"Uniting Academic Research"

ACADEMIC SCIENCE NEWS&REVIEW™

New York Edition

Serving NYU, Columbia, SUNY Stony Brook & Brooklyn, Mount Sinai, Cornell, Rockefeller, Einstein, North Shore, and Cold Spring Harbor & Brookhaven National Laboratories

Dec-Jan◆1997-8

Brookhaven Lab Management Contract Awarded to Stony Brook Team

Stony Brook-Battelle Team to Be Headed by Former Stony Brook President Marburger

by Kathryn Gavin

After suffering through a year during which Brookhaven National Laboratory could seem to do no right, the research lab's staff finally breathed a sigh of relief on November 25, when they learned that a coalition of SUNY Stony Brook and the Battelle Memorial Institute would soon take over the management of the troubled institution.

Although a legal hitch cited by the U.S. Department of Energy will hold up the formal award of the contract until early January, the announcement eased some of the tension at Brookhaven. The official contract award will pave the way for the new team, called Brookhaven Science Associates (BSA), to take over fully 60 days afterward.

In discussing the contract announcement, the Lab's employees and visiting scientists stressed their belief that the changing of the guard and the involvement of a Long Island-based university bodes well for the Laboratory's often rocky relationship with local elected officials, most notably U.S. Representative Michael Forbes and Senator Alfonse D'Amato.

In fact, in response to the announcement, D'Amato deemed the award "magnificent." Forbes was more circumspect, challenging BSA to avoid the mistakes in environmental management and community relations made by the outgoing contractor, Associated Universities Inc.

Energy Secretary Federico Peña announced in April that AUI's contract, which had been renewed consistently since BNL's founding in 1947, would be terminated because of deficiencies in those areas.

Several internal and external environmental investigations have been conducted at the Lab in the wake of the discovery of low-level radioactive groundwater contamination emanating from the spent fuel pool at the 30-megawatt High Flux Beam Reactor, a research reactor

Continued on Page 5

Researchers Discover Another 'Mismatch' Repair Gene Linked to Inherited Cancer

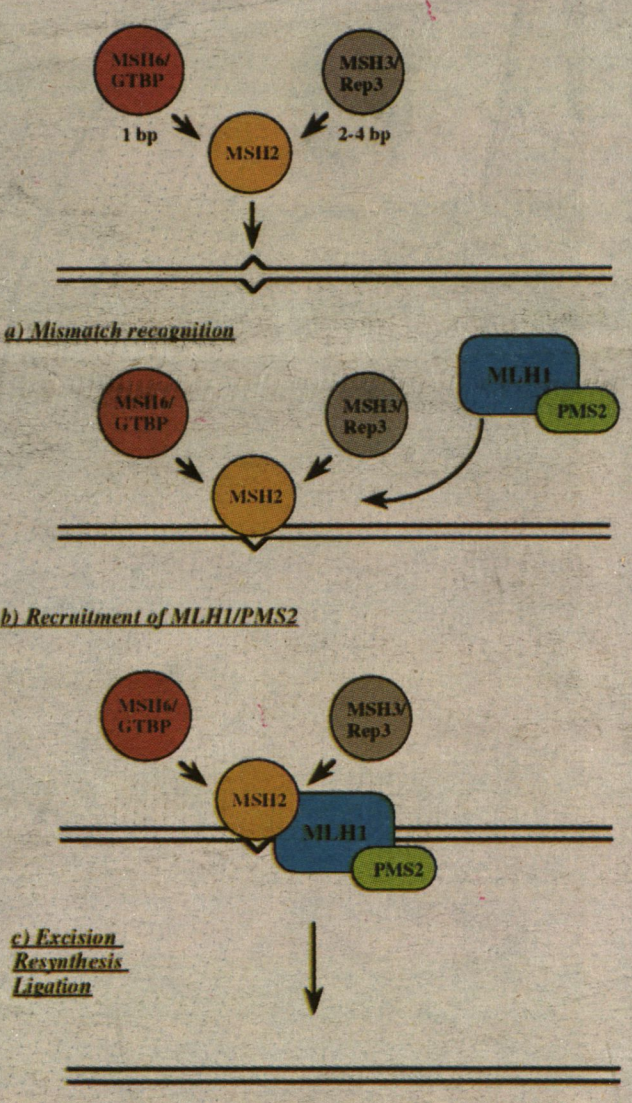
Mutation of the MSH6 Gene Found to Cause Colon Cancer Susceptibility

by Dan Coulter, *ASN&R* Staff Writer

A multi-center team of scientists led by researchers at the Albert Einstein College of Medicine has shown that mutations in a gene called MSH6 — a member of the mismatch repair gene family — can lead to cancer susceptibility, particularly for hereditary non-polyposis colon cancer (HNPCC). The team's finding is reported in the November 14 issue of the journal *Cell.*

The mismatch repair gene family was first discovered in yeast and bacteria, and has been a topic of study for over forty years. Mismatch repair genes and their associated enzymes function to assure the accuracy of DNA replication. In *E. coli*, for example, mismatch correction enzymes encoded by the genes mutH, mutL, and mutS bind together to form a complex. This complex scans newly replicated DNA for mismatched base pairs, and removes the single-stranded segment containing the wrong nucleotide(s). This, in turn, allows DNA polymerase to insert the correct base(s) to fill the gap. For example, the nucleotide adenine (A) normally binds with thymine (T) during replication. If, however, the mismatch enzymatic complex detects an A-A bond, it would replace the incorrect A nucleotide with a T nucleotide in the newly replicated strand of DNA.

Model for Eukaryotic Mismatch Repair



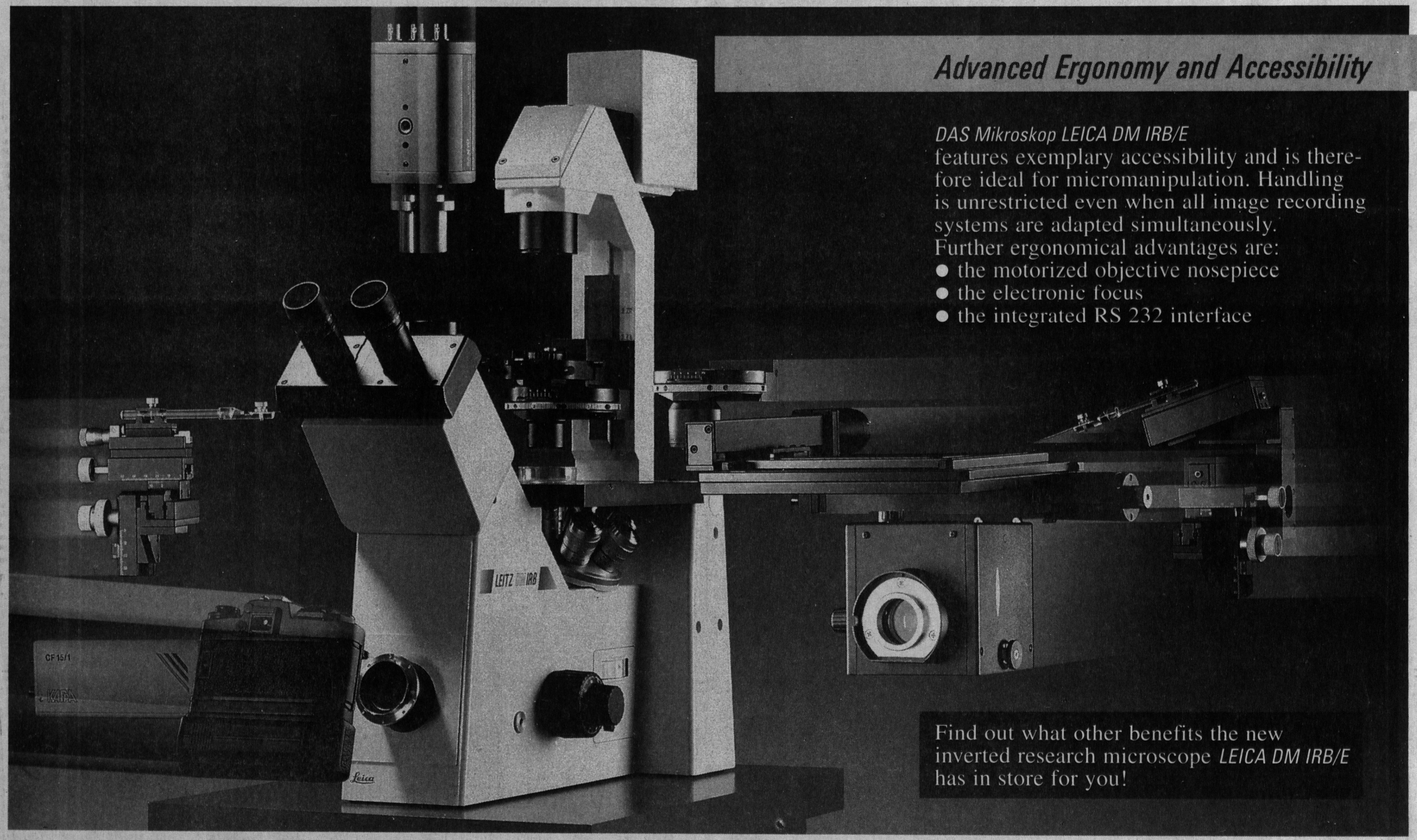
The model depicted proposes that the repair of base-base mismatches is initiated by a complex between MSH2/MSH6, and repair of 2 to 4 base pair insertion/deletions is initiated by a complex between MSH2/MSH3. In subsequent steps a complex between MLH1/PMS2 is recruited and the mismatch is corrected by the excision of the newly synthesized strand, DNA resynthesis and ligation.

Not until the 1990s did researchers discover a family of mammalian mismatch repair genes that are homologous to those found earlier in bacteria and yeast. This family of genes includes: MSH1 - MSH6, MLH1-MLH3, PMS1 and PMS2. Genes such as MSH2, MLH1, and MSH6 have been shown to form a mismatch repair complex that corrects mismatched DNA very much as do the systems found in bacteria and yeast.

Interest in the mismatch repair genes was significantly enhanced in

Continued on Page 4

Inside...



Advanced Ergonomy and Accessibility

DAS Mikroskop LEICA DM IRB/E
features exemplary accessibility and is therefore ideal for micromanipulation. Handling is unrestricted even when all image recording systems are adapted simultaneously.
Further ergonomical advantages are:

- the motorized objective nosepiece
- the electronic focus
- the integrated RS 232 interface

Find out what other benefits the new inverted research microscope *LEICA DM IRB/E* has in store for you!

Leica Inc.
111 Deer Lake Road
Deerfield, Illinois 60015
800/248-0123 FAX 847/405-0147

Leica Canada Inc.
513 McNicoll Avenue
Willowdale, Ontario M2H 2C9
416/497-2460 FAX 416/497-2053

Leica

Earthquake or Nuclear Bomb?

Columbia Scientists Dispute Finding That Aug. 16 "Event" Was Russian Nuclear Test

by Columbia News Services

Two seismologists at Columbia University's Lamont-Doherty Earth Observatory, writing in the British journal *Nature,* have concluded that a seismic event on Aug. 16 north of mainland Russia was an earthquake, not a nuclear test.

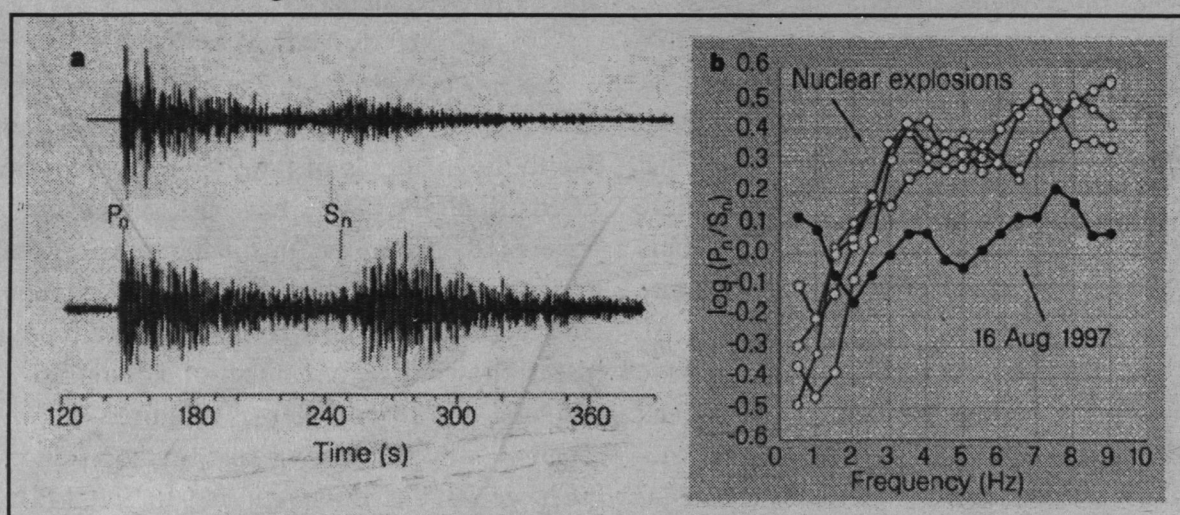


Figure 2 a, Waveforms for a Soviet-era nuclear explosion at the Novaya Zemlya test site (top, 24 October 1990, 1,048 km) and for the 16 August event (bottom, 1,127 km), recorded at the same station, KEV, in northern Finland. b, Spectral ratios for a few nuclear explosions, and for the 16 August event, at KEV. Although no earthquake records from KEV were available for reproduction here, the weaker P/S ratio of the 16 August event is a well documented characteristic of earthquakes[3,5]. KEV is a station in the global network operated jointly by the USGS and the IRIS consortium of US academic institutions.

Seismic monitoring stations detected the event, which appeared to be in the vicinity of Novaya Zemlya, an island that is the site of a Russian nuclear weapons testing facility. Newspaper reports quoted government sources describing the event as having "explosive characteristics" and a Clinton Administration spokesman maintained that technical data could be interpreted to support either the hypothesis of an earthquake or a nuclear test.

Had the event indeed been a nuclear explosion, it would mean the Russian government had violated the terms of the Comprehensive Test Ban Treaty (CTBT), an agreement laboriously negotiated over the last two decades by the United States, Russia and other nations that bans such testing.

Analysis by the two Columbia researchers, Paul Richards and Won-Young Kim, seismologists who specialize in nuclear test verification, shows the seismic event was actually a small earthquake. The research, published in the Oct. 23 issue of *Nature,* demonstrates that scientists have excellent capability to monitor such events in the vicinity of Novaya Zemlya, they said.

Other scientific views at odds with the U.S. government's interpretation of the Aug. 16 event have been reported in the Washington Post and the New York Times. The *Nature* report is based on one of the first independent tests of a new International Monitoring System (IMS) that is being developed to verify the CTBT. The system is a global network of sensitive instruments designed to detect the various physical and chemical fingerprints of nuclear weapons tests.

Data from these instruments are to be analyzed by the treaty participants in order to determine compliance with the test ban. Since nuclear explosions can produce signals that may look like an earthquake, scientists must learn to differentiate between the two, the scientists said.

Dr. Richards, the Mellon Professor of Natural Sciences, saw the Aug. 16 event as an opportunity to test the capabilities of data obtained both from IMS and non-IMS sources to monitor nuclear tests under the test ban treaty. In the *Nature* article, he and Dr. Kim, associate research scientist, state: "The ease of location and identification of the 16 August event, with a magnitude of about 3.5, demonstrates that the CTBT can be monitored near the Russian test site down to magnitude 3, and maybe even lower. . . . So the 16 August event indicates excellent capability to monitor the CTBT." Seismologists use the Richter scale to measure the size of both explosions and earthquakes; a magnitude of 3.5 corresponds to an explosive yield of about one-twentieth of a kiloton.

The Columbia seismologists drew on several lines of evidence to verify that the event was not an explosion. First, the scientists compared seismic recordings of the questioned event with the recordings of a known nuclear explosion set off by the former Soviet Union in 1990. Drs. Richards and Kim noted differences in the delay between the first arriving seismic shocks (P-waves) and ones arriving later (S-waves). The recordings, from a Finnish monitoring station west of Novaya Zemlya, showed that S-waves from the 1997 event took 8 seconds longer to reach the station than those from the 1990 nuclear test, indicating that the more recent event was in fact nearly 100 kilometers, or about 62 miles, east of the test site.

Additional work by other seismologists located the epicenter some 50 kilometers to the southeast of Novaya Zemlya, in a part of the Kara Sea nearly 400 meters deep. An explosion of this size located under water would produce a large acoustic signature that would be picked up by sensitive seafloor microphones maintained by

Continued on Page 18

FEATURES

Dec-Jan 1997-8

Mismatch... Continued from Page 1

the early 1990s by the discovery that mutations in some of the mismatch repair genes, MSH2 and MLH1, lead to a genetic predisposition for HNPCC. Families susceptible to HNPCC pass the mismatch repair gene mutations along to a certain proportion of each generation, and these offspring thereby become far more likely to develop not only cancers of the colon, but of the endometrium, ovaries and other sites as well.

"If you look at patients with colonic tumors," said Dr. Raju Kucherlapati, chairman of molecular genetics at Einstein, " a very large proportion of them — 80 to 85% — develop those tumors from polyps. There is a subset who do not have polyps. These genes — MSH2, MLH1, and MSH6 — are involved in that segment of patients with non-polyposis." Normally, it takes about 10 years for a tumor to develop from a polyp. "In HNPCC cases however, the development of tumors is much more rapid in the sense that you don't see the polyp phase at all" adds Dr. Kucherlapati.

One of the hallmarks of HNPCC is that the tumors show genetic instability — also called microsatellite instability, while other types of tumor do not show this type of instability. Microsatellite instability can be defined as an inconsistency in the amount of "microsatellites" passed onto daughter cells following cellular division. A microsatellite is a segment of DNA where a repeated element such as, for example, a cytosine (C) followed by adenine (A) sequence repeats approximately 10-20 times. On the average, there is one microsatellite every 50,000 base pairs. If a microsatellite in a parent cell has, for example, 15 C-A repeats, the two daughter cells following division should also contain 15 repeats each on that given segment of the genome. Microsatellite instability in the subsequent offspring occurs when the number of actual repeats differs from the expected 15.

Previous studies of HNPCC patients have shown that mutations in genes MSH2 and MLH1 are very common, and are also characterized by a high level of microsatellite instability. Mutations of the gene MSH6, on the other hand, had not been necessarily observed in HNPCC families. Though mutations in this gene had been observed in a small number of human colon tumor cells, mutations in other genes also had been found in those lines. It therefore remained a matter of debate whether mutations in MSH6 play any role in cancer susceptibility. As a result, studies on the mismatch repair complex containing the gene products from MSH2, MLH1, and MSH6 have traditionally focused on genes MSH2 and MLH1, because of their easily detected genetic instability when mutated.

OF MICE AND MANKIND

Scientists such as Dr. Kucherlapati suspected the possibility of a role for the MSH6 gene due to the hundreds of families with predispositions to HNPCC that have not shown mutations in the common mismatch repair genes implicated to that time. "So we ask," explains Dr. Kucherlapati, "how come there is a protein that is known to be a member of a complex — and this whole complex is required for the repair — why is it that we find mutations in the other genes but no mutations in the MSH6 gene?"

To answer this question, the team generated so-called knockout mice — mice that were

Continued on Page 9

Academic Science News&Review–New York Edition

A Monthly Publication Dedicated to Academic Research in the Sciences.

Publishers
Peter S. Bernstein
Matthew S. Seidner

Editor-in-Chief
Peter S. Bernstein

Staff Writers
Elizabeth Belton
Dan Coulter
Ilana Harrus
Jeremy Kay

Contributors to this Issue
Sharon Cleary
Donna Carty
Kathryn Gavin
Chris Verzulli
Faye Yates
Peter Saal

Calendar Editor
Daniel Huber

Advertising
Cheryl Frank, Director
Stephanie Rubino

Academic Science News&Review–New York Edition, 2780 Middle Country Road, Suite 213, Lake Grove, NY 11755
(516) 737-3415 editor@pdpub.com FAX (516) 737-3414

Brookhaven...Continued from Page 1

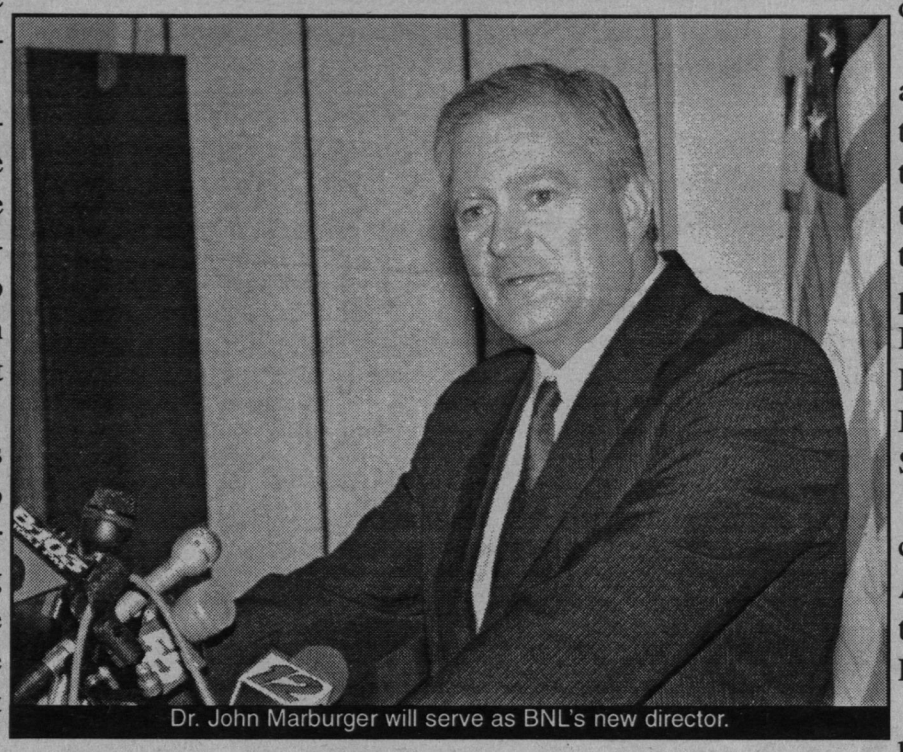
once used by over 250 scientists each year but now off-line awaiting Peña's decision on its fate. The installation of past SUNY Stony Brook president John Marburger as BNL's new director was also met with approval. He emphasized BSA's plans for real change at the Laboratory, not just improved appearances.

"Community involvement, environmental health and safety [which] were less important in the first 50 years are going to be just as important as the science," he said. "And it is possible to give these things the kind of attention that they deserve and need without diminishing the quality of the science."

Marburger added that he "welcomes the opportunity to guide the Lab . . . into a new way of doing things that better fits the kind of world that we are living in today." BSA, he said, has to make Brookhaven "more competitive, more efficient, more effective and must inspire confidence."

He continued, "The kind of attention to detail, the need to know within context, the . . . hunger for being the best that drives good science can also be captured to drive good operations. . . . The elements of caring, of intelligence and of the desire to be the best that already exist here at Brookhaven . . . [can] drive a future that is every bit as glorious as the past."

BSA will operate the Laboratory for the DOE for a fee of $5.3 million, $1 million more than AUI. The increased fee will come out of the Lab's existing $400 million budget, prompting some concern about belt-tightening in an already cash-strapped institution. Peña's April guarantee that the transition to the new contractor would not result in any loss of jobs among the 3,200 employees for one year was somewhat reassuring, but doubts remain about the future beyond that year.



Dr. John Marburger will serve as BNL's new director.

The one-year job guarantee does not apply to the Lab's top management, and the organizational chart unveiled on the Nov. 25 did feature some new faces. Marburger will have two deputies — one, Stony Brook Physics Department chairman Peter Paul, for science, and the other, Battelle's Thomas Sheridan, for operations.

While the three basic-science associate directors will retain their titles, a fourth scientific associate director, Battelle's Adrian Roberts, will fill the new slot for applied science and technology. Two new assistant director positions, for Environment, Safety and Health and Environmental Management, will be taken by Battelle's Kenneth Brog and Michael Schlender, respectively.

To fulfill BSA's goal of improved community involvement, BNL Public Affairs Manager Marge Lynch will rise to Assistant Director for Community Relations and Public Affairs.

Over the on-site directorate will be BSA's board of 16 directors, headed by current Stony Brook president Shirley Strum Kenny. Both Stony Brook and Battelle will appoint five directors each, with the remaining six drawn from core universities Columbia, Cornell, Yale, Harvard, Princeton and the Massachusetts Institute of Technology.■

Examining the Future of Digital Television (DTV)

Conference Attendees Discuss Economics, Content, and Technology

by Sharon Cleary

Digital television (DTV) is beginning to span the globe. The technology is reaching homes via satellite, terrestrial broadcast, cable, Internet and DVD. Will a worldwide standard emerge? Will server-based TV result in a broader spectrum of broadcast voices or will mass-market media companies continue to dominate broadcasting? On November 13th, academics, cable network representatives and electronics manufacturers converged upon the Columbia Institute for Tele-Information at Columbia University to participate in a day-long conference regarding the future of digital television (DTV).

At a conference on the future of digital television held at Columbia, Eli Noam, Professor of Finance and Economics at Columbia University Graduate School of Business, gives his opening remarks.

Attendees remained attentive as four expert panels discussed applications of DTV: The Changing Economics of TV Industries, Impact of DTV on Content and Programming, Delivery Systems and Technology Issues and an International Perspective of the technology. The conference addressed questions sparked by the Telecommunications Act of 1996 in which the Federal Communications Commission requires all television stations in the US to begin converting from analog to digital broadcasting. The panelists attempted to outline the ramifications of the new technology on television broadcasting. Based on the dissent voiced during the panel discussions, the future of digital is unclear and depends upon numerous factors, including consumer interest, federal and international regulations and commercial investment.

The reason digital is now an important option is twofold. First, this sort of transmission results in a picture that contains twice the amount of vertical and horizontal pixels as an analog-transmitted picture. Secondly, numerous analog channels can be transmitted over the bandwidth required for a single digital channel, thus allowing for simultaneous broadcast of different television programs. Some experts hope that this will allow for niche broadcasting. These innovations have varying meanings for broadcasters as well as technological innovators.

Opening remarks at the conference were given by Eli Noam, Professor of Finance and Economics at Columbia University Graduate School of Business, and Director of the Columbia Institute for Tele-Information. His brief introduction stressed DTV content and its potential to reach niche audiences, as well as the possibility of the technology being accessible to compartmentalized industries. Throughout the conference the stress remained on content and technology distribution, but few panelists agreed on their approach.

WHO WILL PROFIT FROM DIGITAL TELEVISION?

The changing economics of the television industries was one of the key issues addressed. W. Russel Neuman, Professor of Communications at the Annenberg School for Communications at the University of Pennsylvania, discussed the allocation of spectrum to broadcasters. Title II of the Telecommunications Act of 1996 gives away about $7 billion dollars worth of spectrum to organizations who have broadcast licenses for unspecified "advanced broadcasting services." Wireless telephone providers, who arrived later in the game, must place bids in a spectrum auction. Why the freebies to the big broadcasters? Neuman states, "the short answer, of course, is that they are politically powerful."

Gary Poon of PBS is not a supporter of the spectrum giveaway because he is concerned that "there is a widening gap between the haves and have nots." Rather than a giveaway, Mr. Poon proposes that the FCC charge broadcasters for spectrum in order to build the infrastructure necessary to transmit digital video. Professors Neuman and Waterman agreed. Waterman added that price discrimination would be a key factor in the widening gap between haves and have nots.

Francine Sommer of Gabelli Multimedia addressed the possibility that the smaller broadcast companies could be squeezed out of business by a spectrum giveaway. She mentioned that there are so many forms of digital distribution — such as wireless caps, line caps, cable, and satellite — that it's too expensive for smaller companies to continue pouring money into potential digital distribution methods without the certainty of financial gain. As a smaller operator, she remarked, "Greed drives me." Larger companies who are receiving spectrum have deeper pockets. A small multimedia company, while happily committed to innovative uses of digital television, is at a distinct economic disadvantage until a single means of distribution is decided upon. An industry standard is needed.

Analysts hope that auctioning spectrum will become the primary form of allocation, but Neuman believes that "the road ahead is not clear and unobstructed. In upcoming years, spectrum allocation may be an intertwined system — legacy and innovative, specific-use and flexible-use frequency fragments in a chaotic spectrum brew." Neuman relies on the future Telecommunication Act of 2006 to determine precisely what that brew will be.

WHAT WILL DIGITAL TELEVISION LOOK LIKE?

The second panel continued the debate between mainstream and niche broadcasting of digital television programming. The economics of digital television cannot be satisfactorily worked out until broadcasters have determined what will air on DTV. Like the Internet, this question is impossible to resolve without a good deal of trial and error. Thus, numerous suggestions were made with differing results. The ensuing differences boil down to two options for the content broadcast. The full amount of bandwidth may be spent to render a digitally clear picture, or the same amount of bandwidth may be used for multicasting, which allows for numerous (3 or 4) analog signals to be transmitted via a single digital channel. The content corresponding to each option is vastly different in terms of approach.

John Carey, Director of Greystone Communications, is a proponent of multi-casting. He discussed the organization and display of content on digital television and envisions a channel page, much like what exists on AOL, which will allow watchers to choose which television feature they would like to watch. Carey's user interface could apply to all sorts of DTV interactive content.

Panelist Robin Mudge, Executive Director of BBC Digital Media, uses a similar interface in his experimental work in BBC education. When viewers tune into a program called "Science Zone," they directly affect what happens in the program they are watching. "Science Zone" offers different versions of a linear narrative, each has the same beginning, but the middle and end vary depending on the choices the viewer makes. Moreover, an intelligence management system builds a profile of the viewer. The BBC technology recuts the principal narrative of "Science Zone" on the fly depending on the profile created. Much like news retrieval intelligent agents on the Internet, the system knows what the viewer is watching and anticipates what decisions the viewer will make.

A second program, an exercise show, encourages viewers to input their height, weight, and level of health and frequency of physical activity via a specialized remote control. The personalized

Continued on Page 19

OVER ONE MILLION OF THE BEST MINDS IN AMERICA HAVE ALREADY CHOSEN THE BEST RETIREMENT SYSTEM.

TIAA-CREF.

Nearly 160 Nobel Prize winners – and 1.8 million other forward thinkers – count on us to help them plan a comfortable future. With $170 billion in assets, we're the world's largest retirement company, the nation's leader in customer satisfaction, and the overwhelming choice of people in education, research and related fields.*

The reason? For more than 75 years, TIAA-CREF has introduced intelligent solutions to America's long-term planning needs. We pioneered portable benefits. We invented the variable annuity and helped popularize the very concept of stock investing for retirement planning.

Today, TIAA-CREF's expertise offers an impressive range of ways to help you create a comfortable and secure tomorrow. From the guarantees of TIAA's top-rated Traditional Annuity** to the additional growth opportunities of our nonguaranteed investment accounts, you'll find the flexibility and diversity you need to help you meet your long-term goals. And they're all backed by some of the most knowledgeable investment managers in the industry.

To learn more about the world's premier retirement organization, speak to one of our expert counselors at **1 800 842-2776** (8 a.m.-11 p.m. ET). Or better still, speak to one of your colleagues. Find out why, when it comes to planning for tomorrow, great minds think alike.

Visit us on the Internet at www.tiaa-cref.org

TIAA CREF

Ensuring the future for those who shape it.℠

*Source: DALBAR, Inc., *1995 Consumer Satisfaction Survey*, in which 96% of respondents expressed overall satisfaction with TIAA-CREF.

**TIAA is one of only a handful of companies that currently hold the highest marks from the nation's leading independent rating agencies for stability, sound investments, claims-paying ability, and overall financial strength: A++ (Superior), A.M. Best Co.; AAA, Duff & Phelps; Aaa, Moody's Investors Service; AAA, Standard and Poor's. TIAA's guarantees are backed by its claims-paying ability. These ratings of TIAA as an insurance company do not apply to CREF. CREF certificates are distributed by TIAA-CREF Individual and Institutional Services, Inc. For more complete information, including charges and expenses, call 1 800 842-2733, extension 5509, for a prospectus. Read the prospectus carefully before you invest or send money.

New Research Suggests Ways to Speed Regeneration of Damaged Nerve Cells

Implications Seen For Patients With Palsies and Other Nervous System Diseases

by Donna Carty, Ph.D.

On October 27, at the annual meeting of the Society for Neuroscience, Dr. David Weinstein, assistant professor of neuroscience at Albert Einstein College of Medicine, presented research demonstrating a way of inducing speedier and more extensive regeneration of damaged myelinated peripheral nerves. Such research offers hope for patients with facial nerve and other palsies caused by damage to the peripheral nervous system and may open the way for progress towards regeneration of nerves in the central nervous system.

As background for this work, it is now clear that damaged myelinated peripheral nerves can regenerate and reinervate their target tissues. However, the greater the damage to the nerve, the slower and the less complete is the recovery of function that occurs.

When a peripheral nerve pathway is damaged, both the nerve axon and the myelin sheath disintegrate and are reabsorbed. The target organ is left without the particular aspect of communication with the central nervous system which had been contributed by that nerve.

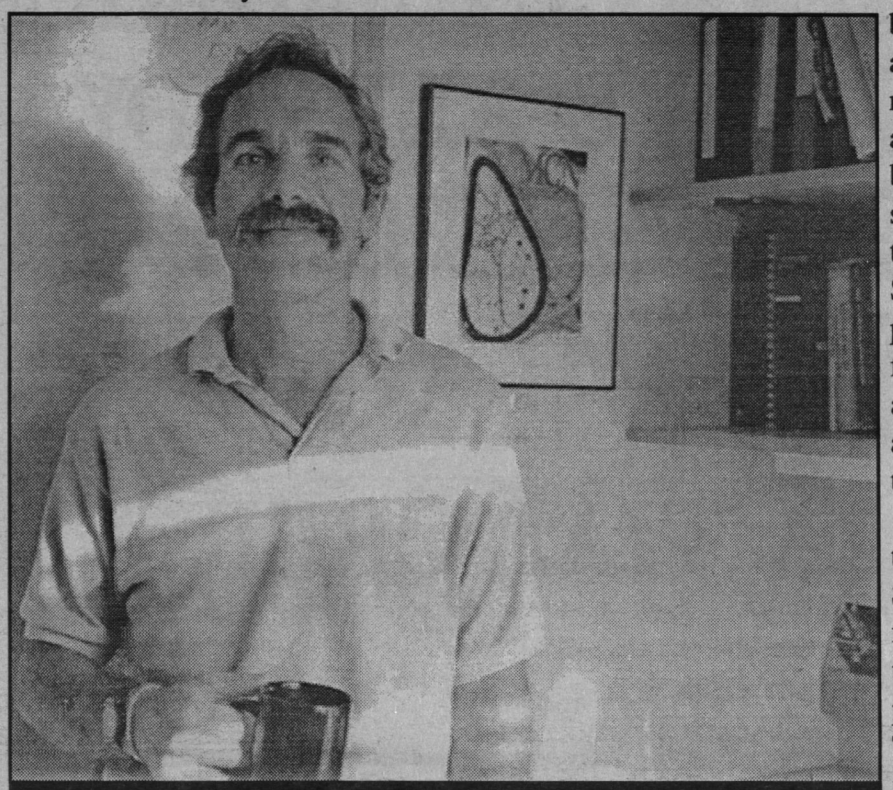
Recovery of function requires not only re-extension of the damaged nerve axon, but the support, guidance and remyelinization of the developing re-extension by Schwann glial cells as well. The re-extending nerve axon follows a pathway of newly proliferated Schwann cells to reach its former target, and is also myelinated by those same Schwann cells. The slowness of regeneration can also contribute to incomplete recovery of function, since the target organ may degenerate during the absence of nerve impulses.

Dr. Weinstein and his colleagues were able to induce improved regeneration of the crushed sciatal nerves in the mouse leg by causing two of the steps in regeneration that usually take place in succession to occur together. To accomplish this, they created a mutant version of the SCIP transcription factor gene that controls the timing and succession of Schwann cell proliferation and the production of myelin.

Under the control of the SCIP (suppressed cyclic-AMP-induced POU) gene, myelin production does not begin until Schwann cell proliferation is complete. The altered gene allows the two events, both essential for effective nerve regeneration, to occur at once in transgenic Schwann cells containing the mutant gene.

To control the pathway of regeneration, Dr. Weinstein and Dr. Robert Goldstein, a microsurgeon at Einstein's Jack D. Weiler Hospital, introduce the transgenic Schwann cells inside a specific conduit. The regenerating nerve axon, following the conduit, is sure to reach its proper target, thus regenerating the crushed sciatal nerve in the mouse leg.

The result of combining the Schwann proliferation and myelin-producing steps, and guiding the regeneration along its proper pathway, is significantly faster and more extensive regeneration of the nerve pathway. Dr. Weinstein and his colleagues hypothesize that this dramatically improved regeneration is due to a a factor produced by the mouse Schwann cell.



Dr. David Weinstein, Albert Einstein College of Medicine

Attempts to expand upon this work are already underway. Marjorie Gondre, a graduate student in Dr. Weinstein's laboratory, is currently involved in searching for a protein with which SCIP associates. In addition, Rita Wu, a postdoctoral fellow, is investigating other molecules that are regulated in pro- myelination, the period of Schwann cell proliferation preceeding myelin production.

Since the altered SCIP gene can be introduced into Schwann cells from the animal which has suffered the nerve damage, there is no problem with immunological incompatibility of the transgenic cells. Dr. Weinstein noted that the same mutant gene can be introduced into human Schwann cells. He added that the his group is currently establishing an experimental plan to introduce the altered cells back into patients with nerve palsy.

Because oligodendrites fill a role similar to Schwann cells in the central nervous system, producing myelin in accord with similar genetically timed events, it is possible that research into such controls could eventually contribute to the development of strategies to encourage regeneration in the damaged central nervous system.

Researchers must also deal with differences in regeneration following crush-injury to the nerve and that following severance. For example, myelinization and nerve-sprouting processes differ here.

Myelinated peripheral nerve axons require the support and guidance of Schwann cells (a type of modified glial cell), in order to re-extend from the point of damage to their target tissues. Schwann cells are also responsible for producing the multilayered myelin sheath of "insulation" that surrounds the nerve axon "wiring". This sheath greatly increases the velocity and conduction of nerve impulses as well as decreasing the metabolic cost of transmission of nerve impuses.

Within 24 hours of an injury, Schwann cells begin dividing, elongating, and migrating as a bundle toward the cut-off end of the nerve. The remaining intact neuronal axon begins to regenerate by reaching out blindly in all directions with a bush of sprouts from the damaged axon stump. If the damage resulted from a crush injury, Schwann cells marking the original nerve pathway may still be in place and easily found by one of the nerve sprouts. Since a Schwann cell will only myelinate one axon, sprouts heading in the wrong direction will degenerate.

A complete break is more difficult to repair. Axonal sprouts, failing to find a Schwann cell for support and guidance, follow confused paths. They may form a tangle with scar tissue, a neuroma, and be painful or obstruct proper reinnervation. They may reach out so far that they find the wrong Schwann cells and end up innervating the wrong tissue. And if the process of regeneration takes too long, the correct target organ may have degenerated. Muscle, in particular, will atrophy and degenerate if left without innervation for longer than 20-24 months.

In general, following a crush injury, nerve regeneration begins within a day and proceeds at the rate of about 1-2 mm/day. In the case of a complete break, regeneration does not begin for one week. It then proceeds more slowly than regeneration following a crush injury.

Once the nerve reaches its target, regeneration of function may be further delayed by the need for remyelinization. A single Schwann cell in the peripheral nervous system provides myelinization for 1 mm of axon. Though Schwann cells begin proliferation within a day of injury, and peak within a week, their speed of proliferation then falls rapidly. In general, regeneration of function proceeds at the rate of 4 cm per month.

Speeding up the process of regeneration by allowing myelination of the re-extending axon, while the proliferation and migration of the Schwann cells extending the pathway to the target is still in process, increases the chance of recreation of the original nerve pathway, and of reaching the target tissue before degeneration has occurred. Further, controlling the pathway of nerve regeneration increases the liklihood of complete functional restoration. Combined with advances in the prevention of CNS deterioration following injury, this research may ultimately contribute to a strategy for restoration of CNS function.■

Mismatch... Continued from Page 4

missing both copies of the MSH6 gene. The team found that 90 percent of the animals developed a spectrum of tumors, especially gastrointestinal tumors and B- and T-cell lymphomas. The team also found that the development of these tumors was delayed in comparison to tumors resulting from MSH2 and MLH1 mutations. Another significant finding was that these tumors did not show any microsatellite instability.

Dr. Kucherlapati explains, "It turns out that there are two types of mismatch repairs that this complex is involved with. The first is insertion/deletion mismatches which are characterized by multinucleotide mismatches, and the second is single nucleotide mismatches. For instance, if a parent cell has a microsatellite with 12 repeating C-A sequences, and the daughter cells have 14 repeating C-A sequences, this is a multinucleotide mismatch that results in microsatellite instability. Both gene products from MSH2 and MLH1 are required to correct this type of mismatch, but the protein from MSH6 is not required. MSH6, on the other hand, is required only when single nucleotide mismatches are present. It therefore has a unique function. However, if a single G-T match occurs — representing one pair of incorrectly matched nucleotides — MSH6 would be required to repair this type of mismatch. Yet if the MSH6 protein is absent, these single nucleotide mismatches cannot be repaired, and an accumulation of mutations in those cells will eventually lead to cancer."

Because the mismatch repair system in mice is homologous to that of humans, the team was eager to learn whether the finding would prove true for people as well. "So what we predicted then, based upon results from the mice experiments," comments Dr. Kucherlapati, "is if you look at human patients who develop these tumors a little bit later than the conventional type of HNPCC patient, you might find mutations in MSH6. We also predicted that the tumors from these patients will not have microsatellite instability like those we are seeing in the other genes. This has been tested and we find that, first, human patients who have mutations in the MSH6 gene develop tumors; second, they do not show microsatellite instability; and third, these people usually develop tumors much later than other HNPCC patients. So basically, we really identified another gene whose absence or mutation would lead to cancer or a predisposition to cancer." There are two other groups in Japan who have reported similar results as well.

The team's findings could have implications not only for hereditary cancers caused by mutations in germ-line cells, but also for certain "sporadic" cancers which are not characterized by microsatellite instability. The finding promises to aid diagnosis, and to open a new path for research in cancer predispositions and development in humans.

Dr. Kucherlapati concludes: "In humans, if you want to study diseases such as colon cancer, it becomes very complex due to the tremendous amount of genetic variability in the human population, coupled with environmental components such as foods, that ultimately influence the development of the disease. Trying to sort out whether it is a genetic difference or an environmental difference is very complex. When you study the mouse, however, you can have a uniform genetic background, and they eat what you feed them. You then can normalize all of those variables. Mouse genetics really helped us and also pointed us in a direction to look at particular classes of human patients - this doesn't happen very often and this is a nice situation."

Dr. Kucherlapati's primary co-author on the *Celll* paper is Dr. Winfried Edelmann, assistant professor in the Department of Cell Biology at Einstein. Another key contributor is Dr. Richard Kolodner, a noted cancer researcher now associated with the Ludwig Instituite for Cancer Research in La Jolla, CA. Other contributors include Kirkland Lau, Joerg Heyer, Wolfgang Liedtke and Jeffrey Pollard, all at Einstein; Kan Yang, Kunhua Fan and Martin Lipkin of Strang Cancer Research Laboratory of Rockefeller University; Asad Umar and Thomas Kunkel of the NIH; Michael Kane, now at the Ludwig Institute; and Nianjun Ye and Gray Crouse of Emory University in Georgia.■

THE WEAKNESS OF C IV ABSORBER CLUSTERING IN KECK HIRES SPECTRA OF ADJACENT QUASAR SIGHT LINES

Crotts APS. Burles S. Tytler D.

Astrophysical Journal. 489(1 Part 2):L 7-L 11, 1997 Nov 1.

We observe with Keek/HIRES the z approximate to 2.5 QSO triplet 1623+27 in order to explore on the scale of 1 Mpc the spatial clustering of C Iv absorbers between adjacent sight lines. We find this signal to be significantly weaker than the clustering in velocity on corresponding scales along single sight lines, assuming that the relative velocity of absorbers in dominated hv the Hubble flow Thin indicates that small-scale clustering (200 km s(-1) < Delta v < 600 km s(-1)) of the C Iv absorbers cannot be interpreted in terms of the positions of the absorbers in space but must be considered as internal motions within individual absorbers or within clusters of absorbers whose internal velocities dominate over Hubble expansion across the cluster scale. If the single sight line signal is due to spatial clustering, it is caused by absorber clusters smaller than would be implied by their velocities if a Hubble flow is assumed. The spatial clustering of C Iv absorbers at z approximate to 2 is consistent with data on Ly alpha forest clustering measured in the same way at the same redshifts. However, present-day galaxy clustering, evolved back to z approximate to 2, is consistent with C Iv spatial clustering but perhaps not with that of the Ly alpha forest. Even so, one cannot as yet distinguish the two absorber populations on the basis of spatial clustering on these small scales.

IN VIVO EVOLUTION OF HIV-1 CO-RECEPTOR USAGE AND SENSITIVITY TO CHEMOKINE-MEDIATED SUPPRESSION

Scarlatti G. Tresoldi E. Bjorndal A. Fredriksson R. Colognesi C. Deng HK. Malnati MS. Plebani A. Siccardi AG. Littman DR. Fenyo EM. Lusso P.

Nature Medicine. 3(11):1259-1265, 1997 Nov.

Following the identification of the C-C chemokines RANTES, MIP-1 alpha and MIP-1 beta as major human immunodeficiency virus (HIV)-suppressive factors produced by CD8(+) T cells(1), several chemokine receptors were found to serve as membrane co-receptors for primate immunodeficiency lentiretroviruses(2-8). The two most widely used co-receptors thus far recognized, CCR5 and CXCR4 are expressed by both activated T lymphocytes and mononuclear phagocytes. CCR5, a specific RANTES, MIP-1 alpha and MIP-1 beta receptor, is used preferentially by non-MT2-tropic HIV-1 and HIV-2 strains(3-7,9,10) and by simian immunodeficiency virus (SIV)(11), whereas CXCR4, a receptor for the C-X-C chemokine SDF-1 (ref. 12, 13), is used by MT2-tropic HIV-1 and HIV-2, but not by SIV (ref. 2-7, 9-11, 14). Other receptors with a more restricted cellular distribution, such as CCR2b, CCR3 and STRL33, can also function as co-receptors for selected viral isolates(4,6,8). The third variable region (V3) of the gp120 envelope glycoprotein of HIV-1 has been fingered as a critical determinant of the co-receptor choice(4,15). Here, we document a consistent pattern of evolution of viral co-receptor usage and sensitivity to chemokine-mediated suppression in a longitudinal follow-up of children with progressive HIV-1 infection. Viral isolates obtained during the asymptomatic stages generally used only CCR5 as a co-receptor and were inhibited by RANTES, MIP-1 alpha and MIP-1 beta, but not by SDF-1. By contrast, the majority of the isolates derived after the progression of the disease were resistant to C-C chemokines, having acquired the ability to use CXCR4 and, in some cases, CCR3, while gradually losing CCR5 usage. Surprisingly, most of these isolates were also insensitive to SDF-1, even when used in combination with RANTES. An early acquisition of CXCR4 usage predicted a poor prognosis. In children who progressed to AIDS without a shift to CXCR4 usage, all the sequential isolates were CCR5-dependent but showed a reduced sensitivity to C-C chemokines. Discrete changes in the V3 domain of gp120 were associated with the loss of sensitivity to C-C chemokines and the shift in co-receptor usage. These results suggest an adaptive evolution of HIV-1 in vivo, leading to escape from the control of the antiviral C-C chemokines.

CRUDE CLOSURE DYNAMICS THROUGH LARGE SCALE STATISTICAL THEORIES

Grote MJ. Majda AJ.

Physics of Fluids. 9(11):3431-3442, 1997 Nov.

Crude closure algorithms based on equilibrium large Scale statistical theories involving only a few constraints are developed here. These algorithms involve the nonlinear evolution of either a single parameter, the energy, for dynamic closure based on equilibrium energy-enstrophy statistical theory, or two parameters, the energy and circulation, for crude dynamic closure based on the equilibrium point vortex statistical theory. The crude closure algorithms are tested systematically through numerical experiments with the Navier-Stokes equations in two dimensions on a rectangular domain with stress-free boundary conditions and strong small scale forcing at moderately large Reynolds numbers. A series of successively more stringent tests is devised with conditions ranging from freely decaying flows to spin-up from rest by random forcing with like signed vortices, and finally to random forcing by vortices with alternating or opposite signs. Comparison of standard spectral simulations with crude dynamic closure based on the two-parameter theory yields at most 5% velocity errors for all of these examples. The velocity errors can be as large as 10% for the one-parameter closure theory but are often comparable to those obtained with the two-parameter closure. The results of numerical experiments with Ekman drag are also discussed here.

EFFECTS OF EXTRACELLULAR CA2+ CONCENTRATION ON HAIR-BUNDLE STIFFNESS AND GATING-SPRING INTEGRITY IN HAIR CELLS

Marquis RE. Hudspeth AJ.

Proceedings of the National Academy of Sciences of the United States of America. 94(22):11923-11928, 1997 Oct 28.

When a hair cell is stimulated by positive deflection of its hair bundle, increased tension in gating springs opens transduction channels, permitting cations to enter stereocilia and depolarize the cell, Ca2+ is thought to be required in mechanoelectrical transduction, for exposure of hair bundles to Ca2+ chelators eliminates responsiveness by disrupting tip links, filamentous interstereociliary connections that probably are the gating springs, Ca2+ also participates in adaptation to stimuli by controlling the activity of a molecular motor that sets gating-spring tension, Using a flexible glass fiber to measure hair-bundle stiffness, we investigated the effect of Ca2+ concentration on stiffness before and after the disruption of gating springs, The stiffness of intact hair bundles depended nonmonotonically on the extracellular Ca2+ concentration; the maximal stiffness of approximate to 1200 mu LN . m(-1) occurred when bundles were bathed in solutions containing 250 mu M Ca2+, approximately the concentration found in frog endolymph, For cells exposed to solutions with sufficient chelator capacity to reduce the Ca2+ concentration below approximate to 100 nM, hair-bundle stiffness fell to approximate to 200 mu N . m(-1) and no longer exhibited Ca2+-dependent changes. Because cells so treated lost mechanoelectrical transduction, we attribute the reduction in bundle stiffness to tip-link disruption, The results indicate that gating springs are not linearly elastic; instead, they stiffen with increased strain, which rises with adaptation-motor activity at the physiological extracellular Ca2+ concentration.

MAXWELL GARNETT THEORY FOR MIXTURES OF ANISOTROPIC INCLUSIONS - APPLICATION TO CONDUCTING POLYMERS

Levy O. Stroud D.

Physical Review B-Condensed Matter. 56(13):8035-8046, 1997 Oct 1.

The effective dielectric function epsilon(e) for a medium of anisotropic inclusions embedded in an isotropic host is calculated using the Maxwell Garnett approximation. For uniaxial inclusions, epsilon(e) depends on how well the inclusions are aligned. We apply this approximation to study epsilon(e) for a model of quasi-one-dimensional organic polymers. The polymer is assumed to be made up of small single crystals embedded in an isotropic host of randomly oriented polymer chains. The host dielectric function is calculated using the effective-medium approximation (EMA). The resulting frequency-dependent epsilon(e)(omega) closely resembles experiment. Specifically, Re epsilon(e)(omega) is negative over a wide frequency range, while Im epsilon(e)(omega) exhibits a broad "surface plasmon" band at low frequencies, which results from localized electronic excitations within the crystallites. If the host is above the conductivity percolation threshold, Im epsilon(e)(omega) has a low-frequency Drude peak in addition to the surface plasmon band, and Re epsilon(e)(omega) is negative over an even wider frequency range. We also calculate the cubic nonlinear susceptibility chi(e)(omega) of the polymer, using a nonlinear EMA. At certain frequencies, chi(e)(omega) is found to be strongly enhanced above that of the corresponding single crystals. Our results suggest that the electromagnetic properties of conducting polymers can be understood by viewing the material as randomly inhomogeneous on a small scale such that the quasistatic limit is applicable.

RECURRENT EXCITATORY POSTSYNAPTIC POTENTIALS INDUCED BY SYNCHRONIZED FAST CORTICAL OSCILLATIONS

Whittington MA. Traub RD. Faulkner HJ. Stanford IM. Jefferys JGR.

Proceedings of the National Academy of Sciences of the United States of America. 94(22):12198-12203, 1997 Oct 28.

Gamma frequency (about 20-70 Hz) oscillations occur during novel sensory stimulation, with tight synchrony over distances of at least 7 mm, Synchronization in the visual system has been proposed to reflect coactivation of different parts of the visual field by a single spatially extended object. We have shown that intracortical mechanisms, including spike doublet firing by interneurons, can account for tight long-range synchrony. Here we show that synchronous gamma oscillations in two sites also can cause long-lasting (>1 hr) potentiation of recurrent excitatory synapses, Synchronous oscillations lasting >400 ms in hippocampal area CA1 are associated with an increase in both excitatory postsynaptic potential (EPSP) amplitude and action potential afterhyperpolarization size, The resulting EPSPs stabilize and synchronize a prolonged beta frequency (about 10-25 Hz) oscillation, The changes in EPSP size are not expressed during non-oscillatory behavior but reappear during subsequent gamma-oscillatory events, We propose that oscillation-induced EPSPs serve as a substrate for memory, whose expression either enhances or blocks synchronization of spatially separated sites, This phenomenon

thus provides a dynamical mechanism for storage and retrieval of stimulus-specific neuronal assemblies.

SELECTIVE OXIDATION OF N-BUTANE TO MALEIC ANHYDRIDE ON VANADYL PYROPHOSPHATE .1. INFLUENCE OF OXIDATION PRETREATMENTS ON THE CATALYTIC PERFORMANCES

Aitlachgar K. Abon M. Volta JC.

Journal of Catalysis. 171(2):383-390, 1997 Oct 15.

A pure and well-crystallized (VO)(2)P2O7 catalyst was oxidized under an oxygen flow at 500 degrees C for different times up to 24 h. These samples were characterized by TGA-DTA, XRD, UV-VIS spectroscopy, and P-31 NMR. Their catalytic performances were compared in the selective oxidation of n-butane to maleic anhydride (MA) as a function of the time of oxidizing pretreatments. The sample oxidized for 1 h displayed an important increase in MA selectivity (from 52 to 84%), whereas the activity remained virtually nonaffected. These results have been discussed in relation with the development of a proper density of selective V-V species associated with the creation of structural disorder in the pyrophosphate lattice.

MUTATIONS IN THE HMINK GENE CAUSE LONG QT SYNDROME AND SUPPRESS I-KS FUNCTION

Splawski I. Tristanifirouzi M. Lehmann MH. Sanguinetti MC. Keating MT.

Nature Genetics. 17(3):338-340, 1997 Nov.

Ion-channel beta-subunits are ancillary proteins that co-assemble with alpha-subunits to modulate the gating kinetics and enhance stability of multimeric channel complexes(1,2). Despite their functional importance, dysfunction of potassium-channel beta-subunits has not been associated with disease. Recent physiological studies suggest that KCNE1 encodes beta-subunits (hminK) that co-assemble with KvLQT1 alpha-subunits to form the slowly activating delayed rectifier K+ (I-Ks) channel(3,4). Because KVLQT1 mutations cause arrhythmia susceptibility in the long QT syndrome (LQT)(5-7), we hypothesized that mutations in KCNE1 also cause this disorder. Here, we define KCNE1 missense mutations in affected members of two LQT families. Both mutations (S74L, D76N) reduced I-Ks by shifting the voltage dependence of activation and accelerating channel deactivation, D76N hminK also had a strong dominant-negative effect, The functional consequences of these mutations would be delayed cardiac repolarization and an increased risk of arrhythmia. This is the first description of KCNE1 as an LQT gene and confirms that hminK is an integral protein of the I-Ks channel.

CONFORMATIONAL LANDSCAPES OF NONPLANAR PORPHYRINS - SUPERSTRUCTURE, LIGATION, BINDING POCKETS AND OXIDATION EFFECTS IN CU(II) PORPHYRINS

Renner MW. Barkigia KM. Fajer J.

Inorganica Chimica Acta. 263(1-2):181-187, 1997 Oct 15.

The crystal structure of the porphyrin pi cation radical Cu(II)OETPP(+)pyl(3)(-). py is reported (OETPP = 2,3,7,8,12,13,17,18-octaethyl-5,10,15,20-tetraphenylporphyrin; py = pyridine). The compound is readily prepared by oxidation of Cu(II)OETPP in CH,CI, with excess I, in the presence of py. The structure exhibits the following features: (1) The porphyrin is oxidized, not the Cu(II). (2) The Cu(II) is pentacoordinated with one py as axial ligand. (3) The sterically crowded macrocycle is saddle shaped. This distortion and the peripheral substituents combine to form superstructural, orthogonal 'trenches' above and below the porphyrin plane. (4) The trenches impose a specific orientation on the ligated axial py along the N-Cu-N axis of the porphyrin and also form a 'distal' binding pocket that traps a second molecule of py. (5) The Cu(II)OETPP+ py radical is diamagnetic because of antiferromagnetic coupling between the unpaired electrons of the Cu d(x2-y2) and the porphyrin pi orbitals which is favored by the nonplanarity of the macrocycle. (6) The radical is more distorted than its nonplanar parent and provides additional support for the thesis that nonplanar porphyrins can easily undergo additional structural excursions. Conformational changes of the type reported here may also influence the reactivities of the rr cation radicals formed in the (photo)catalytic cycles of photosynthetic and hemoproteins also comprised of nonplanar porphyrins. Crystallographic data Cc (No. 9), a=21.706(2) Angstrom, b=16.077(2)Angstrom, c=19.993(2) Angstrom, beta=103.34(1)degrees, V=6789(1) Angstrom(3), Z=4.

VENTRICULAR VOLUME AND ASYMMETRY IN SCHIZOTYPAL PERSONALITY DISORDER AND SCHIZOPHRENIA ASSESSED WITH MAGNETIC RESONANCE IMAGING

Buchsbaum MS. Yang S. Hazlett E. Siegel BV. Germans M. Haznedar M. Oflaithbheartaigh S. Wei TC. Silverman J. Siever LJ.

Schizophrenia Research. 27(1):45-53, 1997 Oct 17.

Magnetic resonance imaging (MRI) was performed in 12 patients with schizotypal personality disorder (SPD), 11 patients with chronic schizophrenia, and 23 age- and sex-matched normal volunteers. MRI slices were acquired in the axial plane at 1.2-mm intervals, and the ventricles were traced on every other slice. The lateral ventricular system was divided into the anterior horn, temporal horn, and dorsal lateral ventricle. Schizophrenic patients had larger left anterior and temporal horns than the normal volunteers. Size of the left anterior and temporal horn in SPD patients was intermediate between those of normal volunteers and schizophrenic patients and differed significantly from schizophrenic patients. The left-minus-right difference was larger in schizophrenic patients than in normal volunteers or SPD patients. Thus, in their structural brain characteristics, as well as in their clinical symptomatology, SPD patients evidence, in attenuated form, abnormalities resembling those found in full-ledged schizophrenia. The findings suggest that decreased left hemispheric volume, in frontal and temporal regions, may characterize both psychotic and non-psychotic disorders of the schizophrenia spectrum.

HIGH-TEMPERATURE PAIRING IN STRIPES

Zachar O. Kivelson SA. Emery VJ.

Journal of Superconductivity. 10(4):373-378, 1997 Aug.

That the superconducting transition in underdoped high temperature superconductors is controlled by phase ordering, implies that pairing is a local phenomenon that occurs on an intermediate length scale, and typically at a temperature above T-c. The discovery of local stripe order in the LSCO family of high temperature superconductors, along with the theoretical suggestion that such structures are a general feature of doped antiferromagnets lead us further to propose that in fact pairing occurs in the vicinity of an individual stripe. The transition to a superconducting state then follows at lower temperature due td Josephson coupling between stripes. In this paper we review our microscopic model of high temperature pairing on individual stripes.

NO SYNTHASE ISOZYMES HAVE DISTINCT SUBSTRATE BINDING SITES

Fan BC. Wang JL. Stuehr DJ. Rousseau DL.

Biochemistry. 36(42):12660-12665, 1997 Oct 21.

The resonance Raman spectra of the carbon monoxide (CO) derivatives of nitric oxide synthases (NOSs), in which CO coordinates to the heme at the site occupied by oxygen under physiological conditions, are very sensitive to the presence of substrates and inhibitors. Significant differences in the modes associated with the bound CO are now found to depend on the isoenzyme. In the presence of L-arginine, the physiological substrate, the frequencies of the Fe-CO stretching mode and the C-O stretching mode in nNOS, the brain enzyme, are detected at 503 and 1929 cm(-1), respectively; whereas in iNOS, the inducible enzyme from macrophage, the modes are detected at 512 and 1906 cm(-1), respectively. The frequencies in eNOS, the endothelial isozyme, are similar to those of iNOS. These results indicate that nNOS has a much more open substrate-binding pocket than iNOS and eNOS. A theoretical simulation based on the interaction between the CO and a positively charged guanidino group on the arginine indicates that the polar environment of the CO differs markedly between the isozymes. This may be accounted for either by an arginine-CO distance that is as much as 1 Angstrom greater in nNOS than in iNOS and eNOS or by a substantial shielding of the charge on the arginine in nNOS as compared to the other isozymes. This is the first reported detection of a structural difference of the substrate binding sites between the isozymes and serves as an initial step in a rational dig design for NOS.

SEDIMENTARY PROCESSES ACROSS THE CONTINENTAL RISE OF THE SOUTHERN ANTARCTIC PENINSULA

Mcginnis JP. Hayes DE. Driscoll NW.

Marine Geology. 141(1-4):91-109, 1997 Sep.

A series of large sediment mounds have been identified along the Pacific portion of the Antarctic Peninsula continental rise. These mounds are composed of sediment delivered to the continental rise during the advance and retreat of grounded ice across the shelf. The stratigraphic development of one of these sediment deposits, the Tula sediment mound, is examined to investigate how the onset of glaciation influenced the deep-sea depositional environment along this portion of the margin. The stratal relationships, associated facies distribution, and the physiography observed along the southern Antarctic margin reflect the waxing, and waning of the Antarctic ice sheets; various processes erode, transport, and deposit sediment along the outer shelf, slope, and rise throughout a glacial cycle. A deep-sea erosional unconformity is apparent at the base of the Tula deposit. This surface may reflect the first onset of intensified bottom water circulation along the margin perhaps induced by the tectonic opening of the Drake Passage. The Tula sediment mound is comprised predominantly of canyon/overbank systems. Evidence for the onset of canyon cutting and the development of the thick overbank deposits (>2 km) is found immediately above the deepsea erosional unconformity. Relating increased canyon cutting across the continental rise to the fluctuation of ice across the shelf implies that the onset of predominantly glacial conditions commenced soon after the onset of intensified bottom water circulation along this margin. The volume of sediment associated with the Tula deposit and the apparent 'point source' distribution of the channel systems suggests that much sediment was transported to the slope and rise perhaps by meltwater processes through these canyons.

COMPARISON OF THE KINETIC EFFECTS OF PHOSPHOLAMBAN PHOSPHORYLATION AND ANTI-PHOSPHOLAMBAN MONOCLONAL ANTIBODY ON THE CALCIUM

REGIONAL CALENDAR OF SEMINARS

DEC 9-12

Dec 9: "Yes, Virginia, There are Creationists-Lots of Them," Dr. Eugenie C. Scott, Executive Director of the National Ctr for Science Education Inc., 12:00, Dept. of Ecology and Evolution, 120 Endeavour Hall, Marine Sciences Research Ctr., SUNY Stony Brook

9: "Biological Consequences of Interactions between Signaling Pathways, Dr. Ravi Iyenger, Dept. of Pharmacology, Mt. Sinai School of Medicince, 12:00, Dept. of Physiology & Cellular Biophysics and Pharmacology, P&S 11-505, Rover Conference Room, College of P&S of Columbia University

10: "Competition and Coexistence of Larval Ant Lions," Dr. Nick Gotelli, Univ. of Vermont, 3:30, Dept. of Ecology and Evolution, Rm. 038, Life Sciences Building, SUNY Stony Brook

10: "TBA," Dr. Predrag Cvitanovic, Neils Bohr Institute, 4:30, Applied Mathematics, Rm. 214, SW Mudd, Columbia University

11: "Ecosim: Null Models Software for Ecologists," Dr. Nick Gottelli, Univer. of Vermont, 10:45, Dept. of Ecology and Evolution, Conference Room 650, Life Sciences Building, SUNY Stony Brook

11: "Myelin-Associated Glycoprotein, MAG, a Sialic Acid Binding Protein and an Inhibitor of Axonal Regeneration," Marie Filbin, Dept. of Biological Sciences, CUNY Hunter College, 12:00, Dept. of Neurobiology and Behavior, N.Y. State Psychiatric Institute, 7th Floor Conference Room, 722 West 168th St., College of P&S of Columbia University

11: "Signaling Mechanisms Controlling Mammalian Gamette Competence, Adhension, and Activation at Fertization, Dr. Gregory Kopf, U. Penn, 12:00, Medical Ctr., Endocrinology and Reproductive Biology Seminar, 301 Weiss, Rockeller University

11: "Resonances for Convex Bodies," Dr. Maciej Zworski, University of Toronoto, 11:00AM, Courant Inst. of Mathematical Sciences, Warren Weaver Hall, Rm. 1302, 251 Mercer St., NYU

12: "Observing the Earth from Space - An Oceanographer's Perspective," Dr. Gene Feldman, Goddard Space Flight Center, 12:30, Marine Science Research Center, Rm 120, Endeavor Hall, South Campus, SUNY Stony Brook

DEC 12-15

12: "Chemokine Receptors in HIV and SIV Disease," Dan Littman, Investigator, HHMI; Skitball Institute of Biomolecular Medicine, 12:00, Cell Biology, 116 Rockefeller Research Laboratories, MSKCC, 420 East 67St., Rockefeller Institute

12: "Condensed Phase Simulations of Biomolecular Systems," Dr. Glenn Martyna, Indiana University, 3:00, Dept. of Chemistry, Rm. 1003, Main Building, 100 Washington Sq. East, NYU

12: "The H-p Mortar Finite Element Method for Second Order Elliptic Problems," Faker Ben Belgacem, Univer. Paul Sabatier, France, 10:00, Courant inst. of Mathematical Sciences, Warren Weaver Hall 1302, 251 Mercer St., NYU

12: "New Principles of Dendritic Function," Dr. Daniel Johnson, Division of Neuroscience, Baylor College of Medicine, 12:00, Dept. of Neurobiology, Neurological Institute Alumi Auditorium, Columbia Univ.

12: "Numerical Analysis Seminar: The h-p Mortar Finite Element Method for Second Order Elliptic Problems," Faker Ben Belgacem, Université Paul Sabatier, Toulouse, France, 10:00, Warren Weaver Hall Rm. 1302, NYU

12: "29th Computational Geometry Day," Speakers include: Jeff Erickson, Duke; Jeff Lagarias, AT&T Labs; Estie Arkin, SUNY Stony Brook. 10:30 - 4:00, Warren Weaver Hall Rm. 109, NYU

15: "The Transport and Acumulation of Low Denisty Lipoprotein and Cholesterol in the Artery Wall," David Rumschitzki, 3:45-5:00, J-418,

15: "Quantum Fields in Curved Space," Dr. Eduardo Franklin, Institutee for Advanced Study, 2:00, Theorical Physics, Rm. 831, Pupin Hall, Columbia Univer.

15: " Functional Significance of Dopamine-Glutamate Interactions in the Prefrontal Cortex," Dr. Bita Moghaddam, Yale Univer. School of Medicine, 12:00, Dept. of Neurology, Meyer Building, Rm 122, Washington Sq., NYU Medical Center

15: "p53 and Cell Death," Kornelia Polyak, M.D., Ph.D., The Johns Hopkins Ocology Center, Howard Hughes Medical Institute, Molecular Genetics Laboratory, 12:00, Humphreys Auditorium, Rm. VC 14-240, College of P&S of Columbia University

DEC 16-29

16: "Structure and Function of Human Proteins Involved in mRNA Splicing and Its Regulation," Dr. Adrian Krainer, Cold Spring Harbor Laboratory, 12:00, Dept. of Cell Biology, Cell Biology Library, MSB 657, NYU Medical Ctr., School of Medicine

18: "Synapse Specific Transcription-Dependent Long-Term Facilitation of the Sensory to Motor Neuron Conection in Aplysia,"Kelsy Martin, Lab. of Dr. Eric Kandel, Ctr. for Neurobiology & Behavior, 12:00, Ctr. for Neurobiology & Behavior, N.Y. State Psychiatric Insitute, 7th floor Conference Room, 722 West 168th St., College of P&S of Columbia University

18: "Epilepsy in the Developing Brain: Consequences and Therapy," Dr. Gregory Holmes, Department of Neurology, Harvard Medical School, Boston. 12:00, Room 901, Kennedy Center, Albert Einstein College of Medicine

19: "Spectroscopy and Dynamics on Large Helium Clusters," Dr. Kevin K. Lehmann, Princeton Univer., 3:00, Dept. of Chemistry, Rm. 1003, Main Building, 100 Washington Sq. East, NYU

29: "Raising Roofs, Crashing Cycles, and Playing Pool: Applications of a Data Structure for Finding Pairwise Interactions," Jeff Erickson, Duke Univer., 10:30-11:15, Courant Inst. of Mathematical Sciences, Warren Weaver Hall 109, 251 Mercer St., NYU

29: " Loose Ends in Knot Theory: The Complexity of Unknotting," Jeff Lagarias, AT&T Labs-Research, 11:30-12:15, (12:30-2:00 Lunch), Courant Inst. of Mathematical Sciences, Warren Weaver Hall 109, 251 Mercer St., NYU.

29: "Approximation Algorithms for Variants of the TSP," Estie Arkin, SUNY Stony Brook, 3:00-3:45, (4:00-5:00Wine &Cheese Recept.13th Floor Lounge), Courant Inst. of Mathematical Sciences, Warren Weaver Hall 109, 251 Mercer St., NYU

29: "Prediction and Management of Chaotic Risks," Graciela Chichilnisky, Columbia Univer., 2:00-2:45 (2:45-3:15 Cofffee Break), Applied Math Seminar, Warren Weaver Hall 1302, 251 Mercer St., NYU

AR 8140A

IN HPLC, NOTHING IS AS GOOD AS GOLD.

Durable, reliable and versatile, System Gold® set the standard in HPLC. Now, Beckman is raising that standard with System Gold *Nouveau*—a new system with new software.

So whether you're buying a new HPLC system, or replacing an old one, ask yourself how it measures up to the Gold standard.

• ***Cost of ownership.*** Replacement cycles are getting longer, and a system isn't a good value if you have to replace it every 5 years. Beckman instruments are known to last.

• ***Ease of use.*** Gold™ *Nouveau* with Windows* takes intuitive software design to a new level, helping you become more productive, more quickly. You'll spend less time training, and more time getting results.

• ***Capability.*** Exceptional microflow performance allows you to save on solvent costs without sacrificing reliability.

• ***Number 1 in service.*** System Gold *Nouveau* comes with 700 unique accessories—our worldwide network of Beckman field service representatives. They're the reason that a recent survey rated Beckman *number one* for responsive service.

• ***No-quibble warranty.*** Beckman offers a full 12-month parts and in-lab labor warranty—not just 90 days or five years of "limited" coverage.

To see System Gold *Nouveau* in action, or to receive a demonstration software disk, just contact your local Beckman office, or reach us through the Internet at http://www.beckman.com. **Windows is a trademark of MicroSoft Corporation.*

BECKMAN

Worldwide Offices: Africa, Middle East, Eastern Europe (Switzerland) (41) 22 994 07 07. **Australia** (61) 2 844-6000. **Austria** (43) 222 7292164. **Canada** (800) 387-6799. **China** (861) 5051241-2. **France** (33) 1 43 01 70 00. **Germany** (49) 89-358700. **Hong Kong, PRC** (852) 814 7431. **Italy** (39) 2-953921. **Japan** 3-5352-2825. **Mexico** 525 559 1635. **Netherlands** 0297-230630. **Poland** (48) 22 408822, 408833. **Singapore** (65) 339 3633. **South Africa** (27) 11-805-2014/5. **Spain** (1) 358-0051. **Sweden** (8) 445 11 20. **Switzerland** (41) 22 994 07 07. **Taiwan** (886) 02 378-3456. **U.K.** (01494) 441181. **U.S.A.** 1-800-742-2345.

SEMINARS CONTINUED

DEC 29-JAN 22

29: "The Challenge of Earth Stewardship: New Knowledge Requiring a New Approach," Peter Eisenberger, Columbia Univer., 3:15-4:00, Applied Math Seminar, Warren Weaver Hall 1302, 251 Mercer St., NYU

Jan 8: "T-box Genes - A New Family With Critical Roles in Mammalian Development," Dr. Virginia Papaioannou, Columbia University, 4:00, Rm. 038 Life Sciences Building, SUNY Stony Brook

8: Neurobiology and Behavior Seminar: Karel Svoboda, Cold Spring Harbor Laboratory, 12:00, Neurological Institute, Alumni Audiorium, 710 W. 168th St., Columbia University P&S

13: "Synaptic Transmission at the First Synapse," Dr. Amy B. MacDermott, Department of Physiology and Cellular Biophysics, Columbia University College of Physicians & Surgeons, 12:00, Rover Physiology Conference Room, P&S 11-505, College of P&S of Columbia University

15: "TBA," Dr. Neil Stahl, Regeneron Pharmaceuticals, 4:00, Rm. 038 Life Sciences Building, SUNY Stony Brook

15: Neurobiology and Behavior Seminar: David A. McCormick, Section of Neurobiology, Yale University School of Medicine, 12:00, Neurological Institute, Alumni Audiorium, 710 W. 168th St., Columbia University P&S

20: "Leptin, Leptin Receptors and the Control of Body Weight," Dr. Jeffrey Friedman, Rockefeller University, 12:00, Physiology & Celluar Biophysics, Rover Physiology Conference Room, P&S 11-505, Columbia University

21: Ecology and Evolution Seminar, Larry Slobodkin, SUNY Stony Brook, Life Sciences Building, SUNY Stony Brook

22: "TBA," Dr. Michael Gilman, ARIAD Pharmaceuticals, 4:00, Rm. 038 Life Sciences Building, SUNY Stony Brook

22: Neurobiology and Behavior Seminar: "Antero-Posterior Patterning in the Zebrafish Embryo," Robert Ho, Biology Department, Princeton University, 12:00, Neurological Institute, Alumni Audiorium, 710 W. 168th St., Columbia University P&S

JAN 23-30

23: "Essential Dynamics of Biological Molecules," Dr. Peter Deuflhard, University of Berlin, 3:00, Rm. 1003 Main Chemistry Building, 100 Washington Square East, NYU

23: "Role of the Rb/E2F Pathway in Cell Growth Control," Joseph R. Nevins, Ph.D, Howard Hughes Medical Institute, Department of Genetics, Duke University Medical Center, 12:00, Humphreys Auditorium, Rm. VC 14-240, College of P&S of Columbia University

26: "Irish Elk Extinction and Nutrient Cycling," John Pastor, University of Minnesota, Life Sciences Building, SUNY Stony Brook

26: "Mice deficient in Ets and bHLH-PAS proteins exhibit abnormal blood cell and blood vessel development," M. Celeste Simon, Ph.D., Howard Hughes Medical Institute, The University of Chicago, Departments of Medicine and Molecular Genetics & Cell Biology, 12:00, Humphreys Auditorium, Rm. VC 14-240, College of P&S of Columbia University

27: "The Role of the Extracellular Matrix in Differentiation of Polarized Epithelia," Dr. Qais Al-Awqati, Dept. of Medicine& Physiology &Cellular Biophysics, 12:00, Physiology & Cellualr Biophysics, Rover Physiology Conference Room, Rm. P&S 11-505, Columbia Univer.

29: "Novel Forms of Protein Glycosylation," Dr. Robert Haltiwanger, SUNY Stony Brook, 4:00, Rm. 038 Life Sciences Building, SUNY Stony Brook

29: Neurobiology and Behavior Seminar: David J. Linden, Department of Neuroscience, Johns Hopkins University School of Medicine, 12:00, Neurological Institute, Alumni Audiorium, 710 W. 168th St., Columbia University P&S

30: "TBA," Dr. Stanley Tabor, Harvard Medical School, 3:00, Rm. 1003 Main Chemistry Building, 100 Washington Square East, NYU

Please send your seminar dates for listing (free of charge) by fax: 516-737-3414, or email: editor@pdpub.com.

PUMP IN PURIFIED CARDIAC SARCOPLASMIC RETICULUM MEMBRANES

Antipenko AY. Spielman AI. Sassaroli M. Kirchberger MA.

Biochemistry. 36(42):12903-12910, 1997 Oct 21.

Protein kinase A-(PKA-) catalyzed phosphorylation of phospholamban (PLN), the protein regulator of the cardiac Ca pump, mediates abbreviation of systole in response to beta-adrenergic agonists. Investigators previously, however, have been unsuccessful in demonstrating an effect of PLN phosphorylation or anti-PLN monoclonal antibody (mAb), which is considered to mimic phosphorylation's well-known effect on K-m(Ca), on microsomal Ca uptake at the (high) Ca2+ concentrations found intracellularly at peak systole. We therefore compared the effects of the catalytic subunit of PKA and anti-PLN mAb on the kinetics of Ca uptake in sucrose gradient-purified cardiac microsomes. Both treatments produced a 33-44% increase in V-max(Ca) at 25 and 37 degrees C, and an 11-31% decrease in K-m(Ca), with comparable changes in Ca2+-ATPase activity. An acceleration of E2P decomposition upon PLN phosphorylation may contribute to the increased V-max(Ca) of Ca uptake at 25 degrees C but not at 37 degrees C, based on measurement of the kinetics of E2P decomposition and steady-state E2P formation from P-i at different temperatures. Our data document almost identical increases in V-max(Ca) of microsomal Ca uptake with PLN phosphorylation or addition of anti-PLN mAb and hence provide insight into the kinetic mechanism of PLN's regulation of the cardiac sarcoplasmic reticulum Ca pump protein.

EXTENSION OF THE PS-GVB ELECTRONIC STRUCTURE CODE TO TRANSITION METAL COMPLEXES

Mainz DT. Klicic JJ. Friesner RA. Langlois JM. Perry JK.

Journal of Computational Chemistry. 18(15):1863-1874, 1997 Nov 30.

We have developed a parameterization enabling ab initio electronic structure calculation via the PS-GVB program on transition-metal-containing systems using two standard effective core potential basis sets. Results are compared with Gaussian-92 for a wide range of complexes, and superior performance is demonstrated with regard to computational efficiency for single-point energies and geometry optimization. Additionally, the initial guess strategy in PS-GVB is shown to provide considerably more reliable convergence to the ground state.

REGIONAL REMODELING OF ATHEROSCLEROTIC ARTERIES - A MAJOR DETERMINANT OF CLINICAL MANIFESTATIONS OF DISEASE [Review]

Birnbaum Y. Fishbein MC. Luo H. Nishioka T. Siegel RJ.

Journal of the American College of Cardiology. 30(5):1149-1164, 1997 Nov 1.

In this review we present the current data on remodeling, based on in vivo ultrasound imaging or postmortem histologic analysis of native peripheral and coronary arteries from animal models and studies in patients (coronary artery saphenous vein bypass grafts, lesions of restenosis after balloon angioplasty and other catheter-based interventions), Histologic and ultrasound imaging studies of arteries with atherosclerosis and after vascular injury reveal that arterial remodeling is common and that the cross-sectional area of the vessel is not constant, Compensatory enlargement, inadequate compensatory enlargement and shrinkage at the site of atherosclerotic lesions occurs in coronary and peripheral arteries, Current studies demonstrate that arterial remodeling is a major determinant of vessel lumen size.

RETINOIC ACID ENHANCES THE EXPRESSION OF INTERFERON-INDUCED PROTEINS - EVIDENCE FOR MULTIPLE MECHANISMS OF ACTION

Pelicano L. Li FS. Schindler C. Chelbialix MK.

Oncogene. 15(19):2349-2359, 1997 Nov 6.

Retinoic acid (RA) and interferons (IFNs) are negative regulators of cell proliferation, In vitro and in vivo, their combination leads to a more potent growth inhibition, However, the molecular mechanisms by which RA and IFNs potentiate each other are not fully understood. As some IFN-induced gene products regulate cell growth and/or antiviral activity, we analysed the effects of RA on their expressions. RA increases the level of 2'5'oligoadenylate synthetase, p68 kinase, the promyelocytic leukemia protein (PML) and Sp100 in both HL-60 and WISH cells. Moreover, RA and IFN act cooperatively to increase the expression of these proteins, RA also inhibits vesicular stomatitis virus replication and induces a higher antiviral state and growth inhibition when combined with IFN. RA stimulates the IFN regulatory factor 1 (IRF-1) gene expression directly through the GAS motif and causes the induction and secretion of IFN alpha. Additional mechanisms could he involved as RA increases the level of signal transducing activators of transcription (STAT) proteins, and enhances the IFN-induced STAT activation, suggesting that cooperative effects by RA and IFN are mediated through multiple pathways.

ENVIRONMENT AND CANCER - WHO ARE SUSCEPTIBLE

Perera FP.

Science. 278(5340):1068-1073, 1997 Nov 7.

Acting in concert with individual susceptibility, environmental factors such as smoking, diet, and pollutants play a role in most human cancer. However, new molecular evidence indicates that specific groups-characterized by predisposing genetic traits or ethnicity, the very young, and women-may have heightened risk from certain exposures. This is illustrated by molecular epidemiologic studies of environmental carcinogens such as polycyclic aromatic hydrocarbons and aromatic amines. Individual genetic screening for rare high-risk traits or for more common, low-penetrant susceptibility genes is problematic and not routinely recommended. However, knowledge of the full spectrum of both genetic and acquired susceptibility in the population will be instrumental in developing health and regulatory policies that increase protection of the more susceptible groups from risks of environmental carcinogens. This will necessitate revision of current risk assessment methodologies to explicitly account for individual variation in susceptibility to environmental carcinogens.

LOCAL STRUCTURAL CHANGES IN KNBO3 UNDER HIGH PRESSURE

Frenkel AI. Wang FM. Kelly S. Ingalls R. Haskel D. Stern EA. Yacoby Y.

Physical Review B-Condensed Matter. 56(17):10869-10877, 1997 Nov 1.

The local structure of the perovskite KNbO3 at 77 and 300 K under high pressure, up to 15.8 GPa, has been investigated using the x-ray-absorption fine-structure (XAFS) technique. It is found that the local-structure symmetry does not change even though the average macroscopic crystal symmetry changes several times over this same temperature and pressure range. The existence of different local and macroscopic structures means that the local distortions from the average structure are disordered. Other unexpected results obtained from the XAFS measurements are evidence for a decreasing Nb-Nb displacement correlation length and a destabilization of the oxygen octahedra with increasing pressure.

ANOMALOUS MAGNETIC RELAXATION IN FERRITIN

Friedman JR. Voskoboynik U. Sarachik MP.

Physical Review B-Condensed Matter. 56(17):10793-10796, 1997 Nov 1.

We report measurements in natural horse-spleen ferritin that provide a detailed mapping of the blocking temperature, T-B, as a function of magnetic field over a broad range up to 20 kOe. Unlike most superparamagnetic materials where it decreases with applied field, T-B increases with increasing field at small fields, reaching a maximum at approximate to 3 kOe before exhibiting the expected decrease. The hysteresis loops are anomalously "pinched" near zero field. Both observations are consistent with an effective energy barrier that is smaller at zero field than in small finite fields. This may arise from tunneling between pairs of states on opposite sides of the anisotropy barrier that are in resonance in zero magnetic field, regardless of particle size. However, direct measurements of the magnetic viscosity yield ambiguous results, leaving open other possible explanations.

A TURBULENT TRANSPORT MODEL - STREAMLINE RESULTS FOR A CLASS OF RANDOM VELOCITY FIELDS IN THE PLANE

Apelian C. Holmes RL. Avellaneda M.

Communications on Pure & Applied Mathematics. 50(11):1053-1088, 1997 Nov.

Probabilistic methods and computer simulation are used to analyze streamline properties of flows defined by a general class of random, incompressible velocity fields. Such fields are stochastically modeled by a superposition of simple shear-flow layers. The resulting flow is governed by a nonstationary, random Hamiltonian with Hurst exponent H = 0.5 and having the form H-0 = Sigma(k=1)(N) b(k)W(k)(n(r) . r) for constants b(k), where the W-k are two-sided continuous-time random walks. The statistical topography of the flow, as characterized by the level sets or streamlines of H-0, is analyzed via an associated Brownian walk space from which asymptotic results are determined. The flow consists of a hierarchy of nested, closed streamlines. For a given box of side length 2L centered at the particle's starting position, an upper bound on the particle's probability of exit, or "noncycling" probability, p(nc), is shown to have a power law dependence on the box size, p(nc)(L) similar to L-alpha, for L >> 1 and positive constant alpha. We also introduce a constant, nonzero mean flow and denote its relative strength with respect to the r.m.s. fluctuations of the random field by rho. In the case 0 < rho < 1, the fraction p(nc)(rho) of noncycling or particles (in an infinitely large box) satisfies the relation rho/rho+1 less than or equal to p(nc)(rho)< 1. All particles percolate in the case rho greater than or equal to 1. Computer simulations for various values of N agree well with earlier work on the N = 2 case by Avellaneda, Elliott, and Apelian, thereby confirming and validating both studies. Numerical results also show the power law exponent alpha to be remarkably robust with respect to changes in topology, including the existence of traps, irregularly spaced modes, and the value of N. All runs yield a common value of alpha approximate to 0.22. Likewise, the mean length of streamlines exiting boxes of size 2L, (lambda(L)), scales Like L-gamma With gamma approximate to 1.28 for all N. These exponent values contrast with those predicted by Isichenko and Kalda yet consistently satisfy a "sum rule" alpha + gamma = 2 - H, relating alpha, gamma, and H, the Hurst exponent of the flow.

Selected Funding Updates

Compiled by Peter M. Saal
Office of the Vice President for Research —SUNY Stony Brook

DK-98-005: Physician and Scientist Training Program in Urologic Research

The Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in cooperation with the American Foundation for Urologic Diseases (AFUD), invites applications for the continuation of a joint program for research training in urology. Each applicant will submit an application for training basic medical scientists in biological sciences related to urologic diseases of interest to the NIDDK and an application for training physicians for a future in urology research. Clinical training programs will not be considered in this initiative.

Areas for research training within this program are limited to those which fall within the primary responsibility of the NIDDK. These areas are broadly defined as: prostate growth control and development including BPH; chronic inflammatory urologic disorders such as prostatitis and interstitial cystitis; the basic science and clinical aspects of urolithiasis; the physiology and pathophysiology of bladder function including voiding dysfunctions as in urinary incontinence, enuresis and vesicoureteral reflux; infections of the urinary tract; male sexual function and dysfunction including the basic aspects of testicular and epididymal function; and pediatric urology. Institutions, program directors and individual applicants should contact the appropriate staff at the NIDDK should there be any question of research areas falling within the purview of the NIDDK. Letter of Intent Receipt Date: February 11, 1998; Application Receipt Date: March 11, 1998.

HL-98-001: Thrombocytopenia - Pathogenesis and Treatment

The purpose of this initiative is to improve the understanding of the pathogenesis of thrombocytopenia in general and HIV-related thrombocytopenia in particular. The long term goal of the initiative is to develop better therapeutic approaches for these conditions. This RFA will use the NIH individual research project grant (R01) mechanism of support. Letter of Intent Receipt Date: January 29, 1998; Application Receipt Date: March 12, 1998.

HD-98-001: Medical Rehabilitation Clinical Trial Grants

The National Center for Medical Rehabilitation Research (NCMRR) of the National Institute of Child Health and Human Development (NICHD) seeks to fund high quality clinical trials of medical rehabilitation interventions. The purpose of the Medical Rehabilitation Clinical Trial Planning Grant is to provide support for the organization of an effective research group and development of essential elements of a successful clinical trial, including plans for recruitment of patients, experimental design and protocols, testing of procedures, data management, analytical techniques, facilities, administrative procedures, and collaborative arrangements. The purpose of the planning grant is not to obtain preliminary data nor to conduct studies to support the rationale for the clinical trial.

Detailed information regarding the rationale of the clinical trial, based on preclinical science and preliminary clinical research, must be included in the application for the Medical Rehabilitation Clinical Trial Planning Grant. Involvement of representatives from the targeted patient population in planning and conducting the trial is highly recommended.

This program will use the exploratory/developmental grant (R21) mechanism. Applicants will be responsible for the planning, direction, and execution of the proposed project. Support may be requested for a single year for up to $50,000 in direct costs, not including facilities and administrative costs for collaborating institutions, if any. Letter of Intent Receipt Date: December 22, 1997; Application Receipt Date: January 21, 1998.

AG-98-001: Minority Dissertation Research Grants in Aging

Small grants to support doctoral dissertation research will be available for minority doctoral candidates. Grant support is designed to aid the research of new minority investigators and to encourage minority individuals from a variety of academic disciplines and programs to study topics relevant to aging.

For the purpose of this RFA, underrepresented minority students and investigators are defined as individuals belonging to a particular ethnic or racial group that has been determined by the grantee institution to be underrepresented in biomedical or behavioral research. Awards will be limited to citizens or non-citizen nationals of the United States or to individuals who have been lawfully admitted for permanent residence at the time of award. In awarding grants for dissertation support, the NIA will give priority to dissertation candidates who are African American (Black), Hispanic American, Native American or Alaska Natives, or Pacific Islanders, or other ethnic or racial group members who have been found to be underrepresented in biomedical or behavioral research nationally. The doctoral candidate must have a dissertation topic approved by the named committee. This information must be verified in a letter of certification from the chair of the candidate's dissertation committee and submitted with the grant application.

The mechanism of support is the NIH small grant (R03). Grants may be made for up to two years. Grants to support dissertation research will provide no more than $30,000 in total direct costs, and no more than $25,000 in direct costs in any one year. Application Receipt Date: February 20, 1998.

HL-98-003: Molecular and Physical Characterization of the Vulnerable Plaque

The purpose of this solicitation is to promote research into the properties of the atherosclerotic vulnerable plaque, especially those that relate to its tendency to progress to erosion or to rupture leading to thromboembolic events, unstable angina, myocardial infarction, and/or sudden death. A special emphasis is placed on multidisciplinary approaches in view of the variety of research disciplines and strategies that are needed to study the vulnerable plaque. Of interest would be studies on pathoanatomical and biochemical issues to identify major determinants of plaque vulnerability to erosion or rupture; humoral and systemic factors involved in coronary thrombosis; the physical forces associated with plaque disruption; and methods to identify and quantify the physicochemical features of plaque in vivo. Letter of Intent Receipt Date: February 2,1998; Application Receipt Date: March 11, 1998.

HL-97-012: Heart Failure Research - New Approaches to Pathogenesis

The National Heart, Lung, and Blood Institute and the National Institute on Aging invite applications to investigate the cellular and molecular underpinnings of heart failure, as well as the multiple tissue interactions leading to the symptoms of this condition. This Request for Applications (RFA) is intended to promote and support research teams with diverse, complementary expertise in molecular, cellular, physiological, and clinical approaches to heart failure research. The overall goal is to stimulate innovative multidisciplinary research to expedite progress in understanding the pathogenesis of heart failure and to facilitate rapid application of new findings to better recognition and treatment of the condition.

The objectives of this program are to: 1) encourage outstanding investigators from various disciplines to apply their expertise to develop experimental techniques and strategies to understand and combat heart failure; 2) foster collaborations (teams of physician and non-physician scientists with different skills, abilities, and talents, who may be from different institutions, and partner to solve problems which require a multifaceted approach and diverse technological skills not typically possessed by a single investigator or department; 3) expedite evaluation and dissemination of emerging findings, methods, and technologies; and 4) promote the standardization of key definitions and assessments in clinical and experimental research methods.

This RFA is to support collaborations in the basic and clinical sciences. The collaborations should focus on a common hypothesis with all component projects contributing scientifically to the central theme. The collaborative projects may include shared resources, and need to demonstrate the interdependence and multidisciplinary nature of the individual components.

Although not an active participant in this RFA, the National Institute on Environmental Health Sciences (NIEHS) has an interest in environmental diseases, including heart failure. Referral guidelines of the NIH will prevail, especially for secondary assignments to NIEHS. Letter of Intent Receipt Date: January 9, 1998; Application Receipt Date: February 20, 1998.

PA-98-008: Exploratory/Developmental Grants for Diagnostic Cancer Imaging

The Diagnostic Imaging Program (DIP), of the Division of Cancer Treatment and Diagnosis (DCTD) solicits exploratory/developmental (R21) grants that articulate highly innovative research concepts in diagnostic cancer imaging. Within each area of importance in imaging, there exists a need for innovative and creative approaches leading to new avenues of research. One way to encourage research into high risk/high impact areas is to provide investigators with the initial resources required to accomplish feasibility and pilot testing of innovative ideas.

Investigators with innovative ideas for research in diagnostic cancer imaging have previously had difficulty identifying potential funding sources. The R21 mechanism will provide investigators at all career levels with a defined level of funding adequate for the initial feasibility testing of high risk/high impact concepts and, if the concepts are viable, for the generation of experimental preliminary data. This would render the investigators competitive for funding through the research project grant (R01) and/or First Independent Research Support and Transition (FIRST) (R29) award mechanisms, thus potentially leading to the establishment of new research programs in areas that might have previously remained unexplored.

HL-98-002: Immunogenetics of Inhibitor Formation in Hemophilia

The goals of this initiative are to be able to predict those patients most likely to develop inhibitors, to specifically and safely block inhibitor formation, and to induce tolerance or neutralize existing inhibitors, so that the risks and suffering caused by antibody inhibitors is reduced or eliminated.

This RFA will use the NIH individual research project grant (R01) mechanism of support. For this RFA, funds must be requested in $25,000 direct cost modules and a maximum of seven modules ($175,000 direct costs) per year may be requested. Any necessary escalation must be included within the number of modules being requested. Only limited budget information will be required and any budget adjustments made by the Initial Review Group will be in modules of $25,000. Applicants may request up to four years of support. The specific number to be funded will, however, depend on the merit and scope of the applications received and on the availability of funds.

Because expertise in both hematology and immunology would be beneficial, collaboration of investigators engaged in these and other appropriate disciplines is encouraged. Particular encouragement is offered to experienced immunologists to apply their research knowledge to the problem of antibody inhibitors in hemophilia. Letter of Intent Receipt Date: February 10, 1998; Application Receipt Date: March 24, 1998.

PAR-98-007: Innovation Grant Program for Approaches in HIV Vaccine Research

Continued on Page 20

New X-Ray Imaging Gives Sharper View of Breast Cancer

Method Uses Both Absorption and Refraction of Rays Through Tissue

by Kathryn Gavin

A new, experimental X-ray imaging technique developed in part at Brookhaven National Laboratory is raising hopes for sharper detail and more information from future mammograms and other imaging procedures.

Although the technique is about five years away from clinical trials, images made at BNL's National Synchrotron Light Source (NSLS) facility gave up to 25 times better contrast than conventional imaging techniques.

The new method, called diffraction enhanced imaging or DEI, is described in the November issue of *Physics in Medicine and Biology* by scientists from BNL, the Illinois Institute of Technology (IIT), North Carolina State University and the University of North Carolina.

"Our studies on DEI have relied on the intense, tunable X-rays produced by the NSLS," said BNL physicist William Thomlinson. "Now, the challenge is to take it from today's experimental stage to future use in mammography, and other medical and materials imaging as well."

Both at the NSLS and in recent tests at the Advanced Photon Source at Argonne National Laboratory in Illinois, DEI produced a dramatic contrast between normal tissue and tumors, an important accomplishment for mammography.

"Mammography presents very difficult imaging problems because of the density of the tissues which often hide tumors," says team member Dr. Etta Pisano, chief of mammography in the department of radiology at UNC. "With our method, we have produced images showing improved detail of cancerous tumors in human breast tissue. The detail is outstanding."

The approach also offers more information than traditional mammography, allowing both the absorption and the refraction of the X-rays to be measured.

In conventional mammograms, differences in tissue densities and composition show up as contrasting areas due to X-ray absorption, allowing physicians to see tumors or changes in tissue. But differences between healthy and cancerous tissues are very small, and scattering of X-rays can lead to blurring and even lower contrast, making it difficult to detect small tumors. The recent DEI tests showed up to 25 times better contrast than normal in a quality-control phantom.

The DEI method uses a single-energy (monochromatic) fan beam of X-rays — instead of the broad-energy beam used in conventional imaging. The object is scanned through the beam.

The key to the new imaging method is an analyzer crystal placed between the object and the X-ray detector. The analyzer can differentiate between X-rays that are traveling much less than one ten thousandth of a degree apart.

"This method of line scan imaging reduces scatter and helps us visualize low-contrast areas that otherwise would be lost," explained Dean Chapman, director of IIT's Center for Synchrotron Radiation Research and Instrumentation.

DEI produces two images. The first, or refraction, image highlights the edges of structures in the object. Objects that have very little absorption contrast may have strong refraction properties, which this image will highlight. An example is the fine, thread-like fibers that characterize some malignant tumors. Normally difficult to see using conventional radiography, they are clearly visible in the refraction image.

The second DEI image, the apparent absorption image, is similar in appearance to a normal radiograph of the object but shows improved contrast. "Since the analyzer rejects X-rays that are scattered through small angles by various types of tissues, this method is sensitive to tissue structure," explained Thomlinson.

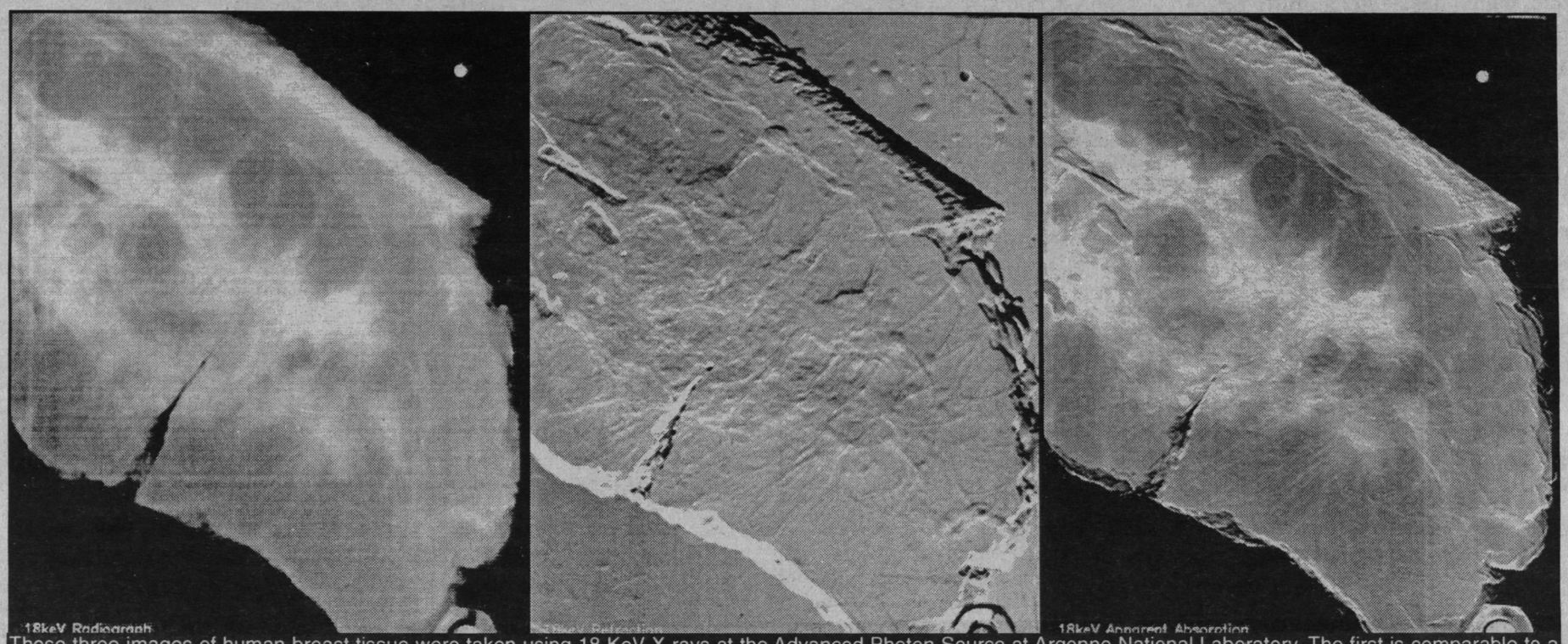
The journal article describes results achieved at the NSLS using a "phantom" breast model, created by the American College of Radiology for quality control in mammography.

More recently, preliminary tests using human breast tissue at Argonne's APS also showed much higher contrast than conventional images. The APS work has already demonstrated that the technique works equally well at the X-ray energy used in conventional mammography and at a higher energy level, although the higher-energy X-rays caused a lower radiation dose to the breast tissue.

The researchers say DEI could be used in experimental clinical trials within five years and possibly in routine mammography in 10 years. In addition to mammography, potential applications of DEI include the imaging of other low-contrast tissues and organs such as kidneys, and in non-destructive testing of materials.

To continue this research, the team has established its own experimental station at the NSLS, on the beam line called X15A. The beam line will provide the necessary experimental time to advance the technology over the next two years or more.

The authors of the paper, titled "Diffraction Enhanced X-ray Imaging," are BNL's Thomlinson, Zhong Zhong, Fulvia Arfelli, Nicholas Gmur and Ralf Menk; IIT's Chapman; Dale Sayers of the physics department at North Carolina State University; and Eugene Johnston, David Washburn, and Pisano, all of the department of radiology at the University of North Carolina.■



These three images of human breast tissue were taken using 18 KeV X-rays at the Advanced Photon Source at Argonne National Laboratory. The first is comparable to a conventional mammogram. The second and third were taken using the DEI method developed by scientists from Brookhaven National Laboratory, Illinois Institute of Technology, the University of North Carolina and North Carolina State University. Note the dramatic increase in contrast between the conventional and DEI images.

Seismic Event... Continued from Page 3

the U.S. government. No such acoustic signature was observed. Neither the large underwater drilling apparatus that would have been necessary for such a test, nor any radioactivity, was observed. Drs. Richards and Kim further noted the presence of several aftershocks in the region, which would not be expected if the event had been a nuclear test.

"Aftershocks are common for earthquakes, but would not be detectable at IMS stations after small nuclear explosions at Novaya Zemlya," Dr. Richards said.

Drs. Richards and Kim also analyzed the seismic waves produced by the event and recorded by seismological monitoring stations scattered throughout Eurasia. These data are collected by various U.S. government and international programs and are available to the scientific research community. Analyzing the size of shock waves at high frequencies, the seismologists found that the ratios of P to S waves were consistent with ratios for known earthquakes with epicenters near Novaya Zemlya. This technique, which has been carefully refined at Lamont-Doherty and elsewhere, provides the most definitive evidence that the Aug. 16 event does not have "explosive characteristics," the scientists said.

The U.S. government needs to provide mechanisms that allow officials to draw on new research in their decision-making, the scientists said.

"When the research community is able to demonstrate a good new method of discrimination, or the need for good communication to non-IMS stations with openly available data, the development must be assessed and operational procedures perhaps revised," Drs. Richards and Kim wrote in *Nature*, adding that the existence of more than 10,000 seismographic research stations across the globe should be able to provide supplementary data on any problem event.

Despite the U.S. government's refusal to acknowledge a mistake, both that government and the IMS have the technology to discern earthquakes from nuclear explosions, the scientists said. "Our capability to monitor the CTBT is magnificent. We have all these discriminants upon which knowledgeable decisions can be based," Dr. Richards said.■

Digital TV... Continued from Page 6

information controls what exercises the viewer sees.

Unfortunately, with current delivery systems, multicasting is impractical, and, in many places, impossible. Transmission of personalized multicasting requires a tremendous amount of bandwidth — the datastream that accompanies the television program contains roughly 1 megabit per second. There are other problems that require attention. What if viewers — when presented with a multi-cast — desire a non-interactive television program? A multi-cast program must still be interesting for those who choose not to choose their own story. So multi-casting is also impractical in terms of production. What network would willingly pay for four programs instead of two? And the time involved to produce all four is definitely more than a forty hour week . Multicasting may be promising for education, but it would be tremendously impractical, not to mention economically infeasible, for mass-market television.

Digital television requires tremendous bit rates to transmit; almost 1 billion bits per second. Finite limitations in bandwidth on a communications channel make compression necessary to transmit the signal over standard lines. Still digital images on the Web are transmitted via the MPEG (Motion Picture Experts Group) compression standard, which enables the images to be transmitted with the least amount of interference. A similar compression standard exists for digital television. The MPEG standard reduces the bit rate, but not without some distortion of the digital transmission. Until delivery systems catch up to the digital television technology, most consumers won't be able to see the transmission at its best.

Richard Bleier, Vice President of Pay TV and Cable at Warner Brothers, spoke last for the first panel. His reaction to the earlier speakers displayed clear skepticism about the future of DTV. "When my glasses are dirty, I can't tell the difference between an analog and digital television," said Mr. Bleier. He added that "a high dose of cold water and reality should be thrown on market considerations." So consider the conference a caveat to investors in DTV: advances in technology determine what new services are possible but a combination of price, regulation (FCC), consumer interest and commercial investment will determine the future of the technology.■

Continued from Page 16

This program aims to encourage the entrance of novel and innovative vaccine discovery and development concepts into the research pipeline. As such, the emphasis of this program is on supporting vaccine research projects that are particularly innovative, novel, high risk/high impact and show clear promise in advancing AIDS vaccine design or evaluation. Applications are especially welcome from young investigators and those not currently active in the field of AIDS research. The INNOVATION Grant Program utilizes a grant mechanism which provides funds to projects of an exploratory nature to generate preliminary data for further studies. In addition, the program utilizes streamlined review and award processes to accelerate the rate of response to these new scientific opportunities. Two general areas of investigation are targeted in this iteration of the program: 1) studies to investigate the structure and immunogenicity of HIV envelope proteins, and 2) studies to investigate mechanisms that affect cellular immune responses to HIV or related lentiviruses during disease progression.

Research projects will be supported with the Exploratory/Developmental Research Grant mechanism (R21). This mechanism provides short-duration support for preliminary studies of a highly speculative nature which are expected to yield, within this time frame, sufficient information upon which to base a well-planned and rigorous series of further investigations. Applicants may request up to two years of support and up to $150,000 per annum in direct costs, although with compelling justification exceptions can be made if specific costly reagents, animals, specimens or laboratory modifications are needed to perform these studies. Program staff may be able to advise prospective applicants concerning NIAID-sponsored resources that may be available to them. The award is non-renewable; however, the hope is that grantees under this program will progress through this exploratory phase further along the research/development pipeline; applicants may elect to seek continuing support for this research through the R01 mechanism.

To help meet the research objectives defined by NIAID and the AIDS Vaccine Research Committee, research applications intended to produce preliminary data or precedent for an idea or a concept are particularly encouraged. Letter of Intent Receipt Date: February 10, 1998; Application Receipt Date: March 10, 1998.

PAR-98-006: Mentored Scientist Development Award in Research Ethics

The National Institutes of Health, Centers for Disease Control, Health Resources and Services Administration, and the Agency for Health Care Policy and Research invite biomedical, behavioral, and public health researchers to apply for the Mentored Scientist Development Award (MSDA). The MSDA will support training in research ethics for health professionals working at academic and other health-related institutions in biomedical, behavioral, or public health research, particularly research involving human participants.

The goals of the MSDA are two fold. First, the award should enhance the career of the candidate such that he or she would become an independent investigator in applied research ethics, and second, the candidate would become a resource on research ethics for the sponsoring institution and its scientific community. As such, applications for the MSDA should include a mentored research experience that will demonstrably enhance the candidate's scientific career as a research ethicist. The award is designed for investigators who would refocus their research careers to the field of applied research ethics.

As used in this program announcement, research ethics refers to ethical, legal, and social principles guiding the proper conduct of research programs, particularly focusing on scientific integrity and protection of the interests of research participants.

The candidate must have a research or a health-professional doctorate or its equivalent and should have demonstrated the capacity or have shown the potential for highly productive, independent postdoctoral research in her or his chosen field prior to applying for this award. The candidate must identify a mentor with extensive research and academic experience in ethical issues related to biomedical research and must be willing to commit a minimum of 75 percent of his or her full-time professional effort to conducting research and pursuing research career development activities for the period of the award.

Candidates must be U.S. citizens or noncitizen nationals or must have been lawfully admitted for permanent residence. Individuals on temporary or student visas are not eligible. Current principal investigators of research grants from NIH or any of the other sponsoring agencies are not eligible.

Awards from this PA will use the K01 mechanism, which provides an additional period of support to a doctoral-level candidate in a new research area or in an area that would enhance the candidate's scientific career. The candidate and mentor are responsible for the planning, direction, and execution of the program on behalf of the applicant institution. Candidates must show the capacity or potential for highly productive, independent research. The project period is for three, four, or five years depending upon prior experience and the need for additional research experience. Awards are not renewable. Letter of Intent Receipt Dates: February 6 and May 22, 1998; Application receipt Dates: March 6 and June 24, 1998.

PAR-98-005: Short-Term Courses in Research Ethics

The National Institutes of Health, Centers for Disease Control, Health Resources and Services Administration, and the Agency for Health Care Policy and Research invite applications for grants to develop, conduct, and evaluate short-term courses on ethical issues in research, particularly those involving human participants. Courses should improve the skills of biomedical, behavioral, social science, and public health researchers in identifying and addressing the ethical, legal, and social implications of their research, especially when human subjects are involved.

Support for this program will be provided through the Continuing Education Training Grant (T15), which funds educational institutions to establish or expand programs of continuing professional education. Grantees may develop, offer, and/or evaluate research ethics courses ranging from three days to six weeks in duration. For organizations wanting to teach research ethics courses, such courses should be offered at least once a year. Alternatively, courses could be developed that would be made available to the student on the Internet, on video, or in another distance-learning format. Applicants may request up to three years of support. The indirect cost rate for T15 awards is eight percent. Letter of Intent Receipt Dates: February 6 and May 22, 1998; Application Receipt Dates: March 6 and June 24, 1998.

PAR-98-009: Supplements for Embryonic Cryopreservation of Rats in Hypertension Research

The objective of this supplement program is to preserve embryos from unique rat strains that have well-defined phenotypic and genotypic characteristics and that are employed in hypertension research. Funds will be provided to investigators with active regular research project (R01), Method to Extend Research in Time (MERIT) (R37), and program project (P01) grants from the National Heart, Lung, and Blood Institute (NHLBI) for the cryopreservation of embryos for future revitalization and use. The rat model to be cryopreserved must already be in use in the parent grant at the time the supplement application is submitted. Application Receipt Dates: March 9 and November 9 each year beginning with March 9, 1998.

RFA: DK-98-007: Cellular and Molecular Approaches to Achieving Euglycemia

The National Institute of Diabetes and Digestive and Kidney Diseases, the National Center for Research Resources, the National Institute of Allergy and Infectious Diseases, the National Institute of Child Health and Human Development, and the National Institute on Aging invite investigator- initiated research grant applications to develop therapies to achieve euglycemia in people with type I diabetes. These applications could include: islet and beta cell transplantation; engineering of regulated insulin secretion in non-beta cell surrogates; hematopoietic stem cell therapy for the induction of tolerance; or development of technologies to preserve beta cell function and stimulate beta cell regeneration. Particular emphasis should be placed on the development of clinically applicable technologies.

This Request for Applications (RFA) is intended to stimulate the application of advances in cell biology, bioengineering, immunology, molecular biology, gene therapy and transplantation to the development of safe and effective therapies to regulate glucose homeostasis in humans. Collaborative efforts linking expertise in these disciplines to expertise in diabetes are strongly encouraged. Two-year pilot and feasibility applications and interactive research projects, which will support the efforts of several independent investigators working in a collaborative manner, are available within this RFA. It is anticipated that results obtained from studies supported by this RFA will aid in the development of improved therapies for the treatment of type I diabetes mellitus. Support of this program will be through the National Institutes of Health Research Project Grant (R01), Interactive Research Project Grant (IRPG), and Exploratory/Developmental Research Grant (R21) award mechanisms. Letter of Intent Receipt Date: February 19, 1998; Application Receipt Date: March 19, 1998.

ES-98-002: Chemical Mixtures in Environmental Health

The National Institute of Environmental Health Sciences (NIEHS) and the U.S. Environmental Protection Agency (EPA) share the common goal of promoting research that will ultimately reduce the extent of adverse human health effects occurring as a consequence of exposure to hazardous environmental agents. The objective of this Request For Application (RFA) is to encourage innovative experimental approaches and/or computational, statistical or predictive strategies for chemical mixtures that focus on the mechanistic basis for chemical interactions and related health effects. It is anticipated that research projects generated as a result of this RFA will provide the scientific foundation necessary to develop biologically relevant risk assessment models for human exposure to chemical mixtures. The issuance of this RFA is a joint announcement by NIEHS and EPA and reflects our common research interests. The program will be managed by both agencies to ensure complementary balance of the research portfolio. Letter of Intent Receipt Date: January 10, 1998; Application Receipt Date: February 10, 1998.

DK-98-008: Glucose Sensors in the Treatment of Type 1 Diabetes

The National Institute of Diabetes and Digestive and Kidney Diseases and the National Center for Research Resources invite investigator-initiated research grant applications to develop a glucose sensor or to create a closed-loop system for regulating blood glucose. Commercial development of needle-based sensors and minimally invasive sensors is underway. Several optical approaches are appealing and are worthy of further development but are unlikely to yield a functioning sensor in the near future. This Request for Applications (RFA) is intended to stimulate the application of advances in chemistry, engineering, cell biology, biochemistry and endocrinology to the development of novel technologies (which may include a combination of cellular and mechanical approaches) to reliably and accurately measure glucose levels as part of a system to maintain euglycemia.

This RFA allows for the submission of applications for two-year pilot and feasibility grants, regular research project grants, and interactive research project grants, which will support the efforts of several independent investigators working in a collaborative manner. Letter of Intent Receipt Date: February 19, 1998; Application Receipt Date: March 19, 1998.

DK-98-010: Immunopathogenesis of Type 1 Diabetes Mellitus

The National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development, and the National Institute of Diabetes and Digestive and Kidney Diseases invite investigator-initiated research grant applications to elucidate the immunopathogenesis of type 1 diabetes. Specifically, this Request for Applications (RFA) focuses on basic research into the role of: viral and environmental factors, the major histocompatibility complex (MHC) in susceptibility to and protection from disease, B cells and autoantibodies in disease pathogenesis, the fetal and neonatal immune response, and interactions of genetic, immune, and environmental factors in development of disease. It is anticipated that results obtained by studies supported by this RFA will enhance understanding of basic mechanisms and the application of this knowledge to the development of novel approaches to immunomodulation and immunoprevention.

This RFA is intended to stimulate the application of advances in immunology, virology, cell biology, molecular biology, and endocrinology to the study of the pathogenesis of type 1 diabetes mellitus. Participation of virologists and infectious disease experts to focus on type 1 diabetes is highly desirable. Collaborative efforts linking expertise in these disciplines to expertise in diabetes are strongly encouraged. Two-year pilot and feasibility applications and interactive research projects, which will support the efforts of several independent investigators, working in a collaborative manner, are available within this RFA. Letter of Intent Receipt Date: February 19, 1998; Application Receipt Date: March 19, 1998.

PA-98-011: Impact of HIV Variation on Immunological Recognition

The National Institute of Allergy and Infectious Diseases, National Institutes of Health, invites applications through this Program Announcement (PA) to support research to address the impact of HIV variation on immunological recognition. The objective is to foster investigations to provide information that will ultimately be useful for identifying the strain(s) of HIV that should be used for vaccine development. Increased understanding of the mechanism of HIV neutralization, identification of neutralization immunotypes, and understanding of the impact of viral variation on CTL recognition is sought. Traditional research project grant (R01) and FIRST award (R29) applications may be submitted in response to this program announcement. ■

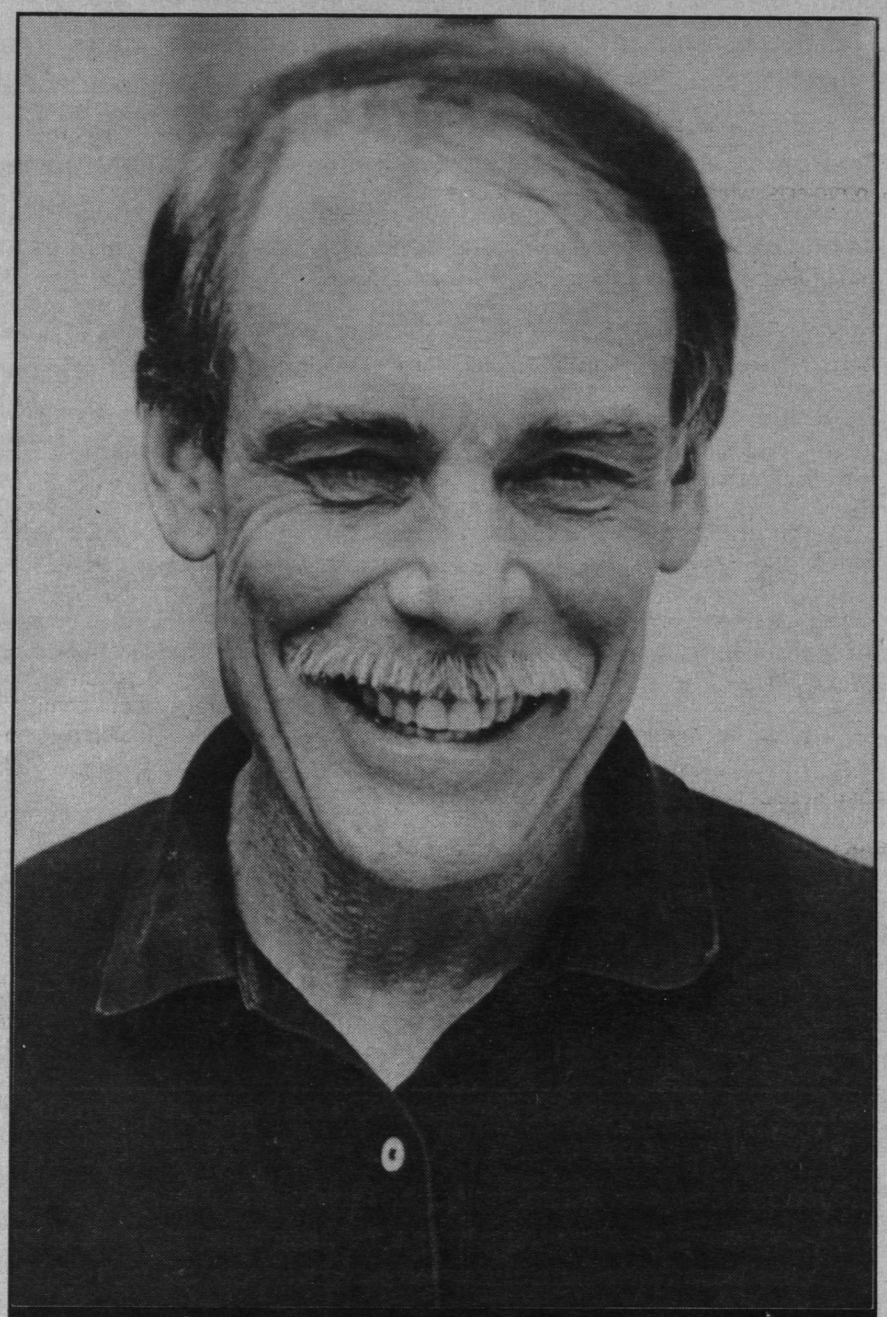
Earth Cools in Persistent, 1,500-Year Rhythm

Working From Sea Cores, Scientists Find Consistent Cycle Even Through Ice Age

by Columbia News Services

Earth's climate cools significantly and abruptly every 1,500 years or so in a persistent, regular rhythm, a team led by scientists at Columbia University's Lamont-Doherty Earth Observatory reports in the Nov. 14 issue of the journal *Science.*

The newfound naturally occurring climate cycle has continued uninterrupted over at least the past 32,000 years, said the scientists, who believe the last such cycle may have taken place 300 years ago. The periodic sudden cold spells have occurred both when the Earth was covered with massive glaciers during the last ice age and have persisted even after human civilization began to flourish in a relatively warm, ice-free era that scientists had previously thought was resistant to dramatic climate shifts.



Gerard Bond, Lamont-Doherty Earth Observatory

The newly discovered cycle appears to be "a pervasive component of the Earth's climate system," the scientists wrote. "The cycle may well be the pacemaker of rapid climate change."

The discovery will prompt a search to explain this recurring, large-scale climate pattern, and finding the cause will provide a fundamentally new understanding of how Earth's climate system can shift abruptly and dramatically, said Gerard Bond, a paleoclimatologist at Lamont-Doherty, Columbia's earth sciences research institute in Palisades, N.Y.

The finding of abrupt climate shifts in the modern era adds an important new factor in predicting future global climate change, he said. And it throws new light on historical events, such as the Little Ice Age, a cold spell that gripped the world in the 17th and 18th centuries and

Continued on Page 22

Earth Cools... Continued from Page 21

might prove to be the most recent manifestation of the phenomenon.

The scientists re-analyzed sediments cored decades ago from the bottom of the Atlantic Ocean by Lamont's legendary research vessel, the Vema, and preserved in Lamont's deep-sea core repository, which holds the world's largest collection of ocean sediment cores from every ocean in the world. The scientists found evidence that on average, every 1,470 years, plus or minus 500 years, cold, ice-bearing waters, which today circulate around southern Greenland, pushed as far south as Great Britain. The polar waters penetrated a warm North Atlantic current that prevails today, and may have disrupted the global ocean circulation pattern that keeps the North Atlantic region warm. The ocean circulation disruption may well have had far-flung, worldwide effects, they said.

The ocean sediment evidence agrees with chemical clues from Greenland ice cored by other researchers, which show that the air above Greenland cooled in precisely the same pattern. The 1,500-year cold snaps dropped average temperatures throughout the North Atlantic region within a century or two, and probably faster, the scientists said. Temperatures stayed cold for several hundred years, then warmed again as quickly as they cooled.

Reporting the finding with Dr. Bond, the lead author, were: Maziet Cheseby, Rusty Lotti, Peter Almasi, Peter deMenocal, Paul Priorie and Heidi Cullen, all of Lamont-Doherty; William Showers of North Carolina State University; and Irka Hadjas and Georges Bonani of ITP ETH in Zurich, Switzerland.

The scientists analyzed two ocean sediment cores from opposite sides of the North Atlantic, one from off the southwest coast of Greenland and the other more than 600 miles to the south, off the coast of England. The found regularly spaced layers of microscopic rock particles that originated from Greenland and Svalbard, an island in the Arctic Ocean, as well as glass from Icelandic volcanoes. The tiny particles had been transported by glacial icebergs and sea ice to the North Atlantic, deposited on the seafloor and buried by subsequent sediments. At times of coolings, the number of particles doubled or tripled in both ocean sediments, indicating that the amount of floating ice increased and extended further south.

At the same time, the scientists also analyzed the sediments for the skeletal remnants of microscopic marine plankton. They found that the abundance of cold-water-loving plants increased and the amount of warmer-water plankton decreased in the same 1,500-year cycle. That indicated that the North Atlantic surface water temperatures dropped as far south as Great Britain.

The increase in floating ice may have resulted from cooler air temperatures that caused glaciers to advance and sea ice to spread. Or cooler ocean temperatures may have allowed more ice to survive long transits before they melted. The melting ice, in turn, may have added fresh water to the North Atlantic and disrupted the delicately balanced global ocean circulation system, known as the Great Ocean Conveyor, which is set in motion by the sinking of denser, salty water in the North Atlantic.

The team was only able to confirm the pattern of abrupt climate shifts to 32,000 years ago, the limit of radiocarbon dating techniques. However, the scientists are currently seeking to learn whether the cycles persisted even before the last ice age began, as far back as the Eemian Period, more than 115,000 years ago, when the Earth's climate was relatively warm like today's.

Dr. Bond, Dr. deMenocal and William B.F. Ryan of Lamont-Doherty will lead an expedition this spring to collect new ocean sediment cores to see if the climate trend has continued to the present. They will use a new coring device that does not ruin the top sections of the sediments, which represent the most recent times, as it is thrust into the ocean floor.

The research was supported by the National Science Foundation and the National Oceanic and Atmospheric Administration. Lamont's Deepsea Sediment Repository is supported by the NSF and the Office of Naval Research.■

BIOMARKERS™

dsDNA SIZING STANDARDS

NEW 10KB MARKER

PROVIDES :

ACCURATE SIZING OF LINEAR dsDNA OVER THE 1-10KB RANGE

9 BANDS OF EQUAL ETHIDIUM BROMIDE INTENSITY

KINASE READY-REQUIRES NO DEPHOSPHORYLATION

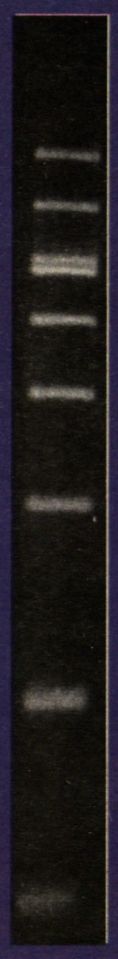
STABLE AT AMBIENT TEMPERATURE

NO DRY ICE SHIPPING CHARGES

NEXT DAY DELIVERY

100 ASSAYS CATALOG NO. M-10KB $85.00

BIOMARKER LOW



ACCURATE SIZING OF LINEAR dsDNA OF 50-1000BP

9 BANDS OF EQUAL ETHIDIUM BROMIDE INTENSITY

ACCURATE ESTIMATION OF PRODUCT YIELDS

KINASE READY-REQUIRES NO DEPHOSPHORYLATION

ALL MARKER BANDS INFORMATIVE

STABLE AT AMBIENT TEMPERATURE

NO DRY ICE SHIPPING CHARGES

NEXT DAY DELIVERY

50 ASSAYS CATALOG NO. M-1 $75.00

TO ORDER OR OBTAIN INFORMATION CALL

BioVentures,Inc.

Phone 800-235-8938 FAX 615-896-4837