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The Rockefeller University

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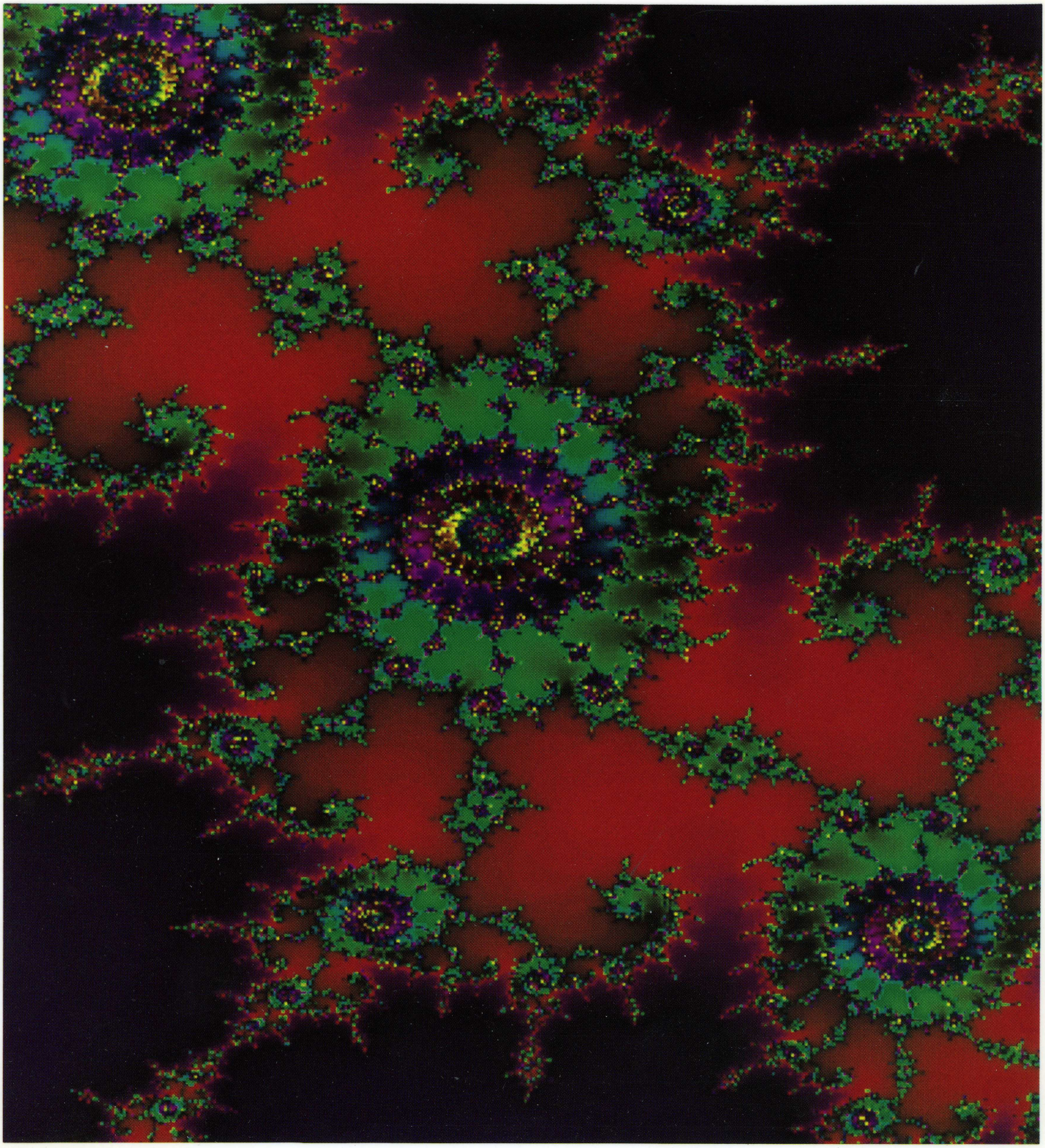

SEARCH

CONTENTS

On Seeing Molecules
by David Baltimore **2**
The Theory of Chaos
by Michael D. Lemonick **3**
Tackling Duchenne Muscular Dystrophy
by Harold M. Schmeck, Jr. **6**
Pursuing Genetic Determinants of Atherosclerosis
by Susan Blum **8**
The Discovery of Ribozymes
by Geoffrey Montgomery **12**
The Gardens of The Rockefeller University
Text by Niloufar Leibel
Photos by Leif Carlsson **14**
Bird Songs and Neurogenesis
by Geoffrey Montgomery **18**
The Delta Agent Story
by Philip DiMauro **20**
The Beginning of Modern Cell Biology
by Catherine Vanchieri **22**
Campus News **23**
Science and Life
by Salvador E. Luria **27**

ON THE FRONT COVER

A computer-generated fractal, a shape that is, in theory, infinitely complex and may help explain the deepest problems of physics. This pattern and the one on page 3 were generated by Anthony M. Popowicz, assistant director for scientific computing, Computing Services.

ON THE BACK COVER

Flowering crabapple with ivy ground cover across from Abby Aldrich Rockefeller Hall. Photo by Leif Carlsson.

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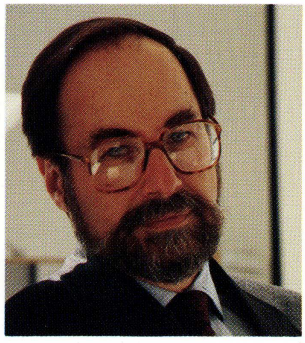
COMMENTARY

ON SEEING MOLECULES

by David Baltimore
President, The Rockefeller University



At a recent lecture I gave to non-scientists, I was asked how a molecular biologist sees the molecules he or she works with. My first reaction was that we use the word "see" as a metaphor—we rarely see molecules at all. We say we see them because in our minds the molecules have the vividness that scenery has to a landscape painter, or the magazine in front of you has to the reader. Our intimate acquaintance with molecules comes not from staring at them in real life, or even in photographic images, but because the techniques we have to study molecules teach us about their size, shape and contours. We use this information to build models, either physically or on a computer, blowing up the molecules to a size we can cope with. Our vivid sense of the molecules really comes from our remembrance of the models.

But, I was asked, isn't there an electron microscope to see molecules? Yes there is, but the sample preparation methods and the problem of fixating on selected images make it a poor way to get routine knowlege about molecules. Also, the resolution of such a microscope is too low to see the detailed structure of molecules. The question, however, raises an interesting philosophical issue. Electron microscopes are not a way of seeing in the usual sense. They use electrons to make an image the way the photons of light make images for us in the ordinary world. We cannot directly sense electrons so we translate the image into photons using a fluorescent screen or photographic paper.

But then, how do we see photons? We do it by virtue first of lenses—the lens in our eye and the lens in our glasses, if we wear them. After passing through the eye's lens, photons impinge on our retina, where the image is translated into electronic impulses. These travel along nerves, are passed to other nerves by chemical transmission, and make the image we sense by a complicated series of stimulatory, inhibitory, and integrative signalling of nerve cells. In fact, the electron microscope sees in a much more direct way than we do because it uses lenses, but then records the image as a point-by-point record, rather than using the complicated machinery of the brain.

The technique we most often depend on to learn about molecules is X-ray crystallography. More recently, nuclear magnetic resonance (NMR) has come into use for determining the structures of molecules. Neither of these methods would seem to be "seeing." There are no lenses to focus the images made by X-rays, and, therefore, complicated calculations are needed to extract structural data from the spots on photographic paper that X-rays leave as a mark of their passsage through crystals. NMR is a method that uses no rays of any kind to create an image; it depends entirely on calculations to extract structural information. But the calculations in both methods are certainly more unambiguous than the complicated processing of images in our brains. For X-rays, the calculations really just take the place of lenses, otherwise X-ray crystallography is basically a photographic process.

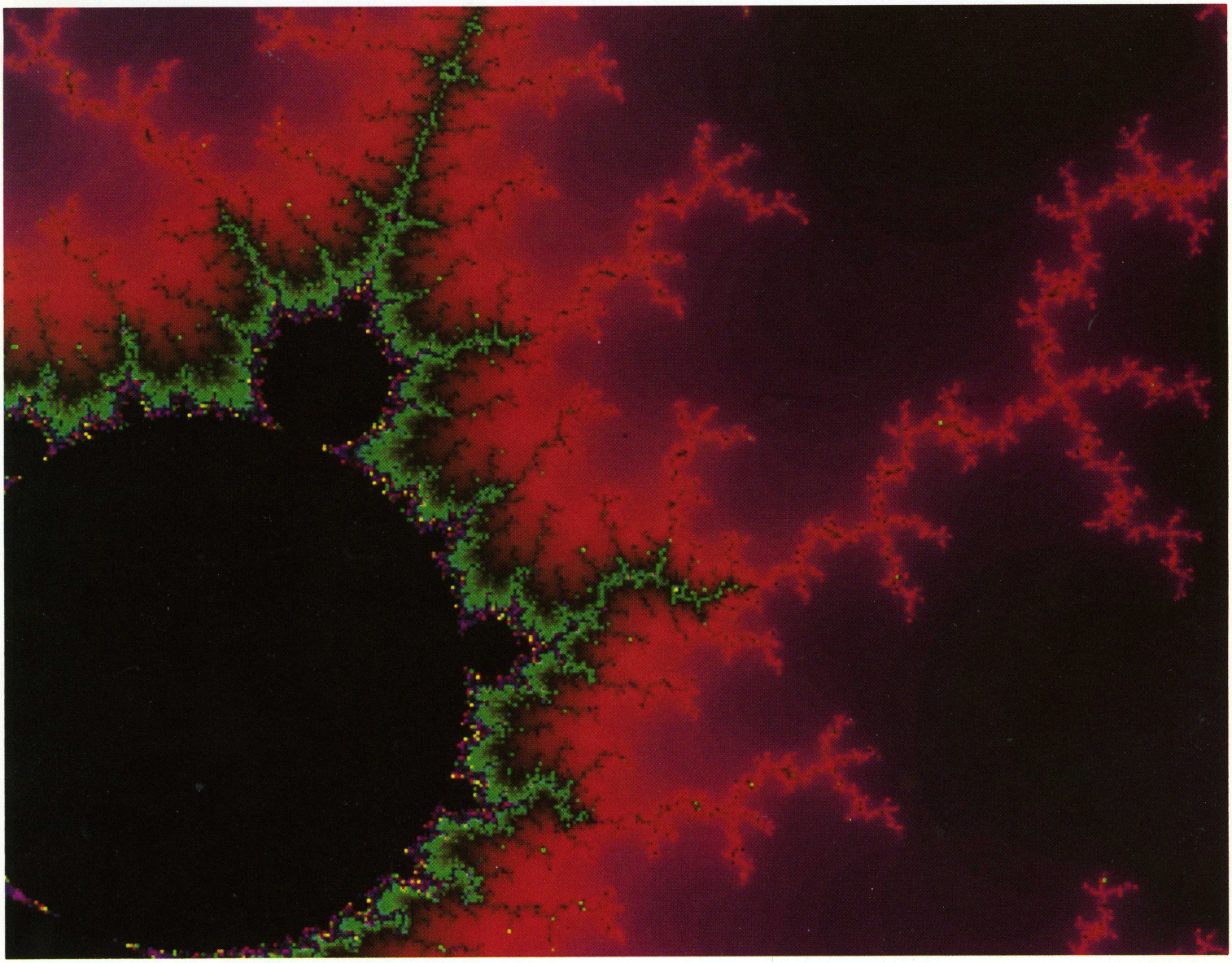
Thus, maybe we really do see molecules. The methods we use are, in a sense, as much "seeing" as the direct use of photons and lenses. It is a philosophical question, but one that most of us settled comfortably without much thought long ago when, as children, we first saw a photograph. Once we got over the amazement of seeing daddy's and mommy's image caught on paper, we became used to the idea of "seeing" by using intermediary instruments. First a camera, then a telescope, then, perhaps a light microscope. For molecular biologists the tools may be less familiar and the methods may depend more on mathematics than on lenses, but the result is the same.

Yes, I guess we do see molecules.

CLOUDS, SANDPILES, AND WATERFALLS:
MITCHELL FEIGENBAUM AND THE THEORY OF CHAOS

by Michael D. Lemonick

Below: Detail of computer-generated fractal pictured on cover. The mathematics of fractal geometry may help Mitchell Feigenbaum and colleagues describe the behavior of complex systems.



Mitchell Feigenbaum is only interested in the deepest problems of physics, which is why he is building sandpiles. "Imagine a table with a pile of sand on it," he says. "And imagine that you start pouring more sand onto it." What happens is obvious: the pile grows until it is so steep that little avalanches begin. Sometimes the avalanches will simply move the sand around on the table; sometimes sand will fall off the edge. "Now," says Feigenbaum, "you start keeping a record of how much sand falls off the table every five seconds." The overflow will be very irregular—again, an obvious point. "The question," he says, "is, 'can you *predict* the pattern of overflow?'"

It turns out that this problem is overwhelmingly difficult—so difficult, in fact, that Feigenbaum and his colleagues work not with a real, three-dimensional sandpile but with a one-dimensional analogue, in which the sand can avalanche in only one direction, operating under extremely simple physical laws; the analogue exists only in a computer. "Even then," he says, "the problem is extraordinarily complex, about as complex as the hardest problems in high-energy physics."

Mere complexity is not the attraction, though. The problem is also a testing ground for new mathematical techniques that could finally solve the utterly baffling problem of turbulence in physical systems—clouds, waterfalls and the like. "The problem was first posed well over 100 years ago," says Feigenbaum, "and many of the greatest physicists of the twentieth century, including

MICHAEL D. LEMONICK, a free-lance writer living in Princeton, New Jersey, has been a science writer for *Time* magazine.

Right: Mitchell Feigenbaum at The Rockefeller University. He is the Toyota Professor at the university

Einstein, Feynman, and Heisenberg, worked on it without making much progress."

Why should Feigenbaum do better? Not necessarily because he and his collaborators are better than their predecessors at finding answers, but because the relatively new science of chaos (pioneered by Feigenbaum, among others) has enabled them to understand the nature of the problem better, and thus to pose the right questions. The right question for clouds, sandpiles and waterfalls is: How can you use statistics to describe the behavior of complex systems? Before you can answer that question, you not only have to know all the possible states the system can be in—all the possible arrangements of individual sand grains in the pile, or of wisps of water vapor in the cloud—but you also have to know how often each arrangement is likely to occur. "The traditional way to do it," he says , "is to assume that each configuration is equally likely. That makes the problem much easier, but it gives you the wrong answers."

Feigenbaum and his colleagues haven't yet worked out a better way, but they suspect that the answer may lie in the mathematics of fractal geometry. A fractal is a shape that, in theory at least, is infinitely complex. No matter how closely you look at it, it always has finer and finer detail. Moreover, a fractal exhibits self-similarity: the details at all scales look the same. A reasonable real-world approximation is a fern, in which the main stem has branches, each of which looks like a miniature fern, and off of which come sub-branches that themselves look like even tinier ferns. Another is a coastline, which looks about equally jagged when viewed from one hundred miles up, ten miles up or one mile up.

There are two remarkable facts about fractals. One is that their intricate shapes can be described by extremely simple mathematical rules, called scaling functions. And the other is that the shapes generated by such rules look very much like real objects—not just ferns and coastlines, but mountains, trees, snowflakes, and clouds. "You can imagine making a cumulus cloud," says Feigenbaum, "out of a spherical blob decorated with smaller spherical blobs. To make the cloud look realistic, you have to make the scales of these smaller blobs different, and distribute them randomly. But you can find a scaling function that will describe a cumulus cloud very accurately."

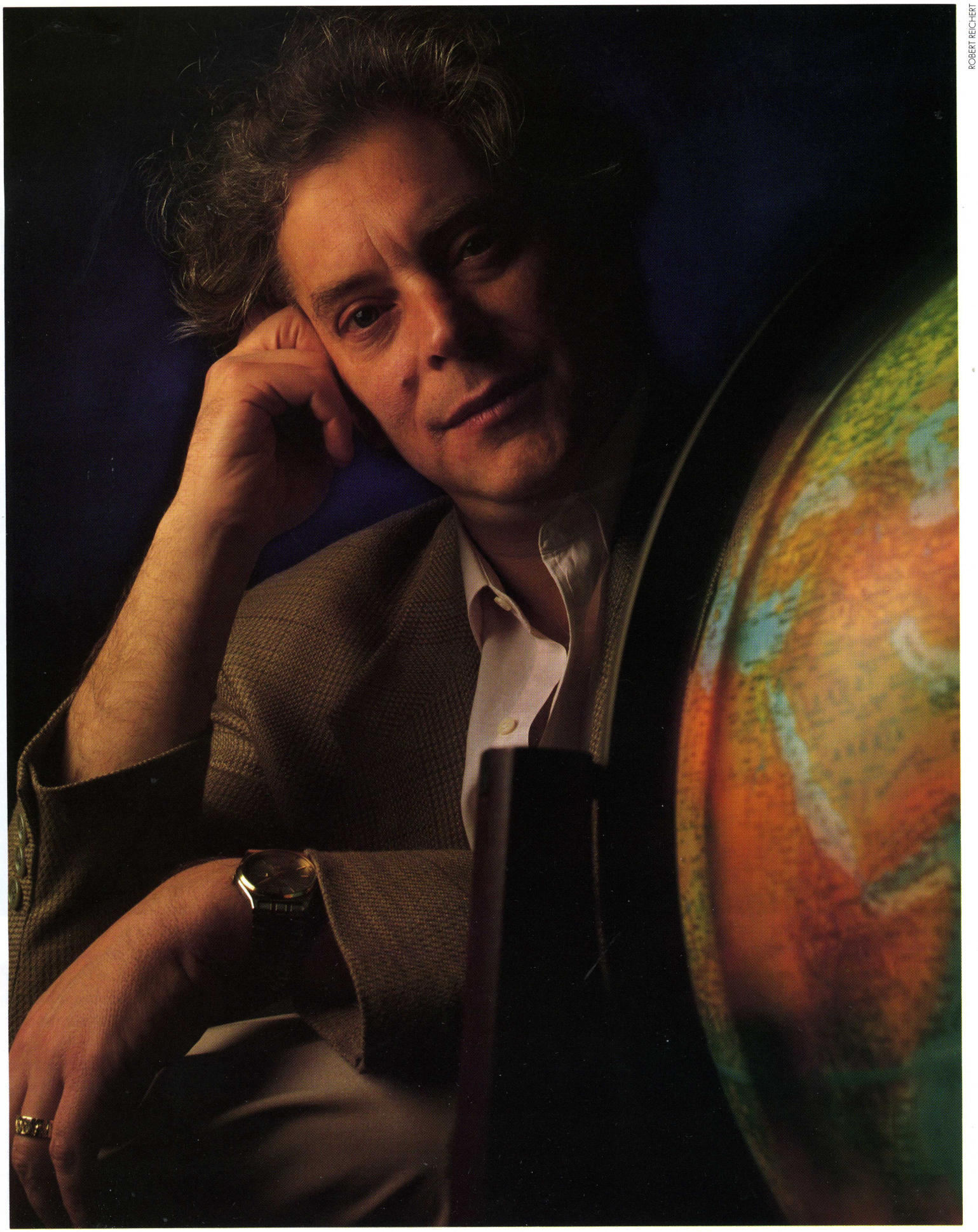
Making a cloud is easy; getting it to evolve realistically over time is not. "Ordinarily, you'd solve the problem with the equations of fluid dynamics, but that means you have to divide the cloud up into imaginary cells, know the density of water vapor and the temperature in each cell, know how each one is moving, and then calculate what each one will look like a short time later." That is much too difficult a problem for even the most powerful computer to solve, but Feigenbaum believes there may be a much simpler way to approach it. "What one wants to do," he says, "is to apply the laws of fluid dynamics, not to the cloud itself, but to the much simpler equations of the scaling function. In other words, you have to understand what the laws of motion look like in *that* world." Again, the answers may be years away, but when they come they may well be generalizable to sandpiles and other real-world phenomena that baffle modern science.

There is, of course, no guarantee that Feigenbaum can crack the problem, but he does have a track record on this sort of thing. His most important and celebrated work came in the late 1970s, when the science of chaos was undergoing its most rapid growth. One major unanswered question was how a physical system makes the transition from orderly to chaotic behavior. In the case of a dripping faucet, for example, a certain flow will produce a steady drip. Open the faucet a little and the drip gets faster, but is still steady. Eventually, though, with more water flowing (though not enough for a steady stream), the drips will become erratic and unpredictable.

Feigenbaum's remarkable discovery was that there is a definite pattern discernible in the changeover from steady to chaotic dripping, and, most important of all, that the simple mathematics underlying the changeover is identical for chaotic systems as seemingly disparate as the fluctuations in animal populations, oscillating electric circuits, and certain chemical reactions. The transition to chaos, he proved, is a universal phenomenon. "If I gave you the numbers for any of these systems without telling you the units—drips per second or population per month—you wouldn't be able to distinguish one from another," he says.

The fact that he works with complex mathematics raises the reasonable question of whether Feigenbaum is really a mathematician or a physicist. His degrees are in physics, but his appointment at Rockefeller is technically as a mathematician. "That happened to be a slot that was vacant when I was hired," he says with a laugh. "I suppose I'd most accurately be described as a mathematical physicist." Working in the physical rather than the biomedical sciences makes him a member of a rather small minority group at the university, but he feels comfortable with that status.

"I have various discussions with biologists," he says. "Some of them go places, some of them don't." One that did was a collaboration in which he and a student helped analyze the electrical fluctuations of a single neuron, with a view to determining whether the cell behaved chaotically or not. Another problem has to do with the behavior of fibroblasts, the cells that form scar tissue in wounds. "If you look at the way they travel to the sites of injuries, the paths are not random, but the data are compatible with the idea that they move chaotically." Feigenbaum has also mused over mutations in viruses and the "software" governing the eye's tracking system. "If you can find someone willing to listen to your ideas," says Feigenbaum, "this is actually a very good place for a physicist to be."



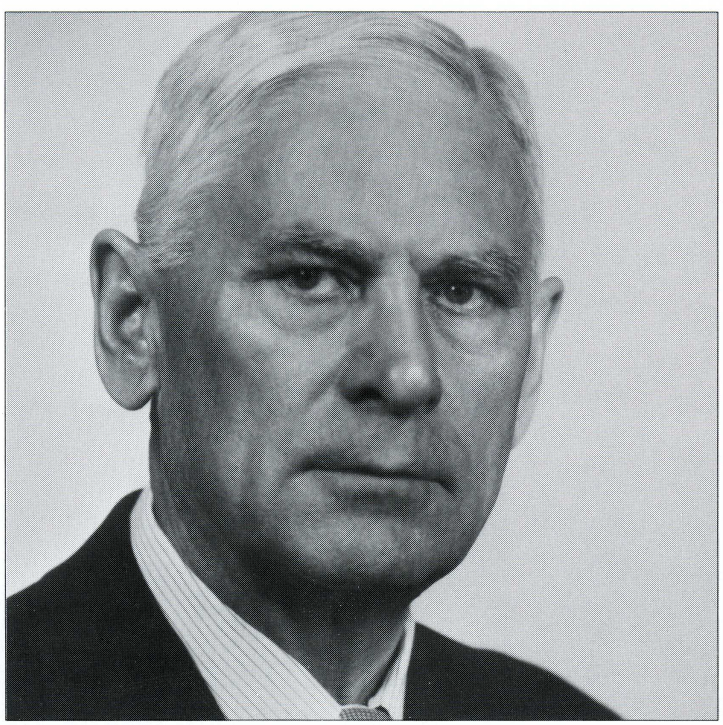
ROBERT REICHERT

HEIR TO A SCIENTIFIC HERITAGE: LOUIS KUNKEL TACKLES DUCHENNE MUSCULAR DYSTROPHY

by Harold M. Schmeck, Jr.

If your grandfather was a noted botanist and plant pathologist at Rockefeller when it was still called an institute, and your father was a research leader in clinical immunology there, what do you do?

If your name is Kunkel, you plunge into molecular biology and make one of the most important advances in the war against genetic disease. It was not a direct progression by any means. The path depended somewhat on the modern need to search high and low for research funds and even more on Louis Pasteur's famous dictum that chance favors the prepared mind. In this case the preparation spanned three generations.



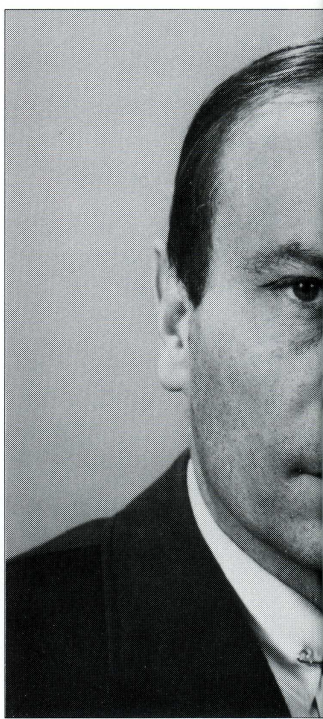
"There was always an interest in our home in understanding the things around us—the flowers, the plants, the birds, the animals," says Louis M. Kunkel, who is now a research scientist at Children's Hospital in Boston and professor of pediatrics and genetics at Harvard Medical School.

Most of his career has been a quest to understand Duchenne muscular dystrophy, one of the most tragic of genetic diseases.

But the progress toward that disease began with botany, partly, no doubt, a legacy from his grandfather, Louis O. Kunkel. Growing up in Crestwood, New York, the younger Kunkel was guided by his father, Henry G. Kunkel, in studying and actually breeding irises as a childhood outdoor hobby. In the process he learned something of the fundamentals of genetics. Both Kunkel's father and grandfather have since died, but as longtime Rockefeller scientists, they both made important contributions to their own fields of research.

Louis O. Kunkel, born in Missouri, received his Ph.D. at Columbia in 1914. He specialized in plant diseases and was a key figure in early study of plant viruses, particularly those of mosaic disease of tobacco and other plants. His son, Henry G. Kunkel, made early contributions to hepatitis research and later did important work in clinical immunology and the structure of antibody molecules. Each scientist trained key people who became scientific leaders of the next generation. Both fields, virus research and the molecular details of antibody formation and function, were to prove crucial to the development of modern molecular biology, Louis M. Kunkel's field.

As an undergraduate at Gettysburg College in Pennsylvania, Louis M. Kunkel was thinking seriously of graduate studies in plant biology. A summer job at Cornell University Medical College across Sixty-Eighth Street from Rockefeller changed that focus forever.



The job was in the laboratory of Alexander Bearn, who had been a fellow in his father's laboratory at The Rockefeller University, and who is currently an adjunct faculty member and a visiting physician, as well as a member of the board of trustees at Rockefeller. The project was to use cell cultures to define the genetic problem in Marfan's syndrome, an inherited disease of connective tissue that can cause abnormalities of the eyes, the bones, and the cardiovascular system.

In a trip to Johns Hopkins to collect biopsies from Victor McKusick's large roster of Marfan patients, the young potential botanist met the famous human geneticist. The effect was to add another human geneticist to the nation's scientific rolls. After graduating from Gettysburg College, Louis Kunkel enrolled at Johns Hopkins. His Ph.D. thesis was on isolating DNA sequences unique to the human Y chromosome.

Next came two years at the University of California, San Francisco, where the new art of gene cloning was blossoming with incredible promise. Kunkel learned the techniques from experts. Later he moved to Children's Hospital in Boston, where scientist Samuel A. Latt wanted to add a strong competence in molecular biology to

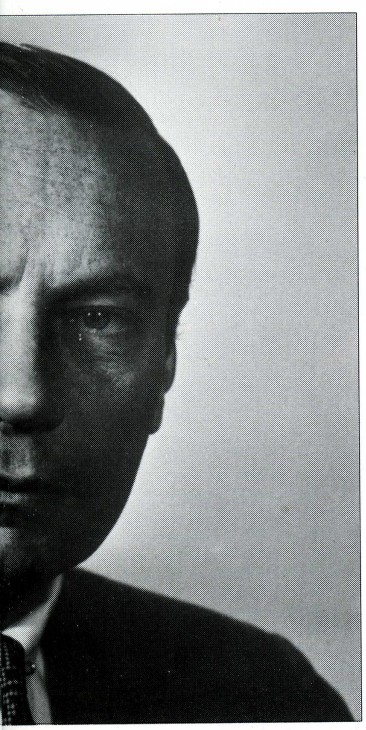
HAROLD M. SCHMECK, JR. is a free-lance writer who retired recently after thirty-three years covering science for *The New York Times*.

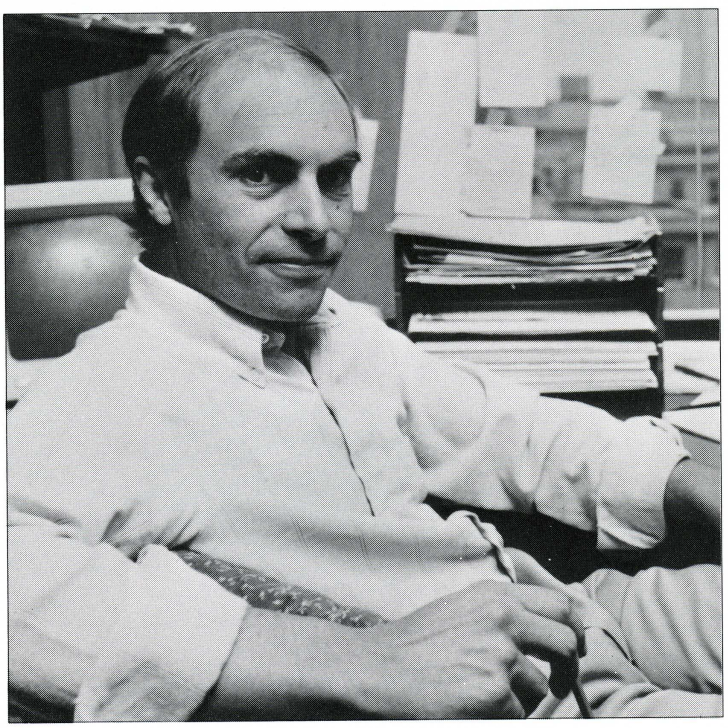
Photos, left to right: Louis O. Kunkel, Henry G. Kunkel, Louis M. Kunkel

his laboratory's already powerful skills in cytogenetics. But Latt could supply research support for only the first year. Kunkel would have to find support of his own.

"One of the things we wanted to do was study the human X chromosome," Kunkel recalls, "and there is a very major disease that is known to be located there."

Maybe they could make progress on that disease—Duchenne muscular dystrophy. Kunkel applied to the Muscular Dystrophy Association for a fellowship. The idea was to work on the X chromosome with Latt and generate markers to follow the still-unidentified Duchenne gene in families at risk for the disease.





"I got the fellowship and started working on the problem," Kunkel recalls, "and as things went along, the problem got more and more interesting and I focused more and more on Duchenne muscular dystrophy and less and less on the X chromosome in general."

As a disease, Duchenne muscular dystrophy is a recipe for tragedy. Boys who seem buoyantly healthy as infants and toddlers later begin to stumble and suffer from inexplicable and increasing weakness of their muscles. Slowly, that weakness progresses and eventually brings death, often from failure of the respiratory muscles and the heart.

As a scientific problem, the disease had always been difficult, almost impenetrable. Patterns of heredity showed there must be a flaw on the X chromosome. But that was cold comfort. Heredity was not a treatable condition.

In the early 1980s, however, the Muscular Dystrophy Association was beginning to see real hope in molecular biology. They enlisted Kunkel and the team he had formed at Children's Hospital as one of about a half dozen research groups who were young, imaginative, and willing to put a major effort into the problem.

In 1986, Kunkel's research team was the first to identify the faulty gene that causes Duchenne muscular dystrophy. Only a year later, they identified the protein that is the product of that gene. Lack of the protein, now called dystrophin, causes the fatal degeneration of muscle in Duchenne muscular dystrophy. The protein proved to be part of the cytoskeleton—the web that keeps the muscle cells spatially organized and structurally intact. Because of many lines of evidence including the crucial fact that the disease develops very slowly, Kunkel believes dystrophin is one of a family of still-unidentified proteins. Those other dystrophin-like proteins presumably fill the breach for a time by doing the job of the missing dystrophin.

Thus, Kunkel's major achievements in identifying the gene and the protein are opening new horizons. Now, the mechanism of Duchenne muscular dystrophy can be better understood and the stage is set for the first rational treatments for the disease.

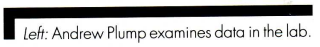
Doctors are attempting transplants of normal myoblasts (muscle cell precursors) to give the muscles of Duchenne patients some dystrophin. In animal experiments, gene transfer has been successful in putting new genes into heart muscle, part of a long-range strategy to protect that muscle against fatal dystrophy.

These are a few of the new ideas made possible by knowledge of the gene and its product. The story of Duchenne muscular dystrophy is entering a profoundly hopeful new stage, thanks to Kunkel's research. But there is one additional dividend from years of scientific effort that gives him particular pleasure. It brings the story of three generations of scientists full circle. Last year, Kunkel became a member of the prestigious National Academy of Sciences—as his father and his grandfather had both been elected before him.

It was the first time that three generations of the same family had ever been honored with membership.

THE HEART OF THE MATTER:
PURSUING THE GENETIC DETERMINANTS OF ATHEROSCLEROSIS

by Susan Blum



Left: Andrew Plump examines data in the lab.

Andrew Plump took a break from medical school to pursue a Rockefeller Ph.D. because he wanted some answers. "I loved my medical studies, but they focused on the 'whats,'" says Plump. "I wanted time to study the 'whys."

He came to the right place. As a graduate student in the laboratory of Jan Breslow, Rockefeller's new physician-in-chief, Plump is part of a team pursuing a major medical mystery: coronary heart disease.

Why do some people live exemplary lives—exercising, eating right, and foreswearing tobacco—yet still develop heart disease in their twenties or thirties? Why do others live sedentary lives and eat and smoke with abandon, yet live to old age free of the disease? And why, when behavioral choices seem to make so little difference for a few, are they so important for most of us in determining whether or not we get heart disease?

The answer lies in our genes, but not in a simple way. Unlike conditions such as cystic fibrosis and muscular dystrophy, which are caused by defects in a single gene, no one gene causes heart disease. Instead, many different genes interrelate to determine susceptibility to the disease.

Naturally occurring variations in these genes lead to differing degrees of susceptibility. Some patterns of variation make heart disease nearly inevitable, while others confer virtual invulnerability to the disease. But these extremes of genetic determinism are far less common than the patterns that permit the influence of exacerbating or mitigating factors such as smoking, diet, and exercise.

The Rockefeller researchers want to learn how these patterns work in atherosclerosis, the condition in which deposits build up in the lining of the arteries and progressively limit blood flow. Blockage to the arteries nourishing the heart is called coronary heart disease. When the blockage becomes severe, the result is often a heart attack, or even death.

A prime component of the artery-clogging deposits is cholesterol, a fatty, waxlike substance that circulates through the body via the bloodstream. In fact, says Plump, the link between blood cholesterol and atherosclerosis is so direct that "some people have made the analogy that cholesterol is to heart disease as smoking is to cancer."

The development of atherosclerosis is determined in large part by the functioning of the system that carries fats and cholesterol throughout the body. Central to this system are the lipoproteins—spherical, protein-coated particles that ferry the insoluble fats and cholesterol within the watery environment of the blood.

There are five kinds of lipoproteins; differences in the patterns of relationships among them help determine susceptibility to heart disease. As most health-conscious people know, high levels of low-density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) are risk factors for developing atherosclerosis. So are high levels of other, less familiar lipoproteins: very-low-density lipoprotein (VLDL); chylomicrons; and a modified form of LDL known as Lp(a). On the other hand, high levels of HDL and low levels of LDL protect against atherosclerosis. Though the subtleties of each pattern vary, the bottom line is that differences among them reflect the relative balance of lipoproteins that carry fats and cholesterol *to* tissues, and lipoproteins that remove cholesterol *from* tissues.

Levels of the various lipoproteins are directly controlled by at least seventeen different genes. Ten of them code for apolipoproteins, proteins on lipoproteins' outer coats that help direct cholesterol traffic. The remaining genes code for proteins involved in other aspects of lipoprotein manufacture, breakdown, and function.

The genes controlling the transport and metabolism of fat and cholesterol are the subject of study in the Breslow lab. A pioneer in the molecular biological approach to atherosclerosis, Breslow in 1982 was the first researcher ever to identify an apolipoprotein gene, elucidate its precise DNA sequence, and analyze variations within it that contribute to heart disease. Since then, Breslow and his Rockefeller colleagues have been instrumental in advancing knowledge about lipoprotein genes on a number of fronts.

One focus of their current research is how the genes function, and how the functions interact. To investigate these questions, the scientists have enlisted the mouse.

With a genetic endowment remarkably similar to that of humans, and a breeding cycle that produces a new generation about every two months, mice have long been a valuable source of naturally occurring genetic variations that can elucidate gene function. Today, mouse studies are more fruitful than ever, for revolutionary new techniques now make it possible to tailor-make genetically altered mice almost at will, rather than waiting for nature to make them slowly and randomly.

The newest technique, called "gene targeting," exploits two of nature's most remarkable phenomena. The first is recombination, the process that enhances genetic diversity by reshuffling the genes. In homologous recombination, similar, or *homologous*, segments of genes trade places by linking up at regions they share in common. The second of nature's contributions is totipotency, the ability of each cell in an early-stage embryo to develop and differen-

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

THE HEART OF THE MATTER

Plump's chimeric mice contain manipulated DNA. Here, a mouse embryo before (*above*) and just after (*below*) the introduction of cells harboring the altered DNA.

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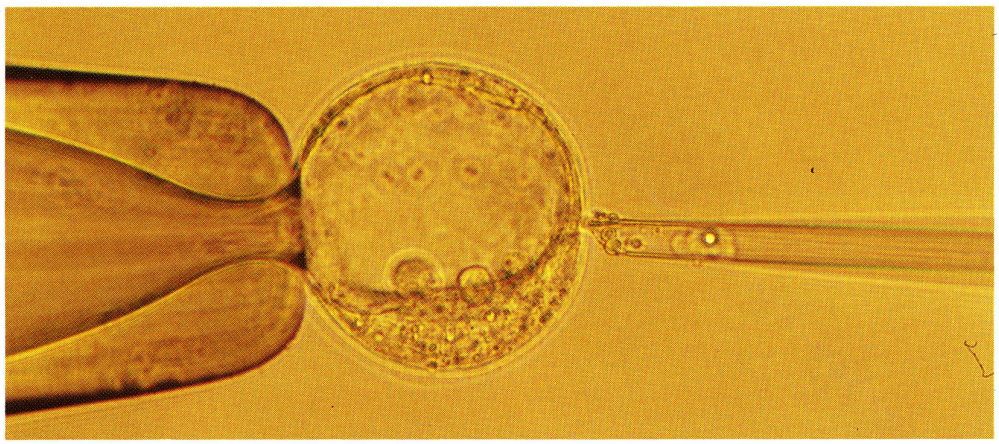

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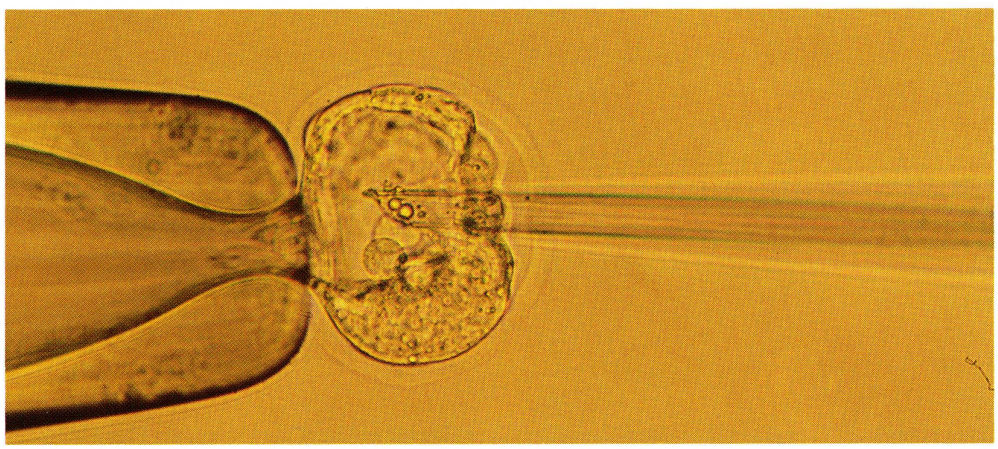


into all the specialized tissues that make up an animal. By yoking these two natural phenomena together, gene targeting lets scientists engineer a specific genetic change in a cell from an early mouse embryo, then "grow" the cell into a mouse that carries the change in each cell of its body.

Gene targeting was made possible by progress in two different areas. Embryologists improved their ability to nurture early-embryo cells in a tissue-culture dish, and geneticists learned how to control recombination not only in yeast cells—where it had been used to great profit for years—but also in the cells of mammals. "About three years ago," Plump reports, "it was the fate of these two fields to cross."

He was well poised at the crossroads when they did. In 1989, after his second year of medical school at the University of California at San Francisco, Plump joined the Breslow lab for a year of research under the sponsorship of the Stanley J. Sarnoff Society of Fellows. During that time, he worked with Rockefeller scientist Jonathan Smith on studies of the gene that codes for an apolipoprotein called Apo E.

By the end of the year, he knew a year would not be enough. "I'd gained the technical skills needed to do science, but I still had a lot of room for improvement as a critical thinker," Plump recalls. So he took an official hiatus from medical school to stay on at Rockefeller and pursue a Ph.D.

He aimed his sights high. "I wanted to do a project that would really make an impact, at least within the lab," Plump says. "Dr. Breslow was intrigued by what he had been reading about gene targeting and so was I, so we agreed I should look into it."

The technique was so new that "looking into it" meant calling and visiting some of the few other labs that were using it. Even then, Plump had to experiment and innovate to discover the strategies that worked best. This process of exploration is still ongoing, but, he reports, "by now we're really starting to optimize our procedures."

Plump is using those procedures to study the mouse genes for two apolipoproteins, Apo E and Apo A-1. Apo E is an important apolipoprotein in a number of lipoproteins including chylomicrons and VLDL; it also plays an indirect role in determining blood levels of LDL. Apo A-1 is the main apolipoprotein in HDL and is an essential determinant of HDL levels.

"There's a lot we know about these proteins, but also a lot we still don't know," says Plump. One way of learning more about them is to see what happens when they do not function at all. Plump is pursuing this path by attempting to create strains of mice with genetic "knockouts" that render Apo E or Apo A-1 inactive.

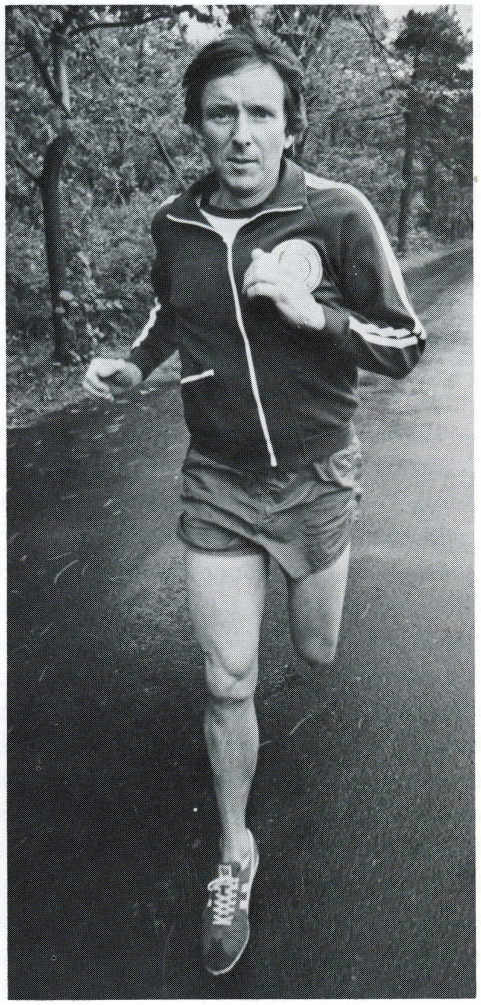
Recombination is the first step in the process. To produce the gene knockout, Plump coaxes cells into swapping a copy of their native Apo E or Apo A-I gene for a defective copy he has engineered. The cells he uses are embryonic stem (ES) cells, early-stage mouse embryo cells that are still totipotent—at least in theory.

It is painstaking work. For one thing, the ES cells may not live up to their totipotent potential. Flushed from an embryo, frozen,

Below left: Winston Churchill did everything wrong—smoking, overeating, drinking, and rarely exercising—yet lived to old age. *Below right:* Runner Jim Fixx did everything right, yet died prematurely of a heart attack. Their differing fates may be a result of their differing genes.

AP/WIDE WORLD PHOTOS

AP/WIDE WORLD PHOTOS



defrosted, and then grown in a tissue-culture dish, the cells suffer many insults that can prompt them to differentiate, or even turn into tumors. Each cell must be carefully screened for any such change. In addition, mammalian cells undergo homologous recombination only rarely, and the strategies used to detect these infrequent events are demanding and time consuming.

Despite the enormous odds, it is possible to achieve homologous recombination in totipotent ES cells, and to multiply the number of these precious cells by growing clones in culture. When this is accomplished, researcher Annemarie Walsh-Mullen injects the ES cells into early-stage "host" mouse embryos, then introduces these embryological constructs into surrogate mouse mothers. Cellular messages from the host embryo cells cue the genetically altered ES cells to respond normally as part of the developing mouse.

The next step is to wait—three weeks for the mouse pups to be born, then one more week for their fur to grow in. A two-tone coat is the sign of success, since the host cells come from a mouse with black fur, while the genetically engineered cells come from a strain that is brown. Thus, a mottled pelt signals that the mouse is a chimera—a creature whose tissue arose from both host and gene-targeted ES cells.

Further tests reveal whether the ES cells have developed into germ-line cells, the cells that carry genes to the next generation. For reasons that are not yet understood, germ-line transmission is very hard to achieve; though the Breslow team has produced chimeric mice, germ-line carriers have not yet been born. But the scientists are confident this event is around the corner, and when it occurs, a few rounds of interbreeding will produce mice that carry only the altered version of the gene in each cell of their body.

"And," says Plump, "once you've made the mouse, the possibilities are almost limitless." Investigating the effects of an Apo E or Apo A-1 knockout will be just the beginning. The researchers will also study how Apo E and Apo A-1 interrelate by interbreeding strains with a knockout of each gene to create a strain with knockouts of both.

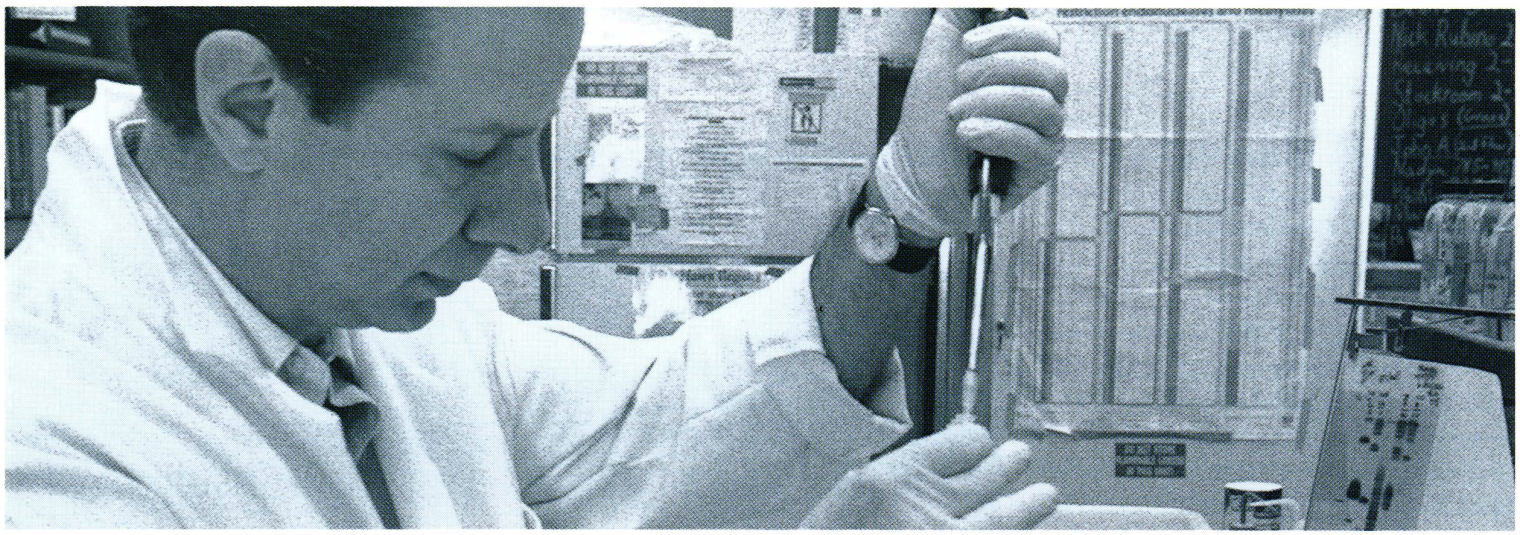
They may even be able to make a mouse that develops atherosclerosis. By nature, the mouse is a high-HDL, low-LDL-animal—one highly resistant to the artery-clogging condition. But by knocking out the genes for both Apo E and Apo A-1, the researchers may invert this protective lipoprotein ratio, generating instead a profile mimicking the low-HDL, high-LDL pattern that so strongly predisposes humans to atherosclerosis.

Such a mouse model would open the door to a wide range of possible discoveries, from a better understanding of the origin and development of atherosclerosis to new and better therapies to treat it, including gene therapy. It would, in short, be an invaluable tool for researchers striving to learn the "whys" that underlie heart disease.

THE DISCOVERY OF RIBOZYMES:
NEW PROMISE FOR GENE EXPRESSION THERAPIES AGAINST CANCER AND AIDS

by Geoffrey Montgomery

Below: Sidney Altman, whose discovery of ribozymes earned him a Nobel Prize, in his laboratory at Yale University.



MICHAEL MARSLAND/YALE UNIVERSITY

When Sidney Altman arrived at the Medical Research Council's (MRC) Laboratory of Molecular Biology in Cambridge, England, in October 1969, the classical age of molecular biology was over. It had begun in 1953 at the MRC's original lab at the Cavendish, where James Watson and Francis Crick deciphered the structure of DNA; it had culminated a decade later with the cracking of DNA's genetic code. By 1969, when Altman walked into the office Crick then shared with Sydney Brenner, it seemed to some that work on the molecular biology of the gene had become more a matter of dotting *i*'s and crossing *t*'s than reading new Rosetta Stones. Still, everyone recognized that important details about the genetic machinery remained to be elucidated. The MRC lab had invited Altman, then a thirty-year-old postdoctoral fellow, to work on one of them. He was to do physical chemical analysis of the structure of a critical genetic intermediary called transfer RNA (tRNA).

Once in their office, however, Brenner and Crick told Altman that the problem he was to work on was no longer a problem. Crystals of tRNA which yielded good X-ray diffraction patterns had just been made. They told Altman to think about another project to tackle, and then come back and see them in a week or two.

To some of his MRC colleagues, Altman seemed disappointed by Brenner and Crick's news. But as Altman, now a professor at Yale, told his audience at Stockholm after winning the Nobel Prize for Chemistry in 1989, "The feeling must have passed quickly, because I only recall being presented with a marvelous opportunity to follow my own ideas." Indeed, the idea Altman hatched that week, and pursued over a series of unanticipated turns, has helped lead to nothing less than a revision of molecular biological orthodoxy and a revolution in our understanding of the origin of life.

The classical age had placed a cell's essential biological molecules into three distinct classes. There were genes, made of DNA; there were enzymes, made of protein; and then there were various kinds of RNA, nucleic acid intermediaries that used the information in the DNA template in directing the synthesis of enzymes. Yet this division of labor left molecular biologists with a chicken-and-egg quandary concerning how living systems originated in the absence of the genetic code. Genes cannot replicate or make proteins without enzymes; and enzymes cannot be made without genes. How could life have arisen out of the primordial soup if both nucleic acid genes and protein catalysts were needed from the very beginning? In 1967, Carl Woese, and in 1968, Crick and Leslie Orgel had speculated that RNA, in addition to storing genetic information, could in principle act enzymatically as well. But they then dismissed the idea because catalytic RNA had never been observed in Nature.

In the early 1980s, however, Altman and Thomas Cech of the University of Colorado, the co-winner of the 1989 Nobel Prize, independently isolated the entities that Crick and Orgel had hypothesized and then dismissed: enzymes made of RNA. Because of these discoveries, most biologists now believe it likely that all life on earth emerged from a cell in which RNA played the role of both gene and enzyme—both chicken and egg. Further, the enzymatic properties of RNA they found have led to novel ways of designing genetic therapies against such diseases as cancer and AIDS.

That first week in England in 1969, however, looking for a new problem to attack, Altman was hardly thinking of gene therapy or the origin of life. "I simply wanted to find something I could do," he says. His thoughts revolved back to tRNA, the molecule whose structure he was supposed to have discerned through physical chemical studies. Brenner, Crick and others had shown that the base sequence information in DNA's template was first copied onto a single RNA strand called messenger RNA (mRNA); specific base

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sequences on the mRNA template then bound to complementary sequences on tRNA. Together, mRNA and tRNA collaborated to translate DNA's code into an enzyme: tRNA serves as kind of adaptor-socket, plugged into mRNA at one end, and plugged at the other end to one of the twenty amino acids that make up a protein chain. Yet how did the base sequences of the tRNA chain allow it to fold up into such an exquisitely effective adaptor? No one knew. As a graduate student, Altman had used a mutagen related to the chemical known as acridine to alter genetic base sequences. If he used this chemical on *E. coli* bacteria to mutate the gene encoding a specific tRNA molecule, he told Brenner and Crick the next time he saw them, he could probe this important issue directly.

Brenner and Crick were not enthusiastic. Brenner and a colleague had already made batches of tRNA mutants using other chemical mutagens. Why make more? they asked. Nevertheless, they allowed Altman to follow his ideas. Subsequently, and using a clever purification strategy, Altman was able to isolate, for the first time, a precursor molecule to tRNA.

The precursor was not tRNA itself, but a larger version, pieces of which had to be clipped off to give tRNA its mature clover-leaf shape. "The next logical step was to find the enzymes that trimmed the extra pieces off," says Altman. Then, collaborating with Hugh Robertson, who trained at Rockefeller and was later a faculty member at the university, he simply mixed the precursor with an extract from *E. coli* cells, and found that something in the extract—a still unidentified enzyme he called "Ribonuclease P"—made a specific cut near the stem of the tRNA clover leaf. "That was the easy part." Altman and Robertson then began to characterize this enzyme. In a paper published in 1972, they noted the curious fact that the enzyme—which of course, following molecular biological dogma, had to be made of protein—seemed to be co-purifying with a chunk of RNA. "In our own minds," says Altman, "we simply thought it was some piece of nucleic acid that just happened to bind very strongly to the Ribonuclease P enzyme, but we were not certain it was actually part of the enzyme."

In 1971 Altman moved to Yale, and the arduous task of completely purifying Ribonuclease P was turned over to a graduate student, Benjamin Stark. "He worked very hard at it for several years, and it was very frustrating." Stark would purify the enzyme; but then found the enzyme he came up with was apparently *not* purified: instead of being composed only of protein, it was attached to RNA as well.

Finally, in 1976, Stark and Altman realized that they were dealing with a new kind of animal: an enzyme made of both protein and RNA. This finding seemed heretical enough; Altman did not even suspect that under some conditions the RNA sub-unit of Ribonuclease P could work alone, serving as a true RNA enzyme.

But that is precisely what another Altman associate, Cecilia Guerrier-Takada, found on September 21, 1983, using the powerful new tools of recombinant DNA technology to examine large quantities of the enzyme's RNA sub-unit. "Cecilia knew what she had immediately"—the RNA sub-unit was clipping the tRNA precursor by itself—"but she was worried she might have mixed up tubes in the experiment the day before." She immediately repeated the experiment; she got the same result. "By then I had been working on this thing for thirteen years," Altman remembers. "And finally I felt I understood what was going on."

The major focus of Altman's lab remains to elucidate exactly how the RNase P ribozyme recognizes its cutting site on tRNA. To aid in this task, his lab has designed artificial sequences of RNA, called external guide sequences, that bind to RNA test molecules. The guide sequences then act as a homing signal for RNase P, which, after sliding along the guide sequence to a specific site on the test RNA, clips its target in two. This strategy could also be deployed against RNA strands made by disease-causing genes, whether from the AIDS virus or a mutant cancer gene. In principle, Altman says, an external guide sequence could be designed to bind to RNA from any disease-causing gene; the RNA would thus be targeted for destruction by the RNase P present and active in all human cells. According to this still-speculative scenario, our cells are already full of potential anti-viral and anti-cancer missiles: the missiles simply need to be guided.

The finding of ribozymes that can both cut and replicate RNA molecules has also led to a new picture of biology's cosmological question: how did life and the genetic code arise? Billions of years before our present universe of DNA, RNA, and protein, it is now thought, there was a world ruled by RNA alone, where strands of RNA could both mutate and replicate their genetic information, as well as fold up into useful enzymatic shapes. A ribozyme like RNase P might have accelerated the evolution of this RNA world, says Altman, "because if you had RNA enzymes that cut long strands of RNA into many smaller pieces, you could generate a larger population of elements for evolution to play around with."

Perhaps the most important of these new RNA elements would have been the first tRNAs. Once these primordial adaptor plugs evolved, cells had a molecule that could carry amino acids to specific sequences on an RNA strand, thus beginning the process by which genes encode proteins. Nature was beginning to evolve the Genetic Code itself. The first proteins made in this new RNA-protein universe then bound to and enhanced the catalytic power of previously existing RNA enzymes—just as the protein component of RNase P helps its RNA sub-unit function in today's cells. Indeed, the enzyme Altman discovered in England after beginning to follow his own ideas is now seen as a living fossil of this world in transition, a relic of the primeval era before DNA's double helix came on the scene, and took over the keys to the store of life.

THE GARDENS OF THE ROCKEFELLER UNIVERSITY

Text by Niloufar Leibel
Photographs by Leif Carlsson

ALLEE OF LONDON PLANES

The formal rows of London planes lining the campus walks and lawns provide the major thematic framework for landscape architect Daniel Urban Kiley's design. The open, wide-spreading, and strong-branching structure of the planes provides a stately, rhythmic, and recurrent pattern throughout the grounds of the university. Their distinctive, dappled bark produces a changing patchwork of color suggesting the play of sunlight. As the outer fawn-colored layer of bark grows older it separates into large, thin plates which are shed to reveal a fresh inner layer of pale green and cream. The planes' flowers and fruits, usually borne in pairs, grow in round clusters on pendulous stalks. The green flower balls ripen into brown, woody fruits that persist throughout winter. In spring, the fruit clusters break up, releasing tiny brown seeds, each capped by a tuft of hairs to aid in dispersal by the wind.

The London plane tree (*Platanus x acerfolia*) is thought to be a hybrid between the oriental plane tree (*Platanus orientalis*) native to Turkey and Greece, and our eastern North American sycamore or buttonwood (*Platanus occidentalis*). Its history dates back to 1663, when it was found growing in London. More vigorous and hardy than either parent, the London plane is remarkably adaptable to a wide range of growing conditions. It is commonly planted along city streets worldwide, and until recently was the street-tree species most frequently planted in New York City.

Just off the southwest corner of The Rockefeller University Hospital is an oriental plane tree propagated from a cutting obtained on the Greek island of Kos and given to Detlev Bronk in the 1950s. The cutting was taken from the tree that legend claims was the one Hippocrates sat under while teaching his students over 2,400 years ago.

AZALEA-BORDERED PATH IN EARLY SPRING

Each spring, the many flowering shrubs and trees and the massed plantings of bulbs create a succession of dazzling floral displays throughout the campus landscape. The azaleas are, perhaps, the most impressive contributors once erupted into their brilliant palette of blooms. The border and foundation plantings feature many different varieties of azalea, with colors ranging from the purple and fuschia of the older and larger shrubs to the white, pink, salmon, and red of the newer types. These newer varieties are smaller and have both lighter wood and foliage. Botanically, all azaleas are considered to be members of the genus *Rhododendron* (rose tree), which includes over 900 species and an enormous multiplicity of varieties and cultivars due to the ability of the species to hybridize freely. In the wild, they grow as understory plants on every continent except South America and Africa, and are most abundant in mountainous southeast Asia.

The Rockefeller University campus has been described as an oasis of beauty and tranquility in a city whose starkness and tumult are legendary. The Rockefeller landscape provides a quiet, contemplative sanctuary of sylvan beauty. Here, the seasonal rhythms of nature which concrete obliterates, become a part of daily life.

During the early 1950s, when the development of The Rockefeller Institute as a graduate university was being planned, the institute's president, Detlev Bronk, and the trustees envisioned the creation of a setting of great natural beauty. As the building of new facilities progressed, architect Wallace Harrison recommended that landscape architect Daniel Urban Kiley of Charlotte, Vermont, be commissioned to landscape the campus grounds. In 1956 when Bronk and Kiley first met, Kiley warned Bronk, "I should tell you at once that I cannot assume any further commitments," and agreed to listen for only fifteen minutes. The meeting lasted five and a half hours after Bronk described his concept for the university's fourteen-acre campus. Kiley declared, "If I cannot participate in this great undertaking, I shall be one of the most disappointed men in America."

Kiley's elegant landscape creation includes spacious lawns; naturalistic border and foundation plantings meant to suggest woodland undergrowth; and a formal, secluded courtyard garden. The design reflects imagination and love of the individual character of plants. The species chosen not only complement each other esthetically and enhance the environment throughout each season, but bring to the attention of the viewer the richness and diversity of the plant world.

The campus grounds are a miniature arboretum of ornamental woody plants. Both native and exotic, evergreen and deciduous trees and shrubs stand together in a harmony of formal and informal plantings. The deciduous shade tree collection includes London planes, lindens, a weeping willow, a Japanese pagoda, ginkgos, and European hornbeams. Among the conifer trees planted on the campus are two especially beautiful and elegant species: blue atlas cedar and Japanese cedar. The extensive understory collection includes dogwoods, magnolias, and shadblows.

Responsibility for maintaining the beauty of the campus belongs to James Sullivan and grounds crew Frank Duffy, Francisco Molina, and Eugene Tarasco.

NATURALISTIC FOUNDATION PLANTING, SOUTHWEST CORNER OF FLEXNER HALL

Two trees beautiful in all seasons, a Japanese flowering cherry and a Japanese dogwood, are surrounded by both evergreen and deciduous shrubs and by ivy ground cover to form a luxuriant, naturalistic planting. Typical of the informal approach Kiley used in his treatment of the border and foundation plantings throughout campus, this corner conveys an impression of woodland undergrowth. There appears to be a random placement of plants; the lines of the composition are curved and gently flowing.

FOUNDATION PLANTING, SOUTHWEST CORNER OF THE HOSPITAL

To provide a sense of order and underlying structure to the campus landscape, Kiley relied on the repeated use of certain plants throughout the grounds. The andromeda (on the left in the photo at right) is one of the plants used most extensively for this purpose. Related to the azaleas and rhododendrons, the evergreen andromeda (*Pieris japonica*) adds a special warmth and beauty to the grounds in all four seasons. In early spring, the shrub is cloaked in flowers which resemble lily-of-the-valley, and which develop into woody, brown fruit capsules. The new leafy growth is a rich reddish-bronze hue which turns a lustrous, dark green by late spring. In summer, the buds for next year's flowers are formed and remain prominently visible on the plant throughout the fall and winter.

The vigorous, deciduous vine which traces intricate patterns across the facades of Founder's, Flexner, and the Hospital is porcelain ampelopsis (*Ampelopsis brevipedunculata*). The leaves of this member of the grape family are bright green in summer and an attractive red in the fall. The vine is at its most beautiful when in fruit during September and October. Its ripening berries offset by ivy-like leaves change from yellow to pale lilac to a final deep blue. Frequently, all three colors are present together in the same fruit cluster.

SHADBLOW

The shadblow *(Amelanchier canadensis)* is another plant used repeatedly in Kiley's campus landscape design. This slender, multistemmed tree, a member of the rose family and native to the deciduous forests of eastern North America, has a graceful habit and attractive gray bark striated with white. In early spring, it produces a fleeting profusion of small, delicate white flowers before the leaves appear. Its common name, "shadblow," derives from the fact that the time of blooming coincides with the time the shad migrate upstream to spawn. The edible purplish fruit matures in June and is sweetish and juicy. Like the flowers, the ripened fruit is also short-lived; birds favor it and will quickly strip a tree of all the blueberry-like fruit.

FORMAL GARDEN, NORTH OF CASPARY AUDITORIUM
The garden area north of Caspary Auditorium is a beautiful example of the formal plantings in Kiley's campus landscape design. The composition is neatly ordered and carefully balanced; clearly defined shapes and lines predominate. The plants selected provide subtle contrasts in color, but dramatic contrasts in texture. The design features an expanse of lawn, hedges of Japanese holly and azaleas meticulously pruned into geometric forms, a majestic Japanese tree lilac, and conifers of distinctive character—the blue atlas cedar and the Japanese cryptomeria.

JAPANESE DOGWOOD
The Japanese dogwood *(Cornus kousa)* is another plant used repeatedly in Kiley's campus landscape design. It blooms later and longer than our own native flowering dogwood. The beautiful, showy blossoms, borne above the dark green leaves, are not flower petals but enlarged leaf bracts that set off a cluster of tiny yellow flowers in their center.

NILOUFAR LEIBEL is a Master Gardener in the Urban Horticulture Program of Cornell University Cooperative Extension in New York City.

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

BIRD SONGS AND NEUROGENESIS

by Geoffrey Montgomery

Right: Arturo Alvarez-Buylla working with canaries in neurogenesis studies at the university's field station in Millbrook, New York.

When Arturo Alvarez-Buylla arrived as a graduate student in Fernando Nottebohm's lab at Rockefeller in 1984, Nottebohm had just reported a discovery so astounding that Alvarez-Buylla himself could not believe it. Nottebohm's lifelong fascination with birds and their songs had earlier led him to identify centers in the bird brain that control song production. He had further found that in adult canaries these song-control centers grew dramatically each breeding season, when male canaries learn a new medley of songs in order to entice a mate.

At first, Nottebohm assumed that this growth was due only to the enlargement of pre-existing neurons in the song-control centers. The dogma among neurobiologists was that all neurons in higher vertebrate brains were generated during embryonic life; once an animal reached adulthood, all production of new neurons—a process known as neurogenesis—had long ago ceased. But then, in 1983, Nottebohm and graduate student Steve Goldman examined the brains of adult canaries during their seasonal growth period, and were stunned to find that thousands of new neurons were being born each day.

"Fernando and Steve had just published their discovery of adult neurogenesis when I came to the university," says Alvarez-Buylla, "but in the beginning, I didn't see how it could be true." How, he wondered, could newborn neurons become incorporated into a brain already tightly packed with interconnected cells? Over the next six years, Alvarez-Buylla not only confirmed adult neurogenesis, but by following the trail newborn neurons make through adult bird brains, he made a further series of discoveries relating to this remarkable cellular process. Indeed, his work has helped raise the hope that the knowledge gained from birds might someday be used to repair or rejuvenate human brains damaged by injury, age or disease.

"It has been a kind of detective story," says Nottebohm, "in which a whole series of things unfolded in a natural, and yet surprising way."

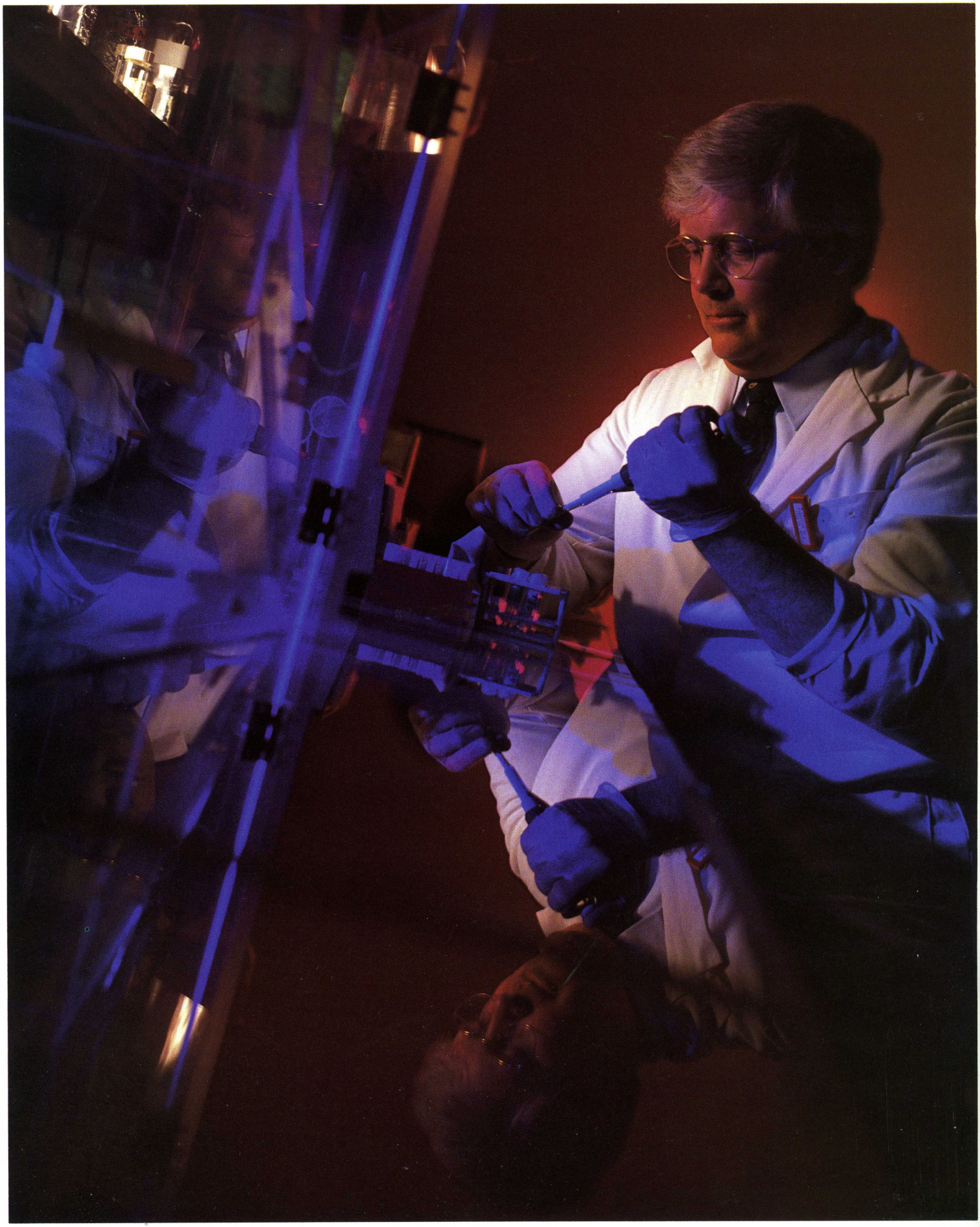
Alvarez-Buylla's sleuth work started in 1985 when he and Nottebohm began to address the most pressing puzzle of adult neurogenesis. Nottebohm and Goldman had found that, as in both bird and mammalian embryos, adult canary neurons are born in specialized brain layers called the "ventricular zone." The newborn neurons would then have to migrate from their birthplace in the ventricular zone to their workplace within various specialized areas of the canary brain. But how? In embryos, neurons began this migration by climbing up long fibers extended by cells called radial glia, which form the scaffolding around which the embryonic brain is built. It was generally thought that this scaffolding was disassembled by adulthood.

But Alvarez-Buylla and Nottebohm found that this was not so. Late one evening, they placed a specially stained slice of adult canary brain under a double-viewing microscope. "Do you see that!" said Nottebohm immediately. Under the double microscope, they both could see blue-stained neurons stretched out along dark-stained radial glia fibers. Over the next two years, Alvarez-Buylla showed that these neurons were newborn, and that they used the radial glia fibers to climb out of the ventricular zone in the initial stage of their migration—research published in 1988 in *Nature*. Then, as reported in a *Science* cover story in September 1990, Alvarez-Buylla showed that these newborn neurons, after migrating to one song-control center, can form long neural connections with a second brain area controlling song, suggesting that these neurons help store the patterns for the new songs canaries learn each breeding season. Yet for Alvarez-Buylla, the most fascinating finding, published last year in *Neuron*, is that neurogenesis occurs only in special "hot spots" in the ventricular zone. Further, and most surprisingly, many of the cells that give rise to new neurons are none other than the radial glia themselves.

"It has traditionally been thought that neurons and glia are two absolutely separate categories of cells," says Alvarez-Buylla. Radial glia formed the scaffolding, and neurons the bricks, out of which the brain was built. "Now it seems that radial cells can be both scaffolding and bricks."

Today, Alvarez-Buylla's major goal is to define the precise conditions under which new neurons are born, and to find markers for the exact cells that give birth to these neurons. "With these markers we could then look for these cells in the ventricular zones of animals that, like humans, normally don't produce new neurons," he says. "They may be there, but are just quiescent—if you give them the right stimuli, you might be able to induce neurogenesis." If the cells are not present, perhaps they could be transplanted. "All this may be very far in the future, but it is something we are thinking about."

Indeed, in the saga of neurogenesis in adult birds, each new discovery has led to a new series of questions and challenges. "It's like a snowball rolling down a hill," says Alvarez-Buylla. "The knowledge on the inside keeps getting bigger, but so do the questions on the surface. Those moments when you encompass some new piece of knowledge—those are the most satisfying moments in science. And I hope," he says, smiling now, "to have many more of them."



ROBERT REICHERT

CAN HEPATITIS BE WORSE? THE DELTA AGENT STORY

by Philip DiMauro

Left: Hugh Robertson, doing research on the delta agent, which causes hepatitis and which he has hypothesized is a viroid-like pathogen.

In the early 1980s, when AIDS emerged as a serious problem among drug addicts who use hypodermic needles, another mysterious killer was already stalking the same population. The disease itself was nothing new: delta hepatitis, a virulent and frequently fatal infection, had been identified in Europe in the 1970s. The agent of this dangerous disease, however, turned out to be something completely unexpected.

Delta hepatitis requires two pathogens, or disease-causing organisms, to develop. The more common of the two is the hepatitis B virus, an infection that is prevalent among drug abusers, but seldom results in rapid decline or death. The other pathogen—the delta agent itself—is still being classified.

In the opinion of Hugh Robertson, an investigator in the biochemistry department of Cornell University Medical College, the delta agent is one of the viroid-like pathogens—simple life forms based on RNA, some of which infect cells on their own, while others always associate with a conventional virus. If he is correct, the delta agent is the first viroid-like pathogen known to infect members of the animal kingdom. All previously known viroids cause disease only in plants.

Robertson received his Ph.D. degree from The Rockefeller University in 1969, working in the field of genetics in the laboratory of Rollin Hotchkiss and Norton Zinder. During this period, he developed an interest in how RNA performs its essential role in the making of proteins. In our own cells, for example, blueprints for the manufacture of proteins are stored as genes made of DNA. Protein synthesis begins when an activated DNA gene is transcribed as a messenger RNA (mRNA) precursor strand. But before the newly transcribed mRNA is dispatched to cellular protein factories, it must be "processed" by specialized enzymes that excise bits of useless information and allow the remaining functional segments to re-attach, forming a messenger that contains the correct protein code. At Rockefeller and during his postdoctoral research, Robertson and colleagues discovered and purified the first two specific RNA processing enzymes, RNase III and RNase P.

Plant viroids, first discovered in the 1920s, fascinated Robertson because they are often small, free-living, circular RNA strands lacking even a protein coat. When he returned to Rockefeller in 1972 after three years of postdoctoral study in Cambridge, England, he and collaborator Andrea Branch began growing plants for viroid research in a rooftop greenhouse that was the domain of Armin Braun, the University's eminent plant biochemist at the time.

One of the important questions being asked at this stage in viroid research was: How do viroids replicate, or reproduce themselves? By the mid-1980s, Branch and Robertson had worked out the replication cycle for viroids. In this "rolling circle" replication style, the circular RNA "parent" generates continuous RNA progeny strands that contain multiple copies of the single viroid unit. Like messenger RNAs, these long progeny strands are cut into unit-length segments by RNA enzymes, or ribozymes. Then they attach at the cleavage points to form mature circular viroids.

Branch, who has joined the Rockefeller laboratory of Mary Jeanne Kreek, an investigator in the field of substance abuse and its correlative problems, and Robertson, who is now a member of the adjunct faculty at Rockefeller, recently completed experiments that elucidate the role of a specific RNA enzyme, or ribozyme, in delta agent replication. In the future, they intend to investigate ways to block the action of delta ribozymes, a potential strategy for development of treatment for delta hepatitis.

This research has even broader implications, Robertson explained, because "the delta agent causes a human disease, and its ribozymes are the only examples known to operate in human cells." Delta ribozymes, he says, "could someday be harnessed and targeted to work against many disease-causing viruses."

The Branch-Robertson delta collaboration is funded in part by a National Institute of Drug Abuse (NIDA) Center grant awarded to The Rockefeller University for the study of addictive diseases under Kreek's direction. She estimates that thirty percent of New York City street addicts have been exposed to hepatitis delta.

The acute phase of hepatitis B is fatal in one to two percent of cases; co-infection with delta raises the death rate to between twenty and thirty percent. Studies conducted by Kreek at The Rockefeller University Hospital indicate that patients with AIDS experience more serious and long-lasting symptoms when co-infected with hepatitis B and delta.

Because the delta agent is infectious only in the presence of acute hepatitis B virus infection, Kreek emphasizes the importance of hepatitis B immunization for health care providers and laboratory workers. If there is any good news to be gleaned from her recent studies, it is the finding that the number of intravenous drug abusers exposed to hepatitis B seems to be decreasing—probably the result of education on AIDS risk reduction directed at addicts. The irony of this is that these individuals have no natural immunity to hepatitis B and are now at risk for co-infection by hepatitis B and delta. For these drug abusers, vaccination against hepatitis B is also recommended.

PHILIP DIMAURO, a writer in The Rockefeller University Development Office, has also worked as a business and entertainment journalist.

ENTERING THE MANSION OF OUR BIRTH
ALBERT CLAUDE AND THE BEGINNING OF MODERN CELL BIOLOGY

by Catherine Vanchieri

In the mid-19th century, microscopic studies of animal and plant tissues revealed the cell as the basic unit of life. The nucleus and a few other faint and tantalizing shapes were visible inside the cell, but for almost a century further observation was hampered by the low resolving power of the light microscope and the inexactness of available biochemical methods. An understanding of the intricacies of cell structure and activity had to await what Albert Claude once called "the accident of technical progress."

Claude, who died in 1983 at the age of eighty-four, is often referred to as the father of modern cell biology, a discipline he helped launch at Rockefeller in the late 1930s and 1940s. Perhaps his greatest legacy was the adaptation and refinement of two complementary technologies that have played critical roles in the exploration of the cell. One was the electron microscope, an instrument that in the 1940s was already forty to fifty times more powerful than the best available light microscope. The other was the centrifuge, used to fractionate cells and make their contents accessible to meticulous biochemical analysis.

Claude traveled to Rockefeller from his native Belgium in 1929, one year after he had earned a medical degree, and eighteen years after he had dropped out of school, at the age of twelve, to become a steelworker. He arrived in New York with the goal of isolating and purifying a biological agent that a few—but not many—scientists believed to be a virus capable of producing tumors in chickens. After several years, he obtained highly concentrated samples of what is now known as Rous sarcoma virus and determined that they contained protein and ribonucleic acid.

As a control, Claude examined the tissues of tumor-free chick embryos. Unexpectedly, in the normal tissues he discovered particles that were similar in size and chemical composition to the viral agent. The serendipitous resemblance between the newly isolated particles, which he named microsomes, and the viral agent led him to focus on the living cell and its internal structures, or organelles.

Both Rous sarcoma virus and microsomes were isolated by centrifugation, a technique that uses centrifugal force to separate the heavier contents of the cell from the lighter ones. A series of centrifugations and separations produced several different fractions. Over the years, comparative biochemical analysis of the different fractions—a concept first introduced by Claude—produced a wealth of information about the organization and activity of the cell.

In the 1940s, while refining centrifugation procedures, Claude also turned his attention to the electron microscope, a powerful imaging instrument that had been developed by physicists a decade earlier. At first, the electron microscope was of little use to biologists, for they did not know how to prepare intact biological specimens that were both thin enough to be accessible to the probing electrons and able to withstand exposure in a high vacuum.

Over a period of several years, Claude experimented systematically with new methods of tissue preparation, pointing the way for other investigators who would soon learn how to use the electron microscope to study all types of cells. During the mid-1940s, Claude completed a series of electron microscopy studies, collaborating at first with industrial microscopist Ernest Fullam and then also with Rockefeller biologist Keith Porter. The results of these experiments were published jointly by Claude, Porter, and Fullam.

The earliest micrographs were of cell fractions containing mitochondria, relatively large intracellular structures that had first been detected with the light microscope in the 19th century. These were soon followed by micrographs of the thin periphery of cultured cells, which disclosed for the first time a "lace-like" network of membranes and channels. Claude and his colleagues also obtained the first micrographs of virus particles inside infected cells.

In 1949, when Claude returned to Belgium to direct the Jules Bordet Institute, in Brussels, his techniques had already influenced a generation of cell biologists, including George Palade, who spent twenty-eight years at Rockefeller, the early ones with Claude. Further study by Palade and his associates, including Philip Siekevitz, currently a professor emeritus at Rockefeller, demonstrated that microsomes are centrifuged remnants of the lace-like reticulum. During the 1950s, they analyzed this formation, now known as the endoplasmic reticulum, and delineated its role in protein synthesis and segregation for eventual secretion. They also isolated the organelles that are now called ribosomes. Often intimately associated with the endoplasmic reticulum, ribosomes are the protein factories of the cell. Palade also delineated the intricate fine structure of mitochondria, the sites of energy production in the cell.

Meanwhile, in Belgium during the late 1940s and early 1950s, Christian de Duve further developed Claude's techniques of differential centrifugation and used them to discover two more cell parts. In 1949, de Duve found a new group of organelles, which he called lysosomes, a sort of cellular digestive system. Several years later, he used the same strategy to find peroxisomes, organelles that metabolize hydrogen peroxide as they break down biologically important chemicals, including amino acids and fatty acids.

De Duve joined the Rockefeller faculty in 1962, while retaining academic ties in Belgium. Today, he is a professor emeritus at Rockefeller and president of the International Institute of Cellular and Molecular Pathology, in Brussels. Palade is dean of science affairs at the medical school of the University of California, San Diego.

Claude, de Duve, and Palade shared the 1974 Nobel Prize for their work on "the structural and functional organization of the cell." In his lecture at the Nobel ceremonies, Claude offered a somewhat more poetic version: "We have entered the cell, the mansion of our birth, and started the inventory of our acquired wealth."

CATHERINE VANCHIERI is a science writer in The Rockefeller University Development Office.

ROCKEFELLER AND PASTEUR SCIENTISTS MEET IN JOINT SYMPOSIUM

by Susan Blum

Forging ties with international colleagues from the Pasteur Institute in France, a group of Rockefeller scientists, led by David Baltimore, met in late May near Lisieux, in Normandy, France. The meeting, "Horizons in Cell Biology," took place at the Pasteur Institute's newly remodeled conference center in a chateau, pictured below.

Rockefeller scientist Gunter Blobel organized the event in cooperation with Daniel Louvard, one of the Pasteur Institute's eminent researchers. The two-day conference was made possible by a grant from Disque Deane, a former member of Rockefeller's board of trustees.

Scientists from the two institutions covered a wide range of topics, including pathogenic bacteria as tools for cell biologists; membrane proteins and intracellular transport; membrane-cytoskeleton interactions; the cell cycle; cell-cell interactions during development and differentiation; and immunodifferentiation. In addition to Baltimore and Blobel, other Rockefeller scientists in attendance were Alan Aderem, Frederick Cross, Kathryn Crossin, Vincent Fischetti, David Luck, Anant Menon, Sanford Simon, Alexander Tomasz, and Michael Young.

According to Baltimore, the connections made were both institutional and personal. "Rockefeller University and the Pasteur Institute learned to appreciate each other as scientific institutions, and warm relationships developed between individual scientists, as well," he added.

A strong possibility exists that these ties will be strengthened next year, with Rockefeller hosting a second joint meeting.

GILBERT GUILLOTIN

Scientists from Rockefeller and the Pasteur Institute gathered for a joint meeting in Normandy, France, in May.

ROCKEFELLER UNIVERSITY HOSPITAL HOSTS DINNERS

Fifty friends of the university gathered at The Rockefeller University Hospital June 12 for the first in a series of small informal dinners that will be held throughout the coming year. Guests at these dinners will include donors to the hospital and others who want to learn more about clinical research under way at the hospital.

Speakers at the first dinner included:

- Attallah Kappas, physician-in-chief from 1974 through June 1991, who provided an overview of the hospital's contributions to advances in science and medicine.
- Jan Breslow, the newly appointed physician-in-chief, who discussed future plans for the hospital and the need to train more young clinicians in laboratory research.
- David Baltimore, Rockefeller's president, who briefly outlined new approaches to research on the aging process.

The evening's host was Ralph Ablon, vice chairman of the board of trustees, who has long taken a special interest in the hospital. Ablon underwrote the cost of the dinner, which featured a three-course "heart healthy" menu planned by Cynthia Seidman, director of dietary services at the hospital.

At the dinner, Ablon announced that a steering committee is being formed to raise funds for the hospital. The enthusiastic response to this announcement prompted him to remark, "It is gratifying to see so many people show an interest in the hospital. I'm not surprised, though, because our hospital is a unique, important facility, and the members of our clinical faculty are both stellar investigators and wonderful human beings."

"Ralph has been a good friend to this institution," said Baltimore, "and I am delighted that he will be providing leadership for a hospital fund-raising initiative, working closely with Drs. Kappas and Breslow."

MEDICAL BENEFITS VS. RISKS

by Kassie Evashevski

- How can data about medical benefits and risks be shared among countries?
- Should patients' willingness to tolerate risks from medical care be proportionate to the risks from the illness?
- What do members of the public need and want to know about medical risks, and how do they most effectively obtain the information?

Answers to questions such as these must ultimately come from an informed society, but first the questions need to be asked. In March, William Lowrance, then a senior fellow and director of the Life Sciences and Public Policy Program at The Rockefeller University, left for Geneva, Switzerland, to do just that. As executive director of the newly formed International Medical Benefit/Risk Foundation, Lowrance says he hopes to provide a "fair and constructive forum for the resolution of controversial issues and a resource for concerned parties."

The International Medical Benefit/Risk Foundation is an outgrowth of an endeavor started by the Ciba-Geigy company in 1988, known as Risk/Benefit Assessment of Drugs—Analysis and Response (RAD-AR), the purpose of which was to improve the quality of information on drug benefits and risks, and to ensure that this information is communicated effectively. The foundation—which is supported by eleven pharmaceutical companies from Europe, Japan, and the United States, with the participation of experts from academic and regulatory institutions as well as other organizations—seeks to improve understanding and change atttitudes toward the management and communication of medical benefits and risks. The foundation's scope will include a wide range of medical benefit/risk issues, such as those surrounding prescription drugs, over-the-counter preparations, diagnostic procedures, vaccines, biotechnological innovations, and therapeutic choices in general.

ROBERT REICHERT

William Lowrance

"Our central concern," says Lowrance, "is the fundamental notion that all of health care is a weighing of risk versus benefit." To promote an informed approach to such matters, the foundation "will emphasize the international dimensions of issues, take a multidisciplinary public health orientation, and actively cultivate broad professional and societal involvement. The foundation will convene workshops and conferences, conduct case studies, and perform analyses," he adds.

Geneva was chosen as the headquarters of the foundation because there are over a thousand health-care organizations there, including the World Health Organization, the International Red Cross, and the International Red Crescent.

Lowrance, who received his Ph.D. from Rockefeller in 1970, has always been interested in what he calls "the social side" of science. After a fellowship at the National Academy of Sciences to write the first book about the concept of "risk," and teaching positions at several universities, including Harvard and Stanford, Lowrance returned to Rockefeller in 1980 to direct the Life Sciences and Public Policy Program, where he remained until he left for Geneva.

KASSIE EVASHEVSKI is a free-lance writer.

MARILYN SMITH APPOINTED CORPORATE SECRETARY

Marilyn T. Smith, elected secretary of the corporation by the board of trustees, plans to keep board members busy learning about university affairs. "We want them to look beyond facts and become involved in the life and spirit of the university," the long-time special assistant to President David Baltimore said. She assumed her new position July 1, replacing Lila Magie, who retired.

"Our hope is that the board members will become more fully engaged with the mission of the university and its people," Smith added. She hopes there will be more opportunities to meet with postdocs and students as well as with faculty members, and to hear about the science going on at the university. "It is important that they be as excited about the work going on here as we are," she said.

Smith's new position adds the responsibility of being the liaison between the university and its board of directors to her present duties of handling issues relating to the Academic Council and assuring close communication among Personnel, the Office of the President, and members of the faculty on vital, sensitive faculty administrative matters.

As liaison with the board, she will interact with its standing committees, including the Executive Committee; the Committee on Scientific Affairs, which reviews faculty appointments of more than three years; and the Nominating Committee.

In her interactions with the Academic Council—which advises the president in matters relating to faculty—Smith will be involved in planning meeting agendas, organizing ad hoc committees, and reporting on Council activities to the president.

Smith, whose previous experience includes having been Special Assistant to Dr. Baltimore when he was director of the Whitehead Institute, and an administrator at the Center for Cancer Research at the Massachusetts Institute of Technology, is a graduate of Denison University, where she majored in political science.

J. RICHARDSON DILWORTH RETIRES FROM ROCKEFELLER BOARD

J. Richardson Dilworth, who has been a trustee of the university since 1960, retired from the board last June, at the time of his seventy-fifth birthday. He has been named a trustee emeritus.

During his thirty-one years on the board—longer than any current member except David Rockefeller—Dilworth held several key positions. In the early years of his tenure, he served as the university's treasurer—a volunteer position at the time—until the university hired a full-time officer. He also served for a number of years as chairman of the Finance and Investment Committee, managing the growth of the university's endowment. During Dilworth's involvement with the board, the endowment rose from about $130 million to nearly $500 million.

J. Richardson Dilworth

Dilworth was a member of two presidential search committees, those that selected Frederick Seitz and Joshua Lederberg to lead the university. He was integrally involved in the expansion of the university's facilities over the years, including the acquisition of the Millbrook field station, the Pocantico Hills facility which houses the university's archives, and the Seven Springs conference center; and the construction of the Detlev W. Bronk Laboratory, the Tower Building, Faculty House and Scholars Residence, the Laboratory Animal Research Building, and the new research tower currently under construction.

Educated at Yale University—receiving a baccalaureate degree in 1938 and a law degree in 1942—Dilworth spent twelve years with Kuhn, Loeb & Co., seven of them as a partner. He left in 1958 to join Rockefeller Family and Associates, where he stayed until his official retirement ten years ago. In his long association with the Rockefellers, he served as senior financial advisor to the family, and as chairman of Rockefeller Center from 1966 to 1982.

Dilworth has had a long and exceptional career as a volunteer in the non-profit sector. He was a trustee of the Metropolitan Museum of Art from 1961 until last fall, including a five-year term as chairman of the board; he has been chairman of the board and a trustee of the Institute for Advanced Study in Princeton; and he was a fellow of the Yale Corporation for twenty-seven years.

ROCKEFELLER'S DEPARTMENT OF LABORATORY SAFETY: A VITAL FORCE IN WASTE MANAGEMENT

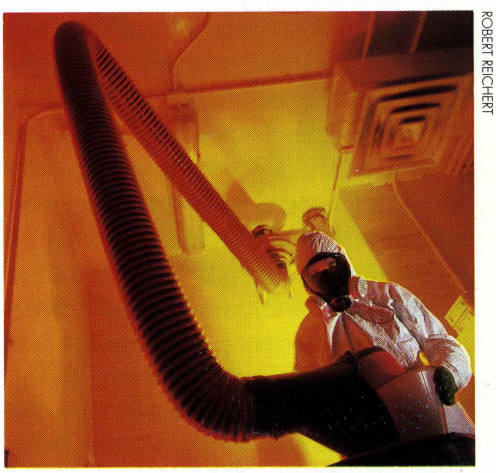
by Ruth Coxeter

"Apart from making sure the university meets growing regulatory demands, we are essentially problem-solvers," says Edward Gershey, head of the university's Department of Laboratory Safety. "We focus our research on assessing the reliability and safety of laboratory equipment," he adds, "and we try to influence the formation of new legislation and regulations in this area."

This research has ranged from finding less toxic and more economical substitutes for chromic acid, a compound used for cleaning glassware, to designing better laboratories and determining whether latex gloves exposed to ethanol lose their effectiveness.

A major part of Lab Safety's program is waste management. By 1993 states will be required to dispose of their own low-level radioactive wastes. Lab Safety began preparing early for the impending waste disposal crisis. In the early eighties Rockefeller made impressive gains, cutting radioactive wastes by ninety-seven percent and reducing total costs for disposal of both radioactive and chemical wastes by sixty percent, despite rising disposal costs. However, Lab Safety notes that future reductions will be more difficult with increased regulations and costs and diminished economic or administrative incentives.

One result of Lab Safety's work is the publication of two books and many articles, including *Laboratory Safety in Practice: A Comprehensive Compliance Program and Safety Manual,* written by Gershey and colleagues Esmeralda Party and Amy Wilkerson, published by Van Nostrand Reinhold in 1991. Each year Rockefeller saves close to a million dollars in waste management, while complying with strict regulations and maintaining a safe working environment for its employees. Because of this success, Lab Safety is often called upon to advise other institutions on a variety of issues ranging from waste management to employee safety.



ROBERT REICHERT

Member of the Department of Laboratory Safety Frank X. Schaefer processing hazardous waste for disposal.

RUTH COXETER is a production editor for *The Journal of Cell Biology*, published by The Rockefeller University Press.

PFORZHEIMER GRANT HELPS EXPAND CIRCULATION OF *SEARCH*


Carl Pforzheimer, Jr.

Combining two of its main interests, publishing and science, the Carl and Lily Pforzheimer Foundation has given *SEARCH: The Rockefeller University Magazine* a grant of $150,000 to help defray publishing expenses and to ensure that the magazine will accomplish its purpose—to improve understanding of science and to convey information about scientific achievements to a broad general public—by increasing its circulation base.

The grant was announced by the foundation's president, Carl Pforzheimer, Jr., who has been a member of The Rockefeller University Council since 1973. Pforzheimer founded Carl H. Pforzheimer & Company, an investment banking firm of which he is senior partner.

The foundation, based in New York City, was formed in 1942 and lists as its focal points publishing and research activities in the general field of American and English literature, higher and secondary education, cultural programs, a national municipal organization, and health care.

The grant will enable *SEARCH* to extend its audience to include additional college and university science departments and some secondary school science departments. Currently the magazine is sent to the Rockefeller community and friends of the university; college and university presidents, science departments, libraries, and minority student career advisement programs; federal, state, and local government education and science committees; and others. Total circulation is approximately ten thousand.

LETTERS TO THE EDITOR

SEARCH welcomes letters from readers and will publish them selectively. Here are excerpts from correspondence we received after our first two issues:

•

I have just received a copy of Volume I, No. 2 of *SEARCH*, and I write to congratulate you on a superb publication.

I was of course pleased to see that the work of two Howard Hughes Medical Institute investigators, Jeffrey Friedman and Michael Young, was discussed. In that regard I would like to note that references on page 5 to Dr. Friedman's work being "supported by grants from the Howard Hughes Medical Institute...." is not correct, as the support for our investigators is not a grant. As a medical research organization the support of research by our investigators, who are de facto employees of the Institute, is not a grant but the direct, active conduct of research by HHMI investigators.

Purnell W. Choppin, M.D.
President
Howard Hughes Medical Institute

What prompts this letter is the signal given by David Baltimore's opening piece, "The Decade of the Mouse" [Spring 1991 issue]. In my years at The Rockefeller Institute for Medical Research (1940—1965) I was the inheritor of the investigative tradition of experimental epidemiology, begun by Dr. Simon Flexner and Dr. Leslie T. Webster. The model we used was the laboratory mouse, literally by the hundreds of thousands. When I resigned my tenure at Rockefeller in 1965 to help found the short-lived Institute for Biomedical Research of the American Medical Association at Chicago, I founded the nation's first laboratory of Experimental Medical Ecology, and continued my involvement with mice.

It is cheering to an old-fashioned organismal-population biologist to hear that the laboratory mouse still commands attention. But, with respect, allow me to suggest that the mouse environment must not be ignored.

Howard A. Schneider, Ph.D.
Professor Emeritus
Biochemistry and Nutrition, School of Medicine
University of North Carolina- Chapel Hill

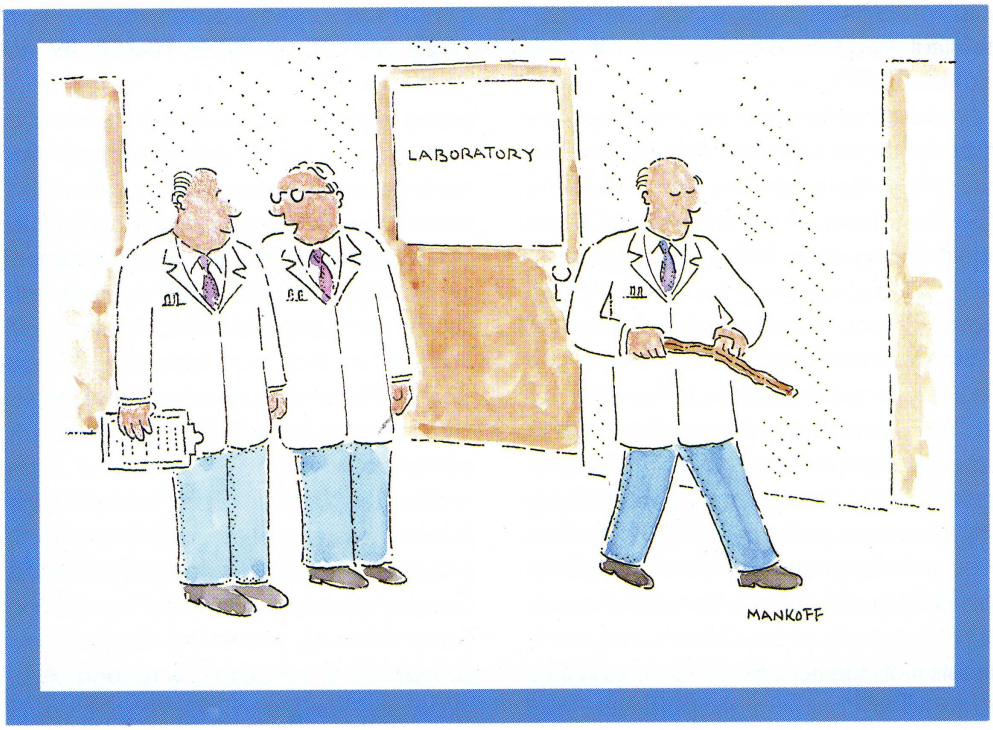
Just a note to tell you how much I enjoyed the premier issue of *SEARCH*. The brief stories are clear and concise, and the photography is excellent. The topics covered were very appropriate, and I look forward to seeing future issues.

Ernest G. Jaworski
Corporate Research
Monsanto Company

Received my copy of *SEARCH* and want to congratulate the editor and her staff on a job well done. I was especially moved by the photograph of the tulips and azaleas on the back cover; it brought back fond memories of the spring flowers on the university grounds.

Thomas J. Kindt, Ph.D.
Laboratory of Immunogenetics
National Institute of Allergy and Infectious Diseases

DOUBLE TAKES



"Don't laugh, he's found funding that way before."

VIEWPOINT

SCIENCE AND LIFE

by Salvador E. Luria

This essay is an excerpt from the introduction to *Life—The Unfinished Experiment,* by Dr. Luria, published in 1973 by Charles Scribner's Sons, an imprint of Macmillan Publishing Company. (Reprinted with permission.)

Science's present grasp of the molecular mechanisms of life, however incomplete, represents a remarkable intellectual achievement, a satisfyingly coherent set of hypotheses and explanations. Moreover, it is intensely relevant—as a source of wisdom as well as of dangers—to a range of problems that already beset modern man or will probably do so in years to come: from the manipulation of his own heredity, to the possible control of his demographic expansion, to the effective learning to live in a balanced environment.

Life has two scientific aspects: life in action and life in time. Life in action is the functioning of living organisms, the molecular and atomic events brought about by the presence of life, and is the subject matter of biochemistry. Life in time is the persistence and disappearance and replacement of organisms, by individual death as well as by the generation and differential proliferation of new species—in one word, evolution. These two aspects, biochemistry and evolution, make life a unique phenomenon in the history of the earth, one that long before the coming of man had impressed its profound mark on the features, the climate, the very structure of the planet earth.

Life is distinct from all other natural phenomena in one feature: it has a program. All other natural phenomena occur more or less at random, like the movement of clouds in the changing winds, or the disintegration of radioactive atoms, or the collision of molecules in a heated fluid. When physical phenomena have a regular trend, it is generally a trend toward increased disorder, in conformity with the physical law that affirms the tendency toward a minimum of molecular order. Even when order appears to increase, as in the crystallization of substances from solutions, it is a repetitious, monotonous, noncreative order. Nonbiological phenomena are characteristically the expression of the statistical behavior of large numbers of units, not of the unique performance of a single object or structure.

Only in life does individuality emerge. Life's program unfolds itself in the wonderful growth of a germ into an organism, in the blossoming of a species to fill an environmental setting, in the creative replacement of species with species in the course of evolution—because life's program has been inscribed in a unique substance, the substance of the genes. This material substrate of life is an exception, not to the laws of physics and chemistry but to the run-of-the-mill types of molecules. It is a substance whose construction insures both stability and almost infinite variety of individual patterns. It provides for copying with an accuracy unattainable in any other known molecular species. At the same time, this program substance is capable of change, and its changes become the basis for biological evolution.

The program of life, embodied in the substance of the genes and expressed in the forms of organisms and in their evolution, is not like the conscious programs of human enterprises, be they works of art or social undertakings. It is not a project for the future: it is an inventory of the present, an array of potentialities embodied in the substance of the genes. As stated by the French geneticist Francois Jacob in *La Logique du Vivant* (1970), "the individual becomes the realization of a program prescribed by heredity." For a single organism, the program is the inborn plan that controls its development and its life functions, modifiable of course by external influences. For a species, the program is the entire range of genetic types it encompasses, a range that determines whether that species, in given surroundings, will persist or flourish or die out.

....Life evolved, reached its present state, and will further develop by the creative interplay of the chemical workings of the genetic material and the historical workings of the natural forces that favor now one species, now another, promoting any biochemical invention that provides increased fitness. Stupendous devices such as the brain and mind of man are biochemical inventions as challenging and as mysterious as those that produced the equally stupendous social organization of insects. To the scientist, the uniqueness of man is purely a biological uniqueness rather than the superposition of something nonbiological—soul or spiritual essence—upon the workings of biological evolution. The nature of the mechanisms responsible for these highly complex phenomena still escapes the biologist, but he is confident that this will not always be so.

The science of heredity is less than one hundred years old, modern biochemistry less than fifty, molecular biology barely twenty, and their progress has been astonishingly rapid. As one looks back at the millennia of ignorance and forward toward the harvest of knowledge still to be gained, both pride and humility are in order. As he gains understanding of life and of himself, man seems to be well on his way to fulfill the prediction of Genesis: "Ye shall be as gods, knowing good and evil."

But man's knowledge of himself is still scanty and is blurred by the fogs of legend and superstition—naive but inevitable attempts of his ancestors to acquire knowledge by intuition rather than by reason. Meanwhile the course of events proceeds swiftly. Man may soon be called upon to make choices on at least some aspects of his own biological future, realizing that the old intuitions do not suffice and that scientific knowledge, partial as it may be, is the truly reliable tool at his disposal....Scientists have a responsibility to inform the public of the state of their knowledge, especially when that knowledge becomes relevant to the welfare of mankind.

SALVADOR E. LURIA, who died this spring, was for many years a faculty member at the Massachusetts Institute of Technology, where he was Sedgwick Professor of Biology and Director of the Center for Cancer Research. Dr. Luria was awarded a Nobel Prize in 1969 for his contributions to "discoveries concerning the replication mechanism and the genetic structure of viruses." The Rockefeller University conferred an honorary degree posthumously on Dr. Luria at commencement ceremonies in June 1991.

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