2-3-1995

NEWS AND NOTES 1995, VOL.5, NO.16

The Rockefeller University

news & notes

February 3, 1995 Volume 5, Number 16 — *The Rockefeller University*

Trager receives Thai medical science award

Rockefeller Professor Emeritus William Trager formally accepted Thailand's Prince Mahidol Award in medical science from Princess Maha Chakri Sirindhorn in a ceremony in Bangkok Sat., Jan. 21.

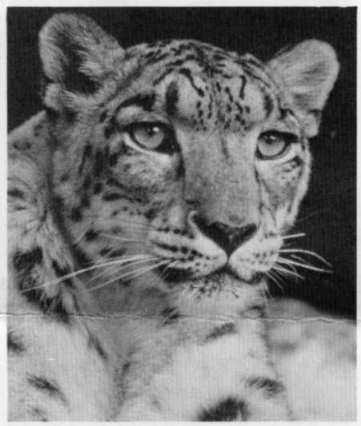
The award honors Trager's "exemplary contribution to the advancement of medicine in malaria," according to the Prince Mahidol Award Foundation. The annual award consists of a medal, a certificate, and $50,000.

"The ceremony was very beautifully done, with a lot of protocol," said Trager. "After the princess gave me the medal, I bowed and my wife gave me a kiss, which was not too serious an infringement of the protocol."

Professor Emeritus William Trager received Thailand's annual Prince Mahidol Award in medical science for his work on malaria.

See ***Award****, page 2*

Lecture series at RU highlights wildlife society centennial



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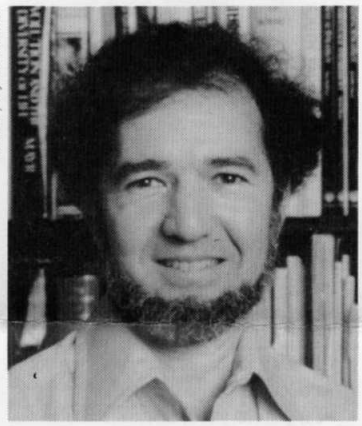


Courtesy of Jared Diamond

Jared Diamond (*right*), physiologist at U.C.L.A. Medical School and science writer, will speak on Tues., Feb. 7 in Caspary Auditorium in the inaugural lecture of the Wildlife Conservation Society's centennial lecture series. Later lectures will address the topic of endangered species, such as the snow leopard.

The struggle to conserve a natural environment under increasing pressure is the theme of the Wildlife Conservation Society's centennial lecture series, which begins Tues., Feb. 7 in Caspary Auditorium.

The six-lecture series, entitled "Conservation at the Crossroads: Man and Nature in the 21st Century," will cover such current topics as biodiversity, ecosystem and species conservation, sustainable use, and global population. The series, which launches a year-long program of activities highlighting the centennial of the Wildlife Conservation Society, continues the tradition of the Fairfield Osborn Memorial Lectures, which are cosponsored every three years by Rockefeller, the Society, and The Conservation Foundation/World Wildlife Fund.

Osborn (1887-1969) devoted his life to furthering human understanding of the natural world. His distinguished role in wildlife management and ecological studies was reflected in his 28-year presidency of the New York Zoological Society (now the Wildlife Conservation Society), as well as his book, *Our Plundered Planet*, published to wide acclaim in 1948. That same year, Osborn established The Conservation Foundation, where he served as president until 1961. The Conservation Foundation was incorporated into the World Wildlife Fund in 1991.

In the 1960's Osborn's fascination with animal behavior found a kindred spirit in Rockefeller's President Detlev W. Bronk. The Institute for Research in Animal Behavior, established in 1965 under the direction of Professor Emeritus Donald R. Griffin, was jointly administered by RU and the Society, and was the forerunner of Rockefeller's Field Research Center at Millbrook, now directed by Professor Fernando Nottebohm.

The lectures, which will be held on Tuesdays at 6:00 P.M., are:

•Voices from the Past: The Ecological Lessons of Ancient Civilizations
Feb. 7
Jared Diamond
U.C.L.A. Medical School;

•Save the Entire Biosphere!
Mar. 7
Norman Myers;

•Nature: Fact or Fiction?
May 8
Michael Soulé
U.C. Santa Cruz;

•The Stork vs. the Plow—Defusing the Population Bomb
Oct. 10
Paul Ehrlich
Stanford University;

•Lemurs of Madagascar: The Lost,

See ***Wildlife****, page 2*

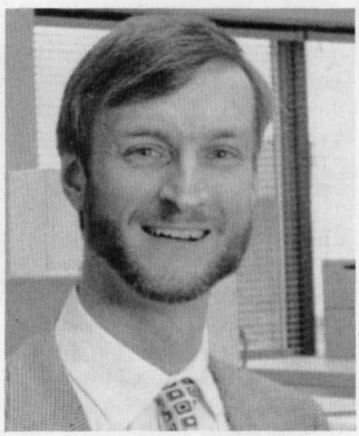
Geneticist to lecture on mice and men today

David C. Page, associate professor at the Massachusetts Institute of Technology (M.I.T.) and member of the Whitehead Institute, will speak on "Germ Cells and Gonads: Genetic Studies in Humans and Mice" today (Feb. 3).

Page and his colleagues use genetic tools to explore development of the germ line and reproductive tract in humans and mice—and especially the roles that sex-chromosome genes play in these processes. In 1992, his laboratory cloned the entirety of the human Y chromosome. Today Page will discuss how genetic studies of infertile humans and mice may reveal roles of RNA- and DNA-binding proteins in the mammalian germ line.

"David has had a long-standing interest in the mechanisms that control sexual differentiation in mammals," said Associate Professor Jeffrey Friedman, who will introduce Page. "He is also a leader in the effort to map the human genome and has completed a map of the entire Y chromosome."

Page received an M.D. magna cum laude from the Harvard Medical School and Harvard-M.I.T. Health Sciences and Technology Program in 1984. He was a visiting student (1981-1983) and postdoctoral associate (1984) in David Botstein's lab at M.I.T. He joined the Whitehead Institute in 1984 as a fellow, and in 1993 became a member. In 1988 he



Courtesy of David Page

David Page gives the Friday lecture today (Feb. 3).

See ***Page****, page 4*

Calling all talent: The ROCKEFOLLIES returns to RU

A casting call for the seventh ROCKEFOLLIES, the university's traditional talent show, was broadcast on campus last week by the ROCKEFOLLIES committee.

Billed by the committee as "an evening of exceedingly diverse light entertainment," the show is "by and for all of us working here," said Yvonne Holland, assistant for research and ROCKEFOLLIES producer. "We're very low key. If you have experience, wonderful. If not, you're welcome too—all you need is willingness."

The committee is eager to book both talent and management for the show, which will take place on the evening of Tues., Mar. 21. Anyone working at the university may participate, and acts may include nonuniversity friends. Acts should be about 10 minutes long ("if you need more time, we're flexible," said Holland), and may include a maximum of 10 people. There will be one rehearsal (full dress) the day before the show.

A few performers have already signed on, and Paul Rosen, desktop computing and electronics manager in the electronics shop, has accepted an invitation to emcee the show again. Said Rosen, "I try to get the audience in the mood by telling jokes. I'm not an extrovert, so I'm surprised that I can even do it." But do it he does, according to Holland: "He's a big drawing card for us. The audience really enjoys his jokes."

She continued, "Anything people want to do is fine; we've had everything from belly dancing to poetry reading to tae kwando demonstrations. It's a chance to show our nonworkday selves. We're not the gong show, and our audience is very supportive. Plus, it's a great way to meet university people you don't ordinarily meet."

To participate, contact Holland, x8396, box 173.

Young devotees of karate, who study the art with Isaiah Curry, waste handler (*not shown*), demonstrated their skill at ROCKEFOLLIES 93.

Wildlife

(continued from page 1)

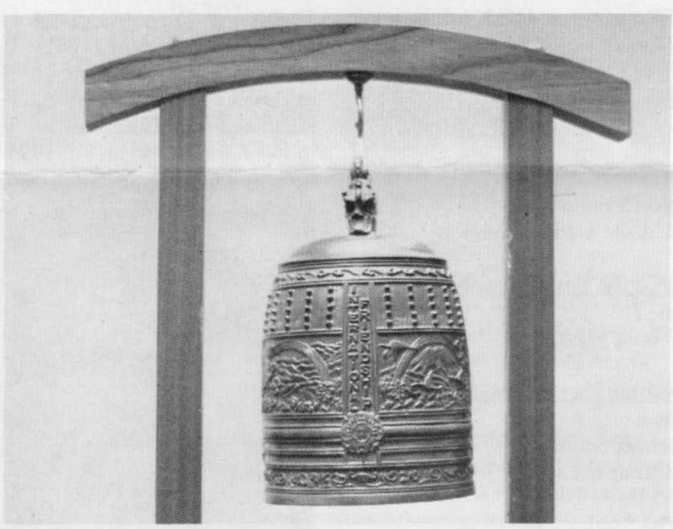
the Living and Lessons They Offer
Nov. 7
Alison Richard
Yale University;

•Forest Fragmentation—The Quiet Crisis
Jan. 23, 1996
John Terbough
Duke University.

The lectures are open to the public. A limited number of complimentary tickets will be available to the RU community; contact the Office of Public Affairs, x8967.

For more information, contact the Wildlife Conservation Society, 718-220-6891.

A bell tolls for peace



A replica of the Peace Bell, a symbol of rapprochement in Japanese and American relations after World War II, now adorns the office of President Emeritus Frederick Seitz. It is one of about 100 replicas of the original bells, which stand in Hiroshima and Oak Ridge, Tennessee. The bells are inscribed with the dates for Victory over Japan Day (V-J Day), Pearl Harbor, and the bombings of Hiroshima and Nagasaki; they also carry affirmations of friendship.

Award

(continued from page 1)

The Prince Mahidol Awards were established three years ago to commemorate Prince Mahidol, a doctor and member of the Thai royal family who brought modern medicine to Thailand in the first half of the 20th century. Two awards are given annually, one in medical science, which Trager received, and the other in public health, given this year to Ho Wang Lee, a Korean doctor honored for his contributions to Hanta virology.

Trager is a protozoologist who studies parasitic diseases transmitted by insect carriers. In 1976, his laboratory achieved the first continuous cultivation in vitro of the parasite responsible for human malaria, a crucial first step toward the development of a vaccine. Malaria afflicts 270 million people world wide, killing one million annually.

As the Mahidol Award recipient, Trager's activities included lecturing at the Mahidol University and Chulalongkorn Hospital, and attending banquets four nights in a row. "At each banquet, I was congratulated and asked for a few words. I tried to thank them differently every night," he said.

Trager and his wife, Ida, traveled to Chiangmai, a mountainous, less westernized region in the north of the country. Trager had previously visited Thailand in 1978, when he gave a course for the World Health Organization (W.H.O.) on cultivating malaria parasites.

Trager, who received his Ph.D. from Harvard in 1933 in biology, has spent his entire professional career at Rockefeller. His first appointment was as a National Research Council Fellow, in 1933; he became assistant professor in 1935, associate in 1940, associate member in 1950, associate professor in 1955, and professor in 1964. During World War II, he served as a captain in the U.S. Army Sanitary Corps, studying and treating servicemen infected with malaria. He became emeritus at Rockefeller in 1980.

Trager was elected to membership in the National Academy of Sciences in 1973. In 1980, the W.H.O. presented him with the 15th Darling Medal and Prize. In 1982, he received the First Rameshwardas Birla Triennial International Award of the Medical Research Centre of the Bombay Hospital Trust and the Leuckart Medal of the German Society for Parasitology.

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.

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Researcher probes resistance to "drug of last resort"

by Susan Blum

The crisis of antibiotic resistance is finally getting the attention it deserves. Much of the credit for raising awareness of the danger is due to efforts of the Rockefeller lab of Professor Alex Tomasz, where he and his colleagues have a long tradition of tracking antibiotic resistance and unraveling the molecular mechanisms that underlie it.

One issue under study in the lab is resistance to vancomycin. Vancomycin is often referred to as "the drug of last resort" because it is used to treat bacterial infections resistant to all other drugs. In 1986, French doctors reported the first appearance of vancomycin resistance, in a bacterium called *Enterococcus faecium*. Since then, enterococci with varying levels of vancomycin resistance have been reported worldwide, and their prevalence is rapidly spreading.

In the hospital setting, enterococci are the second most common cause of hospital acquired infections overall, including urinary tract infections, postoperative wound infections, and blood infections. They also cause infections in the community setting. Because many enterococci are now resistant to all other antibiotics, vancomycin is frequently the only drug available to combat them.

Vancomycin-resistant enterococci thus pose a grave health problem for people infected with the pathogens. But the threat does not stop there. As part of their modus vivendi, bacteria use many methods to transfer genes from one cell to another, and resistance genes are among the ones that travel.

Traveling genes

These genes can spread not only among pathogens of the same genus, but between genera, as well. So far, vancomycin resistance genes have not crossed genera, but there is no intrinsic reason why they could not do so in the future. Should they reach a pathogen such as *Staphylococcus aureus*—a major cause of bacterial infections that is now often resistant to all other drugs—the results could be truly disastrous.

Assistant Professor and clinical scholar Sandra Handwerger, a member of the Tomasz lab, specializes in the study of how vancomycin resistance operates and how it spreads. The story of her work goes back to the years between 1983 and 1985, when she was a postdoctoral fellow in the Tomasz lab. Aware of the lab's long-standing interest in antibiotic resistance, a researcher from elsewhere sent them what appeared to be a specimen of vancomycin-resistant streptococcus. Investigating further, the Rockefeller researchers learned that the bug wasn't strep but rather *Leuconostoc mesenteroides*, what Handwerger called "an organism of very little clinical significance."

Still, the Rockefeller researchers were fascinated. "It just seemed odd that one could have a vancomycin-resistant gram-positive bacterium at all," Handwerger recalled. (Because of differences between gram-positive and gram-negative pathogens, vancomycin is only effective in the former class.) Vancomycin works by binding to the final two amino acids of the molecular precursors used to construct the cell wall, thus blocking any subsequent steps in the complex biochemical reactions involved in building the structure that is vital to the bacterium's survival. Because these precursors were thought to be ubiquitous among all bacteria, and to be essential targets of the cell-wall-building enzymes, it was believed no bacterium could fight back against a drug that bound to them.

When Handwerger's postdoc was over, she took *L. mesenteroides* with her to Beth Israel Medical Center, where she started as a fellow in infectious diseases and rose to assistant division chief of infectious diseases. Given all the headlines now devoted to vancomycin resistance, it is ironic that in those early years, as she hoped to pursue the question of vancomycin resistance, a grant proposal of hers was rejected on the grounds that her topic was "of little biomedical relevance." But interest picked up after the first reports of vancomycin-resistant enterococci appeared in 1986, and Handwerger has continued to pursue the topic, first at Beth Israel and now back at Rockefeller since 1992.

Wide-ranging approach

Her studies have taken a wide range of approaches, from the biochemical to the genetic to the epidemiologic. For instance, she showed that resistant bacteria actually produce cell wall precursors that are different from normal, and pinpointed the exact nature of this difference. She identified and characterized one of the genes involved in the signaling system that tells resistance genes to turn on in the presence of vancomycin. And she is exploring how vancomycin-resistance genes get transmitted from one strain of enterococci to another—a line of research that is her current focus at Rockefeller.

Enterococci possess a number of types of vancomycin resistance. The most common type, and the one that leads to the highest level resistance, is called *vanA*. A host of genes are involved in *vanA* resistance. Some code for the mutant cell wall precursors, while others code for an enzyme that breaks down the normal precursors. Some code for components of the signaling system, and still others code for elements required for gene transfer. As researchers from the Pasteur Institute showed, all these genes reside on a transposon, a mobile element of DNA.

Assistant Professor Sandra Handwerger studies vancomycin resistance in bacteria.

The resistance genes on the transposon can be transmitted in a number of ways. As Handwerger showed in 1990, one way is by means of pheromone response plasmids—elements, unique to enterococci—that were first characterized by researchers at the University of Michigan. Plasmids are circular DNAs that are separate from the bacterial chromosome and can reproduce independently. Pheromones are signaling molecules. In the case of the enterococci, the recipient cell sends out a pheromone to which strains harboring the resistance plasmid respond. As part of this response, an "aggregation substance" is produced that clumps donor and recipient cells together, allowing the plasmid to move, or conjugate, into the recipient cell.

Conjugative mobilization is another mode of transmittal, currently under study by Handwerger and postdoctoral fellow Michael Heaton. In this case, the resistance genes are found on a plasmid that cannot conjugate on its own, but that can be mobilized to do so by another plasmid. "To my knowledge, this sort of mechanism has not been described in enterococci before," Handwerger says. Her team spotted it as part of their molecular epidemiologic studies of vancomycin-resistant enterococcal strains, and they are now trying to find out just how common a mechanism it is.

Worrisome prospect

They may also have identified still another method of transfer — one that Handwerger calls "the scariest." This method utilizes conjugative transposons. This type of transposon, which resides on the chromosome, can cut itself out of the chromosome, form a transient, circular form, move into another cell just as plasmids do, and then integrate back into the chromosome.

Conjugative transposons are so frightening because they are particularly "promiscuous," able to move easily into an unusually wide range of hosts, including *Staphylococcus aureus*. In a New York hospital, Handwerger and her colleagues recently found a vancomycin resistant enterococcal isolate that appears to use this mechanism. Should their analysis confirm its identity, and show it to be widespread, the implications could be dire, indeed.

Along with this work, Handwerger is collaborating with another Rockefeller clinical scholar, Steven Shiff, on the adhesion of vancomycin-resistant enterococci to the intestinal epithelium. Remarkably, the same pheromone response plasmid gene that permits the recipient and donor bacteria to stick together is responsible for mediating the bacterium's adherence to the host's intestinal cells. The researchers hope that it might eventually be possible to block this adherence, in order to reduce infection by vancomycin-resistant enterococci.

Such a strategy will not help people already infected with vancomycin-resistant enterococci. But Handwerger believes that a wide range of strategies are required to help stem the tide of antibiotic resistance. Some of these will be preventive; others, therapeutic. But whatever the approach, the challenge is great. Handwerger said, "The preantibiotic era made for a pretty cruel life. We're not used to the concept of people dying from bacterial infections." But with the rise of resistance, that concept has already become a reality.

World Wide Web opens new oceans of information for RU net surfers

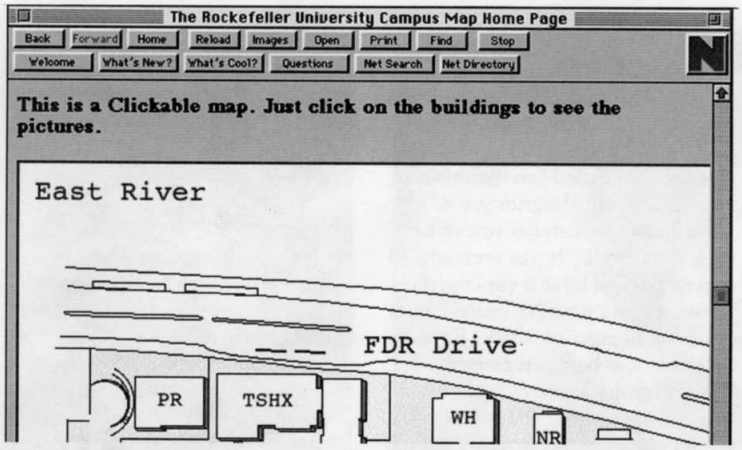
by Joseph Bonner

Click your mouse: You're off to Switzerland to look for a protein sequence. Click again: You get a picture of the protein from the Brookhaven National Laboratory. Click: You're looking into the eyes of the purchasing assistant you talk to every week but have never met. Welcome to the World Wide Web, the latest desktop on-ramp to the information superhighway.

Developed by the European Center for Particle Physics (CERN) as a way to share documents over the Internet, the Web is one of the easiest ways to browse and access information. "It's called a web because no matter where you are on the network, you're connected to everything else," said Anthony Popowicz, assistant director for scientific applications in Computing Services.

"The beauty of the Web is its ease of use," Popowicz continued. The most common entry into the Web is through a "home page" on a local server. Using a mouse, a user clicks on a highlighted word, phrase, or graphic (a "hyperlink"), which requests and retrieves a piece of information. The retrieved document may have links pointing to other documents on another server.

The RU server was produced by several Computing Services staff members (Popowicz, Mark Kowitz, Stuart Cohnen, Anne Duffy, and Alla Minkova.) The Rockefeller home page contains links to a clickable map of campus buildings, Web sites that contain information and tools for chemists and biologists, the Internet, and the RU phone book, which is an on-line version of the new photo directory. Popowicz said, "It's popular. People find it useful to see photos of their colleagues." Popowicz stressed that, for security reasons, access to the phone book is restricted to the university community.



Rockefeller's World Wide Web server contains links to the Internet, the RU phone book, and a map that, when clicked on with a mouse, displays digital images of campus buildings.

But just about everything else on the RU Web is available to people outside the university. Who visits RU electronically? Computing Services noted that for the week beginning Sun., Jan. 22, about 20,000 connections to the server were made and about 15,000 came from American universities. On-campus users requested over 5,000 connections.

The Web has opened up a new world for researchers. Through its network of links to information, scientists can search a data base of sequences, and download the results—whether a picture or a set of structural coordinates—to their desktop computers. David Fenyö, a research associate in the Chait lab, has written a home page called NYC–MASS, which contains links to Swiss-Prot, a data base of protein sequences in Geneva, Switzerland, and the protein structure data base at the Brookhaven National Laboratory. "It's under development now," said Fenyö. "We eventually want to set up our own mass spectrometry data base, which would be accessible to researchers all over the world."

Another Web browser at RU is Douglas Many, database analyst in the library. The library uses the Web to access newsgroups, bulletin boards, and on-line public access catalogs. Said Many, "I haven't used it much, but I was able to find two or three books that I could not have found otherwise."

Anyone using appropriate software can access the Web. Information and recommendations about software, much of which is free, and help with installing it can be obtained from the consultant in Computing Services, x8940.

With the Web, no road maps are necessary on the information superhighway. "The great thing is that you don't have to know the intricate details of how to get anywhere," Popowicz said. "You just point and click."

Potpourri

Tri-Institutional Noon Recital

Marina Piccinini, flute, and William Wolfram, piano, will perform the works of Aaron Copland, Richard Strauss, and Benjamin Godard at the Tri-Institutional Noon Recital today (Feb. 3). The concert, to be held in Caspary Auditorium at noon, is free. All are welcome.

David Hughes

Marina Piccinini (*above*) and William Wolfram will perform at the Tri-Institutional Noon Recital today (Feb. 3).

Clinical Research Seminar

Howard Worman, assistant professor in the Department of Medicine at the College of Physicians and Surgeons of Columbia University, will speak on "Molecular Cell Biology of the Nuclear Envelope: A Target Organelle for Autoantibodies in Liver Disease" Wed., Feb. 8 at noon at the Clinical Research Seminar in Nurses Residence 110B.

RU Concert

The Chamber Orchestra Kremlin will perform at Rockefeller Wed., Feb. 8 at 8:00 P.M. in Caspary. For ticket availability, call x8437.

Workshops

Computing Services workshops resume this month. They are free, but registration is required to ensure a computer to work on.
Introduction to the Macintosh: Thurs., Feb. 9, 10:00 A.M. to noon;
Introduction to Windows: Fri., Feb. 10, 10:00 A.M. to noon;
UNIX for Sequencers, Part I: Fri., Feb. 10, 2:00 P.M. to 4:00 P.M;
UNIX for Sequencers, Part II: Fri., Feb. 17, 2:00 P.M. to 4:00 P.M;
WordPerfect, Part I: Wed., Feb. 15, 10:00 A.M. to noon.
To register, contact Joan Falciano, x8925, or leave voice mail at x7768.

Information Server

The debut issue of *Information Server*, the quarterly newsletter from Computing Services, is now available. Copies may be requested from Amy Steingart, e-mail steinga.

Honor

Professor George A.M. Cross has accepted an invitation to serve as a member of the National Institutes of Health Tropical Medicine and Parasitology Study Section, Division of Research Grants. His term runs from July 1, 1994 to June 30, 1998.

Page

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joined the faculty at M.I.T. as an assistant professor and was promoted to associate professor in 1992. He has been an assistant investigator of the Howard Hughes Medical Institute since 1990 and associate director of the Center for Genome Research since 1992.

Page has received the MacArthur Prize, the Searle Scholar's Award, and the Leon Reznick Award. He is on the editorial board of *Human Mutation* and is a member of the Genome Review Committee of the National Institutes of Health.

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