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March◆1997

HIV May Play Active Role in Promoting Other Diseases

Normally Quiet JC Virus is Activated by HIV Protein, Causing Progressive Neurodegeneration

by Jeremy Kay

Any doctor will tell you that AIDS can't kill you — not directly anyway. What it can do is severely damage the immune system, opening the door for a host of nasty opportunistic infections that are more than capable of causing suffering and death. This, according to conventional medical wisdom, is how the HIV virus operates — it does little more than set the stage for other, more virulent diseases.

However, a recent set of findings indicates that HIV may play a more active role in promoting disease than was previously suspected. Researchers at Mt. Sinai and at Thomas Jefferson University in Philadelphia have shown that HIV can hijack a normal cellular regulatory protein and use it to activate a second virus, known as JCV, which causes a neurodegenerative disorder called progressive multifocal leukoencephalopathy (PML). This is the first known example of an opportunistic infection receiving a biochemical boost from interacting with HIV proteins. And the mechanism by which HIV acts to give JC virus a boost — the "hijacking" of a cellular protein that regulates gene transcription — raises the intriguing possibility that HIV might depend on the same mechanism to regulate its own replication. If this were true, the biochemical pathway that the Mt. Sinai- Jefferson team has discovered might turn out to be an important target for drugs designed to stop HIV.

The study was led by Dr. Edward M. Johnson, a professor in the pathology department at Mt. Sinai, and by Dr. Kamel Khalili, then of of Thomas Jefferson, and currently at the University of the Alleghanies. In an interview, Dr. Johnson described how a lucky twist of fate suddenly spurred his interest in the molecular biology of JCV and HIV, giving rise to the experiments that are now yielding groundbreaking results. "Our lab was working on regulation of the cell cycle — it was nothing to do with JCV. And as part of that work we cloned, sequenced, and described the Purα gene." Purα is a DNA-binding protein expressed in every human cell type. Dr. Johnson's lab showed that it binds DNA preferentially at sites with repeats of a particular nucleotide sequence. Its role within the cell is still poorly understood — "It does so many things we don't know what the primary function is," Dr. Johnson said — but originally it caught the lab's attention because of its role in cell cycle control of DNA replication and transcription.

Meanwhile, Dr. Khalili's lab had started to explore potential links between JCV and HIV at the molecular level. Although conventional wisdom about AIDS would suggest that opportunistic infec-

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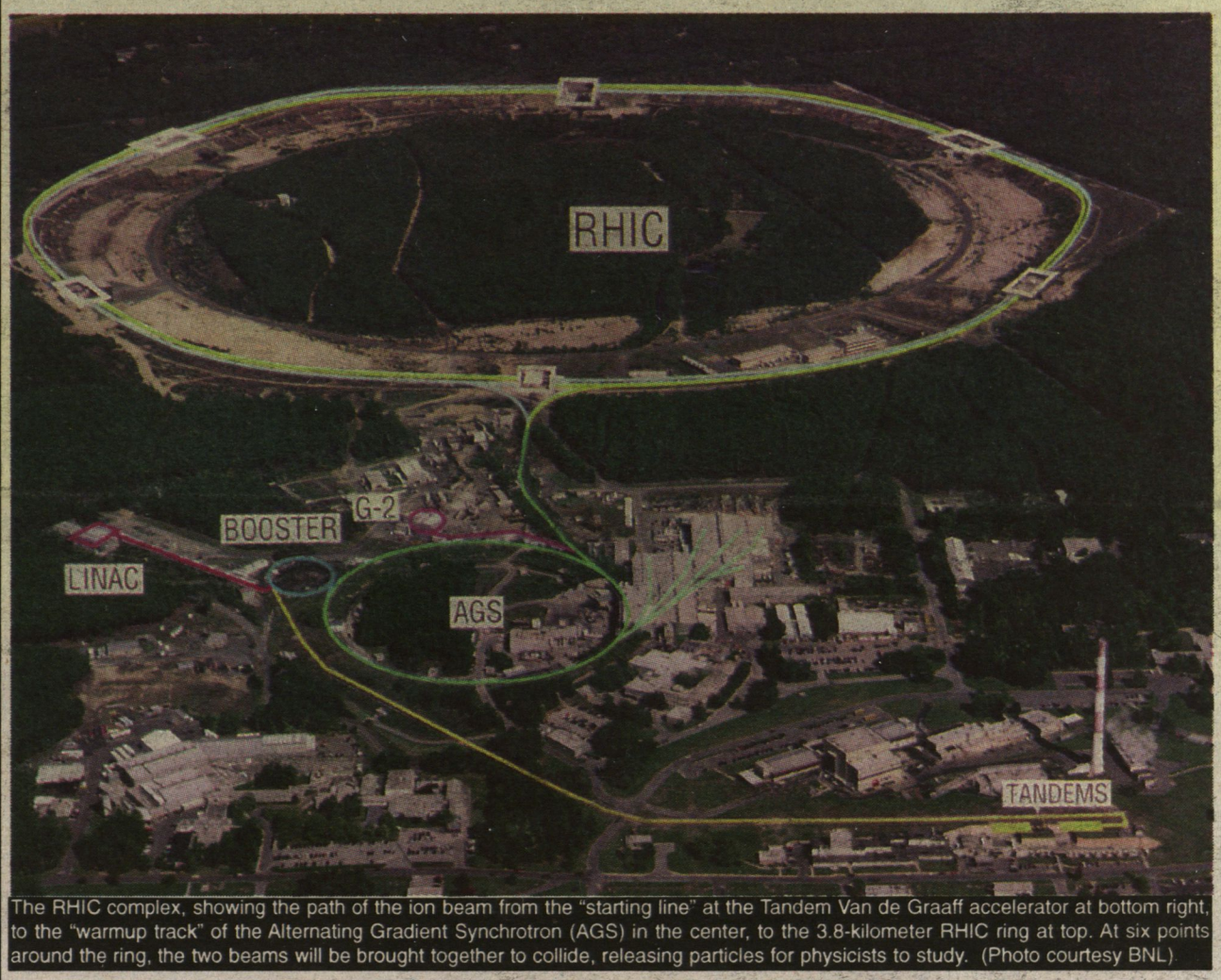
New Brookhaven "Atom Smasher" Gets Ready for 1999 Debut

Heavy Ion Collider to Allow Study of the Physics of the Early Universe

by Kara Villamil

The fastest fast. The coldest cold. The emptiest empty. To describe the Relativistic Heavy Ion Collider at Long Island's Brookhaven National Laboratory (BNL) requires the ultimate in adjectives, and a measure of awe, too.



The RHIC complex, showing the path of the ion beam from the "starting line" at the Tandem Van de Graaff accelerator at bottom right, to the "warmup track" of the Alternating Gradient Synchrotron (AGS) in the center, to the 3.8-kilometer RHIC ring at top. At six points around the ring, the two beams will be brought together to collide, releasing particles for physicists to study. (Photo courtesy BNL)

The $500 million collider, known as RHIC (pronounced "rick"), is still a couple of years away from giving physicists a glimpse of the phenomena that shaped the early universe. By late 1999, beams of speeding ions will collide head-on in its 3.8-kilometer underground ring, and four house-sized experiments will capture the showers of subatomic particles that will rain out onto sophisticated detectors.

But on a brisk Sunday afternoon in January, RHIC got its first chance to prove that a machine so complicated, so full of new technologies, could actually get off its feet. And the appetite of physicists around the world was whetted for a new means of discovery.

Training Run Tests Things Out

The January test could be compared to a race, one that took only a few millionths of a second from start to finish.

Just after two o'clock on January 26, a hundred million gold atoms were stripped of their electrons to become ions. Then, they were loosed from their "starting gate" at BNL's world-renowned particle accelerator complex.

As they rounded the bend in their "warmup track," BNL's Alternating Gradient Synchrotron accelerator, the ions were accelerated to nearly the speed of light —— the fastest that anything can go. That speed is what earns RHIC the first word of its name: relativistic, as in Einstein's theory of relativity.

Speed aside, the real race began when the ions

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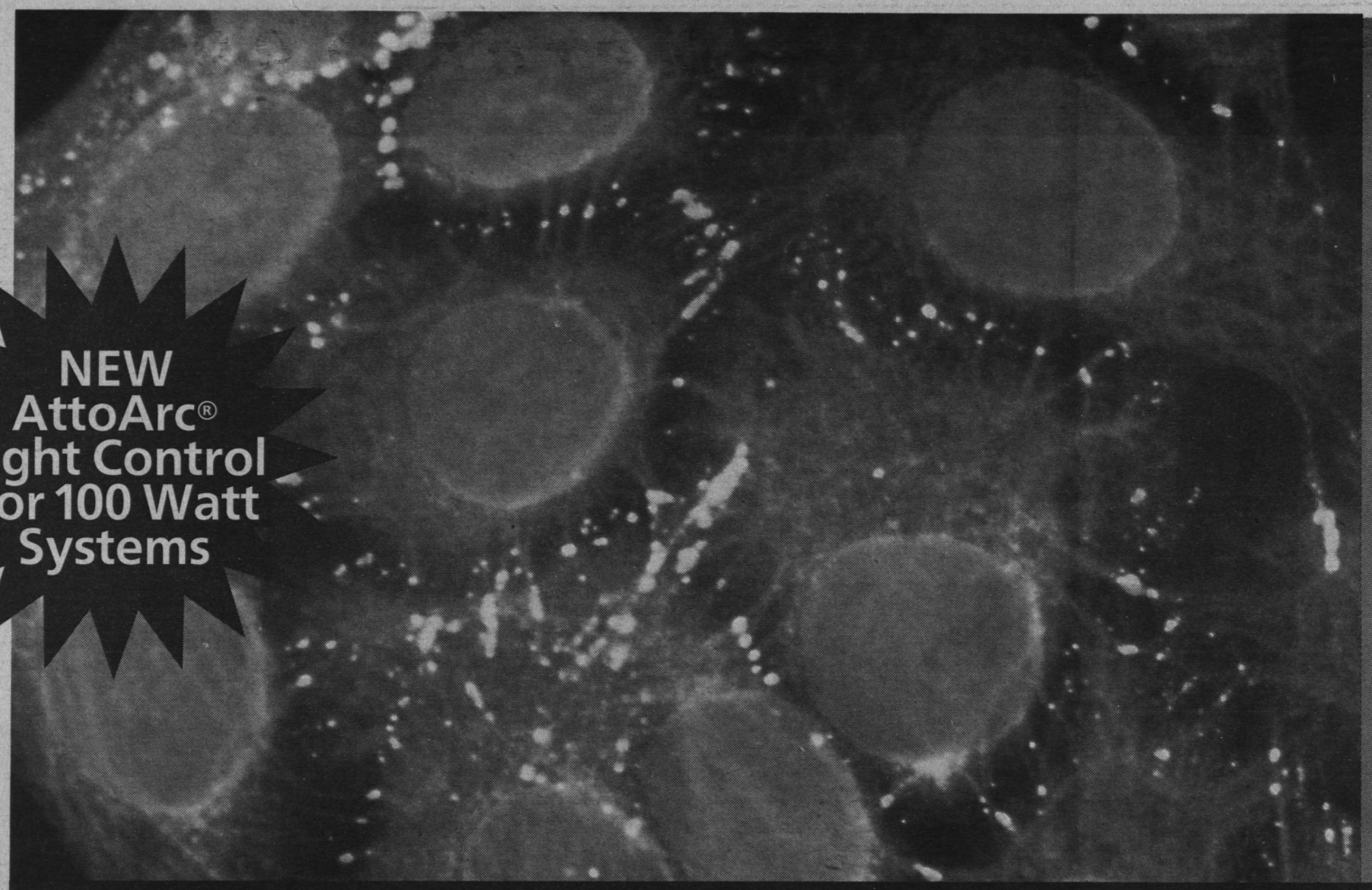

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SEE WHAT YOU'RE MISSING

FEATURES—March 1997

- Tests were performed recently on the Relativistic Heavy Ion Collider (RHIC) at Brookhaven National Lab. The new "atom smasher" is on schedule for a 1999 opening, when it will allow scientists to study the physics of the very early universe. p 1.

- The HIV virus, rather than serving merely to set the stage for opportunistic viruses, appears to promote their activation. p 1.

- "Pleiotropic" effects in gene-altered animals reveal genes whose products are employed in many distinct roles in an organism. Apo B is one such product, and it has led to much investigation. p 3.

- Why is it so hard to leave a career in science for something else? A look at this often trying and emotional choice. p 4.

- Impairment in complex motor function appears to be an early indicator of Alzheimer's disease. p 6.

- A pioneering earth scientist at Columbia's Lamont-Doherty Earth Observatory has died. Marcus Langseth was known for his work on heat flow in the earth's upper layers, and was an early contributor to plate tectonics. p 8.

- Researchers have developed a mouse model for the most common genetic cause of a lipid disorder associated with premature heart disease. p 19.

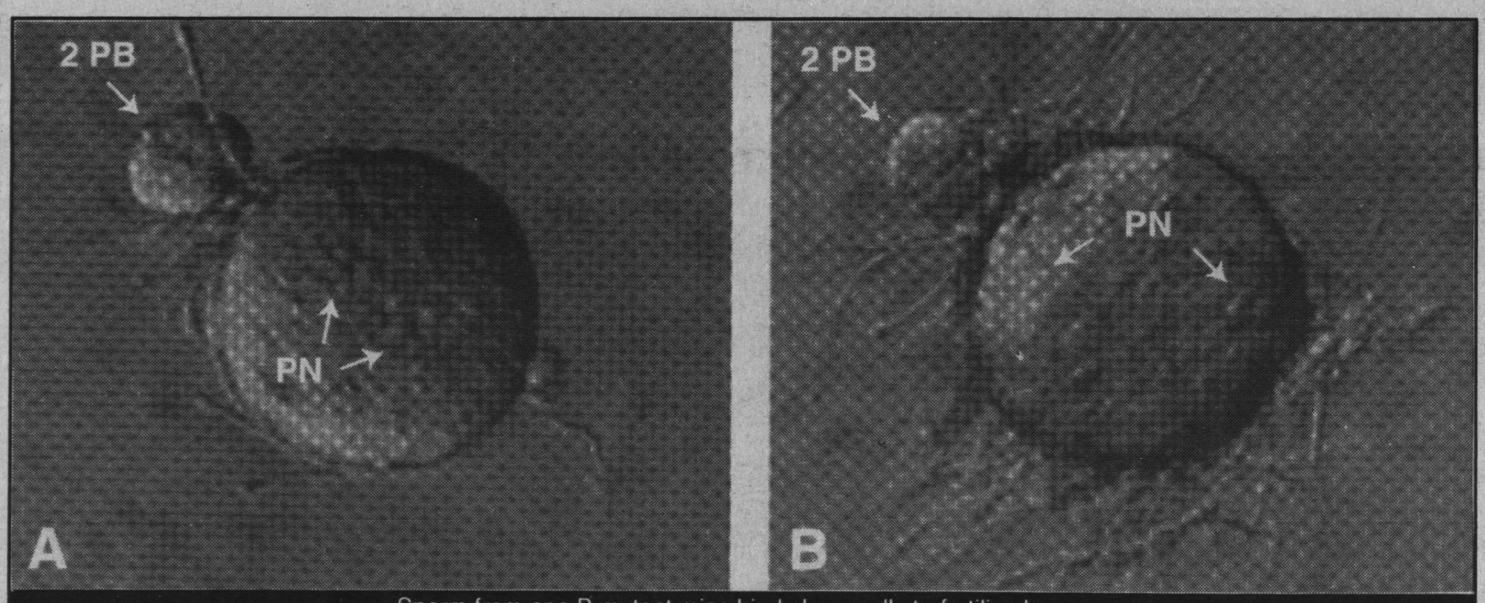
One Gene, Many Responsibilities

An Exploration of apolipoprotein B, Involved in Lipid Metabolism, Neural Tube Development, and Male Infertility

by Alan Packer, Ph.D.

With the advent of gene knockout technology, geneticists have the ability to delete any gene from the genome of a complex organism like a mouse, and determine precisely where and when that particular gene product is required.

Often, the phenotype of the mutant mouse will conform to expectations, with the affected cells or tissues known to be sites where the deleted gene is ordinarily highly expressed. Sometimes the results are less informative, with no observable defects, suggesting that other gene products can compensate for the absence of the deleted gene.



Sperm from apo B mutant mice bind abnormally to fertilized eggs

On occasion, however, the mutant mouse will exhibit a surprising array of abnormalities, opening up new lines of investigation. These pleiotropic effects, as geneticists refer to them, occur because single gene products are often employed in several distinct roles throughout the life of an organism. This precept is illustrated in an ongoing series of studies by Dr. Li-Shin Huang and her colleagues on the function of apolipoprotein B (apo B), a protein involved in lipid metabolism, neural tube development, and male fertility.

Apo B, synthesized in the liver and intestine, is a component of lipoproteins, fatty protein complexes that are required for the transport of cholesterol and other lipids. Low density lipoprotein (LDL) is specifically required for the transport and clearance of cholesterol by LDL receptors on cells in peripheral tissues. It is well established that an elevated level of plasma LDL is associated with an increased risk for coronary heart disease. Apo B, the apolipoprotein component of LDL, is the ligand for the LDL receptor, and when its synthesis or function is altered, it too is associated with a number of disorders, including heart disease when levels are elevated, and ataxia, retinitis pigmentosa, and anemia when levels are reduced.

With this in mind, Dr. Huang — now an assistant professor in the Department of Medicine at the Columbia University College of Physicians and Surgeons — carried out the targeted deletion of the apo B gene in mice, in order to understand better its function in an animal model. The work was published in a 1995 article in the *Journal of Clinical Investigation* [96:5, 2152-2161 (1995)].

In the standard gene targeting protocol, mice carrying only one normal copy of the gene are generated (heterozygotes) and are then interbred to produce mice completely lacking the gene product (homozygous null mice). In the case of apo B knockout mice, however, homozygous pups were never produced, suggesting that mice lacking apo B might be dying during embryonic development. Dr. Huang recalls that "there was a hint from a previous study in which part of apo B was deleted that there might be some neurological problems in the mice. We started to look at embryos, systematically, and we found that the homozygotes were dying in utero by day 9 of gestation."

Surprisingly, then, a protein assumed to be involved in postnatal lipid metabolism appeared to be essential for embryogenesis. Moreover, up to 10% of the apo B heterozygotes also died in utero, although at a later stage. When the mutant embryos were examined, it was noted that there was a failure of neural tube closure. Heterozygotes that were born occasionally exhibited hydrocephaly due to defective closure of the cranium, and died prematurely. "One of the things we are interested in," Dr. Huang comments, "is the nutrient or nutrients that apo B is carrying that is required for proper closure of the neural tube."

One intriguing clue as to the potential role of apo B in the embryonic development of the nervous system has come from studies in mice on the sonic hedgehog gene. Mice lacking sonic hedgehog, a potent secreted factor, exhib-

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– O P I N I O N –

Why is it so Hard to Feel Good About Making a Career Change out of Science?

by Alka Mansukhani, Ph.D.

In recent years, plenty of post-docs and "super"-post docs are looking into the possibilities of a career change from "bench science" in academia to other fields. With the funding situation in research being stiffly competitive, and job prospects after years of post-doctoral training looking increasingly bleak, many young scientists are exploring alternatives. There is always a big crowd at career-alternatives symposia featuring speakers who have made successful moves out of science and into fields such as business, editing, writing and law. In spite of the growing numbers of scientists who no longer see a future in research, there seems to be a prevalent sense of guilt and misgiving associated with leaving a research career that is probably unusual in other fields.

Take the case of Rebecca, who got her Ph.D. in molecular biology in 1993. She went on to do a post doc. According to a friend, "...no one could tell that everything wasn't quite right unless you listened carefully to her cafeteria conversations. It always started with a joke about how stupid we were to be in this field, while younger people in law and business and medicine were being successful and 'raking it in.' It often went on to state how we scientists spent our lives staring at bands on an autoradiogram that few people in the world understood and even fewer cared about. About how what we did was inconsequential in the world 'out there.'"

Somehow the fire fueling the making of a scientist was being slowly put out. Rebecca saw no future for herself in academic science. After four years, she didn't have a good project. Only when she had hit rock-bottom frustration did she look seriously into alternative careers. She applied to law school for evening classes but couldn't bring herself to tell her peers about it. For two months she worked at the bench all day and quietly disappeared at 5pm to her law classes. She probably couldn't have carried on for too much longer without it being noticed. Luckily, Rebecca landed a job with a law firm that was willing to put her through school while she worked as an associate learning technology patent law. Even after she got the offer, she couldn't bring herself to tell the boss or anyone else in the lab until she was weeks away from quitting.

There is something about the culture of academic science that causes tremendous psychological blocks when one is faced with getting out. "It is almost as though you are a deserter to the cause of the pure scientific pursuit."

What was it that prevented her from being honest with her boss and mentor? From sharing her fears and frustrations with her peers?

Susan got a Ph.D. in neuroscience and went on to a 2-year post doc. She was one of the lucky ones in that she made her career switch at a relatively early stage. Susan applied for a job as an editor with a scientific journal and she got it. She is glad that she still has the type of job where she can stay in touch with the research in her field. Her switch was also prompted by what she percieved as bleak opportunities in academic research. With a husband in acadmics as well, she felt at least one of them should be on "hard money". Her advisors in fact were quite supportive of her career moves, although she says she still faces a degree of disdain from authors who think her unqualified to review their

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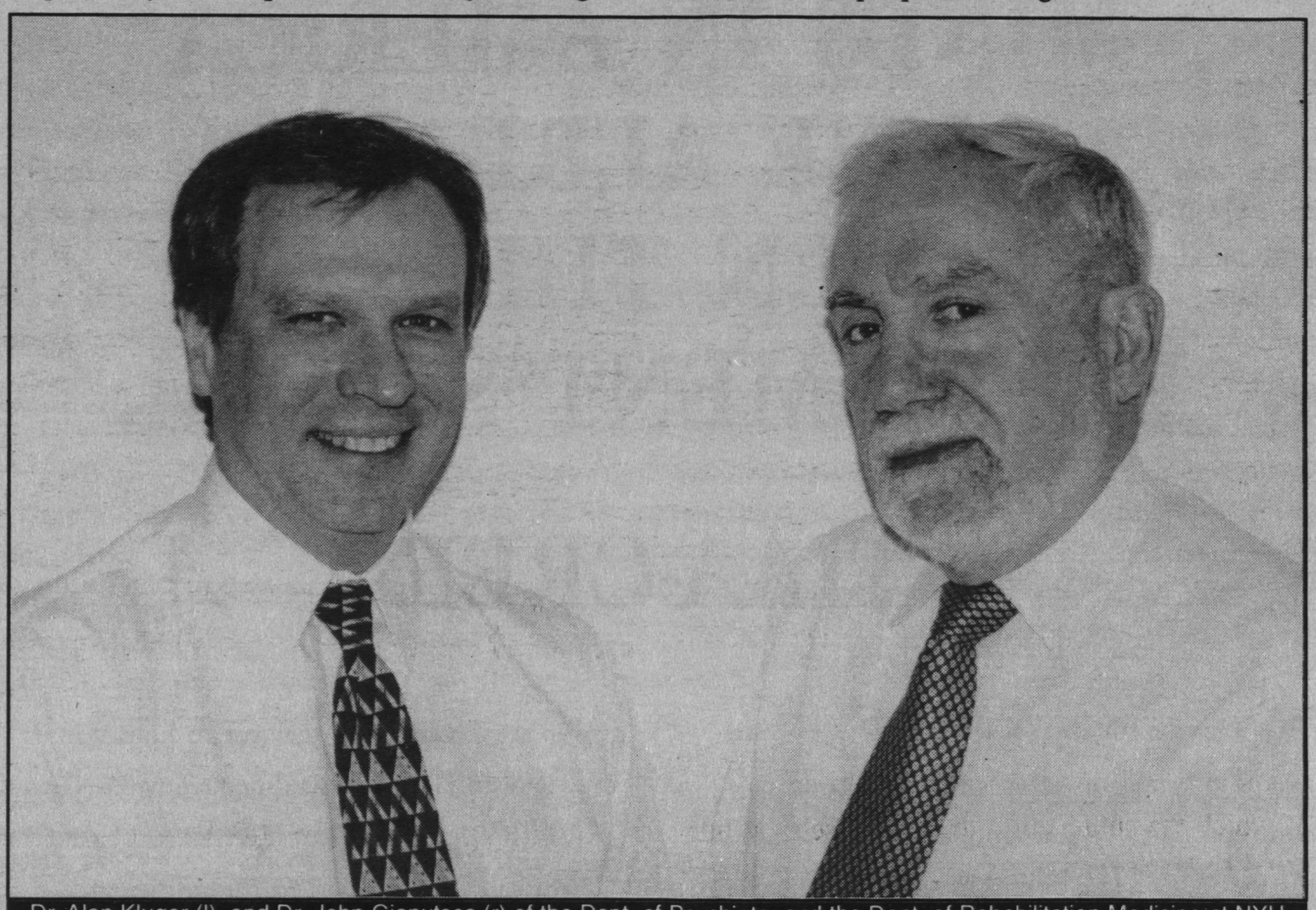
Discovering the Subtle Signs of Early Alzheimer's

Impairment in Complex Motor Function Appears to be an Early Indicator

by Gretel Schueller, *ASN&R* Staff Writer

Your eyes focus on a paper cup of hot coffee sitting on the table. Within fractions of a second, the brain has relayed a multitude of instructions to your arm as it reaches out to pick up the cup. Your arm reaches out to just the right spot; Your hand grasps the paper cup with the correct amount of pressure — squeeze too tightly, the cup crushes and its contents spill; As you lift up the cup, muscles in your arm anticipate its weight — overestimate its weight and the coffee most likely will fly out of the cup; Finally, with perfect aim, the rim of the cup reaches your mouth. What appears to be a simple action that takes a matter of seconds is in reality a very complicated process of events. Each time you move something or pick up something, your brain is anticipating what to expect and planning. "Motor performance is a very sophisticated action," explains John G. Gianutsos, director of research at New York University Medical Center's Department of Rehabilitation Medicine.



Dr. Alan Kluger (l), and Dr. John Gianutsos (r) of the Dept. of Psychiatry and the Dept. of Rehabilitation Medicine at NYU Medical Center

It was the interest in how motor function decreases in patients with white matter lesions in the brain that brought Alan Kluger, chief of neuropsychology at the Aging and Dementia Research Center at NYU's Medical Center, Gianutsos, and several other NYU scientists together. During research that originally began as an effort to study the correlation of white matter lesions in the brain with motor dysfunction, the researchers made a rather serendipitous finding. They found that motor dysfunction was significantly correlated to patients that were classified as mildly impaired or demented. In the January issue of the *Journal of Gerontology Psychological Sciences,* the NYU Medical Center researchers suggest that motor skills can be used along with more traditional cognitive tests to identify people in the earliest stages of Alzheimer's disease.

Alzheimer's disease afflicts some 4 million Americans. Yet, the disease remains poorly understood: no one knows precisely what causes the disease, let alone how to cure it. One of the hallmarks of Alzheimer's is brain lesions consisting in part of clumps of protein called beta-amyloid. This protein is a breakdown product of another protein called amyloid precursor protein, a structural component of neurons and other cells that is constantly being made in normal brains. And normally, beta-amyloid is constantly eliminated. For reasons no one can yet pinpoint, but very likely related to faulty genes, some people can not eliminate the protein. In their brains, bits of beta-amyloid accumulate outside the neurons, ultimately forming insoluble sheets, or plaques, of the protein. Some proteins grow into neurofibrillary tangles, tangles of twisted threads of protein that are thought to destroy the brain's nerve cells. Both plaques and tangles occur in areas of the brain known to be involved in memory and intellectual functioning. More recent evidence now suggests that brain regions serving motor and psychomotor function may also be affected by plaques and tangles.

One of the most persistent challenges in Alzheimer's research is diagnosing people in the earliest stages of the disease. Since it's a degenerative brain disease that often starts with mild forgetfulness, it's often difficult to distinguish early stages of Alzheimer's from normal memory lapses. In addition, several other conditions can also cause the loss of memory or other cognitive deficits. These conditions — most of which are treatable — include thyroid gland problems, drug reactions, depression, brain tumors, and dementia caused by blood vessel disease in the brain.

Detecting individuals in the early stages of Alzheimer's is no easy task. It involves finding an objective method of measuring the potential degeneration of the brain. Traditionally, brain imaging such as CT (computerized tomography) scan, MRI (magnetic resonance imaging), or PET (positron emission testing) are used to detect abnormalities in the brain. Neuropsychological tests are used to evaluate a person's mental abilities in many areas, including memory, problem solving, attention, calculation, and language. Doctors use both types of tests together to identify potential individuals in the early stages of Alzheimer's. However, neither of these methods is foolproof. Many factors, such as diet and the natural shrinking process of the brain with age, can give a false or clouded picture of what's taking place within a person's head. The results of cognitive tests can be skewed by the level of education of the patient.

Motor tests, on the other hand, offer an advantage over cognitive tests, say the scientists. Unlike many of the language and memory tests, motor performance tests are not dependent on a patient's level of education. In addition, Kluger and Gianutsos point out that from a practical standpoint, the early detection of motor dysfunction among nondemented and mildly impaired elderly could help identify individuals who are at risk during physical activities, such as driving a car or operating machinery.

Kluger, Gianutsos, and their colleagues studied 91 elderly individuals in an outpatient setting. The patients were classified according to a series of standard psychological tests, the global deterioration scale (GDS), into one of three groups: cognitively normal, mildly impaired, or demented. In addition to brain scans and standard language and memory tests, the doctors gave the 91 individuals several motor function tests. Relative to the cognitively normal group, the mildly impaired individuals performed worse at tasks involving fine and complex motor function; the demented individuals performed even worse. What was most surprising, says Kluger, was that the combinations of motor tests were as accurate as cognitive tests in identifying the GDS scale of patients.

The motor tests included speed of finger tapping and foot tapping, hand strength, and placing pegs in holes. The most novel and sensitive motor function test used was the head tracking test designed by Gianutsos. Gianutsos developed the head tracking test not just for patients in the early stages of Alzheimer's, but also for stroke and head trauma victims. Much like a virtual reality computer game, the "player" wears a headpiece. The individual must move their head accordingly

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it central nervous system malformations (holoprosencephalic syndrome) that are similar to those observed in humans with cholesterol-deficiency syndromes. The subsequent finding that cholesterol is required for the generation of the mature sonic hedgehog protein links cholesterol metabolism to a key factor in neurogenesis. Dr. Huang's work on apo B, a molecule known to be involved in cholesterol transport, suggests that apo B, cholesterol, and sonic hedgehog might interact in a biochemical pathway that is required for proper development of the neuroepithelium. A letter outlining this hypothesis was published in a recent issue of *Nature Genetics* by J. Herz, T.E. Willnow, and R.V. Farese, Jr [15, 123-124 (1997)].

As for the heterozygous apo B mutant mice that were viable, on average they were found to have 37% less LDL cholesterol, as expected. When intestinal cholesterol absorption was assessed, however, no differences were observed, perhaps suggesting that the remaining apo B is sufficient for normal cholesterol absorption. Another unexpected result was obtained when the levels of apo B messenger RNA and protein in the mutant mice were examined by Dr. Huang. "If you look at these mice that have only one apo B allele, the messenger RNA is at about one half of normal levels," she says. "But if you look at the plasma apo B, that's not the case. It's actually much lower than you would expect. So what I'm doing now is asking why this is the case. I'm using a cellular model, specifically hepatocytes from the apo B heterozygotes to look at the secretion of apo B by cells."

The other major abnormality in the heterozygous apo B mutant male mice — and the subject of a recent paper in the *Proceedings of the National Academy of Sciences* [USA 93, 10903-10907 (1996)] — is their severely compromised fertility. When it was found that a significant proportion of the apo B mutant males were difficult to breed, Dr. Huang initiated a collaboration with Dr. Jon Gordon, an expert on infertility in the Departments of OB/GYN and Pediatrics at the Mt. Sinai School of Medicine.

A series of in vitro and in vivo fertility tests were carried out in order to determine the point at which the subfertility manifests itself. While mating behavior was found to be normal, only 3% of eggs examined were fertilized in vivo by sperm from apo B heterozygotes. The rate of successful in vitro fertilization was 0%. Finally, the overall sperm count was found to be depressed, the sperm less motile, and their survival in vitro lower than sperm from age-matched, wild-type controls.

Interestingly, while the apo B mutant sperm were unable to fertilize intact eggs, when the zona pellucida — the egg's outer glycoprotein coat — was removed, they were able to fertilize 84% of the eggs in vitro. When the sperm binding to these zona-free eggs was examined, however, it was found to be abnormal. Ordinarily, sperm cease binding to the egg surface upon fertilization due to the block to polyspermy — the mechanism that prevents fertilization by more than one sperm. In the apo B mutant mice, many sperm remained bound to the egg after fertilization, indicating some kind of abnormality on the sperm surface.

As Dr. Huang, Dr. Gordon, and their colleagues point out in their paper, male infertility in humans undoubtedly has many causes. Their work now raises the possibility that alterations in apolipoprotein B levels might be one of the underlying factors here. In fact, the abnormalities in sperm motility and fertilization displayed by the apo B mutant mice are similar to those seen in many infertile human males.

Dr. Huang's current work on the role of apo B in spermatogenesis includes an attempt to characterize the pattern of expression of apo B in the mouse testis. She is also interested in exploring the incomplete penetrance of the apo B mutant phenotype, since some of the mutant mice are fertile. "When we made these mice they had a mixed genetic background, so that might explain it," she says. "We are currently testing the apo B knockout on different genetic backgrounds to see if the phenotype is modified."

Further study of apo B in this animal model promises to yield important insights into several aspects of mammalian physiology, and illustrates the potential for genetic approaches to identify "new" roles for "old" proteins.■

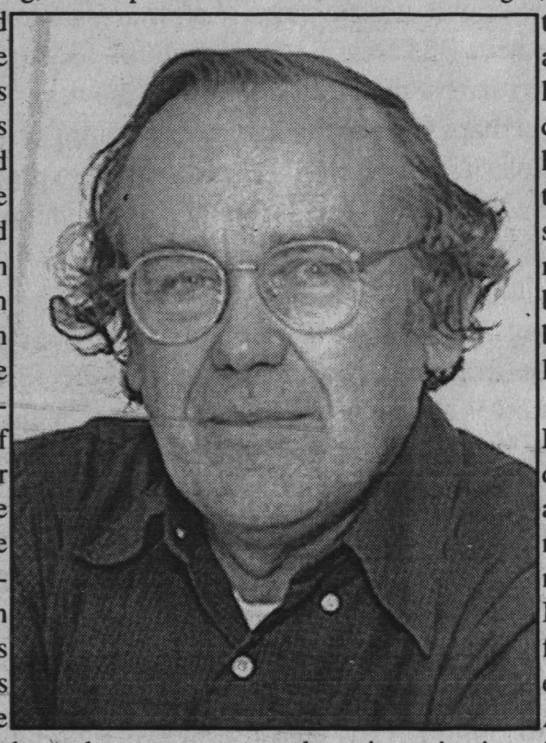
Pioneering Earth Scientist Dies

Marcus Langseth of Lamont-Doherty, an Early Contributor to Plate Tectonics

by Columbia News Services

Marcus Gerhardt Langseth, a pioneering earth scientist at Columbia University's Lamont-Doherty Earth Observatory for 40 years, died on Saturday January 4, 1997 at his home in Palisades, N.Y. He was 64. The cause was lung cancer, said his wife, Lillian Langseth.

In the late 1950's and early 1960's, Dr. Langseth, working at Lamont with Robert "Sam" Gerard and Lamont's founder Maurice Ewing, developed one of the first modern instruments and techniques for measuring the flow of heat through the Earth's upper layers. On numerous cruises in the 1960's aboard Columbia's research vessel, the Vema, he relentlessly gathered heat-flow measurements from all the world's oceans. With these data, he and Richard Von Herzen at the Woods Hole Oceanographic Institution compiled the first global picture of how and where heat flowed near the Earth's surface. The picture they painted helped prove the emerging theory of plate tectonics and revealed how the ocean floor evolved. Dr. Langseth's global heat-flow explorations also ultimately led to the remarkable discovery of hydrothermal vent systems at the mid-ocean ridges, where hot geysers belch mineral-rich, 700-degree water that supports extraordinary biological communities.



Between 1966 and 1975, Dr. Langseth adapted his heat-flow devices to measure the heat escaping from the moon's interior, in an effort to explore the moon's deep structure and evolution. He headed the Apollo Lunar Heat Flow Experiment, which made the only measurements ever of the moon's heat flow. In spite of a series of unlucky mishaps, including a misstep by an astronaut that scuttled the instrument on Apollo 16, the experiment proved that Earth's satellite had dissipated much of its original internal heat and showed no signs of recent volcanic activity.

Dr. Langseth was born in Lebanon, Tennessee, on Nov. 24, 1932. His parents separated three years later under Depression-era strain, and he lived with his siblings until age 12 in the Monroe Children's Home in Nashville, where his mother subsequently got a job.

In the summer of 1953, he walked into the newly founded Observatory, seeking summer employment. He got a job the same day working with the pioneering seismologist Jack Oliver, who was recording seismic waves of explosions being set off to build the Palisades Parkway. After graduating with a B.S. degree from Waynesburg College in 1954, he returned to Lamont for the summer and joined the staff full- time in 1955. After a two-year stint in the Army from 1956-1958, he came back to Lamont as a research staff assistant and the following year decided to pursue graduate studies under Lamont Director Ewing.

"In those days, graduate students were sent out to sea with a mission to collect as much data from as many instruments as possible from every ocean," said Walter C. Pitman III, special research scientist at.Lamont, who was a shipmate of Dr. Langseth's on many of those pioneering voyages. While Dr. Pitman became an expert on magnetic data that confirmed seafloor spreading, for example, Dr. Langseth was assigned the task of launching a research program to collect global seafloor heat-flow measurements until then poorly known.

The rapidly emerging heat-flow measurements from around the world's oceans showed that oceanic rocks were not much colder than continental rocks, as many scientists had assumed because continental rocks are rich in heat-generating radioactive elements. The explanation was that high heat flowed at the mid-ocean ridges, where molten rock rises from the mantle and solidifies to create new seafloor. Dr. Langseth's heat-flow evidence provided corroborating evidence of the heat engine that drives plate tectonics: As young seafloor spreads out from mid-ocean ridges, it gradually cools until it becomes dense enough to sink back into the mantle, 200 million years after it was born.

In the late 1970's Dr. Langseth made the surprising discovery that ocean sediments at the very apex of mid-ocean ridges — the apparent fount of rising hot magma — were cold. Intrigued by this enigmatic finding, scientists were prompted to dispatch the submersible ALVIN to a ridge summit for closer investigations. They found the first hydrothermal vents, which gushed superheated water into the cold, deep ocean and allowed heat to escape. The mineral-rich vents also nourished never-seen-before communities of animals that thrived without sunlight.

Even before Dr. Langseth earned his Ph.D. degree at Columbia in 1964, he was already among the world's few heat-flow experts, so he was asked to lead the lunar heat-flow experiments. For the hard lunar surface, he helped designed special drill equipment to insert the heat- flow probes, which were also specially designed to operate in the moon's airless atmosphere. The instruments were first placed aboard the ill- fated Apollo 13 mission. On the Apollo 15 mission, an obstruction kept the probe at only half its intended depth. On Apollo 16, the instrument was set up and ready to go when an astronaut, walking in a bulky spacesuit and unable to see his feet, accidentally tripped and cut the cable leading to the probe. The experiment was finally conducted on the final Apollo 17 mission and confirmed that the moon had lost much of its internal heat long ago. Dr. Langseth was given NASA's Special Achievement Award.

Dr. Langseth continued his heat-flow studies to the present, most recently finding unusual patterns in subduction zones where plates descend into the mantle. In the 1990's, he chaired a scientific committee that organized the first unclassified scientific missions aboard Navy nuclear-powered submarines. Three missions so far to the Arctic Ocean have given scientists a wealth of new data on a region where permanent ice and frigid weather have deterred extensive exploration in the past.

In 1993, Dr. Langseth was appointed as the Palisades Geophysical Institute Senior Scientist at Lamont. He was also an adjunct professor of earth and environmental sciences at Columbia. Dr. Langseth married Lillian Protz in 1963 and lived in Palisades. In addition to his wife, he is survived by two sisters, Christine Benagh in Nashville, Tennessee And Elva Corbitt in Lewisville, Texas.■

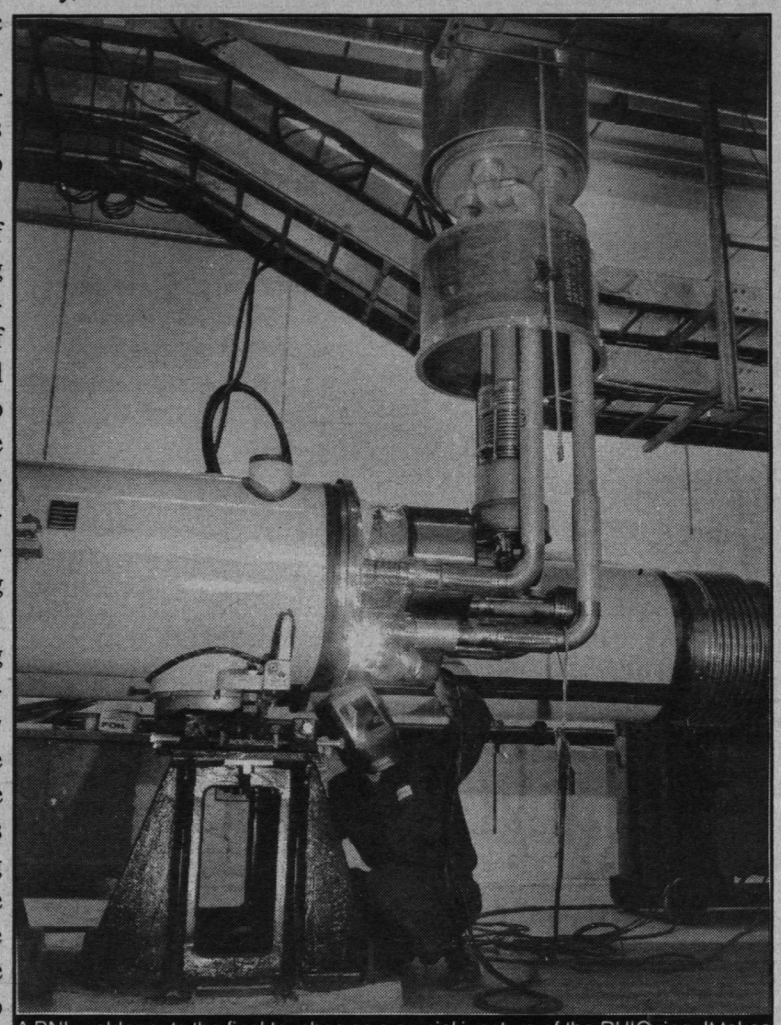
Continued from Page 1

entered RHIC's underground tunnel, traveling through a thin tube that contained the emptiest of emptiness, an extremely high vacuum of 10^{-10} torr. With practically no air molecules as obstacles in their way, the ions continued down the track at high speed, guided by magnetic fields.

The source of those guiding fields — superconducting magnets — is what helps make RHIC impressive, and the January test so notable.

The collider's backbone is a double ring of over 1,700 long, cylindrical magnets, strung together end to end like beads in a double-strand necklace. Each magnet contains yards of niobium titanium filament, which loses all resistance to electricity flow when cooled to about 4 Kelvin, or -269 Celsius. So, with the help of liquid-helium cooling to make the magnets the coolest of the cool, the superconducting cable can carry enough electricity to maintain the beam-guiding field without blacking out all of Long Island's power grid.

The January test "race" sent ions speeding 600 meters down RHIC's tunnel, through a section of magnets that has been completely installed and joined together. The finish line was a block of steel, marking the end of the completed section. But when RHIC's magnets are all linked together, and commissioning begins about two years from now, there will be no finish line — just a never-ending two-lane racetrack, guiding one beam clockwise and one counterclockwise. At six intersections, the two lanes will cross, allowing collisions to occur.



A BNL welder puts the final touches on a crucial juncture of the RHIC ring. It takes 50 electrical connections, 20 welded joints and 4 bolts to make the juncture tight enough to withstand the high-voltage, low-temperature conditions necessary to accelerate the RHIC beam. (photo courtesy BNL)

The Physics of the Early Universe

RHIC's January test was an achievement for the accelerator physicists, engineers, industrial suppliers and technicians who worked for years to design and build RHIC. Their work continues, with more magnets to be installed and connected, and more tests to pass until beam can circulate throughout both rings. By 1999, RHIC should be completely assembled and the ring "conditioned," or prepared for use.

Meanwhile, hundreds of physicists from all over the world are compiling their part of RHIC — the four experiments that will witness the collisions between the ions as they run head-first into one another.

For a layperson, or even a scientist outside the field of nuclear physics, the biggest question might be, "Why do we need to build such a huge machine in order to smash atoms together?" The answer to that question, the physicists say, is our undying curiosity about how matter is put together to make up the universe, and how that matter emerged from the Big Bang at the universe's birth.

Theorists postulate that, at a millionth of a second after the Big Bang, the universe's most elementary particles — quarks and gluons — floated free and unhampered in a souplike state of matter unlike any seen before or since. This quark-gluon plasma, as it is called, lasted only a little while. But out of this primordial particle soup came the organized quark-and-gluon bundles we now call protons, electrons and neutrons. And from those, of course, came atoms.

RHIC's goal, then, is to recreate what hasn't been seen since that fleeting moment after the Big Bang. But it will replay history in reverse. Instead of creating atoms out of particle soup, RHIC will attempt to slam the atoms together so hard and so fast that they will combine into a hot dense soup, and their constituent quarks and gluons will be set free. Using atomic species like gold and lead gives them more bang for their buck — such "heavy ions" mean more protons and neutrons to smash together, and more possibility that a detectable quark-gluon plasma will be formed.

Particle Detectives

So, for a fleeting moment, just as brief as the universe's beginning instant, RHIC's physicists hope that the quark gluon plasma will exist once again.

They also hope they'll be able to see the signs of the plasma if it is created. For a quark-gluon plasma won't hang around for too long before transforming into a shower of millions of other particles. So, the physicists' job will be to capture that particle shower and trace each one back to its origin in the collision zone.

The task is akin to figuring out how a car is put together by picking up the pieces after a demolition derby. Enter the particle detectives, a quartet of house-sized "experiments."

Called PHENIX, STAR, BRAHMS and PHOBOS, each of the four will specialize in finding and interpreting different signs of activity from within the atomic collisions. Several will use arrays of tiny microchips that can capture a flying particle and send the signal of that capture back to a computer, then get ready to capture a new particle millionths of a second later. Some will use huge magnets made of Russian steel, contributed by former Soviet physicists, to allow the detection of ghostly muon particles.

To design and build one of these monstrous experiments requires the cooperation of an international collaboration of hundreds of physicists and engineers, divided into teams that can bring each detector component to fruition.

Each experiment has instilled its own loyalties in its members, and collegial rivalries have sprung up as well. Seventy-two BNL experimenters make up the "home team," but physicists from Columbia University, the State University of New York at Stony Brook and 85 other institutions in 22 states and 18 foreign countries are all taking part. All in all, RHIC will have over 800 "users" poring over particle data for the first signs that quark gluon plasma has been formed.

The experiments are already taking shape in cavernous halls around the RHIC ring, with huge cranes hoisting parts into place. The progress of PHENIX assembly, for example, is tracked every day on the World Wide Web with a digital picture of where things stand. PHENIX members around the world can see their creation taking shape remotely.

The completion of the RHIC ring and the completion of the experiments will roughly coincide, if all goes according to schedule. By late 1999, the dual goals of making RHIC work and using it for groundbreaking physics should be in full swing, both through the heavy-ion program and the Japanese-funded effort to collide spin-polarized protons. When it all comes together, the eyes of the physics community will be on Long Island.■

FUNCTIONAL TRKB NEUROTROPHIN RECEPTORS ARE INTRINSIC COMPONENTS OF THE ADULT BRAIN POSTSYNAPTIC DENSITY

Wu K. Xu JL. Suen PC. Levine E. Huang YY. Mount HTJ. Lin SY. Black IB.

Molecular Brain Research. 43(1-2):286-290, 1996 Dec 31.

Neurotrophins have long been thought to act as target-derived factors that regulate the survival and differentiation of afferent neurons. Recently, brain-derived neurotrophic factor (BDNF) was shown to elicit rapid increases in synaptic activity of cultured hippocampal neurons by enhancing responsiveness to excitatory input. These findings suggest a postsynaptic localization of neurotrophin receptors. In this study, we examined the expression of trkB, a high-affinity receptor for BDNF, in the postsynaptic density (PSD), a proteinaceous specialization of the postsynaptic membrane. Western blot analyses with antibodies to trkB revealed localization to the PSD in adult rat cerebral cortex and hippocampus. Only the full-length, active form of trkB was detected in PSD samples. BDNF treatment of the adult cortical PSD resulted in a 5-fold increase in trkB autophosphorylation, supporting the contention that the PSD contains functional trkB. Truncated trkB, which does not contain the tyrosine kinase signaling domain, though present in membrane fractions, was undetectable in the PSD. The presence of trkB in the PSD is consistent with a role for neurotrophins in the regulation of synaptic activity via direct postsynaptic mechanisms.

QUASI-LIKELIHOOD REGRESSION MODELS WITH MISSING COVARIATES

Paik MC.

Biometrika. 83(4):825-834, 1996 Dec.

his paper presents; methods to handle missing covariates when the quasi-likelihood equations for the complete data are available. Our suggestion is to replace the functions of the missing data appearing in the quasi-likelihood equation with their conditional means given the observed data or with unbiased predictors, so that the resulting equation is unbiased. We focus on two models. One is a random effects model for count data, where random effects are treated as missing covariates. The other is the overdispersed binomial regression model with partially missing covariates. We also investigate the efficiency of the proposed estimates relative to the maximum likelihood estimators.

HYDRODYNAMICAL DESCRIPTION OF 200A GEV/C S+AU COLLISIONS - HADRON AND ELECTROMAGNETIC SPECTRA

Sollfrank J. Huovinen P. Kataja M. Ruuskanen PV. Prakash M. Venugopalan R.

Physical Review C-Nuclear Physics. 55(1):392-410, 1997 Jan.

We study relativistic S+Au collisions at 200A GeV/c using a hydrodynamical approach. We test various equations of state (EOS's), which are used to describe the strongly interacting matter at densities attainable in the CERN-SPS heavy ion experiments. For each EOS, suitable initial conditions can be determined to reproduce the experimental hadron spectra; this emphasizes the ambiguity between the initial conditions and the EOS in such an approach. Simultaneously, we calculate the resulting thermal photon and dielectron spectra, and compare with experiments. If one allows the excitation of resonance states with increasing temperature, the electromagnetic signals from scenarios with and without phase transition are very similar and are not resolvable within the current experimental resolution. Only EOS's with a few degrees of freedom up to very high temperatures can be ruled out presently. We deduce an upper bound of about 250 MeV for the initial temperature from the single photon spectra of WA80. With regard to the CERES dilepton data, none of the EOS's considered, in conjunction with the standard leading order dilepton rates, succeed in reproducing the observed excess of dileptons below the rho peak. Our work, however, suggests that an improved measurement of the photon and dilepton spectra has the potential to strongly constrain the EOS.

FDA REGULATION OF TOBACCO ADVERTISING AND YOUTH SMOKING - HISTORICAL, SOCIAL, AND CONSTITUTIONAL PERSPECTIVES

Gostin LO. Arno PS. Brandt AM.

Jama: Journal of the American Medical Association. 277(5):410-418, 1997 Feb 5.

Perspectives on tobacco control in American society have shifted markedly. As the view that smoking as a voluntarily assumed health risk has declined, the social and political environment has become more conducive to industry regulation. This transformation can be traced to the mounting evidence of the health risks of secondary smoke; the addictive quality of nicotine; the vulnerability and exploitation of young people; and industry knowledge of the harmful effects of tobacco. Regulation of tobacco advertising and promotions by the Food and Drug Administration (FDA) raises serious concerns about constitutional protection for commercial speech. However, the minimal informational value of tobacco advertising suggests that it should be afforded a low level of constitutional protection. The FDA regulations impose reasonable "time, place, and manner" restrictions, leave open alternative channels of communication, restrict messages that are harmful to the public health, do not restrict political speech, prevent misleading messages, and help deter the unlawful sale of tobacco products to miners. The regulations meet the traditional criteria for regulating commercial speech, in that the government's asserted interest is strong, the agency's regulations directly advance that interest, and the regulations are no more extensive than necessary. Thus, the judiciary should defend the FDA's historical social and legislative mission to protect the public health.

AN ANTISENSE TRANSGENIC STRATEGY TO INHIBIT THE MYELIN OLIGODENDROCYTE GLYCOPROTEIN SYNTHESIS

Jaquet V. Gow A. Tosic M. Suchanek G. Breitschopf H. Lassmann H. Lazzarini RA. Matthieu JM.

Molecular Brain Research. 43(1-2):333-337, 1996 Dec 31.

To understand the function of the myelin oligodendrocyte glycoprotein (MOG), a myelin specific protein of the central nervous system, transgenic mice were produced. The transgene is a fusion gene containing 1.9 kb of murine myelin basic protein promoter, 430 bp of rat MOG cDNA. in the reverse orientation and 4.5 kb of human proteolipid protein gene. In spite of high expression of antisense MOG mRNA in the oligodendrocytes, MOG synthesis wets not inhibited in transgenic mice. This lack of inhibition of MOG underlines the difficulties encountered with antisense transgenic strategies.

THE BREAKDOWN OF OLIVINE TO PEROVSKITE AND MAGNESIOWUSTITE

Wang YB. Martinez I. Guyot F. Liebermann RC.

Science. 275(5299):510-513, 1997 Jan 24.

San Carlos olivine crystals under laboratory conditions of 26 gigapascals and 973 to 1473 kelvin (conditions typical of subducted slabs at a depth of 720 kilometers) for periods of a few minutes to 19 hours transformed to the phase assemblage of perovskite and magnesiowustite in two stages: (i) the oxygen sublattice transformed into a cubic close-packed lattice, forming a metastable spinelloid, and (ii) at higher temperatures or longer run durations, this spinelloid broke down to perovskite and magnesiowustite by redistributing silicon and magnesium while maintaining the general oxygen framework. The breakdown was characterized by a blocking temperature of 1000 kelvin, below which olivine remained metastable, and by rapid kinetics once the reaction was activated.

PREPARATION AND MICROSTRUCTURAL STUDY OF CEO2 THIN FILMS

Tian CY. Du Y. Chan SW.

Journal of Vacuum Science & Technology A-Vacuum Surfaces & Films. 15(1):85-92, 1997 Jan-Feb.

Epitaxial and textured ceria films were prepared by conventional electron-beam evaporation on (001) LaAlO3, (1 (1) over bar 02) R-cut sapphire, (001) Au, and (001) Pd substrates using ceramic and metallic sources. Deposition temperature and deposition rate were varied to determine their effects on the formation of the CeO2 films. It was also found that the epitaxial formation of CeO2 films varied with different substrates and evaporation sources. Ceria films grew epitaxially on sapphire with a deposition rate less than 0.5 Angstrom/s in the temperature range of 650-750 degrees C using either ceramic or metallic source. The epitaxial growth of CeO2 on LaAlO3 occurred at deposition rates as high as 1.0 Angstrom/s at a deposition temperature as low as 600 degrees C using a metallic source, while on the (001) Au substrate, only a textured structure was observed between 580 and 700 degrees C and at deposition rates from 0.3 to 1.0 Angstrom/s. On a (001) Pd substrate, the deposited CeO2 films showed a different microstructure corresponding to ceramic and metallic sources at deposition rates of 0.2-0.5 Angstrom/s and from 700 to 750 degrees C. The epitaxial ceria films were achieved using a ceramic source, while the polycrystalline ceria films of multiple twinning were obtained using the metallic source. The epitaxial growth temperature of CeO2 on these substrates was empirically found to be around 700 degrees C (i.e., 0.35 T-m). (C) 1997 American Vacuum Society.

CHINESE HAMSTER CELLS EXPRESSING ANTISENSE TO METALLOTHIONEIN BECOME SPONTANEOUS MUTATORS

Rossman TG. Goncharova EI. Nadas A. Dolzhanskaya N.

Mutation Research - Fundamental & Molecular Mechanisms of Mutagenesis.

373(1):75-85, 1997 Jan 3.

The functions of metallothioneins (MTs) have been debated for at least a decade. Because it seems unlikely that they evolved only to protect cells against exogenous heavy metals, it has been suggested that MTs have roles in scavenging reactive intermediates, controlling zinc and copper homeostasis, and controlling transfer of zinc to transcription factors and other proteins, Previously, we demonstrated that Chinese hamster G12 cells which overexpress MT have greatly reduced spontaneous mutation rates, suggesting that MT evolved to prevent spontaneous mutagenesis induced by free nuclear zinc ions. We have now isolated G12 transfectants which express antisense RNA to MT. Immunofluorescent staining reveals MT protein in both the nucleus and the cytoplasm in parental cells. A clone expressing high levels of antisense RNA (AMT30) shows reduced basal and induced levels of MT protein. AMT30 cells are hypersensitive to cadmium, zinc, copper and mercury chlorides as well as to menadione. Glutathione levels in AMT30 and G12 cells do not differ. AMT30 cells are spontaneous mutators, showing a spontaneous mutation rate 5-10 times that of G12 cells or G12 cells transfectRecent studies utilizing alanine scanning mutagenesis have identified a major ligand binding domain of the secreted recombinant insulin receptor composed of two subdomains, one between amino acids 1 and 120 and the other between amino acids 704 and 716. In order to obtain a more detailed characterization of these subdomains, we examined the binding of an insulin superanalog, des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin, to alanine mutants of the ligand binding determinants of these subdomains. cDNAs encoding mutant secreted recombinant receptors were transiently expressed in 293 EBNA cells, and the binding properties for this analog of the expressed receptors were evaluated. In general des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin binding correlated with insulin binding, suggesting that both peptides bound to the receptor in a similar manner. Alanine mutations of eight amino acids (Asn(15), Phe(64), Phe(705), Glu(706), Tyr(708), Leu(709) Asn(711), and Phe(714)) of the receptor produced the most profound decreases in affinity for des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin, suggesting that interactions with these amino acids contributed the major part of the free energy of the ligand-receptor interaction. Mutation of Arg(14) and His(710) to Ala produced receptors with undetectable insulin binding but an affinity for des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin only 8-23-fold less than for native receptor. Further analog studies were performed to elucidate this paradox. The receptor binding potencies of His-Ag and Asp-B10 insulins for these receptor mutants appeared to parallel their relative potencies for native receptor. In contrast the receptor binding potency of des-(B25-30)-[Tyr-B25 alpha-carboxamide]insulin was disproportionately increased for these mutants when compared with its potency for native receptor.ed with vector alone. Only transfectants which show a high level of MT antisense expression (i.e., AMT30) had greatly elevated spontaneous mutation rates. These results support our hypothesis that a major role of MT is to act as an endogenous antimutagen probably via scavenging of reactive intermediates in the nucleus. AMT30 cells should be useful in delineating the sources of spontaneous mutagenesis.

ANALOG BINDING PROPERTIES OF INSULIN RECEPTOR MUTANTS - IDENTIFICATION OF AMINO ACIDS INTERACTING WITH THE COOH TERMINUS OF THE B-CHAIN OF THE INSULIN MOLECULE

Mynarcik DC. Williams PF. Schaffer L. Yu GQ. Whittaker J.Journal of Biological *Chemistry. 272(4):2077-2081, 1997 Jan 24.*

Recent studies utilizing alanine scanning mutagenesis have identified a major ligand binding domain of the secreted recombinant insulin receptor composed of two subdomains, one between amino acids 1 and 120 and the other between amino acids 704 and 716. In order to obtain a more detailed characterization of these subdomains, we examined the binding of an insulin superanalog, des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin, to alanine mutants of the ligand binding determinants of these subdomains. cDNAs encoding mutant secreted recombinant receptors were transiently expressed in 293 EBNA cells, and the binding properties for this analog of the expressed receptors were evaluated. In general des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin binding correlated with insulin binding, suggesting that both peptides bound to the receptor in a similar manner. Alanine mutations of eight amino acids (Asn(15), Phe(64), Phe(705), Glu(706), Tyr(708), Leu(709) Asn(711), and Phe(714)) of the receptor produced the most profound decreases in affinity for des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin, suggesting that interactions with these amino acids contributed the major part of the free energy of the ligand-receptor interaction. Mutation of Arg(14) and His(710) to Ala produced receptors with undetectable insulin binding but an affinity for des-(B25-30)-[His-A8, Asp-B10, Tyr-B25 alpha-carboxamide]insulin only 8-23-fold less than for native receptor. Further analog studies were performed to elucidate this paradox. The receptor binding potencies of His-Ag and Asp-B10 insulins for these receptor mutants appeared to parallel their relative potencies for native receptor. In contrast the receptor binding potency of des-(B25-30)-[Tyr-B25 alpha-carboxamide]insulin was disproportionately increased for these mutants when compared with its potency for native receptor.

PHASE-TRANSITION BEHAVIOR IN THE RANDOM-FIELD ANTIFERROMAGNET FE0.5ZN0.5F2

Hill JP. Feng Q. Harris QJ. Birgeneau RJ. Ramirez AP. Cassanho A.

Physical Review B-Condensed Matter. 55(1):356-369, 1997 Jan 1.

We present a combined magnetic x-ray and neutron scattering study of the order parameter of the diluted antiferromagnet Fe0.5Zn0.5F2 in an applied field. This system is believed to be modeled by the three-dimensional random-field Ising model. A long range ordered (LRO) state is prepared through a zero-field-cooled procedure (ZFC). The evolution of this LRO state is studied on warming at fixed field. The x-ray order parameter data are well described by a power-law-like transition at all fields with an exponent beta(ZFC) varying from 0.21 to 0.12. The transition region Is broadened and may be described by a Gaussian distribution of transition temperatures, centered at T-C(H), of-width sigma(ZFC)(H). It is found that sigma(ZFC)(H)=AH(2)+B. This rounding is attributed to anomalously slow dynamics, which prevents equilibrium being attained for experimentally relevant time scales for T<T-M(H) where T-M(H) is the temperature below which metastability effects occur. The apparent critical behavior in fact represents a continuous evolution from metastable behavior towards equilibrium behavior. Neutron scattering studies on the same sample allow identification of T-C(H) with the temperature at which the correlation length of the zero-field-cooled fluctuations reaches a maximum value, equal to the corresponding field-cooled value. A qualitative finite size scaling argument is presented to explain the H-2 width dependence. Data showing similar scaling of the width of the ZFC transition region inferred from the temperature derivative of the uniform magnetization as measured by superconducting quantum interference device magnetometry and from neutron scattering measurements of the pseudocritical scattering are also presented. These results lead to an interpretation of indirect specific heat measurements in which the ZFC peak structure, previously attributed to critical fluctuations, is seen instead to arise entirely from a LRO contribution to the measured quantity.

REGULATION OF NF-KAPPA-B BY CYCLIN-DEPENDENT KINASES ASSOCIATED WITH THE P300 COACTIVATOR

Perkins ND. Felzien LK. Betts JC. Leung KY. Beach DH. Nabel GJ.

Science. 275(5299):523-527, 1997 Jan 24.

The nuclear factor kappa B (NF-kappa B) transcription factor is responsive to specific cytokines and stress and is often activated in association with cell damage and growth arrest in eukaryotes. NF-kappa B is a heterodimeric protein, typically composed of 50- and 65-kilodalton subunits of the Rel family, of which RelA(p65) stimulates transcription of diverse genes. Specific cyclin-dependent kinases (CDKs) were found to regulate transcriptional activation by NF-kappa B through interactions with the coactivator p300. The transcriptional activation domain of RelA(p65) interacted with an amino-terminal region of p300 distinct from a carboxyl-terminal region of p300 required for binding to the cyclin E-Cdk2 complex. The CDK inhibitor p21 or a dominant negative Cdk2,which inhibited p300-associated cyclin E-Cdk2 activity, stimulated kappa B-dependent gene expression which was also enhanced by expression of p300 in the presence of p21. The interaction of NF-kappa B and CDKS through the p300 and CBP coactivators provides a mechanism for the coordination of transcriptional activation with cell cycle progression.

NEUTRON AND X-RAY SCATTERING STUDIES OF FIELD-COOLED ORDERING IN THE THREE-DIMENSIONAL RANDOM-FIELD ISING MODEL

Feng Q. Harris QJ. Birgeneau RJ. Hill JP.

Physical Review B-Condensed Matter. 55(1):370-379, 1997 Jan 1.

We report a magnetic neutron and x-ray scattering study of the correlation length and order parameter of the random-field Ising magnets Fe0.5Zn0.5F2 and Mn0.45Zn0.55F2 on field cooling. Fitting the inverse correlation length, kappa, measured above the metastability temperature, T-M(H) in Fe0.5Zn0.5F2, at H=5 and 6 T to a power law yields the exponent nu=1.5+/-0.3 together with the equilibrium transition temperatures, T-N(H), which are found to be well below T-M(H). We also estimate

NEW YORK REGIONAL CALENDAR OF

MARCH 3-5

3: "Development of Columns in Visual Cortex," Michael Stryker, University of California, San Francisco, 12:00, Washington Square, Meyer Building, Room 122, New York University

3: "Essential Cohomology and Group Actions," Alejandro Adem, University of Wisconson at Madison," 1:00, Warren Weaver Hall, Room 613, New York University

3: "Can the Dynamical Chaos Explain the Origin of Thermodynamic Laws?," Geroge Zaslavsky, CIMS aned NYU's Physics Department, 3:45, Warren Weaver Hall, Room 1302, New York University

3: "ATM in Cell-Cycle Regulation, Lymphoid Development, Meiosis, and Tumor Suppression," Yang Xu, Massachusetts Institute of Technology, 12:00, HHSC Building, Room 312, Columbia College of Physicians and Surgeons

3: "Solution Structure of Deoxynucleotide Duplexes Containing 3,N_4-Ethyno-2'-Deoxycytidine Adducts," Dr. Carlos de los Santos, Dept of Pharmacology, USB, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

3: "Quantum Spins and Quantum Links: From Antiferro-magnets to QCD," Prof. Uwe-Jens Wiese, Massachusettes Institute of Technology, 2:10, Pupin, Room 831, Columbia University

3: "Translantional Regulation of Yeast GCN4: A Windon on Factors Controlling Delivery of Initiator tRNA to Ribosomes," Dr. Alan G. Hinnebusch, Chief of Laboratory of Eukaryotic Gene Regulation, National Institutes of Health, 12:00, Life Sciences Building, Room 038, SUNY Stony Brook

4: "Non-Linear Dynamics of Neuronal Ensembles: Periodic Orbits, Generalized Synchrony, and Stochastic Resonance," Steven J. Schiff, George Washington University, 4:00, Smith Hall Annex, B Level Conference Room, Rockefeller University

4: "Measure Value Solutions to the Linear Multi-dimen-sional Transport Equations with Nonsmooth Coefficients," Michael Rascle, University of Nice, 3:30, Warren Weaver Hall, Room 1302, New York University

4: "Neuronal Polarity and the Problem of Protein Localization," Prof. Gary Banker, Univerisity of Virginai Medical Center, 4:00, CUMC, 1300 York Avenue, Rockefeller University

4: "Average Cost Ray-shooting and Minimum Weight Trangulations," Steve Fortune, Bell Labs, 11:30, Warren Weaver Hall, Room 613, New York University

4: "Is Hering's Law Alive? Fast disconjugate Adaptation of Saccades," Lea Averbuch-Heller, MD, Case Western University, 4:00, Life Sciences Building, Room 038, SUNY Stony Brook

5: "Baker-Akhiezer Functions on Singular Riemann Surfaces," Lecture V, Igor Krichever, Landau Instituete for Theoretical Physics, Moscow and Dept. of Math, Columbia, 4:30, Mathematics, Room 507, Columbia University

MARCH 5-7

5: "Systematic Studies of Angiosperm Evolution-Genes, Genomes, and Morphology," Dr. Geeta Bharathan, Katherine Esau Fellow, University of California at Davis, 3:30, Life Sciences Building, Room 038, SUNY Stony Brook

5: "Enhancer-Promoter Fidelity and Chromosome Domains: A Biochemical Approach to Understanding Insulator Function," Dr. Craig Hart, Dept. of Molecualr Biology, University of Geneva, 4:00, NYU Medical Center School of Medicine, Room MSB 393, New York University

5: "Opiate Immunoregulatory Processes," George B. Stefano, SUNY Old Westbury, 11:00, Weiss Building, Room 301, Rockefeller University

5: "Heat Kernels on Riemannian Manifolds," A.A. Grigor'yan, Imperial College, London, 11:30, Warren Weaver Hall, Room 1013, New York University

6: "Coordinated Signaling by Multiple Receptors During Immune Interactions," Dr. Abraham Kupfer, Natinal Jewish Center for Immunology and Respiratory Medicine, Denver, CO, 12:00, Skirball Institute, 3rd floor, Seminar Room, New York University School of Medicine

6: "Ancient Fishes and the Earlies Tetrapods: New Discoveries from Northcentral Pennsylvania (Catskill Fm.; Late Devonian)," Ted Daeschler, University of Pennsylvania, 12:00, Anatomy Dept, HSC T-8, Room 025, SUNY Stony Brook

6: "Status of the Linear Scaling Revolution in Electronic Structure Theory," Prof. Martin Head-Gordon, University of California, Berkely, 4:30, Havenmeyer Hall, Room 309, Columbia University

6: "The Roles of CBP and Associated Coactivators in Retinoic Acid Receptor-dependent Transcription," Christopher K. Glass, University of California at San Diego, 10:00, 116 Rockefeller Research Laboratory, MSKCC, 430 East 67th St, Rockefeller Univeristy

6: "Studies of the Heptahelical TRH Receptor by Molecular Experimental and Computer Analysis," Prof. Marvin Gershengorn, CUMC, Weiss Building, Room 301, Rockefeller University

6: "Inviscid Limits for the Navier-Stokes Equations," Jiahong Wu, Institue for Advanced Studies, 11:00, Warren Weaver Hall, Room 1302, New York University

6: "Consequences of Large Scale Flow in the Earth's Mantle," Richard J. O'Connell, Harvard University, 4:00-5:00, Earth and Space Sciences Building, Room 123, SUNY Stony Brook

6: "Genetic Control of Developmental Timing in *C. elegans*," Victor Ambros, Dartmouth College, 4:00, HHSC Building, Room 301, Columbia College of Physicians and Surgeons

7: "Calcium Channel Modulation," Dr. Kathleen Dunlap, Tufts University School of Medicine," 12:00, Annenberg Building, Room 21-92, Mt Sinai School of Medicine

MARCH 7-11

7: Characterization of the Dynamics and Structure of the Denatured State of Staphylococcal Nuclease," David Shortle, Johns Hopkins University, 12:00, Black Building, Room 523, Columbia College of Physicians and Surgeons

7: "The Centenary of the Discovery of the Electron, 1897-1997," Sam Devons, Columbia, 2:10, Pupin Hall, Room 428, Columbia University

7: "Intraoperative Sarcomere Length Measurement in Human Muscles," Prof. Richard A. Lieber, San Diego VA Medical Center, 7:30am, Front Lecture Hall, HSS 535 East 70th St, Rockefeller University

7: " Branched Covers and Differential Forms on Generalized Manifolds," Juha M. Heinonen, University of Michigan at Ann Arbor, 10:00, Warren Weaver Hall, Room 1013, New York University

7: "Quasiregular Maps with Wild Branching," Seppo Rickman, University of Helsinki, 11:00, Warrene Weaver Hall, Room 1013, New York University

7: "New Theoretical Ideas in Nonequilibrium Statistical Mechanics," David Ruelle, I.H.E.S., 12:45, Warren Weaver Hall, Room 1314, New York University

7: "Some New Stochastic Models for Images," David Mumford, Brown University, 2:00, Warren Weaver Hall, Room 1302, New York University

7: "MHD Waves in the Magnetosphere," Prof. Anthony Chan, Rice University, 3:10, S.W. Mudd, Room 214, Columbia University

7: "From Bioling Stones to Smart Crystals. Supramolecular Photochemistry and Magnetic Resonance Spectroscopy of Organic Molecules Adsorbed on Zeolites," Prof. Nicholas J. Turro, Columbia University, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

10: "Neurotrophic Factors and Cytokines Involved in the Development and Plasticity of Mesencephalic dopamin Neurons," Mariann Blum, Mt. Sinai School of Medicine, 12:00, New York University School of Medicine, Jacob Bleibtreu Seminar Room, Skirall Institute, 3rd Floor, New York University

10: "X-rays, Star Formation, and The Solar Nebula," Eric Feigelson, Penn State University, 1:15, Earth and Space Sciences Building, Room 131, SUNY Stony Brook

11: "Ruminative Coping and Depression," Susan Nolen-Hoeksema, University of Michigan, 3:00-4:30, Pshychology, New York University

11: " A Genetic Analysis of Induction in the Developing Mammalian Forebrain," Dr. Anthony LaMantia, Duke University, 4:00, Life Sciences Building, Room 038, SUNY Stony Brook

SEMINARS & EVENTS

MARCH 12-20

12: "Shellfish-Toxin Interactions," Dr. Sandra Shumway, Southhampton Campus, Long Island University, 5:30, Marine Sciences Research Center, Endeavor Hal, Room 120, South Campus, SUNY Stony Brook

13: "Mass Mortality of Fossil Turtles and Modern Analogs," Prof. Roger Wood, Stockton State College, 12:00, Anatomy Dept, HSC T-8, Room 025, SUNY Stony Brook

13: "Automated Whole Genome Interpretation," Theresa Gaasterland, Argonne National Laborartory, 4:00, HHSC Building, Room 310, Columbia College of Physicians and Surgeons

13: "Multiple Bonds between Metal Atoms in One-Dimensional Polymers and Liquid Crystals," Prof. Malcolm Chisholm, Indiana University, Havenmeyer Hall, Room 309, Columbia University

13: "Transcriptional Control of B Cell Differentiation by EBF and LEF-1," Prof.Rudolph Grosschedl, Howard Hughes Medical Institue, University of California at San Francisco, 12:00, Skirball Institute, 3rd floor, Seminar Room, New York University School of Medicine

13: "Diamonds and Diamonds," Steve haggerty, University of Massachusetts at Amherst, 4:00-5:00, Earth and Space Sciences Building, Room 123, SUNY Stony Brook

14: "The Physics Basis of the ITER Final Design," Dr. Paul Rutherford, Princeton Plasma Physics Laboratory, 3:10, S.W. Mudd, Room 214, Columbia University

14: "Observational Neutrino Astrophysics," M. Koshiba, Japan Society for the Promotion of Science-Washington DC, 2:10, Pupin Hall, Room 428, Columbia University

14: "Structure and Ligand Recognition of Phosphotyrosine Binding Domains, Ming-Ming Zhou, Mout Sinai School of Medicine, 12:00, Black Building, Room 523, Columbia College of Physicians and Surgeons

17: "Neutron Star Atmospheres and their Observational Implications," George Pavlov, Penn State University, 1:15, Earth and Space Sciences Building, Room 131, SUNY Stony Brook

19: "Indirect Calorimetry in Studies on the Thermodynamics of Microbial Growth," Ted Battley, 3;30, Life Sciences Building, Room 038, SUNY Stony Brook

20: "Formation and Evolution of the Continental Lithospherric Mantle: new Evidence from Peridotites, Eclogites, and Diamonds," Steve Shirley, DTM Carnegie Institution of Washington, 4:00-5:00, Earth and Space Sciences Building, Room 123, SUNY Stony Brook

MARCH 20-31

20: "Control of Lymphoid Tissue Structure by Lymphotoxin," Dr. David Chaplin, Howard Hughes Medical Institute, Washington University School of Medicine, 12:00, Skirball Institute, 3rd floor, Seminar Room, New York University School of Medicine

21: "Nicotinic Cholinergic Mechanisms in the Central Nervous System," Dr. John A. Dani, Baylor College of medicine, 12:00, Annenberg Building, Room 21-92, Mt Sinai School of Medicine

24: "Patterns of Sequence Variation and the Structure of RNA Molecules," Robin Gutell, University of Colorado, Boulder, 4:00, HHSC Building, Room 312, Columbia College of Physicians and Surgeons

24: "Cortical Mechanisms of Motion Perception in Primates: Lesion Studies," Tatiana Pasternak, University of Rochester, 12:00, Washington Square, Meyer Building, Room 122, New York University

26: "Elliptic Solutions, Calogero-Moser Systems and Related Many-Body Problems," Lecture VI, Igor Krichever, Landau Instituete for Theoretical Physics, Moscow and Dept. of Math, Columbia, 4:30, Mathematics, Room 507, Columbia University

26: "Exploring Protein-Saccharide Interactins with Synthetic Ligands," Prof. Laura Kiessling, University of Wisconsin at Madison, University, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

27: "Exploring Protein-Saccharide Interactions with Synthetic Ligands," Prof. Laura Kiessling, University of Wisconsin, Havenmeyer Hall, Room 309, Columbia University

27: "The Importance of SIV and HIV Auxiliary Genes for the Pathogenesis of AIDS," Prof. Ronald Desrosiers, Harvard Medical School, 12:00, Skirball Institute, 3rd floor, Seminar Room, New York University School of Medicine

28: "Melting Nuclei Into Quarks-Whate we Know Now and What RHIC Will Tell Us," Barbara Jacak, SUNY at Stony Brook, 2:10, Pupin, Room 831, Columbia University

28: "Two-Dimensional Plasma Flow Past a Laser Beam," Dr. Sandip Ghosal, Los Alamos National Laboratory, 3:10, S.W. Mudd, Room 214, Columbia University

31: "Modulation of Calcium Channels," Kathleen Dunlap, Tufts University School of Medicine, 12:00, New York University School of Medicine, Jacob Bleibtreu Seminar Room, Skirall Institute, 3rd Floor, New York University

31: "Studies of Synthetic EF-Hand Peptide: Fragments of Clabinding D_{28k}," Prof. Karin Akerfeldt, Dept of Chemistry, Rutgers University, Camden, USB, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

gamma=2.6+/-0.5 and <(gamma)=5.7+/-1 for the connected susceptibility, chi, and the disconnected susceptibility, chi(dis), exponents, respectively. The x-ray data reveal a long range ordered component coexisting with short range magnetic order in the field-cooled state, for weak random fields in both samples. The nucleation of the long range order occurs below T-M(H). The intensity of the long range order component decreases with increasing field.

PLANT CYCLINS - A UNIFIED NOMENCLATURE FOR PLANT A-, B- AND D-TYPE CYCLINS BASED ON SEQUENCE ORGANIZATION [Review]

Renaudin JP. Doonan JH. Freeman D. Hashimoto J. Hirt H. Inze D. Jacobs T. Kouchi H. Rouze P. Sauter M. Savoure A. Sorrell DA. Sundaresan V. Murray JAH.

Plant Molecular Biology. 32(6):1003-1018, 1996 Dec.

The comparative analysis of a large number of plant cyclins of the A/B family has recently revealed that plants possess two distinct B-type groups and three distinct A-type groups of cyclins [1]. Despite earlier uncertainties, this large-scale comparative analysis has allowed an unequivocal definition of plant cyclins into either A or B classes. We present here the most important results obtained in this study, and extend them to the case of plant D-type cyclins, in which three groups are identified. For each of the plant cyclin groups, consensus sequences have been established and a new, rational, plant-wide naming system is proposed in accordance with the guidelines of the Commission on Plant Gene Nomenclature. This nomenclature is based on the animal system indicating cyclin classes by an upper-case roman letter, and distinct groups within these classes by an arabic numeral suffix. The naming of plant cyclin classes is chosen to indicate homology to their closest animal class. The revised nomenclature of all described plant cyclins is presented, with their classification into groups CycA1, CycA2, CycA3, CycB1, CycB2, CycD1, CycD2 and CycD3.

HIGH-RESOLUTION STABLE ISOTOPE RECORDS FROM SOUTHWEST SWEDEN - THE DRAINAGE OF THE BALTIC ICE LAKE AND YOUNGER DRYAS ICE MARGIN OSCILLATIONS

Boden P. Fairbanks RG. Wright JD. Burckle LH.

Paleoceanography. 12(1):39-49, 1997 Feb.

Benthic foraminifera in two shallow marine sediment cores from southwest Sweden were analyzed for oxygen isotopes. Several deglaciation events, previously recognized in terrestrial and lake sediments throughout the Baltic region, are identified and radiocarbon dated. An initial Baltic Ice Lake (BIL) drainage at the Mount Billingen threshold is inferred from a distinct 2.4 parts per thousand delta(18)O oscillation in one of the investigated cores. The estimated radiocarbon age for this event is approximately 10,900 C-14 years. The final drainage, which ended BIL history, occurred in two steps during the younger part of the radiocarbon plateau at 10,000 C-14 years. Biostratigraphy suggests that the final drainage took place in the climatically warm early Preboreal. At approximately 11,150 C-14 years, the deglacial trend toward lighter isotopic composition was interrupted and slightly reversed and is interpreted to represent the onset of the cold Younger Dryas period. For a few hundred years prior to the Younger Dryas, melting of the Fennoscandian ice sheet appears to have been rapid. Besides the dramatic drainage events and reduced melting during the Younger Dryas, the records display several other salinity variations. These variations may reflect ice margin oscillations during the Younger Dryas, previously identified throughout Scandinavia as ice marginal deposits. The isotopic records suggest approximately 10 climatically induced ice margin recession/readvances of the southeastern Fennoscandian ice sheet during the Younger Dryas.

POSTNATAL CHANGES IN THE LAMINAR AND SUBCELLULAR DISTRIBUTION OF NMDA-R1 SUBUNITS IN THE CAT VISUAL CORTEX AS REVEALED BY IMMUNO-ELECTRON MICROSCOPY

Aoki C.

Brain Research. Developmental Brain Research. 98(1):41-59, 1997 Jan 2.

Although it is recognized that nearly all synapses in the cerebral cortex form postnatally, little is known about the emergence of molecules necessary to render these synapses functional. This study visualized the emergence of synaptically localized NMDA receptors by immune-electron microscopic labeling of the receptor's obligatory subunit, NMDA-R1, in the developing cat visual cortex. Prior to eye-opening (postnatal day 2-10), NMDA-R1 immunoreactivity is already present within dendritic and axonal growth cones, even though these profiles are devoid of synaptic specializations. This indicates that synthesis and incorporation of NMDA-R1 into plasma membranes are independent of form vision. During the next 2-3 weeks, i.e., preceding the onset of the critical period for ocular dominance plasticity (around the fourth week), NMDA-R1 immunoreactivity changes from a diffuse distribution within dendrites to a more discrete aggregation over postsynaptic densities of axo-spinous junctions. Such clustering of NMDA-R1 at synapses may be a prerequisite for stabilization and strengthening of synapses activated by visual stimulation during the critical period. Furthermore, only during the first several weeks, intensely NMDA-R1-immunoreactive neurons are present in the infragranular layers and the white matter. Enrichment of NMDA-R1 in the deep-layer neurons may reflect the neurons' supportive role in the development of cortical circuitry, serving as transient synaptic targets for geniculate and cortico-cortical afferents while these afferents 'wait' in the infragranular layers for their ultimate, life-long target neurons to become receptive in the upper layers.

VARIABILITY AND SOURCES OF THE SOUTHEASTERN ATLANTIC CIRCULATION

Garzoli SL. Gordon AL. Kamenkovich V. Pillsbury D. Duncomberae C.

Journal of Marine Research. 54(6):1039-1071, 1996 Nov.

The 1992-1993 Benguela Sources and Transport (BEST) time series provide a quantitative view of the Benguela Current transport and the eddy held crossing 30S, as well as an estimate of the relation between its barotropic and baroclinic components. This is done by a simultaneous analysis of the BEST data derived from inverted echo sounders, pressure sensors, current meter moorings, CTD, and ADCP stations. The analysis of the time Series indicates that the annual mean baroclinic transport of the Benguela Current is 13 Sv with a total transport of 16 Sv. Through the combination of instruments the total baroclinic plus barotropic transport of the upper 2600 m was obtained without making any assumption about the level of no motion. Results from this calculation corroborated the assumption that 1000 m as a level of no motion could be used as a fairly good approximation. The stationary flow of the Benguela Current is mostly confined near the African Continent while a transient flow, composed by large eddies shed from the Agulhas retroflection, dominates the western portion of the Benguela Current. In the stationary part of the Benguela Current, both barotropic and baroclinic components are equally important while in the transient part, the barotropic is more substantial. Several rings were observed during the experiment that migrated toward the west. An initial speed of 12 km/day diminished to 6 to 7 km/day at the Walvis Ridge. The water mass source of the Benguela Current includes Indian and South Atlantic subtropical thermocline water; relatively saline, low oxygen tropical Atlantic water; and the cooler, fresher subantarctic water. Changes in thermocline salinity correlate with transport: in general when the northward transport is increasing the thermocline salinity also increases, without a decrease in oxygen. This indicates that the Benguela Current increases in strength by bringing in more subtropical thermocline water. As the Agulhas input is most effective in boosting the salinity of the upper thermocline (the South Atlantic Current water being deficit in salinity relative to the Indian Ocean source) we suggest that the spatial variations in transport are tied to Agulhas water influx, presumably associated with the eddy field.

SEN6, A LOCUS FOR SV40-MEDIATED IMMORTALIZATION OF HUMAN CELLS, MAPS TO 6Q26-27

Banga SS. Kim S. Hubbard K. Dasgupta T. Jha KK. Patsalis P. Hauptschein R. Gamberi B. Dallafavera R. Kraemer P. Ozer HL.

Oncogene. 14(3):313-321, 1997 Jan 23.

Normal cells show a Limited lifespan in culture and the phenotype of cellular senescence, Tumors and tumor cell lines have typically overcome this form of growth suppression and grow continuously as immortal cell lines in culture, We have exploited the DNA virus SV40 to study the mechanism by which human fibroblasts overcome senescence and become immortal, Multiple steps have now been identified, including inactivation of cellular growth suppressors through direct interaction with SV40 large T antigen and through mutation of a gene on chromosome 6 (designated SEN6), In this study, we sublocalize the site of SEN6 to 6q26-27 based on molecular genetic analysis, Twelve SV40-immortalized fibroblast cell lines share a deletion in this area based on assessment for loss of heterozygostiy (LOH) for seven informative markers on 6q, Two immortal cell lines (AR5 and HALneo) appeared to have retained separate single copies of chromosome 6 despite the fact that they are both derived from the same preimmortal SV40-transformant and should share the same mutated allele of SEN6 (Hubbard-Smith et al., 1992), Detailed analysis by polymerase chain reaction, restriction fragment length polymorphism and fluorescence in situ hybridization shows, however, that although they differ for 17 markers from the centromere to 6q26, they share AR5 derived sequences (eight markers) distal to 6q26 including

the minimal deletion region, further supporting the assignment of SEN6 to this region, Since human tumors including non-Hodgkins lymphoma, mammary carcinoma and ovarian carcinoma show LOH in 6q26-27, inactivation of SEN6 may be responsible for immortalization of these tumors as well.

HIGH-FREQUENCY BAROCLINIC WAVE MOTIONS IN AN EQUATORIAL OCEAN CURRENT AND RELATED TEMPERATURE FLUCTUATIONS

Ma H.

Journal of Marine Research. 54(6):1073-1096, 1996 Nov.

This paper uses a theoretical model to demonstrate the existence of a group of equatorially trapped, high-frequency (wave-periods shorter than one week), meso-to-small-scale (wave-lengths shorter than 100 km), baroclinic waves which are embedded in a geostrophic current with only vertical shear. Due to their relatively large vertical and meridional velocities, these high-frequency equatorial waves may play an important role in transporting momentum as well as heat energy in the vertical and transequatorial directions.

POSTSYNAPTIC ELEMENT CONTRIBUTES TO THE DELAY IN SYNAPTOGENESIS IN SYNAPSIN I-DEFICIENT NEURONS

Ferreira A. Li L. Chin LS. Greengard P. Kosik KS.

Molecular & Cellular Neuroscience. 8(4):286-299, 1996.

In a previous study, we reported a retardation in process outgrowth and synapse formation in cultured hippocampal neurons from synapsin I-deficient mice, were we investigated whether this delay in synaptogenesis was attributable to pre- or postsynaptic elements. The experimental paradigm used in this study involved the establishment of heterochronic cocultures of neurons from wildtype and synapsin I-deficient mice. Newly cultured axons from wild-type and synapsin I-deficient neurons established synapses with mature wild-type postsynaptic elements after 24 and 72 h, respectively. In contrast, synapsin I-deficient postsynaptic elements were able to receive synapses only after 9 days in culture, representing a 5-day delay compared to controls. The results suggest a broad role for syplapsin I in the structural development of the synapse, participating directly or indirectly in the maturation of both presynaptic and postsynaptic sites.

IRREGULAR DYNAMICS AND HOMOCLINIC ORBITS TO HAMILTONIAN SADDLE CENTERS

Ragazzo CG.

Communications on Pure & Applied Mathematics. 50(2):105-147, 1997 Feb.

We consider 4-dimensional, real, analytic Hamiltonian systems with a saddle center equilibrium (related to a pair of real and a pair of imaginary eigenvalues) and a homoclinic orbit to it. We find conditions for the existence of transversal homoclinic orbits to periodic orbits of long period in every energy level sufficiently close to the energy level of the saddle center equilibrium. We also consider one-parameter families of reversible, 4-dimensional Hamiltonian systems. We prove that the set of parameter values where the system has homoclinic orbits to a saddle center equilibrium has no isolated points. We also present similar results for systems with heteroclinic orbits to saddle center equilibria. (C) 1997 John Wiley & Sons, Inc.

DECREASED CELLULAR RETINOL-BINDING PROTEIN EXPRESSION COINCIDES WITH THE LOSS OF RETINOL RESPONSIVENESS IN RAT CERVICAL EPITHELIAL CELLS

Tannouskhuri L. Talmage DA.

Experimental Cell Research. 230(1):38-44, 1997 Jan 10.

In response to estrogen the rat cervical epithelium undergoes squamous metaplastic changes, progressing from a resting state through a proliferating, secretory stage and finally to a cornified stage,before sloughing or being reabsorbed. The transition from a secretory to a cornified epithelium is preceded by a dramatic reduction in the expression of the cellular retinol binding protein (CRBP). The associations among retinoids (retinol and retinoic acid), CRBP expression, and estrogen-induced keratinocyte differentiation were explored in cultured cervical epithelial cells. Retinoids supported proliferation of cervical epithelial cells expressing basal keratins. Alone, estrogen had no effect on proliferation and enhanced expression of keratins characteristic of stratified cervical epithelial cells. When added together, estrogen prevented retinoid effects on proliferation, whereas retinoids prevented the estrogen-enhanced expression of differentiation-associated cytokeratins. When CRBP expression was repressed by elevating intracellular cyclic AMP levels, the ability of retinol, but not retinoic acid, to block estrogen-induced changes in keratin expression was severely compromised. These results support a critical role for CRBP in cervical cell responsiveness to circulating retinoids (primarily retinol). We hypothesize that retinol inhibits estrogen-induced keratinization of the cervical epithelium, and the drop in CRBP level results in transient vitamin A deficiency within cervical epithelial cells, permitting the orderly transition from the secretory to the cornified stage. (C) 1997 Academic Press

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INDUCTION OF 8-OXO-7,8-DIHYDRO-2'-DEOXYGUANOSINE BY ULTRAVIOLET RADIATION IN CALF THYMUS DNA AND HELA CELLS

Zhang XS. Rosenstein BS. Wang Y. Lebwohl M. Mitchell DM. Wei HC.

Photochemistry & Photobiology. 65(1):119-124, 1997 Jan.

The levels of 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodGuo) in purified calf thymus DNA and HeLa cells were measured following exposure to either UVC, UVB or WA wavelengths, This DNA damage was quantitated using HPLC coupled with an electrochemical detector, The 8-oxodGuo was induced in purified DNA in a linear dose-dependent fashion by each portion of the UV spectrum at yields of 100, 0.46 and 0.16 8-oxodGuo per 10(5) 2'-deoxyguanosine (dGuo) per kJ/m(2) for UVC, UVB and UVA, respectively, However, the amount of 8-oxodGuo in HeLa cells irradiated with these UV sources decreased to approximately 2.0, 0.013 and 0.0034 8-oxodGuo per 10(5) dGuo per kJ/m(2), respectively. In contrast, the levels of cyclobutyl pyrimidine dimers were similar in both irradiated DNA and cells, Therefore, 8-oxodGuo is induced in cells exposed to wavelengths throughout the UV spectrum although it appears that protective precesses exist within cells that reduce the UV-induced formation of this oxidative DNA damage, Cell survival was also measured and the number of dimers or 8-oxodGuo per genome per lethal event determined, These calculations are consistent with the conclusion that dimers play a major role in cell lethality for UVC- or UVB-irradiated cells but only a minor role in cells exposed to WA wavelengths, In addition, it was found that the relative yield of 8-oxodGuo to dimers increased nearly 1000-fold in both UVA-irradiated cells and DNA compared with cells subjected to either UVC or UVB. These results are supportive of the hypothesis that 8-oxodGuo, and possible other forms of oxidative damage, play an important role in the induction of biological effects caused by wavelengths in the UVA portion of the solar spectrum.

OLFACTORY EPITHELIAL ORGANOTYPIC SLICE CULTURES - A USEFUL TOOL FOR INVESTIGATING OLFACTORY NEURAL DEVELOPMENT

Gong QZ. Liu WL. Srodon M. Foster TD. Shipley MT.

International Journal of Developmental Neuroscience. 14(7-8):841-852, 1996 Nov.

An in vitro slice culture was established for investigating olfactory neural development. The olfactory epithelium was dissected from embryonic day 13 rats; 400 mu m slices were cultured for 5 days in serum-free medium on Millicell-CM membranes coated with different substrates. The slices were grown in the absence of their appropriate target, the olfactory bulb, or CNS derived glia. The cultures mimic many features of in vivo development. Cells in the olfactory epithelium slices differentiate into neurons that express olfactory marker protein (OMP). OMP-positive cells have the characteristic morphology of olfactory receptor neurons: a short dendrite and a single thin axon. The slices support robust axon outgrowth. In single-label experiments, many axons expressed neural specific tubulin, growth-associated protein 43 and OMP. Axons appeared to grow equally well on membranes coated with type I rat tail collagen, laminin or fibronectin. The cultures exhibit organotypic polarity with an apical side rich in olfactory neurons and a basal side supporting axon outgrowth. Numerous cells migrate out of the slices, of which a small minority was identified as neurons based on the expression of neural specific tubulin and HuD, a nuclear antigen, expressed exclusively in differentiated neurons. Most of the migrating cells, however, were positive for glial fibrilary acidic protein and S-100, indicating that they are differentiated glia. A subpopulation of these glial cells also expressed low-affinity nerve growth factor receptors, indicating that they are olfactory Schwann cells. Both migrating neurons and glia were frequently associated with axons growing out of the slice. In some cases, axons extended in advance of migrating cells. This suggests that olfactory receptor neurons in organotypic cultures require neither a pre-established glial/neuronal cellular terrain nor any target tissue for successful axon outgrowth. Organotypic olfactory epithelial slice cultures may be useful for investigating cellular and molecular mechanisms that regulate early olfactory development and function. Copyright (C) 1996 ISDN.

Selected Funding Updates

Compiled by Peter M. Saal
OFFICE OF THE VICE-PRESIDENT FOR RESEARCH—SUNY STONY BROOK

DoE: Program Notice 97-10 - Microbial Genome Program

The Office of Health and Environmental Research (OHER) of the Office of Energy Research, U.S. Department of Energy announces its interest in receiving applications for grants in support of the Microbial Genome Program (MGP). The MGP focus is on developing and using high-throughput microbial genome sequencing that will provide functional genomic sequence and mapping information on microorganisms: with environmental or energy relevance; of phylogenetic significance; and of potential commercial importance and application. Bioinformatics tools relating to complete genomic sequences are also of importance to the MGP.

Preapplications should be received by March 24, 1997. Formal applications should be received by June 9, 1997, to be accepted for merit review and funding in early FY 1998. To provide a consistent format for the submission, review and solicitation of grant applications submitted under this notice, the preparation and submission of grant applications must follow the guidelines given in the Application Guide for the Office of Energy Research. Access to ER's Financial Assistance Application Guide is possible via the World Wide Web at: http://www.er.doe.gov/production/grants/grants.html

NASA: NRA 97-OSS-02 - Astrophysics Data Program

The National Aeronautics and Space Administration, Office of Space Science, is releasing an announcement entitled Astrophysics Data Program (ADP); soliciting basic and applied research proposals for three Types of investigations. The due date is May 27, 1997.

Type 1 is for research involving the NASA space astrophysics data sets currently archived in the public domain; **Type 2** is for applied research to provide new and/or improved tools that enhance space based astrophysical observing, data analysis, and/or data management, and **Type 3** is for Associate Investigator (AI) investigations for the Wide Field Infrared Explorer (WIRE) mission.

The complete text of this NRA may be obtained from the OSS homepage at: http://www.hq.nasa.gov/office/oss; select "Research Announcements." Point of contact for scientific information is: Dr. Guenter Riegler, ADP Program Scientist, Code SR, NASA Headquarters, Washington, DC 20546-0001, E-mail: adp@hq.nasa.gov.

NASA: AO 97-OSS-01 - Science Investigations on the New Millenium Deep Space One Mission

Science Team Members for the New Millennium Deep Space One (DS1) Mission. The National Aeronautics and Space Administration (NASA), Office of Space Science is soliciting proposals for Science Investigations on the New Millennium Deep Space One (DS1) Mission. DS1 is a technology validation mission that will fly by Asteroid 3352 McAuliffe and Comet P/West-Kohoutek-Ikemura. The two principal instruments on the mission are a Miniature Integrated Camera and Spectrometer (MICAS) and a Plasma Experiment for Planetary Exploration (PEPE). Expertise is sought for in-flight instrument calibration; planning of instrument observations; reducing and validating technical and scientific data from the mission; preparing data for archiving in the Planetary Data System (PDS); and analyzing, interpreting, and publishing initial results. Complete AO will be available electronically from the OSS homepage at: <http://www.hq.nasa.gov/office/oss> (select "Research Opportunities").

For further information and printed copies contact: Dr. Walter F. Huebner, Code SR, Office of Space Science, NASA Headquarters, Washington, DC 20546-0001; phone: 202-358-0828 or 0292. Notice of Intent to Propose is due March 18, 1997, with Proposals due May 27, 1997.

NIST: Solicitation Number 97-04 - Digital Data Storage

The NIST Advanced Technology Program (ATP) is soliciting proposals under its focused program competition 97-04, Digital Data Storage. The goal of the Digital Data Storage focused program is to promote U.S. economic growth by supporting sustained, high-risk research and development, which will accelerate the data storage industry. The emphasis of the Program is research that will lead to digital data storage devices exhibiting at least an order of magnitude increase in data storage density (either areal or volumetric), performance, and/or cost advantages over present technology. The goal of the program will be the technology development for future large (multi-gigabyte to terabyte), low cost, high-performance data storage devices. Proposals may address technology to develop components, materials, channel electronics, and software that are specific to the data storage industry.

Topics that may be addressed include new media for magnetic and electro-optical storage devices, new materials to increase storage density and improve performance, high-performance recording heads that are vastly superior to today's state of the art, new lubricants and surface finishes for media, reliable micropositioning devices for high-precision placement of sensing devices over data tracks, channel electronics for signal-processing in order to achieve low error rates, and improved software which significantly advances the state of the art over the range extending from error detection and correction within storage units and disk controllers to management of data storage systems.

The due date for submission of full proposals is 3 p.m. Eastern time on Wednesday, May 28, 1997. An estimated $15 million in first-year ATP funding is available under this focused program competition. This is the second of three competitions planned for this ATP focused program. Only FULL proposals are being solicited under this focused program competition. Abbreviated proposals (pre-proposals) will not be accepted.

NIST: Solicitation Number 97-05 - Technologies for the Integration of Manufacturing Applications

The NIST Advanced Technology Program (ATP) is soliciting proposals under its focused program competition 97-05, Technologies for the Integration of Manufacturing Applications (TIMA). The technical goal of the TIMA focused program is to develop and demonstrate the technologies needed to create affordable, integrable manufacturing software applications those that can be rapidly integrated, reconfigured, and automatically adjust their performance in response to changing conditions and requirements. The intent of this program is to ease the flow of real-time manufacturing execution data among shop-floor software systems, as well as upstream to executive information systems and enterprise resource planning systems, laterally to design and engineering systems, and downstream to equipment control systems. The business goals of this program are to: (1) reduce manufacturing costs and cycle time; (2) reduce time-to-market for new products; (3) reduce the time and cost of starting up new factories and of changing existing factories; and (4) reduce inventories and raise levels of capacity and resource utilization.

This program is open to proposals that develop software interoperability solutions applicable to any or all manufacturing sectors. The scope of this year's competition is enlarged from the previous competition (95-12) to encompass all manufacturing domains including process industries, which were excluded before. This program will support the development of software infrastructure; software development environments; and factory integration. It will not support the development of stand-alone manufacturing applications that do not contribute to the overall goal of an adaptable "plug and play" manufacturing environment.

An estimated $15 million in first-year ATP funding is available under this focused program competition. This is the second of three competitions planned for this ATP focused program. One additional competition is planned. Pre-proposals are due no later than 3:00 p.m. Eastern time on Friday, March 14, 1997, at the address shown below. Written feedback can be expected by April 7, 1997. The due date for submission of full proposals is 3 p.m. Eastern time on Wednesday, May 28, 1997.

NIST: 97-06, Component-Based Software (CBS)

The NIST Advanced Technology Program (ATP) is soliciting proposals under its focused program competition, 97-06, Component-Based Software (CBS). The goal of the Component-Based Software focused program is to promote U.S. economic growth by supporting sustained, high-risk research and development, which will accelerate the development of a commerce in software components. The result of this focused program is expected to be widely available tools and infrastructure supporting sustained electronic commerce in semantic-based software components for large, complex systems. Projects should focus on supplying broadly enabling technology which overcome barriers to enhanced software development productivity such as technology for automatic semantic based composition of components and automated methods and tools for supporting a sustainable commerce in components. Pre-proposals are due no later than 3:00 p.m. Eastern time on Friday, April 18, 1997. The due date for submission of full proposals is 3 p.m. Eastern time on Wednesday, May 28, 1997.

NIST: Solicitation Number: 97-07 - Tissue Engineering

The NIST Advanced Technology Program (ATP) is soliciting proposals under its focused program competition 97-07, Tissue Engineering, and announces a public meeting (Proposers' Conference) for all interested parties. The goal of the Tissue Engineering Focused Program is to promote U.S. economic growth by focusing on the development of a tissue engineering industry that would have global preeminence and thus provide jobs, result in high market revenues and significantly reduce the total national healthcare costs which now exceeds $1 trillion annually. Furthermore, development of new treatment modalities with the use of tissue engineered devices will have significant societal benefits by improving the quality of life for the physically and mentally afflicted population. The acute and chronic shortage of donor tissues and organs, will make these devices life-saving in many instances. To be in scope, business plans of proposals must contribute to the overall goal of reducing direct hospital and medical costs as well as those costs associated with the long-term care of the ill or disabled. Technical plans must address one or more aspects of the design and development of tissue engineered devices for diagnostic and/or therapeutic use including (A) biomaterials, (B) cellular components, (C) manufacturing processes, and (D) implantation/transplantation technologies. The 97-07 focused program booklet is available on a World Wide Web site (http://www.atp.nist.gov). Only FULL proposals are being solicited under this

Continued Next Page

focused program competition 97-07. The due date for submission of full proposals is 3 p.m. Eastern time on Wednesday, June 11, 1997.

DoE/OER: Program Notice 97-07; Atmospheric Radiation Measurement (ARM) Program

The Office of Health and Environmental Research of the Office of Energy Research, U.S. Department of Energy (DOE), hereby announces its interest in receiving applications to support the experimental and theoretical study of radiation and clouds in conjunction with the Atmospheric Radiation Measurement (ARM) Program as part of the U.S. Global Change Research Program (USGCRP). This notice requests applications for grants to support the following four efforts:

(1) Continuation and enhancement of activities previously funded by DOE under the auspices of the ARM program via responses to earlier announcements.

(2) The modeling of clouds and radiation including aerosol effects for use in General Circulation Models (GCMs) and related models. Analysis of ARM and other data for refining, supporting, and validating model development are key aspects of research sought in this category. These activities should be closely tied to the analysis and use of data from the current and planned facilities at three Cloud and Radiation Testbed sites: the first is centered near Lamont, Oklahoma; the second has instruments operating on the Island of Manus, Papua, New Guinea, and later will have other sites in the Tropical Western Pacific; and the third site in the North Slope of Alaska region.

(3) The extension of fundamental research results or methodology to the development and evaluation of new analytic methods and algorithms that take advantage of ARM data. Methods and algorithms that are proposed to evolve from these efforts must be suitable for automated use in the routine processing of ARM data streams. Successful applications will use data from current or projected ARM instruments (singly, in combination, or in combination with data from outside the ARM program, e.g. Satellite data), to provide new ARM community data streams of high credibility and useability within the ARM Science Team.

(4) The development of advanced instrumentation for high accuracy/ precision radiometric observations and for profiling of all three phases of water in the atmosphere and lower stratosphere. Short wave radiometry is of particular present interest.

Formal applications submitted in response to this notice must be received by 4:30 p.m., EDT, April 29, 1997, to permit timely consideration for award in fiscal year 1998. For further information, contact: Dr. Patrick A. Crowley, Office of Health and Environmental Research, Environmental Sciences Division. Telephone: 301-903-3069, fax: 301-903-8519. Program information is available on the ARM WWW page: http://www.arm.gov

American Heart Association

Established Investigator Grant: support is provided to promising scientists who have recently acquired independent status for research projects related to cardiovascular disease and function and stroke that have not had previous funding. Awards are $75,000 per year for four years. Eligible applicants are U.S. citizens or permanent residents who hold an M.D., Ph.D., D.O., or equivalent degree. Awards are four years and provide $75,000 annually for salary, fringe benefits, indirect costs, and project costs (at least $40,000 for project support). Application forms and guidelines may be obtained via Internet: http://www.amhrt.org Deadline: 06/16/1997

Grant-In-Aid Awards: support is provided to encourage the most innovative and meritorious research projects from independent investigators in the broad field of cardiovascular function and disease and stroke. Awards are $55,000 per year for three years. Applicants must hold an M.D., Ph.D., D.O., or equivalent doctoral degree. Eligibility is not restricted by seniority of academic rank. Eligible applicants U.S. citizens, permanent residents, or foreign nationals (holding H1, H1B, or J1 immigrant status) who hold an M.D., D.O., Ph.D., or equivalent doctoral degree. Applicants should be faculty/staff members pursuing independent research. Eligibility is not restricted by seniority or academic rank. Grants are awarded for three years and are $55,000 per year, plus indirect costs at ten percent. Research may be performed outside the U.S., but only by a principal investigator who is a U.S. citizen.

Scientist Development Grant: awards of $65,000 per year for four years support highly promising beginning scientists in their progress toward independence. Activities are in the broad field of cardiovascular function and disease and stroke. Eligible applicants are U.S. citizens or permanent residents who hold an M.D., Ph.D., D.O., or equivalent doctoral degree. Eligible applicants are U.S. citizens or permanent residents who hold an M.D., Ph.D., D.O., or equivalent doctoral degree. Applicants should be faculty/staff members initiating independent research careers, usually at the rank of Instructor or Assistant Professor (or their equivalents). Applications may be submitted for review in the final year of postdoctoral research fellowship or in the initial years of the first faculty appointment. Applicants cannot hold or have held any other national award. Awards are $65,000 per year for four years. Awards cover salary, fringe benefits, indirect costs, and project costs (at least $35,00 for project support).

Application forms and guidelines for these three grant programs are available via Internet: **(http//www.amhrt.org)** or from institutional Sponsored Programs offices. Deadlines: 06/16/1997

HL-97-004: Rat Gene Catalog and Expressed Sequence Tag (EST) Map

The purpose of this Request for Applications (RFA) is to expand the Rat Genome Project by soliciting applications for research projects to accomplish three objectives: 1) arraying and distributing existing rat cDNA libraries, 2) developing Expressed Sequence Tags (ESTs) from those libraries, and 3) mapping a subset of those EST's. The overall goal of this effort is to construct a rat gene catalog and an EST map that will facilitate the mapping of genes in the rat and increase the value of the rat as a biomedical research model. This RFA will use the National Institutes of Health (NIH) individual research grant (R01) mechanism. Applications are encouraged that address any one or all of the objectives listed. $3.5 million (including direct and indirect costs) is available for year -01 and $1 million for year -02. Letter of Intent Receipt Date: March 28, 1997; Application Receipt Date: April 23, 1997.

PAR-97-037: Pilot Grants in Behavioral and Social Science of Aging

The Behavioral and Social Research Program (BSR) of the National Institute on Aging (NIA) is seeking small grant (R03) applications to stimulate and facilitate research in underdeveloped topics in the behavioral and social sciences of aging. This Small Grant (R03) Program provides support for pilot research that is likely to lead to a subsequent individual research project grant (R01) or a First Independent Research Support and Transition (FIRST) (R29) award application and/or a significant advancement of aging research. These R03 projects include, but are not limited to, research that is innovative and/or high risk. Application Receipt Dates: March 17, July 17, and November 17, 1997.

The Small Grant program is designed to support new, junior, and established behavioral and social science researchers interested in conducting research on underdeveloped topics in the behavioral and social sciences of aging. Collection of new data or secondary analysis of existing data is allowed. Areas of interest are limited to the topics following:

- Social Cognition in Adulthood and Old Age
- Personality in Adulthood and Old Age
- Behavior Genetics and Aging
- Interventions to Enhance Self Care in Older People
- Religiousness in Health and Aging
- AIDS in an Aging Society
- Social and Structural Factors in Health Care
- Aging and Work Organizations

PA-97-025: Research on Musculoskeletal Fitness and Sports Medicine

The National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Nursing Research invite investigator-initiated research grant applications to study a broad range of basic and clinical topics related to musculoskeletal fitness, exercise physiology and sports medicine. The National Center for Medical Rehabilitation Research of the National Institute of Child Health and Human Development encourages applications for both basic and clinical studies of musculoskeletal fitness and exercise physiology of persons with physical disabilities. Under this program announcement, the NIAMS and NICHD will support investigator-initiated research project grants (R01), First Independent Research Support and Transition (FIRST) (R29) awards, small grants (R03), program projects (P01), career development grants (K01, K02, K08), and Investigator-Initiated Interactive Research Project Grants (IRPG.) The NINR will support individual research project grants (R01 and R29.)

DK-97-007: Exploratory Grants in Chronic Renal Failure in Children

The National Institute of Diabetes and Digestive and Kidney Diseases recognizes the need to enhance research activities in Pediatric Nephrology. The Division of Kidney, Urologic and Hematologic Diseases (DKUHD) of the NIDDK invites exploratory/developmental (R21) grant applications to encourage and facilitate studies designed to develop and/or apply new promising experimental tools to the understanding of the pathophysiology and pathogenesis of events resulting in chronic renal failure and its complications, in children. Letter of Intent Receipt Date: March 18, 1997; Application Receipt Date: April 18, 1997.

DK-97-003: Helicobacter Pylori and Its Relationship to Digestive Diseases and Cancer

The National Institute of Diabetes and Digestive and Kidney Diseases, the National Cancer Institute, the National Institute of Allergy and Infectious Diseases, and the Office of Research on Minority Health in partnership with the American Digestive Health Foundation invite applications for basic and clinical research focusing on the role of Helicobacter pylori infection in peptic ulcer disease, nonulcer dyspepsia, and gastric cancer, particularly in minority populations. Studies on the epidemiology of Helicobacter pylori in minority populations, genetic susceptibility to and the acquisition of Helicobacter infection, the role of Helicobacter in development and the regulation of the inflammatory response are encouraged. The support for this RFA will be through the NIH research project grant (R01) award, the FIRST (R29) award, and the small grants (R03) award. Letter of Intent Receipt Date: March 21, 1997; Application Receipt Date: April 22, 1997.

MH-97-001: Innovative Approaches for Mircoscopic Tract-Tracing

The National Institute of Mental Health and the National Institute on Aging invite applications for grant support to research and develop innovative tract-trac-

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papers, since they assume she is not a scientist.

David's story is one of a more agonizing switch from assistant professor to an editorial position at a scientific press. After running his own lab for 5 years he had hit an all-time low. His grant funding was not renewed and lab morale was low. He felt he couldn't turn to the chairman or colleagues for help and advice because of the stigma of failure that makes one want to dissappear. David points out that scientists actually have many skills that can be valuable in other fields but are usually very poor communicators, not skilled at selling themselves. "Running a lab requires managerial skills that are highly valued out there — problem-solving, budgeting, personell management, etc. — but most scientists do not recognize that these are translatable skills and see themselves as very narrowly trained and unable to do any other type of work."

There is something about the culture of academic science that causes tremendous psychological blocks when one is faced with getting out. "It is almost as though you are a deserter to the cause of the pure scientific pursuit," said another biochemist who had gone on to work in the industrial liason office of the university where she did her graduate training.

Some years ago this attitude was felt by those who chose the path of industry instead of academia, which was not considered "good enough". Now, however, research in industry is seen as a perfectly honorable alternative. Older scientists and established academics need to be more aware of the changing scientific environment at the more junior levels. There should be a greater openness to the outside world and alternative careers for young scientists. Instead of viewing the move to other fields as a way out from a trapped position when it is sometimes too late, young scientists should be free to envision their career opportunities in several directions and take their scientific skills and apply them elsewhere. When more scientifically trained people switch to other areas without a sense of bitterness and failure, there will be more people outside the university setting who understand the research process, which will eventually lead to better public awareness of the scientific enterprise.

This is the biggest favor the scientific community could do for itself, because it is ultimately the public perception of the importance of basic research that will ensure its survival and continued funding.■

The author is a research assistant professor in the Dept. of Microbiology at NYU Medical Center.

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New Mouse Mimics Disorder Leading to Premature Heart Disease

Genetic Lipoprotein Disorder Leads to Premature Disease

by Elizabeth Belton, *ASN&R* Staff Writer

Heart disease can be caused by a fondness for excessive living, but new research shows that there may also be a genetic predisposition for high cholesterol and triglyceride levels in the human bloodstream. Researchers have developed a mouse model that contains a genetic lipoprotein disorder; this model adds greater credence to the theory that the overexpression of the C-III (APOC3) gene may be responsible for certain types of heart disease.

Studies in the past have suggested that genetics are responsible for familial combined hypolipidemia (FCHL) which causes high cholesterol and triglyceride levels in humans. High cholesterol (VLDL) and high triglyceride levels (LDL) build up when the lipid metabolism in humans is not functioning correctly. Several previous studies of mice had shown that mice lacking LDL receptors had FCHL, but researchers at Columbia-Presbyterian Medical Center, Rockefeller University, and several American pharmaceutical companies decided to take the research further.

"In our case," says Dr. Alan Tall, of Columbia-Presbyterian, and senior author of the current study, "we took mice that had a defect in the LDL receptor and bred 2 parent strains and saw a separate synergistic effect which increased the expression of the gene. We got much higher levels than we thought because of the 2 genetic defects."

Atherosclerosis, which is caused by FCHL, can be controlled in humans by diet and exercise. When that doesn't work, drugs can often help by controlling the expression of the APOC3 gene which results in the disorder, but the results are not always completely successful.

Dr. Tall says that although the study does not point definitively to successful treatments for atherosclerosis, that the study is really an increment in knowledge towards genetic studies in humans. He adds that several avenues of research are currently ongoing study other genetic defects which cause high VLDL and that one practical implication [of the study] is that it may now be possible to screen people for fibrate drugs which may reduce the expression of the gene.

Dr. Tall, who is the Tilden Weger Bieler Professor of Medicine and Chief of the Specialized Center for Research in Molecular Medicine and Atherosclerosis at Columbia-Presbyterian Medical Center, developed this study in conjunction with Dr. Lori Masucci-Magoulas, Dr. Ira J. Goldberg and Dr. Humaira Serajuddin of Columbia University, Dr. Jan L. Breslow of Rockefeller University, Dr. Charles L. Bisgaier of Parke-Davis Pharmaceutical Research, and Dr. Omar L. Francone at Pfizer Inc.■

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ing approaches to study the connectivity of the nervous system at the level of the light and/or electron microscope. Particularly encouraged are applications which propose research and development of novel tract-tracing techniques to be used in post-mortem human and animal tissue, especially aldehyde-fixed tissue. All applications proposing research on innovative tract-tracing approaches will, however, be considered pertinent to this RFA

This RFA is issued in response to the need for better ways to demonstrate neural connections in humans and in nonhuman animal models. Research and development of novel methods and/or reagents to clearly, reproducibly, and rapidly trace distant connections at the level of the light and/or electron microscope in post-mortem tissue would represent a major advance in the understanding of normal and pathological brain organization. Among the opportunities that this would make available would be direct comparisons of the detailed connectivity of circuits that underlie important mental functions across normal animals, aged animals, animal models of disease, non-diseased humans and humans with mental disorders and age-related nervous system disorders. Moreover, the ability to trace connections in aldehyde-fixed tissue would allow such methods to be used in conjunction with a variety of other methods currently used to study the microstructure of the brain. It is estimated that approximately $1,000,000 will be available to fund between eight to twelve research project grants (R01) and small grant (R03) awards. Letter of Intent Receipt Date: April 15, 1997; Application Receipt Date: June 11, 1997.

CA-97-011: Novel Technologies for Evaluation of Molecular Alterations in Tissue

The Technology Development Branch of the Cancer Diagnosis Program, Division of Cancer Treatment, Diagnosis and Centers (DCTDC), National Cancer Institute and the Division of Human Communication of the National Institute on Deafness and Other Communication Disorders invite applications proposing the development of novel technologies to facilitate generation of a comprehensive molecular profile of human tissues. Development of these innovative technologies is intended to impact the discovery process in research on the biology of human disease at the level of both gene discovery and molecular cellular biology. This initiative supports development of efficient, cost effective, sensitive technologies to permit the simultaneous, rapid evaluation of the spectrum of molecular alterations in tissue specimens and, ultimately, in single cells. These technologies can be designed to detect genome-wide molecular alterations at the level of DNA, RNA or protein. Investigators may propose technologies to scan the entire genome of a cell or tissue for constellations of cytogenetic changes or other DNA alterations. They may also propose development of technologies to identify changes in gene expression at the level of both RNA and protein. Technologies to evaluate the function status of proteins including proteins of cellular regulatory pathways are also appropriate. As a secondary goal, this initiative is intended to encourage the development of all components of integrated analytical systems including preparation of samples, sample analysis and appropriate informatics systems for data collection and analysis. Letter of Intent Receipt Dates: February 15, 1997 and August 15, 1997; Application Receipt Dates: May 8, 1997 and November 13, 1997.

AR-97-001: Small Grant Program for the NIAMS

The National Institute of Arthritis and Musculoskeletal and Skin Diseases is seeking small grant (R03) applications to stimulate and facilitate the entry of promising new investigators into targeted, high priority areas of NIAMS research. This one-time solicitation will provide support for pilot research that is likely to lead to a subsequent individual research project grant (R01) or a First Independent Research Support and Transition (FIRST) (R29) award application. It is estimated that $1.0 million (total costs) will be available to support approximately 12 to 15 awards under this program. Awards are contingent on the availability of appropriated funds and on the receipt of sufficiently meritorious applications meeting the stated eligibility requirements. Application Receipt Date: March 18, 1997.

PA-97-026: Aspergillosis, Ehrlichioses and Drug Resistance

The purpose of this program announcement (PA) is to stimulate research on selected topics in three separate areas: aspergillosis, the ehrlichioses, and antibacterial or antifungal drug resistance. For aspergillosis, the goal is to support research on clinically relevant aspects of Aspergillus fumigatus and/or A. flavus. For the ehrlichioses, the goal is to support investigations on the diagnosis and pathogenesis of the agents of human ehrlichiosis. For drug resistance, the goal is to support research projects elucidating the molecular biology and molecular epidemiology of antibiotic resistance mechanisms in health care associated bacteria and fungi, including the molecular mechanisms of acquisition, expression, maintenance, and dissemination of resistance genes. Specific organisms of interest include but are not limited to: vancomycin-resistant enterococci, methicillin-resistant staphylococci, drug-resistant pneumococci, Gram negative bacteria and the fungi of greatest significance in the nosocomial setting. Pathogens covered under other NIAID PA's or recent initiatives (e.g., Mycobacterium tuberculosis) will not be considered responsive to this PA. Research project grant (R01), FIRST award (R29), and small research grant (R03) applications may be submitted in response to this program announcement.

PAR-97-027: Centers for AIDS Research

Participating institutes of the National Institutes of Health invite center core grants (P30) applications to support Centers for AIDS Research (CFAR's). CFAR cores provide infrastructure and promote basic, clinical, behavioral and translational AIDS research activities at institutions that receive significant AIDS funding from multiple NIH Institutes or Centers. CFARs foster synergy and improve coordination of research, support emerging research opportunities, and promote economy of scale through resources shared by multiple independent laboratories. CFARs also encourage other activities that serve the requirements of AIDS research. CFARs are not intended to be "Centers of Excellence" in specific areas of AIDS research, but instead are intended to promote all AIDS research efforts at CFAR institutions. Application Receipt Date: June 18, 1997.

PAR-97-033: HIV, AIDS and Related Illnesses Collaboration Award

The Fogarty International Center is expanding its AIDS International Research and Training Program to provide small individual research grants for collaboration between U.S. and foreign scientists in any country, consistent with U.S. foreign policy considerations. Support is available for research on human immunodeficiency virus (HIV) infection, acquired immunodeficiency syndrome (AIDS), and for research related to AIDS.

Up to $20,000 per year for a maximum of three years is available for U.S. investigators and their foreign collaborators to conduct research mainly at the foreign site. U.S. investigators holding currently active NIH grants for research related to HIV infections, AIDS and other related health problems are eligible to apply with their foreign collaborator for the AIDS Fogarty International Research Collaboration Award (AIDS-FIRCA). A similar program of Fogarty International Research Collaboration Awards (FIRCA) is available in all non-AIDS biomedical sciences research subjects for collaborative projects involving U.S. scientists and investigators in developing countries: see program announcement number PA-95-011.

AIDS-FIRCA grants will provide funds to the foreign collaborator, through the U.S. grantee institution, for supplies at the foreign institution; for expenses incurred at the U.S. institution to support the collaboration; and for research- related travel and subsistence expenses for both the U.S. and foreign investigators. If the foreign collaborator is in a developing country, applicants may also request funds for small pieces of equipment necessary to the AIDS-FIRCA project at the foreign site. For the purpose of this program, developing countries are considered to include those in the following regions: Africa, Asia (except Hong Kong, Japan, Singapore, South Korea and Taiwan), Central and Eastern Europe, Latin America, the Middle East (except Israel and the Persian Gulf states), and the Pacific Ocean Islands (except Australia and New Zealand).

tuberculosis, projects on these topics will not be considered responsive to this PA. This PA will use the research project grant (R01), First Independent Research Support and Transition (FIRST) (R29) award, and Interactive Research Project Grant (IRPG) mechanisms.■

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to move a colored square into a small square outline on the two-dimensional television screen. The square outline randomly appears in different part of the screen every ten seconds. The trick is that up and down have been reversed: moving the head up, moves the square down. This reversal requires a person to ignore and completely inhibit their natural instinct — something a person with Alzheimer's can not understand. This subtle difference can weed out normal demential elderly from those with early stage Alzheimer's. The head tracking test has another advantage. Since it's a novel movement that hasn't been learned from previous experience, it's suitable for all people. "From ditch digger to lawyer, it gets rid of pre-experience biasing results," explains Gianutsos.

It's often hard to engage cognitively impaired patients, says Gianutsos. Many memory tests begin without fully involving the patient. For example, lists of words are read without the patient controlling when the tests begins, sometimes without them even paying attention. Most motor tests, however, require the patient to activate the test, ensuring that, at least at the beginning of the test, the patients are aware of the test. Currently, the researchers have begun reexamining their data and retesting the patients in a follow-up study in order to establish whether the patients who scored low did indeed progress to Alzheimer's. Preliminary results of the follow-up study look promising.

Both Kluger and Gianutsos hope the results of the research will allow doctors to identify healthy people who will ultimately develop Alzheimer's. Although there is currently no effective treatment for Alzheimer's that can stop the progression of the disease, experimental drugs have shown promise in easing symptoms in some patients. Moreover, medications can help control various behavioral symptoms — to improve sleep, reduce wandering, and ease anxiety or depression. Since progression of disease from the first symptoms to death can last up to 20 years, such medications are important in making the disease more comfortable for patients and easier for caregivers. "Lots of scientists talk about pure science and double blind studies, and controls, but a lot of the great contributions [to medicine] come from observing patients and helping them," says Gianutsos.■

Continued from Page 1

tions do not interact directly with HIV, there were several reasons to believe that JCV was different.

First, it was known that JCV has the ability to infect human cells and remain latent there, neither reproducing nor causing any damage. One strain of JCV is often found latent in human kidney cells, and good evidence had accumulated that another strain, the one that causes PML, does the same thing in oligodendrocytes, a type of glial cell that provides myelin insulation to neurons in the brain. According to Dr. Johnson, a large number of us probably have JCV lurking in our glial cells — but since the virus is normally latent, PML is exceedingly rare. Still, there are those occasional cases where JCV becomes active and begins to replicate, killing the cells it has infected. When this happens, the consequences are dire — the loss of oligodendrocytic myelin severely disrupts neural signalling, leading to increasingly severe dementia and, eventually, death.

What might be going awry in the brains of PML victims that prods the normally lethargic JC virus into action? Dr. Khalili and others began to focus on the fact that PML incidence is dramatically higher in AIDS patients than in any other population — between four and eight percent of AIDS sufferers have it, while the rate in the general population is near zero. Even other people with immunocompromising diseases did not seem to develop PML at the same rate as AIDS patients.

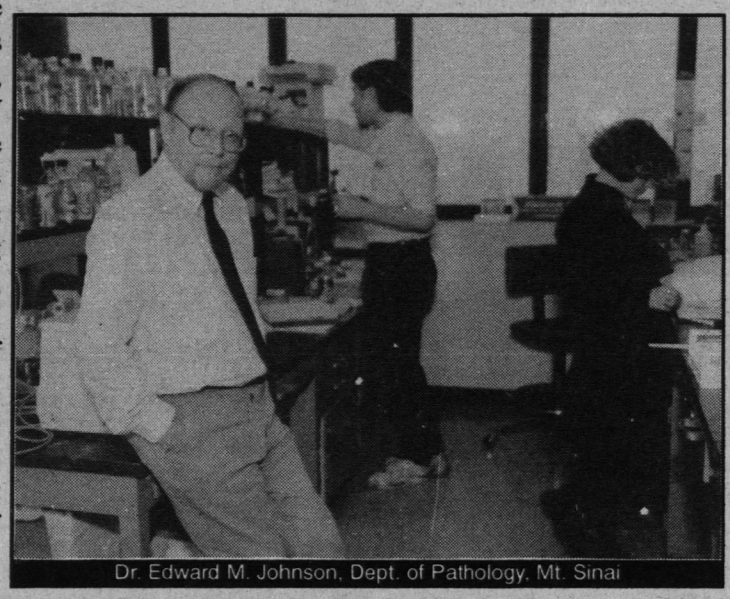
This fact argued against the possibility that PML is just another opportunistic infection, taking advantage of weak immune systems. Instead, it seemed more likely that HIV itself could play a part in causing PML, independent of its role in the immune system. Perhaps, Dr. Khalili hypothesized, HIV somehow interacts with the latent JCV DNA, turning on genes that allow it to replicate and kill. To test this idea, Dr. Khalili's lab began fishing around for HIV proteins that could stimulate transcription of JCV genes. Before long, they found one — a protein called Tat that had previously been known to activate HIV gene transcription.

Having zoomed in on a potentially key protein, Dr. Khalili's lab began trying to figure out exactly what Tat does that allows it to turn on JCV transcription. It soon became clear that Tat could not do the job alone — some other protein or group of proteins was needed to mediate between Tat and the JCV DNA. Until Khalili could identify the rest of this pathway, the possibility remained that Tat's influence on JCV was coincidental — after all, there was no direct evidence that Tat and JCV are ever together in the same cell. "Reviewers constantly point out that JCV and HIV infect different cell types," said Dr. Johnson. "They both infect glial cells, but HIV tends to be found in microglia and astrocytes, while JCV infects mostly oligodendrocytes."

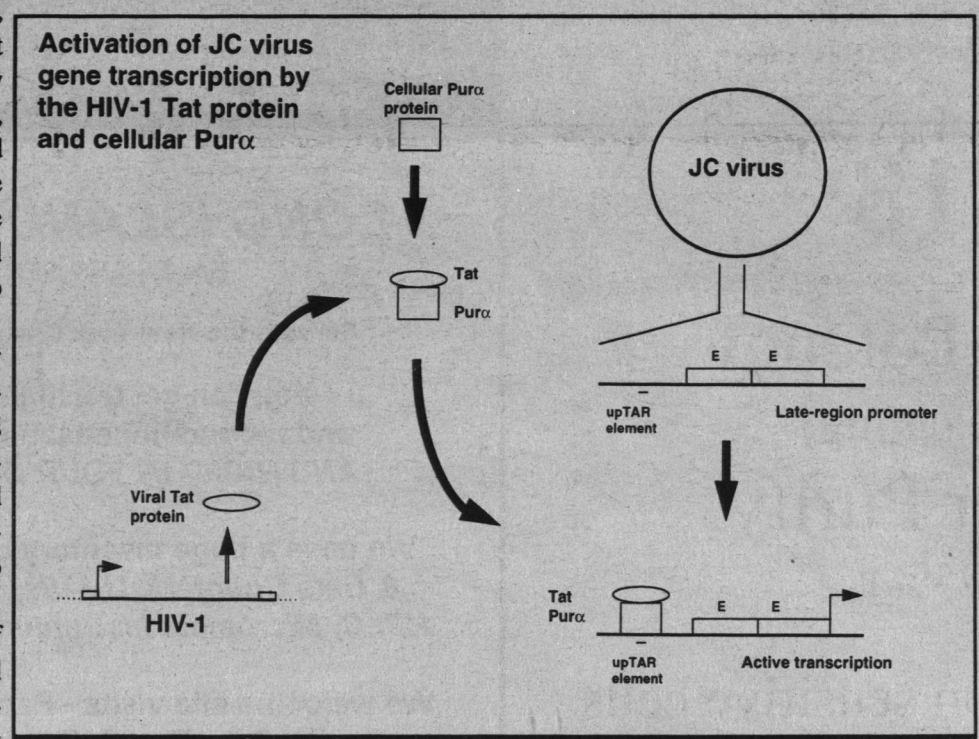
However, Dr. Johnson pointed out, it is well established that HIV-infected cells can secrete Tat protein, and that other cells can take it in. This provides a mechanism by which Tat could influence JCV transcription, Dr. Johnson said — since both HIV and JCV are present in the brain, it is entirely possible that JCV-infected cells are exposed to Tat even if HIV is not present in the same cell.

In 1993, Dr. Khalili's lab published a paper in which they identified a sequence of JCV DNA that appeared to be required for Tat's effect on JCV transcription. They called this sequence the *upTAR* element. Dr. Johnson, who was casually perusing the journals when he came upon this paper, stopped in his tracks. "When we saw the sequence of *upTAR*, we just looked at it and said, 'That's Purα! That's the Purα binding site!' We started taking bets around the lab on how long it would be before Khalili called us up." As it turned out, Johnson and Khalili were on the phone with each other by the afternoon of that very same day, agreeing to collaborate.

If Johnson had never noticed Khalili's article, or if Johnson's lab had never stumbled across the Purα protein in the first place, then things might have been very different. Dr. Johnson might have gone on studying the cell cycle without ever considering HIV or JCV. When he spoke with Dr. Khalili, however, Dr. Johnson realized he would be wise to alter the direction of his research. The fact that *upTAR* contained an apparent Purα binding site suggested immediately that Purα was the missing mediator between Tat and the JCV DNA, and proving this, Dr. Johnson said, would require experimental techniques very similar to ones his lab was already using on Purα. "I told [Khalili] we had developed the tools to really analyze Purα binding and activity," he recalls. Before long, the two had devised experiments to test whether Purα and Tat together could activate JCV transcription.



Dr. Edward M. Johnson, Dept. of Pathology, Mt. Sinai



Interaction of HIV-1 and JC Virus (JCV) which can occur in brains of HIV-1-infected individuals. An expanded region of JCV genome shows the late-region promoter containing the upTAR element, a small DNA sequence responsible for activation by the Tat protein. While Tat alone does not bind this sequence, the Tat-Purα complex does, thereby activating JCV late-gene transcription. This interaction may help explain why AIDS patients suffer a high rate of infection with JCV, a virus which does not normally cause a virulent infection in humans.

In a paper published at the end of last year in the *Proceedings of the National Academy of Sciences* USA, Khalili, Johnson and their collaborators present evidence confirming this hypothesis. They show that Tat and Purα bind to each other with high affinity, that Purα can bind to the *upTAR* element, and that binding of Tat to Purα increases the affinity of Purα for *upTAR*. In the most conclusive part of the experiment, they show that cells transfected with Tat and Purα genes express substantially higher levels of an *upTAR*- linked reporter gene than do cells transfected with Purα alone. Although Purα could, under some circumstances, induce transcription in the absence of Tat, Tat could never stimulate transcription in cells lacking Purα.

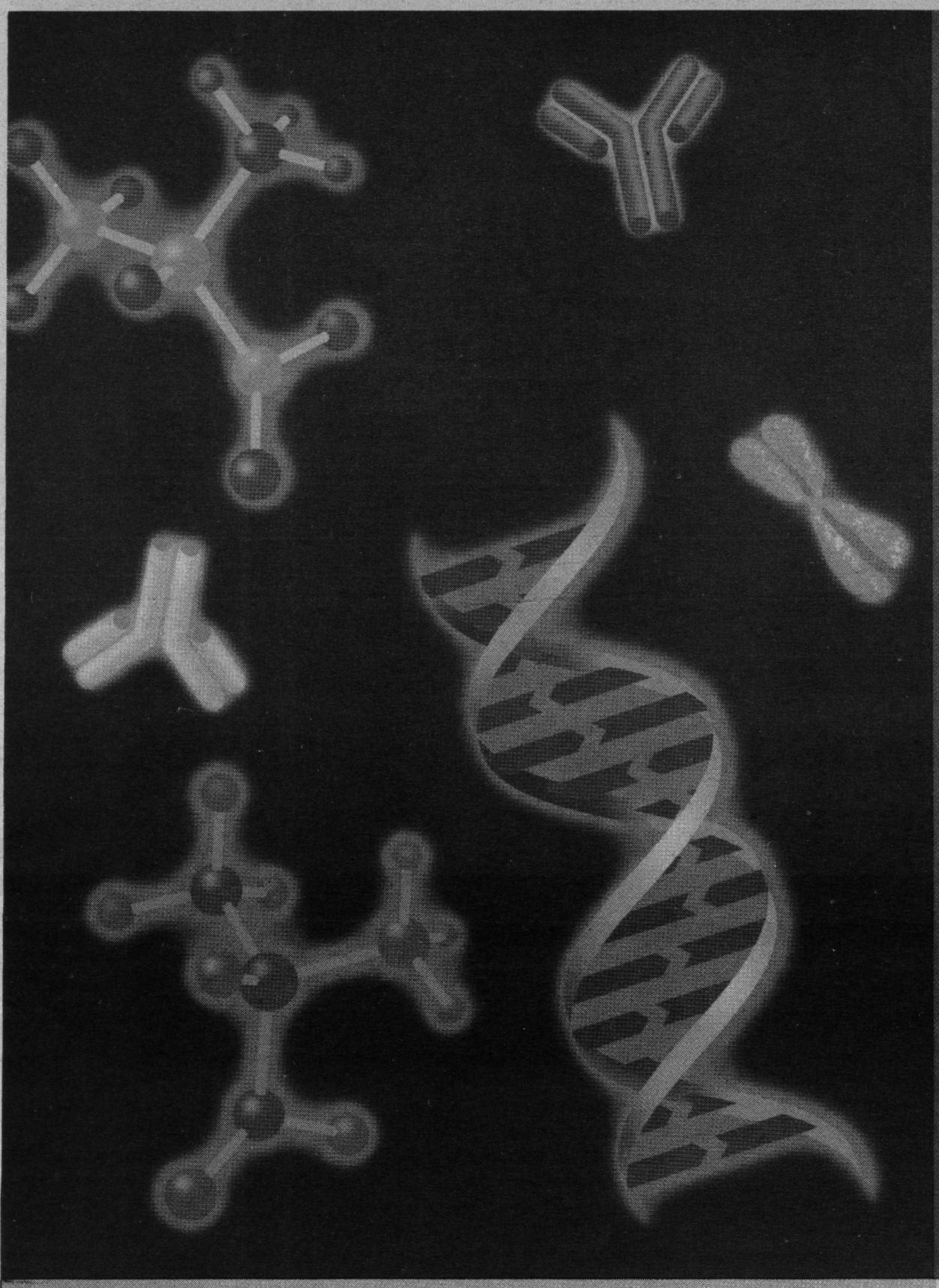
In light of these results, Dr. Johnson and collaborators have proposed the model of JCV activation pictured in the figure that accompanies this article. Cells infected by HIV synthesize the Tat protein, which can be secreted and taken up by a cell infected by JCV. In this cell, the Tat protein "hijacks" Purα by increasing its affinity for the JCV *upTAR* element, and by making it competent to initiate transcription there. Binding of the Tat-Purα complex to *upTAR* seems to allow transcription of proteins involved in viral replication. When the virus replicates, its host cell dies — in other words, the virus is no longer latent, and PML is in the patient's future. People without HIV are spared from all this, because they have no Tat protein. In the absence of Tat, Purα may occasionally bind to *upTAR*, but if it does, not much is transcribed.

If Tat, an HIV protein, can hijack Purα to transcribe some other virus's genes, wouldn't it make sense if Tat could hijack Purα to transcribe its own genes? "It makes a lot of sense," Dr. Johnson says, "But it hasn't been proven."

Circumstantial evidence, however, does exist. Tat is known to play a role in HIV transcription similar to its role in JCV transcription — it stimulates transcription by interacting with a particular nucleic acid element, although it does not bind to this element itself. This element, known as *TAR*, is actually an RNA element rather than DNA — it is found in an untranslated region of all HIV transcripts. Apparently Tat interacts with the *TAR* element of the RNA strand as the strand is being transcribed, and this interaction somehow encourages transcription to continue normally. How might Tat interact with the *TAR* element? It turns out that *TAR*'s sequence contains a potential Purα binding site. The Johnson and Khalili laboratories are now working hard to find out whether the Tat-Purα complex can bind *TAR*, and if so, whether this binding might stimulate transcription.

If Tat does in fact hijack Purα to allow transcription of important HIV genes, then it might be possible to block viral replication by preventing the Tat-Pura interaction. "Because we can identify the regions of each molecule involved in the interaction, we can try to devise specific ways to interfere with binding," Dr. Johnson said. For example, a drug that blocks the Purα binding site for Tat might be able to prevent the two from linking without interfering with Purα's normal functions.

Of course, this hypothetical drug is still a long way from becoming a reality. And even when it does, there is no guarantee it will block HIV replication — Tat's control of HIV transcription may depend on a far more complicated set of interactions than does its control of JCV transcription. Blocking its binding with Purα may prevent only a small number of transcriptions, or it might not prevent any. Still, Dr. Johnson points out, this type of intervention could at least be used to arrest neurodegeneration in HIV patients with PML. And maybe, if we are lucky, it could be used to stop the HIV virus in its tracks.■



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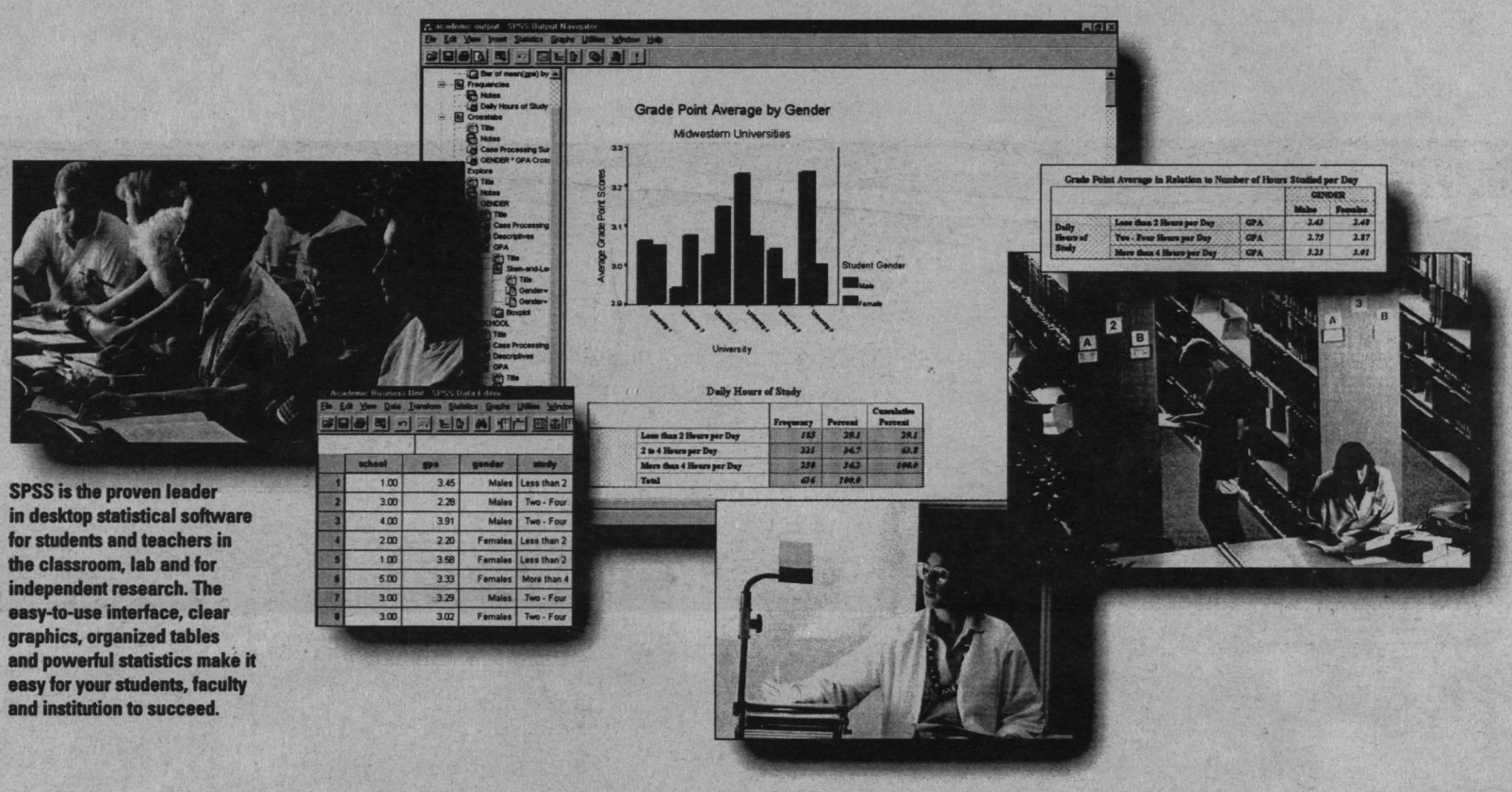

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