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April◆1997

Childhood-Onset Obsessive-Compulsive Disorder Linked to Autoimmune Origin

by James L. Ulrich

It starts with a simple bacterial infection. Group A beta-hemolytic streptococcus sets up residence in the mucous membranes of a child's throat. The child's immune system, encountering the foreign invader for perhaps the first time, deploys antibodies to fight off the infection. The antibodies do their job, killing the streptococcal antigen. But then, in certain children, something goes haywire. The antibodies aren't content to attack just the infection. They proceed to an area of the brain, the basal ganglia, buried deep beneath the cerebral cortex. Once there, they begin to make war on the caudate nucleus, a bundle of nerve fibers which, along with the rest of the basal ganglia, helps to regulate body movement. In these children, the lining of the caudate cells bears a strong resemblance to that of the streptococcus cells, so much so that the child's antibodies mistake the caudate cells for those of the invading infection itself. Months after the infection has gone, the child begins to develop locomotive difficulty: nervous tics, joint swelling, perhaps difficulty walking — a collection of symptoms known as Sydenham's chorea.

For some time it has been possible to identify children with this autoimmune disorder which results in Sydenham's chorea. In children with the disorder, which is believed to run in families, a certain protein on the surface of the immune system's B-cells — cells which play a role in the production of antibodies — is present to a far greater extent than is found in the general population. In these children, the B-cell surface protein is said to be "overexpressed" and thus serves as a marker for susceptibility to Sydenham's chorea.

Now, however, researchers led by Dr. Susan Swedo of the National Institute of Mental Health (NIMH) and Dr. John Zabriskie of Rockefeller University have discovered that the same surface protein is present in children who have developed obsessive-compulsive disorder (OCD) after being infected with streptococcus bacteria. The research group's findings, published in the January edition of the *American Journal of Science,* suggest that the autoimmune disorder which causes Sydenham's chorea may also be responsible for some forms of OCD. The findings may lead to the use of new preventative and therapeutic strategies for the treatment of childhood-onset OCD.

According to the fourth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV), an individual suffering from OCD experiences "intrusive and inappropriate thoughts, impulses, or images" (obsessions) which cause marked anxiety or stress,

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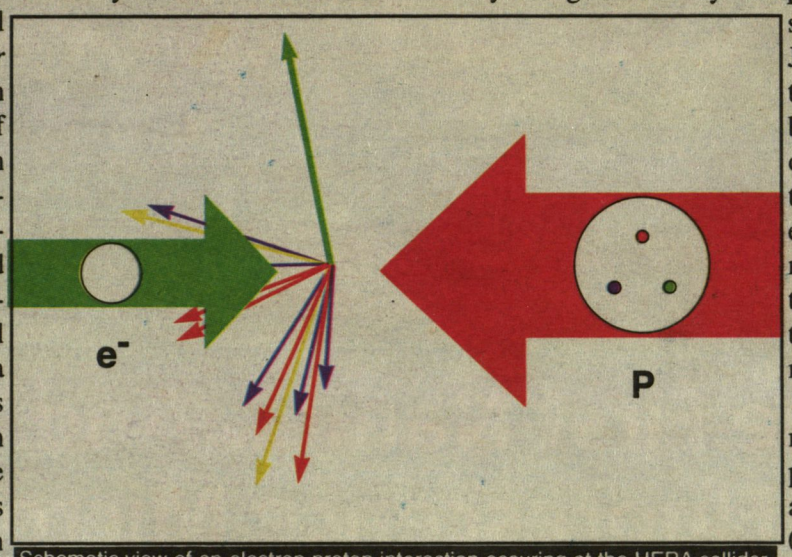
Physicists Report Unusual Particle Collisions

Findings May Indicate New Physics of Quarks and Positrons

by Ilana Harrus, Ph.D.

Members of an international particle physics collaboration (ZEUS) working at the high energy particle accelerator (HERA, or Hadron-Electron Ring Accelerator) in Hamburg, Germany announced in papers submitted on February 24th to the German physics journal *Zeitschrift für Physik* an excess in the number of events detected in one particular configuration of interaction when compared to theoretical predictions. Several Columbia University scientists headed by Alan Caldwell, Associate Professor of Physics and the spokesman for the ZEUS collaboration; Steven Ritz, Associate Professor of Physics; and Franck Sciulli, Professor of Physics were involved in the announcement.



Schematic view of an electron-proton interaction occuring at the HERA collider.

It may be a window opening on a new physics — and a revolution in the standard model of particle physics — or it may be just a statistical fluke. As Professor Ritz said, "something very interesting is going on here, and if it is not a statistical fluctuation there are a lot of possibilities for it being new physics."

The HERA is an accelerator four miles in circumference in which electrons and anti-electrons (called positrons) collide with protons. The electrons and positrons are accelerated to energies of 27.5 billion electron-volts — or the equivalent of 55,000 times their mass — while the protons acquire an energy of 820 billion electron-volts. (Since protons are 1840 times heavier than electrons this energy represents only 875 times their mass.) Within the accelerator, a packet containing 25 billion positrons collides with another packet containing 50 billion protons 10 million times a second.

According to the standard model of particle physics, the proton is made up of quarks and gluons confined by strong interactions. At the high energies reached within the accelerator a positron collides with one of the quarks and is scattered at a certain angle, much like the result of a collision among billiard balls. If the positron collides with a quark carrying a large portion of the energy of the proton, it will make an almost perfect U-turn and come back with a much greater energy. Indeed, in some of the events detected by the ZEUS collaboration the positron comes back with more than 10 times its initial energy.

According to current theories, however, this should be extremely rare, despite the billions of particles colliding, and the 10 million crossings per second. For example, the detection of 5 such events is unlikely enough that it may well provide evidence for some new physics. Just how significant this difference between the number of events now and the number predicted by existing theory is at the heart of the issue raised by the new announcement.

Depending on how much energy the positron has gained after its "U-turn", 0.9 or 0.14 such events were expected. The ZEUS collaboration, and analysis by Dr. Bruce Straub, a Postdoctoral Fellow at the Hamburg facility, detected 4 and 2 events respectively. The probability that deviations of this size could have occurred by chance is around one percent, small enough to support a claim that the excess seen is real. However, the probability for an excess to happen for randomly-selected angles of deviation (and energies) associated with the interaction is around six percent. That is, if 100 groups were to repeat this experiment, 6 of them would be expected to report an excess of events detected around one random value of the angle of deviation of the positron (or its energy). It is of added interest that this increase in the number of events detected was found in a previously unexplored domain of energy. "You may have a certain probability of having a pain somewhere in your body, but when it is right in your chest, you call the doctor," said Dr. Ritz.

In this case, the "doctor" is the large number of theorists rushing to explain the findings. If the excess turns out to be true, it can have a huge impact on current knowledge of particle physics.

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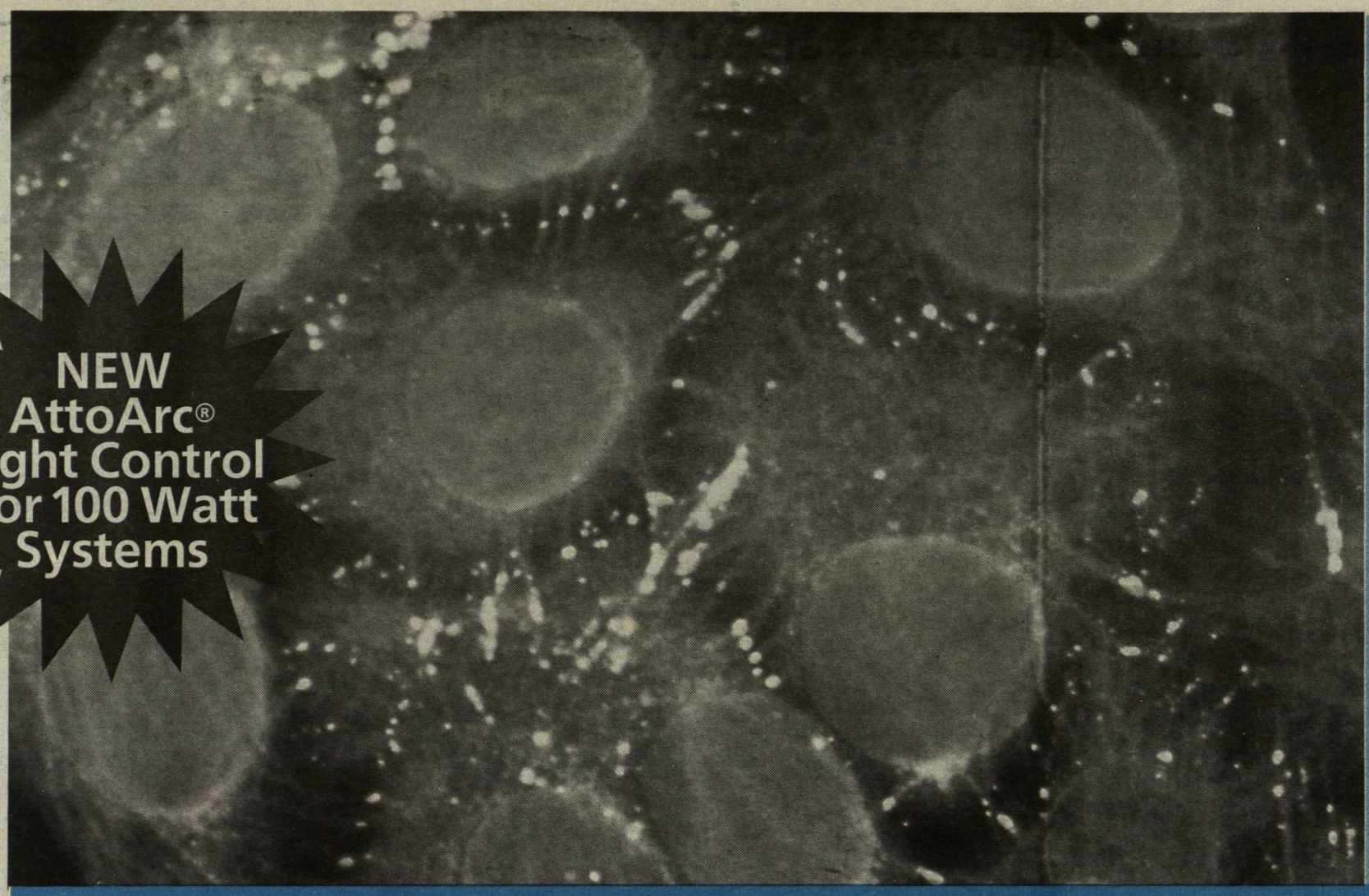

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SEE WHAT YOU'RE MISSING

MRI: It's Not Just for Diagnosis Anymore

Nuclear Magnetic Resonance Imaging Provides a Look at the Functioning Brain

by Kara Villamil

When President Clinton underwent an MRI, or magnetic resonance imaging, exam after injuring his knee in March, news reports barely had to explain what the technique entailed.

After all, most Americans have had or know someone who has had MRI, whether for a tendon injury like the President's or for something even more serious. In the past 15 years, medicine has embraced MRI as a noninvasive way to help physicians "see" injury in soft tissue, much as X-rays allow them to visualize broken bones.

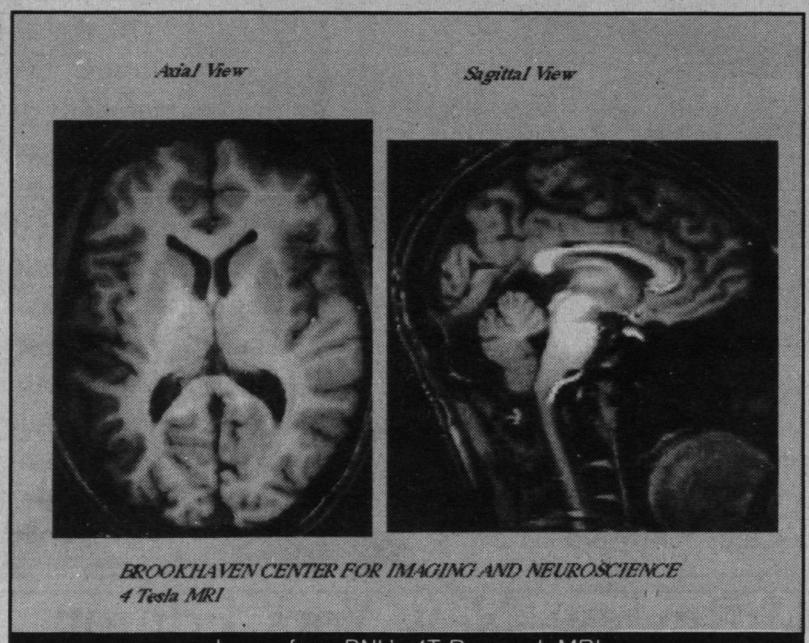

Image from BNL's 4T Research MRI

But even as MRI gains wider and wider use in clinical settings, it is leading a less well-known, but no less important, double life as a research tool. The result is an intriguing interplay of physics, brain chemistry, neurophysiology and cognitive neuroscience that may even help us probe consciousness itself.

That was the message of Robert Shulman, Sterling Professor of Molecular Biophysics and Biochemistry at Yale University, in his recent Brookhaven National Laboratory 50th Anniversary Lecture. Shulman described how MRI, or in vivo nuclear magnetic resonance (NMR) as it is better known to researchers, has allowed scientists to study the human brain's most basic functions.

Shulman noted that his lecture's location was appropriate — Brookhaven recently became home to one of the most powerful research MRI machines in the world, with a four-Tesla magnetic field strength more than twice that of a hospital MRI magnet. He also discussed several achievements made by his introducer, Charles Springer, a chemist at both BNL and the State University of New York at Stony Brook. And he noted that MRI was first developed at Stony Brook, through the work of Paul Lauterbur.

Where Does the Blood Flow?

Modern-day scientists who use NMR to investigate the brain, Shulman said, go by the same principle as 18th century physicians who noted a curious coincidence when treating head-injury patients: When the patients opened their eyes, blood flow to the brain increased.

More specifically, NMR uses the fact that, in order to command activity anywhere in the body, such as opening the eyes and processing visual information, the brain must fire some of its neurons. More specifically, the neurons release and capture chemicals called neurotransmitters in order to communicate the brain's message to neighboring neurons.

To power that communication, the neurons must receive more energy, in the form of glucose. And that glucose (and the oxygen to metabolize it) must be delivered through increased blood flow to the part of the brain where the firing neurons are located.

NMR can look at all aspects of that process, Shulman explained, from basic blood flow to the metabolism of glucose to the travels of the neurotransmitters. In each case, NMR surrounds the brain with a pulsing radiofrequency magnetic field, in addition to the instrument's static magnetic field, then measures the physical response, or resonance, from molecules in the brain. Since each kind of molecule has its own unique resonance frequency, NMR makes it possible to zero in on one molecular species.

Most often, research NMR specialists and hospital MRIs use the resonance signal from the body's ubiquitous water protons. The proton signal can be translated to a blood flow signal, and where there is transient increased blood flow, there is brain activity. This kind of approach allows resolutions of a few cubic millimeters of brain tissue.

"Where the Mysteries Reside"

For a basic NMR study, Shulman said, the interest lies in the difference between blood flow when the subject is being stimulated in some way, and when the stimulus is taken away. So, an NMR study might involve taking a series of images when the person is at rest and then another series when they are doing a task. Then, the researchers can subtract the activity seen at rest from the activity seen during the task, to show the area of the brain that controls the task.

This kind of approach, called functional MRI or fMRI, is allowing science to "move toward the center of the brain where all the mysteries reside," Shulman predicted.

For example, a study that asked subjects to look at random projected images, and to push a button when an image appeared a location twice, led scientists to theorize that the right prefrontal cortex might play an important part in spatial working memory, the kind of memory that allows the short-term remembrance of a piece of information while it is needed. A control experiment that had no memory demands allowed the researchers to subtract out the signals used in button pushing and reading visual input.

This kind of work is the "camel's nose under the tent of cognitive neuroscience," Shulman said,

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FEATURES

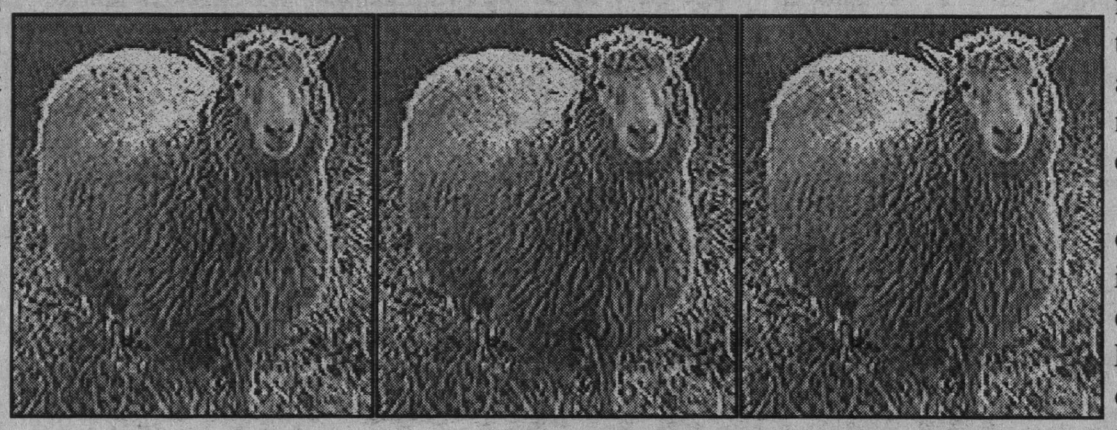
April 1997

– O P I N I O N –

Only the Clonely

by Douglas G. Adler, M.D.

By now everybody knows the news: researchers at Scotland's Roslin Institute have managed to create an identical copy, a clone, of an adult sheep using just one of its cells. This made headlines around the world because, until then, it was thought that adult cells could not be used in such a manner; their nuclei were believed to have long since become too specialized in function to be able to be stimulated to become a whole organism in the way that the nucleus of a fertilized egg can become an entire baby. Those beliefs now appear to have been false.



Almost as amazing as the scientist's feat itself was the near-immediate public backlash and outcry in many circles. The evening news, the editorial pages, and the World Wide Web were inundated with the words from people who were concerned, frightened, and in some cases angered by the implications of this work. Words of praise for the scientists and their labors were hard to find. References to the genetic dystopia populated by cloned humans of Aldous Huxley's *Brave New World* abounded, as did those to the seminal 1970's novel about a group of clones of Adolph Hitler, *The Boys From Brazil.*

While such scenarios and the inevitable jocular suggestions that followed (an Elvis on every bandstand, a Cindy Crawford on every high school boy's arm, etc.) may sell newspapers or amass Nielson points, they do little to help us truly evaluate what has really occurred. As history has shown, it is extraordinarily difficult to foresee what the long term technological, societal, and cultural ramifications of new technology will be. Few could have predicted in, say, 1970, that the microchip revolution would result in incredibly powerful computers in virtually every home. Even fewer could have predicted that those same computers would mostly be put to work playing games such as *DOOM!* or *Duke Nukem.* On another level, our understanding of atomic theory has led to both nuclear weapons and the CAT scanner. While few among us could be grateful for the proliferation of such weapons, it is almost certain that a great num-

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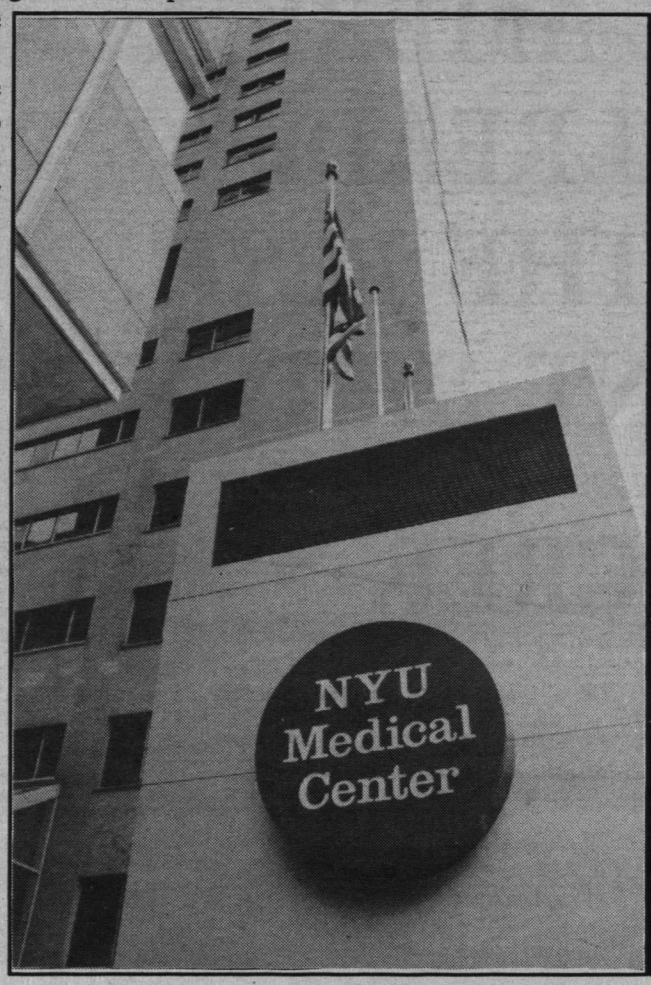
The Collapse of a 'Mega-Merger'

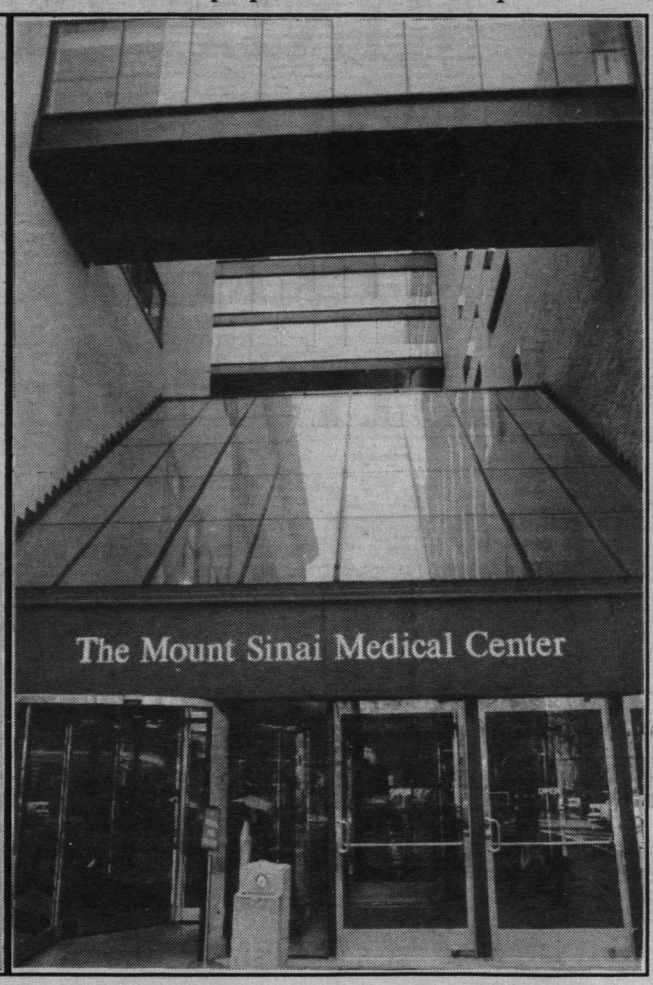
NYU and Mt. Sinai Medical Schools Could Not See Eye to Eye

by Dan Coulter, *ASN&R* Staff Writer

In June of 1996, New York University (NYU) and the Mt. Sinai School of Medicine announced plans to merge their hospitals, medical schools and affiliated health systems. The idea was to create one of the largest academic medical centers in New York and one of the nation's premier medical schools. The proposed merger between NYU and Mt.Sinai was designed to avert problems due to steadily declining Federal and State support as well as cost cutting pressures exerted by managed care companies.

The driving force behind NYU's and Mt. Sinai's decision to merge was their shared vision to create an institution whose prestige and power would virtually guarantee enough revenue to keep its medical research alive at a time of diminishing financial support and increasing uncertainty. The merger would enable both schools to boost their rankings of 22nd and 30th respectively (according to XXX) to be one of the top ten research centers in the country with combined revenues of more than $2 billion.





Shortly after the announcement of the NYU and Mt. Sinai merger, The New York Hospital (NYH) and Presbyterian Hospital announced their intention to merge, thereby confirming that even the most prestigious institutions are not immune to the changing healthcare environment and increased pressure towards consolidation and cost-cutting. Unlike the NYU and Mt.Sinai plan however, NYH and Presbyterian decided to merge only their hospitals —keeping their medical schools separate. Columbia and Cornell medical colleges are ranked 4th and 10th respectively in the nation with respect to federal grants and contracts. Both Columbia and Cornell felt that there was no real need to combine the medical schools at that time.

In February of this year, NYU and Mt.Sinai released a joint statement saying that their merger had been called off. It was reported that efforts to merge the hospital were less complicated than the medical schools' merger, and it was the latter that eventually caused the proposed union's demise.

DIFFERENCES OVER GOVERNANCE

According to representatives from both NYU and Mt. Sinai, the primary reason for the failed merger was the issue of governance over the new medical school. Although other issues regarding rankings and finances were considered during negotiations, they were secondary and probably would not have hindered the merger had the issues concerning governance been resolved.

In an article that appeared in the *New York Times* last year, Dr. William T. Speck, president and Chief Executive of Presbyterian Hospital, observed that the marriage between Mt. Sinai and NYU would have been ideal. He pointed out that Mt. Sinai was regarded to have the stronger hospital and NYU the stronger medical school. At the time that the merger was announced, the partners agreed that the new hospital would be called the Mt. Sinai-NYU Medical Center and that the new medical school would be called the NYU-Mt. Sinai Medical School.

From the beginning of the talks, NYU was apparently under the impression that the new medical school would be located at their site and that the existing facilities at Mt. Sinai would be used solely for clinical research. NYU wanted the proposed medical school to be an integral part of their university, very much like the law school, business school and film school. Degrees for graduating students would be conferred by the NYU-Mt. Sinai School of Medicine.

Mt. Sinai, on the other hand, envisioned a medical school in which students would attend classes at both sites with no provision of choice. Dr. John Rowe, president of Mt. Sinai, indicated in a recent statement to the press that they sought to develop a partnership with NYU — a partnership in which both parties shared responsibility for the school without one party being in control over the other. NYU apparently didn't agree with Dr. Rowe's vision and felt that the idea to keep the school divided at both sites would inhibit their goal to create a stronger school and diminish their ability to attract leading faculty and scientific investigators. Dr. Rowe pointed out that the disagreement over governance was the primary reason why the two medical schools could not see eye to eye.

DIFFERENCES IN RANKINGS

NYU's medical school began in 1841 while Mt. Sinai's school opened in 1968. Although both institutions are renowned for their extensive research in a broad spectrum of areas, the Gourman report's reputation-based ranking puts NYU at 13 and Mt. Sinai at 57 out of 125 schools. In a survey conducted by the Association of American Medical Colleges, it was found that 90% of the students that were accepted to both NYU and Mt. Sinai would choose to attend NYU. According to Dr. Herbert Samuels, Professor of Medicine at NYU and a participant in the negotiations, "this difference in national recognition of the two medical schools was probably one factor that made the merger a difficult one."

Despite these significant differences in rankings however, both schools receive approximately the same amount of financial grants from the National Institutes of Health. Last year, Mt. Sinai received $ 63.3 million and NYU received $ 63.8 million. It has also been reported in the *New York Times* that Mt. Sinai's grants have been steadily growing at a rate of 25% over the last five years while NYU has lost money over the last few years. NYU, however, states that its funding has remained even in recent years.

FINANCIAL DIFFERENCES

After talks began between the two institutions, it was later found that Mt. Sinai has a $325 million debt carried by the medical school in the form of investment-grade bonds. According to a representative from NYU, this debt was structured and reported in such a way that it was not readily evident. Mt. Sinai, on the other hand, maintains that it is fully capable of meeting its debt obligations. In fact, on February 14 of this year, The New York Post ran an article stating that Mt. Sinai is "financially struggling." In response to this, Gary Rosenberg, Senior Vice President of Mt. Sinai wrote a letter to the editor stating that "Mt. Sinai is one of the financially strongest of New York's health-care institutions, with resources more than adequate to meet its debt obligation." Dr. Rosenberg went on to say that the value of endowment and similar funds benefiting Mt. Sinai School of Medicine has increased 64% over the last five years and is now in excess of $330 million. He also indicated that the medical school recorded an operational surplus of nearly $9 million and its available reserves have increased 35% over the last five years to a total of $204 million. NYU maintains, however, that Mt. Sinai School of Medicine's financial strength is based on revenues from faculty clinical practices.

When asked whether the two sides will eventually re-visit the possibility of merging the two hospitals, Dr. Rowe said he wouldn't rule it out, while several representatives of NYU said they could not envision the merger occurring in the future. Despite these reported differences of opinion, a joint press release from NYU and Mt. Sinai concludes with the following statement: "We fully expect to continue the many areas of collaboration that pre-existed our talks, as well as others we discovered in the process. We embarked upon this effort as two of the leading academic medical centers in the nation, and each will continue to flourish, as we serve all of our vital constituencies with the very finest medical care, research and education."■

Continued from Page 4

ber of the readers of this article, or at least their friends and relatives, have benefited from the diagnostic acumen possible with modern CAT scans.

Horror and humor aside, there are many potential benefits to cloning technology. More than likely, some of the first applications to reach the marketplace will involve animal husbandry. Humans have been manipulating the bloodlines of domesticated animals for millennia without arousing much controversy. Virtually any kind of animal breeder, from those raising cattle to thoroughbred racehorses, would jump at the chance to keep an especially productive or gifted animal available for generations. Beyond simple financial gain, one could foresee cloned livestock having a tremendous effect on problems as monumental as world hunger. Livestock resistant to certain common third-world diseases, such as malaria, or animals unusually productive of milk could be cloned and disseminated to regions in need of food. Some scientists foresee the day when so- called transgenic animals, those with modified, added or deleted genes, could be cloned and used to provide specialized products ranging from cholesterol-free milk to blood serum rich in human clotting factors, hormones, monoclonal antibodies, and pharmaceuticals.

Clearly, if a mammal such as a lamb could be cloned, a mammal such as a human could be cloned. Despite laws in many nations to the contrary, it seems likely that, eventually, humans will themselves be cloned. While, theoretically, a billionaire *could* build and staff his own lab to clone a replica of himself so that he could pass on his financial empire *to himself* when he dies, it doesn't take much effort to envision some scenarios where the cloning of a human might more clearly be of benefit.

What if, for example, a woman lost her husband and newborn child in an automobile accident? In the period of time shortly after the accident, cells from the child could be harvested and used to create a clone. The cloned child, carried to term in the uterus of his own mother, would be an identical twin to the child she lost. Does this in any significant way differ from the production of twins via *in vitro* fertilization techniques already employed around the world today? If the technology existed, could we deny this woman the chance to salvage a semblance of the family she had lost?

Much of the fear surrounding human cloning seems to stem from a fear that humans themselves might come to be looked upon as commodities with valuable traits to be reproduced at will, bought, and sold. It is rarely noted and worth mentioning here that even if humans with precious attributes were cloned, the clones themselves might not necessarily manifest those same qualities which made them so desirable. While we could create a clone of the physicist Stephen Hawking, we could never hope to duplicate all of the events of his lifetime, both good and bad, that spawned his particular personality, intellect, and insights. While it is widely known that Mr. Hawking was unfortunately afflicted in his youth with amyotrophic lateral sclerosis (AML), also known as Lou Gehrig's Disease, we have no idea what role his physical illness played in the development of his mind. Was it the overwhelming nature of his physical ailment that stimulated such achievement on a cerebral level? If he had not become so ill, might he have simply gone on to become a clerk at a video rental store in downtown London?

Clearly, we are at the dawn of a new era in biological science. Cloning is real and here to stay. Now is not the time to panic and jump to rash and often unwarranted conclusions. It is a time when the realities and possibilities of cloning, both good and bad, must be assessed. It would be a great shame indeed to miss out on some of the benefits of this new and unexplored technology if we let fear and superstition influence our decisions. These days, few can recall the furor and controversy that surrounded the birth of the first "test tube" babies via *in vitro* fertilization techniques in the late 1970's. Today, IVF is an accepted fact of life and has made parents out of thousands of couples who would have been otherwise childless. It would have been wrong to heed the advice of those who endorsed abandoning IVF back then, as it would be wrong for us today not to investigate fully what cloning is really about and what it could potentially do for all of us.■

Neuronal Communication: Strengthening Circuits

Neurons and Synapses Yield Mechanisms Underlying Development, Learning and Memory

by Wendy Goldstein

The central nervous system is often compared to electrical wiring. And indeed it is true that impulses carried throughout our bodies are like electrical charges coursing to and from our brains. But a very significant difference between the nervous system and copper wiring is that while a lamp needs only to be plugged into an outlet in order to receive a charge, most of the cells in the nervous system do not even touch one another. Signals need to cross over gaps between cells, called synapses, in order to carry the message to the next cell.

Cline group: back row l. - r.: Elly Nedivi, Indrani Rajan, Barry Burbach, Jamie Edwards, Gang-Yi Wu, Dong-Jing Zou. front row, l. - r.: Irena Miloslavskaya, Rukhsana Bari, Holly Cline. (Photo: Marlena Emmons)

Neuronal plasticity is the process by which neurons grow and change, and as they change so too does their function. Two groups at Cold Spring Harbor Laboratory are studying this complex physiological process from two different, but related, perspectives. Hollis (Holly) Cline's lab, in the modern Beckman Neuroscience Building, studies the molecular events involved in the development of neurons and synapses while Roberto Malinow's group, located in the vintage 1893 Jones laboratory, is looking at molecular mechanisms thought to underlie learning and memory. The two groups recently identified a surprising and fascinating common element.

Malinow group: back row l. - r.: Robert Malinow, Shahid Zaman, Thillai Koothan, Zach Mainen. front row, l. - r.: Aneil Shirke, Mirjana Savatic, Nancy Dawkins, Yasunori Hayashi. (Photo: Marlena Emmons)

Holly studies neuronal development and communication in the visual system of the Xenopus frog. In a unique approach, she and her staff study single neurons in a whole-animal system. They look at growing, functioning cells in live frogs by injecting DiI (pronounced die-I), a fluorescent dye visible under a confocal microscope. By watching neurons grow in live animals, this group has been able to film and document some remarkable aspects of their development.

The neurons in developing frogs' visual systems do not grow like most other cells. Nerve cells must develop axons for sending out signals to other cells. Axons in a mature neuron are similar to the branches on a tree. But as the neuron develops, it does not grow one set of branches the way, say, a maple tree does. The cell grows and retracts many branches, reaching out and then retracting its arms until it develops a set with which it is happy. Only a small fraction of the generated axon branches will remain in the mature structure. But how does the cell determine which axons to retract and which to leave as permanent extensions?

"There are a few possibilities," Holly explains. "One is that if the branch sends out signals and gets no response from potential receptor cells, the branch is withdrawn. Another possibility is that the axon branch needs to sense that its impulses coincide with simultaneous inputs from nearby, more mature neurons." This would help to identify an appropriate target for a new neuronal connection.

In the frog central nervous system, as in human's and other species', neurons receive a signal then pass it along to the next neuron or other target cell. Some cells relay messages to the brain — what the organism sees, hears, smells, feels or tastes — others carry messages from the brain to another destination, i.e. 'telling' a muscle to contract.

In order to study synaptic transmission — the neurological communication between cells — both the Cline and Malionw groups sometimes listen in. They use a technique called patch-clamp recording (similar to the old eavesdropping trick of pressing a glass against a wall) in which they gently press the tiny tip of a glass pipette against the neuron's cell membrane where it naturally forms a tight seal. The pipette is hooked up to an amplifier which broadcasts the crackle of electrical signals passing through minuscule holes in the membranes called ion channels. In this way, scientists can actually hear electrical impulses moving through a cell.

Synaptic transmission can be broken down, for the sake of study, into units consisting of two cells and a synapse: the 'sender' of the neurological signal is the pre-synaptic cell; the 'receiver' the postsynaptic cell. The presynaptic cell initiates a signal by releasing neurotransmitter. In the cells studied by these two labs the neurotransmitter is the amino acid glutamate. There are two types of receptors for glutamate: NMDA and AMPA (see Acronym Box).

Holly and Robert recently discovered that initially only NMDA receptors are present in developing neurons. As they mature they gain AMPA receptors. These added receptors appear to strengthen the electrical pathway. Synapses in which AMPA receptors have not arrived are known as 'silent synapses.' They are dubbed silent because they do not respond to all passing stimuli. The requirements for a silent synapse (NMDA receptors only) to transmit a signal are more complex than the requirements in a cell that has both AMPA and NMDA.

Silent synapses require both the release of neurotransmitter and depolarization of the postsynaptic cell, a process that calls for coincident synaptic activity resulting from simultaneous input from other cells to the same postsynaptic cell. Depolarized cells are sometimes said to be excited, and are characterized by an increase in positive charge at the cell membrane. The complex requirements for immature synapses to communicate assure that they do not transmit information unless other, more mature synapses happen to fire at

Continued on Page 22

Continued from Page 1

and which the individual seeks to reduce through the performance of repetitive and ritualistic behaviors (compulsions) such as hand washing, counting, or incessant checking. Everyone may experience such OCD-like symptoms from time to time, of course, but in true OCD they become a major disability. For example, a person with OCD might have a fear of germs so great that it can only be offset by three or four hours of hand washing per day.

It was once believed that all forms of OCD were purely psychological in origin. The NIMH/Rockefeller study, however, provides evidence that at least some forms of childhood-onset OCD are the result of an autoimmune disorder. Beyond this, it also suggests that treatments which have proved effective for

Dr. John Zabriskie, Rockefeller University (Photo: Robert Reichert)

Sydenham's chorea may also be of use in treating childhood-onset OCD. Zabriskie suggests that it might be appropriate to give children identified as carrying the B-cell surface protein "prophylactic dosages of penicillin in order to prevent an infection which might lead to the onset of OCD." Zabriskie noted that children already suffering from OCD might benefit from plasma pheresis, in which the caudate-attacking antibodies are removed from the blood stream, a technique already used to treat Sydenham's chorea.

Dr. Kenneth Bonnet, a neuropsychologist at New York University who is familiar with the NIMH/Rockefeller research, noted that whether a child with the autoimmune disorder develops Sydenham's chorea or OCD in response to a strep infection may be a function of the area of the caudate nucleus targeted by the child's attacking antibodies. "If the attack hits the anterior on both sides of the caudate, it tends to result in OCD. If it hits just one side, then Sydenham's chorea tends to result." Bonnet confirmed that in either case, plasma pheresis would be an effective treatment. "There's a report of one case in which an adult male with Sydenham's chorea actually presented an inflamed caudate. Within minutes of removal of the offending antibodies, the caudate shrank back to normal size, and the chorea disappeared."

Of course, Zabriskie noted that the findings "do not suggest that all cases of OCD are the result of immunological disorders." Such an etiology is only likely in those individuals who test positive for the overexpressed B-cell surface protein.

Zabriskie explained that the presence of the B-cell surface protein is actually detected via another antibody, known as D8/17, which tends to bind to the protein. In a whole-blood sample drawn from an individual with the autoimmune disorder, between 4 and 7 times more D8/17 antibody will bind to B-cells than in a person without the disorder. The extent of D8/17 binding is determined by staining the D8/17 antibody with a green dye and the B-cells with a red dye. The ratio of green cells to red cells can then be measured by inspecting the blood sample under a microscope.

Curiously, the D8/17 antibody itself is created by injecting human B-cells into mice, which produce the antibody in response to the presence of the B-cell surface protein. "The mouse sees the antigen [the human B-cell] as foreign, but the human body does not make an antibody to this antigen!" Zabriskie emphasized. Hence the D8/17 antibody can be used to test human blood for the autoimmune disorder leading to Sydenham's chorea and OCD.■

ISOMERIZATION, BUT NOT OXIDATION, IS SUPPRESSED BY A SINGLE POINT MUTATION, E361Q, IN THE REACTION CATALYZED BY CHOLESTEROL OXIDASE

Sampson NS. Kass IJ.

Journal of the American Chemical Society. 119(5):855-862, 1997 Feb 5.

The putative active site base of cholesterol oxidase from Streptomyces has been removed by site-directed mutagenesis and the mutant enzyme characterized. When glutamate-361 is mutated to a glutamine, the isomerization chemistry catalyzed by cholesterol oxidase is suppressed and the intermediate cholest-5-ene-3 one is isolated. The specific activity for oxidation is 20-fold slower than the wild-type reaction;though the specific activity for isomerization is 10 000-fold slower. Furthermore, incubation of cholest-5-ene-3-one with the E361Q cholesterol oxidase resulted in the production of cholest-4-ene-6 beta-hydroperoxy-3-one (6%), cholest-4-ene-3,6-dione (32%), cholest-4-ene-6 beta-ol-3-one (36%), and cholest-4-ene-6 alpha-hydropesoxy-3-one/cholest-4-ene-6 alpha-ol-3-one (13%), in addition to cholest-4-ene-3-one (13%). Measurement of reaction Stoichiometry eliminated the possibility that H2O2 or the C4a-hydroperoxy flavin was the oxygenation agent. It is proposed that cholest-4-ene-6-hydroperoxy-3-one is the product of radical chain autoxidation and that cholest-4-ene-3,6-dione and cholest-4-ene-6-ol-3-one are decomposition products of the hydroperoxy steroid radical. The characterization of the E361Q mutant chemistry has illuminated the importance of intermediate sequestration in enzyme catalysis. The mutant enzyme will be used to obtain information about the structure of the enzyme in the presence of the reaction intermediate. Moreover, the altered activity of E361Q cholesterol oxidase will facilitate its application in studies of cell membranes.

ISOLATION OF A COMMON RECEPTOR FOR COXSACKIE B VIRUSES AND ADENOVIRUSES 2 AND 5

Bergelson JM. Cunningham JA. Droguett G. Kurtjones EA. Krithivas A. Hong JS. Horwitz MS. Crowell RL. Finberg RW.

Science. 275(5304):1320-1323, 1997 Feb 28.

A complementary DNA clone has been isolated that encodes a coxsackievirus and adenovirus receptor (CAR). When transfected with CAR complementary DNA, nonpermissive hamster cells became susceptible to coxsackie B virus attachment and infection. Furthermore, consistent with previous studies demonstrating that adenovirus infection depends on attachment of a viral fiber to the target cell, CAR-transfected hamster cells bound adenovirus in a fiber-dependent fashion and showed a 100-fold increase in susceptibility to virus-mediated gene transfer. Identification of CAR as a receptor for these two unrelated and structurally distinct viral pathogens is important for understanding viral pathogenesis and has implications for therapeutic gene delivery with adenovirus vectors.

THREE NEW LIMAX AMOEBAE ISOLATED FROM MARINE SURFACE SEDIMENTS - VAHLKAMPFIA CALEDONICA N SP, SACCAMOEBA MARINA N SP, AND HARTMANNELLA VACUOLATA N SP

Anderson OR. Rogerson A. Hannah F.

Journal of Eukaryotic Microbiology. 44(1):33-42, 1997 Jan-Feb.

Three new limax amoebae, isolated from marine, surface sediment samples are described using light microscopic and fine structural features. One species, characterized by eruptive locomotion typical of the family Vahlkampfiidae, is assigned the name Vahlkampfia caledonica (47.4 +/- 16.0 mu m x 12.1 +/- 3.2 mu m). The other two monopodial species move with steady locomotion characteristic of the family Hartmannellidae. One is a Saccamoeba with a distinct posterior bulbous uroid, vacuoles containing prominent crystals, glycocalyx with cup-like components, and spherical nucleus with central nucleolus. It is assigned the name Saccamoeba marina (72.5 +/- 14.9 mu m x 20.7 +/- 4.5 mu m). The other hartmannellid limax amoeba moves by steady locomotion and has a rather constant monopodial form, lacks a uroid, but has occasional trailing masses of cytoplasm, contains cup-like structures in the glycocalyx, and is characterized by numerous vacuoles. Based on the latter characteristic, it is assigned the name Hartmannella vacuolata (32.8 +/- 6.8 mu m x 8.5 +/- 1.8 mu m). Few limax amoebae have been described from marine environments and these data provide additional evidence that limax amoebae may be more abundant in marine sediments than realized previously.

RUBISCO OF DUNALIELLA TERTIOLECTA IS REDISTRIBUTED BETWEEN THE PYRENOID AND THE STROMA AS A LIGHT/SHADE RESPONSE

Lin S. Carpenter EJ.

Marine Biology. 127(3):521-529, 1997 Feb.

We used an immunofluorescence technique to investigate the effects of varying light regimes on ribulose 1,5-bisphosphate carboxylase/oxygenase (Rubisco) in individual cells of the chlorophyte Dunaliella tertiolecta Butcher. These studies were carried out between September 1995 and February 1996. The population was heterogeneous with respect to Rubisco localization in the pyrenoid, i.e. in some cells Rubisco staining was highly concentrated in the pyrenoid while in others it was evenly distributed throughout the chloroplast stroma. When light intensity was varied sevenfold, the fraction of the cell population that displayed distinct Rubisco staining in the pyrenoid (PR-index) was correlated with light intensity, although the average Rubisco abundance per cell or per total cellular protein appeared fairly constant. In darkness, or when treated with 3-(3,4-dichlorophenyl)-1,1-dimethyl urea (DCMU), the PR-index decreased markedly during the first 4 and 3 h, respectively, and then remained at low levels, while the cell division cycle progression remained unaffected. We conclude that D. tertiolecta probably possesses an adaptive mechanism, i.e. the redistribution of Rubisco between the pyrenoid (probably the active site of Rubisco activation and CO2 fixation) and the stroma (probably a reservoir of deactivated Rubisco that is readily available for transport to the pyrenoid and activation), to respond to variations in irradiance or photosynthetic inhibition. Our results also suggest that this mechanism is insensitive to slight variations in growth irradiance and to seasonal changes in photoperiod and temperature.

CONTROL OF MACROMOLECULE DISTRIBUTION WITHIN SYNTHETIC AND BIOGENIC SINGLE CALCITE CRYSTALS

Aizenberg J. Hanson J. Koetzle TF. Weiner S. Addadi L.

Journal of the American Chemical Society. 119(5):881-886, 1997 Feb 5.

The ability of organisms to exercise control over crystal growth is wonderfully exemplified by skeleton formation in echinoderms. A sea urchin spine is a unique composite of a single crystal of calcite and glycoproteins intercalated inside the crystal during its growth. Here we performed a detailed morphological and high-resolution synchrotron X-ray diffraction study of the textures of synthetic and biogenic calcite crystals. We show that the intracrystalline macromolecules from sea urchin spines, when allowed to interact with growing calcite crystals in vitro, selectively reduce the coherence lengths and degrees of alignment of the perfect domains in specific crystallographic directions. These directions also correspond to the newly-developed stable faces. In contrast, the defect distribution of young sea urchin spines composed entirely of spongy stereomic structure is much more isotropic. In mature spines containing secondarily filled-in wedges of calcite, the degree of anisotropy is intermediate between that of the synthetic crystals and the young spines. The macromolecules extracted from young and mature spines are, however, very similar. These observations demonstrate the inherent capability of occluded matrix macromolecules to finely differentiate between crystal planes by stereochemical recognition processes. They also show that in biologically-produced calcite crystals this process can be overridden to produce a more isotropic material.

A TOPOLOGICAL INVARIANT FOR NONLINEAR ROTATIONS OF IR(3)

Pecou E.

Nonlinearity. 10(1):153-158, 1997 Jan.

In this paper, we consider germs at O is an element of IR(3) of C-1 diffeomorphisms which fix the origin and such that their linear part at zero generates a rotation. We provide a condition on the dynamics under which the angle of the rotation is a topological invariant. We give an application to germs of C-infinity vector fields of IR(3) whose linear part generates a rotation.

THE DIVERSITY OF BACTERIA, EUKARYOTIC CELLS AND VIRUSES IN AN OLIGOTROPHIC LAKE

Corpe WA. Jensen TE.

Applied Microbiology & Biotechnology. 46(5-6):622-630, 1996 Dec.

An in situ transmission electron microscopic study of biomass samples concentrated from oligotrophic lake water revealed a variety of virus-infected microbial cells and many free viruses and virus-like particles. The most abundant group of microorganisms in screened and filtered water-column samples were 2 mu m or less in diameter, and included representatives of several oligotrophic genera, Prosthecomicrobium, Ancyclobacter, Caulobacter and Hyphomicrobium. Among the prokaryotic host cells, which included both heterotrophs and autotrophs, on the basis of electron microscope observations, approximately 17% were infected with bacteriophage or bore adherent phage particles on their surfaces. Several bacterial morphotypes were observed among the prokaryotic hosts. Water samples passed through a 20-mu m Nitex screen allowed

us to concentrate and examine the larger host cells as well, including several species of single-celled algae and two amoeba species. The infected algal cells included those Chlorella-like in appearance, photosynthetic flagellates and others that could not be positively identified. About one-third of the eukaryotic cells were infected by viruses that were larger (150-200 nm) and structurally more complex than bacteriophages (50-60 nm). None of the viruses have been isolated, but when 0.2 mu m filtrate from a biomass sample was spotted onto lawns of four representative heterotrophs and a Chlorella, the clearing observed was taken as evidence of lysis. Cyanobacterial lawns showed no plaques. Thin sections of two amoeba showed food vacuoles containing what appeared to be virus particles of a type seen in certain prokaryotic and eukaryotic cells in the biomass.

CORRELATION BETWEEN PATTERNS OF HORIZONTAL CONNECTIVITY AND THE EXTENT OF SHORT-TERM REPRESENTATIONAL PLASTICITY IN RAT MOTOR CORTEX

Huntley GW.

Cerebral Cortex. 7(2):143-156, 1997 Mar.

Plasticity of representational maps in adult cerebral cortex has been documented in both sensory and motor cortex, but the anatomical basis for cortical plasticity remains poorly understood. To investigate horizontal connectivity in primary motor cortex (M1) as a putative anatomical substrate for short-term, functional plasticity of adult motor cortical representations, a combination of electrical stimulation and biocytin labeling was used to examine pre-existing patterns of intrinsic connections in adult rat M1 in relationship to the pattern of reorganization of the motor movement map induced by transection of the contralateral facial nerve. Two hours after nerve cut, small, circumscribed regions of the forelimb representation expanded medially into territory previously devoted to the vibrissae representation. Outside of this novel, expanded forelimb region, no forelimb movement could be evoked from the former vibrissae representation at any time over the period of hours tested, thus representing silent cortex. Injections placed into vibrissae cortex representing the newly expanded forelimb representation gave rise to labeled axons and dense terminal fiber labeling which crossed the forelimb/vibrissae border and extended up to 1.2 mm within the low-threshold forelimb representation. In contrast, injections placed into silent vibrissae cortex gave rise to labeled axons and terminal boutons which remained mostly restricted to the original vibrissae representation, with only sparse projections that crossed into the low-threshold forelimb representation. Thus, these results suggest that the extent of short-term, functional reorganization of M1 induced within the first several hours following peripheral nerve cut is mediated, and constrained, by an anatomical framework of pre-existing, horizontal projections which traverse representation borders.

EVOLUTION OF SHAPE DIFFERENCES BETWEEN THE MAJOR AND MINOR CHELIPEDS OF UCA PUGNAX (DECAPODA, OCYPODIDAE)

Rosenberg MS.

Journal of Crustacean Biology. 17(1):52-59, 1997 Feb.

Geometric morphometrics were used to analyze shape differences between the major and minor chelipeds of the fiddler crab Uca pugnax. Although the major and miner chelipeds had similar allometric developmental trajectories, the form of the major cheliped was not an allometric extrapolation of the minor cheliped. The changes in shape associated with the formation of the major cheliped have functional relevance; they allow the major cheliped to produce relatively more power than the minor cheliped. This result suggests that selection for combat effectiveness has played an important role in the evolution of the major cheliped.

DISSOLUTION OF THIN IRON OXIDE FILMS USED AS MODELS FOR IRON PASSIVE FILMS STUDIED BY IN SITU X-RAY ABSORPTION NEAR-EDGE SPECTROSCOPY

Virtanen S. Schmuki P. Davenport AJ. Vitus CM.

Journal of the Electrochemical Society. 144(1):198-204, 1997 Jan.

This paper reports results from x-ray absorption near-edge spectroscopy (XANES) studies during polarization of thin sputter-deposited iron oxide films in acidic solutions. The dissolution rate of iron oxides in acidic solutions was found to be strongly increased by the presence of Fe2+ in the oxide. During anodic polarization in acidic solutions, it is found that dissolution is accelerated by chloride anions in comparison with sulfates. In HCl solutions of increasing concentration, not only does the pH decrease, but also the increasing chloride concentration accelerates dissolution. On the other hand, the dissolution rate in sulfuric acid does not depend on the sulfate (bisulfate) concentration. During anodic polarization, the dissolution rate is fairly independent of the potential, except at very high anodic potentials, and the XANES spectra reveal no changes in the average oxide valence during anodic polarization. Thus the dissolution that takes place is mostly chemical rather than electrochemical. During cathodic polarization, the dissolution rate is independent of the anion in the electrolyte. The findings are interpreted in terms of the negative surface charge of n-type oxides at potentials lower than the flatband potential, retarding anion adsorption on the surface. Hence it is suggested that the detrimental role of chloride anions on the stability of iron oxide films is due to a surface complexation effect. The findings and their relevance to the stability of natural passive films on iron surfaces are discussed.

RELATIONSHIP BETWEEN SUBCELLULAR CADMIUM DISTRIBUTION IN PREY AND CADMIUM TROPHIC TRANSFER TO A PREDATOR

Wallace WG. Lopez GR.

Estuaries. 19(4):923-930, 1996 Dec.

We tested the hypothesis that exposure-related alterations in the subcellular Cd distribution in prey relate to changes in Cd absorption by a predator. Oligochaete worms, Limnodrilus hoffmeisteri were exposed for 1 wk or 6 wk to 0.5 mu g Cd l(-1), 47 mu g Cd l(-1), or 140 mu g Cd l(-1) (including Cd-109 as a tracer) and relationships between oligochaete subcellular Cd distribution and Cd absorption by a predator, the grass shrimp (Palaemonetes pugio), were determined. Concentration and duration of Cd exposure had direct effects on oligochaete subcellular Cd distribution. Changes in oligochaete subcellular Cd distribution were characterized by increases in both the amount and proportion of Cd bound to the cytosolic fraction. The induction of Cd-binding proteins (e.g., metallothioneins) were suspected to be responsible for these changes. We found 1:1 relationships between the amount and percentage of Cd in oligochaete cytosol and the amount and percentage of Cd absorbed by shrimp. These results demonstrate that only metal bound to the soluble fraction of prey is available to higher trophic levels, and that factors influencing subcellular metal distribution in prey will directly alter metal trophic transfer to predators.

STIMULUS GENERALIZATION OF FEAR RESPONSES - EFFECTS OF AUDITORY CORTEX LESIONS IN A COMPUTATIONAL MODEL AND IN RATS

Armony JL. Servanschreiber D. Romanski LM. Cohen JD. Ledoux JE.

Cerebral Cortex. 7(2):157-165, 1997 Mar.

The conditioning of fear responses ta a simple acoustic stimulus (pure tone) paired with footshock can be mediated by the transmission of auditory information to the lateral nucleus of the amygdala from either the auditory thalamus or the auditory cortex. We examined the processing capacity of the thalamo-amygdala pathway by making lesions of the auditory cortex and testing the extent to which conditioned fear responses generalized to tones other than the one paired with footshock. Two studies were performed, one in an anatomically constrained computational model of the fear conditioning network and the other in rats. Stimulus generalization was unaffected in both. These findings support the validity of the model as an approach to studying the neural basis of conditioned fear learning, and in addition suggest that tbe thalamo-amygdala pathway, possibly by the use of population coding, is capable of performing at least crude stimulus discriminations.

TEMPERATURE-STIMULATED ABNORMAL ANNEALING OF NEUTRON-INDUCED DAMAGE IN HIGH-RESISTIVITY SILICON DETECTORS

Li Z. Li CJ. Verbitskaya E. Eremin V.

Nuclear Instruments & Methods in Physics Research Section A-Accelerators Spectrometers Detectors & Associated Equipment. 385(2):321-329, 1997 Jan 21.

Neutron-irradiated high-resistivity silicon detectors have been subjected to elevated temperature annealing (ETA). It has been found that both detector full depletion voltage and leakage current exhibit abnormal annealing (or "reverse annealing") behaviour for highly irradiated detectors: increase with ETA. Laser induced current measurements indicate a net increase of acceptor type space charges associated with the full depletion voltage increase after ETA. Current deep level transient spectroscopy (I-DLTS) and thermally stimulated current (TSC) data show that the dominant effect is the increase of a level at 0.39 eV below the conduction band (E(c) - 0.39 eV) or a level above the valence band (E(v) + 0.39 eV). Candidates tentatively identified for this level are the singly charged double vacancy (V-V-) level at E(c) - 0.39 eV, the carbon interstitial-oxygen interstitial (C-i-O-i) level at E(v) + 0.36 eV, and/or the tri-vacancy-oxygen center (V3O) at E(v) + 0.40 eV.

MELATONIN PREVENTS DEATH OF

NEW YORK REGIONAL CALENDAR OF

APRIL 1-3

1: "New Quantum Algorithms," Umesh Vazirani, University of California at Berkeley, 12:00-1:00, Warren Weaver Hall, Room 1302, New York University

1: "Neural Control of the Heart: Function, of Intrinsic Cardiac Neurones," Dr. David J. Adams, University of Queensland, Australia, 4:00, Life Sciences Building, Room 038, SUNY Stony Brook

1: "Protein Translocation Associated with Channel Gating," Dr. Alan Finkelstein, Albert Einstein College of Medicine, 12:00, Physicians &Surgeons, 11-505, Rover Conference Room, Columbia University

1: "New Quantum Algorithms," Umesh Vazirani, University of California at Berkeley, 12:00, Warren Weaver Hall, Room 1302, New York University

1: "Einstein's Legacy and Physics Beyond the Standard Model," WIlliam Marciano, Brookhaven National Laboratory, 4:00, Meyer Hall, Room 122, New York University

1: "Canonical Theorems for Convex Sets," Janos Pach, City College and CIMS, 6:15pm, Warren Weaver Hall, Room 613, New York University

1: "Melting Nuclei Into Quarks-What We Know Now and What RHIC Will Tell Us," Barbara Jacak, USB, 4:15, Harriman Hall, SUNY Stony Brook

1: " Optical Microcavities in Photonic Crystals," Pierre Villeneuve, Massachusetts Institute of Technology, 4:00, B Level Conference Room, Smith Hall Annex, Rockefeller University

2: "DNA Cleavage and Joining in V D J Recombination," David B. Roth, Baylor College of Medicine, 11:00, Weiss, Room 301, Rockefeller University

2: "Materials for High Temperature Electronics," Emil Arnold, GFN, 1;30-2:30, 633 Mudd Building, Columbia University

2: "A Fusion Power Plant Without Plasma-Material Interactions," Sam Cohen, Princeton Plasma Physics Laboratory, 1:30, Warren Weaver Hall, Room 813, New York University

2: "Transport and Mixing in the Stratosphere," Alan Plumb, Massachusetts Institute of Technology, 3-5:00, Warren Weaver Hall, Room 1302, New York University

2: "Integrable Systems with Discrete Time, Bethe-Anzatz, and Quantum Integrable Models," Igor Krichever, Landau Institute for Theoretical Physics, Moscow and Columbia University, 4:30, Mathematics, Room 507, Columbia University

3: "Chemical Dynamics of Alignment and Control," Prof. Stephen Leone, Colorado-JILA, 4:00, Meyer Building, Room 122, Columbia University

3: "Embryo-maternal Dialogue in the Primate: Modulation of the Uterine Environment," Prof. Asgi Fasleabas, University of Illinois College of Medicine, 12:00, Weiss, Room 301, Rockefeller University

3: "Molecular Identity of Developmentally Regulated Potassium Currents," Angeles B. Ribera, University of Colorado, 12:00, Neurological Institute's Alumni Auditorium, 710 West 168th St, College of Physicians & Surgeons, Columbia University

APRIL 3-8

3: "Guidance of Longitudinal Cell Migration in C. *elegans*," Scott Clark, University of California at San Francisco, 4:00, HHSC, Room 301, College of Physicians & Surgeons, Columbia University

3: "Global Bifurcation in Noncompact Problems," Maria Esteban, Universite Paris-Dauphine, 11:00, Warren Weaver Hall, Room 1302, New York University

3: "Distribution of the Limiting Gibbs Measures in the Hopfield Model," Veronique Gayrard, Centre de Physique Theorique, Marseille, 3:30, Warren Weaver Hall, Room 1302, New York University

3: "Electrical Noise to Study the Molecular Dynamics of Ionic Channels," Adrian Parsegian, National Institutes of Health, 4:00, Meyer Hall, Room 122, New York University

3: "Pricing Path-dependent Options Through Stochastic Time Changes and Laplace Transforms: Comparisons with Monte-Carlo Simulations," Helyette Geman, Universite paris Dauphine and ESSEC, 5:30-7:00, Warren Weaver Hall, Room 101, New York University

3: "Mineralogy and Design of Glass-Ceramic Materials," Linda pinckney, Corning Ceramics, 4:00-5:00, Earth and Space Sciences Building, Room 123 SUNY Stony Brook

4: Graduate Research Conference, Talks on Computer Networks/Internet, Databases, Concurrent Systems, Computer Graphics and Virtual Reality, JAVA, Logic Programming, Dr. James Simons, President of Renaissance Technologies, 9-5, Computer Science Building, Room 1306, SUNy Stony Brook

4: "Alfred Nobel's Will-Initial Difficulties and Risk of Early Collapse of his Prize Project," Gosta Ekspong, University of Stockholm, 2:10, Pupin Hall, Room 831, Columbia University

4: "Macroscopic Disorder and the Dielectric Properties of Organic Conductors," Ohad Levy, CIMS, 2:00, Warren Weaver Hall, Room 1302, New York University

7: "Regulation of p53-dependent Apoptosis by Members of the Bcl-2 Family," Dr. Eileen White, Center for Advanced Biotechnology & Medicine," 12:00, Life Sciences Building, Room 038, SUNY Stony Brook

7: "Bridging the Gap Between Long-Term Potentiation and the Operation of Neuronal Circuitry Studies: In Olfactory Cortex," Lew Haberly, University of Wisconsin,12:00, Meyer Building, Room 122, New York University School of Medicine

8: "Bose-Einstein Condensates-Laser-like Atom," Wolfgang Ketterle, Massachusetts Institute of Technology, 4:15, Harriman Hall, SUNY Stony Brook

8: "Topics in Quantum Computing," Davi Geiger and Ian Jermyn, NYU, 12:00-1:00, Warren Weaver Hall, Room 1302, New York University

8: "Regulation of Intracellular Calcium Release Channels," Dr. Barbara E. Ehrlich, Yale University School of Medicine, Physicians &Surgeons, 11-505, Rover Conference Room, Columbia University

8: "Quantal Analysis of Early and Late Forms of Hippocampal LTP," Dr. Steven A. Siegelbaum, Columbia University College of Physicians & Surgeons, 4:00, Life Sciences Building, Room 038, SUNY Stony Brook

APRIL 9-15

9: "Role of Mixedness in Solid State Kinetics," R. Riman, Rutgers University, 1;30-2:30, 633 Mudd Building, Columbia University

9: "Demography of Florida Scrub Plants: Interacting Influences of Microhabitat, Fire, and Landscape," Eric Menges, Archibald Biological Station, 3:30, Life Sciences Building, Room 038, SUNY Stony Brook

9: "Hamiltonian Approach and Symplectic Forms," Igor Krichever, Landau Institute for Theoretical Physics, Moscow and Columbia University, 4:30, Mathematics, Room 507, Columbia University

10: "The Role of Tyrosine Kinases in Calcium Signaling Pathways in the Nervous System," Sima Lev, Sugen Pharmaceutical Company, 4:00, HHSC, Room 301, College of Physicians & Surgeons, Columbia University

10: "Computing and Analyzing Neural Images in the Visual Cortex," Anthony J. Movshon, New York University, 12:00, Neurological Institute's Alumni Auditorium, 710 West 168th St, College of Physicians & Surgeons, Columbia University

10: "Comets, Dinosaurs, and the Galaxy," Michael Rampino, New York University, 4:00-5:00, Earth and Space Sciences Building, Room 123 SUNY Stony Brook

10: "Lewis-Acid- and Palladium-Catalyzed New Reactions of Acetylenes and Enzymes," Prof. Yoshinori Yamamoto, Tohoku University, 4:00, Meyer Building, Room 122, Columbia University

10: "Multifunctionalized Organosilanes: From Reagents to Pharmaceuticals," Prof. Scott McN. Sieburth, USB, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

11: "New Ventures in Asymmetric Processes, or Following One's Nose," Prof. Philip Magnus, University of Texas, 4:00, Meyer Building, Room 122, Columbia University

11: "Ultrafast Computation Using Flux Quantization and Superconductors," Prof. K. Likharev, SUNY Stony Brook, 2:10, Pupin Hall, Room 831, Columbia University

14: "A developmentally Regulated MAP Kinase Signaling Pathway in Yeast," Dr. Edward Winter, Thomas Jefferson University, 12:00, Life Sciences Building, Room 038, SUNY Stony Brook

15: Columbia University's Chapter of Sigma Xi, The Scientific Research Society, Leon Julian Lidofsky, Columbia, Faculty House of Columbia University, 5:00 reception, 5:30, Induction of New Members, 6:30, Dinner, Immediately Following: "Chien Shiumg Wu: A Retrospective." Cost-$30, Make Reservations by Calling Liz at 212-854-2204

15: "Regulation of mRNA Decay in Yeast," Dr. Allan Jacobson, University of Massachusetts Medical School, 12:00, Cell Biology Library, MSB-657, New York University Medical Center School of Medicine

15: "From Classical to Quantum Information Theory," Nicolas Cerf, California Institute of Technology, 12:00-1:00, Warren Weaver Hall, Room 1302, New York University

SEMINARS & EVENTS

APRIL 15-22

15: "Quantum Computing-From Theory to Experiment, Artur K. Ekert, Oxford University, 4:15, Harriman Hall, SUNY Stony Brook

15: "Pathogenesis in the Central Nervous System Arising from Infection of Selected Targets by a Coronavirus," Dr. Samuel Dales, Rockefeller University, Physicians &Surgeons, 11-505, Rover Conference Room, Columbia University

15: "Selfways: Cultural Diversity in Self Evaluation," Dr. Hazel Markus, Stanford University, 3:00-4:30, Psychology, Room 101A, New York University

16: "Birth Order, Family Dynamics, and Creative Lives: From Darwinian Evolution to World History," Frank J. Sulloway, Massachusetts Institute of Technology, 5:00, Main Library, Alliance Room, SUNY Stony Brook

16: "Effects of Ecosystem Productivity on Biodiversity and Trophic Structure: A Comparative Test of Four Theoretical Models of Community Structure," Matthew Liebold, University of Chicago, 3:30, Life Sciences Building, Room 038, SUNY Stony Brook

16: "Seiberg-Written Solutions to N=2 Sypersymmetric Gauge Theories," Igor Krichever, Landau Institute for Theoretical Physics, Moscow and Columbia University, 4:30, Mathematics, Room 507, Columbia University

17: "Ellagitannin Chemistry," Prof. Ken S. Feldman, Pennsylvania State University, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

17: "Molecular Dynamics in Systems with Polarizable Force Fields," Prof. Bruce Berne, Columbia, 4:00, Meyer Building, Room 122, Columbia University

17: "Constraints on the Nature of Mantle Convection from Tomographic Imaging,: Rob van der Hilst, Massachusetts Institute of Technology, 4:00-5:00, Earth and Space Sciences Building, Room 123 SUNY Stony Brook

17: "Proteolysis and Long-Term Memory," Ashok Hedge, Columbia University, 12:00, Neurological Institute's Alumni Auditorium, 710 West 168th St, College of Physicians & Surgeons, Columbia University

18: "The Metastable Antiprotonic Helium Atomcule and the Deeply Bound Pionic Atom.Nucleus-Miraculously Long-Lived Hadronic Atoms," Prof. T. Yamazaki, JSPS, Japan, 2:10, Pupin Hall, Room 831, Columbia University

21: " Studies on the Molecular Mechanism of the Drosophilia Biological Clock," Charles Weitz, Harvard Medical School, 12:00, Jacob Bleibtreu Seminar Room, Skirball Institute, 3rd Floor, Meyer Building, Room 121, New York University School of Medicine

22: "Non-heme Iron and the Biological Oxidation of Methane," Prof. Stephen Lippard, Massachusetts Institute of Technology, 4:00, Meyer Building, Room 122, Columbia University

22: "Error Correction in Quantum Computing," David DiVincenzo, IBM, 12:00-1:00, Warren Weaver Hall, Room 1302, New York University

APRIL 22-30

22: "Genetic Analysis of Pattern Formation in the Zebrafish Embryo," Dr. William S. Talbot, NYU School of Medicine, 12:00, Cell Biology Library, MSB-657, New York University Medical Center School of Medicine

23: "Platinum Antitumor Drug Binding to DNA: Structure, Mechanism, and Combinatorial Synthesis," Prof. Stephen Lippard, Massachusetts Institute of Technology, 4:00, Meyer Building, Room 122, Columbia University

23: "Advanced Electronics Thru' Improved Si," Kimerling, Massachusetts Institute of Technology, 1;30-2:30, 633 Mudd Building, Columbia University

23: "Non-Linear WKB Methods and Topological Field," Igor Krichever, Landau Institute for Theoretical Physics, Moscow and Columbia University, 4:30, Mathematics, Room 507, Columbia University

23: "Feeding Patterns of Parent Redwinged Blackbirds: Do parents Feed Young Randomly and Does it Matter," Anne B. Clarke, SUNY Binghampton, 3:30, Life Sciences Building, Room 038, SUNY Stony Brook

24: "Neural Patterning During the Development of the Drosophila CNS," Nipam H. Patel, Howard Hughes Medical Institute, University of Chicago 12:00, Neurological Institute's Alumni Auditorium, 710 West 168th St, College of Physicians & Surgeons, Columbia University

24: "Future of Graduate Education and Research in the USA," George Klein, George Klein & Assoc., 4:00-5:00, Earth and Space Sciences Building, Room 123 SUNY Stony Brook

24: "New Group IV Organometallic Chemistry with Tetraazamacrocyclic Complexes," Prof. Stephen Lippard, Massachusetts Institute of Technology, 4:00, Meyer Building, Room 122, Columbia University

28: "Neuromodulation and Cortical Memory Function: Modeling the Physiological Basis of Behavior," Michael Hasselmo, Harvard University, 12:00, Meyer Building, Room 122, New York University School of Medicine

28: "Structure and Function of THDP-Succinyltransferase: A Left-Handed Enzyme," Prof. Steven Roderick, Albert Einstein College of Medicine, 4:00, Graduate Chemistry Building, Room 412, SUNY Stony Brook

29: "Quantum Computing," Peter Shor, ATT, 12:00-1:00, Warren Weaver Hall, Room 1302, New York University

29: "Bicontinuous Mesophase Material," Sol Gruner, Princeton University, 4:15, Harriman Hall, SUNY Stony Brook

30: "Phylogeny of Protostome Worms, Implications for the Evolution of Segmentation and the Diversity of Body Plans," Damhnait McHugh, Harvard University, 3:30, Life Sciences Building, Room 038, SUNY Stony Brook

NEUROBLASTOMA CELLS EXPOSED TO THE ALZHEIMER AMYLOID PEPTIDE

Pappolla MA. Sos M. Omar RA. Bick RJ. Hicksonbick DLM. Reiter RJ. Efthimiopoulos S. Robakis NK.

Journal of Neuroscience. 17(5):1683-1690, 1997 Mar 1.

Studies from several laboratories have generated evidence suggesting that oxidative stress is involved in the pathogenesis of Alzheimer's disease (AD). The finding that the amyloid beta protein (A beta) has neurotoxic properties and that such effects are, in part, mediated by free radicals has provided insights into mechanisms of cell death in AD and an avenue to explore new therapeutic approaches. In this study we demonstrate that melatonin, a pineal hormone with recently established antioxidant properties, is remarkably effective in preventing death of cultured neuroblastoma cells as well as oxidative damage and intracellular Ca2+ increases induced by a cytotoxic fragment of A beta. The effects of melatonin were extremely reproducible and corroborated by multiple quantitative methods, including cell viability studies by confocal laser microscopy, electron microscopy, and measurements of intracellular calcium levels. The importance of this finding is that, in contrast to conventional antioxidants, melatonin has a proposed physiological role in the aging process. Secretion levels of this hormone are decreased in aging and more severely reduced in AD. The reported phenomenon may be of therapeutic relevance in AD.

DEFORMATION QUANTIZATION AND NAMBU MECHANICS

Dito G. Flato M. Sternheimer D. Takhtajan L.

Communications in Mathematical Physics. 183(1):1-22, 1997 Jan.

Starting from deformation quantization (star-products), the quantization problem of Nambu Mechanics is investigated. After considering some impossibilities and pushing some analogies with field quantization, a solution to the quantization problem is presented in the novel approach of Zariski quantization of fields (observables, functions, in this case polynomials). This quantization is based on the factorization over R of polynomials in several real variables. We quantize the infinite-dimensional algebra of fields generated by the polynomials by defining a deformation of this algebra which is Abelian, associative and distributive. This procedure is then adapted to derivatives (needed for the Nambu brackets), which ensures the validity of the Fundamental Identity of Nambu Mechanics also at the quantum level. Our construction is in fact more general than the particular case considered here: it can be utilized for quite general defining identities and for much more general star-products.

B-CELL GENE REARRANGEMENT IN BENIGN AND MALIGNANT LYMPHOID PROLIFERATIONS OF MUCOSA-ASSOCIATED LYMPHOID TISSUE AND LYMPH NODES

Torlakovic E. Cherwitz DL. Jessurun J. Scholes J. Mcglennen R.

Human Pathology. 28(2):166-173, 1997 Feb.

The polymerase chain reaction (PCR) with polyacrylamide gel electrophoresis was used to study patterns of immunoglobulin heavy chain (IgH) gene rearrangement (CR) in formalin-fixed, paraffin-embedded specimens of lymphomas and reactive conditions of mucosa-associated lymphoid tissue (MALT) and lymph nodes. DNA amplification was performed directly on sections obtained from paraffin blocks. Five patterns of PCR products were observed: a single band, two or more discrete bands, smearing, a single band overlying a smear, and two or more bands over a smear. A pure polyclonal pattern (smear) was observed in all of the reactive lymph nodes but in only 15% of cases of Helicobacter pylori (HP) gastritis with lymphoid hyperplasia, 25% of cases of HP gastritis without lymphoid hyperplasia, and 37% of colonic specimens of various types. Patterns consisting of multiple bands with or without background smearing were common in gastritis, colitis, and gastric lymphomas. Single bands or dominant bands were present in all lymph node and salivary gland lymphomas, 12 of 14 cases of gastric lymphoma, and 17 of 20 cases of HP gastritis with lymphoid hyperplasia. These bands were reproducible in deeper sections from the same paraffin block or similar areas sampled in different blocks in all of the lymph node and salivary gland lymphomas, 11 of 12 gastric lymphomas, but only 1 of 17 cases of HP gastritis with lymphoid hyperplasia. Bands were also found in 3 of 20 cases of HP gastritis without lymphoid hyperplasia and 17 of 38 colonic specimens, but these were not reproducible. The complexity of patterns of IgH GR in acquired MALT compared with lymph nodes may be the result of a relative paucity of B-cell clones or preferential proliferation of B-cell clones with a limited area of distribution. HUM PATHOL 28:166-173. This is a US government work. There are no restrictions on its use.

SUDAKOV FACTORIZATION AND RESUMMATION

Contopanagos H. Laenen E. Sterman G.

Nuclear Physics B. 484(1-2):303-327, 1997 Jan 20.

We present a unified derivation of the resummation of Sudakov logarithms, directly from the factorization properties of cross sections in which they occur. We rederive in this manner the well-known exponentiation of leading and non-leading logarithmic enhancements near the edge of phase space for cross sections such as deeply inelastic scattering, which are induced by an electroweak hard scattering, The relevant factorization theorems are known to hold for many such cross sections of interest, and we conjecture that they apply even more widely. For QCD hard-scattering processes, such as heavy-quark production, we show that the resummation of non-leading logarithms requires in general mixing in the space of the color tensors of the hard scattering. The exponentiation of Sudakov logarithms implies that many weighted cross sections obey particular evolution equations in momentum transfer, which streamline the computation of their Sudakov exponents. We illustrate this method with the resummation of soft-gluon enhancements of the inclusive Drell-Yan cross section, in both DIS and <(MS)over bar> factorization schemes.

ADVANCES IN HUMAN MITOCHONDRIAL DISEASES - MOLECULAR GENETIC ANALYSIS OF PATHOGENIC MTDNA MUTATIONS

Davidson E. King MP.

Trends in Cardiovascular Medicine. 7(1):16-24, 1997 Jan.

The mitochondrial diseases are a heterogeneous group of disorders that have been defined by specific morphological alterations in muscle and by deficits of the mitochondrial respiratory chain. The morphological hallmarks of these diseases include ragged-red fibers (an extensive proliferation of mitochondria in muscle fibers) and abnormal paracrystalline inclusions and membrane structures in mitochondria. The identification of pathogenic mutations in mitochondrial DNA (mtDNA) has resulted in a genetic classification of mitochondrial diseases. Investigations are being conducted to understand the molecular basis for the biochemical and morphological alterations mitochondria associated with mtDNA mutations. (C) 1997, Elsevier Science Inc.

IMPLICATIONS OF THE FEEDING CURRENT STRUCTURE OF EUCHAETA RIMANA, A CARNIVOROUS PELAGIC COPEPOD, ON THE SPATIAL ORIENTATION OF THEIR PREY

Fields DM. Yen J.

Journal of Plankton Research. 19(1):79-95, 1997 Jan.

Many marine planktonic organisms create water currents to entrain and capture food items. Rheotactic prey entrained within these feeding currents often exhibit escape reactions. If the direction of escape is away from the feeding current, the prey may successfully deter predation. If the escape is towards the center of the feeding current, the prey will be re-entrained towards its predator and remain at risk of predation. The direction of escape is dependent on (i) the ability of the prey to escape in a direction different than its pre-escape orientation and (ii) the orientation caused by the interaction of the prey's body with the moving fluid. In this study, the change in orientation of Acartia hudsonica nauplii as a result of entrainment within the feeding current of Euchaeta rimana, a planktonic predatory copepod, was examined, When escaping in still water, A.hudsonica nauplii were able to vary their pre-escape direction by only 10 degrees. This allows only a limited ability to escape in a direction different than their pre-escape orientation. Analyses of the feeding current of E.rimana show the flow speed to be most rapid in the central region with an exponential decrease in speed distally. In contrast, flow vorticity is minimal in the center of the feeding current and maximal at 1.75 mm along the antennae. As a result, the degree of rotation of the prey towards the center of the feeding current shows a strong dependency on the prey's location within the feeding current. The feeding current of E.rimana rotated the prey 14 degrees when near the center of the flow field and up to 160 degrees when located more distal in the feeding current. Since the prey's escape abilities cannot compensate for the rotation due to the flow, this mechanism will maintain the escaping prey within the feeding current of their predator. Therefore, the feeding current facilitates predatory copepods in capturing prey by (i) increasing the amount of water which passes over their sensors and through their feeding appendages and (ii) controlling the spatial orientation of their prey prior to escape.

A FAMILY OF CYCLIN-LIKE PROTEINS THAT INTERACT WITH THE PHO85 CYCLIN-DEPENDENT KINASE

Measday V. Moore L. Retnakaran R. Lee J. Donoviel M. Neiman AM. Andrews B.

Molecular & Cellular Biology. 17(3):1212-

1223, 1997 Mar.

In budding yeast, entry into the mitotic cell cycle, or Start, requires the Cdc28 cyclin-dependent kinase (Cdk) and one of its three associated G(1) cyclins, Cln1, Cln2, or Cln3. In addition, two other G(1) cyclins, Pcl1 and Pcl2, associate with a second Cdk, Pho85, to contribute to Start. Although Pho85 is not essential for viability, Pcl1,2-Pho85 kinase complexes become essential for Start in the absence of Cln1,2-Cdc28 kinases. In addition, Pho85 interacts with a third cyclin, Pho80, to regulate acid phosphatase gene expression. Other cellular roles for Pho85 cyclin-Cdk complexes are suggested by the multiple phenotypes associated with deletion of PHO85, in addition to Start defects and deregulated acid phosphatase gene expression. Strains with pho80, pcl1, and pcl2 deletions show only a subset of the pho85 mutant phenotypes, suggesting the existence of additional Pho85 cyclins (Pcls). We used two-hybrid screening and database searching to identify seven additional cyclin-related genes that may interact with Pho85. We found that all of the new genes encode proteins that interacted with Pho85 in an affinity chromatography assay. One of these genes, CLG1, was previously suggested to encode a cyclin, based on the protein's sequence homology to Pcl1 and Pcl2. We have named the other genes PCL5, PCL6, PCL7, PCL8, PCL9, and PCL10. On the basis of sequence similarities, the PCLs can be divided into two subfamilies: the Pcl1,2-like subfamily and the Pho80-like subfamily. We found that deletion of members of the Pcl1,2 class of genes resulted in pronounced morphological abnormalities. In addition, we found that expression of one member of the Pcl1,2 subfamily, PCL9, is cell cycle regulated and is decreased in cells arrested in G(1) by pheromone treatment. Our studies suggest that Pho85 associates with multiple cyclins and that subsets of cyclins may direct Pho85 to perform distinct roles in cell growth and division.

DISSOCIATION OF LPL AND LDL - EFFECTS OF LIPOPROTEINS AND ANTI-APOB ANTIBODIES

Choi SY. Pang L. Kern PA. Kayden HJ. Curtiss LK. Vannireyes TM. Goldberg IJ.

Journal of Lipid Research. 38(1):77-85, 1997 Jan.

We have shown previously that the activity of lipoprotein lipase (LPL), the major enzyme responsible for hydrolysis of triglyceride contained in circulating lipoproteins, is associated with lipoproteins in postheparin plasma. In other studies, microtiter plate assays showed that LPL interaction with low density lipoprotein (LDL) and very low density lipoprotein (VLDL) was decreased by antibodies to apolipoprotein (apo)B. To test whether antibodies to apoB affected LPL-LDL association in solution, two types of assays were performed, gel filtration and coprecipitation. First we showed that LPL activity and immunoreactive mass co-eluted during gel filtration of normal postheparin plasma, approximately with the peak of low density lipoproteins. Then LPL was used for gel filtration studies in the presence and absence of LDL and anti-apoB monoclonal antibodies. LPL association with LDL was diminished by antibodies to the amino-terminal region of apoB; antibodies to the carboxyl-terminal LDL receptor binding region of apoB were less effective. LDL binding to LPL containing heparin-agarose was also disrupted by the amino-terminal antibodies to apoB. To determine the LPL-lipoprotein association in situations in which the distribution of plasma lipoproteins was altered, we studied plasma from two types of subjects with dyslipidemias. The addition of I-125-labeled LPL to type 1 postheparin plasma produced two peaks of radioactivity, one peak eluted in the void volume of the column (with the chylomicrons) and a second peak eluted just prior to the normal elution of low density lipoproteins. In postheparin plasma from an abetalipoproteinemic subject, LPL eluted with HDL. We conclude that LPL associates primarily with apoB-containing lipoproteins. The reason for this appears to be that LPL interacts with the apoB.

PRIMITIVE MODELS OF CHEMICAL ASSOCIATION .2. POLYMERIZATION INTO FLEXIBLE CHAIN MOLECULES OF PRESCRIBED LENGTH

Kalyuzhnyi YV. Lin CT. Stell G.

Journal of Chemical Physics. 106(5):1940-1949, 1997 Feb 1.

The structural properties of the totally flexible sticky two-point (S2P) model for polymerization into chain molecules of fixed length are studied. The model is represented by an n-component mixture of hard spheres of the same size with species 2,...,n-1 bearing two attractive sticky sites A and B, randomly distributed on the surface. The hard spheres of species 1 and n have only one site per particle, site B for species 1 and site A for species n. Due to the specific choice for the attractive interaction, which is present only between site B of the particles of species a and site A of the particles of species a + 1, this version of the S2P model represents an associating fluid that polymerizes into freely jointed tangent hard-sphere chain molecules. The correlation functions of this model are studied at all degrees of association using a recently obtained general solution of the polymer Percus-Yevick (PPY) approximation [Yu. Kalyuzhnyi and P. Cummings, J. Chem. Phys. 103, 3265 (1995)]. Comparison of the results of the present theory in the complete association limit with corresponding computer-simulation results and results of other theories is presented and discussed. The complete-association results constitute a quantitatively successful theory of the mean monomer-monomer distribution functions for less than or equal to 16 but for n = 50 these functions are no longer quantitatively accurate. (C) 1997 American Institute of Physics.

THE SECOND CASE OF A T(17-22) IN A FAMILY WITH NEUROFIBROMATOSIS TYPE 1 - SEQUENCE ANALYSIS OF THE BREAKPOINT REGIONS

Kehrersawatzki H. Haussler J. Krone W. Bode H. Jenne DE. Mehnert KU. Tummers U. Assum G.

Human Genetics. 99(2):237-247, 1997 Feb.

A reciprocal t(17;22)(q11.2;q11.2) was found in a female patient with neurofibromatosis type 1 (NF1) and in her affected daughter. Sequence analysis of cloned junction fragments traversing the breakpoints allowed the identification of the structures involved in the rearrangement. Aberrant bands in Southern hybridizations of restriction enzyme-digested DNA of the patient pointed to the disruption of the NF1 gene in intron 31. Semispecific polymerase chain reaction analysis of the genomic DNA of the patient with the specific primer anchored at NF1 exon 31 was used to obtain the breakpoint-spanning fragment of the derivative chromosome 17. The intron 31 sequence turned out to be interrupted within a large irregular (AT) repeat. The chromosome 22-derived sequence of the der(17) junction fragment allowed us to identify cosmids of the corresponding region from a chromosome 22-specific cosmid library. With the support of the break-point-spanning cosmids, the chromosome 22 region upstream of the fragment carried by the der(17) was characterized. Primers deduced from the sequence of this up-stream region were used in combination with a primer in NF1 intron 31 distal to the breakpoint on chromosome 17 to amplify the der(22) junction fragment. The structure of the junction sequences suggested that the translocation had arisen by unequal homologous recombination between (AT)-rich repeats on chromosome 22 and on chromosome 17 in intron 31 of the NF1 gene. However, our data support the assumption of additional rearrangements prior to, or in the course of, the recombination event, leading to a loss of the sequences between the involved (AT) repeats on chromosome 22. In the direct vicinity of these (AT) repeats, two members of a previously undescribed low-copy repetitive sequence have been found, copies of which are also present on human chromosome 13.

STRUCTURE OF CHAIN D OF THE GIGANTIC HEMOGLOBIN OF THE EARTHWORM

Xie Q. Donahue RA. Schneider K. Mirza UA. Haller I. Chait BT. Riggs AF.

Biochimica et Biophysica Acta - Protein Structure & Molecular Enzymology. 1337(2):241-247, 1997 Feb 8.

The extracellular hemoglobin of the earthworm has four major O-2-binding chains, a, b, c and d, together with additional non-heme structural chains that are required for assembly. Although the abc trimer self-associates extensively at least to (abc)(10), addition of chain d results in the formation of a discrete 280 kDa complex corresponding to (abcd)(4). Thus a primary function of chain d is to cap the abc association and convert an abc trimer that binds O-2 with weak cooperativity to a highly cooperative (abcd)(4) complex. Amino-acid sequences of the major globin chains a, b, c have been determined previously by peptide and cDNA analysis. However, the peptide sequence reported for the major chain d (Shishikura, F., Snow, J.W., Gotoh, T., Vinogradov, S.N. and Walt, D.A. (1987) J. Biol. Chem., 262, 3123-3131), has a calculated molecular mass 134-167 Da higher than masses for components of chain d determined by mass spectrometry (Ownby, D.W., Zhu, H., Schneider, K., Beavis, R.C., Chait, B.T. and Riggs, A.F. (1993) J. Biol. Chem. 268, 13539-13547). Reverse-phase HPLC confirms the presence of two distinct polypeptides, d(1) and d(2), together with d(1), a variant of d(1). cDNA-derived amino-acid sequences have been determined for chains d(1) and d(2) by application of the polymerase chain reaction with primers based on the NH2-terminal sequences and oligo-dT. Each of the two cDNA-derived sequences has 140 residues and they differ by 28 substitutions. The data show that the sequence originally reported had been derived from peptides generated from both polypeptides.

Selected Funding Updates

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

NASA: AO-97-OSS-02 - Research for Design and Construction of Unique Instrument for Use at the Keck Observatory

The Office of Space Science, has issued a Request for Proposal AO-97-OSS-02, for research proposals for a scientific investigation at the W. M. Keck Observatory (WMKO). An integral part of this research program is the design and construction of a unique instrument for use at WMKO. Each successful proposer will conduct a feasibility study with an option for implementation. A detailed description of the general area of interest and specific guidance for proposal preparation will be available electronically on the WWW site after March 14, 1997. The URL address is: http://www.hq.nasa.gov/office/oss/research.htm Further information is available from: Dr. Sethanne Howard, Code SR, NASA Headquarters, Washington, DC 20546-0001; telephone: 202-358-0359. This opportunity will be open for a period through June 16, 1997.

NASA: NRA 97-OSS-06 - Origins of Solar Systems Program

The Office of Space Science has released NRA 97-OSS-06 which solicits basic and applied research proposals for the Origins of Solar Systems Program (OSSP) to conduct scientific investigations related to understanding the formation and early evolution of planetary systems and to provide the fundamental research and analysis necessary to detect and characterize other planetary systems. This announcement will be available on the OSS Homepage at URL: http://www.hq.nasa.gov/office/oss/research.htm. Proposals are due by June 20, 1997.

NASA: NRA-97-OSS-05 - Research to Analyze Scientific Data from the Compton Gamma Ray Observatory

NASA Headquarters, Office of Space Science, has issued a Request for Proposals for basic research proposals for participation in the NASA program to analyze scientific data from the Compton Gamma Ray Observatory (Compton) and to conduct correlative and theoretical research closely tied to Compton observations. Proposals are due by June 12, 1997. This NRA will be available electronically through the selection "Research Opportunities" on the OSS homepage on the internet, at the URL address: http://www.hq.nasa.gov/office/oss/research.htm

NASA: NRA-97-OSS-04 - Exploration of the Solar System: Research in Planetary Sciences

The National Office of Space Science, solicits proposals for basic research to conduct scientific investigations in the areas of planetary astronomy, planetary atmospheres, cosmochemistry, and planetary geology and geophysics. A detailed description of the general areas of interest and specific guidance for proposal preparation will be available at URL address: http://www.hq.nasa.gov/office/oss/research.htm. This opportunity will be open through June 6, 1997.

DoE Program Notice 97-08: Innovations in Fusion Energy Confinement Systems

The Office of Fusion Energy Sciences of the Office of Energy Research, U.S. Department of Energy announces its interest in receiving grant applications for innovative experiments in fusion energy confinement systems. Organizations with research projects funded under previous Notice 95-10 which are now due for continuation funding need not submit; however, those seeking renewal funding should submit a renewal application under this Notice. Successful applications will be funded early in FY 1998.

The Office of Fusion Energy Sciences is interested in applications for innovative experimental research that has the possibility of leading to improved fusion energy power plants (this includes tokamak based power plants with qualitatively improved performance). The research should be aimed at experimentally elucidating the physics principles involved. Research projects are sought which are unique, first of a kind and which provide new scientific insights. Although the main thrust of this initiative is experimental, consideration will be given to applications which are directed at scientific assessment of new concepts which are not ready for experimental investigation. Applications for research on existing large tokamaks, separate theory investigations, or initiatives in Inertial Fusion Energy should not be submitted in response to this notice. Collaborative applications submitted from different institutions which are directed at a single proposed experiment will be "bundled" and reviewed collectively.

Applications submitted in response to this notice must be received no later than May 15, 1997. General information about development and submission of applications, eligibility, limitations, evaluations and selection processes, and other policies and procedures may be found in the Application Guide for the Office of Energy Research Financial Assistance Program via the Internet using the following Web site address: http://www.er.doe.gov/ production/grants/ grants.html

DoE: Prog. Notice 97-12 - Atmospheric Chemistry Program

The Office of Health and Environmental Research of the Office of Energy Research, U.S. Dept. of Energy has announced its interest in receiving applications to support the continuation of its Atmospheric Chemistry Program (ACP). The applications should address the continuation of experimental and theoretical study of atmospheric chemistry processes affected by energy-related air pollutants (i.e., sulfur oxides, nitrogen oxides, aerosols, and ozone). The Atmospheric Chemistry Program is part of the DOE's Global Change Research Program and is closely linked with other national and international programs. Collaborations are maintained with global change counterparts in other agencies, particularly NASA, NOAA, and the NSF. Internationally, the DOE ACP links with the World Meteorological Organization's (WMO) Global Atmospheric Watch (GAW) program, particularly through the North American Regional Experiment (NARE), the Aerosol Chemistry Experiment (ACE) 1 and 2, North American Research Strategy for Tropospheric Ozone (NARSTO), and the Southern Oxidant Study (SOS).

Detailed descriptions of ACP plans, rationale, and foci are provided on the DOE ACP homepage at: http://www.atmos.anl.gov/ACP. Research applications that demonstrate the continuity and progress of the DOE ACP during the 1993-1997 period (see research abstracts in http://www.atmos.anl.gov/ACP) addressing midlatitude tropospheric ozone and heterogeneous chemistry, atmospheric chemical-conversion processes, and wet-removal and air/surface exchange is encouraged. More so, applications addressing ozone research that is in support of the NARSTO are also encouraged.

This notice requests applications for grants to support: (Category 1): Research to understand the fundamental scientific phenomena associated with atmospheric ozone formation and removal processes. (Category 2): Ozone and UV-B trend analysis, using past and emerging data sets. (Category 3): Research to understand the fundamental scientific phenomena associated with aerosol radiative forcing and climate change. It is anticipated that approximately $3 million will be available for multiple grant awards in FY 1998, contingent upon availability of appropriated funds. Applications may request project support up to three years, with out-year support contingent on availability of funds, progress of the research, and programmatic needs. Annual budgets are expected to range from approximately $50,000 to $500,000. Applications should include detailed and justified budgets for each year of support requested. Grant applications must follow the guidelines given in the Application Guide for the Office of Energy Research, which may be found via the World Wide Web at: http://www.er.doe.gov/production/grants/grants.html. Formal applications submitted in response to this notice should be received by 4:30 p.m., June 12, 1997.

National Inst. for Occupational Safety & Health: Research and Demonstration Grants
Occupational Safety and Health

The National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC) is soliciting grant applications for research and demonstration projects related to occupational safety and health. The purpose of this grant program is to develop knowledge that can be used in preventing occupational diseases and injuries. Thus, NIOSH will support the following types of applied research projects: causal research to identify and investigate the relationships between hazardous working conditions and associated occupational diseases and injuries; methods research to develop more sensitive means of evaluating hazards at work sites, as well as methods for measuring early markers of adverse health effects and injuries; control research to develop new protective equipment, engineering control technology, and work practices to reduce the risks of occupational hazards; and demonstrations to evaluate the technical feasibility or application of a new or improved occupational safety and health procedure, method, technique, or system. The types of grants NIOSH supports are as follow:

1. Research Project Grants (R01)
2. Demonstration Project Grants (R18):
3. First Independent Research Support and Transition (FIRST) Grants (R29)
4. Special Emphasis Research Career Award (SERCA) Grants (K01)
5. Small Grants (R03)

The NIOSH program priorities, listed below, are applicable to all of the above types of grants listed under the section Mechanisms of Support. Approximately 500 organizations and individuals outside NIOSH provided input into the development of the National Occupational Research Agenda (NORA). The conditions or examples listed under each category are selected examples, not comprehensive definitions of the category. Investigators may also apply in other areas related to occupational safety and health, but the rationale for the significance of the research to the field of occupational safety and health must be presented in the grant application. The Agenda identifies 21 research priorities. The NORA document is available through the NIOSH Home Page; http://www.cdc.gov/ niosh/nora.html.

The research grant application Form PHS-398 (OMB Number 0925-0001) is to be used in applying for these grants. Receipt dates* are: **Research and Demonstration Project Grants:** Feb. 1, June 1, and Oct. 1; **SERCA and Small Grants:** Mar. 1, July 1, and Nov. 1. (* Deadlines for competing continuation applications or revised applications are 1 month later).

To receive additional written information call 404-332-4561. You will be asked to leave your name, address, and telephone number and will need to refer to announcement #729. This and other CDC Announcements can be found on the CDC home page at http://www.cdc.gov

PAR-97-042: Innovation Grant Program for Approaches in HIV Vaccine Research

Continued Next Page

The National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH) on the recommendation of the AIDS Vaccine Research Committee (AVRC), seeks to implement a new program aimed at rapidly exploiting new scientific opportunities to broaden the base of scientific inquiry in areas related to vaccine discovery and development.

This program announcement represents the first step in establishing the Innovation Grant Program. The NIAID invites applications, including those from researchers previously outside the field of AIDS research, for research projects that involve a high degree of innovation, risk and novelty— as well as a clear promise of helping to improve vaccine design or evaluation — in the following three general areas: (1) the structure/function of HIV envelope protein; (2) creation/improvement of animal models for vaccine evaluation and pathogenesis studies; and (3) mechanisms of directing antigen processing in vivo. This Innovation Grant Program utilizes a grant mechanism which provides the resources to carry out preliminary tests of feasibility for new research hypotheses, and a rapid and streamlined review and award process. This approach will be evaluated by the AVRC for suitability and responsiveness following this initial offering. If successful, other announcements may be made in the future. Research projects will be supported with the exploratory/developmental research grant mechanism. Application Receipt Date: May 23, 1997.

PAR-97-040: NIA Pilot Research Grant Program in Neuroscience and Biology

The National Institute on Aging (NIA) is seeking small grant (R03) applications to: (1) stimulate and facilitate the entry of promising new investigators into the neuroscience and biology of aging and (2) encourage established investigators to enter new targeted, high priority areas in these research fields. 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 (R29) award application and/or a significant advancement of aging research.

PAR-97-041: Pilot Grants in Geriatrics

The Geriatrics Program of the National Institute on Aging (NIA) is seeking small grant (R03) applications to stimulate and facilitate research in underdeveloped topics in specific areas of aging research. 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 (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.

CA-97-005: Chemoprevention in Genetically-Identified High-Risk Groups - Interactive Research and Development Projects

The purpose of this initiative is to establish integrated, multidisciplinary research programs that define and evaluate chemopreventive strategies in asymptomatic subjects at high risk for cancer. This Request for Applications (RFA) seeks programs with administrative core functions supporting at least three independent but integrated research projects that share a common focus directed at designing and evaluating chemopreventive strategies in high-risk cohorts. This includes groups with on-going administrative clinical trials core functions and laboratory support such as cooperative groups, CCOP Research Bases and NCI designated cancer centers. At least two of the individual projects must involve Phase I/II or Phase II clinical chemoprevention trials or translational research needed for chemoprevention applications. It is anticipated that approximately $3 million in total costs will be committed specifically to fund three to four research program cooperative agreement (U19) awards in response to this RFA. Letter of Intent Receipt Date: April 3, 1997; Application Receipt Date: May 22, 1997.

DK-97-008: Chronic Protatitis Collaborative Clinical Research Studies

The Division of Kidney, Urologic and Hematologic Diseases of the National Institute of Diabetes and Digestive and Kidney Diseases invites research project grant (R01) applications for five interactive Clinical Research Centers (CRC) and one biostatistical support center (BSC) to participate as an interactive chronic prostatitis clinical research group (CPCRG). The purpose of this request for applications (RFA) is to provide support for investigators to study patient self-reported symptoms and the objective diagnostic findings in men with chronic prostatitis (i.e., pain or discomfort in the pelvic area, no demonstrable infection using routine clinical methodology). One area of emphasis is the development of state-of-the-art techniques to characterize the prostatic secretions of men with chronic prostatitis. Another area of emphasis is the development and validation of a survey instrument to assess self-reported severity of illness in these men. For FY 1997, $1,100,000 will be committed to fund applications submitted in response to this RFA. It is anticipated that up to five awards for Clinical Research Centers (CRC) and one award for a Biostatistical Support Center (BSC) will be made under this RFA. The award for the clinical component of each Clinical Center will not exceed $140,000 direct costs for the first year (protocol development phase). The direct costs awarded for the BSC for the first year (protocol development phase) will not exceed $180,000 direct costs. Letter of Intent Receipt Date: March 17, 1997; Application Receipt Date: May 14, 1997.

CA-97-014: Pivotal Clinical Trials for Chemoprevention Agent Development

The Division of Cancer Prevention and Control (DCPC), National Cancer Institute invites applications to further the drug development efforts of the Chemoprevention Branch by carrying out intermediate-sized Phase II/III efficacy trials of promising chemopreventive agents in major cancer target organs, particularly prostate, breast, lung, colon, and bladder. Approximately $3 million in total costs for the first year of support for the program will be committed specifically to fund three to four cooperative agreement (U01) applications submitted in response to this RFA. Letter of Intent Receipt Date: April 3, 1997; Application Receipt Date: May 22, 1997.

PA-97-045: Pilot Projects or Feasibility Studies for Genomic Mapping, Sequencing and Analysis

The National Human Genome Research Institute (NHGRI), formerly the National Center for Human Genome Research, invites applications for exploratory/developmental grants (R21) to develop new, and/or significantly improve existing, technologies that will accelerate the genome mapping, sequencing and analysis goals of the Human Genome Project (HGP) in the most expeditious and economical manner. The purpose of this program announcement is to encourage high risk/potential high payoff applications that are not yet developed fully enough to successfully compete for a standard R01 grant. This program announcement supersedes the program announcement: PAR-94-046, Pilot Projects or Feasibility Studies for Genomic Analysis, NIH Guide, Vol. 23, No. 10, March 11, 1994.

PA-97-043: Research on the Origins and Pathways to Drug Abuse

This program announcement encourages research exploring the origins of and pathways to drug abuse. Of particular interest are multidisciplinary, integrative and developmental approaches. A keen understanding of the factors and processes that predispose and protect an individual from drug abuse from initial use through different stages of drug involvement is essential to the successful prevention and treatment of drug abuse. Investigators from diverse scientific disciplines are encouraged to apply either individually (e.g., as individual projects) or collectively (e.g., as a program project). Support mechanisms include: Project Grants (R01), Small Grants (R03), Exploratory Grants (R21), First Independent Research Support and Transition Awards (R29), Program Projects (P01) and Research Centers (P20, P30, P50, and P60).

PA-97-044: Technologies for Genomic Mapping, Sequencing, and Analysis

The National Human Genome Research Institute (NHGRI), formerly the National Center for Human Genome Research solicits applications for research project grants (R01) and First Independent Research Support and Transition (FIRST) (R29) awards to develop new technologies, and/or significantly improve existing technologies, that will facilitate and accelerate the genome mapping, sequencing and analysis goals of the Human Genome Project (HGP) in the most expeditious and economical manner. The resources produced will be used to further studies of diseases and other biological phenomena. This program announcement supersedes the following two program announcements: PA-94-045, New and Improved Technologies for Genomic Mapping and Sequencing, NIH Guide, Vol. 23, No. 10, March 11, 1994 and PA-92-59, Genome Informatics Program, NIH Guide, Vol. 21, No. 12, March 27, 1992.■

Continued from Page 3

because it helps localize cognitive activity using an empirical technique.

A Look at Metabolites, Neurotransmitters

Shulman also discussed work using glucose and its metabolite glutamate, and the neurotransmitter couple of glutamate-glutamine, as the objects of NMR spectroscopic scans. Because such species are much less prevalent than water protons, the resolution of such scans is on order of 5 or 6 cubic centimeters.

To look at metabolites and neurotransmitters, Shulman explained, one must start with glucose that is "labeled" with carbon-13 — one of the molecule's six carbon-12 atoms has been replaced with the stable, magnetic isotope C-13. By following the C-13's magnetic resonance signal, the location of glucose and glutamate becomes readily visible and the areas where the metabolic rate is highest can be seen.

Neurotransmitter studies also use C-13, to allow measurement of the rate of transformation of glutamate into glutamine. Communication between many neurons starts when the sending cell releases glutamate into a synapse. Then, the receiving neuron takes up the glutamate and transfers it to an adjacent glial cell, which uses an enzyme to convert it into glutamine, and then returns the glutamine into the sending neuron to complete the communication.

So, Shulman said, by measuring the cycling rate of glutamate and glutamine, more valuable clues about brain activity can be gleaned. And, the measurement can be tested by anaesthetizing an animal subject and confirming that neurotransmitter activity diminishes practically to zero.

All in all, Shulman summarized, NMR "enables us noninvasively to get quantitative measurements in regions of the brain of the parameters which have been used to characterize brain activity. Each of these opens important different directions for more medical applications, and for more applications involving different activities of the brain."

Between water-proton-based MRI scans that open questions in cognitive neuroscience and studies based on metabolism and neurotransmitters, Shulman concluded, "We are presented with great opportunities to study the functioning brain when there is no conscious output. This is access to that great, deep, epistimologically inaccessible consciousness."■

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Research on Hold at BNL Reactor for Groundwater Investigation

Radioactive Leak Leads to Intensely Negative Public Reaction

by Kathryn Gavin

Research is on hold at one of Brookhaven National Laboratory's (BNL) main scientific facilities, the High Flux Beam Reactor (HFBR), following the discovery of radioactive tritium contamination in groundwater near the reactor building and the subsequent political and media uproar over the pollution.

Nearly 300 researchers from BNL and other institutions are facing at least a year without access to the HFBR's neutron scattering beam lines and sample irradiation facility.

Since first going on-line in 1965, the reactor has supported research in high-temperature superconductivity, structural biology, nuclear medicine, surface chemistry and materials science. But a routine maintenance shutdown was extended indefinitely in January when tritium, an isotope of hydrogen with a half life of 12.3 years, was found unexpectedly in two groundwater monitoring wells near the reactor's domed building.

The wells had been installed last year as part of BNL's comprehensive groundwater protection program, an offshoot of its Superfund cleanup efforts. While groundwater contamination, largely organic chemicals, has been found elsewhere on the Lab site and targeted for cleanup, the HFBR was not a suspected groundwater pollution source. But samples taken from the wells last fall, analyzed in December and confirmed in January showed otherwise.

Since the initial tritium finding, hydrogeologists have installed more than 100 new groundwater monitoring wells "downstream" of the HFBR, to allow them to delineate the plume's extent.

Based on this extensive groundwater sampling and analysis, the contamination appears to extend several thousand feet south of the reactor building, though still within the BNL site and out of reach of any drinking water supply. As a result, investigators from the Environmental Protection Agency have repeatedly stated that the public's health is not at risk from the tritium.

An intense search for the tritium's source has paralleled the groundwater sampling efforts. Officials now suspect that tritiated water may have been leaking imperceptibly for over a decade from a 68,000-gallon pool in the building's lower level that is used to store spent HFBR fuel. The reactor's core is not leaking.

Operation of the HFBR won't begin for approximately a year, officials say, so that investigators can track the contamination's extent, plan for cleanup, and install an impermeable stainless-steel liner in the pool to prevent future leakage.

Before the liner can be installed, 800 spent fuel elements and the surrounding water must be removed from the pool and shipped off-site for storage, a process expected to take several months. Over the same period, pumps will begin extracting contaminated groundwater from the ground to stop its flow southward toward inhabited areas.

BNL's efforts to address the tritium contamination have been accompanied by negative community reaction, intense media coverage and close attention from politicians. Senator Alfonse D'Amato and U.S. Rep. Michael Forbes have both taken an intense interest in the situation, arranging for neighbors of the lab to be hooked up to the public water supply to ease their anxiety about the quality of their own well water.

In public hearings and press conferences, both have repeatedly condemned BNL's delay in recognizing that the spent fuel pool posed a potential threat to goundwater. The pool was built in the mid-1960s using a tile, felt and concrete construction that was acceptable at the time, but was never upgraded to meet changing standards.

The announcement that BNL director Nicholas Samiois plans to retire at the end of April has been colored by the tritium issue, with media reports attributing his decision to exterior pressure over the Lab's handling of the situation. In fact, Samios had been planning for about a year to retire at the end of 15 years as BNL director, an anniversary that falls on May 1.

As the controversy boils on, HFBR users are seeking alternate neutron sources to accommodate their research, including reactors at Oak Ridge National Laboratory and the National Instititute of Standards & Technology. Those institutions are reportedly making an effort to shoehorn displaced HFBR users into their already tight schedules.■

Fed Gov't to Pay NY Hospitals Not to Train Residents

New Attempt to Control Oversupply of Physicians

by Elizabeth Belton, *ASN&R* Staff Writer

American healthcare commissions and institutions have been grappling for several years about how to solve the problem of resident overstaffing in teaching hospitals; in response, the federal government has proposed a radical and experimental solution. On February 17, the Department of Health and Human Services announced a new plan in which the government will pay the majority of New York State teaching hospitals to not train residents; in exchange for 400 million dollars, these hospitals will cut back their residency positions to ease the oversupply of new physicians.

This approach, likened by the *New York Times* to the federal government's paying corn farmers to let fields lie fallow, means that there will be less unemployed doctors. Furthermore, hospitals will not suffer a lack of resources by cutting back their staff, and will gain funds which they can use for a variety of purposes.

The plan, called the Medicare Graduate Medical Education Demonstration Project, proposes that each hospital will cut down, over a period of 6 years, 20 to 25 percent of their residency programs. Forty-one teaching hospitals in New York state are participating in the plan, the majority of them in New York City and surrounding areas.

These hospitals are responsible for training 10,286 residents statewide and currently receive 900 million dollars annually from Medicare specifically for graduate medical education. With the new plan, 2500 resident positions could be cut statewide by 2003.

In New York City, the participating hospitals include: the Mt. Sinai Consortium (Cabrini Medical Center, Elmhurst Hospital Center, Mt. Sinai Medical Center, and Queens Hospital Center), and the New York University Consortium (Bellevue Hospital Center, Brooklyn Hospital, Hospital for Joint Diseases and Orthopedic Institute, Lenox Hill Hospital, New York Downtown Hospital, and New York University Medical Center).

Other hospitals in the New York metropolitan area include Columbia-Presbyterian Hospital, Maimonides Medical Center, St. Luke's Hospital, the New York Eye and Ear Infirmary, Coney Island Hospital, and the Long Island Jewish Medical Center. The only major hospital consortium participating in the project outside the New York City metropolitan area is a group of hospitals upstate in Buffalo.

For several years, major healthcare corporations and institutions have disagreed about not only the severity of the resident overstaffing problem, but what methods should be used to solve the problem. In November, 1995, the Pew Health Professions Commission released a report called Critical Challenges: Revitalizing the Health Care Professions for the 21st Century. Among other issues, the commission recommended that some medical schools be closed to decrease the large amount of physicians entering the workforce.

In a response to the Pew commission's report, the Association of American Medical Colleges released a report the following February agreeing that there were a current oversupply of physicians, but disagreed that schools should be closed down entirely.

Warning that there was less need now for physicians, the AAMC stated that there could be a need for more in the future, stating that all existing evidence suggests that the disease burden in the population will continue to increase, and recommended that medical schools merely decrease the size of their entering classes. The AAMC also made the observation that students denied admission to medical school because of limited enrollment could very well attend medical school in countries adjoining the United States, such as Mexico, and then return to the United Stated to pursue a residency, thus perpetuating the current problem.

In June, 1996, the Council on Medical Education released a report detailing the tripling of medical school student in the last thirty-five years, the current unstable financing of medical school education, and urged the federal government to find more stable funding for graduate medical education.

The Medicare Graduate Medical Education Demonstration Project is the first such concrete plan introduced by the government to combat the problem of overstaffing; it may also positively influence hospital staffing in other areas.

In the last few years, hospitals' tight budgets, have forced residents to assume responsibilities otherwise performed by others on the hospital staffs. A recent editorial in the *New York Times* written by a resident physician in Los Angeles complained of doing less training as a physician and performing non-medical tasks that ordinarily would be done by other personnel, including filling out paperwork and transporting patients around in the hospital. Although the competition may now be greater for residency positions in New York teaching hospitals, the new money will enable hospitals to expand their resources so that residents can concentrate on training to be better physicians.■

Continued from Page 1

The explanation which has received the most attention is the so-called "leptoquark hypothesis" (electrons and positrons are members of the "lepton family," hence the name). In this view, quark and positron interact directly, forming a new particle which then decays back into positron and quark. No such particle was thought to exist in the current model, and the families of quarks and leptons were not thought to mix. The popularity of this hypothesis is to be traced to this unification of the two classes.

For the moment, there are more than a dozen fundamental particles detected, and most particle physicists find this number too large to be the final one. The general belief is that there must be some more fundamental force or particle which would unify and simplify this picture. (In much the same way one can explain the complete periodic table with electrons, protons, and neutrons.) The new particle would be very heavy (more than 200 times the mass of the proton), which would explain why it has not been detected before in other accelerators around the world.

The leptoquark is just one of the possible explanations for what is now reported. Another explanation suggests a different possible substructure of quarks or electrons. This too involves a change from earlier thinking and would imply the existence of a new force, strong enough to confine this new particle in the quarks. The existence of substructures for the quarks or electrons would also provide an explanation for the large number of particles seen, and would reduce the number of fundamental particles needed as "building blocks".

The announcement has generated considerable excitement in the scientific community and in particle physics facilities around the world — even more so since a second experiment (called H1), also operating at the HERA collider, reported a similar excess. However it is difficult to compare the results of the two groups directly because the H1 team used a different method to reconstruct the events, and have different errors associated with their method. Moreover, their analysis was done using the equivalent of only 60% of the data collected by the ZEUS collaboration.

For the moment, no one is claiming a discovery of any sort, and the most conservative opinion is that, as Professor Ritz expressed it, "a statistical fluctuation is the most likely explanation for all of this." A new run of data collection will start this month and be completed by the end of the year. At that time, the data-set will have been doubled, and researchers will see if the excess has diminished or has remained.

Everyone awaits the analysis of the additional data. Until then, as Professor Ritz said, "We are stuck with the statistics."■

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the same time.

Holly and Robert have found that when a synapse matures it gains AMPA receptors. They've determined that this happens when calcium enters the cell through the NMDA channels and activates the CaMKII enzyme, which in turn stimulates the arrival of AMPA receptors. In an experiment designed to test the role of CaMKII, a postdoctoral fellow, Gang-Yi Wu, working with Holly and Robert, found that when the enzyme is inserted into a developing neuron the cell reacts by developing characteristics of a mature cell — the axons stabilize and the synapse acquires the second receptor, AMPA.

As each group looked at the role of AMPA receptors, and the molecular elements involved in their arrival, they found a striking common element. In addition to showing that CaMKII appears to stimulate the arrival of the AMPA receptors, they also found that activation of CaMKII is necessary for maturation of synapses during development and later for establishement of LTP (long term potentiation), a process thought to be critical to the formation of memories.

Acronym Box

AMPA: a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; a neurotransmitter receptor.
CaMKII: calmodulin-dependent kinase II; an enzyme that modifies cellular proteins.
GFP: green fluorescent protein, a fluorescent tag which can be attached to specific proteins in order to make them visible for study.
LTP: long term potentiation; the strengthening of electrical pathways characterized by greatly enhanced response in the affected postsynaptic cell(s).
NMDA: N-methyl D-aspartate; a neurotransmitter receptor.

What is LTP? In order to understand LTP, imagine for a moment the lawn of a corner house. If passers-by occasionally cut across the lawn in random places the lawn will likely not show any significant change. But if each day a series of walkers cut across the lawn in the same diagonal line, eventually a pathway will appear, worn into the lawn. The repeated use of a given path establishes, then reinforces, that path's existence. This is also the case in neurological transmission across the myriad of neurons that make up the brain and central nervous system. The establishment of such a pathway in the brain is LTP.

The Malinow lab studies LTP in the hippocampal region of rats' brain. The hippocampus is a region of the mammal brain that is implicated in learning and memory. It has been shown that when the hippocampus is damaged the ability to form long term memory is impaired; when it is destroyed on both sides of the brain the ability to form new memories is lost.

In order to test the effect of repeated stimuli and a sudden strong stimulus on the formation of LTP, they set up an experiment in which they delivered a series of mild electrical charges to a slice of rat hippocampal cells at a rate of one charge per 15 seconds. The strength of sequential synaptic transmission remained constant. They then delivered a rapid fire 'buzz' charge equivalent to 100 impulses in one second. Synaptic response peaked dramatically, then upon returning to the original (one charge per 15 seconds) stimuli the postsynaptic responses were consistently twice as strong. Something about the jolt increased the strength of the synaptic communication. This is the achievement of LTP and with the help of a graduate student in Robert's lab, Dezhi Liao, the researchers have shown that LTP appears to be due, in part, to the arrival of AMPA receptors.

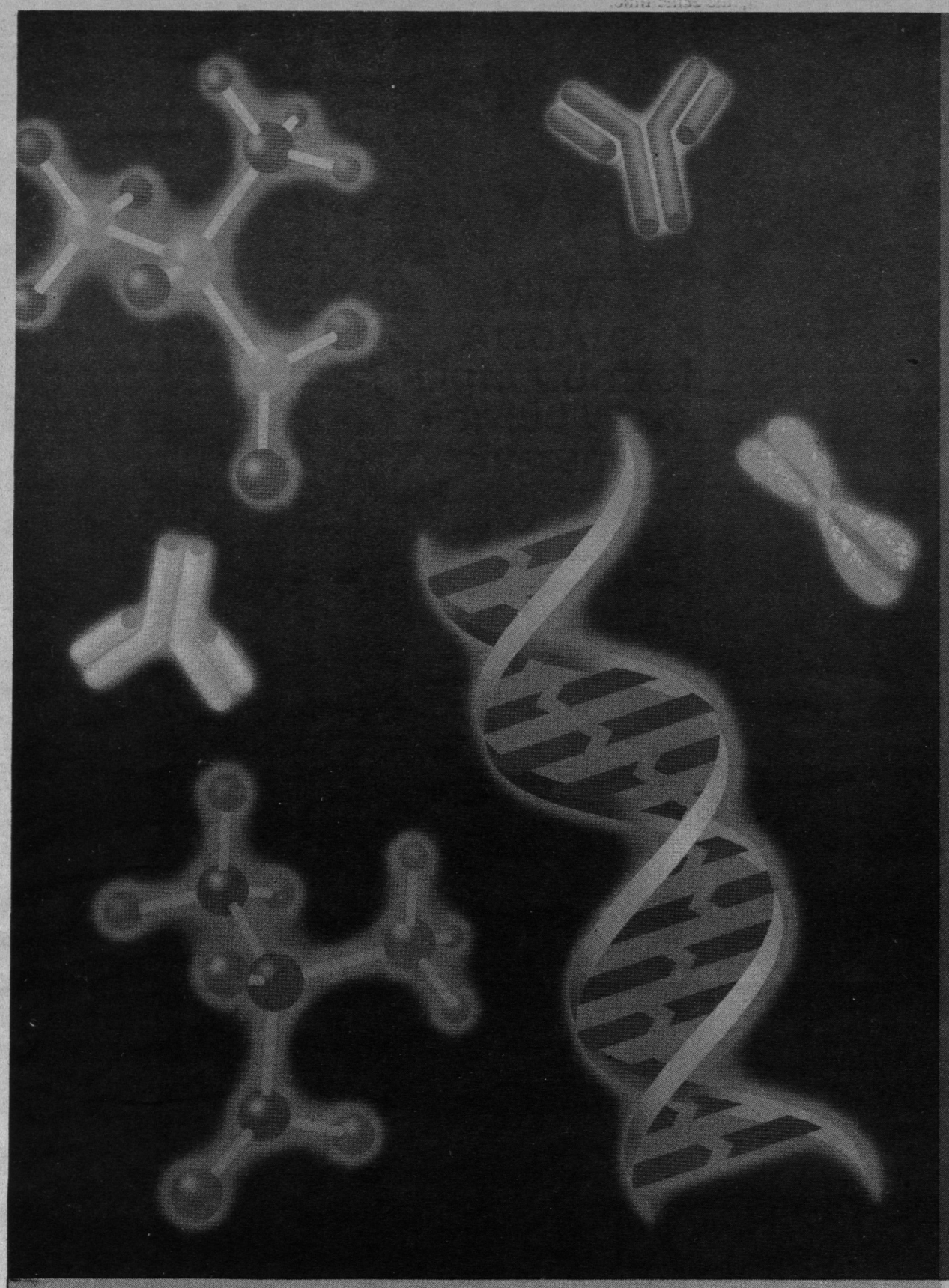
But what exactly causes the arrival of these secondary receptors? "The process is very fast — less that one minute," Robert reports, "and we are testing the idea that AMPA receptors may be in vesicles in the postsynaptic cell and, upon a calcium stimulus, vesicles move closer to the membrane and fuse with it, delivering AMPA receptors to the postsynaptic membrane." The Malinow group has attached green fluorescent protein (GFP) to AMPA molecules in order to look at their location and movement. GFP is a fluorescent protein that allows scientists to look at specific proteins in living cells. These experiments will help to determine where AMPA originates, and how and when it arrives at the synapse.

LTP is thought to be an important underlying process of learning and memory. Such complex requirements for LTP, therefore, can provide a selective process for the formation of memories. If you imagine the brain as the hard drive of an organism's computer, and everything that it saw and heard was committed to memory, the hard drive (or brain) would become overloaded in no time. This would explain why repetitions or shock — which lead to LTP — are necessary in order to commit something to memory: if you repeat a fact or telephone number enough times it will eventually be committed to memory. A close call with an oncoming truck at a given intersection will likely create a lasting impression. These are some of the bases for the formation of long term memory.

"It's interesting," Robert notes, "that two ostensibly different research projects — one to determine how synapses are formed and stabilized (Holly's work) and the other to understand an important mechanism of learning and memory — could reach such common observations." The fact that AMPA is required for both types of changes in the brain and that CaMKII is instrumental to both processes raises questions about the relationship between neuronal development, maturity, learning and memory.

"Cells have a certain repertoire of molecular events," Holly points out. "In this case the cell uses particular parts of that repertoire during development, then goes on to use the same mechanisms later to strengthen the connections that it developed earlier. So you have genes that are important in development playing a different but equally important role later on."

These two labs use the same molecular biological tools and techniques to study the very same components in two processes once thought to be quite different. Their continued and intersecting research on these not so different processes promises to bring us closer to understanding both of these important neurological events — neuronal development and the achievement of learning and memory.■



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