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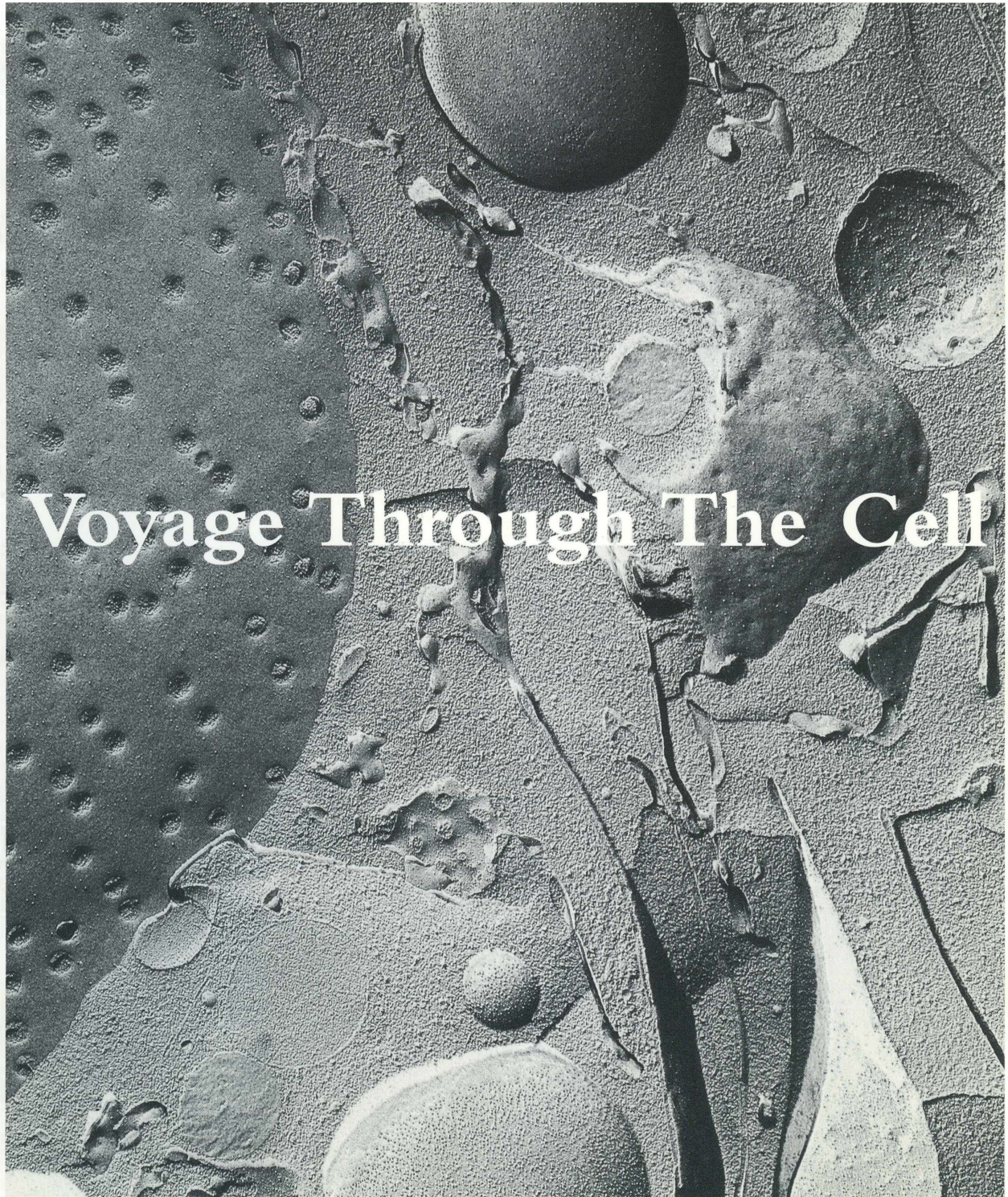
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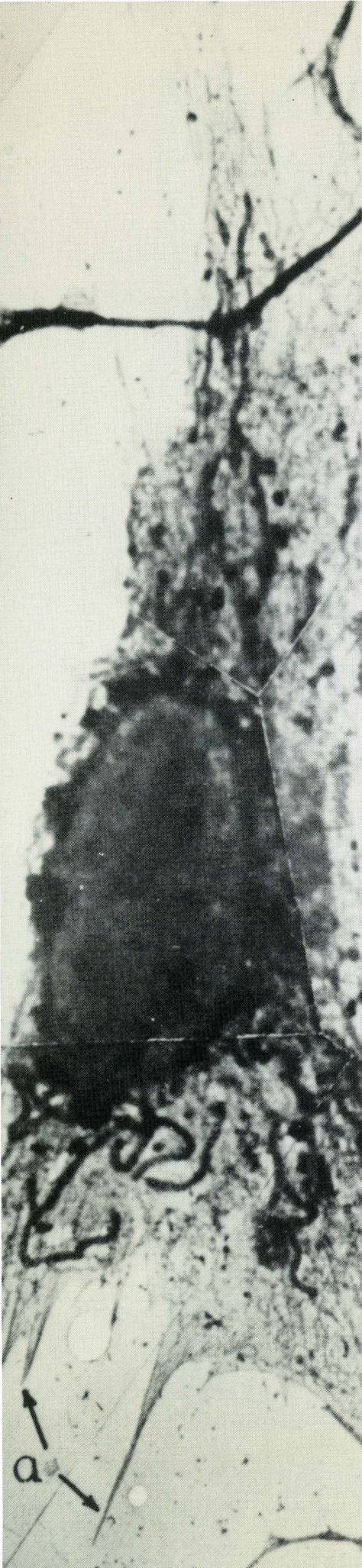


# SEARCH

THE ROCKEFELLER UNIVERSITY MAGAZINE







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1996

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## Celebrating the Origins of Cell Biology

Torsten N. Wiesel, *President*

“The key to every biological problem must finally be sought in the cell,”

wrote the great classical cytologist E.B. Wilson in 1925. Yet until the advent of biological electron microscopy, most of the interior landscape of the cell remained a *terra incognita*, beyond the level of the light microscope’s resolution. It was only when Rockefeller scientists Albert Claude and Keith Porter, in collaboration with Interchemical Corporation

electron microscopist Ernest Fullam, published the first electron micrograph of a whole cell in 1945 that biologists had their first glimpse of the cell’s astonishingly intricate inner structure.

The historic micrograph, combined with improvements in techniques for cell fractionation and preparation of tissue specimens for electron microscopy, launched the modern era of cell biology. In 1995, The Rockefeller University celebrated the birth of this central scientific discipline with a special three-day symposium, which included lectures by Nobel laureates George Palade and Christian de Duve, a historical roundtable discussion, lectures on current problems in cell biology, and a public lecture for the general community.

This issue of *Search* traces the origins of cell biology from the cancer research of Albert Claude, who in seeking to purify a cancer-causing virus serendipitously discovered a mysterious cellular structure, the “microsome,” present within the cells of all plant and animal species. The possibility of seeing the structure of the microsome was a key impetus for the collaboration that produced the first electron micrograph.

Modern cell biology is one of the university’s great and enduring legacies in science. This issue’s main article, “A Voyage Through the Cell,” takes us on a journey from the cell’s nucleus to its receptor-laden surface, showing how Rockefeller scientists are probing critical questions about cellular function in health and disease at each point along the way. The article brings the cell to life with images from our laboratories and specially commissioned illustrations.

*Search* also contains a tribute to David Rockefeller, who retired in 1995 as chairman of the Board of Trustees’ Executive Committee after 55 years on our board and was honored at the 1995 convocation. While officially “retired,” David continues to play a leadership role at the university as honorary chairman of the board, life trustee and chairman of The Rockefeller University Council.

Finally, we introduce a new section to *Search*, “Sixty-Sixth and York,” that highlights some recent scientific activities in our laboratories as well as other developments on campus.

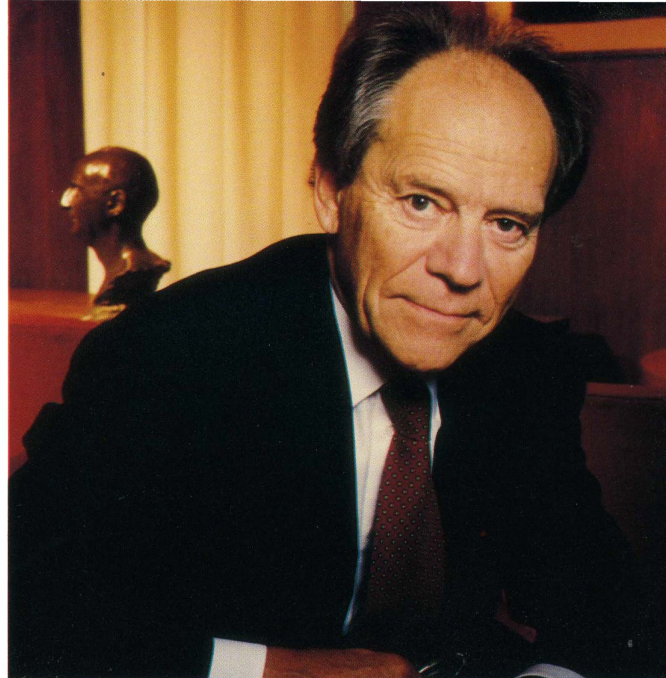


Photo of Torsten N. Wiesel: Robin Thomas

Cover: This freeze-etch electron micrograph of an onion root-tip cell reveals the nuclear surface with its pores, at left, and several fractured organelles in the surrounding cytoplasm. Courtesy of Daniel Branton.

At left: The first electron micrograph of an intact cell taken at Rockefeller in 1945. Magnified 1,600 times, this cell reveals mitochondria, the Golgi apparatus and the “lace-like reticulum” later named the endoplasmic reticulum.



# Far Better Than Dreams

## *The Founding of Modern Cell Biology*

by Geoffrey Montgomery

Philip Siekevitz



Top: Pictured in an early electron micrograph, these fragments of the endoplasmic reticulum are studded with ribosomes, cellular factories for protein synthesis.

Above: Albert Claude, at the then Rockefeller Institute for Medical Research in the mid-1940s, at the time of the first electron micrograph of an intact cell.

When Albert Claude began breaking open animal cells in the 1930s in search of the source of a strange form of cancer, he could scarcely have imagined how far this journey would take him. His quest for the secret of cancer led him into the unexplored interior of complex cells, where he became the first to navigate the territory of a new science, the modern discipline of cell biology.

Claude's original ambition was simple. He wanted to purify and characterize the agent that caused a transmissible form of cancer in chickens, today called the Rous sarcoma virus. Claude came to Rockefeller in 1929 to conduct his research because it was here that Peyton Rous discovered the virus in 1911.

For more than a decade, Claude pursued the virus, but was unable to isolate it with the techniques of the day. In attempting, however, he revealed the cell was not a bag of enzymes, a formless "biochemical bog," as many biologists believed, but an organized entity with substructures, called organelles, with specialized functions. His work led to the historic viewing of a cell with an electron microscope in 1945, considered the birth event of cell biology. Beginning with the discoveries by Claude and his fellow cell biology pioneers, many of whom worked or trained at Rockefeller, cell biology grew to become a foundation for modern biology and medicine. To honor this achievement, the university celebrated the 50th anniversary of the field last year with a three-day meeting of cell biology experts, including several of the field's pioneers.

"The place of birth of cell biology is clear. It's The Rockefeller Institute for Medical Research [now The Rockefeller University]," said Christian de Duve, a former colleague of Claude's and Rockefeller professor emeritus, at the university's symposium. "The name of the father and mother is [also] clear: Albert Claude and Albert Claude."



Claude's work led to the building of the two major pillars on which the nascent field of cell biology would rest: electron microscopy and the examination of purified cell components by a technique known as cell fractionation. Claude pioneered cell fractionation in his attempt to isolate the inner components of chicken tumor cells. Working within the cancer research laboratory of James B. Murphy, Claude broke open the tumor cells' protective outer membranes, placed their spilled innards in a tube and spun the tube in a high-speed centrifuge. The cell pieces separated in distinct layers, or fractions, within the tube according to their mass, with the heaviest spinning to the bottom. In this way, Claude hoped to segregate and purify the cancer's infectious agent—whose viral nature was highly controversial.

Indeed, by the late 1930s, Claude succeeded in obtaining a fraction that was 50 times more effective in producing new tumors than the original tumor tissue. Though the presumed viral components of the fraction were too tiny to see with the light microscope, Claude could test the fraction's biochemical characteristics. He found the fraction contained ribonucleic acid (RNA)—a mysterious substance whose function, like that of DNA, was then unknown.

But Claude then performed a crucial control experiment. He applied the fractionation procedure to healthy chicken cells derived from a normal chick embryo. Claude discovered, to his great surprise, that the normal RNA fraction was strikingly similar to the tumor cell fraction, except the normal fraction failed to produce tumors.

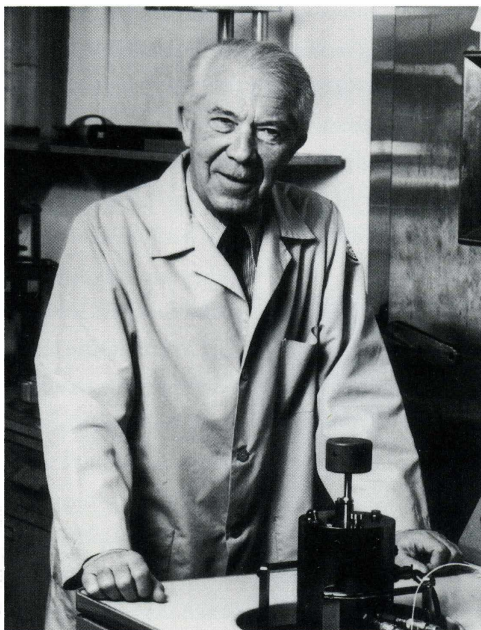
In further studies he found that in every cell type examined, a fraction could be separated by high-speed centrifugation that would contain RNA, protein and phospholipids, the major component of cell membranes. He called this material a "microsome," for "tiny body."

Microsomes became a portal for Claude and a growing host of colleagues into the uncharted interior of the cell. These mysterious microsomes were present in all animal cells, yet what was their function and structure? Where did the microsomes reside in the terrain of the intact cell? To answer these new and paramount questions, novel techniques for studying cells were required. Although the scientists could estimate the minuscule size of microsomes and probe aspects of their chemistry, microsomes could not be seen with existing light microscopes. They were too tiny. Like the islands of the Caribbean before Columbus, the microsome lay beyond the horizon of the visible.

In 1943, however, Claude was offered a ship to the New World. Claude had just published a paper in *Science* describing his microsomes, which, he speculated, "like the other nucleic-acid-containing structures [in the cell], may be endowed with the property of self-duplication...."

His speculation turned out to be incorrect, but it caught the attention of Albert Gessler, director of the Interchemical Corporation's research laboratories in New York City. Gessler contacted Claude and asked if he wanted to use an instrument theoretically capable of visualizing microsomes and other fine cell structures. The instrument was in Interchemical's possession for use in the top-secret Manhattan Project to develop the atomic bomb. The instrument was the electron microscope, which, by projecting short-wavelength electron beams at a sample, created images of structures 100 times smaller than those perceptible with visible light.

A collaboration commenced between Claude and Interchemical's electron microscopist, Ernest Fullam. They looked at cell fractions containing mitochondria, the power stations of higher cells that Rockefeller's



Christian de Duve discovered lysosomes, cell organelles that specialize in recycling and waste disposal.

Ingbert Grütner





Rollin Hotchkiss had shown to contain enzymes essential to oxygen-consuming respiration.

A young colleague from the Murphy laboratory, Keith Porter, soon joined Claude and Fullam. Porter, a

1970 Horwitz Prize honoring the historic work. By occupying this open space in the wire grid, the cell was in a clear path for the electron beam. The beam could pass unimpeded through the cell's interior to a photographic plate.

"Men have visited the moon...but we were the first...to see particles, to see structures that the light microscope had not been able to resolve. And there were Claude's microsomes, and there was the lace work of [what] eventually came to be known by that

**"Men have visited the moon...but we were the first...to see particles,**

zoologist, had developed great expertise in the fine art of growing and studying cultured cells.

"On one of Claude's early visits," Porter would later remember, "I tagged along to see this remarkable instrument and learned such basic points as a) the specimen [under study] had to be dry [to prevent evaporation within the electron microscope's vacuum chamber] and b) it had to be thin [to allow penetration by the microscope's electron beam]." Porter, who knew that cultured cells had a tendency to spread out to extreme thinness on their growth plates, "began to dream about ways to get cultured cells into the electron microscope."

Porter devised a method both ingenious and historic. He grew embryonic chick cells on a layer of Formvar plastic that covered a glass petri dish. When he found cells that spread especially thin, he used watchmakers' forceps to peel back a disc of the plastic underlying the cells and inserted a wire specimen grid suitable for electron microscopy beneath. He then removed the three-layered sandwich of wire grid, plastic and cultured cells, drying them and chemically stabilizing their structure in preparation for viewing with the electron microscope.

"Within a short time we discovered on one grid — which had only three or four cells on it — a cell in an opening in the grid, and it became the most micrographed cell in history," Porter recalled when, with Claude and George Palade, he received the

horrendous term 'endoplasmic reticulum,'" remembered Porter.

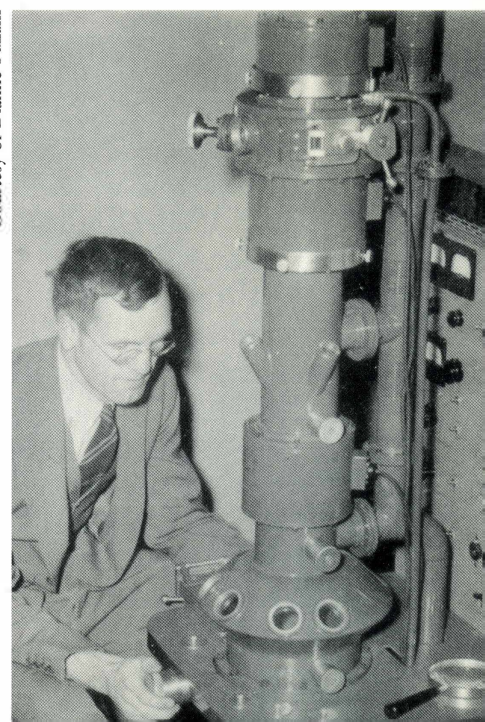
Indeed, Porter soon correctly suggested that Claude's microsomes were actually fragments of the endoplasmic reticulum (ER), a labyrinthine series of channels extending from the nucleus of the cell. Seen clearly with the electron microscope, the microsomes became membranous tubes usually studded with peppercornlike particles. By 1956, Palade and Philip Siekevitz showed definitively that not only were these particles the source of the microsomes' RNA, they also were the sites of protein creation. Consequently, they were dubbed ribonucleoprotein particles or ribosomes.

By the early 1960s, an integrated picture of protein synthesis — the central process by which cells maintain their structure and manufacture the thousands of enzymes used for every biological process from digestion to human thought — emerged from these studies at Rockefeller and at a handful of other vanguard research groups.

Within the cell's nucleus, DNA's genetic message is transcribed into

*Above: Keith R. Porter in 1939, the year he arrived at Rockefeller. Porter invented key techniques in the art of electron microscopy. Right: Ernest F Fullam, at the electron microscope, collaborated with Rockefeller biologists Albert Claude and Keith Porter in creating the first electron micrograph of an intact cell.*

Courtesy of Dianne Fullam





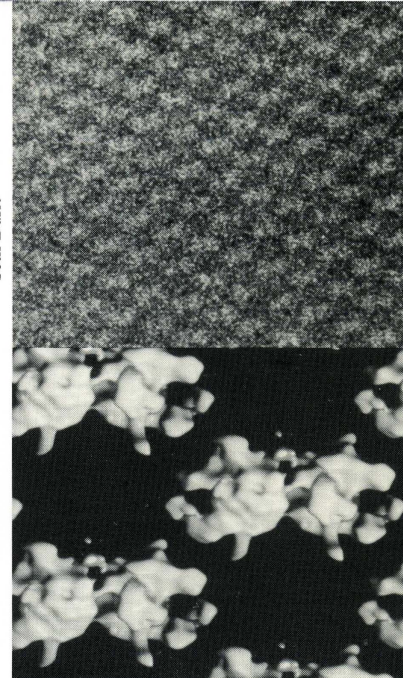
strands of messenger RNA, which is then translated on the ribosome into chains of amino acids — the units that comprise protein molecules.

Ribosomes exist both freely in the cell's cytoplasm and bound to the ER membrane. If the ribosome is attached to the ER, the new protein enters the ER's internal channels for further use in the cell or for export. Before leaving the cell, proteins are packaged in another cellular miniorgan, or organelle, known as the Golgi apparatus.

Laboratory for Cell Biology, then headed by Porter and Palade.

"Lee Peachey was the first, followed by others including Jim Jamieson, David Luck, Peter Satir and David Sabatini," Palade recalled. "These special graduate students, together with the post-doctoral fellows and research associates of that period, who included

Seth Darst



to see structures that the light microscope had not been able to resolve."

Palade recalled at the university celebration that the improvements in techniques for preparing cells for fractionation and electron microscopy launched a revolution. "Essentially the entire garden of creation was open for study at the new levels of resolution," he said, "and prospectors for anticipated scientific gold nuggets rushed to the newly open fields in ever-increasing numbers, much like the '49ers in the gold fields of California."

Claude's cell fractionation techniques, previously improved by Palade, George Hogeboom and Walter Schneider in their work on mitochondria, were adopted and refined by de Duve, who used them to discover and characterize a previously unrecognized cell organelle, the lysosome, which serves as the cell's waste and recycling facility.

Claude's enhancements allowed not only for the study of organelle structures, but their functions as well. "Just the idea that you could actually take mitochondria in a test tube and ask them to do there what they do in the cell — it was something fantastic," de Duve remembered thinking after first learning of this work from Claude.

With the addition of new knowledge about cells came a new generation of cell biologists, careers facilitated with the transformation of the Rockefeller Institute for Medical Research to a graduate university in 1954. Many of the students joined the

Günter Blobel, Nam-Hai Chua and Marilyn Farquhar, became the most active, imaginative and enterprising crew in the history of the Rockefeller cradle for cell biology."

Today cell biology has merged with molecular biology and genetics to offer a unified scientific front for the exploration of life and disease. As Claude, who died in 1983, said on receiving the Nobel Prize for Medicine with Palade and de Duve in 1974: "Looking back...the facts have been far better than the dreams. In the long course of cell life on this Earth, it remained for our age, for our generation, to receive the full ownership of our inheritance. We have entered the cell, the mansion of our birth, and started the inventory of our acquired wealth."



Top Right: Today RU biologist Seth Darst uses the electron microscope to image single-layer view crystals of a DNA transcription enzyme, RNA polymerase II, whose molecular structure is then modeled on the computer. Right: Nobel Prize-winning cell biologists Christian de Duve (center) and George Palade (right) talked with President Torsten Wiesel, also a Nobel laureate, at RU's 50th anniversary celebration of modern cell biology.

# A Voyage

## Through the Cell

by Susan Blum

Peroxisome  
Endosome  
Nucleus  
Nucleolus  
Nuclear Pore  
Nuclear Membrane  
Microtubule  
Plasma Membrane  
Ion Channel



Half a century ago, Rockefeller scientists Albert Claude and Keith Porter, together with Ernest Fullam, revealed a new biological world. Their image of an intact cell, taken with an electron microscope, beckoned researchers to explore hitherto-unseen intracellular structures. In the years that followed, electron

microscopy, combined with laboratory techniques, carried researchers on a voyage throughout the cell to survey its newly discovered structures and investigate their functions.

To mark the anniversary of those early voyages, *Search* takes an excursion through the cell.



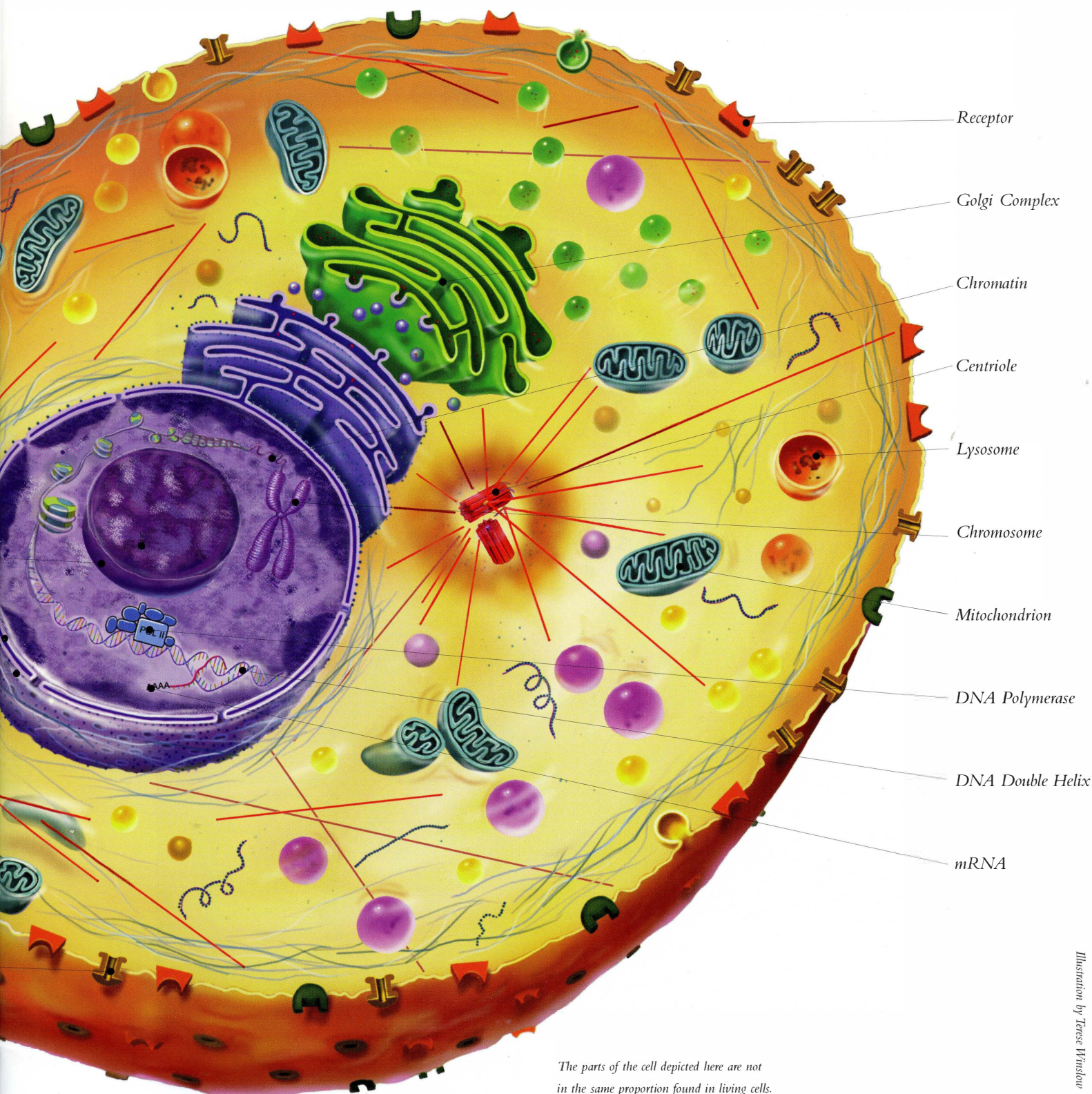


Illustration by Terese Winslow

Our trip's route will lead from the cell's innermost structure — the nucleus — to its outermost border — the surface membrane. Our itinerary highlights the work of Rockefeller researchers studying aspects of cell structure, function and behavior. Today, the field of cell biology has grown

so large and has merged with so many other disciplines that no single article can encompass all the investigations at the university. But in the pages that follow, we invite you to sample some of the discoveries emerging from the innovative cell research at Rockefeller.





*Professor Fred Cross, left, and Bert Oehlen, postdoctoral associate, investigate the molecular events underlying the cell's decision to commit to a new round of gene duplication, which takes place in the nucleus.*



# Home Port:

## *In the Nucleus*

At the heart of plant and animal cells is the nucleus, set — as the Latin roots of its name imply — like a little nut in the cell's cytoplasm. Nestled within the nucleus' membranous shell are six feet of DNA that contain commands for manufacturing proteins and the workbenches on which they are forged.

ple, the instructions embodied in DNA are duplicated each time the cell divides, as it does when a developing embryo takes shape or an injured tissue replenishes itself. Professor Fred Cross investigates the molecular events underlying the cell's decision to commit to a new round of gene duplica-

place the clamp onto the DNA. Using the techniques of X-ray crystallography, which reveal the 3-D position of every atom within a molecule, Kuriyan and his collaborators determined the shape of the clamp and three subunits of the clamp-loading machinery. Their ultimate aim is to reveal the structures of

### **As guardian of the cell's DNA, the nucleus serves as its Information Central.**

Not all cells have a nucleus, but possession of this substructure, one of many cell organelles, confers many benefits upon a cell. For instance, a nucleus protects precious genetic cargo from the mechanical forces generated by the cell's internal framework. It also enables the cell to undertake the extremely complicated molecular processing that produces a repertoire of proteins to serve many needs.

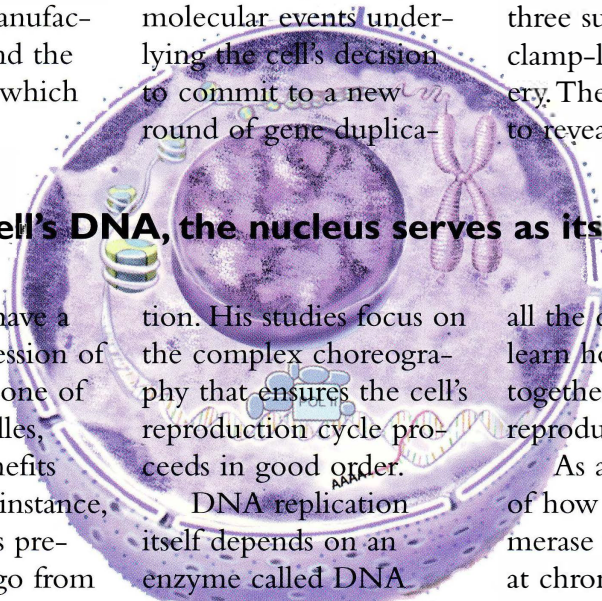
As the guardian of DNA, the nucleus serves as the cell's Information Central. Here, for exam-

tion. His studies focus on the complex choreography that ensures the cell's reproduction cycle proceeds in good order.

DNA replication itself depends on an enzyme called DNA polymerase, under study in the lab of Professor John Kuriyan, an investigator of the Howard Hughes Medical Institute. This complex biological machine consists of three different components — a core catalytic engine, a protein that forms a sliding clamp to grip DNA and accessory proteins that

all the components and learn how they function together to accurately reproduce DNA.

As a consequence of how the DNA polymerase works, the DNA at chromosomal ends cannot be copied. Moreover, if left unprotected, the ends of the chromosomes are subject to loss through fusion or degradation. Telomeres, complexes of specialized proteins and repetitive DNA sequences that cap chromosome ends, solve both of these potential problems. They protect the tips of chromosomes





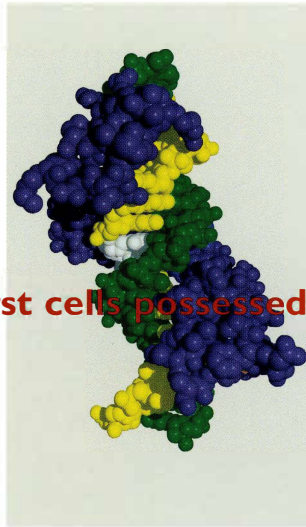
and interact with an enzyme called telomerase that adds back the DNA lost with each round of duplication.

Associate Professor Titia de Lange studies telomeres and recently cloned — that is, pulled out from the chromosomes — the first gene coding for a vertebrate telomere protein. She also investigates the telomerase enzyme itself. Until recently, researchers thought that telomerase did not function in nor-

determined by which of its genes are transcribed. Thus, the cell must tightly control this process — a control under study in a number of labs at Rockefeller. Among the researchers investigating aspects of transcription are Robert Roeder, James Darnell, Jan Breslow, Nat Heintz,

cell type at one distinct time in a cell's developmental program.

During transcription, a gene's DNA information is read out into a closely related molecular cousin called messenger RNA (mRNA) that then leaves the nucleus to be translated into protein. But before the mRNA makes an exit, it undergoes processing on spliceosomes, molecular machines made up of protein and RNA. Spliceosomes snip out



*In order for RNA production to begin with the correct sequence during translation, a protein (shown in purple) wraps around double helixed DNA (yellow) and recognizes the beginning of a gene (white).*

mal mature cells. Only cancer cells, which grow out of control, were thought to produce the chromosome-building enzyme. But de Lange and her colleagues found telomerase remains active in certain healthy cells, indicating a more complex role for the enzyme than previously known.

In the nucleus, genes are not only duplicated. The information encoded within them is “read out,” as well, in a process known as transcription. The individual identity of a cell — as, say, a liver cell or a heart cell — is

Stephen Burley, Nam-Hai Chua and Claude Desplan. Their studies span a range of topics, from the general transcription factors that prompt transcription in all cells to the factors that turn on a gene or set of genes in one particular

mRNA sequences called introns, which remain in the nucleus, but rapidly degrade.

Associate Professor Magda Konarska is studying the splicing process, stripping spliceosomes down to their bare minimum to better understand how they work. One question she aims to answer is whether the cuts are catalyzed by the spliceosome's protein components, its RNA portions or both. Should the research reveal that the action depends on RNA, it will provide additional

**Many scientists believe the first cells possessed genes made of RNA, not DNA.**

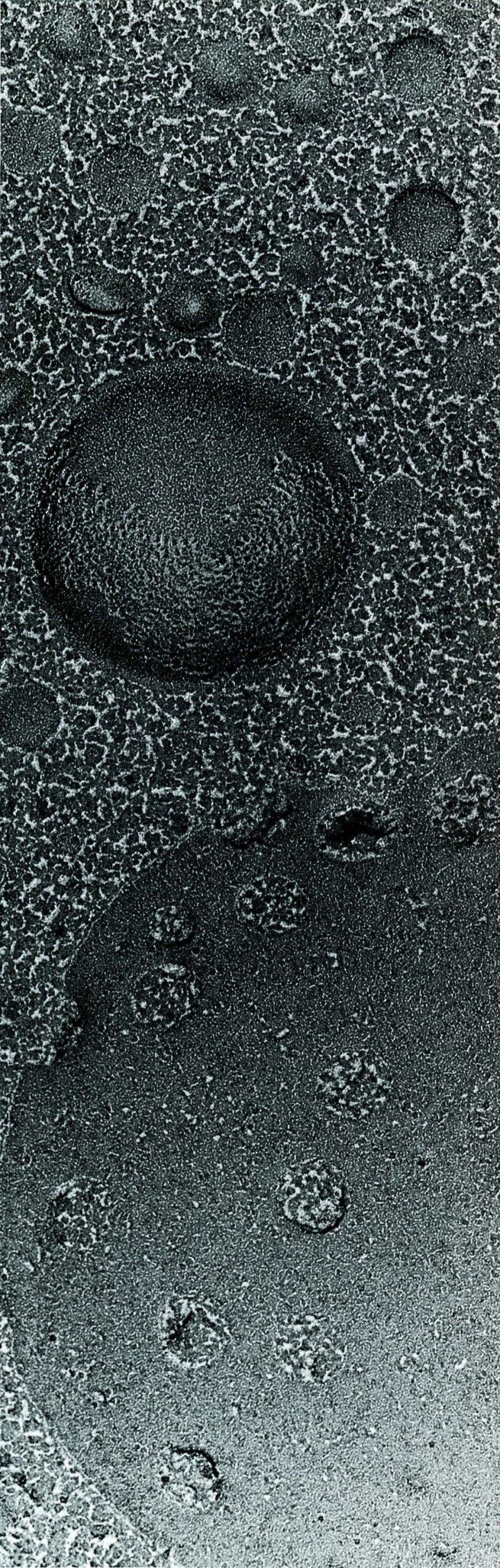


**Should research reveal that spliceosomes, molecular editing machines, depend on RNA, it would provide additional support for one theory on how life began.**

*Magda Konarska, associate professor, studies the RNA splicing process.*







## A Hole in the Wall: Exploring the Complexities

The nucleus is the cell's *sanctum sanctorum*, wherein are cached the genetic text of life and the molecular clerics that transcribe its message.

"It's a great privilege to be in the nucleus, so entry and exit into this inner sanctuary must be highly regulated," says Professor and Howard Hughes Medical Institute Investigator Günter Blobel.

He and his colleagues study the portal through which worthy molecules pass — the nuclear pore complex whose interplay of struts, rings and buttresses rivals the engineering feats of many a Gothic cathedral. The number of nuclear pores varies among cell types, but scientists estimate that each pore mediates as many as 10 import and 10 export events per second.

Each pore consists of up to about 100 proteins called nucleoporins. Researchers, including Blobel, have characterized a number of them. For instance, the Rockefeller scientists found that some nucleoporins sport repeated patterns of peptides, short stretches of amino acids. They also identified proteins found outside the nucleus — in the cell's fluid cytosol — that play a role in nuclear traffic.

One of those cytosolic molecules, called Ran, belongs to a protein family that cycles between on and off states. Another cytosolic protein is karyopherin, which sports two parts called alpha and beta. Alpha can bind to the address label found on all proteins destined to enter the nucleus, while beta can recognize certain peptide repeat regions of the pore's nucleoporins.

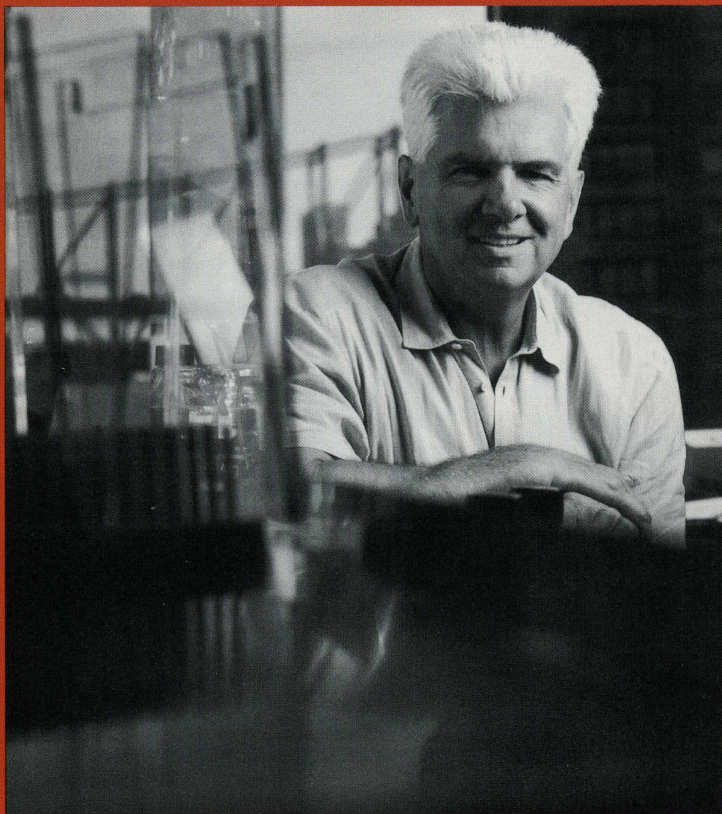
"We still don't know exactly how all these proteins control transport, but we're beginning to have some ideas," Blobel says. One of the researchers' most intriguing ideas is that nuclear traffic works through a series of docking and undocking events that ferry substances from one side of the nuclear membrane to the other.

Going into the nucleus, complexes made of the molecule to be imported, Ran, and karyopherin's alpha and beta subunits might dock and undock sequentially to nucleoporin regions recognized by the beta subunit. Ran's on and off switch might control the docking and undocking action and

*A freeze fraction electron micrograph reveals the nucleus and its pores, bottom, surrounded by the cytoplasm and organelles, top.*



# of Nuclear Pores



Professor Günter Blobel, an investigator of the Howard Hughes Medical Institute, and his colleagues study the portal through which worthy molecules pass — the nuclear pore complex, whose interplay of struts, rings and buttresses rivals the engineering feats of many a Gothic cathedral.

could direct the sequential disassembly and reassembly of the package at each docking site along the way. The same general principles could hold for traffic out of the nucleus, with transport simply occurring in the opposite direction.

On and off docking may not just get substances through the nuclear pore, but deeper within the nucleus, too. There, researchers in the Blobel lab spied what appear to be molecular "tracks" that might be docking sites in interchromosomal regions. Blobel cautions, however, that "the nature of these structures is still completely obscure."

That's just one of the many tantalizing puzzles about nuclear transport that remain to be solved. "Not only the details, but some of the major questions are still open for exploration," says Blobel.

support for one theory of how life began. Many scientists think that the very first cells possessed genes made of RNA, not DNA. In such a world, RNA would have served both as a genetic template and as a catalyst for its own reproduction and, perhaps, splicing. Scientists already know that a few rare single-celled microorganisms use RNA to catalyze their gene splicing. If it turns out, however, that all nucleated cells rely on such processes, the arguments for RNA's role in life's origins become strong.

Edited mRNAs are just one of the many substances that voyage out of the nucleus. In fact, the traffic both out of and into the cell's largest organelle never lets up. In addition to mRNAs, for instance, ribosomes — complexes of RNA and protein — are exported into the cytoplasm, where they serve as the site for protein production. Although all proteins are manufactured outside the nucleus, some of them must be transported back into the nucleus. This process of nuclear import and export is the subject of study in the lab of Professor Günter Blobel, an HHMI investigator. There, researchers study the nuclear pore complexes that permit the bustling nuclear traffic. See *"Exploring the Complexities of Nuclear Pores"* at left. ●





*Professor Ralph Steinman and Associate Professor Melissa Pope explore how certain immune system cells import antigens, fragments of cells and disease-causing organisms, including HIV, that can stimulate immune response.*



# Setting Out to Sea:

## *The Cytoplasm*



**This cellular soup is peppered with organelles, small structures with diverse functions.**

Outside the nucleus, but within the cell membrane's sheltering perimeter, lies the watery substance known as the cytoplasm. This cellular sea is peppered with diverse organelles, or small membrane-bound structures.

Among the cell's organelle inventory are mitochondria, the power plants generating the energy-packed molecules that drive cellular reactions. Lysosomes are enzyme-filled organelles that work as garbage disposals to degrade pathogens, foreign particles and defunct intracellular structures. Other organelles are peroxisomes, the oxidative reactors that detoxify poisons and break down fatty acids, and the endosomes that serve as important way stations and processing centers for substances entering and leaving the cell. The endoplasmic reticulum (ER), an organelle forming a labyrinthine, lace-

like network, is where lipids and many proteins are created and processed. The Golgi complex is an organelle that modifies proteins, packages them and sorts them for dispatch to their proper destination.

As even this brief catalogue indicates, organelles are specialists. Each organelle owes its characteristic capacities to the particular proteins that stud its membrane and fill its interior space.

Lysosomes, for example, are chock-full of highly acidic and destructive proteins, peroxisomes possess enzymes that generate hydrogen peroxide and the inner membranes of mitochondria are dotted with energy-creating enzymes. While some organelles handle civic duties, such as garbage disposal or energy production, others are diplomats, helping mediate relationships with the world. For instance, many organelles participate in importing materials from

the environment, called endocytosis, or in exporting them out of the cell, known as exocytosis.

The cell endocytosizes many different substances for various purposes. In some cases, materials get incorporated into a cell to maintain structures or help regulate cell processes. In others, specialized eating cells known as phagocytes use endocytosis to destroy invading pathogens or clear away dead or destroyed cells and tissues.

Sometimes, the first step in endocytosis occurs when the cell simply pinches in its membrane and envelopes the material destined for incorporation. In other cases, endocytosis proceeds only after a specialized receptor on the cell's surface latches on to its extracellular prey. Regardless of the initial step, the end result is the complete enclosure of the substance by a region of the fatty cell surface membrane.





This membranous packet, called a vesicle, then starts on its long voyage inward, with many potential stops along the way. For instance, vesicular contents may end up at the endosomes, where the substances are sorted and recycled back to the cell surface. Other materials make it all the way to the lysosome, for destruction by enzymes.

Much of the current knowledge about endocytosis comes from the work of Rockefeller researchers, such as

cells called antigen-presenting cells. See *"Presenting a New Kind of Receptor,"* at right.

Just as the cell takes a multitude of substances in from the outside world, it also exports an array of materials. In many ways, this process, which culminates in the budding of vesicles outward from the membrane, is the reverse of endocytosis, which begins with the formation of vesicles pinching inward.

A complex but order-

## AS THE CELL TAKES IN A MULTITUDE OF SUBSTANCES

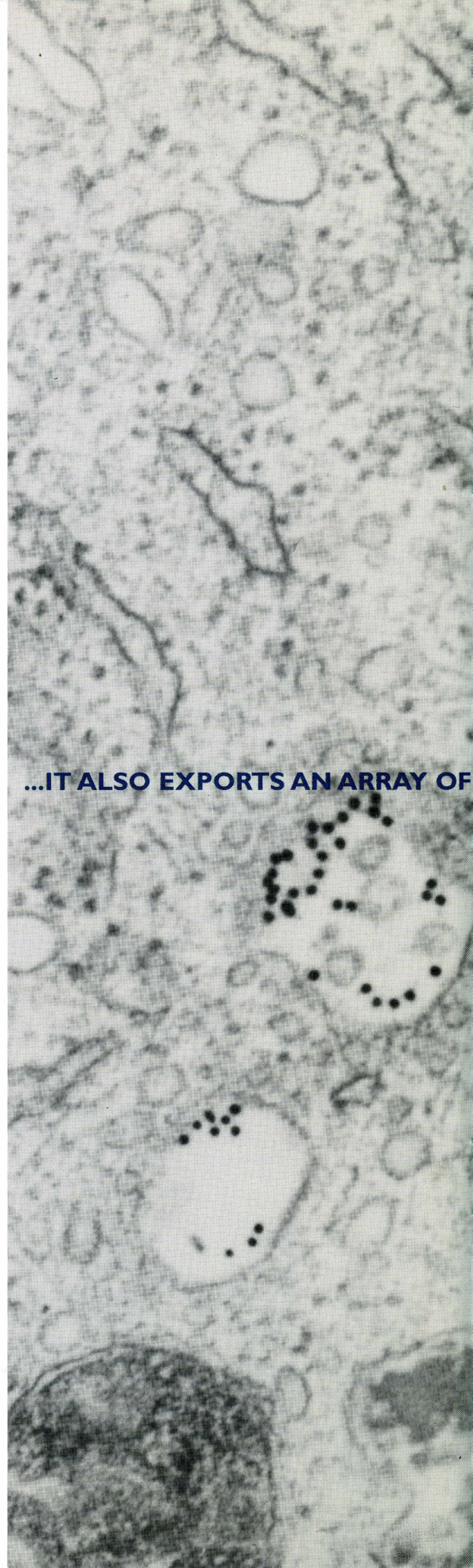
Christian de Duve, who discovered the lysosome and the peroxisome, and Zanvil Cohn and James Hirsch, who traced the pathways by which the membranes of vesicles — and, often, some of their contents — are recycled. Today, work on the endocytic pathway is continuing in the collaborative efforts of Professor Ralph Steinman and Associate Professor Michel Nussenzweig, an assistant investigator of the Howard Hughes Medical Institute. The scientists explore how receptor-mediated endocytosis works in immune

ly progression known as the secretory pathway guides the process of exocytosis. In the 1950s and 1960s at Rockefeller, George Palade and his colleagues elucidated the steps by which proteins destined for secretion are delivered from the ribosomes to the inside of the ER, passed through the Golgi complex for further processing and sorting and then stored in specialized secretory vesicles, which fuse with the cell surface membrane upon receipt of an export signal.

As their work on secretion advanced, the

## ...IT ALSO EXPORTS AN ARRAY OF

*Cellular vesicles called endosomes, center, transport complexes of receptors and antigens within the cell. The receptors bind the antigens at the cell surface, which then pinches in its membranes to make the endosomes.*





# Presenting a New Kind of Receptor

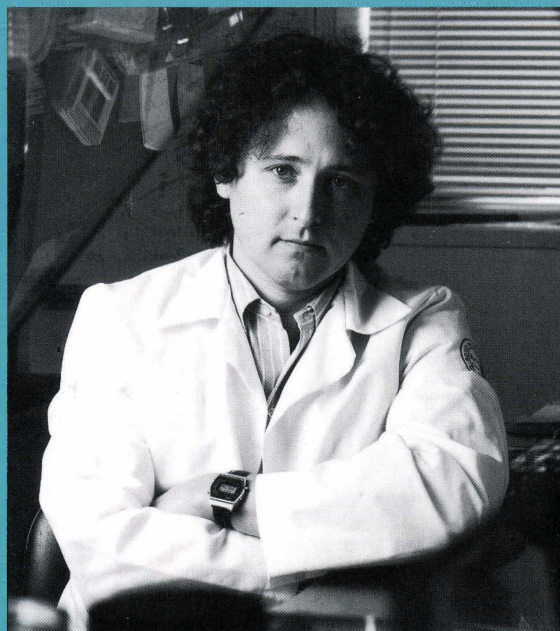
As the guardian of the body's integrity, the immune system has two different tasks. One is to rally its formidable destructive forces to destroy pathogens and the cells they infect. The other is to ensure that those forces mobilize only against threatening elements and not against healthy cells.

This delicate balancing act requires that antigens — fragments of substances belonging to an invader or to the self — be captured by immune cells, processed within their organelles and presented on the cells' surface with a protein called the MHC molecule. Although the importance of this process has been known for some time, the way it occurs in two specialized antigen-presenting cells remained a mystery until recently. Those cells are the dendritic and thymic epithelial cells.

Dendritic cells are sentinels that scout out antigens and present them to the immune system's various kinds of T cells. To mature T cells, they proffer fragments of foreign invaders, thus stimulating the T cells to take destructive action. To developing T cells, dendritic cells display self-antigens, thereby setting in motion the destruction of newborn T cells, which would have responded too strongly to the body's components. Thymic epithelial cells, found in an immune-system organ called the thymus, play a similar role, teaching the body to retain the nascent T cells that will not react too strongly against the self.

Researchers knew that to serve all these roles dendritic and thymic epithelial cells must capture a range of antigens for intracellular processing. But they wondered whether this capture occurred through receptor-mediated endocytosis and, if so, what the receptor would look like.

Thanks to the collaborative studies of Professor Ralph Steinman, discoverer of



*Associate Professor and HHMI Associate Investigator Michel Nussenzweig examines dendritic cells, the sentinels that scout out antigens and present them to the immune system's various kinds of T cells.*

dendritic cells, and Associate Professor and HHMI Associate Investigator Michel Nussenzweig, in whose lab a receptor protein was cloned, the researchers found the molecule on both dendritic and thymic epithelial cells and dubbed it DEC-205.

"DEC-205 appears to be a new type of antigen receptor," Nussenzweig says. The molecule is composed of 10 different carbohydrate-binding domains, which likely confer upon it the ability to capture a wide range of foreign and self-antigens.

The researchers aim to delineate the steps by which DEC-205 and its antigen cargo are processed within the antigen-presenting cells. Much of the action may take place in recently discovered structures called multivesicular endosomes. The intracellular structures contain many MHC molecules and may be the site where antigen fragments are loaded onto MHC molecules for delivery to the cell surface.

**MATERIALS.**



# Combating Resistance to Chemotherapy

researchers realized that cells use at least part of this pathway not only for proteins ordained for exocytosis, but also for the synthesis, transport and delivery of proteins destined to remain in the cell's organelles.

How does each protein know where it belongs — be it in an organelle involved in the secretory pathway or an organelle with other functions such as a mitochondrion or peroxisome? Furthermore, how does a protein reach its proper place inside or on the membrane of that organelle?

These questions Professor Günter Blobel and his colleagues posed and answered. As his research showed, newly synthesized proteins possess certain sequences that target them to their proper destination. Blobel and Sanford Simon, then a postdoc in his lab and now an associate professor at Rockefeller, also disclosed the existence of a watery channel through which nascent proteins move on their way through the network of the endoplasmic reticulum. They now seek similar channels that proteins might move through into other organelles, such as the mitochondria or peroxisomes.

Simon also studies how certain proteins are stitched

When cancer strikes, physicians can draw on an arsenal of chemotherapeutic drugs. The trouble is, sooner or later, cancer cells usually resist the medications. But the research of Associate Professor Sanford Simon may lead to new ways to thwart drug resistance, thanks to work tying together Rockefeller's tradition of studies on exocytosis with Simon's own research on membrane proteins.

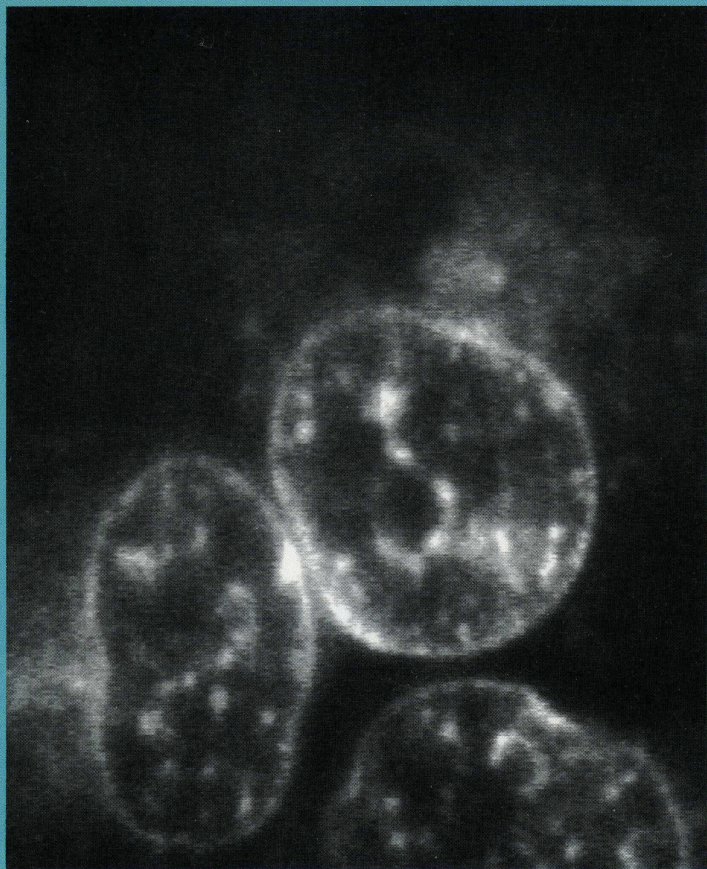
The studies focus on levels of intracellular acidity. In healthy cells, the organelles of the secretory pathway — including the endosomes and the Golgi complex — are more acidic than the watery cytosol that surrounds the organelles. The compartments' acidic environments help them route newly synthesized proteins through and eventually out of the cell. In cancer cells, though, the pattern is different. The cytosol is more acidic than in normal cells, but the organelles fail to acidify, which confers certain growth benefits on the renegade cells.

But although this strategy may initially help cancer cells, there's a downside to it. Chemotherapeutic drugs, which prefer an acidic environment, fail to enter the secretory pathway and get exocytosized from the cell. Instead, they are trapped in the cytosol's relatively more acidic environment. They also enter the nucleus, where they do the damage for which they are designed and kill the cancerous cell.

To resist the drugs' onslaught, drug-sensitive tumor cells then mount a paradoxical countermove: They revert to a more normal cell type to resist the drugs. They re-acidify their organelles and can rid themselves of the drug by secreting it.

What might be causing this reacidification? Simon's studies of a membrane protein called the p-glycoprotein may provide the answer. This protein is overexpressed in drug-resistant cancer cells. The majority view held that the p-glycoprotein pumps drugs out of the cell, but Simon was unconvinced by the evidence for this scenario. Rather, the protein's similarity to a type of chloride channel (CFTR, studied by Professor David Gadsby's lab) led Simon to think the p-glycoprotein might serve the same function. By letting ions in through the membrane, these channels would then help the organelles to acidify.





Sanford Simon

These drug-resistant cancer cells have been manipulated to reduce the acidity of their organelles. This process allows the drug tamoxifen to enter the cell's nucleus and damage or kill the cells.

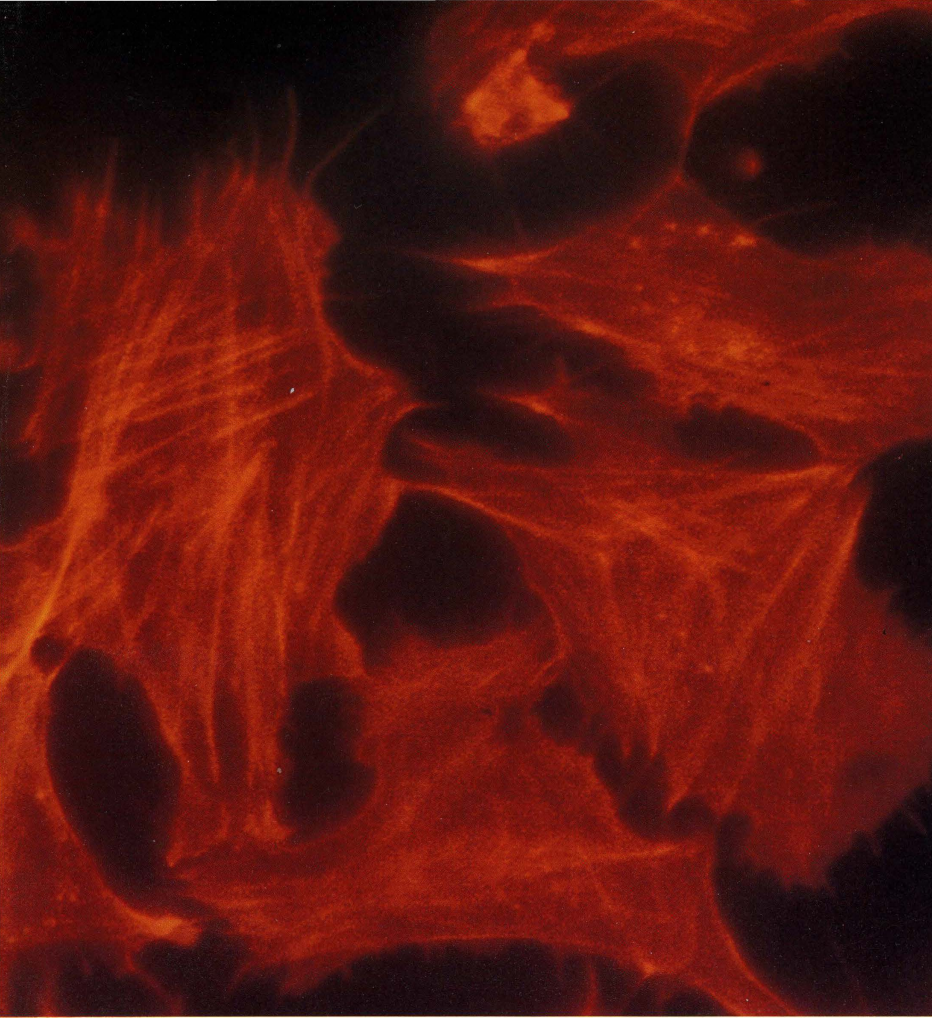
If this view is correct, drug resistance might be reversed by reducing acidity within the relevant organelles. And, in fact, *in vitro* studies by Simon and colleagues have shown that drugs that reduce the acidity of the Golgi complex can resensitize resistant tumor cells to drugs by as much as 50-fold. The next step is to test this potential therapy in mice, a project that will soon begin with collaborators at other institutions.

In the end, Simon says, "No one drug will be the magic bullet," because every anticancer drug has side effects. Combinations of therapies that aim at different cancer cell strategies will likely turn out to do the best job. The greater the number of therapeutic guns to fight with, the better the chances of finally winning the war against cancer.

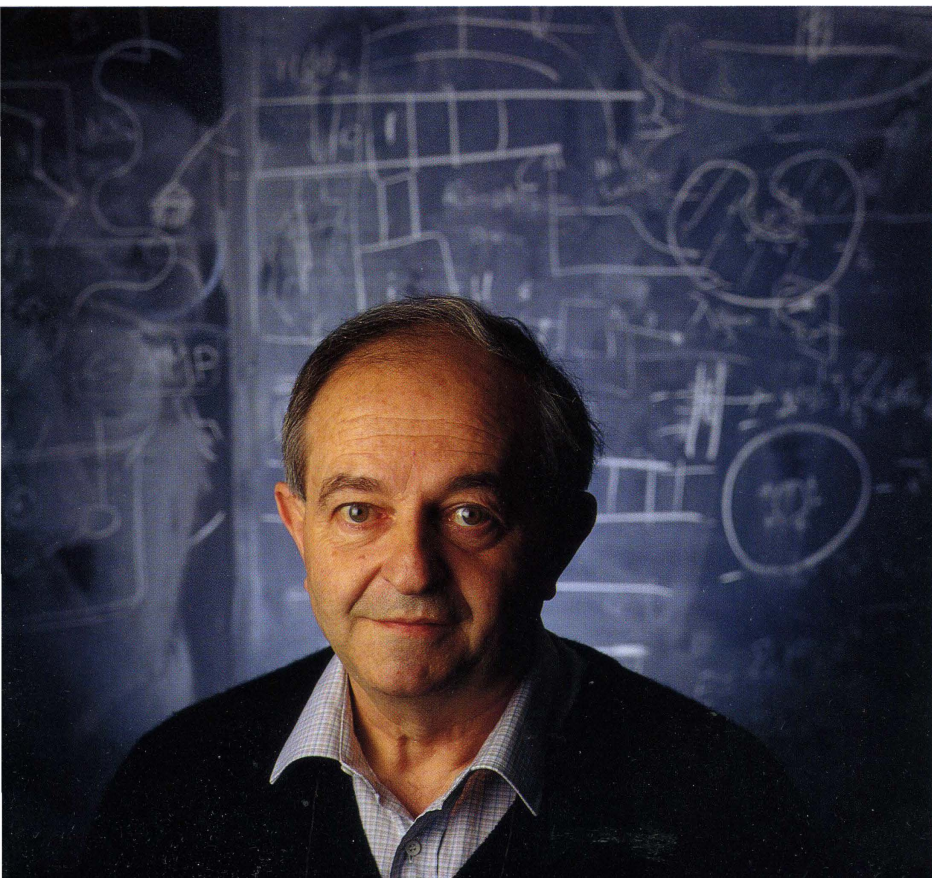
into the membranes of organelles (and the membranes surrounding the cell itself) rather than passing through them. So vital are these membrane proteins — they serve as receptors and channels, for instance — that a hitch anywhere in their production or insertion can spell disaster for a cell. For example, cystic fibrosis is most often caused by a mutation that prevents a channel protein from reaching the membrane of epithelial cells. And retinitis pigmentosa, the most common form of inherited blindness, frequently is traced to problems in the transit to the cell surface of opsin, a component of a receptor in the eye's retina.

Scientists in Simon's lab use opsin as one model molecule for their studies of the synthesis, transport and integration of membrane proteins. Their other exemplary protein is the p-glycoprotein. Simon's initial interest in this molecule stemmed from its membership in a family of proteins that are involved in helping other proteins cross membranes. But as work on the p-glycoprotein progressed, his studies also generated unexpected insights into cancer — and potential new ways to outsmart malignant cells that become resistant to chemotherapeutic drugs. See "Combating Resistance to Chemotherapy," at left. ●





**WEAVING THROUGH THE CELL IS A WEB COMPOSED OF STIFF**



*Top: Fibroblasts, cells that comprise connective tissue, are stained to reveal their cytoskeletons. The flexible fibers are made of the protein actin.*

*Bottom: Professor Albert Libchaber studies the interactions of proteins of the cytoskeleton.*



# Rigging the Cell:

## *The Cytoskeleton*

Weaving through the cell is a complex web composed of stiff hollow tubes, tough ropelike cords and flexible fibers. This meshwork, called the cytoskeleton, is endowed with prodigious capabilities. It gives a cell shape, which can vary with changing circumstances. It lets a cell crawl, reach and squeeze — movements vital for

thin microfilaments formed from the protein actin and intermediate filaments constructed from various proteins — is highly dynamic.

These cytoskeletal fibers assemble, disassemble and reassemble as needed. For instance, each time a cell starts to divide, microtubules form a spindle-shaped apparatus to pull duplicated chromosomes away from each other. When its task is finished, the spindle disintegrates, only to be rebuilt with the next turn of the cycle. And each time a cell makes a move — to approach an invader, squeeze through a vessel or migrate during development — parts of its actin cytoskeleton reorganize to spur the cell onward.

Moreover, hundreds

and microfilaments.

Various forms of the motor protein myosin move actin fibers against one another or carry cargo along the length of the microfilaments, while proteins called dyneins and kinesins ferry loads on microtubules.

A new member of the kinesin family was recently identified by Assistant Professor John Hall, working in the lab of Professor and Vice President for Academic Affairs David Luck, where studies have long focused on structures called flagella. These long, microtubular whips propel cells as varied as sperm cells and the single-celled algae *Chlamydomonas*. Evidence suggests flagella elongate through additions to their ends, so components

### **HOLLOW TUBES, ROPE LIKE CORDS**

development, immune response and wound healing. It choreographs the dance of chromosomes during cell division and moors organelles to parts of the cell. It serves as the tracks for transport within the cell and relays messages from outside the cell to regions deep within it.

How can the cytoskeleton accomplish so many tasks? For one thing, its rigging — thick microtubules made of the protein called tubulin,

### **AND FLEXIBLE FIBERS. THIS**

### **MESH WORK HAS A PRODIGIOUS RANGE OF CAPABILITIES.**

of proteins work with cytoskeletal elements to foster their many cellular functions. For instance, motor proteins associate with both microtubules

required for growing must somehow be transported up the lengthening structure.

The kinesin discovered by Hall and his



colleagues is required for building a flagellum. Without it, assembly and maintenance of the *Chlamydomonas* propeller grinds to a halt. So far, the scientists don't know kinesin's cargo, but they are searching for it. They also are pursuing evidence that the protein may play a role in constructing the microtubular spindle upon which chromosomes array themselves during cell division.

Motor proteins such as the kinesins are just one class of molecules that work with cytoskeletal compo-

actin from its cross-linked state and free the actin microfilaments from contact with the cell membrane. These changes provide the combination of cytoskeletal plasticity and on-and-off contact that let the macrophage draw near and engulf the invader.

The synapsins, under study in the lab of Professor Paul Greengard, are yet another protein family that can interact with the cytoskeleton. The effect of these molecules varies according to the life stage of the cell. In developing

described in Newtonian physics. Within the noisy world of the cell, no inertia exists to help movement along. Rather, friction reigns supreme, and force is required to maintain any intracellular motion. In this world, molecular machines such as motors are essential. Without them, organization, and thus life itself, would stop.

Libchaber and his colleagues study the interactions of actin and myosin that lead to muscle movement. Several years ago, they designed a system for

## Cytoskeletal fibers assemble, $d^i s_a s_s e_m b^l e$ and reassemble as needed.

nents. Other such protein families include the MARCKS brothers. MARCKS and Mac MARCKS proteins integrate messages transmitted by two common cellular signaling pathways and use those messages to help regulate the cell's cytoskeleton. For instance, in immune-system cells called macrophages, signals from pathogens modify MARCKS' activity. Upon stimulation from a foreign invader, MARCKS — which can bind to both actin and cell membranes — alter in ways that release

cells, the synapsin's interactions affect cell structure, while in mature cells they affect cell functions. See "Synapsin's Cytoskeletal Impact," at right.

Most Rockefeller researchers who study the cytoskeleton and its associated proteins are biologists. But scientists in the Center for Studies in Physics and Biology bring the theories and techniques of physics to these biological interactions.

There, in the labs of Professor Albert Libchaber and others, the scientists investigate a realm very different from the one

visualizing the dynamics of this relationship. Then, collaborating with mathematician Marcello Magnasco, another center member, they measured the force of the myosin motor on actin filaments. More recently, Libchaber conducted experiments that help explain how motor proteins achieve movement in one direction, despite constant random buffeting by water molecules. Such investigations help the researchers understand how precise and efficient organization emerges and is maintained within the cell's turbulent world. ●



# Synapsin's Cytoskeletal Impact

Clustered at the tips of nerve cells are little membranous sacs filled with the chemicals that transmit thoughts, dreams and feelings. These substances, the neurotransmitters, are the nervous system's messenger molecules. Upon receipt of the proper signal from a neighboring nerve cell, the sacs, or vesicles, merge with the cell's outer membrane and spill their neurotransmitter cargo, which floats away to communicate with other nerve, muscle or gland cells.

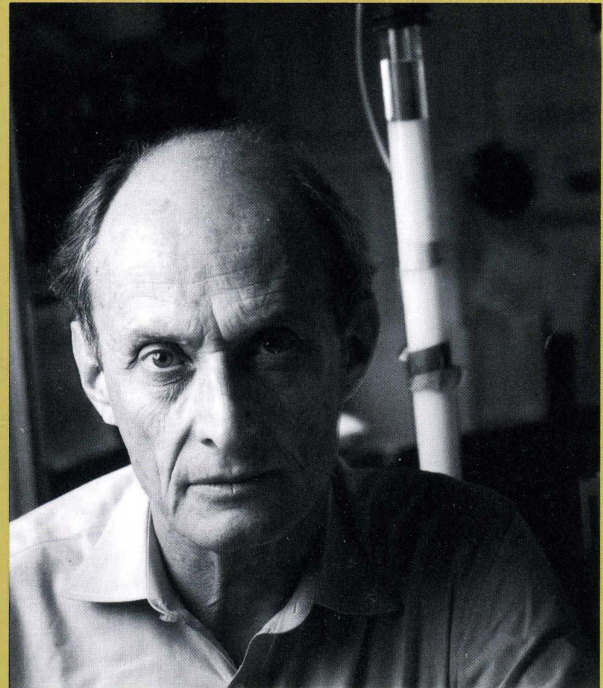
Neurotransmitter release must be strictly controlled, and research in the lab of Professor Paul Greengard shows how interactions between the cytoskeleton and certain proteins help regulate when and how much neurosecretion occurs.

The scientists' studies focus on a family of neuron-specific proteins called synapsins, which can exist in two forms: phosphorylated (decorated with phosphate molecules) and dephosphorylated (lacking the phosphate trimming).

During the last decade or so, research in Greengard's lab showed that when molecules of a synapsin family member called synapsin I are dephosphorylated, they stick both to neurotransmitter-filled vesicles and to strands of the actin cytoskeleton. In this way, the synapsin tethers the vesicles within an actin cage, preventing them from joining the pool of sacs that stand ready to race to the cell's surface.

But when synapsin I is phosphorylated, it changes shape, freeing the vesicles from their cytoskeletal jails. A complex cascade of biochemical events — reflecting the nerve cell's state of excitation — controls the extent of phosphorylation and, therefore, carefully regulates the magnitude of the message the nerve cell sends.

Recently, the researchers found evidence that synapsins are vital not just for controlling a neuron's functions, but for shaping and maintaining its structures as well. One line of experiments disclosed that synapsin is needed to form and preserve synapses, the cell-to-cell junctions across which nerve signals

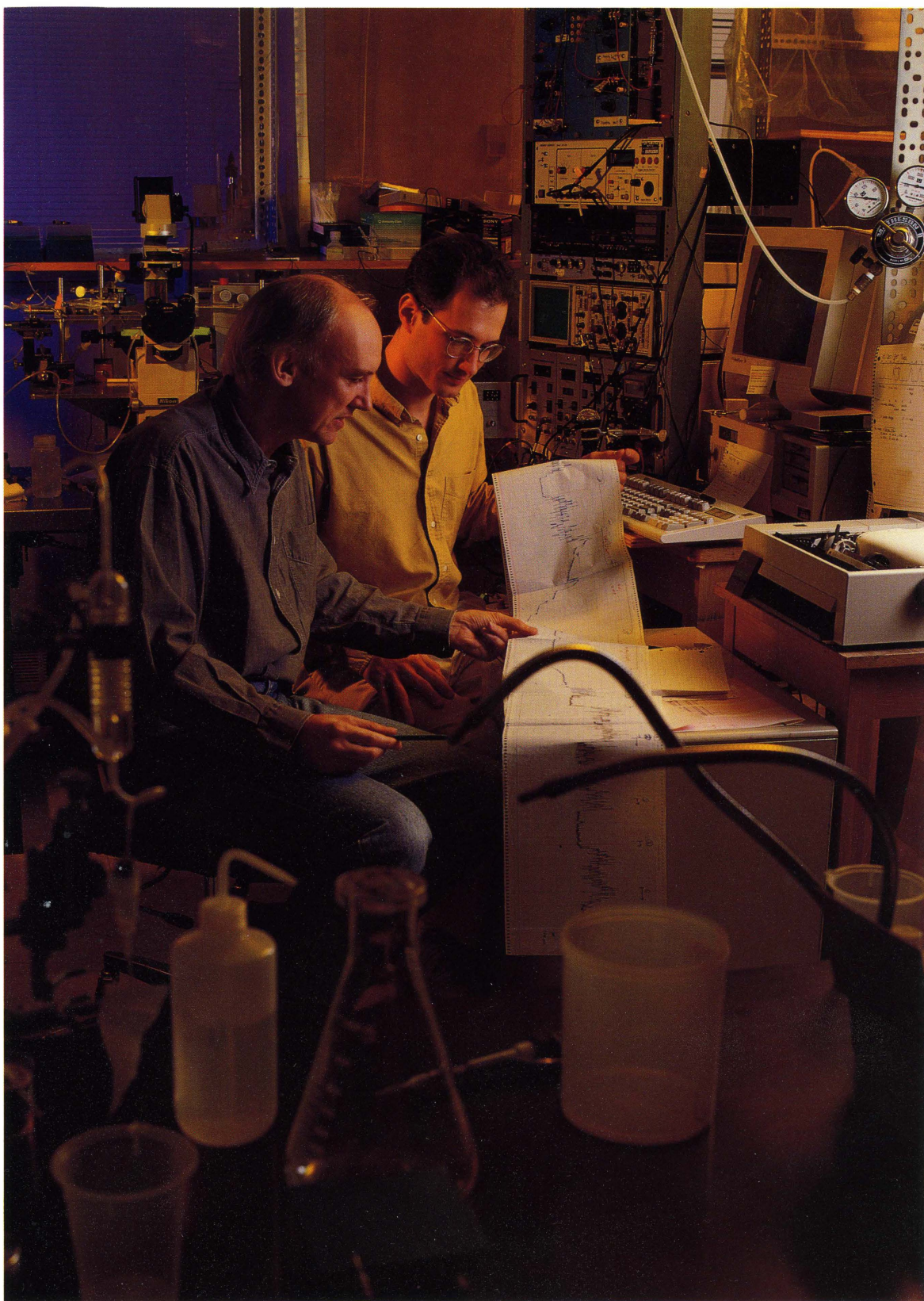


*Research in the lab of Professor Paul Greengard shows how interactions between the cytoskeleton and certain proteins help regulate neurosecretion.*

pass. Another series of studies shows that synapsin may play a central role in the development of axons and dendrites, the structures that radiate from a nerve cell's body and mediate its capacity to receive and send messages.

When the scientists introduced synapsin I into nonneural cells, the altered cells developed elongated structures reminiscent of axons and dendrites. A key characteristic of this dramatic shape change was the reorganization of actin into thick, cablelike bundles. Given synapsin's action on the cytoskeleton in neurotransmitter release, "it seems reasonable to hypothesize that the effect of synapsin on neural growth, maturation and differentiation might also be achieved through interactions with the actin cytoskeleton," Greengard says. "We don't have direct evidence for that yet," he adds — but experiments on the subject are proceeding apace in the lab.





*Professor David Gadsby and Biomedical Fellow Athanasios Dousmanis investigate how proteins serve as conduits for ions, one of the ways cells communicate.*



# At the Horizon:

## *The Cell Surface*

At the frontier of each cell is the plasma membrane, which serves a dual role. On the one hand, it safeguards the integrity of the cell's internal environment, which is chemically quite different from the one the cell lives in. On the other hand, it

of messages, which they then transmit to realms deep within the cell. Still others form direct passageways across the membrane for nutrients, such as glucose and amino acids, and for molecules carrying an electric charge, called ions.

that form pores in the membrane, called channels, and proteins that act as pumps. Channels are rather like drainpipes, but with a gate that opens and closes. When open, they let ions flow in and out of the cell following their concentration (and

**A cell interacts with its surroundings primarily through proteins in its surface.**

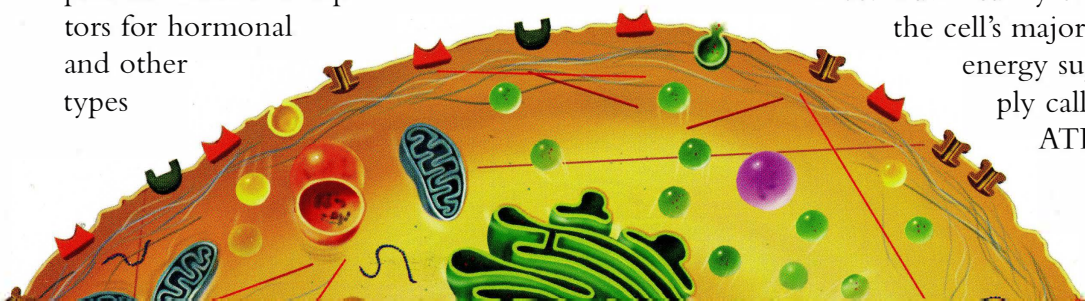
facilitates many kinds of exchange between the cell and the world around it.

Nearly all interactions between a cell and its surroundings occur thanks to the myriad of proteins embedded in the cell's surface. Some of these proteins play a structural role, guiding cells to their proper position during embryonic development, or keeping mature cells connected as tissues and organs. Other proteins serve as receptors for hormonal and other types

Ions such as sodium, potassium, chloride and calcium are crucial to the proper functioning of every cell in the body. Without them, for example, nerve cells could not communicate and muscles could not contract. The proteins that serve as conduits through the membrane for several of these ions are the focus of research in Professor David Gadsby's lab.

These conduits are of two basic types: proteins

electrical) gradients from higher concentration to lower concentration. The opening and closing of their gates requires relatively small amounts of electrical, chemical or mechanical energy. Pumps, on the other hand, like the sodium/potassium exchange pump studied by Gadsby and his colleagues, actively transport ions uphill, against their concentration gradients. To perform this task, pumps must draw heavily on the cell's major energy supply called ATP.





But now work in Gadsby's lab has found that there is a channel that draws on ATP. The channel is called the cystic fibrosis transmembrane conductance regulator or CFTR. Mutated versions of this channel are well known as the cause of cystic fibrosis. They are the underlying reason for the buildup of thick, dehydrated mucus in the patients' lungs that makes them so susceptible to life-threatening infections.

It has long been known that CFTR is present in

Molecules aren't the only things that move through the membrane. Information does too, to alert cells to changes in their environment and instruct them how to respond.

Such environmental cues are crucial during an organism's development, when messages from neighboring cells play a central role in determining the intracellular events and cellular migrations required to build a multicelled body. These cell-cell interactions

These commands are transmitted to receptor proteins — tens or even hundreds of millions of them — that stud the cell membrane. Stationed on the cell's boundary with their arms open wide, receptors permit the cell to sample its environment through direct cell-cell contact or by means of molecules — such as hormones, growth factors or neurotransmitters — that swim through the bloodstream.

Each type of receptor is stimulated by only one

## **Molecules aren't the only things that move through the membrane.**

epithelial cells like those in the lungs, pancreas, colon and testes. But recently Gadsby and his colleagues made the surprising discovery that CFTR also is expressed in the heart — in very small amounts. That has turned out to be an advantage. Because the channels are so few and far between, the scientists studied them one molecule at a time. The behavior of CFTR, they found, is far more complex than that of any other channel. They now study precisely how ATP regulates its activity and what physiologic purpose it serves in the heart.

are the subject of study in the lab of Professor Mary Beth Hatten, who investigates how a brain region called the cerebellum establishes its complex form during embryogenesis. See *"Molecular Cues for Migration,"* page 28.

But the communications that determine a cell's fate and position during development are just the first of many relationships it establishes with other cells near and far. Throughout its lifetime, a cell receives countless messages that tell it to grow, change its metabolism, turn on new sets of genes or even die for the good of the whole.

or a few special messengers. When the signaling molecule meets its matching receptor, it sets off a cascade of events that ultimately affects a cell's behavior. But exactly *which* kind of behavior is triggered depends on the types of receptors expressed on the cell's surface. For example, while all cells display some common receptors, a kidney cell also expresses certain cell-surface proteins that an immune-system cell does not. It's the same for immune cells, of course, which sport their distinctive collection of receptors.

Intriguingly, though most receptors pass just one

*Right: A tentative molecular model of the 11-cis-retinal-binding pocket of rhodopsin, the receptor in rod cells, the retinal cells responsible for vision in dim light. Associate Professor Thomas Sakmar, an HHMI associate investigator, and his colleagues study rhodopsin to better understand the general mechanisms by which messages are sent, also called transduction, by all of rhodopsin's molecular cousins, the G-protein-linked cell-surface receptors.*



Information does as well, alerting cells to environmental changes and instructing them on responses.





## Molecular Cues for Migration

One of life's greatest enigmas is the process by which a single fertilized egg becomes a complex multicellular organism. The mystery wrapped within that enigma is how, in a developing creature, the brain's many types of nerve cells derive their specific identities and how its complex architecture organizes.

The lab of Professor Mary Beth Hatten studies these questions. There, researchers focus on the development of the cerebellum, the brain region responsible for balance, movement and some forms of memory. Specifically, they investigate how cerebellar neurons of one particular sort, the granule cells, acquire their identity and find their rightful place in the brain.

Cell-cell interactions are key to the process. "Signals within the community of cells tell them to progress to their next stage of development," Hatten explains.

For instance, communication is vital for directing the long migration that leads granule cells from their birthplace in zones of proliferation to their final position in the cerebellum.

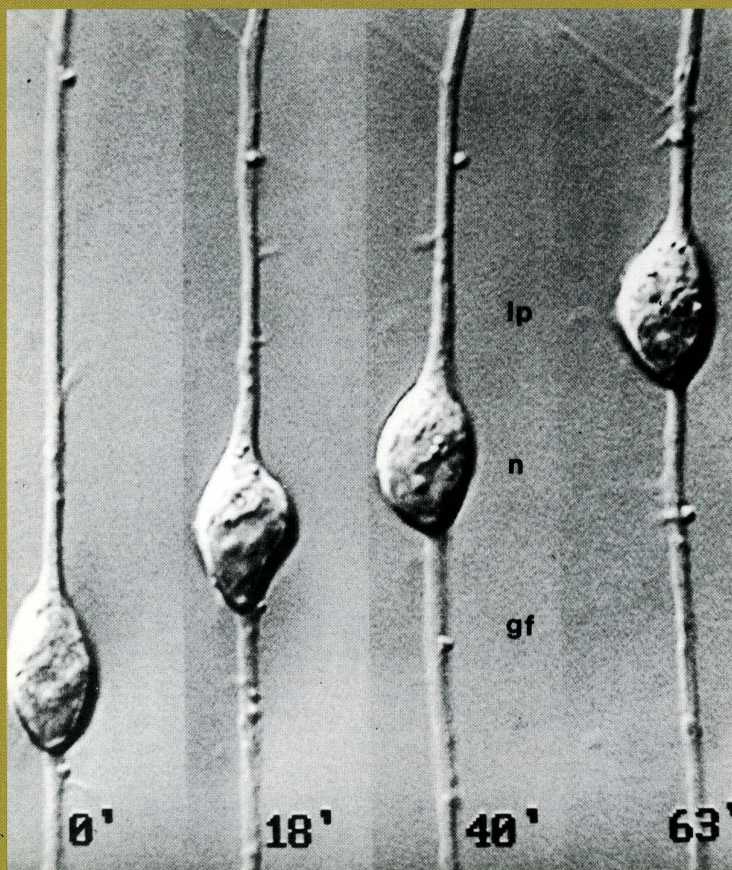
"It's an unbelievably tortuous process," says Hatten. "In relative terms, the distance the cells travel in the brain is about as far as the trip between New York and Chicago." To make their long trek, nascent granule cells inch along a highway composed of the brain's glial cells.

Granule cells hook onto this thruway by means of a protein called astrotactin. The molecule is encoded by one of the more than 100 genes that Hatten and Professor Nathaniel Heintz, an investigator of the Howard Hughes Medical Institute, collaboratively identified as marking different stages of granule cell development. The scientists found that nascent granule cells turn on their astrotactin gene the moment they leave the proliferative zone and step out onto the glial fibers. Dramatic videos made by Hatten show just how important the molecule is: When astrotactin's action is blocked by antibodies, granule cells stop dead in their tracks and fall off the glial turnpike.

The researchers have found that astrotactin is a cell-surface protein with an unusual structure, boasting some characteristics of a cell-surface signaling molecule and others of a cell-surface adhesion molecule. They are eager to learn

*The lab of Professor Mary Beth Hatten studies the development of the cerebellum, the brain region responsible for balance, movement and some forms of memory.*





This four part photograph shows the movement of a young nerve cell on a glial fiber highway at 18, 40 and 63 seconds. This journey, of about one-thousandth of an inch, helps a neuron find its correct position in the growing brain.

how this uncommon protein promotes communication between granule and glial cells, for the relationship between the two cell types seems remarkably complex. Not only does astrotactin keep granule cells hooked onto glial cells, but it maintains the health and identity of glial cells, too. Without their connection to astrotactin, glial cells simply collapse.

"The two cell types seem to signal each other 'I'm OK, you're OK,'" Hatten says. Once their mechanisms are better understood, interactions like these may go a long way toward explaining the mysteries of development.

message along, certain receptors of the immune system's B and T cells prompt many different kinds of behaviors over the course of a cell's life. Take the case of the B cell receptor (BCR). During the early stages of B cell development, the BCR transmits messages for a variety of events: the gene rearrangements that underlie immune-cell diversity, the deletion of self-reactive B cells that keeps the immune system from attacking the body and the exit of cells from the bone marrow into the blood. Once the cell matures, however, signaling through the BCR triggers a completely different set of behaviors: cell proliferation in response to an antigen, the internalization of the antigen and antibody secretion.

Michel Nussenzweig, associate professor and associate investigator of the Howard Hughes Medical Institute (HHMI), studies this multitasking receptor. He and his colleagues dissected the functions and interrelationships of the BCR receptor and two proteins closely associated with it, to assess the role each component plays in sending signals. They now seek to learn how these few components can send so many different messages at different times.



Another cell surface receptor is rhodopsin, found in the rod cells of the retina that facilitate vision in dim light.

Rhodopsin is a two-part molecule. One part, opsin, weaves through the cell's surface membrane. Retinal, the other component, is chemically linked to opsin. When a packet of light energy called a photon hits the receptor, retinal changes its conformation and rhodopsin is activated.

Thomas Sakmar, associate professor and HHMI associate investigator, studies the molecular interactions set in motion

more than 200 of these receptors — each with a particular function, but all sharing certain characteristics.

Rhodopsin and the immunoglobulin protein are just two among the veritable forest of receptors planted within the cell's membrane. Each different receptor stands ready to transmit a message when an appropriate signaling molecule nests upon it. But how is that message transmitted to its ultimate destination within the cell — most often into the nucleus? Signal transmission involves complex biochemical

### **Most receptors pass one kind of message along...others pass many during a cell's life.**

when a photon tickles rhodopsin. For instance, work in his lab has pinpointed exactly which chemical groups in opsin shift protons around as they undergo their characteristic conformational changes upon activation. The researchers also located the specific regions in rhodopsin that appear to play a key role in sending light's signal further into the cell.

In conducting such studies, the scientists plan to shed light on a broader subject as well: the general mechanisms whereby messages are sent by rhodopsin's molecular cousins, collectively known as the superfamily of "G-protein-linked cell-surface receptors." So far, scientists have identified

pathways that move the message towards its goal. One of the most important of those circuits — the Jak-STAT pathway — has recently been revealed through work in the lab of Vincent Astor Professor James E. Darnell Jr. *See "Holding Hands All the Way to the Nucleus," at right.*

The more scientists learn about how signals are communicated from the cell surface inward, the better the chances of finding new treatments for a host of ills such as cancer, diabetes, heart disease and immune system disorders. For it is when cell signaling goes awry that the cell's orderly processes break down, and disaster all too often ensues.



# Holding Hands All the Way to the Nucleus

Like the fingers of a pianist striking keys to produce tones, signaling proteins outside the cell contact receptors in a cell's membrane to evoke responses deep within. The messenger molecules' ultimate site of action is often the cell's nucleus, where genes are read out, or transcribed, as the first step in protein production.

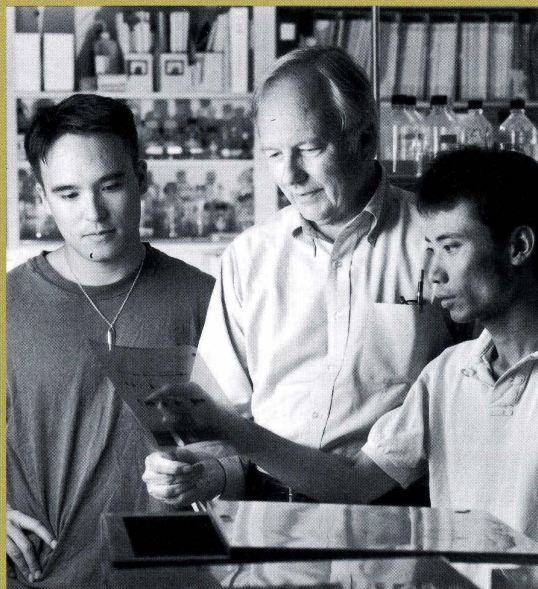
To maintain harmony within a cell — and in the larger organisms that cells comprise — each signaling molecule must prompt the readout of a specific gene or set of genes. But how is such specificity orchestrated?

Part of the answer lies at the cell surface, where a signaling molecule docks only at the receptor designed to receive it. Specificity also resides in the nucleus, where proteins called transcription factors control the readout of particular genes.

But between the cell surface and the nucleus, scientists know much less about events involved in passing along a messenger's singular signal. Until recently, many researchers thought most signals are conveyed by "second messengers" — small molecules, such as calcium, whose changing concentrations send a message through the cell.

This explanation never satisfied Professor James E. Darnell Jr., however. "If all the information received at the cell surface converged in a pool of a small number of second messengers, the specificity of the information would be lost and could never be recovered," he says.

Over the past few years, a new line of research — much of it conducted by Darnell and his colleagues — has disclosed that many extracellular signaling molecules can direct their message from the receptor to the nucleus through a pathway of protein-protein interactions that never let go of the specificity. Instead, the proteins "hold hands" all the way to the gene's DNA.



*Professor James E. Darnell Jr. (center) discusses the results of an experiment with Zilong Wen (right), graduate fellow, and Daniel Weinstein, a postdoctoral fellow who received his Ph.D. from Rockefeller in 1995. The scientists investigate events involved in passing along a messenger's signal between the cell surface and the nucleus.*

This pathway involves two new families of proteins, the Jak enzymes that put highly charged phosphates on molecules and the STAT proteins — first discovered in Darnell's lab — that lie waiting inactive within the cell.

All the steps in the Jak-STAT pathway are not yet known. But research by Darnell's group showed that when certain signaling molecules dock with their receptors, Jak enzymes place phosphate molecules on the receptors. This phosphorylation lures specific STATs to the receptors, upon which the STATs themselves are phosphorylated. Once phosphorylated, the various STAT proteins can bind together in units of two — called dimers — that move to the nucleus. There, by themselves or combined with still other proteins, the dimers serve as transcription factors to trigger gene readout. Because the Jak family is numerous, and the STAT family even more so, the range of Jak-STAT combinations can contribute to specificity.



1901

John D. Rockefeller,  
David Rockefeller's  
grandfather,  
establishes  
The Rockefeller  
Institute for  
Medical Research

1936

David  
Rockefeller  
earns B.S. from  
Harvard

# DR

As the university celebrated its 37th commencement in June of 1995, the month also marked David Rockefeller's 80th birthday. He announced that he would scale back his activities on campus, retaining his position as chair of the Rockefeller University Council but stepping down as chair of the Board of Trustees' Executive Committee. With gratitude, the trustees elected him honorary chairman of the board and lifetime trustee, one of many ways members of the RU community signaled their respect and admiration during the two days in which the university honored him.

In this modern era of term limits, rapid turnovers and abrupt takeovers, David Rockefeller's 55 years of service to the university is almost anomalous. David Rockefeller — or, to use the university community's affectionate moniker, DR — joined the institution's Board of Trustees in 1940, served for 20 years as chairman of the trustees and 25 as chairman of the board's Executive Committee. He also has served since 1973

as chairman of the RU Council, a group of friends of the university.

DR's dedication continues a family tradition of support, dating back to 1901, when his grandfather, John D. Rockefeller, and father, John D. Rockefeller Jr., created the institute. During the June festivities last year, alumni created a scholarship in his honor and faculty presented a bust they commissioned. The bust resides in the lobby of the Rockefeller Research Building next to one of his father. Expressing his appreciation, DR noted that he and his father had between them served the university for 106 years. "This must be some kind of record," he mused.

But DR's longevity at RU is not the essence of his relationship to the institution, for he has served science at RU with perpetual zeal and love. As a new board member in the 1940s, he took charge of an extensive assessment of the institution's future, which ultimately resulted in its transformation into a university. Working



1940

David Rockefeller earns Ph.D. in economics at University of Chicago

1940

David Rockefeller joins Board of Trustees of Rockefeller Institute for Medical Research

1940s

David Rockefeller initiates Rockefeller Institute for Medical Research self-examination



*David Rockefeller, shown here in 1957 with Detlev W. Bronk, has always taken a great deal of interest in the architecture, art and landscaping of the changing university as well as its science.*

with President Detlev Bronk during the 1950s, DR shepherded the institution through this transformation, as well as through a major expansion of the faculty and the physical plant.

He helped lead Rockefeller when the genetic revolution unfolded in the 1950s and 1960s. DR has worked hand in hand with six university presidents: Herbert Spencer Gasser (1935–1953), Detlev W. Bronk (1953–1968), Frederick Seitz (1968–1978), Joshua Lederberg (1978–1989), David Baltimore (1989–1991) and Torsten N. Wiesel (1992–present). During this time, 14 scientists associated with the institution received Nobel Prizes and another 14 won the prestigious Albert Lasker Award, which the press dubs the “American Nobel” because of the high percentage of Lasker recipients who later earn the Swedish honor.

As the century progressed, the changing

economics of the United States threatened the independence of private institutions. DR led the effort to maintain the university’s excellence. Perceiving the university’s need for an organized community of friends, DR conceived of and initiated the RU Council, whose members he envisioned as ambassadors for Rockefeller’s scientific mission. Additionally, he saw the need for an organized development program, which he supported with generous gifts.

In 1975, on the 35th anniversary of DR’s appointment to the Board of Trustees, board chairman William O. Baker, now chairman emeritus of the Board of Trustees of AT&T Bell Telephone Laboratories, Inc., attributed David Rockefeller’s commitment to “a belief in excellence, a fascination with genius, a captivation in seeing the mind travel where none has gone before. . . . [His] devotion is as individualistic in



1950s

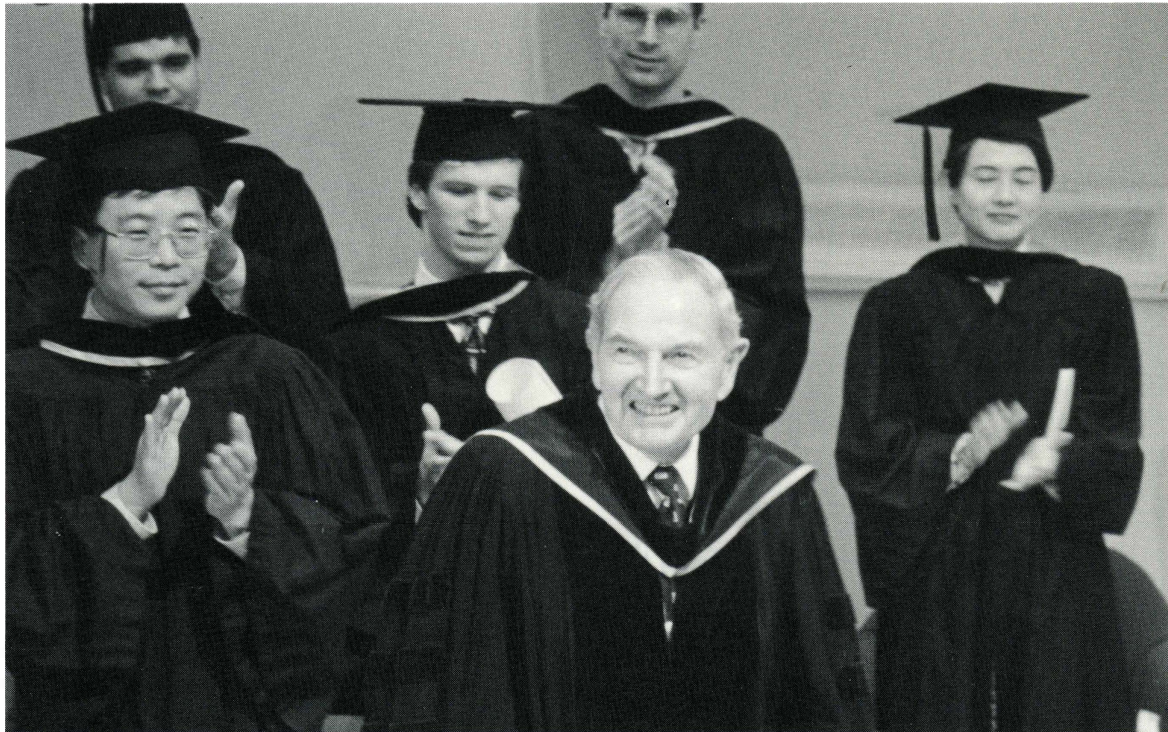
David Rockefeller encourages the formation of a graduate program and building of a modern campus

1970

David Rockefeller becomes chair of Board of Trustees

1980

David Rockefeller establishes and chairs the Rockefeller University Council



*DR never misses a convocation and takes pride in the individual tributes made to young scientists receiving their Ph.D.s.*

its finest manifestations as the most exquisite painting or music, sculpture or poetry.”

Five years later, when the university awarded DR an honorary doctor of laws, Rockefeller scientist Maclyn McCarty, who with colleagues discovered that DNA is the hereditary material, lauded DR’s “devotion and commitment, which are essential to the fostering of research.”

When the university celebrated the 50th anniversary of the 1944 paper authored by McCarty, Oswald Avery and Colin MacLeod to report that DNA, not protein, comprised genetic information, DR told *The New York Times*, “This great discovery has, in my judgment, more than justified all by itself the great hope and aspiration of my grandfather and father when they established this institution in 1901. It has, in fact, given to the world what they hoped for:

The beginning of the understanding of the inner mysteries of life and disease.”

What special qualities are necessary to keep a research institution at the fore amid social and scientific change of all kinds?

At the 1995 convocation ceremonies, President Wiesel put forward a hypothesis: “David is an excellent sailor, and one can view his guidance in nautical terms. Through 55 years, David has helped us steer a steady course — not in any predetermined direction, because that is not the way science moves. Rather, David has helped us turn our sails where the winds of new scientific discoveries and innovations were blowing, to turn our tiller away from danger and stagnant waters, toward the challenges and opportunities of promising but uncharted seas.

“David has always recognized that science is



1992

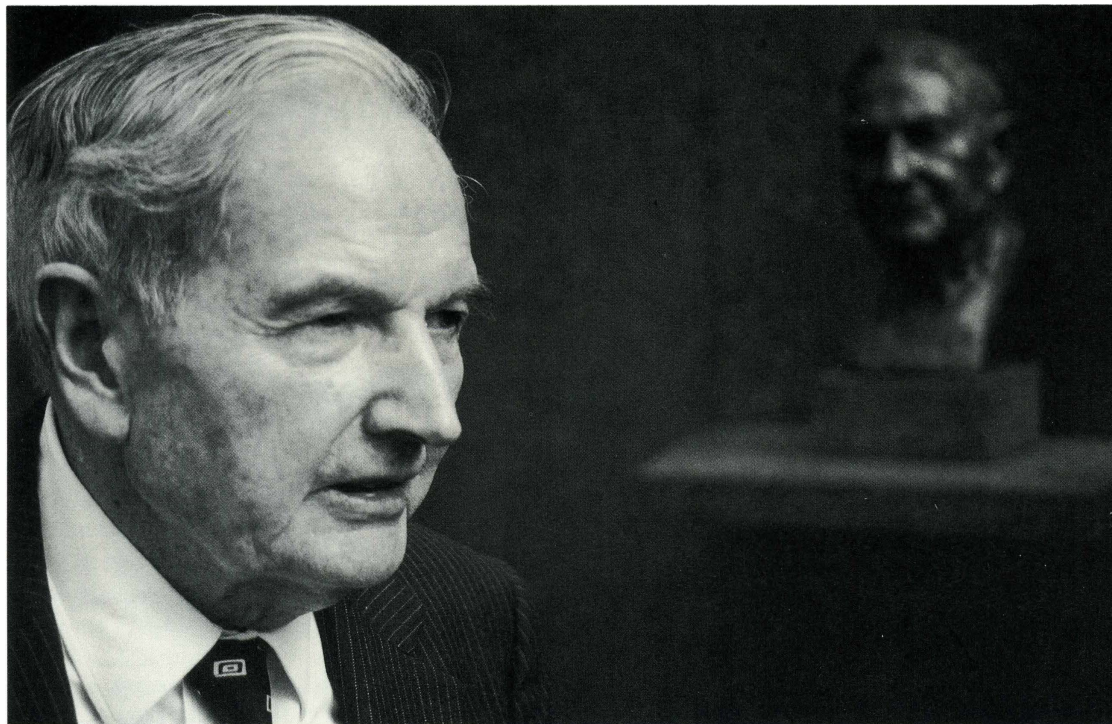
University dedicates  
new laboratory  
building to  
John D. Rockefeller Jr.  
and David Rockefeller

1995

David Rockefeller  
steps down as  
chairman of the  
Executive Committee  
of the RU board, but  
continues as chair of  
the RU Council

1995

During June convocation  
festivities, RU alumni  
create a scholarship in  
DR's honor



*RU faculty  
members presented  
DR a bust in  
his likeness which  
resides in the  
lobby of the  
Rockefeller  
Research Building  
next to one  
of his father.  
Expressing appre-  
ciation, he noted  
that together they  
have served the  
university for  
106 years.*

never static, but must always sail forward into the unknown. This requires courage, resources and a steady purpose, and David has provided all three."

During the June celebration of DR's birthday and extraordinary service, he repeatedly stressed that he would not be leaving altogether, telling *The New York Times*, "I would miss it if I were going to walk away and never see the university again. But I will continue to come to meetings. So while it is sad in one sense, I don't feel as if I am leaving."

Heartfelt tributes, humorous anecdotes and fond memories of his stewardship through the university's evolution abounded during the two days. One of the commemorations was a scientific symposium organized by and featuring alumni, a gesture conceived as a way of

recognizing DR's historical support of graduate students. Opening the symposium, alumnus Robert Barlow, '67, professor of neuroscience and ophthalmology at SUNY, Syracuse, recalled the moment he understood the depth of David Rockefeller's commitment:

"My father was a banker. Back in the early 1970s, he met with David Rockefeller at Chase Manhattan Bank to discuss mutual business. They were having a very mundane conversation about banking, and my father mentioned that he had a son who had recently graduated from Rockefeller University. He told me that at that point David Rockefeller's face just lit up. They began talking about the university and biomedical research, and the conversation never returned to banking."



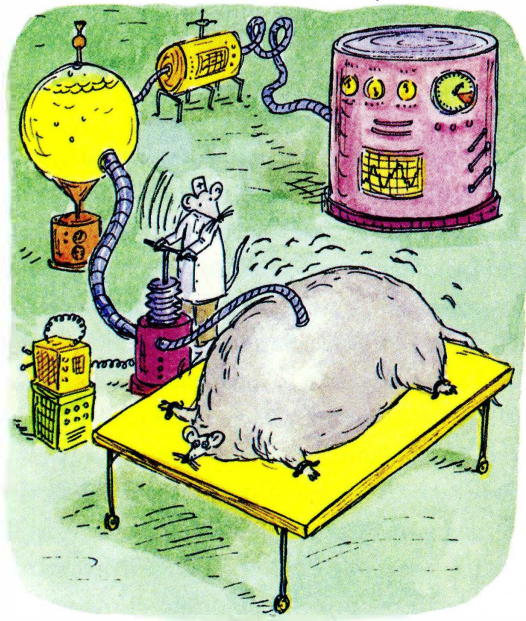


# ALTERNATIVE TREATMENTS *for* FAT MICE

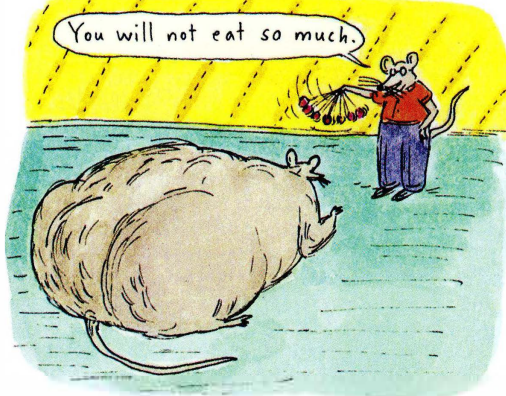
Many mice have simply changed their wardrobes.



For others, liposuction is the only way to shed unwanted pounds.



Some have found hypnosis to be a helpful dieting aid.



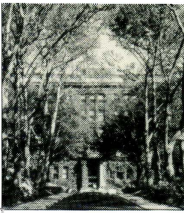
For a long-term solution, however, most will have to revamp their life styles.



R. Chazt

Professor Jeffrey Friedman's discovery of leptin caught the attention of people worldwide, including a few cartoonists. Above is Roz Chazt's cartoon from The New Yorker. At right is Steve Kelley's cartoon, appearing in the San Diego Union-Tribune. (Cartoons reprinted with permission.)





## Rockefeller Weighs in on Obesity Research

Just two weeks of therapy on leptin, a newly identified protein made by fat tissue, made genetically fat mice drop 30 percent of their weight by making the mice eat less and exercise more, found Rockefeller scientists.

But don't expect to buy leptin at a store soon. New therapies for weight control in humans require more studies and years of testing, says Professor Jeffrey Friedman, Howard Hughes Medical Institute (HHMI) associate investigator.

Nonetheless, since Friedman and his colleagues reported their findings in the July 28, 1995 *Science*, more than 900 people from around the world have written asking to be volunteers for any future human trials of leptin.

Since leptin's identification, Friedman has determined that the hormone's weight-reducing effects result from an interaction with a receptor in the brain's hypothalamus, known to regulate food intake and body weight. Publishing in the Feb. 15, 1996 *Nature*, he and his colleagues reported six different forms of the leptin receptor, known as Ob-R. One form, Ob-Rb, is expressed at a high level in the hypothalamus. While Ob-Rb appears to be critical for the weight-reducing effects of leptin, the functions of other forms of Ob-R are not yet known, Friedman says.

Across campus at the RU Hospital, Associate Professor Rudolph L. Leibel also investigates obesity. Using genetic mapping techniques and gene analysis, he determined that the *diabetes* gene in mice and the *fatty* gene in rats are not only the same genes, they also carry instructions to make a leptin receptor, work reported in *Science* Feb. 16, 1996.

In earlier, human clinical studies, Leibel, Professor Jules Hirsch and Assistant Professor Michael Rosenbaum found that the body works hard to keep its set point, regardless of what a person eats.

"Obesity is not just a problem of will power," says Leibel, whose findings come from a small study of 41 patients at the Rockefeller University Hospital.



In the hospital investigations, the team found that men and women, thin and fat, had a strong metabolic opposition to maintaining an altered body weight. Moreover, the resistance appears to stem from apparent changes in efficiency with which muscle burns calories.

A few steps from the Hospital in the Rockefeller Research Building, Friedman and collaborators continue to make headway on the biological basis of obesity.

Using mice, Friedman cloned in 1994 the *obese* (*ob*) gene, which if defective results in overweight mice. The team found the *ob* gene makes a protein, which they called leptin from the Greek root *leptos* meaning thin, that appeared to signal the brain that enough fat is stored and to stop eating.

The amount of leptin highly correlates to how much fat is

stored in the human body, with greater levels found in individuals with more fat and reduced levels in those who dieted. However, not all obese patients have increased levels, which suggests there may be important differences in the causes of obesity, explains Friedman. His findings from a small human study of leptin levels appeared in the November 1995 *Nature Medicine*.

Differences in the fat's production rate of leptin, resistance to leptin at its site of action or a combination of these factors could influence eating behaviors and energy use to cause obesity or other nutritional abnormalities, such as diabetes.

Reduced sensitivity to leptin in some patients could explain why more leptin is found in obese people. "Some obese people may make leptin at a greater rate to compensate for a faulty signaling process or action," Friedman says. "If resistance to leptin is partial, rather than complete, more leptin may be required for action."

In addition, obesity may occur if genetic or environmental factors affect body chemistry after leptin acts.

Obesity, defined as being more than 20 percent over an ideal weight, is a major risk factor for diabetes, heart disease, high blood pressure, stroke, sleep apnea and gallstones as well as some cancers and forms of arthritis. In the United States, more than one third of adults — 50 million people — are obese, reports the National Institute of Diabetes and Digestive and Kidney Diseases, which helped support the Friedman and Leibel studies. — MEG

Science  
and other  
news from  
the RU  
campus.



The setting and running of the daily body clock comes from the delicate affinity of two proteins, reported Rockefeller scientists in a trio of papers in the Nov. 3, 1995 *Science*. The clock, called the circadian rhythm, influences cell and body biochemistry, health, aging and behavior.

Like people, fruit flies have daily rhythms lasting approximately 24 hours. In 1971, scientists at the California Institute of Technology discovered a fly gene, dubbed *period* (*per*), involved in the clock, but exactly how it worked was unknown. In 1984, Rockefeller and Brandeis University scientists cloned the

joined, the proteins enter the cell nucleus, a process that sets the time and duration of the circadian cycle," says senior investigator Michael W. Young, professor and director of the Laboratory of Genetics at RU. He also is an HHMI investigator and directs the National Science Foundation (NSF) Science and Technology Center for Biological Timing at Rockefeller. NSF supported the studies.

All cells in the fly have *per* and *tim* genes, but the cells in the fly's brain set the body's clock. The two genes become active at midday and in the cell's nucleus, the genes' DNA code is transcribed into two

of the *tim* and *per* RNAs during several hours, as well as from the attraction of the PER and TIM proteins for each other.

"The PER and TIM proteins have an affinity for each other, but it is not a strong link," Young says. "Only if the two proteins are available in sufficient quantities do they begin to bind. Most importantly, the proteins can only survive and enter the cell nucleus when they are bound to each other. Therefore, about six to eight hours lapse between the time of peak RNA accumulation, which occurs around dusk, and the peak in the nuclear protein

## Circadian Rhythm Set by Pairing of Two Proteins

*per* gene and characterized the protein it makes. In 1994, the RU team identified a second clock gene, *timeless* (*tim*).

In the new studies, investigators from Rockefeller, the University of Pennsylvania and Harvard Medical School cloned the *tim* gene, determined the order of nucleic acids in its DNA structure and characterized the protein it makes, TIM. By investigating what happens when *tim* and *per* are damaged in mutated flies, the researchers also established how the TIM and PER proteins together set the body clock.

"The *tim* and *per* genes, through the proteins they make, have a true partnership in operating the body's clock. Part of the TIM protein binds to the PER protein and once

RNA molecules, *per* RNA and *tim* RNA, which accumulate over several hours.

At dusk, the levels of RNAs peak and only then does the cell use the RNAs to stockpile PER and TIM proteins. In the evening, the proteins join and cross into the cell's nucleus. About four hours before dawn, the PER and, presumably, TIM proteins in the nucleus reach their maximum amounts, an achievement that signals the *per* and *tim* genes to stop making the RNA. Near dawn, the nuclear proteins begin disintegrating, the cycle begins again and throughout the daylight hours the *per* and *tim* genes produce new RNA to make replacement proteins.

The pace of the clock appears to stem from the gradual, coordinated accumulation

levels, shortly before dawn."

This pattern of late binding of the proteins sets up daily cycles of RNA and protein production, because only after the bound proteins enter the cell nucleus can they turn off further synthesis of RNA from the *per* and *tim* genes.

Additional mechanisms and other, as yet unidentified, proteins also may influence the interaction between the PER and TIM proteins, which could affect the timing. For example, scientists know that light affects circadian rhythms and, Young notes, evidence exists that the PER/TIM protein union is affected by light. This sensitivity may help explain how body clocks are reset after jet lag, which occurs as a traveler crosses time zones. — MEG



## Structural Biologists Gather at Rockefeller University to Honor Pasteur

More than 400 scientists from around the world gathered at Rockefeller University for a structural biology conference honoring the 100th anniversary of Louis Pasteur's death in September 1995.

The Institut Pasteur and the United Nations Educational, Scientific and Cultural Organization (UNESCO) designated 1995 as "The Year of Louis Pasteur," and held six symposia in locations around the world to address current progress in the fields of Pasteur's major discoveries.

conferences to take place in the United States — focused on "Stereospecificity and Molecular Recognition."

Several Nobel Prize winners and other experts discussed their latest findings about the shape and structure of molecules, which strongly influence their function in the body. Such information is vital, for example, when designing drugs and investigating how viruses cause disease.

"The conference focused attention on research at the interface

On the meeting's second day, John Kuriyan, RU professor and an HHMI investigator, chaired a session on molecular recognition and response. Also, Henri Buc, professeur at the Institut Pasteur, chaired a section on design of biomolecules.

During the third day, Burley chaired a session focusing on macromolecular assemblies. Researchers also heard presentations on RNA biology in a section chaired by Dinshaw Patel of the Sloan-Kettering Institute.

The symposium closed with a session called "A Chiral World," chaired by William Agosta, RU professor. Burley presented closing remarks.

Abstracts from the conference, organized by the Institut Pasteur,

**The conference focused attention on research at the interface between chemistry and biology, which is playing an increasingly important role in modern molecular and cellular biology.**

The conferences allowed "the scientific community to pay a tribute to one of the outstanding figures of science, a man who revolutionized the fields of biology and medicine during the second half of the 19th century," said Maxime Schwartz, director general of the Institut Pasteur.

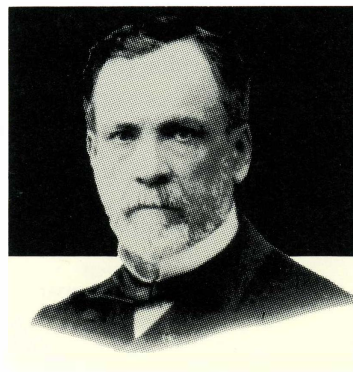
Popularly, Pasteur is perhaps most frequently recognized in the United States for developing the technique "pasteurization," first used to help the French control microbes in wine, and today used to purify beer and milk as well. However, Pasteur pioneered chemistry, agriculture, industry, medicine and hygiene, established many specialized scientific fields and developed a vaccine for rabies, among other things.

The meeting at Rockefeller — the only one of the six Pasteur

between chemistry and biology, which is playing an increasingly important role in modern molecular and cellular biology," says Stephen Burley, professor and Howard Hughes Medical Institute (HHMI) investigator.

Nobel laureate Arthur Kornberg, professor emeritus at Stanford University, opened the meeting with a keynote address, "Coalescence of the Biological Sciences." He discussed how advances in chemistry revolutionized biology and medicine, illustrating that the results of basic science investigations yield solutions to problems and questions. However, he said, basic science must be cultivated and strengthened, noting that lack of funding for further investigations could damage the health of people the world over.

Rockefeller and UNESCO, are available from the RU Office of Public Affairs or the RU home page: <http://www.rockefeller.edu/>. UNESCO and the European Commission sponsored the year-long celebration, which also received support from 24 organizations. — MEG



Institut Pasteur



## **Student Take Honors at RU Fair and Westinghouse Competitions**

Aaron Wong and Ting Luo, seniors at Stuyvesant High School, captured the first and second place awards, respectively, at the New York City regional competition of the International Science and Engineering Fair (ISEF), which RU hosted in March 1996. Saif Ahmed and Zhen Huang, juniors at Midwood High School, garnered the first place team project. Ten other students received top honors as well.

All four students planned to compete in the 47th ISEF, held during May in Tucson, Ariz., in which nearly 1,100 students from the United States and 41 other countries participate.

"The ISEF fairs encourage young people to learn more about biomedical and physical sciences and the research process by encouraging them to explore a question or problem by conducting an investigation to seek answers," says Bonnie Kaiser, Ph.D., director of science education outreach programs at RU.

Working in the Laboratory of Molecular Genetics, headed by Associate Professor Claude Desplan, a Howard Hughes Medical Institute associate investigator, Wong studied "The Anterior Development of the *Drosophila* Embryo in Absence of the Morphogen Hunchback."

Second place at the RU event went to Stuyvesant senior Ting Luo, who worked in the Laboratory of Biochemistry and Molecular Biology, headed by Robert G. Roeder, Arnold and Mabel Beckman Professor. His project was called "Identification and Characterization of a Novel Human General Transcription Factor: Implications in Gene Expression

Regulation, Transcription-Translation Linkage, Host Cell-Virus Communication and Programmed Cell Death." Luo's research also earned second place and a \$30,000 scholarship in the Westinghouse Science Talent Search.

Ahmed and Huang's team project focused on "To What Extent Does Coliphage T4 IIRA Mediate the Partial Reversal of UV Damage in *E. coli* K12?"

RU and the NYNEX Foundation supported the regional fair, which had 60 judges, including 30 university faculty and 30 high school science teachers. The nonprofit Science Service Inc. sponsors ISEF, with support from the Andrus Foundation-American Association of Retired Persons, Intel Foundation, Merck Research Institute and the NYNEX Foundation. In addition to sponsoring ISEF, Science Service, founded in 1921, publishes *Science News* and administers the Westinghouse competition.

## **The Books Balance**

In fiscal year (FY) 1996 RU balanced its financial operations for the second time in two years.

"In fiscal year 1995 we eliminated the long-standing deficit in ongoing university operations and we are now in the happy position of achieving renewal and expansion of our scientific enterprise within our financial means," says Fred Bohen, executive vice president, who foresees a balanced budget for FY 97 as well. "We claim this hard-won victory not because of major new income but because of continued control and reduction of routine expenses."

Adds President Torsten Wiesel, "From this sound financial position,

we intend to pursue our ambitious program of faculty development as laid out in the Academic Plan."

The FY 97 expenditures will run an estimated \$125.1 million, with sources of revenue coming from government grants and contracts, endowment income, development gifts and private sources.

"Putting our house in order and living within our means has inspired our trustees and other friends of the university to give more generously to support the faculty development program," says Wiesel.

During FY 96, the university met its \$21 million goal for the second year of the current campaign, the most successful fund-raising year in the institution.

## **RU Rates!**

In a national ranking of doctoral programs in the United States, the National Research Council ranked the university's cell and developmental biology program as number two in scholarship and four in effectiveness of teaching and the neurosciences program as number 13 in scholarship and nine in teaching. The study examined more than 3,360 academic programs at 274 institutions. More than 8,000 faculty participated in the rating.

## **At Home on the Web**

RU's homepage on the World Wide Web is just brimming with information. Included at the Internet site are the *Scientific and Educational Programs* report, issues of *News&Notes*, a campus map, news releases, event-related items and much more. Stop by for a visit at <http://www.rockefeller.edu/>.



## **RU's On Ramp to Internet Information**

Rockefeller's library provides greater and faster access to six biomedical databases thanks to a new computer collaboration with Cornell University Medical College, Hospital for Special Surgery and Memorial Sloan-Kettering Cancer Center.

"The collaboration allows shared access of equipment, software and databases that will greatly enhance the research capabilities of faculty and clinicians as they pursue and exchange information," says Francis C. Lees, chief information officer and director of Rockefeller's Information and Computing Services, which oversees the daily operations of the project.

The institutions acquired licenses jointly for the electronic databases MEDLINE® and five of the seven science editions of Current Contents®. In addition, the access from the RU server is top speed, allowing faculty and staff access at 10 megabits, about 750 typewritten pages, each second. Currently, Lees tallies more than 200 RU accounts, which total more than 700 weekly logins. With each account representing five to 10 people, the use is "gigantic," he adds.

## **Seven Springs Sold**

Real estate entrepreneur Donald Trump purchased Seven Springs, the university's 200-acre property in Mount Kisco, N.Y. The university shared the proceeds, \$7.5 mil-

lion, with Yale University, a former owner of the estate. The RU portion, when added to a preexisting separate endowment fund for the property, will cumulate to about \$10 million and then constitute a new unrestricted endowment to support research.

Seven Springs was the home of the late Eugene I. Meyer, Jr., who owned *The Washington Post*. In 1970, his widow donated the estate, which includes two mansions, orchards and a swimming pool, to Yale. The Eugene and Agnes Meyer Foundation ran the estate for Yale as a conference center and gave the property to RU in 1984.

## **Hospital Celebrates 85th**

The Rockefeller University Hospital marked its 85th year on Oct. 27, 1995. The 30-bed research center is the oldest such institution in the United States and served as the model for the Clinical Center at the National Institutes of Health.

## **Garden Laurels**

The East Side Association of New York City presented its Green Thumb Award to the university for its achievements in landscaping, making special mention of the Azalea Festival held in May 1994. At the university's annual event, guides from the New York Botanical Garden offer tours of the grounds, designed by Daniel Kiley.

## **Tower Renamed for Weiss**

The university rededicated the Tower Building as the Benjamin and Irma G. Weiss Research Building. The renaming honors the \$10 million bequest by the late Benjamin Weiss, a Rockefeller University Council member. Home to research labs and the university cafeteria, the Weiss building also houses *The Tail*, a sculpture by Frank Stella, in a newly renovated lobby.

## **1996 Enrollment Increases**

In September 1996, RU will welcome 25 students to campus. Applications in 1996 tallied 415, up 15 percent from the previous year and included students from institutions in the United States and abroad. The Dean's Office extended offers to 49 students, after screenings by the admissions committee and visits of candidates to the campus. A three-day open house, new this year, drew 37 of the applicants and was very well received. Of the incoming students, 11 are women and 10 students have completed undergraduate work in foreign schools.





## HONORS

John D. Rockefeller Jr. Professor and HHMI investigator **Günter Blobel** shared the 1996 King Faisal International Prize from Saudi Arabia with Hugh Pelham of the MRC Laboratory of Molecular Biology in Cambridge, U.K. and James Rothman of the Memorial Sloan-Kettering Cancer Center in New York City.

**Jan Breslow**, Frederick Henry Leonhardt Professor and head of the Laboratory of Biochemical Genetics and Metabolism, was elected to the National Academy of Sciences in May 1995. He also is president of the American Heart Association.

Professor **Stephen K. Burley**, head of the Laboratory of Molecular Biophysics and HHMI investigator, was elected a fellow of the Academy of Sciences of the Royal Society of Canada.

Vincent Astor Professor **James E. Darnell Jr.** was elected as foreign member of the Royal Society of London.

Assistant Professors **Robert Darnell** and **Markus Stoffel** received Irma T. Hirshl Career Scientist Awards.

Assistant Professor **Seth Darst**, also the Jack Fishman Professor, received a Pew Scholars Award.

Professor **Vincent Fischetti** presented *Expression of Foreign Proteins on the Surface of Gram-positive Bacteria for Mucosal Vaccine Delivery* at the Institut Pasteur. The speech was part of the meeting "Vaccines, 100 Years after Louis Pasteur," held September 1995. He is the codirector of the Laboratory of Bacterial Pathogenesis and Immunology.

The Membrane Biophysics Group of the Biophysical Society presented Professor **David Gadsby** with its K.S. Cole Award for his contributions to the field. He heads the Laboratory of Cardiac/Membrane Physiology.

The University of California Board of Regents named **M.R.C. Greenwood**, '73, chancellor of the University of California, Santa Cruz.

The Japanese government presented the Bunka Kunsho, Japan's Order of Culture, to **Hidesaburo Hanafusa**, Leon Hess Professor and head of the Jeanette Warren Davidson Laboratory of Molecular Oncology. The prize honors artistic or scientific contributions to world culture.

Assistant Professor **Ali Hemmati-Brivanlou** has been selected as a 1996 McKnight Scholar.

Assistant Professor **Peter Mombaerts**, a neurobiologist, has been named a 1996 Searle Scholar.

President Emeritus and Professor Emeritus **Joshua Lederberg** presented the concluding remarks at the "The Year of Louis Pasteur Symposium" in Rio de Janeiro. The Institut Pasteur hosted the meeting. Lederberg received the 1995 Allen Newell Award from the Association for Computing Machinery for his path-breaking contributions to the application of computer science research to chemistry and biology. Also, he was elected a director of the Council on Foreign Relations. Lederberg directs the Laboratory of Molecular Genetics and Informatics.

Professor **Bruce McEwen** is the president-elect of the Society of Neuroscience. He heads the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology.

A street in Hamburg, Germany has been named after the late **Marie Nyswander**, who died in 1986. She

was the wife of Professor Emeritus **Vincent Dole**. During the 1960s, Dole and Nyswander, then a research associate in his lab, pioneered the use of methadone maintenance for the treatment of heroin addiction. A group of recovering heroin addicts in Hamburg petitioned the city to honor Nyswander.

Arnold and Mable Beckman Professor **Robert Roeder** and Robert Tjian of the University of California at Berkeley received two awards honoring their contributions to understanding the control of genetic expression: the Lewis Rosenstiel Award for Distinguished Work in Basic Medical Research and the Passano Award. Roeder heads the Laboratory of Biochemistry and Molecular Biology.

The American Society of Photobiology gave Associate Professor **Thomas Sakmar**, head of the Laboratory of Molecular Biology and Biochemistry and HHMI associate investigator, its Young Investigator Award.

The University of Rome presented an honorary degree to President Emeritus **Frederick Seitz**. He also received the Order of the Brilliant Star with Violet Grand Cordon for his service on behalf of the advancement of science and technology in the Republic of China.

Professor Emeritus **William Trager** received Thailand's Prince Mahidol Award in medical science, which honored his contributions to the advancement of medicine in malaria. He directs the Laboratory of Parasitology.

Wesleyan University presented RU President **Torsten N. Wiesel** with an honorary degree. He also heads the Laboratory of Neurobiology.

The RU chapter of Sigma Xi hosted a lecture by U.S. Senator Barbara D. Boxer, D-Calif., who discussed



"Investing in the 21st Century." She received a certificate of recognition from the RU chapter for her conservation efforts in Congress.

## PUBLICATIONS

Professor **William Agosta** has authored *Bombardier Beetles and Fever Trees: A Close-up Look at Chemical Warfare and Signals in Animals and Plants*. *Library Journal*, the publication for book buyers, selected the text as 1995's Best Scientific and Technical Book for General Readers, Biology-General. One reviewer lauded it as a "perfect balance of science, fact, big words and the all-important 'Cool! Gross!' factor."

Professor **Joel E. Cohen's** *How Many People Can the Earth Support* explores the complexities of ecology, economy and epidemiology in determining the world's capabilities to host an expanding population. He heads the Laboratory of Populations.

Professor Emeritus **Christian de Duve's** *Vital Dust: Life as a Cosmic Imperative* provides a history of four billion years on Earth.

*The Hostage Brain*, by Professor **Bruce McEwen** and Harold M. Schmeck Jr. and published by the RU Press, received two awards: the Award of Excellence from the Association of Medical Illustrators and an honorable mention for excellence in book design and production from the Professional/Scholarly Publishing Division of the Association of American Publishers. McEwen heads the Harold and Margaret Milliken Hatch Laboratory of Neuroendocrinology.

RU President Emeritus **Frederick Seitz** has translated and annotated *Ten Years in a Golden Cage*, the memoir of Nikolaus Riehl, a radiochemist who purified uranium in Germany

during World War II and then worked as a captive scientist in the Soviet Union for 10 years. The new volume, *Stalin's Captive: Nikolaus Riehl and the Soviet Race for the Bomb*, includes information Seitz gleaned from Riehl's family and contemporaries as well as scientific, historical and political archives in the United States and abroad.

Professor **Alexander Tomasz** is the editor of a new journal, *Microbial Drug Resistance*. RU researchers on the editorial board include **Gilla Kaplan** and **David S. Thaler**. Tomasz directs the Laboratory of Microbiology.

## FACULTY

### New Graduate Deans

Professor **George A. M. Cross** is the new dean of graduate studies. He directs the Laboratory of Molecular Parasitology. Professor **John Kuriyan**, head of the Laboratory of Molecular Biophysics and an HHMI investigator, serves as associate dean.

### Promotions

#### To Professor:

**Frederick R. Cross**, head of the Laboratory of Yeast Molecular Genetics.

**Jeffrey Friedman**, head of the Laboratory of Molecular Genetics. He is an HHMI investigator.

#### To Associate Professor:

**Arturo Alvarez-Buylla**, head of the Laboratory of Developmental Neurobiology.

**Ambrose Cheung**, member of the Laboratory of Bacterial Pathogenesis and Immunology.

**James G. Krueger**, head of the Laboratory of Investigative Dermatology.

### In other news...

**Brian T. Chait**, head of the Laboratory for Mass Spectrometry and Gaseous Ion Chemistry, is the new Camille and Henry Dreyfus Professor.

**Stephen Duncan** has been appointed assistant professor in the Laboratory of Molecular Cell Biology, headed by James E. Darnell Jr., Vincent Astor Professor.

**A. James Hudspeth** joins the university as the F. M. Kirby Professor.

**Maria Karayiorgou** joins the university as an assistant professor. She heads the Laboratory of Human Neurogenetics.

**Albert J. Libchaber**, head of the Laboratory of Experimental Condensed Matter Physics, is the new Detlev W. Bronk Professor.

**Peter Mombaerts** is the new head of the Laboratory of Vertebrate Developmental Neurogenetics. He joins RU as an assistant professor.

**Thomas Muir** is the new head of the Laboratory of Synthetic Protein Chemistry. He joins the university as an assistant professor.

**Vincent A. Pieribone** has been appointed assistant professor. He is a member of the Laboratory of Molecular and Cellular Neuroscience, directed by **Paul Greengard**, Vincent Astor Professor.

**Melissa Pope** has been appointed assistant professor in the Laboratory of Cellular Physiology and Immunology, headed by Ralph M. Steinman, Henry G. Kunkel Professor.

**Andrej Šali** is the new head of the Laboratory of Molecular Biophysics. He joins RU as an assistant professor.



**Ralph Steinman**, head of the Laboratory of Cellular Physiology and Immunology, is the new Henry G. Kunkel Professor.

**Markus Stoffel** is the new head of the Laboratory of Metabolic Diseases. He joins RU as an assistant professor.

**Norton Zinder**, former head of graduate studies, has become special assistant to the president. He is a John D. Rockefeller Jr. Professor and cohead of the Laboratory of Genetics.

## ADMINISTRATION

### Board Adds Members

The board of trustees elected investor **Jeffrey E. Epstein**, neurobiologist **Eric R. Kandel**, Nancy M. **Kissinger**, philanthropist **David H. Koch** and Morehouse College President **Walter E. Massey** as new members.

President of J. Epstein & Co., a private holding company, Epstein is the director of the Wexner Foundation and of the Wexner Heritage Foundation. Kandel is University Professor in the Columbia University Department of Biochemistry and Molecular Biophysics and a senior investigator at the Howard Hughes Medical Institute. Kissinger is a member of the board of overseers of the Nelson A. Rockefeller Institute of Government at the State University of New York, Albany. She is a trustee of the MacKay-Shields MainStay Series Fund and Tax Free Bond Fund, of the Animal Medical Center and of The Masters School. Koch is executive vice president of chemical technology of Koch Industries Inc., a diversified energy company founded by his father, Fred C. Koch, who invented a refining process. Massey, in addition to his Morehouse presidency, is a director of Motorola, Amoco and Bank of America.

### In other news...

**Penny Cook** has returned to RU as the assistant vice president for faculty and community affairs and as corporate secretary.

**Marion E. Glick** is the new director of communications in the Office of Public Affairs.

**Lauren Hackett** is the new director of the Office of Research Administration.

**John Harrigan** has been promoted to vice president for finance and controller.

Sherman M. Fairchild Professor **Jules Hirsch** steps down from his position as Physician-in-Chief at the RU hospital, effective July 1, 1996. He will continue to co-head the Laboratory of Human Behavior and Metabolism with Associate Professor Rudolph Leibel.

**David Lyons**, vice president for business and finance, retired at the end of 1995 after 26 years of service. He will serve as a part-time consultant for RU and other academic institutions.

**Ingrid Reed**, vice president for public affairs and corporate secretary, departs Rockefeller to direct the New Jersey Project, an initiative of the Rutgers University Eagleton Institute of Politics.

**David Soles** is the new director of housing operations and services.

## PASSINGS

**Reynard Biemiller**, 85, former assistant director of the RU Press, died Dec. 15, 1995. Biemiller, who retired in 1974, received many awards for his designs of university publications.

**Teruko Hanafusa**, senior research associate and a founding member in the Laboratory of Molecular Oncology, headed by her husband Leon Hess Professor Hidesaburo Hanafusa, died January 26, 1996 of cancer at her home. She was 67.

Assistant Professor **Sandra Handwerker**, a member of the Laboratory of Microbiology headed by Professor Alexander Tomasz, died at home April 15, 1996, of metastasized breast cancer. She was 41.

**Ann Quatela**, former RU executive secretary, died April 21, 1996, from cancer. After working with Robert Leader and Atallah Kappas, Quatela served four RU presidents: Frederick Seitz, Joshua Lederberg, David Baltimore and Torsten Wiesel.

Professor Emerita **Maria Rudzinska** died at her home in New York on February 9, 1996, at age 92. In her career of more than 40 years at RU, she made numerous contributions to the understanding of the cell biology of protozoa and particularly malaria parasites.

**Elizabeth A. Straight**, 60, director of nursing at the RU Hospital from 1977 to 1990, died Nov. 17, 1995, from cancer. She joined the hospital in 1960.

**Igor Tamm**, 72, Abby Rockefeller Mauzé Professor Emeritus, died Feb. 6, 1995 of chronic lung disease at his home in Watch Hill, R.I. A pioneer in the study of biochemistry and replication of viruses, he directed the Laboratory of Cell Physiology and Virology.

Professor Emeritus **Hao Wang**, 73, head of the Laboratory of Logic, died May 13, 1995 at New York Hospital of lymphoma.





*Caspary Auditorium's blue dome is visible through the London plane trees that line the walkway along the Graduate Students Residence, at right.*





# SEARCH

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