Spring 1991

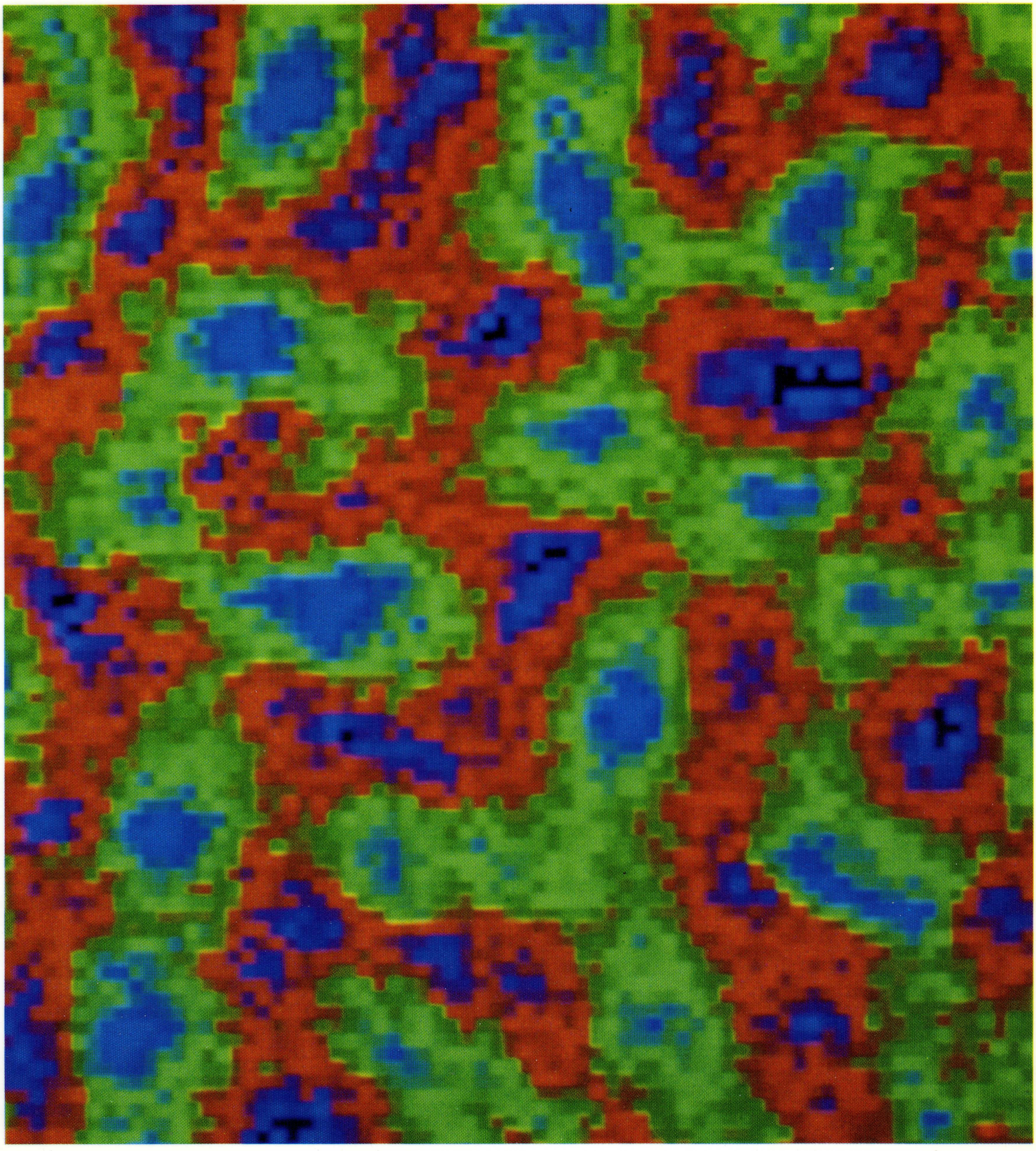
SEARCH MAGAZINE 1991, VOL.1, NO.1

The Rockefeller University

Premier Issue
Spring 1991

SEARCH

THE ROCKEFELLER UNIVERSITY MAGAZINE



SEARCH

EMBARKING

This first issue of *SEARCH: The Rockefeller University Magazine*, is launched in the true spirit of exploration. It is to be a quarterly magazine, issued with the seasons, attempting to discover and then convey the importance and excitement of research and education—particularly biomedical research—in contemporary American society.

This is not the first magazine published by this university. During its nine decades, The Rockefeller University has sponsored numerous publications. They were unfailingly right for their times, served their purpose, and, when times changed, they retreated to the archives.

The times now are right, we believe, for this magazine. Biomedical research and education accelerate in complexity, cost, and importance. For this university, the times cry out for a publication that can explain simply and thoroughly to our friends the research revolution going on here and elsewhere, and place it in perspective.

We have compiled our initial mailing list from a variety of sources. We hope you receive this magazine at your correct address, that you will enjoy it, and share it with others. If you would prefer not to receive it, please let the editor know and she will promptly remove your name from the list.

If you have comments about the magazine, we would be glad to hear them. We want the magazine to enlighten in an entertaining way. We want it to be attractive, and sometimes provocative. And while we hope it will spur some to join The Rockefeller University community as financial supporters, we don't wish to be obtrusive in communicating our needs.

You, our readers, are the best judges of our performance. We invite you to be our critics.

David Baltimore, President
Alfred G. Kildow, President's Assistant for Communications

CONTENTS

ON THE COVER

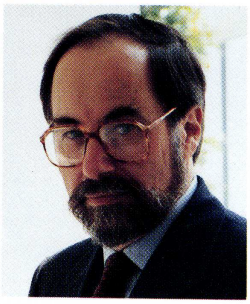
A view of a three-millimeter portion of the area of the brain responsible for vision. The blue patches show cells that process color information. The red and green areas contain cells that are not selective for color, but rather for orientation. The image is colored artificially by computer. (See story on page three.)

SEARCH: The Rockefeller University Magazine is published quarterly by The Rockefeller University Press, 222 East 70th Street, New York, NY 10021-5405. Application to mail at second class postage rates is pending at New York, NY, and additional mailing offices. POSTMASTER: Send address changes to Search, Box 68, The Rockefeller University, 1230 York Avenue, New York, NY 10021-6399. ISSN 1054-9358

Phone (212) 570-8969. Fax (212) 570-7876. Electronic mail—INTERNET: Rock-search@rockvax.rockefeller.edu; BITNET: Rock-search@rockvax.bitnet.

EDITORIAL

THE DECADE OF THE MOUSE



When it comes to disease, the lowly mouse, a pest to many, is man's and woman's best surrogate. Although so different from us—four-footed, not very intelligent, a life span of two or three years, a gnawing rodent—it is a mammal and therefore much closer to us in evolution than a worm or a fly or a fish or a bird. But flies and worms have great advantages when it comes to doing experiments: they breed rapidly and are relatively inexpensive to keep in large numbers. Those two traits mean that they lend themselves to analysis by the most powerful tool a biologist has, genetics. To do genetics requires large numbers of organisms, a few of which will have altered genes, and a way of rapidly analyzing the genes by selective breeding. To do fancy, modern genetics requires an ability to add and subtract genes.

The mouse as an experimental organism fails on two basic counts: a new generation requires months of waiting, and the animals are available in limited numbers because they are so costly to maintain. But recently new experimental capabilities have altered the situation. We learned about five years ago how to add genes to a mouse, and we learned over the last two years how to subtract genes. This last capability is still rudimentary, but is being improved rapidly. Together, these new approaches have compensated for the slow breeding and cost of mice, and promise to make the 1990s The Decade of the Mouse.

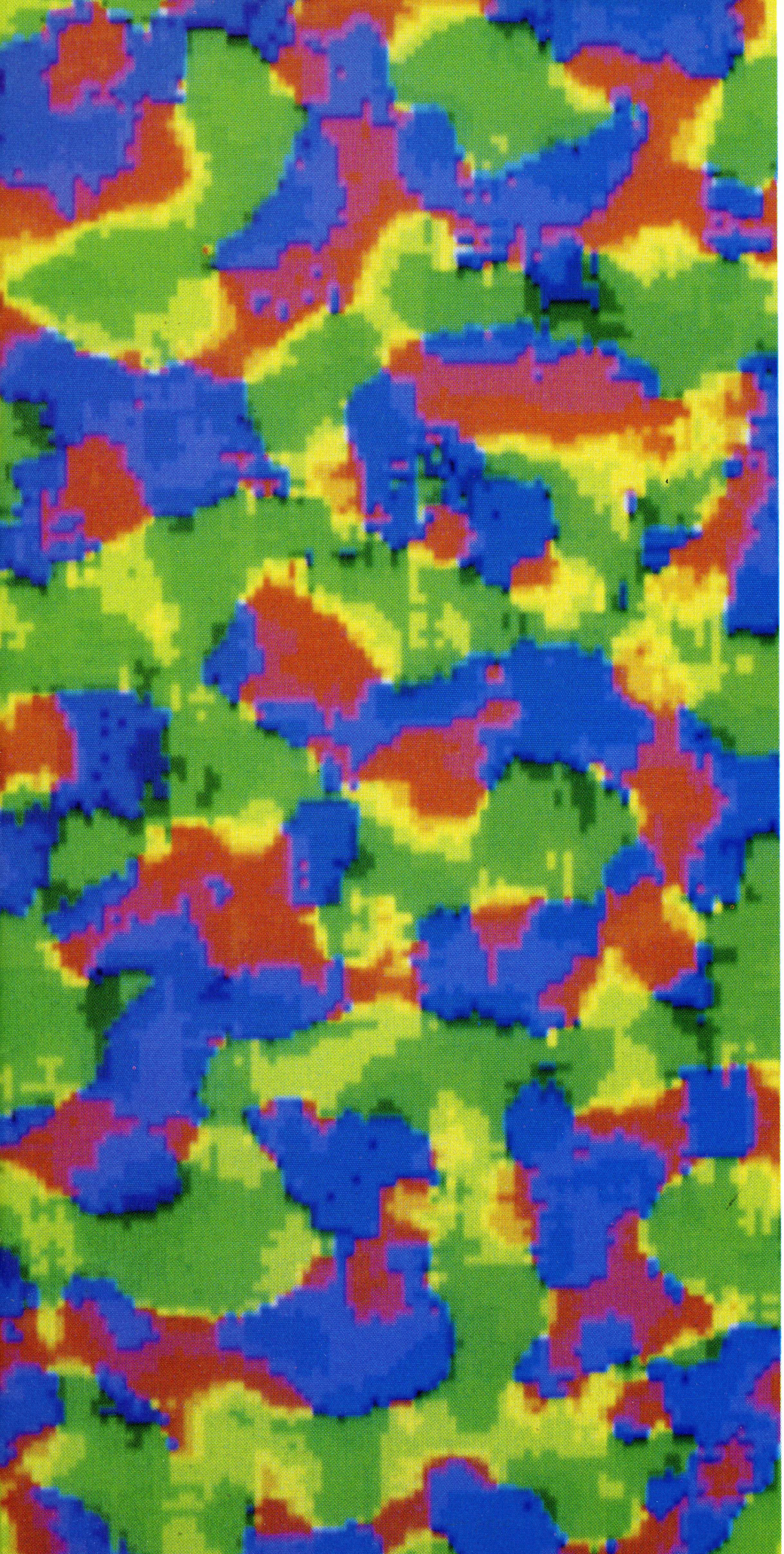
The recombinant DNA revolution of the last fifteen years provided us with the skills to isolate genes at will from a mouse (or a human, for that matter) and to alter them to order. Now that we can add or subtract them at will, a major problem posed by the mouse is no longer an issue—we do not need the impossibly large numbers previously required to find one with a given altered gene. We just alter the gene as we wish. This capability is sufficient to make many investigators willing to cope with the long breeding time and great expense of mice in order to gain the advantage of working with a true human surrogate. Human genetic diseases are, one by one, being mimicked in the mouse, providing an invaluable tool for understanding and treating disease.

The genetically altered mouse provides the ideal tool for investigating the functions of all mammalian genes, whether or not they have been associated previously with disease. Already, genes involved in the development of a fertilized egg into an adult—genes active in both mice and humans—have been altered and their roles defined by examining the defective mouse embryos. Genes involved in the functioning of that most complex system of our bodies, the nervous system, are soon to follow.

For experimental biologists, this adds up to a future of fulfillment of our most fanciful dreams. We can analyze the effect of a normal or altered gene in the context of a complete, living mammal.

The institutional consequences of this new technology are profound. We need to revivify old skills like animal pathology. We need to build new mouse facilities to house the animals who will show us the genetic roots of human biology and human disease. We need investigators willing to invest the years of preparation required to generate the altered mice. We need new resources for these very expensive experiments. Fully realizing the potential of The Decade of the Mouse will test both our institutional flexibility and America's commitment to rapid progress in health research.

DAVID BALTIMORE, President, The Rockefeller University



HOW WE SEE

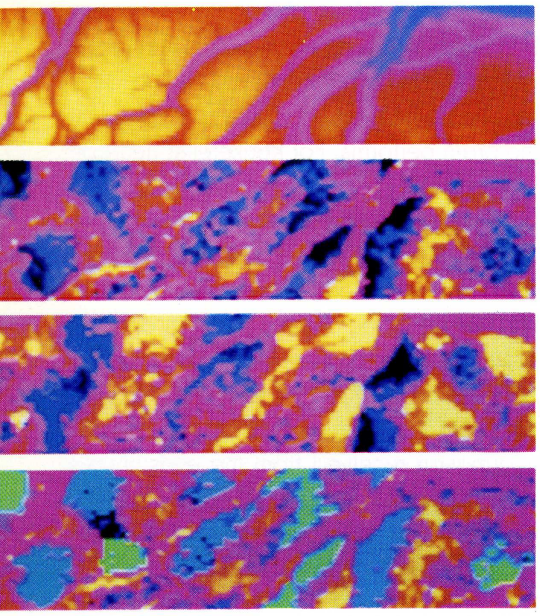
by Sana Siwolop

Since the mysteries of the brain are too difficult to tackle all at once, most neurobiologists have narrowed their studies to focus on one of the many complex functions that the brain performs. For Rockefeller neurobiologist Daniel Ts'o, that focus is vision—the precious and remarkable ability of our brain together with our eyes to see and perceive light from the world around us. In the gradual unravelling of the secrets of vision and the brain, perhaps the most fruitful research has centered on the visual cortex—the region of the brain that is the processing center for information received from the eyes. Ts'o's special contribution to the field has been to develop and employ new experimental methods combined with computer technology to understand how brain cells in the visual cortex interact and cooperate with each other. Says Ts'o, "The way that cells in the visual cortex cooperate and signal each other is what makes the visual system work."

What fascinates Ts'o is that the visual system is so complicated, yet seeing is so deceptively simple. "The amazing thing about vision is that we see and recognize objects so easily—look, here's a desk, here's a chair," says the California-born scientist. "And yet if an engineer were to begin to try to build a machine that can see, it would become obvious that vision is a very difficult thing to do. Even the most sophisticated present-day computer has a hard time recognizing letters, let alone reading and interpreting literature."

The brain's visual system, Ts'o explains, is very much more complicated than an ordinary TV camera. "That is because the brain actually has to recognize objects and make sense of the visual world, rather than just relay pictures. It's true that if you look at how cells in the retina of the eye respond to a visual scene, they only see spots of light, much like a TV camera," says Ts'o. "But a remarkable change happens in the primary

SANA SIWOLOP is a freelance science writer living in New York City. She has been a reporter for *Discover* magazine, and a staff writer for the Science and Technology section of *Business Week*.



Above: Color-enhanced view of the second visual cortical area (top), with stripes (shown in blue) that are sensitive to spatial frequency (whether an object is large or small).

Previous page: Optical map of orientation selectivity in a seven-millimeter portion of the visual cortex. Each different patch of color indicates a region of cells that is selective for a particular orientation—horizontal, vertical, or oblique.

visual cortex," the first stage of processing in the brain. "Cells no longer respond just to spots of light, as in the retina, but rather to the edges of light and dark that form the borders of an object, and only at a certain angle, whether vertical or horizontal or in between."

To make his point, Ts'o picks up a pencil. "Cells in the visual cortex are particularly interested in the borders of this pencil and at what angle they are positioned," he says. To Ts'o, the fact that the primary visual cortex can respond selectively to those borders was "the first clear evidence that the cortex does very sophisticated processing" of visual information, rather than merely receiving it like a TV screen. The implication is that the visual cortex begins to break down a visual scene into distinct objects by detecting the angled lines that form the borders of the objects. Interestingly, more than a century ago, the Impressionist painter Vincent Van Gogh painted pictures that were composed entirely of little, angled lines of color. Perhaps the famous Dutchman had an intuitive sense of how the visual cortex analyzes the visual world.

Ts'o has spent ten years charting that portion of the brain, first as a graduate student in the laboratory at Rockefeller of the pioneering, Nobel Prize-winning neurobiologist Torsten Wiesel, and now as a thirty-four-year-old assistant professor at the university. His research is an effort to carry forward the work that Wiesel, in collaboration with Harvard neurobiologist David Hubel, began some thirty years ago, when they discovered the first architectural principles of the visual cortex. But Ts'o has added a special contribution of his own. Drawing on a long-standing interest in electronics and computers, Ts'o has come up with a number of computer-based technologies that have given the research work powerful new tools to study the visual cortex. Says Wiesel, "Dan has the skill and training to use the computer like you'd use a pen. He represents a new generation of systems neurobiologists."

Ts'o is, in fact, a rare hybrid, part biologist, part computer scientist. The son of immigrants who fled southern China during the Communist takeover, he first tinkered with computers as a teenager growing up in Baltimore. Later, as an undergraduate at Harvard, he started out studying mathematics, then switched to biochemistry, and finally to neurobiology. "Somewhere along the way, I fell in love with the immediacy of physiology," he explains. "You give a stimulus, and the system responds. It's not like biochemistry, where you do a manipulation, grind up some tissue, then hours or weeks later look for some sort of change."

For Ts'o, the journey probing the secrets of the brain began when he joined Wiesel's lab after graduating from Harvard College with an undergraduate degree in electrical engineering. He spent much of his time building a computer system that permitted the display and analysis of the three-dimensional shape of brain cells and their wiring—unlike the flat, two-dimensional view seen in a microscope. But soon Ts'o became even more intrigued with how the brain functions and is interconnected, and so he enrolled in Rockefeller's graduate program, with the Wiesel lab as his base.

During his graduate student years, Ts'o employed another new technique, cross-correlation analysis, to measure just which brain cells were connected to which other brain cells. Those studies revealed that cells in the visual cortex form a buddy system: cells that respond to lines and borders of the same angle talk to each other, and cells that respond to the same color also talk to each other.

No one knows how much more specialization exists among cells within the brain's visual cortex. Is it possible, for example, that somewhere in the brain there is a cell so incredibly specialized it can recognize a specific object, say someone's grandmother? For years, researchers have mused over the possibility of such a "grandmother cell." But

most neurobiologists now doubt such a cell exists. Says Ts'o: "The brain's ability to recognize a certain object or person probably depends more on the cooperation of hundreds of thousands of brain cells, all processing different aspects of visual information, then pooling that information together."

Unfortunately, it still is not easy to study how large groups of brain cells work together. Even a highly sophisticated imaging technology such as positron electron tomography (PET) does not provide a detailed enough picture to study many of the brain's anatomical features. The resolution of these PET scans, for example, is typically on the order of a centimeter or so. By contrast, the columns of cells within the visual cortex that Ts'o has been studying are only fractions of a millimeter wide.

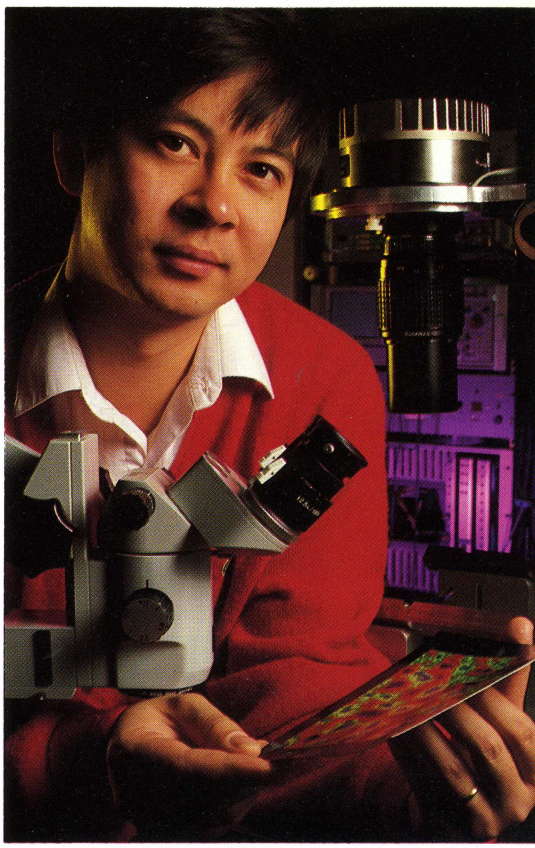
Until recently, researchers who wanted to study the organization of the brain in more detail had to stick a tiny electrode into dozens of different places in the brain, measure the electrical response of individual brain cells to visual stimuli, then piece all this information together. To find a better method, Ts'o pursued another imaging technology by working as a postdoctoral fellow in the laboratory of Amiram Grinvald, a visiting professor at Rockefeller from the Weizmann Institute of Science in Israel. Called "optical imaging," this technology maps brain activity by monitoring changes in optical properties—or light signals—that occur when the brain is active.

Optical imaging used to have a major drawback: it traditionally relied on the use of certain potentially toxic dyes to produce the optical signals needed for the technique, and thus carried the risk of damaging brain cells. However, Ts'o and Grinvald were able to refine the technology to use optical signals that occur naturally in the brain, and therefore eliminate the need for toxic dyes. Says Ts'o, "It still amazes me that without adding anything foreign, in a matter of five or ten minutes you can get a detailed picture of the patterns of brain activity and structure, information that previously took weeks or months of work."

Now, as an assistant professor, Ts'o has already used this new version of optical imaging to collect hundreds of different portraits of the visual cortex within his computer. With a few taps on the keyboard, he can call up these pictures on his computer screen. One shows a polka-dotted pattern of cells that respond to color. Another picture is full of colorful squiggles; each squiggle represents a group of brain cells that likes to see lines and borders at particular angles, whether vertical, horizontal or in between. Still another shows a bold pattern of two alternating bands, light and dark, corresponding to cells that are connected to the two eyes, left and right.

Over the next few years, Ts'o hopes to refine optical imaging technology so that it can be used to study visual processing while a behavioral task is carried out. Eventually the technology may make its way into the operating room; a few neurosurgeons have already asked Ts'o about the technique. At the moment, this new method of optical imaging is helpful to Ts'o and his colleagues, Charles Gilbert and Torsten Wiesel, in their studies probing the workings of the next stage of visual processing in the brain, beyond the primary visual cortex. These studies have already revealed an elaborate and rich organization in the brain for handling the form and color of objects, as well as their position in depth or distance from an observer.

The task of revealing the brain's mysteries may seem too difficult at times. But Ts'o feels he has been given a special mandate. His father, a researcher studying the chemistry of genes, once told him, "My generation will solve the secrets of the cell and the gene. It is up to your generation to solve the secrets of the brain and the mind." Ts'o and his colleagues continue to press on, with new and powerful tools that promise to make the work easier.



Daniel Ts'o studies an optical map of the visual cortex, photographed using the special camera seen on the right. To the left is an operating microscope.

PHOTOGRAPH BY RALPH GABRINER

WHAT CAUSES CANCER?

by Susan Blum

Below, left: Bruce Mayer pursues the puzzle of why normal cells turn cancerous. *Opposite page:* The protein Mayer studies is indicated by the white areas in this computer-generated microscope image of a cell.

ARTHUR LAVINE

To grow, or not to grow? That is the ultimate question for each cell in the body.

A complex biochemical communications network tells a cell how, where, and whether to grow and multiply in response to the body's needs. Is the body still growing? Then cell multiplication must exceed cell death. Is the body full grown? Then cell birth and cell death must be balanced. Is a tissue injured? Then many new cells are needed—and quickly.

While the message varies according to factors like these, one thing remains constant: its communication is normally under strict control. But the regulation can break down, and when it does, the result can be deadly. For, as Rockefeller scientist Bruce Mayer, a thirty-year-old postdoctoral fellow, explains, "cancer is caused by normal growth control mechanisms gone awry."

Why this happens used to be one of science's most perplexing questions. "Ten years ago, if you'd asked cancer researchers why a cell was growing out of control, they'd have said, 'We have no idea.' Today, we can say, 'This is wrong, and that is wrong.' And a lot of our understanding has come from what we have learned about oncogenes," Mayer says.

Oncogenes are once-normal genes that have changed in a way that can make a cell cancerous. They can be transmitted to a cell by a virus, or arise directly within a cell. To understand how oncogenes contribute to cancer, it is important to recall that genes contain a DNA code that provides instructions for making proteins. And it is mainly through proteins that cellular messages are communicated, including the message to grow.

The signalling chemicals the body sends when it is time for a cell to grow, the receptors that register the signals, the messengers that transmit them to the nucleus, and the "transcription factors" that help implement them—all these are proteins, each one coded for by a different gene.

"Growth pathways are very complicated, so a lot of genes have the potential to be oncogenes in a certain cell at a certain time," says Mayer. In fact, he reports, most of the more than fifty oncogenes whose functions are known have turned out to code for proteins involved in growth pathways. Many other oncogenes with as yet unknown functions are also believed to be involved in growth.

Mayer has been studying oncogenes since coming to the university as a graduate fellow in 1984, when he worked in the lab of Hidesaburo Hanafusa, a major figure in oncogene research. Among Hanafusa's contributions is a greater understanding of the oncogene, called "src," first identified in the early 1970s in the virus isolated by Rockefeller's Peyton Rous in 1911. So it was fitting that, while working in Hanafusa's lab, Mayer studied the oncogene contained in CT-10, a virus isolated at the university in 1927—and then forgotten.

The virus became more memorable when Mayer re-examined it using the theories and techniques of modern molecular biology. Like many other scientists doing basic cancer research, Mayer looked at how cells in culture can be transformed, and how they can develop abnormalities in shape, mobility, and other characteristics that make them good models of cancer in humans and animals.

Mayer found that the oncogene in the CT-10 virus, called "crk," coded for a protein that transformed normal cells by changing the activity of other proteins. This was surprising because the crk protein had no "business end"—no region that could account for its function. What it *did* have was two domains, or regions, called SH2 and SH3.

Because similar, though not identical, domains are also found in a number of other growth pathway proteins—including some that can become oncogenic—Mayer and his colleagues believed they might be conferring a function in a modular way. "The question was, *what* function?" he recalls.

Mayer pursued that question when he became a postdoctoral fellow in David Baltimore's laboratory at the Whitehead Institute in Cambridge, Massachusetts. To do so, he studied the SH2 and SH3 regions of the protein coded for by the "abl" oncogene. A form of this oncogene is found in the Abelson murine leukemia virus which, as its name implies, causes leukemia in mice. Another form of the oncogene, one that arises through nonviral mechanisms, is associated with the human disease of chronic myelogeous leukemia.

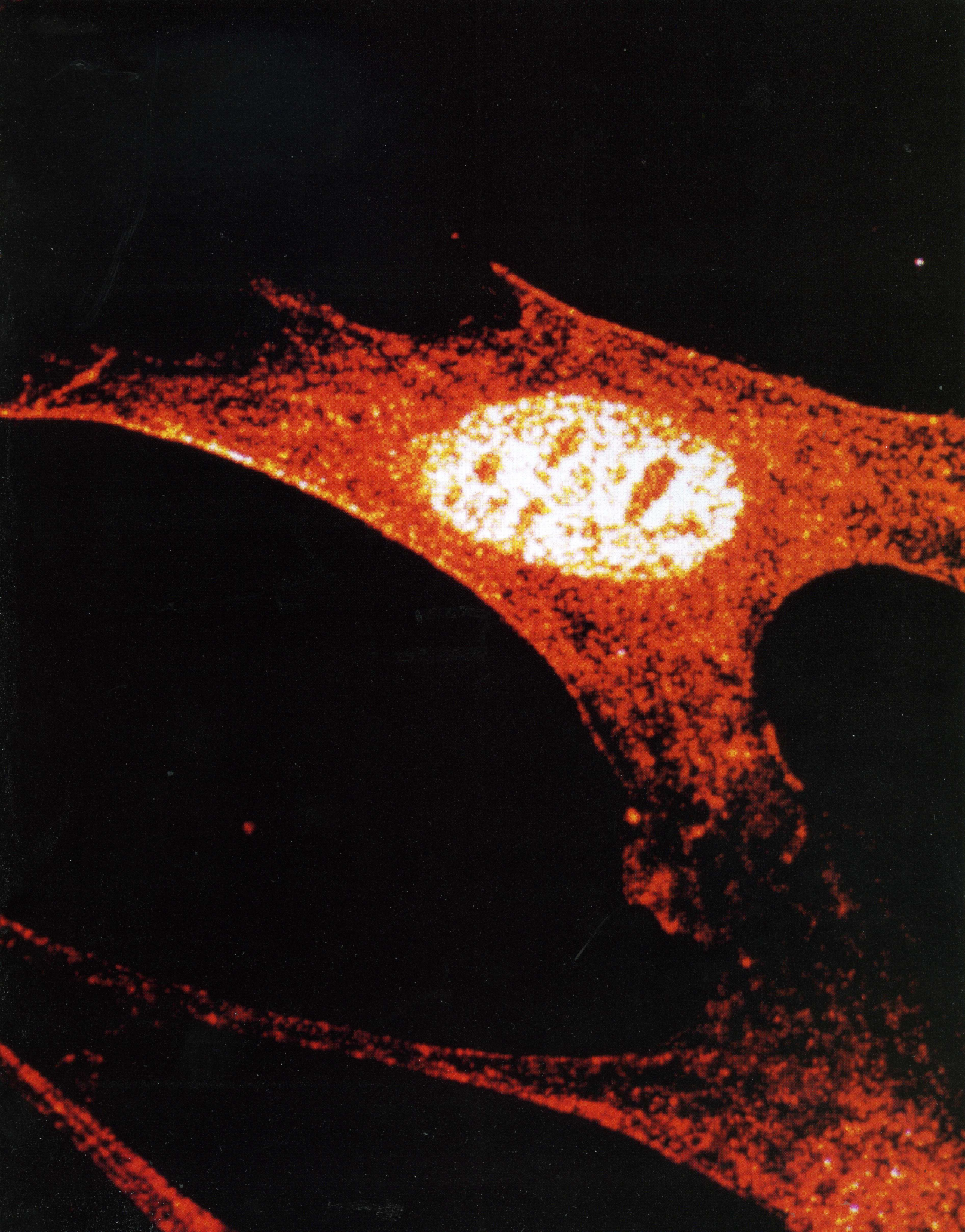
Mayer found that abl's SH2 domain bound to proteins of a particular kind, called tyrosine phosphorylated proteins. This was significant because these kinds of protein play a crucial role in growth pathways. Meanwhile, researchers elsewhere were discovering the same function for the SH2 domain in other proteins.

Now back at the Rockefeller, where Baltimore is moving his lab, Mayer is working to identify the tyrosine-phosphorylated protein that most strongly binds to abl's SH2 domain. "Because it binds with the greatest avidity, this is the protein that is most likely to be physiologically relevant, both in terms of what the normal abl protein might be doing and how the oncogenic protein might be transforming cells," he says.

As a first step in the process, Mayer is purifying the SH2-binding

RICHARD A. VAN ETTEN/PETER JACKSON

SUSAN BLUM is a science writer in The Rockefeller University Public Affairs Office.



protein. When he has enough of it, he plans to locate the gene that codes for it, using the techniques of genetic engineering. With the gene in hand, he will be able to determine the protein's entire amino acid sequence—a first step toward determining its form and function.

Another of his projects is to explore the relationship between abl's SH2 and SH3 domains. "The SH2 domain seems to be the part that's required for transformation, while the SH3 domain seems to inhibit or regulate its function," says Mayer. Indeed, it is mutations or other changes in the part of the gene coding for the SH3 domain that can change the abl protein's normal function (which is still unknown) into a carcinogenic one.

To study the interactions of these two domains, Mayer is working with computer models of the regions produced by colleagues in the Baltimore lab. "The models help clarify your thinking," he said. "They give you a feel for which parts of the protein may be important."

He is also also inducing bacteria to produce the SH2 and SH3 domains, then "putting them through their paces" by making mutations and observing the effects. "Basically, it's a submolecular dissection of how this region of the protein is put together and how it works," Mayer says. "We want to understand it as a little machine. What's this here for? What does that do? What happens if you fiddle with it? Then we'll do structural analyses of the mutations that don't bind, to see what is different and, by extension, what is critical."

Mayer and his colleagues hope some of these investigations will eventually move from the test tube to the living organism.

Researchers in the Baltimore lab have engineered in mice a mutated form of the abl oncogene taken from human chronic myelogenous leukemia (CML) cells. The mice carrying this mutated abl oncogene develop a disease that closely resembles human CML. By studying how SH2 and SH3 mutations affect the oncogene's ability to cause CML in mice, it may be possible to gain important insights into how the human disease develops, and how it might be treated.

These advances will not occur overnight. But the basic research itself keeps Mayer committed."How is a cell stimulated to grow, or not to?" Mayer asks. "It's a fascinating question, one that's relevant not only to cancer, but to development, too. How do you get an egg to grow into a recognizable human being? Some of the cells have to grow at the right time, and others not.

"To me, this is simply the most interesting question in biology, Mayer says. "Why the cell grows, and why it doesn't."

The Making of an Oncogene

Oncogenes are normal genes somehow gone wrong.

Retroviruses can cause genes to change in ways that contribute to cancer. Retroviruses are unusual viruses that carry their genetic information in the form of RNA (ribonucleic acid) rather than DNA (deoxyribonucleic acid). As part of their life cycle, retroviruses are integrated into cellular DNA. While there, they may incorporate a cellular gene or interact with its normal regulatory mechanisms.

The normal cellular gene is known as a proto-oncogene. It becomes an oncogene when its association with the virus changes it in a number of possible ways, all related to the protein for which the gene codes. The change may cause the protein to be produced at a higher-than-normal rate, or it may alter the structure of the protein itself. Either way, the change can help make the infected cell cancerous. In addition, viruses that incorporate the oncogene can transmit it to other cells.

Oncogenes can also arise by means other than infection. A proto-oncogene may be mutated by radiation, chemicals, or spontaneous DNA changes. In this case, too, the cell is pushed toward becoming cancerous by changes in the nature or production of the protein for which the gene codes.

Oncogene-containing viruses are associated with many animal cancers, but the case for viral involvement in human cancers is much less clear. The human T-cell leukemia retrovirus and the Epstein-Barr, hepatitis B, and papilloma viruses (DNA viruses that work differently from retroviruses) are known to be linked with cancers in humans. But so far, most of the major forms of human cancer do not seem associated with viral infection and may depend more on oncogenes that arise in the cell.

Whatever their source, oncogenes are not the whole story in cancer. Other genes, called anti-oncogenes, normally work to suppress cancerous changes, and scientists now believe that they, too, must be mutated or suppressed in some way before cancer develops. Moreover, it seems very likely that more than one oncogene must be activated, and more than one anti-oncogene deactivated, for cancer to occur.

PEYTON ROUS, INQUIRING NATURALIST: CANCER AND THE SARCOMA VIRUS

by Carol L. Moberg

Eighty years ago, a young Rockefeller scientist named Peyton Rous discovered that a virus can cause cancer. This finding challenged half a century of research and 2,500 years of assumptions about cancer as a spontaneous, noninfectious growth. Yet another half century was needed to convince disbelievers that cancer could be caused by a virus, and to consolidate much perplexing knowledge about viruses.

Rous was foremost a naturalist, who was portrayed as "hungry for facts" by his Rockefeller colleague René Dubos. A scrutinizing observer, Rous did not passively witness nature. He generated opportunities where he could explore its complex relationships. At age twenty, he reflected in a wildflower column he wrote for the *Baltimore Sun*, "Naturally, in the strife for existence all sorts of wiles are resorted to." Rous attended Johns Hopkins Medical School at a time when the origin of many diseases was a mystery. Once he became a pathologist, Rous admitted that "everything [he saw] had scientific worth." He described his naturalist's attitude in the tumor virus discovery—turning around Louis Pasteur's famous phrase—as a matter of a "prepared mind making its own chances."

In 1909 Simon Flexner, director of The Rockefeller Institute (now The Rockefeller University), asked Rous to take over cancer research in his laboratory. Despite an early warning in medical school from William Welch, "Whatever you do, don't commit yourself to the cancer problem," Rous accepted Flexner's offer. Institute researchers were then focused on acute infectious diseases such as pneumonia. Experiments concerning degenerative diseases like cancer were considered unproductive by the scientific community. Rous entered a laboratory where the study of viruses was just beginning, yet, within two years, Flexner isolated the virus that causes poliomyelitis, and Rous found a virus that causes a sarcoma tumor.

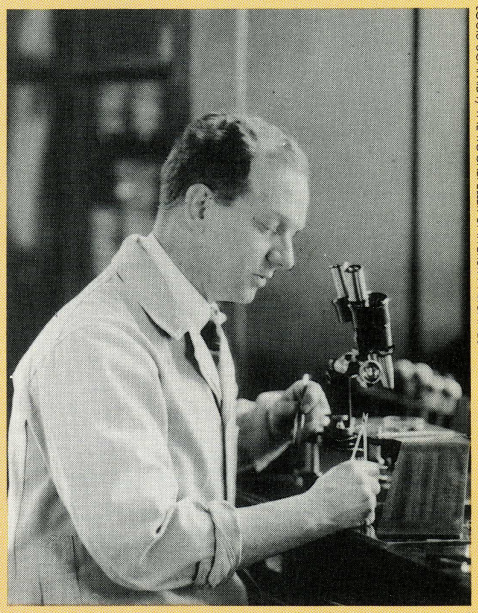
The sarcoma story began by chance. A poultry breeder brought to the Institute a valuable, purebred Plymouth Rock chicken bearing a large breast tumor. Rous was the only Rockefeller scientist interested in the problem. "I transplanted the growth as an aside," he recalled, into some healthy blood relatives of this hen, and they developed the same spindle-cell sarcoma. This was the first known case of the transfer of avian tumor cells from one bird to another.

"About a year after growing this thing," Rous reported, "I began to make experiments on whether an inciting agent could be separated from it....There might be something in that tumor which was different." So Rous inoculated other chickens with a filtrate of this tumor, from which he removed all cells, including cancer cells. Sarcoma tumors grew exactly like the original, and Rous concluded that a virus, too small to be seen with the microscopes of the day, was the cause. What he called the "tumor-producing agent" is now known as Rous sarcoma virus, or RSV. Rous turned a chance experiment into a revolutionary observation about nature.

Reactions to Rous's findings were violent and critical. All previous experience was against a viral hypothesis of cancer causation, though all Rous's evidence was for it. Other scientists dismissed the disease as an inflammation peculiar to chickens. A visiting Englishman scoffed at Rous, "Why, my dear fellow, it can't be a tumor. You've found the cause." In 1922 Rous remarked, "Their offish attitude still goes on...their position [is] impregnable."

Discouraged even further by his unsuccessful attempts to cultivate the virus, Rous admitted it "nearly broke me down," and he wanted to abandon tumor work. Flexner sympathized, saying, "The next most important thing to a good problem is knowing when to quit it." Rous spent more than a decade on other fruitful research. His curiosity about cancer, however, kept him poised to perform a "concrete experiment" with the virus that would prove his theory about the infectious nature of this disease.

In 1932 a major barrier to belief in Rous's theory fell when Rockefeller colleague Richard Shope discovered a virus-caused tumor in mammals. Rous resumed tumor research on these Shope papillomas. "Watching and listening to him," close Rockefeller associate John Kidd remembered, "you perceived at once that the tumor was an evolving biological entity, a part of nature now gone wrong."



LOUIS SCHMIDT/THE ROCKEFELLER UNIVERSITY ARCHIVES

Peyton Rous (1889-1970), a Rockefeller pathologist and Nobelist, isolated a virus in 1911 that can cause cancer.

For the next thirty years, Rous and his colleagues kept the viral theory of cancer causation alive. They discovered that normal cells become cancerous in several stages, and that viruses can collaborate with carcinogens, such as tar, to induce certain types of cancer. Then, after the 1960s, molecular biologists, chemists, and geneticists found other viruses that cause some human cancers. They also learned that viruses act by invading the genes of normal cells. Later, researchers isolated from the Rous sarcoma virus an oncogene, or the gene that causes cells to become cancerous. At long last, the young investigator's discovery had advanced to a dominant place in cancer research.

In 1965, a year before he was awarded the Nobel Prize for finding the relation between viruses and cancer, Rous characterized the paradigmatic nature of his cancer discovery: Viruses are on the down side of life; yet they yield knowledge that soars."

CAROL L. MOBERG, research associate at Rockefeller, is co-editor with Zanvil A. Cohn of *Launching the Antiobiotic Era* (The Rockefeller University Press, 1991). Her current work includes writing an annotated bibliography of the works of René Dubos.

NEW WAYS TO THWART RESISTANT BACTERIA

by Susan Blum

The United States and the Soviet Union may be reducing their nuclear forces, but there is still an arms race going on. It is the one between humans and bacteria and, according to Rockefeller professor Alexander Tomasz, "There is no sign of peace."

In fact, at the moment the bacteria seem to be gaining. Once easily controlled by a variety of antibiotics, many disease-causing bacteria are becoming resistant to one or more drugs.

Take the case of the pneumococcus, a bacterium that can cause pneumonia, meningitis, and middle-ear infections. With the introduction of penicillin in the late 1940s, infections with this organism were easily treated. Then, in 1967, reports out of Australia documented the emergence of a strain of penicillin-resistant pneumococcus. Still, infectious disease experts were not overly concerned, for they believed it highly unlikely the aberrant bacterium would spread.

They were wrong. In 1977, public health officials in South Africa reported the outbreak of pneumococcal disease caused by strains with a thousandfold-greater resistance to penicillin, and by the end of the 1980s, Tomasz says, "penicillin-resistant pneumococci had become worldwide pathogens." The latest evidence comes from Hungary, where a report in 1989 showed that seventy percent of the pneumococcal strains infecting sick children and nearly sixty percent of those found in adults are resistant to penicillin—the highest percentages found so far in the world.

Resistance figures like these are nothing new for another bacterium, *Staphylococcus aureus*. Strains of this bacterium, which can cause serious infections in hospital patients, first developed resistance to penicillin soon after the drug was introduced; by now, says Tomasz, "penicillin-resistant staph is all over the place." To counter the resistance, a related drug called methicillin was developed in 1960; within five years methicillin-resistant bacteria could be found in Europe, Japan, Australia, and the United States, and today methicillin-resistant staphylococci are a major problem in many hospital settings.

"These bugs travel," Tomasz says. "The rule seems to be that whenever resistance is reported in some corner of the world, as time goes by it will find its way to other parts of the world as well."

The problem is compounded by the fact that many bacteria, including pneumococci and staphylococci, are becoming resistant to more than one antibiotic. Some, such as the enterococci (another frequent cause of hospital infections) are resistant to all but one commonly used drug—and some strains of enterococci have been isolated that are resistant to that one, too.

It is not just the organisms' geographic spread and increasing multi-resistance that are causing concern. Researchers are equally struck by the varied and sophisticated mechanisms bacteria have developed to outwit their antibiotic opponents.

In pursuing the arms race, drug designers aim to destroy the bacterium by "finding a target that is in the bug, but not in us," Tomasz explains. In response, the "bug" may use one of two counter strategies: protect its target by preventing the drug from arriving, or change the target itself so the drug will not react with it.

Scientists have long understood many of the ways bacteria achieve the former strategy. But only lately have they discovered the newer, more complicated, and quite extraordinary measures bacteria such as pneumococci take to achieve the latter.

Pneumococci need a sturdy cell wall to survive. Penicillin works by binding to (and thus blocking) the enzymes the bacteria use to bring the wall's building blocks together. By changing the enzymes, pneumococci have been able to foil penicillin, but at a price: they also must change the cell wall components used by the enzymes. According to Tomasz, this strategy represents nothing less than "a real evolutionary change, because so much more of the bacterial physiology is involved."

The implementation of this strategy is remarkable, indeed. "To rebuild the target protein, pneumococci have borrowed big blocks of foreign DNA from other, as yet unidentified bacteria," Tomasz reports. Moreover, they must develop mutations in their "native" genes, to direct production of the altered cell wall components.

Many bacteria are becoming resistant to antibiotics. Alexander Tomasz is on the forefront of research exploring how this resistance develops and spreads.

RALPH GABRINER

Methicillin-resistant staphylococci pursue similar strategies to outfox their chemotherapeutic combatant, as do other bacteria such as the one that causes gonorrhea.

Tomasz and his team of international researchers have made major contributions to the current understanding of how antibiotic resistance develops and spreads. For instance, the Rockefeller group discovered the pneumococcus's ability to change its penicillin target enzymes and build an altered cell wall, and, with collaborating labs in the United States, Britain, and Germany, showed how a resistant strain can spread from one country to another.

Today, the team's work on antibiotic resistance continues on a number of fronts. The lab is the center of a major project to document the incidence of highly resistant pneumococci in the former Eastern Bloc countries. "There is reason to believe the situation in Hungary is just the tip of the iceberg," Tomasz says. To gauge the extent of the problem, Tomasz is coordinating a network of investigators in Hungary, Czechoslovakia, Poland, Rumania, Bulgaria, (formerly) East Germany, and the Soviet Union, who will collect and analyze strains of pneumococci. A fund to support this effort has been established by the university and Tomasz and his colleagues are now garnering contributions for this vitally important international research.

In the best of all possible worlds, such international cooperation would help curtail the major cause of antibiotic resistance: the overuse of the drugs in humans and animals. Whether for economic, sociological, or cultural reasons, too many countries make antibiotics too easy to get. And unless all countries stop, none can be safe. "It's an environmental issue. You can't handle it locally," Tomasz says.

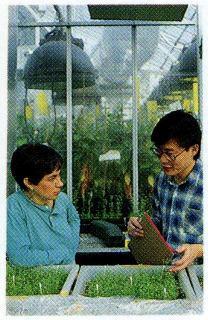
But Tomasz believes such a unified stance is unlikely. That means researchers must keep the arms race escalating to maintain control on the bacterial battleground.

Fortunately, humans are still smarter than bacteria. The organisms may have evolved more sophisticated resistance strategies, but scientific understanding has evolved, as well. With the concepts and techniques of molecular biology, it is possible to explore such questions as how bacteria import foreign DNA, how they use it to produce new wall-building enzymes, and how they mobilize and mutate their own genes to accommodate the new conditions created by the foreign imports. Tomasz believes the answers to these and other questions will provide fundamentally new approaches to the design of antibiotics

"Bacterial resistance will provide a new rallying point for molecular biologists interested in basic research to join forces with people concerned with public health problems," Tomasz says. It is clear he has high hopes for this new strategic alliance.

REMODELLING PLANTS TO FEED THE WORLD

by Catherine Vanchieri



New York City may seem an unlikely destination for a scientist who wants to help launch a new agricultural revolution. For biochemist Loreto Holuigue Barros, though, the Rockefeller University campus was an obvious choice.

In January 1990, Holuigue, age thirty-four, began a postdoctoral fellowship with Professor Nam-Hai Chua, whose work focuses on plant molecular biology. An emissary from the biological sciences faculty of the Catholic University of Chile, in Santiago, Holuigue has come to master the recombinant DNA technology that is being used with increasing success to genetically transform plants, and that one day soon may transform world food production as well.

Before that day arrives, though, Holuigue and her colleagues must learn more about the structure of plant genes and the molecular mechanisms that regulate their activity—a prerequisite for the strategic transfer of genes carrying desirable traits from one species to another. There is a lot to learn. The genetic endowment of plants may be even more complex than the genomes of bacteria or animals. It is certainly larger: a cell from a string bean probably contains ten times more DNA than a human cell.

For the most part, Holuigue works with tobacco and a small weed known as *Arabidopsis thaliana*, favorite laboratory specimens of the plant molecular biologist. One of her projects builds on a long-term effort by Chua and his research team to understand at the molecular level how various aspects of plant development and function are regulated by light.

Scattered throughout the genetic material of a green plant are DNA sequences that act as light-responsive switches: when the plant is exposed to light, the genes associated with these switches, or LREs (light-responsive elements), become activated. Having identified several LREs, scientists in the plant molecular biology laboratory are trying to sort out the complex interactions that must occur between these DNA sequences and various plant cell proteins in order to trigger light-regulated genetic activity.

To identify a few more pieces of this molecular puzzle, Holuigue is studying a mutant strain of *Arabidopsis* that undergoes what are normally light-dependent developmental processes even when the plants are kept in darkness. She makes her own light-responsive genes by attaching various LREs to a bacterial gene. After introducing these gene constructs into both mutant and normal *Arabidopsis* plants, she compares their activity to determine which LREs play a role in normal development.

On a second major project, Holuigue recently teamed up with Xiao-Feng Qin, a twenty-six-year-old scientist who is also far from home. Qin arrived at Rockefeller in October 1989 from the People's Republic of China, where a year earlier he had earned a master's degree in molecular virology and genetic engineering from the Academia Sinica, in Beijing. A member of the first research team to create transgenic plants in China, Qin is one of a series of investigators from the Academia Sinica who have spent time in the Chua laboratory. Both Qin and Holuigue note that successful young scientists in their homelands normally travel to the state-of-the-art laboratories of the United States or Western Europe to augment their training.

Qin is especially intrigued by molecular similarities in the biochemical and genetic regulatory circuitries of plants and animals. His collaboration with Holuigue is aimed at delineating the series of molecular events that occurs when a plant mounts a defense response to a bacterium, fungus, or virus.

More than ten years ago, researchers discovered that exposure to a pathogen sometimes increases a plant's resistance to subsequent pathogen attack. A similar effect can be provoked by spraying even a few leaves of a plant with salicylic acid, a chemical closely related to common aspirin. Recent evidence from other laboratories suggests that endogenous salicylic acid may play an important role in the plant defense response, acting as a systemic chemical signal that announces the presence of a pathogen and activates biochemical defense mechanisms that constitute the plant-equivalent of the human immune system.

Recently, Qin and Holuigue found that several genes involved in the plant defense system contain a regulatory sequence responsive to salicylic acid. In studies with transgenic tobacco plants, they are working to trace the series of molecular signals that begin with salicylic acid and result in the activation of these plant defense genes. A better understanding of this signal pathway may provide clues for improving the plant defense response.

Paradoxically, the salicylic acid produced by plants in response to pathogen attack

CATHERNIE VANCHERI is a science writer and fundraising writer in The Rockefeller University Development Office.

ARTHUR LAVINE

Opposite, left: Loreto Holuigue and Xiao-Feng Qin discuss *Arabidopsis* plants in their laboratory's rooftop greenhouse. *Right:* Holuigue examines a tobacco plant. She and her colleague Qin study genetically engineered tobacco plants to unravel the mechanisms plants use to fight viruses and other pathogens.

may increase the intensity of some viral infections. Holuigue and Qin have discovered that the genetic material of several common plant viruses contains the same salicylic acid-responsive regulatory sequence found in the plant defense genes. Future studies in this laboratory will explore the possibility that the presence of this sequence in the viral DNA may play a role in the ability of certain viruses to circumvent the plant defense system.

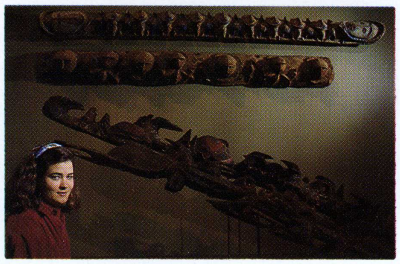
In June 1991, Holuigue will return to her post as an assistant professor in Santiago, where she will continue her research, resume teaching, and play a central role in developing her university's new program in plant molecular biology. She believes that her investigations of the pathogen defense response, in particular, may have important implications for Chile, which depends heavily on agricultural productivity.

Holuigue points out how important it is for developing nations to have their own scientists who can interpret and contribute to the biotechnological advances that are helping to improve living conditions around the world. Qin, who is applying to doctoral programs at Rockefeller and other universities in the United States, also stresses the importance of basic research, which will provide the foundation for future advances in plant engineering.

Before long, an intellectual harvest of research by Holuigue, Qin, and their colleagues around the world may make it possible to design new crop plants that will withstand disease and unfavorable growing conditions, require less fertilizer and fewer pesticides, produce higher yields per acre, and offer increased nutritional benefits to the world's rapidly expanding population.

RESEARCH IN NEW YORK: A MANHATTAN SERENADE

by James M. Keller



Top: Marcia Simpson at work in a laboratory at The Rockefeller University. Her research focuses on the gene in fruit flies that determines where and in what shape body parts are formed. *Above*: Relaxing after the rigors of laboratory work, Simpson visits The Michael C. Rockefeller Wing for Primitive Art at The Metropolitan Museum of Art, within walking distance of the university.

Much of Marcia Simpson's professional activity centers around the intersection of York Avenue and Sixty-eighth Street. Simpson, age twenty-seven, is a fourth-year student in the Rockefeller-Cornell M.D./Ph.D. program. For Simpson, this corner has come to symbolize her career goals—the merging of scientific research and medical practice: The Rockefeller University, with its emphasis on biomedical research, extends to the south, and the New York Hospital-Cornell Medical Center, a hospital and medical school, occupies the expanse to the north.

During her first two years in the M.D./Ph.D. program, Simpson spent most of her time on the Cornell side of the intersection, fulfilling the basic medical school requirements that would lead to the Level I medical boards. A four-week subclinical internship followed, during which Simpson made medical rounds with attending physicians. "An internship of that length can't make you an expert," she says, "but it can provide a flavor of various clinical areas."

Simpson still crosses the street to Cornell for occasional classes and seminars, or to discuss medical cases with her medical school adviser, Cornell's Dr. Roy Silverstein. She will return to Cornell's wards for a fifteen-month total immersion in medical studies at the end of her training. But for the past year and a half, Simpson has been engaged mostly in working towards her Ph.D. in the laboratories and libraries on the Rockefeller side of the street.

Her lab work these days focuses on pattern formation in *Drosophila*, or fruit flies. She is studying a gene that contributes to the correct formation of body parts in their proper locations. Simpson presented portions of her research work in poster sessions at the *Drosophila* Research Conference, sponsored by the Genetic Society of America last spring in Monterey, California, and will do so again at the same conference this spring in Chicago.

Molecular biology has not always been high on Simpson's list of interests, but she changed her mind when she encountered Claude Desplan, an energetic young Rockefeller scientist doing research in this area. "I was the second student to become seriously involved in his projects," reports Simpson. "Since then, three more students have joined him, and in the past two years his lab has doubled in size." It is not unusual for that to happen around Rockefeller—a specialized, self-standing enterprise develops around the work of a single, magnetic researcher.

What drew Simpson to this program in the first place? "To start with," she explains, "there was the double-degree program, which in six or seven years leads to both the M.D. and the Ph.D. This fit in with my goals. Then, too, Rockefeller has a reputation for encouraging students to devise their own customized educational programs. The university provides the faculty and facilities and resources, but

In addition to writing on the arts for *Musical America*, *The Piano Quarterly*, *Hudson Valley*, and *The New Yorker* (where he works on staff), JAMES M. KELLER has written widely on pharmaceuticals and biotechnology for public corporations.

doesn't dictate how the students have to use them. This makes the students themselves responsible for their education, and I like that."

And finally, there was New York City itself, with its unlimited cultural and recreational opportunities. Simpson is a native New Yorker who grew up in the City. "When I was in college at Amherst," she says, "I realized that if I were going to commit to spending seven years somewhere, New York was one of the few places that I knew could sustain my interest that long. Don't get me wrong; I loved my years at Amherst. But I knew that I wouldn't have much time for leisure activities in an M.D./Ph.D. program, and I didn't want to be somewhere where I'd have to drive forty-five minutes just to get to these activities."

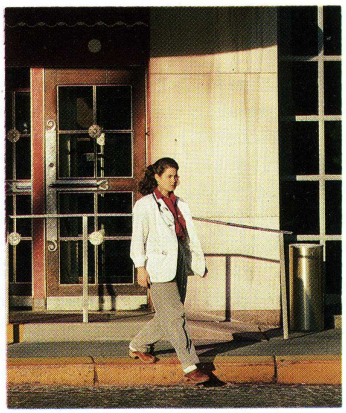
One would assume that a person learning to be a research scientist and a physician would have very little time for such activities, but Simpson is much involved in the educational and cultural life of New York. For a starter, there is her extracurricular science. During her undergraduate summers and "winter term" each January, Simpson was involved in an electron microscopy project at the New York University Medical Center. Still fascinated by the project, she often takes the short bus ride downtown to keep involved.

Then there is her physical well-being. "I run four or five times a week," she reports. Is this a leisurely jog, we wonder? "Well," she continues, "a year ago I ran the New York City Marathon. Now I'm taking a running class in Central Park with the New York Road Runners Club. I also take advantage of the gym and the Nordic track here at Rockefeller, so maybe I'll go for the Marathon again in '91."

Every now and then Simpson rewards herself with a trip to the theater or to one of the City's many museums. It is a pleasant stroll from Sixty-eighth and York to the Frick Collection or the Metropolitan Museum. More often, though, Simpson finds herself at the Producer's Club, in the Broadway theater district, where she volunteers as an associate producer for "Sneakers," a professional rock group for children.

"Sneakers puts on shows targeted at kids between three and twelve years old," she explains. "Our shows encourage kids to have good feelings about themselves, and to help them appreciate people who may have characteristics different from their own."

Simpson will be getting married this August. In thinking about her future in medicine and research, she reflects, "The whole field is changing so quickly! I don't believe that the practice of medicine will go on as we know it, with the enormous changes in people's attitudes and in society. Already there's a change in medical education—towards more complete understanding of the patient, as well as the disease. For me, the future may involve both fundamental research and/or something resembling a medical practice, which is why I chose this double-degree program in the first place. Just how I will end up, I can't say for sure, but this I do know: I'll be prepared for the opportunities, wherever they are."



Top, left: A marathoner, Marcia Simpson takes an early morning run along the East River next to the university. *Top right:* Simpson leaves New York Hospital and heads towards Rockefeller across the street. Though currently engaged primarily in laboratory research at the university, she still spends time at Cornell, attending seminars and classes, or discussing medical cases. *Above:* Volunteering as an associate producer for the rock group *Sneakers* affords Simpson the opportunity to work with children.

PHOTOGRAPHS BY CATHERINE NOREN

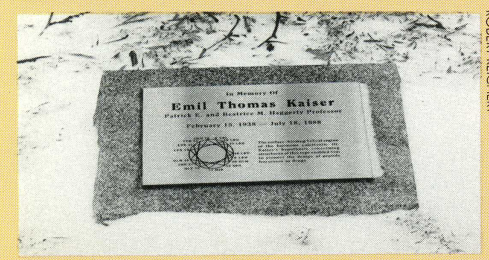
CAMPUS NEWS

EMIL THOMAS KAISER REMEMBERED

Rockefeller professor Emil Thomas Kaiser was a scientist of tremendous creativity and originality. His research focused on the chemical, physical, and biological properties of proteins, and his work on synthetic enzymes and other polypeptides advanced scientific understanding in ways that had important implications for medicine.

Kaiser's sudden and premature death in July 1988 from complications following a kidney transplant was a blow to the entire Rockefeller community. "Not only was Tom Kaiser a brilliant and innovative scientist, but he also had a deep personal regard for his colleagues and friends at the university," said John Taylor, assistant professor in the laboratory Kaiser founded in 1982.

Soon after Kaiser's death, members of the lab planted an "October glory" maple tree in front of Caspary Hall to serve as a living tribute to his memory.



ROBERT REICHERT

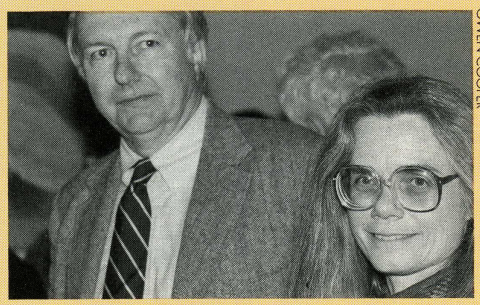
The memorial plaque dedicated to Dr. Kaiser.

On December 3, 1990, the tree graced the path to a day-long symposium held in Kaiser's honor, entitled "Proteins: Design and Function."

Organized by Taylor and Stephen Burley, assistant professor and head of laboratory, the symposium was attended by some 200 persons. It brought together six scientists working in research areas directly related to the design of new protein catalysts, Kaiser's special field of interest. The speakers were David Eisenberg, University of California, Los Angeles; William Lipscomb, Harvard University; James Rothman, Princeton University; Angela Gronenborn, National Institutes of Health; William DeGrado, E.I. du Pont de Nemours and Company; and Donald Hilvert, Research Institute of Scripps Clinic.

Rockefeller's president David Baltimore introduced the symposium saying, "The program for this meeting very effectively traces Tom's development from a pure chemist, to a biochemist, to one of the most audacious and one of the first protein designers. Meanwhile, the wonders of modern molecular genetics have made amateur protein chemists out of many biologists such as me, providing through DNA sequence a wedding together of the black arts of biochemistry and cell biology. Tom was at that interface even before its existence was recognized by most of us."

As a complementary tribute to Tom Kaiser's career, his former graduate students and postdoctoral colleagues contributed summarized accounts of many of his most important publications. These accounts, which were presented in the symposium's program, provided



OWEN COOPER

Vice President for Academic Affairs James Darnell and Bonnie Kaiser, widow of Emil Thomas Kaiser, at the symposium held in Kaiser's honor last December.

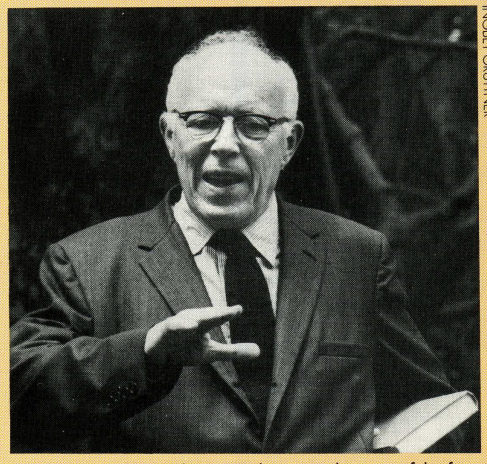
an eloquent description of the development of Kaiser's research career from its early insightful contribution to bioorganic chemistry, through its visionary period at the University of Chicago, to the maturing stage that was just beginning at the Rockefeller University before Kaiser's untimely death at the age of fifty.

At midday, those assembled to remember Kaiser and his work gathered outside Caspary Hall. There, in the presence of Kaiser's widow, Bonnie, and his father, Emil Kaiser, Sr., John Taylor dedicated the memorial plaque in front of the tree that symbolizes the scientist's enduring presence on campus.

FROM THE ROCKEFELLER UNIVERSITY PRESS

Almost everyone today owes his or her life or health to treatment with an antibiotic. Infections that only fifty years ago meant certain death can now be cured. While much is known about the "miracle cures" resulting from the use of antibiotics, very little has been published about how these drugs were discovered.

A new book, *Launching the Antibiotic Era: Personal Accounts of the Discovery and Use of the First Antibiotics*, edited by Carol L. Moberg and Zanvil A. Cohn and published by The Rockefeller University Press, brings together for the first time the several human accounts of the efforts that launched what is now called "the antibiotic era." Six pioneering scientists describe the excitement of a time in which one biological or chemical triumph after another led to a transformation in the therapy of infectious diseases.



INGBET GRÜTTNER

René Dubos (above) discovered gramicidin, one of the first antibacterial agents to be used clinically and produced commercially. The fiftieth anniversary of Dubos's discovery was celebrated in 1989 with a commemorative symposium at the university. *Launching the Antibiotic Era* represents the proceedings of that symposium.

SCIENCE BRIEFS

DEVELOPING A VACCINE AGAINST GONORRHEA

by Ruth Coxeter

It may be surprising to learn that people have more bacteria than cells in and on their bodies. Generally, these guests seek to be commensal, or to live in harmony with their host. At times, however, bacteria invade the skin or mucous membrane, escape destruction by the body's immune system, and cause infection.

Assistant Professor Lee Wetzler's fascination with this kind of host/parasite interaction brought him to The Rockefeller University to work with Professor Emil Gotschlich in developing a vaccine against *Neisseria gonorrhea*, the bacteria responsible for causing gonorrhea. Gotschlich had already received the prestigious Lasker Award for developing a vaccine against another Neisserial strain, *Neisseria meningitidis*, which causes meningococcal meningitis.

RALPH GABRINER

Lee Wetzler

Gonorrhea bacteria infect about one million people in the United States each year, costing close to one billion dollars annually for diagnosis and treatment. These figures may rise because of the increase in the resistance of gonococci to penicillin, an antibiotic used to treat it. In addition, it is suspected that infections such as gonorrhea increase the likelihood of the transmission of AIDS.

Developing a vaccine against gonorrhea is not an easy task. As humans appear to be the only host of the gonococcus, research using animal models is not adequate to test a vaccine. Methods of preventing the infection may only be tested in humans. Wetzler, age thirty-four, working with Gotschlich and another university scientist, Milan Blake, has discovered what may prove to be an effective vaccine against gonorrhea. The team is currently planning a human trial of the vaccine at The Rockefeller University Hospital. They will innoculate about fifty volunteers with the vaccine. This will test the ability of the vaccine to induce immunity. This phase of the testing process will take at least one year. If successful, it would still take several

more years of testing before the vaccine could be placed on the market.

RUTH COXETER is a production editor for *The Journal of Cell Biology*, published by The Rockefeller University Press. She is currently working on her master's degree in English literature at City University of New York.

SCIENCE BRIEFS

PREVENTING ENDOTOXIC SHOCK

by Susan Blum

The cells of the immune system work in a remarkably complex way to guard against infection and other illnesses. Generally the system's vigilance helps maintain health. But sometimes elements of the immune system overreact to cause serious illness or even death.

That is what happens in endotoxic shock, a potentially life-threatening condition.

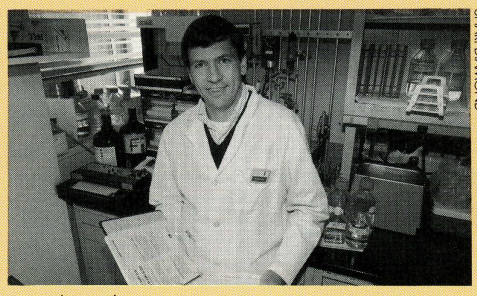
Endotoxic shock is particularly common in patients hospitalized for cancer, AIDS, trauma, or surgery. It occurs when cells of the immune system respond to endotoxins, molecules produced by gram-negative bacteria. As part of this response, immune cells called macrophages produce a flood of substances including prostaglandins, leukotrienes, interleukin-1, and tumor necrosis factor (TNF). An overabundance of these substances can cause a spiral of events that results in the multiple organ failure and plummeting blood pressure characteristic of endotoxic shock.

There is currently no treatment for endotoxic shock. But research conducted by Samuel Wright, age thirty-eight, an associate professor at the university, is pointing the way to one new approach to the problem—stopping the overproduction of TNF before it begins.

Wright and colleagues at The Research Institute of Scripps Clinic discovered that a special protein in the blood, called LBP, combines with the endotoxin in gram-negative bacteria. The LBP/endotoxin complex can then link up with receptors on macrophages. These receptors, called CD14 receptors, directly or indirectly trigger the TNF response.

Researchers had known about CD14 receptors for many years. The surprise came when Wright discovered that rather than being "benign," as had been believed, the receptors are actually involved in the chain of events that can lead to endotoxic shock. The therapeutic implications of this discovery are exciting. It may be possible to use antibodies directed against the CD14 receptor and block its ability to link up with the LBP/endotoxin complex, thus short-circuiting the pathway to disease.

Wright believes his discoveries may have implications for infections with gram-positive bacteria, as well. These bacteria do not produce endotoxins, but can produce reactions that are clinically indistinguishable from endotoxic shock. Wright speculates that the mechanism for this reaction may also involve the CD14 receptor and an overproduction of TNF. If that turns out to be true, receptor-blocking strategies may protect against a wide range of potentially fatal threats.



SHARI DIAMOND

Samuel Wright

PHILANTHROPY'S ROLE IN RESEARCH: THREE CASE STUDIES

by Thom Hunter

Members and guests of The Rockefeller University Council learned firsthand of the impact of philanthropy on scientific programs at the university this fall. Featured speakers at the October 4 program were representatives of three philanthropic organizations and the Rockefeller scientists whose work they have chosen to sponsor.

During the program, the philanthropists offered these observations:

"Scientific research is simply not getting the financial support that it needs."—Irene Diamond, President, The Aaron Diamond Foundation.

"It is important to get your feet wet, not to wait until you know everything about an area, but to seek advice from people working in the field."—Vincent McGee, Executive Director, The Aaron Diamond Foundation.

"The way to make innovation happen is to take the shackles off and encourage people to take risks."—Rebecca Rimel, Executive Director, The Pew Charitable Trusts.

"The best and the brightest are here (at Rockefeller) and if you want to have an impact, I think this is the place to begin."—Anne Dyson, President, The Dyson Foundation.

Scientists who have received support from the foundations described how grants from private organizations served as a catalyst for discovery in their research programs. The grants supported an advance in pediatric medicine; a new study of AIDS; and a program in nutrition, a neglected area of research.

CASE 1

JAUNDICE IN NEWBORNS
The Dyson Foundation

As a pediatrician, Anne Dyson was interested in biomedical research that would have clinical applications for children. She had spent a year of her medical residency at Rockefeller and knew that two scientists here—Professor Attallah Kappas, physician-in-chief at the hospital, and Associate Professor George Drummond—had been conducting basic research that might be applicable to pediatrics. Their findings suggested that it might be possible to block the body's production of a toxic substance—bilirubin—that causes problems in newborns ranging from jaundice to brain damage and death.

Kappas and Drummond had conducted much of their basic research with funding from the National Institutes of Health. The NIH grant, however, would not allow them to extend their research to clinical investigation. At this critical juncture, in December 1981, the Dyson Foundation stepped in. As Dyson put it, her foundation was able to support "a clinical application in pediatrics that is still bearing fruit."

For more than a dozen years, Kappas has studied the biochemistry of heme, a compound involved in many basic cellular functions. Perhaps best known as the red pigment in blood, heme has a four-ring molecular structure with an iron atom at its center. When red blood cells break down, heme is degraded in a two-step enzymatic pathway to bilirubin, the yellow pigment of jaundice. Normally, bilirubin is processed by the mature, healthy liver and excreted in bile. But if the liver is impaired by hepatitis, cirrhosis or other disease, or if the liver is immature, as in many newborns—bilirubin accumulates dangerously, resulting in jaundice, neurological abnormalities and sometimes death.

Kappas and Drummond produced a synthetic heme with tin, rather than iron, at its center. Tin-protoporphyrin, they found, is not converted to bilirubin when broken down. Moreover, tin-protoporphyrin prevents the breakdown of natural heme and thwarts the production of bilirubin.

Eventually, Kappas and Drummond established the safety and effectiveness of tin-protoporphyrin in animals tests and received Food and Drug Administration approval to administer it to adults. The support from the Dyson Foundation permitted its later application in pediatric medicine.

Clinical trials with infants in Athens, Greece, were successful, attracting the notice of pediatricians around the world. The Dyson Foundation continues to provide the funding Kappas and Drummond need to extend their studies and apply their findings to important problems in pediatrics. This support, Kappas says, "gives us a great sense of satisfaction," for it is helping to advance research that may ultimately benefit millions of children.

CASE 2

EARLY AIDS RESEARCH
The Aaron Diamond Foundation

During the past decade, outstanding scientists in increasing numbers have switched their attention to AIDS research. At Rockefeller, the first to tackle the disease were Professors Zanvil Cohn and Ralph Steinman. Cohn is widely regarded as an expert on macrophages, large scavenger cells that play an important role in the immune system. The long-time collaborators are also known for their discovery of the dendritic cell, a key component of the immune system.

As immunologists, Cohn and Steinman believed their AIDS project was a logical extension of previous studies in immunology. Their knowledge and techniques were directly applicable to research on the

human immunodeficiency virus, HIV, the causative agent in AIDS, but when they applied for NIH funding in the mid 1980s, the response was a classic Catch-22: because the Rockefeller scientists had not studied AIDS in the past, the NIH was not enthusiastic about funding their study. Of course, few had done AIDS research; it had only been recognized as a disease for a few years.

Eager to start what they believed was a vitally important research effort, Cohn and Steinman turned to a new private foundation for help: the Aaron Diamond Foundation. AIDS has been a primary concern of the Diamond Foundation since its founding in 1985. Today, the foundation is the largest private source of support for AIDS research in the United States, because, as its president, Irene Diamond, explains: "If we ever find answers to this catastrophic disease, they will come from scientific research. Unfortunately, this research is simply not getting the financial support that it needs."

The work that the Diamond Foundation has funded at Rockefeller builds on a long history of retrovirus research and studies in immunology and related fields that come together in the university's AIDS research. "This is the kind of pattern we have been looking for in research institutions," Vincent McGee said.

In 1986, with Diamond support, the Cohn-Steinman laboratory launched its new study of AIDS. Later, NIH joined in funding the research. Since then, the laboratory has made a number of important findings and focused considerable attention on interleukin-2, or IL-2, a protein molecule that plays a crucial role in effective immune response. The Cohn-Steinman laboratory is now conducting experiments to determine if the immune responses of HIV-infected individuals can be enhanced with regular skin injections of a long-acting form of IL-2. Their earlier work suggests that IL-2 may help these patients produce some of the cells and molecules that could help them fight the secondary infections that eventually kill people with AIDS. This work continues to receive support from the Diamond Foundation.

CASE 3

NUTRITIONAL SCIENCE
Pew Charitable Trusts

Each year, Americans spend more than $30 billion on diet pills, spas and a variety of products and services to help them lose weight. By contrast, the NIH allocated only $60 million last year for all research related to nutritional science.

According to Rockefeller professor Jules Hirsch, research in nutritional science has lagged far behind studies in other fields where new data and techniques from molecular biology and genetics have been used to tackle clinical problems. Equally important, Hirsch said, students in science and medicine show little interest in nutritional science research.

To help correct these disparities, Hirsch wanted to encourage young people to enter the field and enlist their help in finding new ways to build bridges between basic research in biology and clinical investigations in the nutritional sciences. His ideas were greeted with enthusiasm at the Pew Charitable Trusts—a foundation that had made a serious commitment to funding research in neglected areas of science and to developing programs to encourage young people to pursue careers in the health sciences.

The Trusts' Rebecca Rimel said that the foundation considered the nutritional sciences an important, yet neglected field of research. To promote individual and institutional excellence in this field, she said, the Trusts launched a program that established centers for excellence in nutrition at five research institutions.

Rockefeller became the site of one of these centers, with Hirsch as the program director. Each year, the university recruits four fellows who have completed their third year of medical school to spend a year at Rockefeller, where they learn to apply the new methods of molecular biology to clinical problems in the nutritional sciences. During their stay at the University, the Pew Fellows learn by conducting a laboratory research project and by working in a hospital setting with Hirsch and his colleagues. With their new knowledge and a strengthened interest in clinical studies of nutrition, the students return to medical school to complete their fourth and final year.

One of the first Pew Fellows to come to the university became intrigued by an enzyme that breaks down fatty particles in the bloodstream and transports them into fat cells. During his year at Rockefeller, this student provided an important and somewhat surprising piece of information about how the production of this enzyme is affected by a chemical that acts like the body's own adrenal hormones. Another Pew Fellow provided new insights into the relationship between food intake and a chemical produced in the hypothalamus.

Each of these findings, Hirsch explained, represents a "small step in understanding a complex process, but an important and extremely instructive one for the student. At the same time, Hirsch said, "The rest of us learn something we didn't know before—which helps to keep our own research going."

At the Council meeting, David Rockefeller also had advice for those who may be interested in helping to build increased private support for the university. He said that the university "offers many ways to derive great satisfaction and enjoyment—even fun—from providing support for biomedical research. A donor, for example, who provides fellowship support for a young scientist is generally invited to visit the scientist's laboratory, have lunch, and get to know both the scientist and his or her work. Through these meetings and the reports that are regularly issued on the scientist's progress, many donors come to feel personally involved with young investigators, following their careers for many years, whether they remain at the university or move on to other leading institutions."

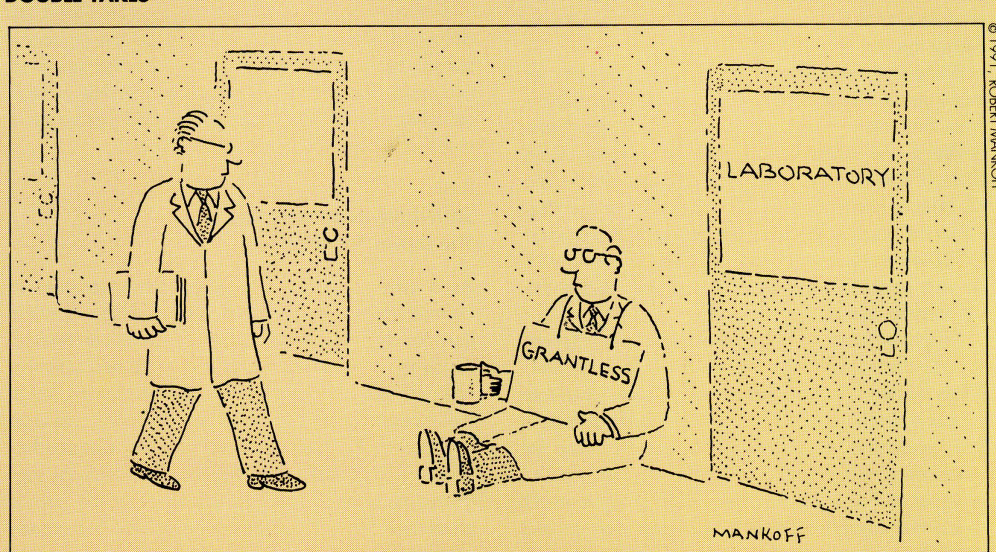
Speaking from his own experience, Rockefeller described how gratifying it can be to get to know the outstanding scientists who work at the university. "You can imagine," he said, "what a thrill it was for me when Bruce Merrifield—a senior scientist at The Rockefeller University who holds a chair named for my father—won the Nobel Prize in Chemistry in 1984."

I think we all have a stake in the future of biomedical research," Rockefeller concluded, "and I urge you all to do what you can to make that future as bright as possible."

THOM HUNTER is a writer and editor in the Development Office at the university. His fiction has been published in *Long Shot* and will soon appear in two other magazines, *The Guide* and *Crazy Quilt*.

ROBERT MANKOFF is a cartoonist whose work has appeared in *The New Yorker*.

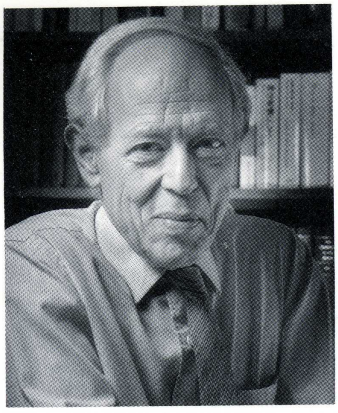
DOUBLE TAKES



REFLECTIONS ON BOHR AND EINSTEIN

This article is excerpted from an address by Dr. Pais to the Royal Danish Academy of Sciences and Letters in December 1989. He repeated the lecture at The Rockefeller University in April 1990.

by Abraham Pais



RALPH GABRINER

Niels Bohr and Albert Einstein were in their early and late sixties, respectively, when I first met them. Since I am one (perhaps the last) of those who knew both men rather well personally in their later years, it is hardly surprising that I have been asked off and on how, in my view, they compared. That question used to make me mildly uncomfortable, and in the past I tended to respond evasively, simply because the better one believes he understands people, the more superficial and hopeless comparisons tend to become. That remains true today. I must admit, however, that a comparison between Bohr and Einstein is far more interesting than similar, more frivolous ones of the kind we physicists, a competitive breed, often indulge in: Who is smarter, A or B? After all, we are dealing here with men who were arguably the two leading figures in physics in this century. So, abandoning my reservations, I shall reflect on what kinds of men they were.

First, let me discuss physics, by which both Bohr and Einstein were possessed, if not obsessed. Both would speak with intense enthusiasm and optimism about work they were engaged in, and had enormous powers of concentration. Both realized quite early not only the importance, but also the paradoxes resulting from Max Planck's discovery of his radiation law. In younger years, Einstein's spectrum of scientific activities was broader than Bohr's. Also in their younger years, both had an urge for doing experiments, at which Bohr did better. Bohr published approximately 200 papers in scientific journals; Einstein, about 270. All their respective most important papers appeared under their own name only. Both men were indefatigable workers, driving themselves on occasion to states of exhaustion which would lead to illness, more serious in the case of Einstein. Both taught courses in their younger, but not their later years. Neither had his own Ph.D. students. Neither experienced difficulty or pain in admitting to himself, if not to others, that occasionally he had been on a wrong scientific track. Neither was in the least overwhelmed by medals, prizes, honorary degrees, or other distinctions showered upon them. Their prime concern was always with what they did not understand, rather than with past achievements.

Their life spans were almost identical. Bohr lived to be seventy-seven; Einstein, seventy-six. Both chose to be cremated. Einstein remained scientifically active until, literally, the day he died. From the point of view of science, Bohr was more spectator than actor in his later years.

Both Bohr and Einstein were a-religious. Bohr left the Lutheran Church in 1911, just before he got married. Einstein said that he did not believe in a God who concerns himself with fates and actions of human beings. He would often invoke God in his spoken and written words. ("God does not play dice.") When, in the 1930s, the celebrated actress Elizabeth Bergner asked Einstein whether he believed in God, he replied, "One may not ask that of someone who with growing amazement attempts to explore and understand the authoritative order in the universe." When she asked why not, he answered, "Because he would probably break down when faced with such a question." Imagery like that would never have occurred to Bohr.

On general social issues, both men spoke up and took action on behalf of the downtrodden. Beginning in 1914, but most especially after World War II, Einstein co-signed numerous politically oriented declarations. Bohr did so only once, in his open letter to the United Nations in 1950. Both were highly sympathetic to the cause of Israel, though not uncritically so.

Einstein had a lifelong interest in philosophy. As a schoolboy, he had read Kant. With his friends in Bern he had studied Spinoza's ethics, Hume's treatise on human nature, Mill's system of logic, Avenarius's critique of pure experience, and other philosophical works. He never wrote articles that may be called philosophical in a technical sense, however. In fact, his reading of philosophy led him to develop a dim view of the subject. As he once said, "Is not all of philosophy as if written in honey? It looks wonderful when one first contemplates it, but when one looks again, it is all gone. Only mush remains."

As for Bohr, less well read in philosophy than Einstein, philosophizing was part of his nature from boyhood on. His first preoccupation with philosophical problems did not arise from his physical investigations, but from general epistemological considerations about the function of language as a means of communicating experience. How to avoid ambiguity—that was the problem that worried Bohr. Shortly before his death, he spoke about his youthful philosophical considerations. When asked how significant those were to him at that time, he replied, "It was, in a way, my life."

To conclude, in some respects Bohr and Einstein were extreme opposites. They differed in their needs with regard to contact with other physicists. Einstein, rarely lonely, mostly alone, did not really care for teaching classes and never delivered a Ph.D. He did have collaborators. I have, in fact, counted more than thirty physicists with whom he published jointly. Nevertheless, it was his deepest need to think separately, to be by himself. Bohr, always in need of other physicists, especially young ones, to help him clarify his own thoughts, was always generous in helping them to clarify theirs. He was not a teacher of courses nor a supervisor of Ph.D.'s, but was forever giving inspiration and guidance to postdoctoral and senior researchers.

They differed in their views regarding the interpretation of quantum mechanics. They argued frequently about it, particularly over the concept of complementarity. And they also differed in one other most significant way. To Bohr, one and only one place was home: Denmark. Einstein never fully identified with any one country or nation. He lived in—rather than visited—many places, Germany (Ulm, Munich, Berlin), Switzerland (Aarau, Bern, Zurich), Milan, Prague, and Princeton. He called himself a gypsy, or a bird of passage.

By and large, however, similarity outweighed disparity. Both had a deep need for simplicity, in thought and in behavior. Each had a lifelong boyish—not juvenile—curiosity, and pleasure in play. They took science very seriously, but to them it was ultimately a game. The greatest similarity, though, was that Einstein and Bohr were both scientists without whom the birth of that uniquely twentieth-century mode of thought, quantum physics, is unthinkable.

ABRAHAM PAIS, a theoretical physicist, is The Detlev W. Bronk Professor Emeritus at The Rockefeller University. He is the author of *Subtle is the Lord...The Science and the Life of Albert Einstein*; *Inward Bound: Of Matter and Forces in the Physical World*; and *Niels Bohr's Times, in Physics, Philosophy, and Polity*, to appear in the autumn of 1991.

SEARCH
The Rockefeller University Magazine
The Rockefeller University, Box 68
1230 York Avenue at 66th Street
New York, NY 10021-6399

Forwarding and Return Postage Guaranteed
Address Correction Requested

Non Profit
Organization

U.S. Postage
PAID

Montpelier, VT
Permit No. 225

INGBET GRÜTTNER

Flexner Hall, The Rockefeller University