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The Rockefeller University

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news & notes

April 8, 1994 Volume 4, Number 23

The Rockefeller University

Board promotes two to professor, elects trustee

Several faculty job offers made; academic plan favorably received

In its meeting Mar. 23, The Rockefeller University Board of Trustees voted to promote Stephen Burley and Mary Jeanne Kreek to the rank of full professor. In addition, the board elected a new trustee, Leon Levy, general partner of Odyssey Partners, L.P. and chairman of the board of Oppenheimer Mutual Funds.

"I am very pleased by the addition of Stephen Burley and Mary Jeanne Kreek to the senior faculty," said President Torsten Wiesel. "Dr. Burley has made outstanding contributions to the field of structural biology and Dr. Kreek has provided leadership in the scientific understanding of the biological basis of drug addiction. I offer my sincere congratulations to them both.

He continued: "I would also like to express my pleasure at the election of Leon Levy to the Board. Given his long-standing leadership in and support of nonprofit and educational institutions, I believe Mr. Levy will serve the university with intelligence and creativity. I look forward to working with him."

In other business at the board meeting, the trustees agreed to extend a number of offers for positions on both the junior and senior faculty. In addition, the trustees favorably received a preliminary report of the academic plan, which aims to ensure that the strength of



Stephen Burley and Mary Jeanne Kreek were promoted to the rank of professor at a trustee meeting Mar. 23.

scientific research at the university is maintained and enhanced into the 21st century. A final version of the report will be presented in June.

Stephen Burley

Burley's work focuses on the process by which biomolecules recognize each other and coordinate diverse biochemical events. Using x-ray crystallography, he is studying the role of the molecular recognition process in regulating the expression of genes in eukaryotes. Recently, he was the first to show the three-dimensional structure of the TATA-box binding protein, the key protein underlying all eukaryotic gene transcription, and how it recognizes the DNA TATA sequence. The lab also recently determined the structures of Max, a key transcription factor involved in cancer, upstream stimulatory factor, a similar protein, and hepatocyte nuclear factor-3, which also influences transcription.

Burley received a B.Sc. in physics from the University of Western Ontario in 1980, a D.Phil. as a Rhodes scholar from the University of Oxford in 1983 and an M.D. from Harvard Medical School in 1987. He then worked as a research resident in internal medicine and protein crystallography at Brigham and Women's Hospital and the Department of Chemistry at Harvard University. He received an appointment from Rockefeller, and from Howard Hughes Medical Institute, in December 1990. He was promoted to associate professor in March of last year.



Mary Jeanne Kreek

Kreek's laboratory group focuses on the fundamental mechanisms of cocaine as well as opiate and alcohol addiction. The group has found that abstinent cocaine addicts display an abnormal response to stress at the level of the brain's neuroendocrine system. In addition, using rats as subjects, Dr. Kreek and her co-workers have found that one type of opioid receptor in specific brain cells increases when the animals are given cocaine in binge-pattern doses.

Kreek received a B.A. from Wellesley College in 1958 and an M.D. from Columbia University College of Physicians and Surgeons in 1962. Kreek has been affiliated with Rockefeller since 1964, first as guest investigator (1964) and associate physician (1964-72), then as

See **Board**, page 2

Seminars to focus on eukaryotic gene expression

A joint symposium of The Rockefeller University and Sweden's Karolinska Institutet [sic], entitled "Eukaryotic Gene Expression and Regulating Signals," will be held Mon., Apr. 11 and Tues., Apr. 12, from 9:00 A.M. to 5:00 P.M., in Caspary Auditorium.

The first of a series of exchanges between the institutions, the symposium will address recent advances in signal transduction and the mechanisms regulating transcriptional control. The Karolinska Institutet will organize the next symposium, to take place in Sweden, in approximately two years' time.

"There has been an unofficial long-term relationship with The Karolinska Institute stretching back many decades," said Professor James Darnell who helped organize the symposium. "Our institutions share a similar devotion to basic research and to the transfer of knowledge to human betterment, particularly in medicine. The symposium will provide us a framework in which to exchange our views both informally and formally in a concentrated area of interest."

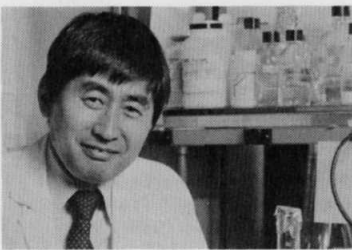
The symposium will be introduced by President Torsten Wiesel, an alumnus of the Karolinska Institutet. See the box on page 2 for a schedule of the lectures in each of the four sessions. Admission is free. All are welcome to attend.

Lecture on ethics to celebrate 50th anniversary of DNA discovery

Nancy Wexler—professor at Columbia University, adviser to the Human Genome Project and a leader in the field of research into Huntington's disease—will speak on "DNA Technology and its Social Consequences" on Mon., Apr. 18. The lecture will be part of the year-

long 50th anniversary celebration of the discovery by Rockefeller University investigators Oswald Avery, Colin MacLeod and Maclyn McCarty that genes are made of DNA. The lecture, which will be held at 6:00 P.M. in Caspary Auditorium, is free and open to the public.

2 Hanafusa to give Friday lecture



3 Research on fast track to nucleus

Hanafusa to speak at Friday lecture

Professor Hidesaburo Hanafusa, head of the Laboratory of Molecular Oncology, will speak on "Virus-Induced Cancer: Heritage and New Perspectives" at the Friday Lecture today (Apr. 8).

Hanafusa's research focuses on cellular mechanisms that prompt normal cells to become cancerous following induction by oncogenes, or genes that cause cancer. One of the oncogenes under study is *src*, originally found in the Rous sarcoma virus, a virus isolated in 1912 by Peyton Rous at what was formerly The Rockefeller Institute for Medical Research. Another oncogene under study is *crk*, a gene first identified by the Hanafusa lab. The gene comes from the avian sarcoma virus CT10, yet another virus first discovered in the early 1930s by Albert Claude at Rockefeller.

"Many of the principles of cancer were elucidated thanks to a heritage of research in virology at Rockefeller," said Hanafusa. "These early studies are what led this laboratory to realize that transformation of a single gene can cause cancer in a process called transduction. The concept of oncogenes thus established has made it possible to elucidate inherent causes of cancer such as mutation, amplification and chromosomal translocation." Set against a backdrop of research at The Rockefeller Institute, Hanafusa's talk will cover recent studies from his lab on the *src* and *crk* oncogenes as well as novel structural and functional influences on cellular transformation.

A graduate of Japan's Osaka University (B.S., 1953; Ph.D., 1960), Hanafusa completed his postdoctoral studies at the University of California, Berkeley, in 1964. He spent the next two years as a visiting scientist at the Collège de France then, joined the Public Health Research Institute of the City of New York as an associate member in 1966 then member, in 1968. In 1973, Hanafusa joined the faculty of The Rockefeller University as professor and was named Leon Hess Professor in 1986. Hanafusa has served on many editorial boards, and won numerous awards and honors, including the Albert Lasker Basic Medical Research Award in 1982, and the Sloan Prize from the General Motors Cancer Research Foundation last year.

The lecture will be held in Caspary Auditorium at 3:45 P.M. and preceded by tea in Abby Aldrich Rockefeller Hall at 3:15 P.M. All are welcome.

Schedule: "Eukaryotic Gene Expression and Regulating Signals"

Session I (Mon., Apr. 11), "Essential Proteins in Transcription," chaired by Professor James Darnell:

- Introductory remarks by President Torsten Wiesel, 9:00 A.M.;
- "Regulation of Eukaryotic Transcription: General Initiation Factors, Regulatory Factors and Co-Factors" by Professor Robert Roeder, 9:15 A.M.;
- "X-ray Crystallographic Studies of Eukaryotic Transcription Factors" by Professor Stephen Burley, 10:15 A.M.

Session II, "Families of Factors: Steroid/Thyroid Receptors and Homeobox Proteins," chaired by Erling Norrby, dean of the Karolinska Institutet:

- "Functional Architecture of the Glucocorticoid Receptor and Characteristics of Some Novel Members of the Steroid/Thyroid Hormone Receptor Superfamily" by Karolinska Professor Jan-Åke Gustafsson, chairman of the Department of Medical Nutrition, 11:30 A.M.;
- "Mechanism of Signal Transduction by the Basic Helix-Loop-Helix Dioxin Receptor" by Karolinska Associate Professor Lorentz Poellinger, 2:00 P.M.;
- "V-erb A Induces Tumors and Hypothyroidism in Transgenic Mice" by Karolinska Professor Björn Vennström, 3:00 P.M.;

- "Modulation of the Activity of the Bicoid Homeoprotein by a Signal Transduction Pathway" by Associate Professor Claude Desplan, 4:00 P.M.

Session III (Tues., Apr. 12), "Signals and Transcription," chaired by Karolinska Professor Bertil Daneholt, chairman of the Department of Cell and Molecular Biology:

- "Phosphorylation of Cellular Proteins by c-Src and v-Crk" by Professor Hidesaburo Hanafusa, 9:00 A.M.;
- "SH2 Structure and Function" by Rockefeller Professor John Kuriyan, 10:00 A.M.;
- "The NF- κ B Family of Transcription Factors and the Expression of Opioid Peptide Precursor Genes" by Karolinska Professor Lars Terenius, 11:30 P.M.;
- "The JAK-STAT Pathway" by Darnell, 2:00 P.M.

Session IV, "RNA Events in Regulation," chaired by Hanafusa:

- "Structure and Function of Two Adenovirus Encoded RNA Splicing Factors" by Karolinska Professor Göran Akusjärvi, 3:00 P.M.;
- "Ordered Translocation of a Premessenger RNP Particle Through the Nuclear Pore" by Daneholt, 4:00 P.M.

Board promotes two faculty to professor; elects new trustee

(continued from page 1)

assistant professor (1967-72) and senior research associate (1972-83). She was promoted to physician in 1972, lab head in 1975 and associate professor in 1983. Kreek has been affiliated with The New York Hospital-Cornell University Medical College since 1962. Since 1987, Kreek has been principal investigator and scientific director of an NIH-NIDA Research Center on the biological correlates of addiction. Kreek has served on many committees of the NIH and currently is on the National Advisory Council of the National Institute on Drug Abuse.

Leon Levy

A graduate of the City College of New York (B.B.S., 1948), Levy served in the U.S. Army from 1945 to 1947 before joining Hirsch & Company as a security analyst. In 1951, he moved to Oppenheimer & Co. (now Odyssey Partners, L.P.) as general partner. He is currently chairman of the board of Oppenheimer Mutual Funds and Avatar Holdings, and former chairman of the board of Oppenheimer Management Corporation. In addition, he is director of Electra Investment Trust, P.L.C., Mercury Assets Management, Ltd., Seneca Insurance Company, S.G. Warburg

& Co., Ltd. (Jersey Funds) and the United Kingdom Fund, and former director of Hotel Carlyle Owners Corporation.

Levy is also affiliated with a number of nonprofit institutions. These include: American Schools of Oriental Research, Bard College, International Foundation for Art Research, Institute for Advanced Study, Institute of Fine Arts and Institute for Fine Arts Foundation (both at New York University), Jerome Levy Institute for Economic Research at Bard College, John Simon Guggenheim Foundation and Century Association.

Bunny brings babes Easter bounty



Jennifer Horne King

Children begin their quest for chocolate eggs on the steps of Founder's Hall on Easter Sunday. The annual event is organized by the Rockefeller University Faculty Tenant Association.

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Research at RU illuminates fast path into cell nucleus

by Susan Blum

Like the fingers of a pianist striking the keys to produce tones, extracellular signaling proteins (ESPs) contact cell surface receptors to evoke responses within the cell. The ultimate site of action of ESPs is the nucleus, where genes are transcribed as the first step in the production of proteins. To maintain harmony within the organism, each specific ESP prompts the transcription of a specific gene or set of genes.

How is such specificity orchestrated? Part of the answer lies at the cell surface, where each different messenger docks only at the receptor designed to receive it. Specificity also resides in the nucleus, where different transcription factors control the transcription of different genes.

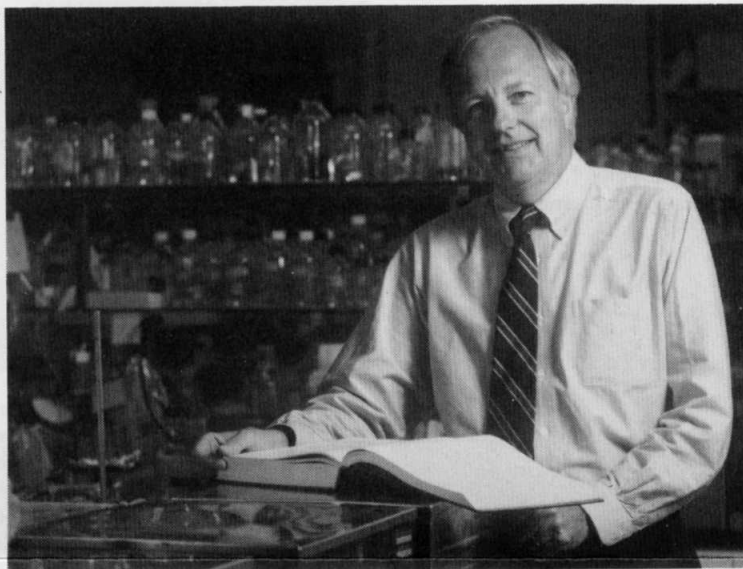
But between the cell surface and the nucleus, much less has been known about the events involved in passing along, or transducing, an ESP's singular message. Many scientists had long believed that most messages were conveyed by changes in the intracellular concentration of "second messengers," small molecules such as calcium and cyclic AMP. But this explanation never seemed sufficient to Rockefeller University Professor James Darnell. "If all the information received at the cell surface converged in a soluble pool of a small number of second messengers, the specificity of the information would be lost and could never be recovered," Darnell said.

Direct pathway is disclosed

Over the past decade, a new line of research—much of it conducted by Darnell and his colleagues—has disclosed that messages can reach genes in the nucleus through a pathway of protein-protein interactions that never let go of the specificity. This "JAK-STAT" pathway is turning out to be used by an ever-growing list of polypeptide signaling molecules. It is also turning out to be remarkably straightforward, providing what Darnell calls "a fast route" into the nucleus.

In outline, the JAK-STAT pathway works as follows. An ESP binds to its designated receptor. This event activates one or more members of the JAK family of tyrosine kinases, which put phosphate molecules on the amino acid tyrosine. The molecules that receive this phosphate are members of the STAT family of proteins. STAT proteins are always present in the cell's cytoplasm, but are usually inactive. Phosphorylation activates them and causes them to bind together in units of two, called

John H. Sholtis



Professor James Darnell's research has helped illuminate how extracellular signaling proteins send messages to a cell's nucleus.

dimers. These dimers then move into the nucleus where, alone or sometimes in combination with still other proteins, they serve as transcription factors. From this dual function—Signal Transducers and Activators of Transcription—comes the name of the protein family.

A flood of papers on the JAK-STAT pathway has been published recently by Darnell's lab and about half a dozen others, many headed or staffed by former Darnell postdocs and graduate students. The field has progressed with great rapidity since October 1990, when a paper by Darnell and a postdoc, David Levy, first proposed the existence of such a pathway that would operate for all polypeptide signals. A mere three and a half years ago, this idea was so novel that their article was published under the rubric, "Theory and Hypothesis."

Interferon studies lead way

The hypothesis was based on work done in the Darnell lab on the intracellular events evoked by interferon- α . Beginning in the mid-1980s, Darnell's lab and scientists elsewhere showed that a specific set of genes was turned on in a matter of minutes when IFN- α docked at its cell-surface receptor. The Darnell lab then cloned two of these genes, and initially identified the region of DNA that proved responsible for controlling the transcription of all IFN- α responsive genes. Next, they and researchers elsewhere identified the transcription factor that bound to the DNA, and Darnell's lab determined that this factor was actually a multi-unit complex made up of two members of a new protein family (now dubbed STAT 1 and STAT 2), and a third, unrelated protein called p48. Another part of the IFN- α

puzzle fell into place when Darnell and his colleagues reported that the activation of STAT 1 and STAT 2 occurred by means of tyrosine phosphorylation.

Parallel to the latter part of their work on the IFN- α pathway, Darnell and his colleagues started exploring the pathway set in motion by interferon- γ , a completely different polypeptide with its own receptor and its own set of inducible genes. These studies showed that the general principles of the pathway were the same, although the details varied. For instance, the DNA control region was different, and the transcription factor was composed simply of two subunits of STAT 1.

Meanwhile, researchers led by Ian Kerr and George Stark at the Imperial Cancer Research Fund in London were using genetic rather than biochemical techniques to identify molecules connected with the interferon response. They first discovered that a mutant cell unable to respond to IFN- α lacked the Tyk-2 kinase, a JAK family member. Two more JAK proteins were subsequently found to be required: JAK 1, which acted in both the IFN- α and IFN- γ pathways, and JAK 2, involved only in the IFN- γ pathway.

Many details remain to be learned about how IFN- α and IFN- γ send their messages into the nucleus. But even before these details are in, work on the IFN- α and IFN- γ pathways has paved the way for a wealth of new discoveries supporting Darnell and Levy's prediction that the signaling strategies used in these pathways would prove true for many other extracellular signaling polypeptides. Since last September, a spate of papers has reported that at least one compo-

nent of the JAK-STAT pathway—STAT 1—is activated by a number of cytokines and growth factors, including EGF, PDGF, CSF-1, CNTF, IL-10, and IL-6.

If STAT 1 is involved in so many JAK-STAT pathways, how is the specificity of each message maintained? Darnell asserted, "The answer will come in finding additional STAT and JAK proteins," each of which can interact with their respective receptors in various combinations to ensure specificity.

New family members are found

In fact, such discoveries are already occurring. In the April 1 issue of *Science*, Darnell and two graduate students, Zhong Zhong and Zilong Wen, report the first new member of the STAT family, called STAT 3, which is activated in response to EGF and IL-6, but not by IFN- γ . Darnell's lab has also discovered STAT 4, and another group has found STAT 5.

"These recent discoveries give us every reason to believe that there will be a sizable number of STAT proteins, not just a few," said Darnell. The same is true for the JAK family; a new JAK was reported last month. Add to this the fact that the expression of many of these proteins is likely to be tissue-specific (STAT 4, for instance, is found only in testis, thymus and spleen) and that additional multiple-member protein families may be involved (such as those in the family to which p48 belongs) and the possibilities for specificity-ensuring combinations ramify greatly. Such possibilities are discussed in a review article, co-authored by Darnell, scheduled to appear in the April 15 issue of *Science*.

Ultimately, research on the JAK-STAT pathway promises to yield insight not only into how cells register a specific signal, but how they integrate many messages coming from different signaling molecules. For instance, Darnell said, "many polypeptides may regulate both overlapping and unique sets of genes by activating both shared and specific proteins that assemble into multi-unit transcription factors." In addition, there are numerous possibilities for interactions between components of the JAK-STAT pathway and other signal transduction pathways, such as the ras pathway involved in many cell growth and differentiation events. For example, some of the proteins that activate STAT 1 also activate the ras pathway. In this way, the notes evoked by each messenger can blend into chords, and the chords can be composed into the melodies that make complex multicellular organisms hum.

Potpourri

Tri-Institutional Noon Recital

The Chester String Quartet will perform works by Franz Joseph Haydn and Franz Schubert at the Tri-Institutional Noon Recital today (Apr. 8). The quartet, made up of violinists Aaron Berofsky and Kathryn Votapek, violist David Harding and cellist Thomas Rosenberg, won top prize at the Munich and Portsmouth International Competitions. The concert, to be held in Caspary Auditorium at noon, is free.

Spraying

Weather permitting, the trees and shrubs on campus will be sprayed Sat., Apr. 9 from 6:00 A.M. to noon. The Grounds Department recommends that those on campus that day stay out of direct contact of the spray, close windows, turn off air conditioners and keep pets inside. The rain date is Sat., Apr. 16. For more information, call James Sullivan, x8001.

Sunday film

Viridiana (Spain, 1961), directed by Luis Bunuel, will be shown in Caspary Auditorium at 7:30 P.M., Sun., Apr. 10. The film is the story of an innocent woman who is drawn into the depraved world of her uncle. Her eagerness to do good results in tragedy. Admission is free.

Clinical Research Seminar

Andrew Shenker, senior research investigator in the Molecular Pathophysiology Section of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, will speak on "Activating Receptor and G Protein Gene Mutations as a Cause of Human Disease" at the Clinical Research Seminar, Wed., Apr. 13, at noon, in Nurses Residence 110B.

RU Concerts

Violinist Benny Kim and pianist

Jaime Bolipata will perform at The Rockefeller University Concerts, Wed., Apr. 13 at 8:00 P.M. in Caspary Auditorium. The program will feature works by Jean-Marie LeClair, Johannes Brahms, Antonín Dvořák, Frédéric Chopin and Manuel de Falla. Kim has received numerous awards, including the Young Concert Artists International Auditions. Admission is \$17 per person; \$7 for students and postdocs from the Tri-Institutions. For more information or reservations, contact Cathy Rogers, x8971.

Cohn Forum

David Skinner, president and chief executive officer of New York Hospital-Cornell Medical Center, will speak at the Zanvil A. Cohn Forum on Health Affairs, Thurs., Apr. 14 in the Faculty and Students Club. His lecture is entitled "The Future of Academic Health Centers." The presentation will begin at 5:30 P.M. and will be followed by discussion. Sherry will be served at 5:00 P.M.

Club hours

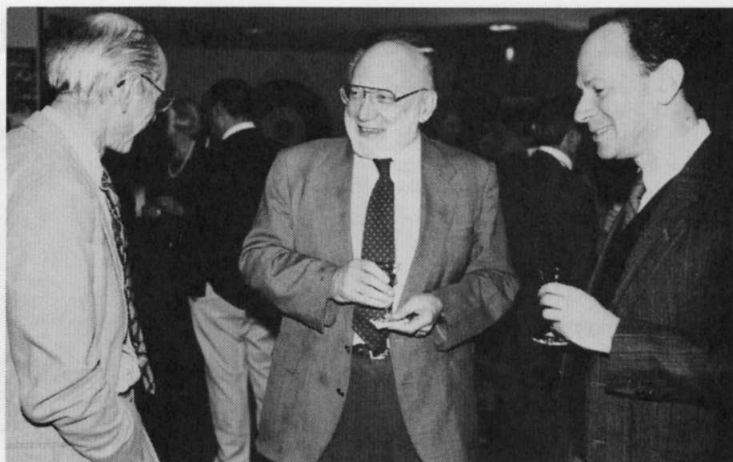
The Faculty and Students Club will open at 8:00 P.M. instead of 4:00 P.M., Thurs., Apr. 14.

Marble walkways

Plant Operations has scarified a small section of the marble walkway between Bronk Laboratory and the tennis court to determine if this process will succeed in making the walkways more slip-resistant. The department invites members of the Rockefeller community to test the surface for themselves and to send or call in reactions to either Gene Roth, x8606, or Bob Francis, x8001.

Electronics Shop move

The Electronics Laboratory and Shop have moved to Smith Hall C-13 and C-28. Senior Research



The first Zanvil A. Cohn Forum on Health Affairs last month featured Joshua Lederberg (center), university professor and former president, here chatting with Visiting Professor Robert Olby (left) and Senior Research Associate Jesse Ausubel before the lecture. The next Cohn Forum, on Thurs., Apr. 14 at 5:30 P.M. in the Faculty and Students Club, will feature David Skinner, president and chief executive officer of New York Hospital-Cornell Medical Center (see announcement, this page).

Associate Paul Rosen and Administrative Assistant Anne Conners are located in C-28. Engineers Herb Cohen and Mike Chen, as well as technicians Mike Perrino and Bjorn Gullaksen are located in C-13. All telephone numbers will remain the same.

Computing Services move

Computing Services will be situated for 10 weeks in Smith Hall B1 (the former Electronics Shop) while construction is under way; after that time the department will move back into Smith Hall B4. Computing Services apologizes for any inconvenience. (Please note

that the User Area/Classroom is not affected by the move.)

Birth

Research Associate Iddo Wernick of the Program for the Human Environment and his wife, Lisa, became parents to a son Gamliel Aryeh, 8 pounds, 14.5 ounces, on Feb. 2. Gamliel is their third child.

Rockefeller University Today

The winter 1994 issue of *The Rockefeller University Today* has been published. Copies are available during business hours from the Public Affairs Office, Caspary 3C.

Clarence Morley Connelly (1916-94)

Clarence Morley Connelly, a member of the faculty at The Rockefeller University for 30 years, died last week.

At the time of his retirement in 1984, Connelly was dean of the graduate program at Rockefeller. His efforts to select top-notch students and mentor them during their studies at the university shaped the graduate program for two decades. Connelly came to Rockefeller in 1954 as assistant professor and was promoted to associate professor in 1960. He became associate dean in 1962 and dean in 1980.

A graduate of Cornell University (A.B., 1938) and the University of Pennsylvania (Ph.D., 1949), Connelly conducted research which focused primarily on the relations between oxidative metabolism and the electro-



Clarence Morley Connelly

chemical properties of nerve cells that generate action potentials and regulate nerve excitability. One of his most cited experiments shed light on the sodium pump, a physiological mechanism which increases electrical potential across cell membranes.



David Wesolowski, administrative secretary in the Laboratory for Investigative Dermatology, celebrates his birthday with a free lunch in Abby Aldrich Rockefeller Hall. On the right is Research Nurse Mary Brust. The treat was part of a special new offer in which birthday celebrants dine free with a party of four or more. For more information, contact Alzatta Fogg, x8894.