1-28-1994

NEWS AND NOTES 1994, VOL.4, NO.16

The Rockefeller University

news notes

50 YEARS OF DNA

January 28, 1994 Volume 4, Number 16 The Rockefeller University

RU celebrates 50th anniversary of historic DNA discovery

Feb. 2: Leading geneticist speaks on science behind human genome project

David Botstein, professor and chairman of the Department of Genetics at Stanford University School of Medicine, will speak on "The Human Genome Project in its Scientific Context" on Wed., Feb. 2 at 5:00 P.M. in Caspary Auditorium. The public lecture is part of Rockefeller University's celebration of the 50th anniversary of Oswald Avery, Colin MacLeod and Maclyn McCarty's discovery that genes are made of DNA.

"It is fitting that Dr. Botstein will speak at our 50th anniversary celebration, because—like Avery, MacLeod and McCarty's research—his work made the human genome project possible," said Professor Norton Zinder, chair of the faculty committee that helped plan the celebration. "Dr. Botstein's idea on the use of restriction fragment length polymorphisms provided us with the insight necessary to consider mapping the whole human genome. Before this, we did not know how to obtain enough genetic markers to do so."

Botstein was educated at Harvard University (A.B., 1963) and the University of Michigan (Ph.D., 1967). He joined the Massachusetts Institute of Technology, where he rose to the rank of professor. In 1987 he moved to Genentech, Inc. as vice president for science and in 1990 assumed his present position.

Courtesy of Stanford University School of Medicine

Professor David Botstein will speak on the human genome project Wednesday.

Botstein's research has centered on genetics, especially the use of genetic methods to understand biological functions. The bacteriophage P22 was the focus of his earliest research, which included studies of DNA replication, recombination, head assembly and evolution of temperate bacteriophages. In the early 1970s Botstein turned to budding yeast (*Saccharomyces cerevisiae*) and devised novel genetic methods to study the functions of the actin and tubulin cytoskeletons. Other scientific interests of the Botstein laboratory include protein secretion (both in bacteria and yeast) and the use of localized random mutagenesis technologies to understand protein structure-function relationships.

Botstein began making theoretical contributions on linkage mapping of the human genome beginning in 1980 by suggesting, with collaborators, that restriction fragment length polymorphisms could be used to produce a linkage map of the human genome and to map the genes that cause disease in humans. With R. W. Davis, Botstein is currently helping to organize and administer the Stanford Yeast Genome Project, whose aim is to sequence the entire genome of *Saccharomyces cerevisiae*.

A member of the National Academy of Sciences, Botstein has won many awards. He presently serves on the Advisory Council of the National Center for Human Genome Research.

Feb. 3: Experts discuss 1944-53 period

How did Oswald Avery, Colin MacLeod and Maclyn McCarty's discovery that DNA is the genetic substance affect the field of genetic research between 1944 and 1953? Six of the world's leading scientists active in this formative period will participate in a roundtable discussion of this topic Thurs., Feb. 3, at 4:00 P.M., in Caspary Auditorium.

"This unique event brings together those pioneers who took the first steps in the molecular revolution of 20th-century biology," said President Torsten Wiesel. "It will explore the field of genetics in the period between the Avery lab's discovery and James Watson and Francis Crick's finding of DNA's double-helical structure."

Robert Olby, visiting professor at Rockefeller and author of *The Path to the Double Helix*, who will moderate the panel, said: "After a brief outline of their work, the panel will be invited to recall the impact upon them of the discovery that the transforming principle is DNA, and to describe how their research was directed thereafter. I hope this discussion will yield valuable information on this great episode in modern science and will bring to life the personalities of those names known to many only as authors of famous papers."

Participants in the panel discussion, who will be introduced by Professor Norton Zinder, include:

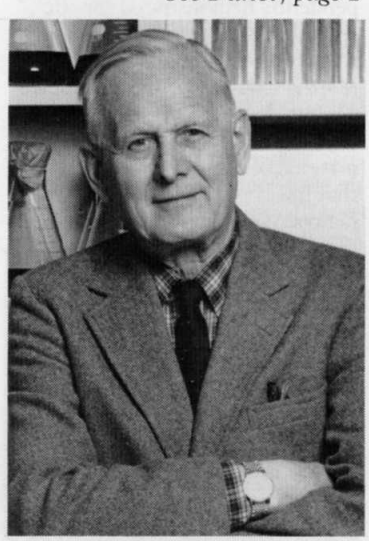
• Erwin Chargaff. Chargaff, an eminent biochemist, is currently professor emeritus at Columbia University. Educated at the University of Vienna (Ph.D., 1928), he was a fellow at Yale University (1928-30); assistant at the University of Berlin (1930-33); and research associate at the Pasteur Institute (1933-34). In 1935 he went to the College of Physicians and Surgeons at Columbia University where he moved up the ranks to become professor and department chairman.

Initially, Chargaff was interested in a range of biochemical fields, including lipid metabolism and blood coagulation. Following the Avery lab's paper, Chargaff focused on DNA. Using paper chromatography and ultraviolet spectroscopy, he found the composition of DNA to be constant within a species but to differ widely between species. In addition, Chargaff discovered that, no matter what species was examined, the number of purine bases (adenine and guanine) always equaled the number of pyrimidine bases (cytosine and thiamine); the number of adenine bases always equaled the number of thiamine bases; and the number of guanine bases equaled the number of cytosine bases. Chargaff's discovery of base-pairing, announced in 1950, was critical for the development of the double-helical model of DNA.

A member of the National Academy of Sciences (NAS), Chargaff has received many honors, including the National Medal of Science.

• Seymour Cohen. Cohen, a prominent biochemist, is currently American Cancer Society Research Professor Emeritus at SUNY, Stony Brook. A graduate of the City College of New York (B.S., 1936), Cohen's doctoral training at Columbia University (Ph.D., 1941), was guided by Chargaff. From 1941 to 1942 Cohen was affiliated with Wendell Stanley's lab at Rockefeller, where he was the first to find an RNA larger than a tetranucleotide. From 1942 to 1943 he worked at Columbia. He then accepted a position at the University of Pennsylvania (1943-71), moving up the ranks to Hartzell Professor of Therapeutic Research and department chair-

See ***Panel****, page 2*



Ingbert Grutner

Professor Emeritus Maclyn McCarty, co-author of the 1944 paper showing genes are made of DNA, will participate in the panel Feb. 3.

Feb. 4: Symposium

The university will host a scientific symposium focusing on areas pursued by the Avery lab—immunology, infectious disease and molecular medicine—on Fri., Feb. 4 at 3:45 P.M. in Caspary Auditorium. More information will be published in the next issue of *News&Notes*.

Panel to discuss historic DNA period

(continued from page 1)

man. In 1971 he accepted a position at the University of Colorado School of Medicine. In 1976 he joined SUNY, Stony Brook.

In 1946 Cohen began a series of studies using radioactive labeling. These studies were aimed at understanding how, shortly after an *E. coli* organism was infected with a bacteriophage called T2, the bacterial cell would burst, releasing several hundred replicas of the invading organism. These studies suggested the importance of DNA synthesis in viral multiplication. In 1952, Cohen and a colleague, G. Wyatt, discovered a new pyrimidine in viral DNA and went on to find the enzyme that made this novel compound. Cohen's group showed that this enzyme did not exist before viral multiplication.

A member of the Institute of Medicine of the NAS, Cohen is the recipient of many awards and honorary degrees.

• Alfred Day Hershey. Hershey was awarded a Nobel Prize for his discoveries concerning the replication mechanism and the genetic structure of viruses. After graduating from Michigan State University (B.S., 1930; Ph.D., 1934), Hershey worked at the Washington University School of Medicine (1934-50), as an assistant bacteriologist, instructor, then associate professor. Next, Hershey moved to the Carnegie Institute, where he was a staff member of the Genetic Research Unit (1950-62) then director (1962-74).

In 1945 Hershey and Salvador Luria independently showed that spontaneous mutations occur in bacteriophages. The following year Hershey and Max Delbrück independently demonstrated genetic recombination between phages in the same cell. Collaborating with Martha Chase, Hershey conducted a seminal experiment in 1952 showing that DNA is the genetic material of bacteriophage (viruses that infect bacteria). Using radioactive tracer techniques, they demonstrated that only DNA enters the bacterial cell; the virus's protein coat stays attached to the cell wall's exterior.

A member of the NAS, Hershey has received many honors in addition to the Nobel Prize (won with Delbrück and Luria), including the Albert Lasker Award.

• Rollin Hotchkiss. Hotchkiss, a pioneering biochemist and geneticist, is currently professor emeritus at Rockefeller. He received a B.S. in 1932 and a Ph.D. in 1935, both from Yale. He then joined Rockefeller as a fellow and was appointed professor in 1955.

Hotchkiss's early research dealt with the immunochemistry of bacterial polysaccharides and protein chemistry. He pioneered the exploration of variant types of DNA that cause bacteria to undergo specific genetic changes from sensitivity to resistance to sulfonamide and other drugs. From 1939 to 1943 he worked with René Dubos on the development and purification of gramicidin and tyrothricin, the first natural antibiotics to be isolated. Shortly after the Avery lab's 1944 discovery, Hotchkiss began working with Avery to develop methods for the quantitative study of transformation, to investigate the mechanism by which DNA enters a cell and expresses its function, and to refine methods for following the fate of DNA during transformation.

Hotchkiss has received many honors including election to the NAS and several honorary degrees, including one from Rockefeller.

• Joshua Lederberg. Lederberg, University Professor and former president of Rockefeller, is a distinguished geneticist and Nobel laureate. A graduate of Columbia College (B.A., 1944) and Yale (Ph.D., 1947), Lederberg joined the faculty of the University of Wisconsin in 1947. In 1959 he joined the Stanford University School of Medicine, where he founded the Department of Genetics. In 1978, he came to Rockefeller as its fifth president, serving until 1990. Throughout his career, Lederberg has taken important advisory roles in government.

While a Ph.D. student at Yale working with Edward Tatum, Lederberg discovered a "sexual breeding" system whereby two bacteria conjugate and form a connecting bridge through which one passes a chromosomal strand to the other. This discovery helped to make bacteria available for genetic research, and eventually for biotechnology. Subsequent research with Zinder showed that bacterial genetic material is exchanged not only by conjugation, when the entire complement of chromosomes is transferred from one bacterial cell to another, but also by transduction, when only fragments are transferred. Today, Lederberg heads a research team investigating how DNA can vary in its conformation, how this is influenced by the environment, and how this may affect the localization of gene mutations.

In addition to the Nobel Prize, Lederberg's honors include the National Medal of Science, election to the NAS, and charter membership in its Institute of Medicine.

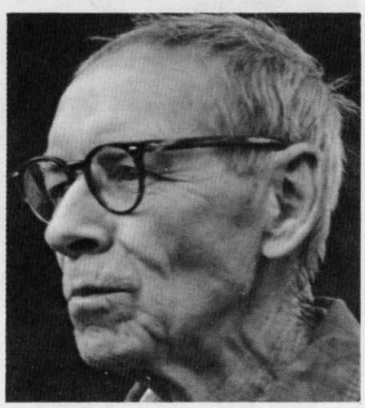
• Maclyn McCarty. McCarty, professor emeritus at Rockefeller and a co-author of the historic 1944 paper, is a renowned microbiologist. McCarty graduated from Stanford University (A.B., 1933) and the Johns Hopkins University (M.D., 1937). At Johns Hopkins, he was successively intern, assistant resident and assistant in the pediatrics department. He was a medical fellow, researching sulfonamide drugs at New York University from 1940 until he joined Rockefeller in 1941. At Rockefeller, he rose to professor and senior physician, then physician-in-chief of The Rockefeller University Hospital.

His work with Avery and MacLeod was significant because transformation—the artificial transfer of genetic material from one bacterium to another—was brought about in a test tube by a highly refined substance consisting principally of nucleic acid. This was the first direct evidence that DNA, a substance then thought to lack the necessary chemical diversity, was responsible for genetic continuity. A corollary of this discovery, that nucleic acid in some way controls the cell's synthesis of certain products, has had wide-ranging implications. McCarty has also studied streptococci and isolated both extracellular and cellular components of this organism.

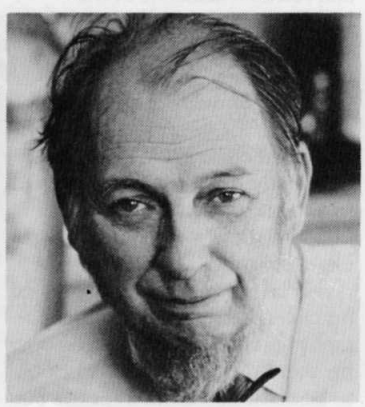
A member of the NAS, McCarty has received many honors, including a number of honorary degrees; the Medal of the New York Academy of Medicine; and the Who's Who in America Achievement Award.

Courtesy of Erwin Chargaff

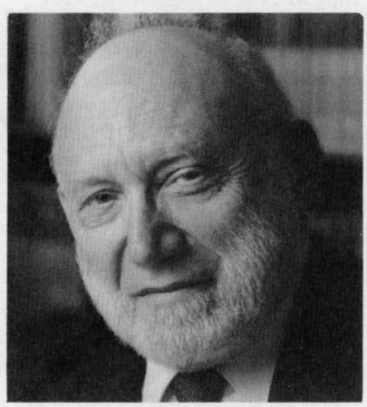
Panelists will include distinguished biologists Erwin Chargaff *(left)* and Seymour Cohen.



CSHL Archives



Ingbert Gruttner



Eminent scientists participating in the discussion of DNA research between 1944 and 1953 will include *(left to right)* Alfred Day Hershey, Rollin Hotchkiss and Joshua Lederberg.

News&Notes is published each Friday throughout the academic year by The Rockefeller University, 1230 York Avenue, New York, NY 10021. Phone: 212-327-8967.

Torsten Wiesel, President
Ingrid Reed,
Vice President for Public Affairs and Corporate Secretary
Doron Weber, Director of Communications

Mika Ono Benedyk, Editor
Jennifer Horne King, Assistant Editor
Heather Leahy, Design
Robert Reichert, Photography
Media Resource Service Center, Processing

Ideas and submissions can be sent interoffice (Box 68), by electronic mail (newsno), or by fax (212-327-7876).

The Rockefeller University is an equal opportunity/affirmative action employer.

Mirsky lectures link Da Vinci and Darwin to today's biology

By Susan Blum

More than 300 high school students took a voyage of scientific discovery during their winter vacation, thanks to the 1993 Alfred E. Mirsky Christmas Lectures given by Rockefeller researchers John Kuriyan and Stephen Burley.

The four talks, on "Da Vinci and Darwin in the Molecules of Life," explored how Da Vinci's anatomical studies and Darwin's work in evolutionary biology informs much of today's research on the structure and function of biological macromolecules. While the speakers' talks focused on the scientific contributions of these historical giants, their discussions also gave the young audience insight into how Burley's and Kuriyan's own scientific careers had developed, linking their professional histories to the biological questions they now pursue.

Professor John Kuriyan *(left)* and Associate Professor Stephen Burley speak at the Mirsky Christmas Lectures for high school students, this year part of the "50 Years of DNA" celebration.

X-ray 'scalpels' are described

Burley, who initially trained as a physician, began his first lecture with a description of Da Vinci's pioneering practice of moving beyond the body's surface to dissect—and then draw—the structures lying underneath. Focusing on one anatomical region, the hand, Burley showed some of Da Vinci's exquisite sketches and then recounted how—four centuries after Da Vinci—Roentgen's discovery of X-rays let scientists peer inside the human body without cutting it open. Later still, Burley told the group, Lawrence and William Bragg showed that the X-ray is "not merely a scalpel that allows us to look inside tissue at bone." Rather, Burley explained, with a technique called X-ray crystallography "we can overcome the limits of the human eye and disclose the atom-by-atom structure of single molecules."

Burley then surveyed the "molecular anatomy" of various proteins that have been dissected by that high-tech scalpel, including myoglobin, hemoglobin and a number of enzymes. Highlighting some of these proteins' most salient features, Burley pointed out their linear composition as strings of amino acids, their twists and turns into α-helices and β-sheets, their areas of positive and negative charge, and their water-loving and water-shunning, or hydrophobic, regions. A number of factors influence a protein's ultimate shape, but it is the sequestering of hydrophobic regions deep within a protein's core—as far away as possible from the cell's watery environment—that is mainly responsible for the complex process of protein folding, Burley said.

Kuriyan, who began his undergraduate studies as a zoology major before shifting to chemistry, commenced his first lecture by telling the audience, "Had I started my career in the late 19th century, I would undoubtedly have been a naturalist, driven by the thrill of discovering undreamed of plants and animals in the rain forest." Today, he said, discoveries of that sort do not have quite the same appeal, but "it is possible to recapture the wonder of seeing strange new forms before anyone else by exploring the 'tropical rain forest' within the cell."

Darwin's greatest accomplishment, Kuriyan said, was his recognition that nature possesses a mechanism for generating variation within a particular population, from which the environment can select those specimens best suited for it. Genetic mutation is the engine driving that mechanism, and it occurs (or is perpetuated) during the process by which genes are duplicated before a cell divides. Errors in the duplicating system occur at the rate of about one mistake per million DNA base pairs, and these mutations in genes lead to changes in the proteins for which they code. Some of these changes are harmful, but often enough they make the organism "fitter" to survive and thrive in its environment.

Proteins evolve in a context

Just as in an ecosystem living organisms—say, predator and prey—evolve in relation to one another, so proteins evolve in the context of the cell's biochemical environment. For instance, trypsin—an enzyme that chews up protein—cuts only at certain specific points in a protein's linked chain of amino acids, while elastase, another protein-splitter, cuts only at other specific amino acids. The reason? Though many features of both enzymes are the same, the nooks and crannies of their "active sites" are so different that they interact with—in a molecular sense, "prey upon"—different protein regions. "Nature took the same protein scaffolding for both enzymes and changed certain of their amino acids by mutation. It's an example of evolution at work," Kuriyan said. He explained that gene duplication is another force driving evolution. Such duplications result in the production of additional proteins (or protein regions, called domains), each of which can then mutate, and all of which can join together in various configurations to perform more complex biological functions, or perform vital functions more efficiently.

Ultimately, whatever function a protein serves is due to its structure. That structure is encoded in the sequence of base pairs in DNA, which in turn embody the instructions for the protein's unique sequence of amino acids, whose particular characteristics cause the protein to take shape spontaneously.

So far, nature has a much better idea about how proteins take shape than do scientists, the lecturers stressed. "How does nature know that a particular amino acid sequence leads to a particular three-dimensional structure?" Kuriyan asked. As Burley had told the audience earlier, this question, which refers to what is known as "the folding problem," remains one of the "great frontiers" of structural biology—a frontier both scientists agreed may be crossed within the next decade.

Lectures explore protein–nucleic acid interactions

On the second day of the lecture series, the scientists moved from considerations of proteins in themselves to discussions of proteins' interactions with other proteins and with the nucleic acids DNA and RNA. Such multi-molecular assemblies, which Burley likened to cellular "machines," perform many of life's most essential functions, such as the replication of DNA, the readout of the genetic code ("transcription") and the transformation of that code into protein ("translation").

Burley's lecture explained transcription and translation. Included in his discussion of transcription was a review of his own lab's groundbreaking work in elucidating the structure of the TATA-binding protein, or TBP—an essential cog in the transcription machine. Like other transcription factors, TBP interacts directly with DNA—in this case, sitting astride it like a saddle. But unlike any other known transcription factor, TBP dramatically distorts its DNA partner, twisting it at a 90 degree angle. As Burley pointed out, "now we know that proteins can not only recognize DNA, but change its shape, too." This adds further complexity to the protein-folding problem, since scientists must now fathom how nature "predicts" that a linear sequence of amino acids will configure itself into a protein that can effectively distort its DNA partner.

Kuriyan's final lecture included a discussion of DNA replication and the multi-component machines, called polymerases, that accomplish this task. He described the ongoing research he and his colleagues are conducting on determining the structures of one component of polymerases—the molecular "clamps" that let the duplication machine work in long sweeps.

The first structure they solved—the clamp for a bacterial polymerase—showed a surprising degree of symmetry, Kuriyan reported. Such symmetry, beautiful in itself, also beautifully illustrated a number of points made throughout the days' lectures. Some aspects of the clamp's structure can be understood through yet another wrinkle in the folding problem: two different chains of amino acids may share virtually no unit-by-unit similarity, yet may fold up into identically shaped proteins due to similar characteristics of the amino acids. Other structural aspects of the bacterial clamp can best be explained by gene duplications, which produce multiple copies of particular protein domains. Furthermore, Kuriyan said, the anatomical and evolutionary insights gleaned from analysis of the bacterial clamp recently helped the researchers predict the structure of the clamp in a polymerase of higher organisms, including humans. Such a prediction is a striking example of Da Vinci's and Darwin's enduring influence on contemporary studies in structural biology.

RU offers new supplemental insurance policy

The Rockefeller University Personnel Office is now offering a new benefit, a supplemental insurance policy for cases of accidental death or dismemberment. Employees have until Fri., Feb. 18 to enroll in the plan for this year.

"For a very reasonable monthly contribution ranging from 26 cents to 26 dollars, depending on the type of coverage, the new policy can supplement the insurance which is already available through the university," said Ginny Hansen, benefits specialist. "The new policy has a much higher maximum coverage, provides for accidents causing dismemberment, and enables employees to insure their spouse or children as well as themselves. We are very pleased to offer this extremely competitive plan to our faculty and staff."

Employees eligible for the new supplemental insurance include non-faculty staff, professors, associate professors, assistant professors and research associates who work at least 910 hours per year. Their spouses, domestic partners and unmarried dependent children up to age 21 (age 25 if they are full time students) are also eligible.

Employees who choose to insure their family members as well as themselves receive the additional insurance of several benefits, including special education for dependent children, spouse retraining and day care.

The accidental death and dismemberment policy covers losses resulting from any type of accident occurring in the course of business or pleasure; on or off the job; in or away from the home; while traveling by train, commercial airplane, automobile or other conveyance; and anywhere in the world, 24 hours per day, 365 days per year.

According to policy guidelines, the accident must occur while coverage is in force and the loss must occur within one year of the accident. The policy does not cover any loss resulting from intentionally self-inflicted injuries, suicide, war, service in the armed forces, illness or air travel other than in a commercial aircraft.

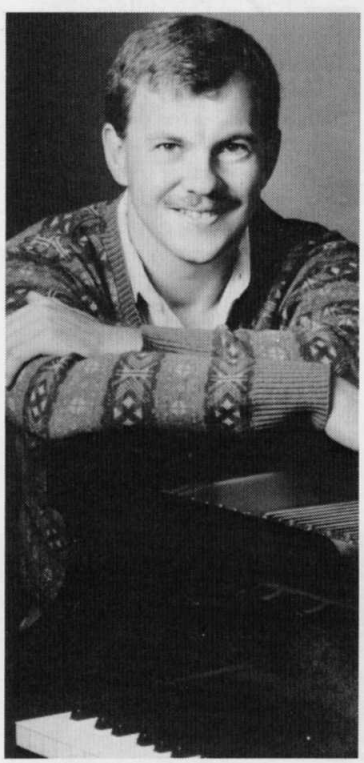
For more information, contact the Personnel Office, Founder's Hall 103 or x8300.

Potpourri

Tri-Institutional Noon Recital
Pianist Anton Nel, first place winner of the 1987 Naumburg Piano Award, will play works by Claude Debussy, Ludwig van Beethoven and Franz Liszt at the Tri-Institutional Noon Recital today (Jan. 28). The concert, to be held in Caspary Auditorium at noon, is free and open to the public.

Superbowl Sunday
The Faculty and Students Club will be open Superbowl Sunday, Jan. 30, from 4:00 to 11:00 P.M.

Christian Steiner



Pianist Anton Nel will perform at the Tri-Institutional Noon Recital today (Jan. 28).

Children's School applications
The Rockefeller University Children's School is accepting applications for the 1994-95 school year for children ages six months to six years. The deadline for priority enrollment for Rockefeller University families is Mon., Jan. 31. For more information or application forms, stop by the Children's School on the first floor of Graduate Students Residence, or call Marjorie Goldsmith, x8580.

RU Concerts
Soprano Harolyn Blackwell and pianist Warren Jones will perform at the Rockefeller University Concerts Wed., Feb. 2, at 8:00 P.M. in Caspary Auditorium. The program will feature works by Obradors, Rachmaninoff, Richard Strauss and Ricky Ian Gordon. Blackwell, who performed alongside Luciano Pavarotti in *Un Ballo in Maschera* at the Metropolitan Opera during her 1990-91 season, has made numerous appearances with the San Francisco, Baltimore, St. Louis, Cincinnati and Toronto symphonies, and has given recitals in Europe and Japan. Admission is $17 per person; $7 for students and postdocs from the Tri-Institutions. For more information or reservations, contact Cathy Rogers, x8971.

Promotions
Five people have received promotions in Plant Operations:

- Brendan Bolger, who was chief engineer, is now chief engineer and manager of Power House services;
- Elbin Diaz, previously foreman, is now manager of maintenance services;
- James Doyle, who was assistant chief engineer, is now associate chief engineer;
- Erika Mueller, previously supervisor of office administration, is now manager of office services;
- James Schaefer, who was assistant foreman, is now assistant manager of maintenance services.

Courtesy of Columbia Artists Management, Inc.

Soprano Harolyn Blackwell will perform at the Rockefeller University Concerts on Wed., Feb. 2.

Westinghouse finalist
Mariya Minkova, 17, the daughter of Alla Minkova, a programmer in Computing Services, has been selected as a finalist in the 53rd Westinghouse Science Talent Search. Mariya, who attends Midwood High School at Brooklyn College, is one of the 14 selected New York students.

Friday lecturer to focus on ion-channel function

Richard Aldrich, professor of molecular and cellular physiology and Howard Hughes associate investigator at Stanford University School of Medicine, will speak on "Biophysical and Molecular Mechanisms of Voltage-Gated Ion Channel Function" at the Friday lecture today (Jan. 28).

Ion channels, crucial components of all cell membranes, are key players in regulating movement of ions, such as sodium, calcium and potassium, into and out of cells. Voltage-gated ion channels, which open and close in response to changes in electrical potential across the cell membrane, are responsible for relaying, often practically instantaneously, most of the vital electrical signals in the body.

The Aldrich laboratory has helped to throw light on the delicate mechanisms underlying channel "gating," the conformational changes that open and close the ion pathway. The lab uses electrophysiological methods such as single-channel recording, which, on a millisecond time scale, can record the opening and closing of individual channel molecules, in combination with the molecular genetic method called "site-specific mutagenesis," in which channels are altered one amino acid at a time to learn which regions of the channel molecule influence its gating behavior.

"Rick is a pioneer in this field," said Professor David Gadsby, who is hosting the lecture. "He was among the first to successfully use site-specific mutagenesis to determine, on a molecular level, details of the relationship between ion channel structure and function."

A graduate of the University of Arizona (B.S., 1975) and Stanford University (Ph.D., 1980), Aldrich studied at Yale University School of Medicine as a postdoctoral fellow with W. K. Chandler and Rockefeller alumnus Charles Stevens from 1980 to 1983. He then became assistant professor there. In 1985, Aldrich returned to Stanford as assistant professor. In 1990, he was named associate professor and Howard Hughes Medical Institute associate investigator. He became full professor in 1993. Aldrich recently won the Jacob K. Javits Neuroscience Investigator Award.

The lecture, to be held in Caspary Auditorium at 3:45 P.M., will be preceded by tea at 3:15 P.M.