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The Rockefeller University

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SEARCH

THE ROCKEFELLER UNIVERSITY MAGAZINE

SEARCH

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ON THE COVER

Tobacco seedling into which a gene has been artificially introduced. Work on this "transgenic" plant is being done by Rockefeller scientist Gloria Coruzzi and a student intern in her laboratory. (See page 18.)

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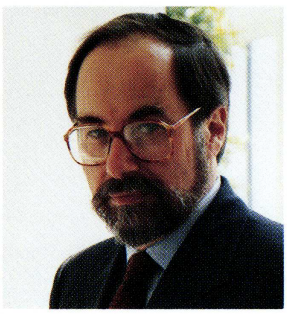
EDITORIAL

AFTER A YEAR



It was almost a year ago that I started as president of The Rockefeller University, and it seems a good moment to comment on what I have discovered and what I hope for in the future.

As I have learned about the various scientific programs on campus, I have been very excited by their vibrancy and diversity. The university laboratories are grappling with the deepest problems of life: how the nervous system functions; how a complicated, integrated organism develops from a single cell; how organisms tell time; how the body regulates its weight. There are laboratories studying the structure of biological molecules, how cell growth is regulated and why it goes awry in cancer, how birds learn song and how brains process sensory information, how microorganisms cause disease and how the body fights back. It will take *Search* forever to do justice to our research efforts because more is learned in a year than *Search* can chronicle.

Not only is the breadth of research astonishing, but the styles of research are remarkably diverse. There are scientists studying disease at the bedside and at the chemical bench. There are physicists, mathematicians, geneticists, biochemists, cell biologists, clinicians, and a myriad of hybrids. Some are driven by a need to understand a particular disease; others by a need to uncover principles at work in living and inanimate systems.

In the midst of all the excitement and activity on the campus, however, I became increasingly aware of a very disturbing problem we must solve in the next few years. Many of the faculty who lead the exciting programs of the university are due to retire during the next decade. Replacing them with people of equal insight and achievement will be difficult. Some replacements can be recruited as senior investigators, but I believe that what we need most are junior faculty members who can grow to become our leaders in the future. Luckily, the new building we are in the process of constructing over the East River Drive will give us the expansion space needed to provide a cadre of beginning, independent scientists the opportunity to develop strength and maturity. Moreover, the faculty has changed its procedures to enable a greater number of young researchers to become the tenured professors of tomorrow.

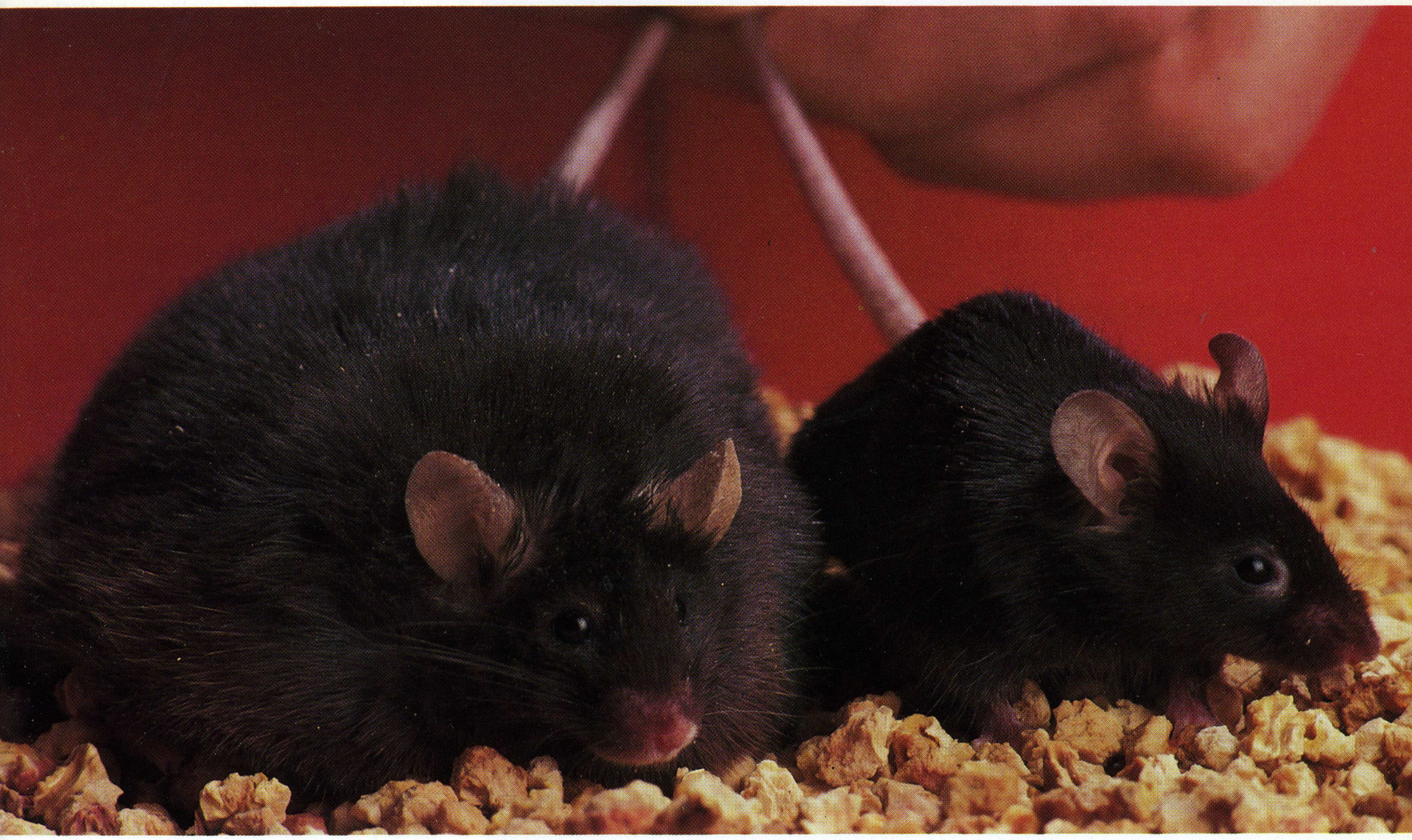
To carry out this plan will involve an extensive financial commitment to talented scientists, necessitating a major fund-raising effort. Although the Rockefeller family has been generous to the university, and will certainly continue to help, it can provide at best a small fraction of what is needed. Similarly, the federal government, the major supporter of research in this country, does not today provide sufficient funds to initiate new laboratories. It is evident that channeling private investment into the future of science will be a central element of my mission here. Already, the Board of Trustees has committed its assistance to this task. But the board cannot do the job alone. It will take the effort and involvement of many of America's most enlightened citizens to make it happen.

DAVID BALTIMORE
President, The Rockefeller University

UNDERSTANDING OBESITY

by Harold M. Schmeck, Jr.

The animals below are genetically identical except for a mutation that has caused the one on the left to become obese. Rockefeller scientists Jeffrey Friedman and Rudolph Leibel are looking for several genes that cause obesity in mice.



ROBERT REICHERT

Few human health problems are as obvious, yet as mysterious, as obesity. Even a layman can diagnose a severe case at a glance. In a superficial way the cause seems clear. To gain weight a person must take in more calories in food than he or she expends. But that does not really explain obesity. Why does one person reach a weight plateau at 350 pounds, including large deposits of fat, while another levels off at a lean 150? The mystery begins in questions like that. Obesity used to be viewed simply as a quirk of behavior, a lack of willpower. Scientists today think that explanation is far too simplistic.

"It may be tantamount to asking why some people are six-foot-four, while others are five-foot-two," says Rockefeller scientist Jeffrey M. Friedman. He and his university colleague Rudolph L. Leibel are looking for the real answers in a population that knows nothing of diet fads, exercise clinics, or carbohydrate binges. The scientists are studying mice, searching for the individual genes that make some laboratory animals grow so fat they can hardly move, while litter mates, lacking the obesity gene mutations, scamper about, lean and agile as their wild ancestors.

The work at The Rockefeller University is basic research, valuable for its own sake in seeking clues to how a creature regulates one of the most crucial of all life's functions—the balance between food intake and energy use. The scientists also expect the work to help explain human obesity, one of the major public health problems of Western civilization today.

Depending on just how obesity is defined, experts estimate that as many as one American child in five is obese, while the same is true of almost one of every three adults. Excess obesity has been linked to high blood pressure, heart disease, and type-two diabetes, the most common variety. Adding to the mystery, however, is the fact that a few patients so seriously obese that they are hospitalized for treatment show no evidence of high blood pressure or the other common risks of their condition.

Nonetheless, there are compelling health reasons for excessively fat people to take off some of the excess, and most do it. The real problem is in keeping it off. At this, most obese people fail. In serious obesity, the relapse rate is over ninety-five percent. There is some evidence, and much speculation,

HAROLD M. SCHMECK, JR. is a free-lance writer who retired recently after thirty-three years covering science for *The New York Times*.

UNDERSTANDING OBESITY

ROBERT REICHERT

Jeffrey M. Freidman

that each individual may have a "set point," a natural gauge that dictates body composition, and that the person, slim or fat, naturally returns to that set point.

For an obese person, the problem is aggravated by the cruel paradox that many who have serious obesity appear to be extra efficient in their use of energy, particularly after they have lost weight. To maintain low weight they must actually eat less than people of equal body size who have never been obese.

The same is true of the animals. One afflicted with a double portion of an obesity gene will survive starvation that kills ordinary mice. There may be a lesson in evolution in this. For most species, including humans, food shortage has usually been a fact of life. Have obesity genes persisted because they help a species survive a famine? That question, like many others in obesity, is a sure spark for controversy. The short answer is: nobody really knows.

Like everything else in life, human obesity is influenced by heredity; but how much of the problem can be laid to that? Estimates of heritability range between thirty and eighty percent. But no one knows what is being inherited.

The biology of obesity is difficult to study in humans. It is the net result of a slow, subtle process. Imbalance between food consumed and energy used takes months to show its effects. In addition, serious obesity tends to distort the human picture, masking causes with effects.

That is why scientists turn to mice. In some special laboratory breeds, the whole problem seems to be focused on single-gene mutations. An animal that carries two copies of that spelling error in a gene becomes extraordinarily fat. Litter mates without the variant gene do not. The actual genes have not yet been discovered, although the team at Rockefeller is closing in on them via large-scale breeding experiments, sophisticated gene mapping, DNA reading, and many other techniques that are new fruits of the revolution in molecular biology.

One spectacular skill is that of physical dissection of chromosomes—the threadlike strands that carry the genes in every cell nucleus. Rockefeller researcher Nathan Bahary has become a master surgeon of these strands, cutting them apart under the microscope with thin glass probes invisible to the naked eye. In experiments that take many hours, he searches out pieces of DNA that may prove to be genes linked to obesity.

The scientists at Rockefeller are on the track of two mouse genes, already known to exist through breeding studies. The goal is to pin down the actual chemical identity of those two genes. All genes are pieces of DNA, the substance that constitutes the hereditary instructions, or blueprints, in every living thing. Once identified, the DNA of those two genes will reveal much about how they function, perhaps how body composition is regulated.

The two genes are named *ob* (for obesity) and *db* (for diabetes). They produce effects by disturbing slightly different aspects of the metabolic signal system that tells the animal it has eaten enough. A gene is the genetic blueprint for making some specific substance—the gene's product. At present, nobody knows what specific chemicals are the *ob* and *db* gene products, or even where they function.

"No one has been able to state with certainty in animals, man, or anything, what the relevant system is, where it is, or what molecules are involved," says Leibel. "In this very critical system, no one really knows at a fundamental level any of the major players

in terms of anatomy, physiology, or molecular biology."

By painstaking studies and much computer work, the scientists have narrowed the locations of the *ob* and *db* genes to specific portions of two mouse chromosomes. When the mapping work is far enough advanced, they hope to be able to capture the actual DNA of the genes, themselves. Then many copies of the genes can be grown in the laboratory—the process called cloning. The DNA strands can be studied to find out what proteins they make and how these function in the body. With that achievement, the team will have captured the first known obesity genes. But what will they actually be?

"I hope that one of these genes encodes a signal molecule that in some way monitors the nutritional state of an individual," Friedman says. If such a signal molecule could be found, it might open the door to many new avenues of treatment for obesity, but the "if" is still large.

"I say that with very great caution," Friedman states. "That's a hope, not a conviction."

One great advantage of cloning genes is that the result is not shackled to any theories the scientists may have had at the outset. A gene is a physical thing—a piece of DNA. It exists in a particular place on one of the chromosomes. Once the scientists have that piece of chemical evidence in hand, it should tell them an important truth.

"We can sit here all day and speculate on what we think it might be," Leibel says, "but, in fact, it doesn't really matter what we think."

Their line of attack on the obesity puzzle is unusual. They are not aware of any large cadre of other researchers following quite the same strategy. But they work at an all-out pace, as though others were breathing down their necks. The work is exciting. It exacts that kind of commitment. Others are impressed by it, too. The research is supported by grants from the Howard Hughes Medical Institute, and two units of the National Institutes of Health: the Human Genome Project and the National Institute of Diabetes and Digestive and Kidney Diseases.

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Rudolph L. Leibel

Implicit in the total enterprise is the conviction that equivalents of the mouse genes probably exist in other species, too. Recently the scientists have taken their latest refinements of the genes' locations on the mouse chromosome map and have found comparable genes in a particular strain of obesity-prone rat. There are many common traits in the genetics of mice, rats, and humans. The success of the rat study raises hopes that comparable human genes may exist and can be found with the help of the animal studies. At least the researchers will be able to narrow down greatly the places in the chromosomes to search.

Human obesity is almost certainly a problem to which multiple genes and many aspects of life-style and environment may contribute. It will never be as simple as the single-gene mutations that seem to function in some breeds of mice.

But nature has a way of using its gene designs over and over again. Once the mouse genes *ob* and *db* are found, the scientists hope to discover similar human genes that may play roles in the complex regulation of human body fat or the balance between energy intake and outflow.

That is where the ultimate hope and vision lie: once the biological system is understood, it may prove possible, someday, to manipulate that system—even to re-set an obese person's "weight-control gauge," to give a lower "normal" weight.

FASCINATING RHYTHMS:
STUDYING BIOLOGICAL CLOCKWORK

by Susan Blum

Right: Rockefeller scientist Mary Baylies readies fruit flies for studies of their sleep/wake cycles.

Walk through the door of the fourth-floor lab in Rockefeller's Smith Hall and you are surrounded by music—the stately rhythms of Bach or Beethoven in the morning, and a bouncier beat—say, the Talking Heads—in the afternoon.

This musical montage is a fitting introduction to the laboratory of Rockefeller scientist Michael Young, where Mary Baylies, age thirty, has just completed her graduate work on biological clocks in the fruit fly. For as surely as songs and sonatas move to set tempos, so do all living creatures march to the beat of internal drummers, biological "clocks" that set periodic rhythms for many cellular, physiological, and behavioral events.

Most of us are aware of our own inner clocks through the daily cycle of sleeping and waking. But our clocks set many other rhythms, too, which cycle on varying time scales. Our hearts beat every second or so; our dreams come in waves every ninety minutes; and our body temperature, mental alertness, pain sensitivity, and hormone production peak and wane every day. The ticking of clocks is also in evidence in a wide range of cyclic events seen throughout nature, from the daily rise and fall of a plant's leaves to seasonal cycles in animal breeding.

Why did these natural clockworks evolve? Scientists can only speculate, of course, but it it is clear that internal timing confers many benefits on living creatures, including the ability to anticipate positive conditions (such as food availability and warm, balmy weather) and avoid negative ones. In short, says Baylies, "Clocks help you adapt to your environment so your species can survive."

Dominating earth's environment is the sun, and its daily rising and setting is reflected in the circadian rhythms that underlie much of an organism's functioning. In natural conditions, many circadian rhythms have a twenty-four-hour periodicity that is set by sunlight. But though light can affect the rhythm, it does not cause it. In fact, in the absence of light or other environmental cues, most circadian rhythms "free run" with periods that are slightly longer or shorter than twenty-four hours.

In animals, the circadian clockwork has been traced to various brain regions—the hypothalamus in mammals, for instance, and the pineal gland in birds. But how many components the circadian clock contains, and how this clock relates to other biological timekeepers throughout the body, are still open questions for chronobiologists such as Young and Baylies. "Everyone's still just building models," Baylies says. "We're testing them and refining them bit by bit."

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

An important contribution to this process is Baylies's graduate work on a fruit fly gene called *per* (short for period)—a gene that carries the code for a large and powerful clock protein.

Remarkably, the per protein is involved in regulating at least three distinct rhythmically timed phenomena: the fly's sleep/wake cycle (which normally recurs about every twenty-four hours); the male's courtship song (which usually lasts sixty seconds); and the hatching of the adult fly from its cocoon (which usually occurs at around 6:00 a.m.).

Perhaps even more remarkably, three different mutations in the *per* gene cause three different changes in the events its protein helps regulate. One mutation, called per^s, speeds up the clock so that the fly's sleep/wake cycle occurs every eighteen hours, the song lasts just forty seconds, and hatching occurs before dawn. The second mutation, per^l, slows the clock down, while a third, per^o, knocks out the timing completely so that none of the events is predictable.

The *per* gene and the effect of its mutations were first identified in 1971. But it was not until the mid-1980s that Young, just arrived at Rockefeller, was able to harness then-new techniques of molecular biology to clone and sequence the gene—that is, to pull it out from its locus on the X chromosome, identify each of its more than 7,000 DNA constituents, called bases, and determine what the protein it coded for would look like.

Soon after this accomplishment, Baylies joined the lab and received her first assignment: to determine the specific DNA changes that distinguish per^s, per^l, and per^o from the normal *per* gene. It was an ambitious undertaking for a new graduate student. But, says Baylies, "Mike's like that. He pushes you to accomplish what you might never have thought you could do."

Using isolated DNA from the three *per* mutations, Baylies discovered that each mutation occurred in a different part of the gene, and was due to a change in just one DNA base. According to Baylies, "This was a really exciting finding, but it opened up a thousand more questions." For instance, were those single-base changes the only ones that could alter clock function? Or might other mutations elsewhere in the relevant gene regions result in proteins that made the clock speed up or slow down?

To pursue the question of how gene structure relates to protein function, Baylies had to narrow it down. Earlier work in the lab had shown that the clock could be slowed by lowering the amount of the normal per protein. "You could imagine that a 'sick' protein could also make a clock run slower, but what kind of protein could make it run faster? The question intrigued me," says Baylies. "Besides," she

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Mary Baylies at work.

adds with a quick grin, "I'm an energetic person myself, so the fit just seemed right."

An avid game player who loves to build experiments, Baylies laid out a strategy that would let her introduce mutated genes into flies "and then ask them, 'Well, now, what are you going to do?'"

Her first step was to make new mutations in the per^s region. Guided by her well-travelled road map of the *per* gene, she concentrated on an area about sixty bases on either side of the original per^s mutation she had analyzed. Using techniques of molecular biology that draw on a wide range of tools—from computers that identify made-to-fit DNA "scissors," to automated synthesizers that generate snippets of new DNA, to bacteria that serve as DNA "factories"—Baylies generated about forty different mutations, from which she chose around one-third for the next step, transformation.

Transformation creates "transgenic" flies by adding new genes to an animal's native genetic endowment. In this case, Baylies added her mutated *per* genes to embryonic flies bred to have only per^o.

As miraculous as this process sounds, it actually took place in a long, narrow room of remarkable ordinariness, distinguished only by its cool, damp atmosphere designed to coddle transgenic flies-to-be. At one end of the lab is a microscope, and here Baylies bent for countless hours, carefully peeling the protective outer casing from hundreds of embryos magnified thousands of times.

Even with its casing off, there is not much to see in a an hour-and-a-half-old fly embryo. But Baylies knew just what she was looking for—a region toward one end that eventually develops into germ cells, the sex cells (eggs or sperm) that transmit genes to the next generation.

Using a narrow glass needle, Baylies injected DNA carrying one of her new mutations into each embryo, knowing that the gene would ultimately be transmitted to a certain percentage of the fly's offspring.

It was these transgenic descendents that Baylies put through their paces. Housed in incubators, two to a narrow glass tube, the flies nestled in computer-connected "cradles" that registered their activity each time they crossed an invisible infrared beam of light. Since their other parent had been carefully bred to have no rhythm, Baylies knew that any rhythmic activity these flies showed would be due to the mutation she had introduced one generation back.

Analysis of their activity rhythms showed that the descendants who received the mutations in the per^s region did indeed have fast-running sleep/wake cycles. Similarly, other transgenic flies given these mutations showed an earlier-than-normal hatching time.

In other words, Baylies had shown that it was not just a single-base

mutation in DNA that made the gene code for a fast-clock protein. Rather, a number of different changes within a whole region of the *per* gene could lead to a speeded-up cycle. Because of the way genes are "translated" into proteins, this actually meant that one or more amino acids within the protein region might differ, yet yield the same result—a faster-than-normal clock.

Baylies's experiments mark another step in the Young lab's attempts to penetrate the still-unsolved mystery of what, exactly, the per protein does—and how it does it.

Research conducted by Young, Baylies, and others at Rockefeller has already led them to a general understanding of the protein's role. They believe it affects biological timing by influencing the conditions for, and the rate of, cell-to-cell signalling. As Baylies explains, "The current thinking is that the per protein serves to couple clock function to the various rhythmic behaviors."

But just where the protein fits into the signalling pathway—and what its particular function may be—is as yet unknown. "It's all very interesting, but we still can't say, 'Oh, yes, per takes A and turns it into B,'" Baylies says. "We wish it were that simple, but it's not."

Simple it may not be, but by helping to delineate the region of the per protein that quickens the clock, Baylies has deepened the understanding of how the per protein might work. When she leaves Rockefeller this fall to become a postdoctoral fellow at Cambridge University in England, others in the lab will continue to add more pieces to the puzzle. Eventually, the mystery of per function—as well as the function of other clock proteins—will be solved.

So far, per-like proteins have been found in creatures as different as snails, fruit flies, and rodents; and the hope is that these molecules will prove relevant to higher mammals, too. The benefits of understanding how clocks tick in the highest mammals—humans—cannot be overstated, for scientists are discovering that these internal timekeepers play a large role in our health and well-being.

When we cross too many time zones too fast, our clocks cannot catch up and we battle jet lag. When our clocks are out of step with the earth's yearly orbit around the sun, we may suffer the sadness of "seasonal affective disorder." If we face the challenge of a fight against cancer, the success of our treatment may depend on how well its timing matches our cells' innate cycles of growth. And as we age, our clocks slow down, sometimes leading to disorders of sleep and of mood. The more we learn about how these clocks function, the better the chances for creative tinkering that can change their inner workings as needed—perhaps even muting the ongoing beat of the years which, like clockwork, eventually will affect us all.

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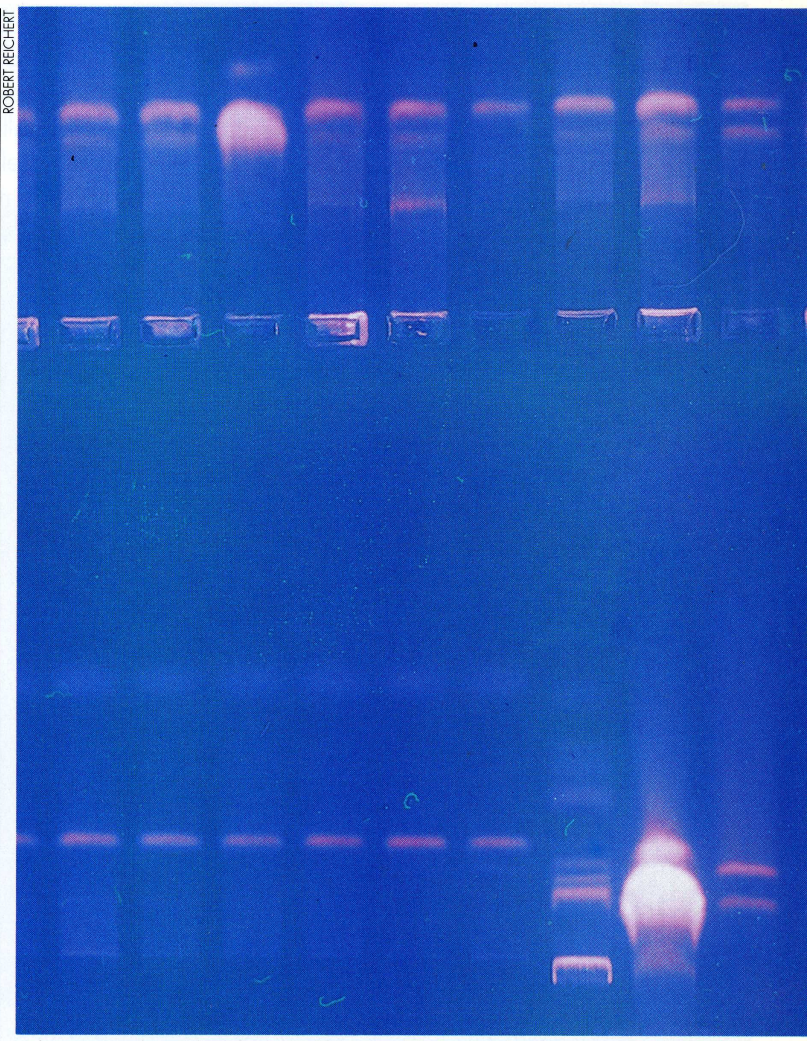


Gel separation technique shows fragments of the *per* DNA, which will be used for further experimentation.

JOINING FORCES IN THE FIGHT AGAINST DISEASE IN DEVELOPING COUNTRIES:

MANUEL PATARROYO AND COLLEAGUES AT THE ROCKEFELLER UNIVERSITY

by Robert Applebaum

The founder of one of Latin America's premier research facilities, Manuel E. Patarroyo has formed alliances with politicians and scientists the world over in his campaign against third-world disease. Breakfast with the president of Colombia or a meeting with Queen Sofia of Spain are not unusual events for the seemingly tireless immunologist, who is just as likely to be on the road discussing peptides with health ministers or journalists as he is to be in Bogota directing a staff of sixty researchers.

The forty-four-year-old Patarroyo—who has maintained close professional and personal relationships with several Rockefeller scientists for more than two decades—has captured the attention and admiration of scientists throughout Latin America, sending tremors of pride through their ranks. He has not only galvanized financial support for a research institute outfitted with state-of-the-art technology and staffed with top-notch local talent—no simple feat on a continent that traditionally loses its brightest minds to the "brain drain"—but the energetic scientist has also pioneered a potentially effective synthetic vaccine to combat the malaria parasite.

"Dr. Patarroyo is a role model for researchers in South America," says Alberto Moreno, a Colombian immunologist and former member of Patarroyo's team. "It's very difficult to do science here—to get financial backing for a laboratory and to pursue extensive research. He has proven that high-quality research can be done in Latin America and has given us a sense of pride and identity as scientists. It is very important for us and our countries to know that we can take risks and be successful."

Raised in a small village in central Colombia (five of his eleven siblings are physicians, four are medical researchers), Patarroyo was introduced to Rockefeller scientist Henry Kunkel in 1967 while studying virology at Yale University as part of his medical education at Bogota's National University. Kunkel was so impressed with the young man's "intensity and drive," recalls university scientist John Zabriskie, that he agreed to take him under his wing. Their relationship lasted until Kunkel's death in 1983, with Patarroyo spending several months a year at The Rockefeller University.

"It was a very beautiful friendship," Patarroyo says. "We were mentor and student for seventeen years. Dr. Kunkel was a man with spectacular vision. He taught me basic immunology, put me in contact with the world's foremost immunologists, and pushed for my working with third-world microbes. I credit him with putting me on track for my work on developing a vaccine against malaria."

Patarroyo's rise to prominence as both an administrator and researcher is inextricably linked to his ongoing connection with The Rockefeller University, where he is now an adjunct professor. In the mid-1970s, taking advantage of a $5,000 annual stipend that Kunkel provided—a significant sum of money in Colombia at the time, Patarroyo says—and salvaging equipment that was being replaced at Rockefeller, Patarroyo started a modest immunology unit at Bogota's San Juan de Dios Hospital. Subsequently, while collaborating with Zabriskie, the Colombian scientist gained widespread recognition for identifying an antigen in a large majority of rheumatic fever patients he studied in Bogota. This discovery won him the Colombian National Science Award and sparked government interest in his work. By the early 1980s, several million dollars had been allocated for Patarroyo's Institute of Immunology—its laboratories furnished with high-tech equipment, and a team of microbiologists, chemists, immunologists, physicists, and computer scientists hired. This windfall also

ROBERT APPLEBAUM, a New York-based free-lance writer, has a long-standing interest in Latin American affairs.

Left: Manuel Patarroyo
Below: An aotus monkey, from the Amazon region, being used in a study of the malaria vaccine Manuel Patarroyo has developed and is testing.

financed a field station located in the Amazon River Basin and an auditorium named in honor of Henry Kunkel.

"I admire Manuel intellectually and for his tactical ability to get things done," says Rockefeller's Bruce Merrifield, who was awarded a Nobel Prize in Chemistry in 1981. "He's driving hard all the time and has a knack for getting people to help him," Merrifield continues. "He's not shy about telling the [Colombian] president what he needs and why his work is important. I was there at the inauguration of his lab and the president treated Manuel just like a son."

Patarroyo has targeted third-world afflictions, particularly leprosy, tuberculosis, and malaria, as his top priority. Drawing on knowledge and techniques he has been exposed to at The Rockefeller University—immunology and immunochemistry in Henry Kunkel's lab, microbiology with John Zabriskie, peptide chemistry with Bruce Merrifield, and methods of cultivating parasites developed by William Trager—Patarroyo set out in 1983 to develop an antimalarial vaccine. He first isolated scores of proteins comprising the malaria parasite

Below: The Institute of Immunology, headed by Manuel Patarroyo. It is part of the San Juan de Dios Hospital in Bogota, Colombia.

and then determined which induced protective immunity in owl monkeys at his jungle field station. He and his team next mapped the amino acid sequence of individual protein fragments in order to synthesize four peptides, which were linked together and polymerized into a larger molecule. The result is a synthetic vaccine engineered to block the malaria parasite at both the sporozoite and merozoite stages, Patarroyo explains.

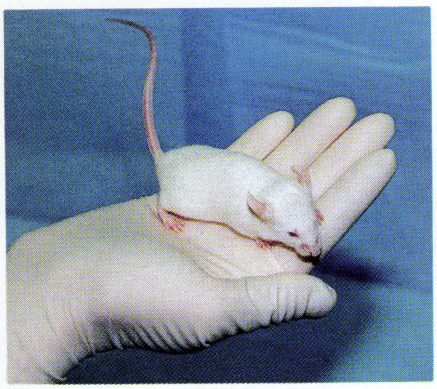
Several preliminary tests of this vaccine indicate that it may provide eighty percent protection against a disease that affects an estimated 300 million people, causing as many as five million deaths annually. Double-blind randomized placebo trials of the vaccine are currently being carried out on more than 4,000 people in Colombia, Ecuador, Venezuela, and Brazil under guidelines suggested by the Pan American Health Organization. The vaccine has stirred controversy as well as enthusiasm among scientists throughout the world, with many reserving judgment until the tests are complete.

"While the trials, which are controversial, need to be continued and the results confirmed," says Zabriskie, "we can say one thing for certain: he is a man with drive and determination who started with very little and has become a guiding light for Latin American science. Anyone would agree with that."

OF SCID-HU MICE AND MEN

by Catherine Vanchieri

Below left: The SCID-hu mouse, developed by Rockefeller alumnus Mike McCune.



Immunologists at Stanford University announced in 1988 that they had made what is promising to be an extraordinarily useful mouse. Their creation—a laboratory animal endowed with a functioning human immune system—may dramatically accelerate the development of effective treatments for acquired immune deficiency syndrome (AIDS), cancer, and many other diseases, while providing scientists with an invaluable tool for understanding basic human biology.

This remarkable new mouse is the brainchild of Rockefeller alumnus Joseph M. (Mike) McCune, a physician-researcher whose imagination was spurred by the urgent need for a suitable animal model to use in the fight against the human immunodeficiency virus (HIV), the virus that causes AIDS. Efforts to understand and control HIV have been severely hampered by the virus's fidelity to the cells of human beings and chimpanzees—an endangered species that is too scarce, expensive, and unmanageable for widespread laboratory use.

McCune "humanized" his mouse by transplanting the essential pieces of the human immune system into an animal that had inherited no working immune system of its own. The strain of mouse chosen—called SCID, because of its severe combined immune deficiency—is susceptible to many of the same opportunistic infections that threaten people with AIDS, especially *Pneumocystis carinii* pneumonia, or PCP, a common cause of death in AIDS patients.

Working with Stanford colleagues and a scientist from the Jackson Laboratory in Bar Harbor, Maine, McCune surgically implanted tiny pieces of human fetal lymph nodes, thymus, and liver under the fatty capsules that surround the mouse kidneys. Within weeks, the transplanted tissues developed into functional counterparts of human organs, supporting human immune system cells that were able to protect the SCID mice against diseases like PCP—and make them susceptible to infection with the AIDS virus.

The genesis of the SCID-hu mouse, as McCune calls his creation, was first reported in *Science* in September 1988 in a paper that was dedicated to the memory of two scientists whom McCune describes as "gods of medical research." One was Henry S. Kaplan, who had directed the Stanford laboratory where McCune and developmental immunologist Irving Weissman first worked on the SCID-hu mouse. The other scientist was Henry Kunkel, McCune's thesis adviser in the M.D./Ph.D. program that Rockefeller cosponsors with the Cornell University Medical College.

Today McCune is scientific director of SyStemix, in Palo Alto, California. The company's contract drug-testing facility, opened in March 1990, offers AIDS researchers the opportunity to evaluate anti-HIV compounds in infected animals, a crucial intermediate step between test-tube experiments and costly, time-consuming clinical trials.

One study recently reported in the *Journal of Infectious Diseases* provided evidence that AZT, the only federally approved anti-HIV drug, can have prophylactic effects if administered immediately after infection—information that may be critical for health care and laboratory workers exposed to the virus while on the job. SyStemix is currently screening potential new anti-HIV drugs for clients that include pharmaceutical companies, academic laboratories, and the National Institutes of Health. According to McCune, future tests will focus on combinations of antiviral compounds in an attempt to forestall the drug resistance that is almost certain to develop in a virus able to mutate as rapidly as HIV.

SyStemix researchers also plan to use their mouse in new approaches to fighting other human-specific viruses, including those associated with hepatitis, leukemia, and cervical cancer. First on their list, though, is cytomegalovirus, or CMV, a virus that is believed to interact with HIV and often causes blindness in AIDS patients.

Not all the investigations at SyStemix are so directly AIDS-related. One major line of research is closing in on the stem cell that is the common precursor of a spectrum of blood and immune cells in the human body. The identification of the human stem cell and the growth factors that stimulate its differentiation (a related project at SyStemix) would bring medical research much closer to a long-sought goal: learning how to reconstitute the human immune system—in a human being.

Researchers at SyStemix are also expanding "SCID-hu technology" by learning how to coax human pancreas, intestine, skin, lung, and other transplanted tissues to develop and function in the immunologically tolerant SCID mice. They plan to create an array of animal models that may eventually shed light on many aspects of human health and disease. McCune notes, "Most of what we do is biologically interesting, and we have a lot to choose from. But we only want to pursue projects that can take us to meaningful applications in the clinic."

CATHERINE VANCHIERI is a science writer and fund-raising writer in The Rockefeller University Development Office.

AN ARCHITECTURAL TOUR

"USEFUL TO THE WHOLE WIDE WORLD":

THE BUILDINGS OF THE ROCKEFELLER UNIVERSITY

Photos by Robert Reichert
Text Research by Daniel Koplowitz and Lynn Sampsell
Layout by Corrine O'Neill
Photographic Printing by Leif Carlsson

COLUMN AT ENTRANCE TO FOUNDER'S HALL

IONIC COLUMN TOP AT THE MAIN ENTRANCE TO FOUNDER'S HALL
Like the other early structures—The Rockefeller University Hospital, Nurses Residence, Flexner Hall, and Theobald Smith Hall—Founder's Hall was built in a highly eclectic period of architecture, in a style called Second Renaissance Revival. This style is marked by symmetrical composition, recessed stone joints, roughly textured stones, a variety of window types, projecting cornices, and heavy railings worked into the exteriors of walls and roofs. Shown is a detail from the building's façade.

"Here is an institution whose value touches the life of every man that lives....Who has not felt the throbbing of desire to be useful to the whole wide world?" These words, spoken by Frederick T. Gates—John D. Rockefeller's financial advisor who first suggested that Rockefeller found a medical institute—imply that from the beginning, utilization was a chief goal of the institute.

In keeping with this purpose, the original architecture of the institute was meant to be utilitarian. According to George W. Corner, in *A History of The Rockefeller Institute*, the earliest trustees determined that the style of the first building, Founder's Hall, "be as simple as is consistent with its present purpose, future additions, and general utility."

While the earliest buildings, as well as the more recent ones, are not without a certain degree of charm, even beauty, the functionalism of the structures is apparent: there is little wasted space, and interiors are shaped to accommodate laboratory equipment and ventilating systems. Even the foundations of the buildings are utilitarian. All the structures are connected by tunnels, which also house a variety of plant operations and other functions.

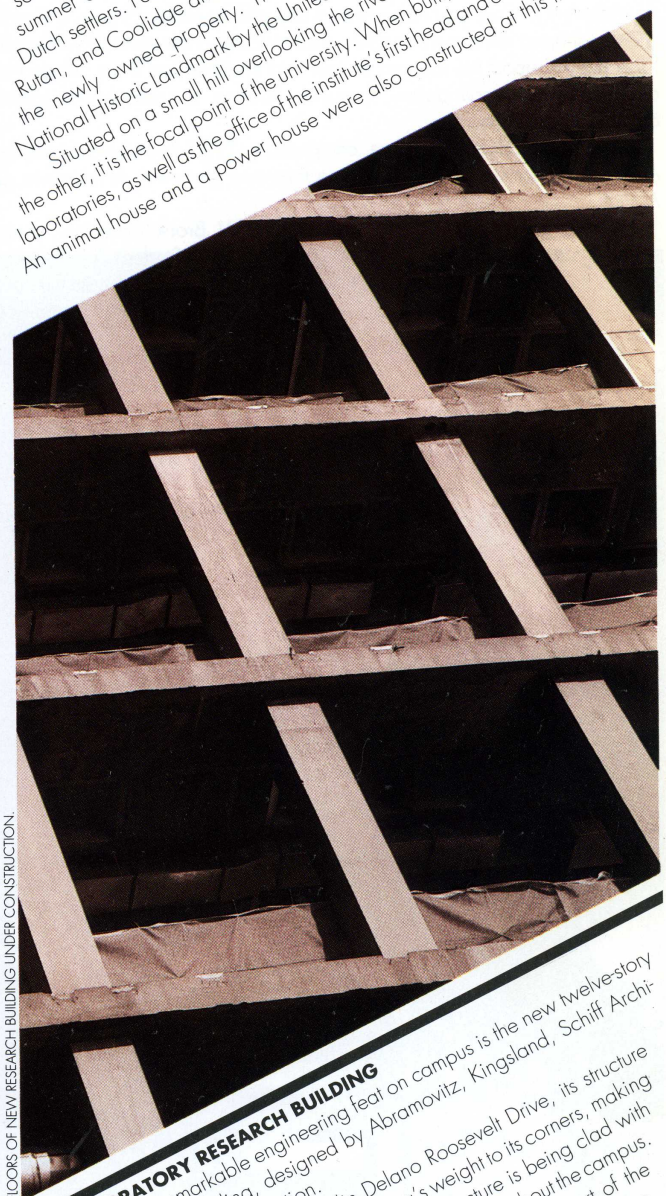
Over the nearly ninety years of its existence, the Rockefeller campus on York Avenue has attracted much interest. We are, therefore, pleased to offer a building-by-building tour of the university, with certain prominent external architectural features, utilitarian or otherwise, noted.

FOUNDER'S HALL

FOUNDER'S HALL

The Rockefeller Institute for Medical Research, founded in 1901, was first located in two brownstone town houses at Lexington Avenue and Fiftieth Street. The institute soon acquired thirteen acres of land on the East River which once belonged to the summer estate of William Schermerhorn, a descendent of seventeenth-century Dutch settlers. Founder's Hall, designed by the Boston architectural firm Shepley, Rutan, and Coolidge and completed in 1906, was the first building erected on the newly owned property. The brick and stone structure was designated a National Historic Landmark by the United StatesDepartment of the Interior in 1975.

Situated on a small hill overlooking the river on one side and the campus on the other, it is the focal point of the university. When built, Founder's Hall contained laboratories, as well as the office of the institute's first head and other administrators. An animal house and a power house were also constructed at this time.



FLOORS OF NEW RESEARCH BUILDING UNDER CONSTRUCTION.

NEW LABORATORY RESEARCH BUILDING

Perhaps the most remarkable engineering feat on campus is the new twelve-story laboratory research building, designed by Abramovitz, Kingsland, Schiff Architects and currently under construction.

Resting on a platform over the Franklin Delano Roosevelt Drive, its structure depends on steel arches which transfer the building's weight to its corners, making it very strong and rigid. The modernist façade of this structure is being clad with Alabama limestone and granite, materials commonly used throughout the campus.

This building is housed among those buildings on the southern part of the campus (the Tower Building, the Laboratory Animal Research Center, and the two faculty residences), all of which are clad in limestone.

CASPARY HALL DOME

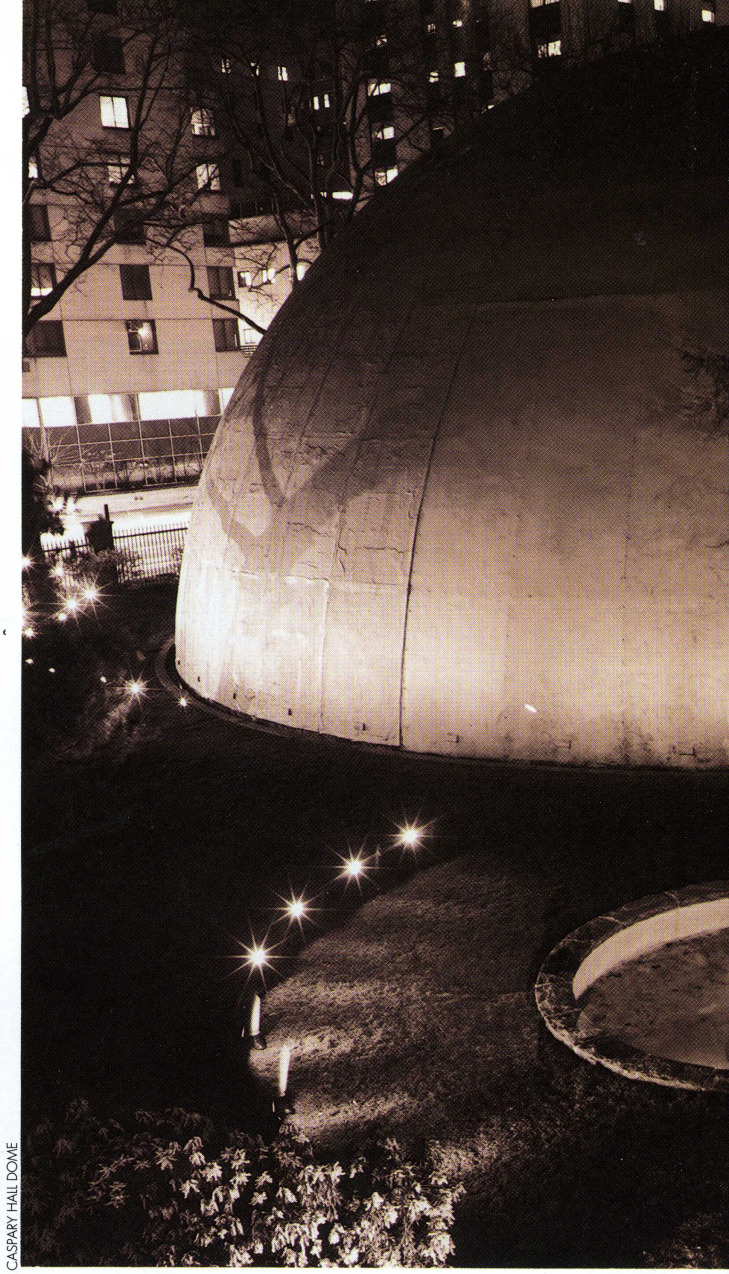
Near the university's main gate at Sixty-Sixth Street and York Avenue are several buildings in the modern style: Caspary Hall/Abby Aldrich Rockefeller Hall, and the Graduate Students Residence. Situated on the lower slope of the campus, these buildings are appropriately scaled to blend in with the Second Renaissance Revival buildings. The modern style, characterized by rounded corners, flat roofs, and horizontal windows, conveys a streamlined effect, modeled after industrial design.

Caspary/Abby Aldrich, although carrying two names, is really one building. Its artificial division is marked in the interior by connecting steps. Designed by Harrison and Abramovitz Architects and completed in 1958, it is composed of two stories plus a basement. Limestone spandrels and aluminum window-curtain walls define the exterior. Inside the double building are a dining room, reception rooms, a small library and conference room, the offices of the president and other administrators, the Faculty and Students Club, and guest accommodations.

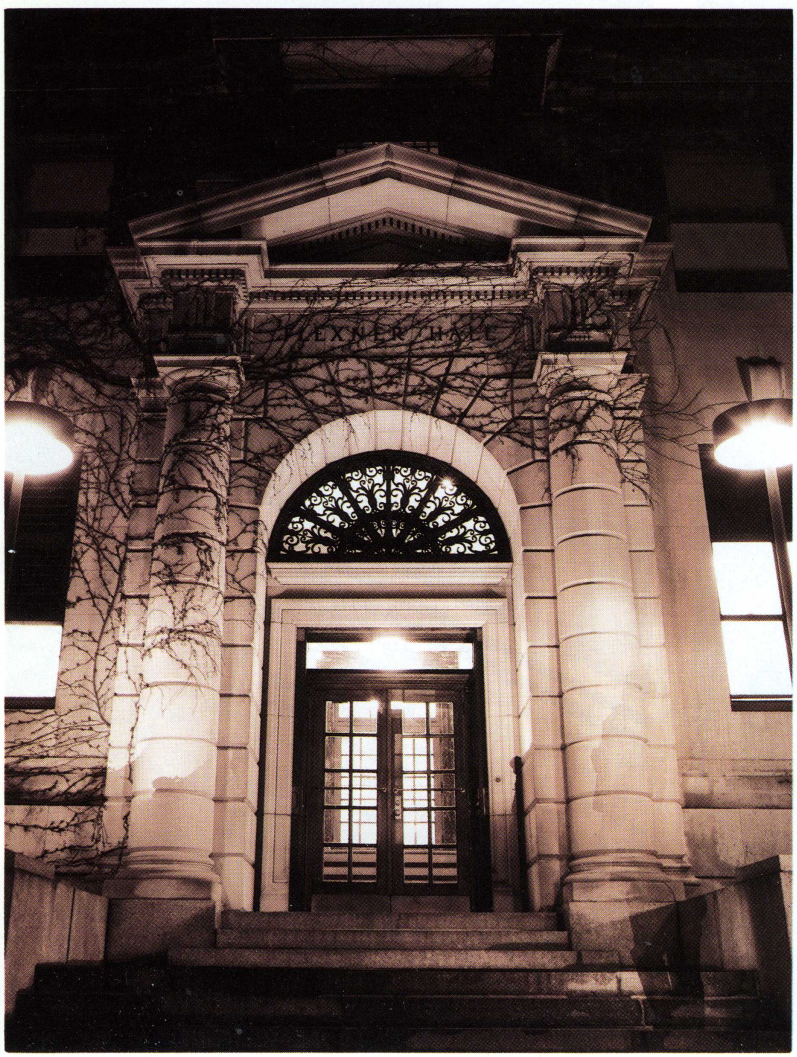
Adjacent to Caspary/Abby Aldrich and also connected inside is Caspary Auditorium, a dome-shaped reinforced concrete shell structure once covered with mosaic tiles, which have not withstood the ravages of time and weather and have popped off. Beneath the auditorium is a small gallery, presently housing a collection of scientific instruments developed at Rockefeller.

Graduate Students Residence, completed in 1959 and also designed by Harrison and Abramovitz, forms a continuum of limestone and glass with its near-twin, Caspary/Abby Aldrich.

Three other modern buildings are the Detlev W. Bronk Laboratory, completed in 1959 and located just south of the Hospital and Graduate Students Residence; the President's House, designed by Harrison and Abramovitz and built in 1957 on the northeast corner of the campus; and Sophie Fricke Hall, built in 1964 and located south and west of Bronk Lab.



CASPARY HALL DOME



ENTRANCE TO FLEXNER HALL

TRANSOM GRILLWORK AT ENTRANCE TO FLEXNER HALL

Flexner Hall was built to house chemistry, pathology, and bacteriology laboratories (moved from Founder's, which was then altered to contain experimental physiology and experimental biology laboratories). It was designed by Coolidge and Shattuck Architects and built just north of Founder's Hall in 1917, on the site of what was formerly the research animal facility.

The next building to be constructed was Welch Hall, east of and connected to Founder's Hall, in 1929. It contained a library, an early dining room, and an assembly hall. Theobald Smith Hall, to the north of Flexner, was built in 1930 for use as laboratories. Both were designed by Coolidge, Shepley, Bulfinch, and Abbott Architects. Another building, the Sixty-Seventh Street Animal House, was constructed in the 1930s between Smith and Flexner Halls. It was renovated in the mid-1980s into research and administrative offices around a three-story atrium and is now called the Smith Hall Annex.

NURSES RESIDENCE

Designed by the architectural firm York and Sawyer, Nurses Residence was constructed in 1910, the same year as The Rockefeller Institute Hospital to which it is connected. It was built as a two-story isolation building for the hospital to house patients with infectious diseases. Worried about airborne contagion, the institute's board of trustees had the building constructed so that air could be vented directly through the roof. Additional floors were added in 1926 as living quarters for the hospital's nursing staff. No longer a residence hall, Nurses Residence now houses many functions, ranging from clinical research and telecommunication facilities to the offices of the Public Affairs and Security Departments and emeritus professors. Like the other early structures, this building exhibits classical proportions and rich masonry details.

NURSES RESIDENCE

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CORRINE O'NEILL is the manager of the Department of Graphic Design at the university.

LEIF CARLSSON is a free-lance photographer from Sweden currently living in New York City.

COMBATTING THE SCIENTIFIC BRAIN DRAIN:
INTERESTING HIGH SCHOOL STUDENTS IN RESEARCH

by Susan Wensley

Attracting the best and the brightest youngsters into careers in science has become a high priority for the nation, faced with declining numbers of scientists graduating from our universities. It is also a concern for many universities, confronted by rising numbers of faculty vacancies created by retirements and the "brain drain" of scientists flocking to more lucrative industry jobs.

To infuse youngsters with the excitement of science, some Rockefeller researchers are mentoring several New York City high school students, helping them to contribute to ongoing biomedical research. Three of these students, featured below, have been interns at Rockefeller for the past two years. After graduating this month, all three will head for college to prepare for science careers.

ROBERT REICHERT

Helen Shigemitsu and Gloria Coruzzi

HELEN SHIGEMITSU, STUYVESANT STUDENT

Helen Shigemitsu, a student at Stuyvesant High School (one of the City's selective public schools), joined the laboratory of Rockefeller's Gloria Coruzzi with a more sophisticated science background than most high school students. Nevertheless, her first months were devoted to learning the background of the laboratory's research and to honing the skills she would need in order to contribute to the effort.

Coruzzi's laboratory has been investigating the genes that regulate the mechanism by which plants assimilate nitrogen from the soil. The goal is to learn how environmental signals activate genes. Shigemitsu's work focused on the expression of the plant gene encoding GS2 (glutamine synthetase), an enzyme which converts ammonia into amino acids the plant can use. Her task was to find which segments of the gene are essential to its function.

Shigemitsu learned how to clone genes into the bacteria *E.coli*, and she used the process to produce fifteen genetic mutations in the controlling elements of the gene. She transferred the mutated genes into a soil bacterium, which she then used to transfer the genes into tobacco plants to make transgenic plants for each genetic mutation. Because of a quirk in the process by which transgenic plants are produced, Shigemitsu had to produce ten plants for each mutation and average out the results before she could compare them with plants carrying the naturally occurring unmutated gene.

"Simply learning theory wouldn't have had the same impact for Helen," says Coruzzi. "Her lab work made the science dramatic and real—and more understandable. Preparing plant tissue culture requires skill and a good understanding of the process. And I'm amazed at how much she knew. I had to keep reminding myself that she's a high school student."

Shigemitsu submitted a paper, "The Expression of the Plant GS2 Gene: Essential Regulatory DNA Elements and Transcription Factors," to the fiftieth Westinghouse Talent Search in December 1990. She was one of only 300 semi-finalists selected nationally in that prestigious competition (see sidebar).

MARCOS VASQUEZ AND QAISAR AHMED, JULIA RICHMAN STUDENTS

Two students from the university's neighbor, Julia Richman High School, began their internships in the laboratory of Rockefeller scientist John Taylor in the spring of 1990, while they were juniors. Taylor has been instructing the students in physics and organic chemistry, as well as laboratory pro-

SUSAN WENSLEY is a science writer living in New York City.

Marcos Vasquez and John Taylor

cedures. Working after school and during the summer, Vasquez and Ahmed have been engaged with Taylor on a research project concerning *apolipoprotein B*, the protein component of low-density lipoproteins (LDL) that controls the function of these cholesterol-carrying particles in the blood. They are attempting to determine how this protein is anchored to the LDL surface. LDL is a major component of plaques that build up on arterial walls and block the flow of blood to the heart. These plaques can cause heart attacks.

Vasquez acknowledges that "synthesizing got a little monotonous," but says that "the experiments were fun, and it was interesting to see how the molecules take shape." By the time they got to the end of their experiments, Vasquez and Ahmed could appreciate the whole research process, from preparing to do an experiment to seeing the results. In March, Vasquez entered his work in the Manhattan Division of the New York City Science Fair, and was awarded second place.

In all, Coruzzi and Taylor found their experiences with the high school students both demanding and rewarding, and they consider the time they contributed well spent. "We invested a lot of energy and time in teaching these students, but we also benefitted," says Coruzzi. "Helen reached the point where she could plow through a lot of the time-consuming basic lab work required in our research. I was impressed by her dedication; she came in every day after school last year and all summer."

Because of other commitments, Vasquez and Ahmed could come to the lab only one or two afternoons a week during the school year, and a little more during the summer. "I found working with them very rewarding, but a little bit frustrating," says Taylor. "I had forgotten how busy young people are. But I enjoyed going all the way back to high school level in chemistry. It was a challenge to think of something that isn't trivial for a nonexpert to undertake in the lab."

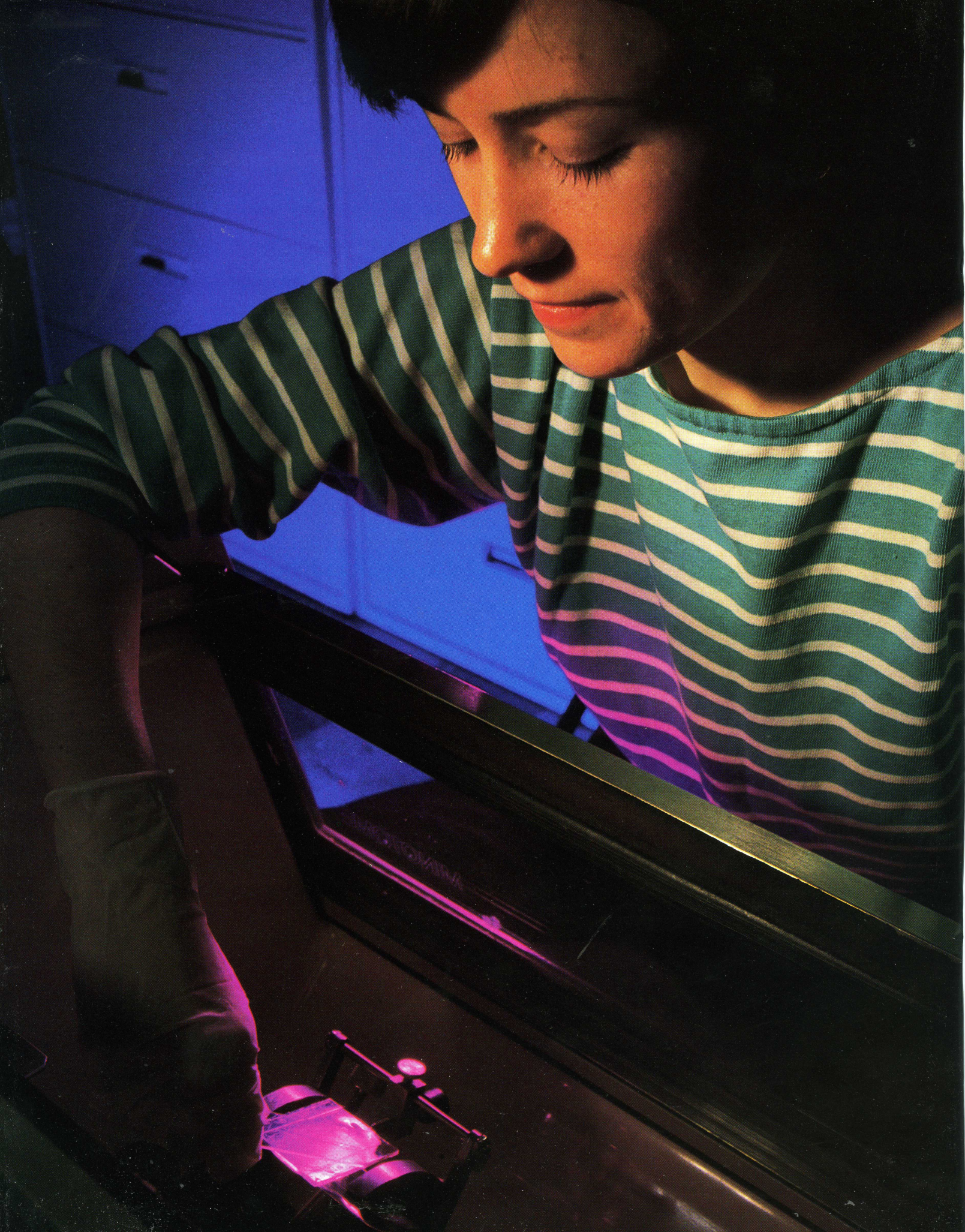
"Science can benefit from these internships," says Coruzzi, who was herself a high school intern at the university. "The more we encourage bright, motivated students, the more likely they'll think of research when they choose a career."

THE WESTINGHOUSE SCIENCE TALENT SEARCH
by Ruth Coxeter

This spring marked the fiftieth anniversary of the Westinghouse Science Talent Search, sponsored by the Westinghouse Educational Foundation. The contest had its origin at the1939 World's Fair, held in New York City. According to a spokesman for the foundation, two science journalists, Watson Davis and G. Edward Pendray, met and agreed that science was "too important for the nation and the coming generation to be neglected in the high schools." Hoping to encourage young people to choose science careers, and to provide recognition for science teachers, they conceived of the competition.

The contest is unique in that each student designs and carries out a science project and writes a research paper which is judged by scientists. Currently, about 1400 entries are submitted each year. Three hundred honors winners and forty national winners are chosen; the national winners display their work in Washington, D.C., and are considered for the top ten awards—college scholarships. More than $2.5 million in scholarships and awards has been granted since the contest's inception.

Over the years, dozens of Rockefeller graduate students, postdoctoral fellows, and faculty members have been former Westinghouse winners.



ROMANCING THE RAT:
HORMONAL CONTROL OF MATING BEHAVIOR

by Susan Blum

Left: Lori Flanagan prepares tissue sections to study the effect of hormones on the rat brain.

Nature proffers the female rat a bouquet of hormones to put her in the mood to mate. Rockefeller scientists are studying this natural nosegay to learn how the interplay of hormones orchestrates rodent romance.

Much of a female rat's short life span is devoted to making and mothering babies. In rats (as in all mammals, including humans) the ovarian hormones estrogen and progesterone are the major players in preparing for a pregnancy and maintaining it. For labor and nursing, another hormone, oxytocin, kicks in. Produced in the brain and secreted into the bloodstream, oxytocin causes contractions in tissues of the uterus and the mammary glands.

This much has been known about oxytocin for decades. But in the 1980s, research conducted at Rockefeller and elsewhere disclosed a much greater role for the substance. Scientists learned that oxytocin can also act as a messenger within the brain itself to foster a wide range of social, sexual, and nurturing behaviors in both males and females.

No one yet knows how the biochemistry of oxytocin translates into behavior in animals, let alone humans. But Rockefeller researchers are helping to answer this question. Both Bruce McEwen and Donald Pfaff study the effect of hormones on the brain and on behavior, and their labs frequently collaborate.

In the mid-1980s, Dutch scientists working in the laboratory of Ron de Kloet, a former postdoctoral fellow with McEwen, discovered that brain cells must be prepared by estrogen before they can respond to oxytocin. Estrogen primes the brain cells by prompting them to make the cell-surface receptors that latch onto oxytocin.

But though estrogen is necessary for oxytocin to work, it is not sufficient; progesterone also plays a crucial role. Two Rockefeller postdoctoral fellows studied this hormonal interaction as it relates to lordosis, the arched-back, rear-showing posture female rats assume to signal their interest in mating.

Homing in on the cells of the brain region controlling lordosis, Michael Schumacher and Hector Coirini, working with McEwen and Pfaff, found that while estrogen prompts the production of oxytocin receptors, progesterone expands the area over which these receptors spread, and makes the receptors bind oxytocin more avidly. Only when both estrogen and progesterone have acted does oxytocin strongly induce lordosis.

Underlying the complicated interactions of all these hormones is the beautifully simple strategy of coordinating physiologic events to maximize beneficial behavior.

Each four-to-five-day estrous cycle (the rat equivalent of the human menstrual cycle) starts with a slow estrogen buildup, followed by a rapid surge in progesterone. In the reproductive tract, the estrogen buildup serves mainly to mature the eggs and the uterine lining, while the progesterone surge is related to the release of the eggs from the ovary. Meanwhile, in the brain, the gradual rise in estrogen promotes the production of oxytocin receptors over the course of about two days, while the progesterone surge elicits the additional changes in receptor area within about half an hour.

At that point—with both eggs and brain fully prepared—oxytocin can swing into action and spur the rat to assume her alluring position. This linkage of ovulation and lordosis boosts the chances for fertilization, and furthers nature's overall goal of perpetuating the species.

Both Schumacher and Coirini have left Rockefeller this year, but a newly arrived postdoctoral fellow in the McEwen lab is taking up where the two former postdocs left off. Twenty-eight-year-old Lori Flanagan is investigating exactly how progesterone affects oxytocin receptors. She is also tracing the pathway oxytocin takes from the time it is made to the time it reaches its cell-surface receptors in the brain region controlling lordosis.

All in all, according to Flanagan, the hormonal bouquet of estrogen, progesterone, and oxytocin is turning out to offer an intriguing bunch of intermingled biological insights.

For instance, the study of progesterone's rapid effects on cell-surface receptors is bolstering a new understanding of how hormones work. Scientists used to believe that steroid hormones (such as progesterone and estrogen) and protein-like hormones (such as oxytocin) work very differently. They thought steroid hormones always work slowly by affecting DNA's control over protein synthesis, while protein-like hormones always work quickly through cell-membrane interactions that affect already-existing proteins. Recently, though, it has become clear that steroid hormones can have rapid cell-membrane effects, and that protein-like hormones can act more slowly to affect DNA.

The experiments at Rockefeller are giving new depth to these concepts. "Normally, studies of hormonal membrane effects are pretty far removed from behavior," says Flanagan. "The beauty of the lordosis studies is that they focus on a behavior that is very well characterized and is easy to control in the lab. This made it possible to show, for the first time, that steroid effects on the membrane can activate a behavior."

The research is also helping to reshape long-standing assumptions about the brain. "The dogma used to be that once the brain is formed, it stays pretty much the same throughout life. But studies in our lab and by others at Rockefeller are showing that, on the contrary, changes in the adult brain are fairly common," says Flanagan. In fact, this brain plasticity, in large measure regulated by cyclical fluctuations of hormones, may account for a good deal of the behavioral variation most creatures of both sexes display at different times and in different circumstances.

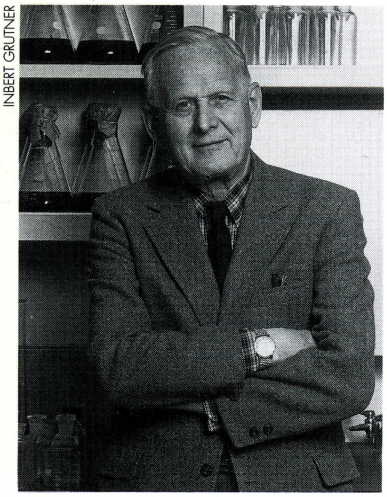
Surely, the wellsprings of behavior are far deeper in humans than in rats. But by studying how a hormonal bouquet leads to rodent romance, scientists may gather preliminary clues to such mysteries as the effect of a dozen real roses on a prospective human mate.

FROM ROCKEFELLER'S PAST

DISCOVERING THAT DNA IS THE GENETIC MATERIAL:

THE WORK OF AVERY, McCARTY, AND MacLEOD

by Kassie Evashevski



INBERT GRUTNER

Maclyn McCarty

"Forty years have passed since Oswald T. Avery, Colin M. MacLeod, and I published our paper identifying the substance responsible for the transformation of pneumococcal types as deoxyribonucleic acid (DNA)," writes Rockefeller Professor Emeritus Maclyn McCarty in the preface to his book *The Transforming Principle: Discovering that Genes Are Made of DNA*, published in 1985. "Because of the nature of pneumococcal transformation, this finding carried with it the implication that DNA must be functioning as a carrier of genetic information," he continues, "and the paper thus presented the first experimental evidence for the nature of genetic material."

"This single discovery," comments scientist and essayist Lewis Thomas in the introduction to the McCarty book, "opened the way into the biological revolution which continues to transform our view of nature in the most intimate details, and continues as well to cast up, in its wake, one biotechnology after another for the comprehension and, it can be hoped, the reversal of human disease processes."

The story of this discovery started fifty years ago, when Avery, a member of The Rockefeller Institute, as the university was then called, was investigating the chemistry of the pneumococcus, the bacterium that causes pneumonia. Avery and his colleagues had already discovered what the bacterium's capsule—its protective coating—was made of, and how this coating is involved in causing the disease. In the hope of further understanding pneumonia, they turned their attention to the process of "transformation," a seemingly mysterious process in which one strain of pneumococcus could change another.

Transformation was first reported in 1928 by the British bacteriologist Fred Griffith. While working with two strains of the bacterium *Streptococcus pneumoniae*, Griffith observed that one, which had a protective capsule, caused pneumonia; while the other, which did not have such a capsule, did not. Griffith heat-killed samples of the virulent strain and found that they did not cause the disease in mice. However, when he mixed the cells from the heat-killed strain with the avirulent strain, the latter became pathogenic.

Avery was intrigued by this report and asked his Rockefeller associate Martin Dawson to look into it. Dawson confirmed Griffith's finding and in 1931 he and his colleagues were able to induce heat-killed pneumococci to transform living organisms in a test tube instead of in a mouse. The following year, J. Lionel Alloway, of Avery's group, provided another important clue when he broke down whole dead cells and repeated the phenomenon using a cell-free extract. Thus, the transforming agent seemed to be a chemical substance.

Avery himself soon joined the search for the transforming agent, working closely at the institute with MacLeod and, later, McCarty. Growing large quantities of a virulent type of pneumococcus, the investigators began their exhaustive analysis by systematically extracting and breaking apart the chemical ingredients to test the transforming power of each one.

McCarty recalls, "There's no question that it was an exhilarating time. As we began to narrow down the possibilities of what might be in those extracts, we got very excited." In 1944 they finally hit upon a substance that possessed the transforming power. This substance, first discovered in 1869 and later defined chemically at The Rockefeller Institute by Phoebus A. Levene and Walter A. Jacobs, proved to be the nucleic acid now commonly called DNA.

That a nucleic acid had caused a heritable change in a living organism surprised the investigators because nucleic acids were thought to be structurally important, but functionally inert; at the time, only proteins were considered capable of producing such an effect. Therefore, Avery and his colleagues could not rule out the possibility that a small bit of protein in the DNA had, in fact, induced the transformation. Knowing that the enzyme DNase would destroy the DNA without affecting the protein, McCarty succeeded in the difficult task of isolating a quantity of DNase from beef pancreas suitable for testing purposes. After treating the substance with the enzyme, the investigators observed that it had lost its transforming power. In their search for a cure for pneumonia, these investigators had uncovered the secret of life itself: the genetic material.

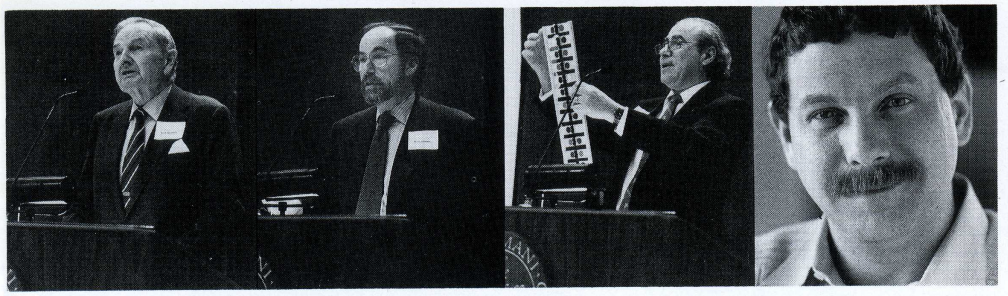
It is a great irony that Avery and his colleagues were never awarded the Nobel Prize for their work. Nevertheless, the legacy of their monumental discovery has already altered almost every aspect of biological research. In reflecting on the value of this discovery, McCarty writes in *The Transforming Principle*, "It is often pointed out that research in the basic sciences provides the base of new knowledge essential for the development of the applied sciences, including medicine. We are less frequently reminded that the reverse can also occur. Research directed against a specific medical problem [in this case, pneumonia] has resulted in contributions to fundamental biological knowledge. The most dramatic example of this is the discovery that deoxyribonucleic acid (DNA) is the substance that transmits genetic information."

KASSIE EVASHEVSKI works in The Office of Sponsored Programs at The Rockefeller University.

CAMPUS NEWS

ROCKEFELLER UNIVERSITY COUNCIL MEETING EXPLORES THE HUMAN GENOME PROJECT

by Susan Blum



Participants in The Rockefeller University Council meeting on the Human Genome Project are, from left, David Rockefeller, David Baltimore, Norton Zinder, and Eric Lander.

The human genome—the repertoire of the 50,000 to 100,000 genes contained in each cell's nucleus—is the human book of life, encoding within its pages all the instructions our cellular machinery uses to build and maintain our bodies. Passed on to each new generation via egg and sperm cells, the human genome encompasses both our past and our future.

The Human Genome Project is an attempt to read this vast book from beginning to end. Participants collaborating on the project in the United States and abroad hope to find the exact position of each gene on the chromosomes and to spell out the exact sequence of DNA that gives each gene its meaning. The endeavor is ambitious—and controversial.

The project's aims and methods were the topics when The Rockefeller University Council gathered at Caspary Hall on April 4. The Council, a group of more than 150 distinguished men and women, promotes understanding of, and inspires private support for, the university's scientific endeavors.

President David Baltimore's introduction to the session provided perspective on the Human Genome Project's history. Calling the endeavor "a splendid concept," he reminded the group that it was, nonetheless, "born in sociological and scientific controversy." The roots of this controversy extend from Darwin's time—when the English scientist's theory of evolution disturbed humankind's view of its place on earth—to the Nazis' perversion of genetics, which shook humankind to its moral core. Ever since World War II, Baltimore said, moral considerations "have pervaded everything we do in genetics."

Indeed, many of the concerns about the Human Genome Project revolve around fears that knowledge of the minutest details of our genetic endowment will lead to attempts to manipulate it directly, select for desirable health or behavioral traits it supposedly "causes," or use it as a basis for discrimination.

These concerns, though understandable, are largely based on an oversimplified understanding of what a gene can and cannot do, meeting participants reported. "A gene does not equal a disease," said Rockefeller scientist Norton Zinder, chairman of the Program Advisory Committee on the Human Genome.

Many other factors may be involved in determining whether a particular person develops a particular disease. Jan Breslow, a Rockefeller scientist who is a pioneer in applying molecular approaches to research on atherosclerosis, explained, "With many complex diseases, such as heart disease, it is not a single gene, but rather the interaction of three or four genes that heightens susceptibility." Moreover, he continued, it is not just the genes but the interaction of the genes with the environment that may transform susceptibility into disease.

Nor does a gene determine behavior or personality. "Genes have subtle effects on biology, and these are then acted on by society," said Eric Lander, a member of the Whitehead Institute for Biomedical Research and a biologist at the Massachusetts Institute of Technology. "We are the product of an interaction of nature and nurture," he continued.

If our genetic endowment does not define us, then what do we gain by defining it? A great deal, agreed meeting participants.

Mapping the entire genome and determining the structure of each individual gene will provide scientists with potent medical tools. Identification of the genes that contribute to disease will boost doctors' diagnostic powers, and knowledge of the function of genes (gleaned from determinations of their structure) will make better treatments possible. Even the DNA that does not code for genes—deemed by some to be "junk"—may yield "little gold mines" of information resulting in important insights into disease mechanisms, said Rockefeller scientist Titia de Lange.

Basic science will benefit, too. Meeting participants lauded the cooperative scientific infrastructure the Human Genome Project is creating, with its labs and working groups pursuing related research worldwide, its computerized databases providing an encyclopedic catalogue of the genome of humans and animals such as the mouse, and its technological advances speeding the process of gene analysis. "The Human Genome Project will make it possible to lay big challenges in front of bright young researchers," Lander said. "Freed from methodological limitations, they'll be able to leverage their ideas and run with them."

"PREHISTORIC" CAVE DRAWINGS DISCOVERED AT THE ROCKEFELLER UNIVERSITY

by Robert Reichert

Which came first? The "cave drawing" on the left, unearthed in a steam tunnel at The Rockefeller University, is dated "9 million B.C." The drawing on the right, which was discovered in 1940 in Lascaux, France, is thought to have been drawn 20,000 years B.C.

You follow the Rockefeller guide with some trepidation, knowing this door has not been opened for a long time. Looking at all the keys on the guard's ring, you are certain he will never find the right one. He does. On the second try, Frank Colosi, an electrician in the Maintenance Department, gets the key to turn. Your eyes wander to the sign bolted to the door: "Live Steam." The door opens, and Colosi gestures his satisfaction as a wave of heat envelopes your body. You enter what looks like a cavern. The tunnel is dark, and you are amazed at how narrow the space is. Large steam pipes hiss inches from your head.

Glancing at the walls, you wonder if the drawings are still here. Colosi haphazardly scans the walls with his flashlight. The others are ready to give up at a fork in the tunnel.

You think about the location of the famous prehistoric cave drawings at Lascaux, France: they were far from the entrances, in the darkest recesses, and very difficult to reach. They were discovered in 1940 by four boys playing in the fields at Lascaux, when their dog fell into a shaft that led to sanctuaries that man had not visited for thousands of years. A dim memory tugs at your mind: your excited art history professor telling you that these drawings must have served a magical purpose, not a decorative one, because of their obscure location. Were they most likely created some 20,000 years B.C. to help ensure a successful hunt? The thought of Cro-Magnon man creating images in the womb of the earth by the mysterious light of his torch gives you a chill. Did our ancestors want to possess or control the animals' spirits—the very animals that were crucial to their survival?

You walk down the darkest corridor, running your hand on the wall as you go forward. Your heart beats a little faster, and then, suddenly, staring back at you are drawings of animals, just like the ones at Lascaux. They are dated "9 million B.C." You remember why the Lascaux drawings are so important. They are the first evidence of man using symbolic thought, and the very beginning of art history.

The Rockefeller drawings, though, were done as a prank some twenty years ago by Kathryn Holmes, a graduate student at the time.

You worry that like the drawings in the caves of Lascaux, which have been closed to visitors, the drawings in the steam tunnel will also be lost to human view. Having begged Colosi to let you bring your camera into the cave to record these drawings deep in the bedrock under Abby Aldrich Rockefeller Hall, you release the shutter in the darkness and the flash goes off like a small nuclear explosion. Seconds afterward you hear animal sounds coming from somewhere nearby. Mice. You sense they are not enthralled with flash photography, and you are saddened when you think about how close prehistoric man was to the animal world, and how far modern man is from it.

ROBERT REICHERT, the Rockefeller Public Affairs Department photographer, is an art history buff.

JOURNAL OF CELL BIOLOGY ADOPTS NEW FORMAT

by Ruth Coxeter

The Journal of Cell Biology had its beginnings in rejection. In 1953 Rockefeller Institute investigators Don W. Fawcett and Keith R. Porter submitted a paper detailing their electron microscope study of the structure of cilia—work that foreshadowed the recognition of the cytoskeleton—to *The Journal of Experimental Medicine*, the first journal published by The Rockefeller University Press. The journal rejected the paper because it did not print papers on cell form and structure.

The article finally appeared in the *Journal of Morphology*, but the men were unhappy with the quality of reproduction of their electron micrographs, which were to have played an important role in telling the story of their research.

Porter and others proposed to Detlev W. Bronk, the new director of the institute, that The Rockefeller Press publish a journal that would reproduce the fine details of electron micrographs, and that would emphasize the importance of the study of cell form and structure. After much debate, *The Journal of Biophysical and Biochemical Cytology* was established in 1955. As cell biology became a recognized discipline, the list of submissions and subscribers grew. In 1962 the journal's name was changed to *The Journal of Cell Biology*.

Looking back to the journal's first issue, Rockefeller Professor Emeritus Philip Siekevitz notes, "It hardly seems possible that in so short a time we have come to view the cellular world as familiar terrain."

Cell biology continues to evolve, and *The Journal of Cell Biology* along with it. This year it is delivering scientific developments faster and more clearly as a result of its new format and a semi-monthly publication schedule. Students, medical residents, and postdoctoral fellows can subscribe to *The Journal of Cell Biology* at a special rate by contacting The Rockefeller University Press (212-570-8572).

UNIVERSITY HONORS 1991 GRADUATES

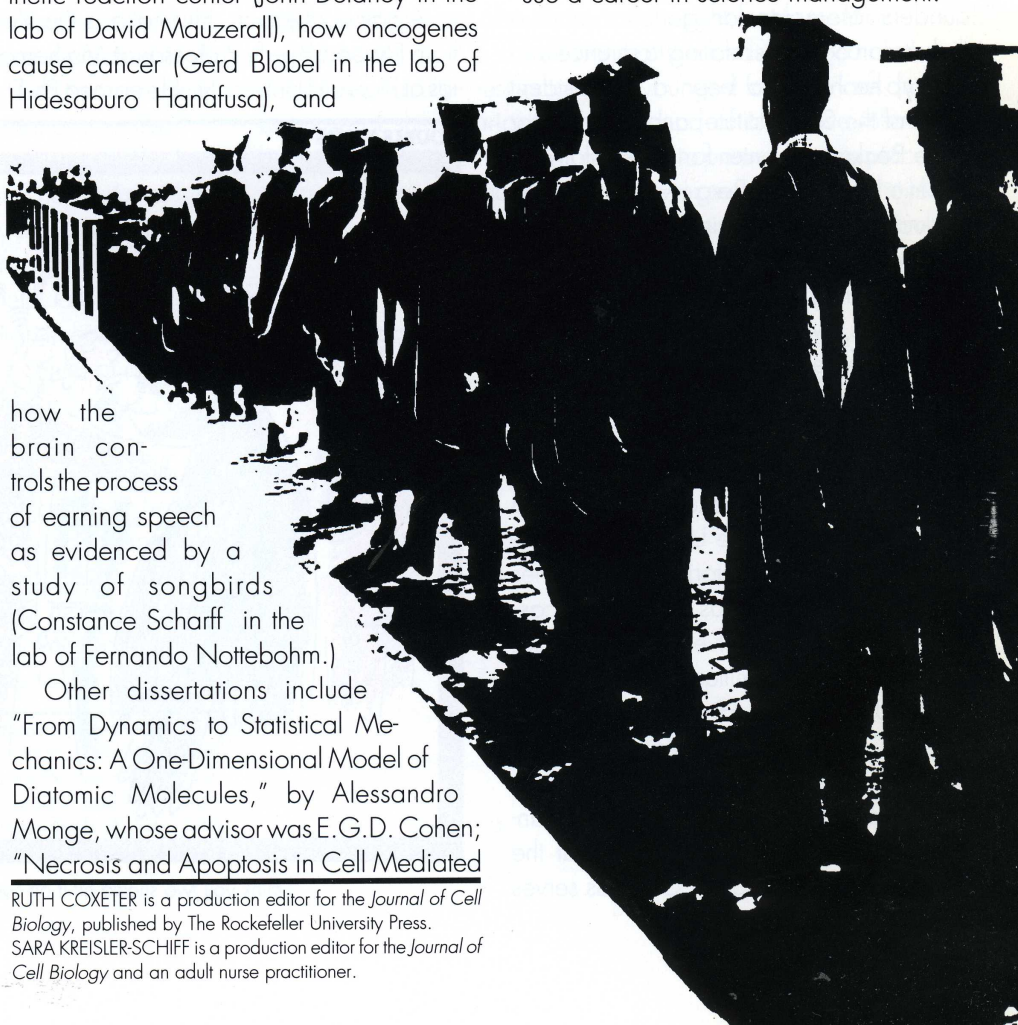
by Ruth Coxeter and Sara Kreisler-Schiff

Fresh from their studies in subjects as diverse as the tse tse fly and gravitons, the members of one of the largest classes in the university's history were honored at Rockefeller's thirty-third commencement ceremony June 5. Twenty-three Ph.D. students and four M.D./Ph.D. students received Rockefeller degrees. As is customary, each graduate student's mentor spoke about his or her advisee's work.

The students earned their degrees in part by fulfilling a research requirement resulting in the completion of a doctoral dissertation. This year's class worked in a variety of areas and laboratories at the university. Some samples of their thesis work are a study of a model system for the photosynthetic reaction center (John Delaney in the lab of David Mauzerall), how oncogenes cause cancer (Gerd Blobel in the lab of Hidesaburo Hanafusa), and how the brain controls the process of earning speech as evidenced by a study of songbirds (Constance Scharff in the lab of Fernando Nottebohm.)

Other dissertations include "From Dynamics to Statistical Mechanics: A One-Dimensional Model of Diatomic Molecules," by Alessandro Monge, whose advisor was E.G.D. Cohen; "Necrosis and Apoptosis in Cell Mediated Cytotoxicity," by Arturo Zychlinsky, a student of John Ding-E Young; and "The Processing of Contrast in Primate Visual Cortex," by David P. Edwards, working in the laboratory of Ehud Kaplan.

Most of the graduates will assume postdoctoral positions in an array of academic institutions throughout the world, continuing their study of science. The M.D./Ph.D. students will complete their clinical training at Cornell University Medical College. One student, Jessica Hopfield, whose dissertation on the nervous system was done under the direction of Paul Greengard, plans to enter the M.B.A. program at Harvard University in the fall, and hopes to pursue a career in science management.



RUTH COXETER is a production editor for the *Journal of Cell Biology*, published by The Rockefeller University Press.
SARA KREISLER-SCHIFF is a production editor for the *Journal of Cell Biology* and an adult nurse practitioner.

ROCKEFELLER BOARD SELECTS FOUR NEW TRUSTEES

The Rockefeller University Board of Trustees has elected four new members since last July, reports its chairman, Richard M. Furlaud. The new trustees are Paul Berg, Gustavo A. Cisneros, Pehr Gyllenhammar, and Heisuke Hironaka.

The Sam, Lulu and Jack Willson Professor of Biochemistry at Stanford University School of Medicine, Berg won the Nobel Prize in chemistry in 1980. He is the recipient of many other awards as well, including the Albert Lasker Basic Medical Research Award and the New York Academy of Sciences Award. Before joining the Stanford faculty, he was a member of the Department of Microbiology at the Washington University School of Medicine in St. Louis. One of the founders of molecular genetics and a spokesman on issues relating to science and society, he has also been a non-resident fellow of the Salk Institute, and is a director of the Beckman Center for Molecular and Genetic Medicine. Berg was an undergraduate at Pennsylvania State University, and received his Ph.D. from Western Reserve University.

Cisneros, who has been a member of The Rockefeller University Council since 1980, is president and chief executive officer of Organizacion Cisneros, the parent organization of more than fifty companies operating in Venezuela, other Latin American countries, the United States, Europe, and Asia, with factories and branches around the world. He was born in Caracas, Venezuela, and is involved with numerous civic groups and committees in Latin America and the United States. He is also a trustee of Babson College, where he earned his B.S. and B.A. degrees; United World Colleges; and the Joseph H. Lauder Institute of Management and International Studies at the University of Pennsylvania. Cisneros serves as president of the Simon Bolivar Foundation, based in New York, which supports social and educational campaigns throughout Latin America.

Gyllenhammar has been chairman and chief executive officer of Volvo since 1983. A native of Sweden, he was educated at the University of Lund, graduating in 1959, and studied international law in England and maritime law in the United States and Switzerland. He is the author of four books on humans at work and industrial policy, and has contributed articles to the Swedish and international press. Gyllenhammar holds directorships in several companies and is chairman of the board of Swedish Ships Mortgage Bank.

A native of Japan, Hironaka is the William Elwood Byerly Professor of Mathematics at Harvard University. He earned Ph.D.s at both Harvard and Kyoto Universities, and has been on the faculty of Brandeis and Columbia Universities and a research fellow at the Institute for Advanced Studies in Princeton. Hironaka is the recipient of many honors and awards, including the Fields Medal Prize in mathematics, the Japan Academy Award, and the Japanese Order of Culture Award. He has been elected to membership in many societies, including the American Academy of Arts and Sciences, and the Japanese and American Mathematical Societies.

Furlaud, president of the Bristol-Myers Squibb Company and a university trustee since 1976, was elected chairman of the board in July 1990, succeeding William O. Baker, who retired from the post after serving as chairman for a decade. Baker is also retired chairman of Bell Laboratories.

DOUBLE TAKES

"I think you two should hit it off - you have 98% of your DNA in common."

VIEWPOINT

SCIENCE WITH BELLS ON

by Lewis Thomas

This essay is an excerpt from an address by Lewis Thomas at the installation of David Baltimore as president of The Rockefeller University.

Lewis Thomas

The direct significance of basic biological science for medicine, and now the possibilities for not only comprehending the mechanisms of disease, but doing something to correct them, seem to me brighter today than ever before.

Even the work in the most arcane regions of pure biology is beginning to catch the attention of those among us most obsessed with human medicine. Who would have guessed, when Rockefeller scientist Donald Griffin and his colleagues started a small-scale project in animal behavior, that within a couple of decades we would find ourselves with beautiful models for exploring the two deepest puzzles in human biology: the cellular basis for language itself—surely as basic a problem for human biology as any I can think of—and the phenomenon of regeneration of neuronal networks within the substance of the brain. The studies reported by scientist Fernando Nottebohm and his colleagues at the university, dealing with canaries in the lab and song sparrows in the field, are providing astonishing information about language acquisition in early life, the lateralization and cellular structure of a language center or centers, and the mechanisms of cell death and regeneration in proper brain cells, all thanks to song sparrows and canaries.

It is now one of the great truths in all of nature. At the nestling stage, a song sparrow hears the song of his species. He needs to hear it for only a brief period, a few days. Then, even if kept in silence for the next ten or so months, now ready for real life, at the moment of his mating season, he begins singing precisely that song, the complex melody of song sparrows. But if he is confined to quarters at that early stage of learning, and exposed only to the song of a swamp sparrow, he will sing, when the season arrives, a flawed swamp sparrow melody, maybe mixed with fragments of what would have been his proper song. And if in early life he is confined in total silence, hearing no song at all, when mature he will be able to sing nothing but a crude, unmelodious sort of buzz. What is more, at the time when a songbird or canary comes into the season of song, a mass of new brain cells and their connecting fibers appears deep in the left side of the brain. When the season is over, the cells die off and away; then, next season, a new assemblage of the same cells develops in the same region of the brain. This, I assert, is hot stuff.

I would predict that this level of basic science—the kind of enterprise former Rockefeller scientist Jim Shannon used to call "undifferentiated research"—will sooner or later lead to related studies on the wards and clinics of The Rockefeller University Hospital.

The same can be said, with even more confidence, about the eventual outcome of the new focus on neurobiology at large, to which the university has committed extensive resources. Give it twenty years, I'd estimate, maybe less, and we should be able to make good guesses about a human thought, not to mention a word.

For the future, it is a safe bet that the kinds of research that the Rockefeller faculty—especially the youngest faculty—are drawn to because of sheer curiosity and the kind of obsessive interest that causes endless insomnia, will continue to preoccupy this place. And almost as safe a bet that science done for such reasons is the likeliest to lead to surprise, and surprise—on the best of days astonishment—is the only way to get along in science.

LEWIS THOMAS is scholar-in-residence at the Cornell University Medical College and president emeritus of Memorial Sloan-Kettering Cancer Center. He has served on the faculties of five schools of medicine. He received the National Book Award in Arts and Letters for *The Lives of a Cell*, and the American Book Award and Christopher Award for *The Medusa and the Snail*. His memoir about his career, *The Youngest Science*, has been followed by two more books of essays, *Late Night Thoughts on Listening to Mahler's Ninth Symphony*, and *Etcetera, Etcetera: Notes of a Word-Watcher*.

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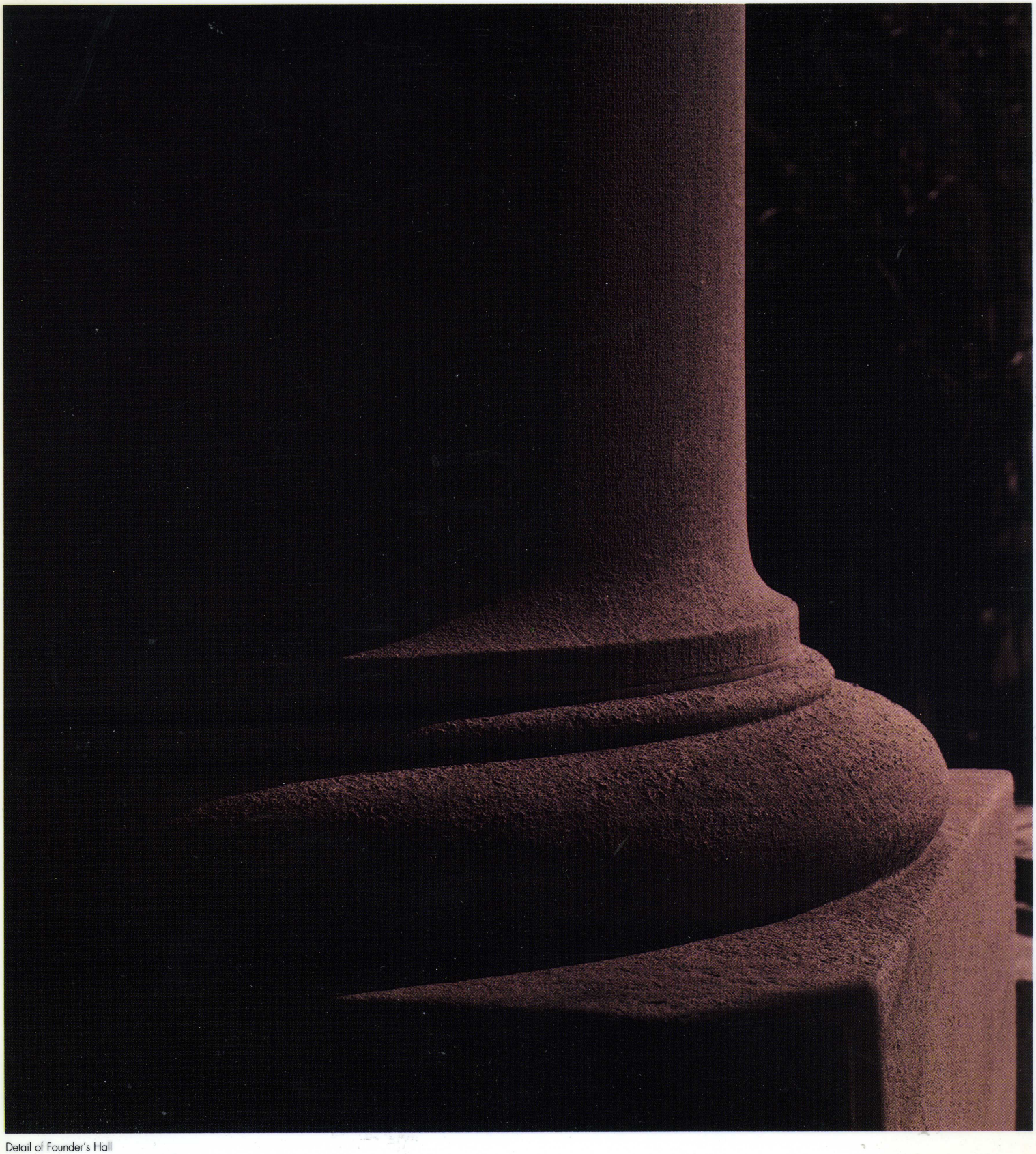

Detail of Founder's Hall