENUES

Governmental grant and contract revenues were approximately the same as the previous year, reflecting keen competition for these funds as well as reductions in awards imposed by Federal agencies. Endowment resources utilized, including interest, dividends, and capital gains to support fiscal 1991 operations, totaled $40.8 million, or about eight percent of the market value.

To preserve the buying power of the endowment, the Board of Trustees set a target of five percent of a three-year moving average of the endowment market value as an appropriate spending rate. The actual fiscal 1991 expenditure was $15.8 million higher than this target and is a measure of the additional financial progress that must be made.

BOND ISSUE

The university, with the assistance of the Dormitory Authority of the State of New York, issued bonds totaling $49.7 million in July 1991. This will permit the return to the endowment of approximately $46 million of funds previously advanced for construction of the new research building. The bonds had serial maturities with the longest maturity—thirty years—priced at an interest cost of $6\ ^{7}/_{8}$ percent. The university is one of only a few nonprofit institutions in the country to have received an AAA credit rating from both major rating agencies. This strength elicited strong investor demand for the bonds and permitted favorable pricing.

ENDOWMENT

The market value of pooled endowment assets on June 30, 1991, was approximately $521 million. Endowment assets are under the stewardship of the Finance Committee of the Board of Trustees. During the year, the committee allocated the funds among four separate investment managers who make day-to-day investment decisions under guidelines established by the committee.

THE LONG-TERM CHALLENGE

The immediate budgetary and financial imbalance problems necessarily commanded the immediate attention of those responsible for charting the university's direction over the last year. While these problems will require continuing control and attention, the administration will also focus on longer-term research, development and management challenges, in particular attracting the most outstanding scientists to advance their careers here. To achieve that goal, faculty committees are engaged in intense searches for talented researchers in emerging areas of emphasis. Overall, the university is committed to a program to attract the financial support critical to support such future leaders in science, as well as to maintain and communicate its position of eminence in scientific research and scholarship.

RETIREMENTS AND DEPARTURES

Finally, even as we look to the future, the administration would like to acknowledge the long and faithful service of a number of key members of the administrative staff who retired over the last fiscal year. These include:

Lila Magie, Secretary to the Corporation and
Director of Faculty Administration
Sonya Mirsky, University Librarian
John O'Donnell, Vice President for Personnel
Jeremiah Barry, Director of Food Services

The following key employees also departed during the year:
Rodney W. Nichols, Executive Vice President
Robert Van Valer, Vice President for University Relations
Philip Sun, Vice President for Facilities Management
Dennis Stark, Director of the Laboratory Animal Research Center

Each of these individuals contributed significantly to the success of the university over the years and their dedication to this institution is deeply appreciated.

David Baltimore, President
Frederick M. Bohen, Executive Vice President

STATEMENT OF EXPENDITURES AND RESOURCES UTILIZED

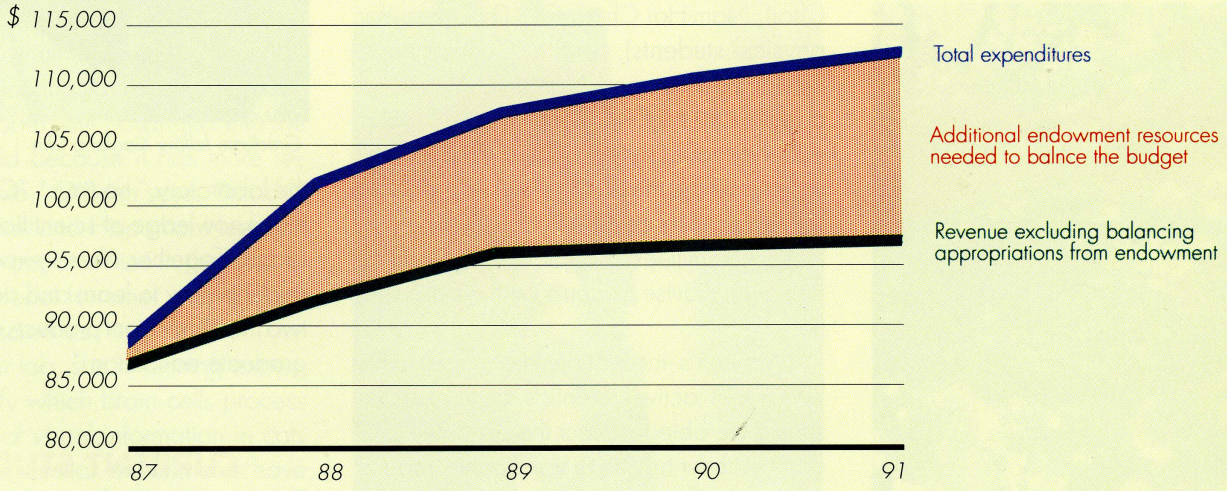
Five years ended June 30, 1991
(000's omitted)

EXPENDITURES	**1987**	**1988**	**1989**	**1990**	**1991**
Research and education	$ 56,100	59,100	61,200	63,600	62,900
Operations and maintenance of plant	11,500	12,300	14,100	14,600	14,900
General administrative and institutional	9,700	10,400	12,000	12,800	13,700
Auxiliary enterprises	7,700	11,100	12,400	14,7000	15,900
Debt service	1,200	1,200	1,200	1,300	1,300
Capital expenditures	$ 3,100	8,600	7,7000	4,500	4,800
Total Expenditures	$ 89,300	102,700	108,600	111,500	113,500
RESOURCES UTILIZED					
Government grants and contracts	$ 38,200	37,700	41,500	37,100	36,800
Private gifts, grants and contracts	18,000	19,5000	18,300	20,100	18,700
*Endowment income	20,600	24,200	24,500	25,000	25,100
Auxiliary enterprises	7,900	8,500	9,600	12,200	13,800
Other sources	2,800	3,100	3,100	3,100	3,300
Total Income	$ 87,500	93,000	97,000	97,500	97,700
Additional endowment resources needed to balance budget	$ 1,800	9,700	11,600	14,000	15,800
TOTAL RESOURCES UTILIZED	$ 89,300	102,700	108,600	111,500	113,500

*Endowment income is defined as five percent of a three-year average market value.

FINANCIAL SUMMARY

Five years ended June 30, 1991
(000's omitted)



The university issues annual audited financial statements. A copy for 1990-91 can be obtained from the Controller's Office, The Rockefeller University, 1230 York Avenue, New York, New York 10021.

NEW DEANS INVIGORATE STUDENT PROGRAM

REPORT FROM THE OFFICE OF GRADUATE STUDIES

One of the first things Bruce S. McEwen did as the new dean of graduate studies was to change an apostrophe. He converted the "Dean's Office" to the "Deans' Office" and joined forces with his two associate deans, Peter Model and Marjorie Russel, to form a team that is breathing new life into the functions they manage.

One of their goals is to spread deaconal administration among a larger number of faculty. For a starter, they have divided up the traditional responsibilities of the Office of Graduate Studies into three functions: McEwen takes care of overall coordination, interaction with the university administration, and fund-raising; Model is in charge of curriculum; and Russel handles admissions and recruitment of new graduate students.

In addition, the Deans' Office includes Claude Desplan, assistant dean, who arranges seminar programs and activities for postdoctoral fellows and junior faculty; and Ralph Steinman, who coordinates and directs the Rockefeller component of the Tri-Institutional M.D. Ph.D. Program, co-sponsored by the university and its neighbors, Cornell University Medical College, and the Cornell University Graduate School of Medical Sciences, which includes the Sloan-Kettering Institute.

Dean Bruce S. McEwen, Associate Dean Marjorie Russel, and Associate Dean Peter Model (left to right) *confer at a spontaneous meeting on campus.*

In a further effort to involve senior faculty with the graduate program, the Deans' Office has initiated the Senior Tutors Program, which provides immediate and individual guidance to incoming students. The tutors meet one-on-one with students and discuss courses, laboratories, and campus life.

Current senior tutors are professors Brian Chait, Nam-Hai Chua, E.G.D. Cohen (for physics students), Bruce Cunningham, David Gadsby, and Nathaniel Heintz, in addition to McEwen and Model. After students have settled in their thesis lab, usually toward the end of their second year, the senior tutors cede their duties to the pre-thesis committees, groups of faculty members who advise students on their dissertations.

McEwen's innovations are a result of his belief that active scientists at Rockefeller should be able to direct the graduate program without having to significantly reduce the time or effort they spend on their scientific research. By dividing responsibilities, these scientists can contribute to the Office of Graduate Studies and maintain their commitment to laboratory work.

This emphasis on laboratory research is the mainstay of the university, a lesson that is important to communicate to incoming students, says McEwen. "The focus of students at Rockefeller traditionally has been

Graduate fellow Xiaofeng Qin

the laboratory," he says. "Courses expand their knowledge of scientific principles and facts. Together, these experiences teach students how to learn and do research, the two most important products of a Rockefeller graduate education."

CURRENT STUDENTS

The twenty-two Ph.D. candidates and eleven biomedical fellows who make up the entering class this year are a diverse group. Some came straight from college, others came after years of research experience. Some are natives of the area; others traveled from countries as far away as Japan and the Soviet Union.

But the students have some striking similarities. They are all bright, independent

individuals driven by their interest in the natural world. The students were all attracted by Rockefeller's excellent reputation in scientific circles and flexible course of study. Those entering the Tri-Institutional M.D.-Ph.D. Program also were drawn by the opportunity to choose to work in any lab at the three institutions.

A DRIVE TO UNDERSTAND THE BRAIN

Estela O'Brien, a Ph.D. candidate in the entering class, is from Long Island. She came to Rockefeller to pursue the question which had intrigued her during medical school: how does the brain interpret visual information?

O'Brien was not always a biologist. She earned an undergraduate degree in physics from Harvard College and a master's degree in astrophysics from Rensselaer Polytechnic Institute before going on to complete two years at Cornell Medical College.

"It was fascinating to try to understand how stars are born, but I changed into the biomedical field because it has more relevance to people," O'Brien says. "In addition, as I'm black and Hispanic, I feel that there are more opportunities in this field to act as a role model for other young black and Hispanic scientists."

In the Knight lab, she is running experiments to identify which brain cells process different types of visual information in cats and monkeys. Similar experiments have revealed that some cells specialize in responding to a specific type of image; for example, some cells fire only in response to a horizontal image, others only to a vertical or diagonal one.

"Right now I look at small groups of cells at one time," O'Brien says, illustrating her point on the chalkboard in her office. "Later, I hope to pursue a technique called "imaging," which enables a researcher to see which cells fire simultaneously in a larger area of the brain. I am interested as well in understanding how the brain integrates visual images with cognition—for example, seeing a chair and understanding that it is used for sitting on."

MOVING QUICKLY TO THE FRONTIERS OF RESEARCH

Like Estela O'Brien, Xiaofeng Qin—a student from Beijing, China—is already immersed in research. In fact, the ability to begin research immediately was one of the factors that attracted him to Rockefeller's Ph.D. Program.

"Here students are able to move quickly to the frontiers of research, where science is most exciting," he says. "Students do not have to follow a slow, formal path."

Qin is no stranger to research. Before becoming a student, he worked two years in the Chua lab at Rockefeller as a guest investigator. Before that, he earned an undergraduate degree from Nanjing University and a master's from Academia Sinica. Qin is now performing a small research project on the immune system in the Nussenzweig lab.

"There are two to five different classes of immune responses," he explains. "Which response is used depends on what is attacking the body—a virus or a bacterium, for example. We do not yet understand how the body determines which response to use, but it is an interesting and important question."

Graduate fellow Henrik Tommerup.

LEAVING THE EASY LIFE FOR SCIENCE

The same independence of mind and interest in research that characterizes O'Brien and Qin can be seen in Henrik Tommerup. After graduating from Copenhagen University, Tommerup performed basic research on plants for Carlsberg Research Center in Copenhagen, where he worked with John Mundy, a researcher who had been a postdoc at Rockefeller.

Tommerup applied to Rockefeller because "a Ph.D. from Rockefeller is well respected all over the world." Although he wanted to broaden his horizons by studying outside Denmark, he remarks, "life is so easy in Copenhagen. You really have to want to do research to leave it—or any wealthy Western European country, for that matter."

Tommerup plans to pursue research in the de Lange lab on molecular kinetics, but has not yet begun running experiments.

"I think that students are quite happy with their experience here," Tommerup com-

ments. "The faculty, even senior faculty, are accessible. We have all the equipment we need. And it's great to jog along the East River, attend classical music concerts on campus, and explore New York's nightlife."

He continues: "I am impressed by my colleagues in the entering class. Even in fields they are not familiar with, they grasp new ideas quickly and are able to manipulate them."

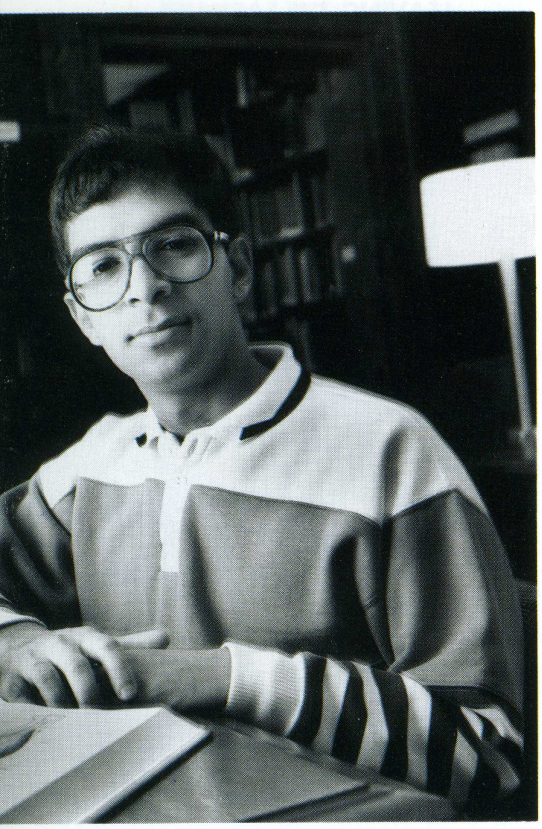
COMBINING RESEARCH AND MEDICINE

Ron Bose has wanted to be a scientist since he was a teenager. His interest in medicine developed in college, when he was a member of the volunteer ambulance corps. The Tri-Institutional Ph.D. Program enables him to pursue both interests.

"M.D.-Ph.D. students can choose to do their lab work at any of the three institutions —Rockefeller, Cornell, or Sloan-Kettering," says Bose. "The large selection of labs was one of the factors which attracted me to the program. I also had a good impression of the faculty, who believe in offering students both flexibility and guidance."

Last summer, after graduating from the University of Rhode Island, Bose did research at Rockefeller in the Edelman-Cunningham lab. "We worked with mice, trying to find out how altering a gene disrupts the normal patterns of protein expressed in the tissue," he explains.

Now taking courses to fulfill Cornell Medical College's first-year curriculum requirements, Bose is already thinking ahead to his Ph.D. work. He wants to investigate a topic in developmental biology or immunology from a molecular point of view.



M.D.-Ph.D. candidate Ron Bose.

Ph.D. student Estela O'Brien

INTELLIGENCE, CURIOSITY, AND A STRONG TECHNICAL BACKGROUND

The intelligence and self-motivation of these students are no surprise to Marjorie Russel, associate dean in charge of admissions at Rockefeller.

"We look for three things when reviewing applications: intelligence, curiosity, and prior research experience," she says. "All the indicators—such as recommendations and grade-point averages—are used together to assess the character and preparation of the individual."

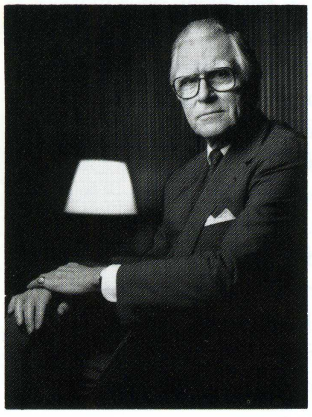
Even though the admissions committee—made up of about seven faculty members including Russel—receives around 300 applications for twenty openings in the Ph.D. Program, and 200 applications for ten openings in the Tri-Institutional M.D.-Ph.D. Program, Russel claims that there are few candidates that meet their simple yet rigorous criteria. Most applications are weeded out during the first review.

This year's class contains slightly fewer women than normal—five of twenty-two Ph.D. candidates and two of eleven M.D.-Ph.D. candidates—and more international students than usual—sixteen Ph.D. candidates with another two in the M.D.-Ph.D. Program.

"Statistical anomalies are bound to crop up when you deal with such small numbers," Russel says. "Although we welcome diversity, our philosophy is that it is more important to admit the most qualified individuals and let the statistics fall where they may. This admissions policy seems to be paying off by attracting students with the potential to one day be leaders in their field."

'90-91 TOPS FOR FUND-RAISING

REPORT FROM THE DEVELOPMENT COMMITTEE CHAIR, ALEXANDER D. FORGER



I am very pleased to report that the university has experienced the most successful period of fund-raising in its history, receiving more than $40 million in gifts and pledges since David Baltimore became president on July 1, 1990. This total includes:

- A $20 million gift from David Rockefeller, the largest contribution ever made to the university by an individual.
- $11.3 million in gifts and pledges raised during the 1991 fiscal year—a twenty-three percent increase over the previous year.
- $9.2 million in new gifts and pledges raised in the first quarter of the current fiscal year (FY 1992).

Richard M. Furlaud, chairman of the board of trustees, reported this success at the October 17 meetings of the board and The Rockefeller University Council, an organization of 150 friends and benefactors of the university.

"These fund-raising efforts will continue to be intensified in the months and years ahead in order to help the university strengthen its position as a premier scientific institution," said Mr. Furlaud. "Under Dr. Baltimore's leadership, and through dedicated efforts by the faculty and the administrative staff, the university over the past year has made significant progress in achieving financial stability, while, at the same time, embarking upon a drive to expand the number of independent laboratories conducting biomedical research."

When he announced the contribution that David Rockefeller made, Mr. Furlaud commented that the receipt of *any* gift of this magnitude would be a landmark event at the university. "This particular gift is especially meaningful, though," Mr. Furlaud pointed out, "because it comes from an individual who has faithfully served the university for more than fifty years." A member of the board since 1940, David Rockefeller served as its chairman for twenty-five years, then went on to serve as the chairman of the executive committee of the board and the chairman of The Rockefeller University Council.

Over the years, Mr. Rockefeller has provided continuous major support for the university, and his most recent act of generosity has provided a great boost not only to the university's finances, but also to its spirits. This is particularly important now as we launch a major effort to raise $250 million in private gifts and grants by the end of the decade.

Alexander Tomasz, David Baltimore , Vincent Fischetti, and Elaine Tuomanen (left to right) *participating in a panel discussion on antiobiotic-resistant bacteria and what scientists can do to combat them. The panel discussion was part of the program presented at The Rockefeller University Council meeting October 17.*

DEVELOPMENT REPORT

The more than $40 million we have raised to date also includes a number of other significant gifts and pledges, among them:

- A $5 million pledge from an anonymous donor who has never before made a gift to the university.
- A challenge grant from a trustee who will donate $2 million to the university if The Rockefeller University Council raises $10 million during the next two years.
- Approximately $1 million in personal commitments from three trustees: Mr. Furlaud, Ralph Ablon, and John Whitehead.
- A $1.1 million grant from the Annenberg Foundation that will be used to endow an assistant professorship for the head of a new laboratory, and a related gift of $90,000 that will be used to bring high school science teachers to the university during the summer to learn and work in our laboratories.
- A major commitment from Jack Fishman, who headed a laboratory on campus for many years. A founder of a publicly held pharmaceutical company, IVAX Corporation, Dr. Fishman has made a gift that will be used to create a permanently endowed assistant professorship for the head of one of our new laboratories.

The university has also received gifts of $100,000 or more from several members of The Rockefeller University Council, including Alexander Abraham, Arnold Beckman (through the Arnold and Mabel Beckman Foundation), Marshall Cogan, William Mazer, Carl and Carol Pforzheimer (through The Carl and Lily Pforzheimer Foundation), Beatrice Renfield, Morris Schrier, and Paulo Villares.

Gifts at this level have also been provided by William Hewlett, another friend of the university, and Librarian Emeritus Sonya Wohl Mirsky.

I am also pleased to announce that a special fund-raising initiative to provide support for the hospital has brought in an additional $1.5 million. Launched in March 1991, this effort is headed by Trustee Emeritus Ralph Ablon, who is working closely with Dr. Attallah Kappas, Sherman Fairchild Professor and physician-in-chief emeritus of The Rockefeller University Hospital.

At a time when harsh economic realities, declining Federal support of research, intense public scrutiny, and fierce competition for philanthropic funds are challenging many leading institutions, I am happy to say that hundreds of enlightened individuals and organizations are continuing to provide major private support for biomedical research—and many of them are offering that support to the research under way at The Rockefeller University.

Clearly, the philanthropic community understands that the promise of biomedical research has never been greater. In the near future, we can expect to see dramatic advances in the effort to understand fundamental biological processes and improve human health. Many of those advances will undoubtedly be made either on The Rockefeller University campus or by scientists who have worked or studied here.

I know that the talented scientists and staff assembled at the university join me and my colleagues on the board in expressing our deep appreciation of the support the university has received during the past fiscal year from the many individuals, foundations, and corporations listed here.

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*July 1, 1990—June 30, 1991 **

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