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November◆1997

Lorenz Delivers Talk on Climate Prediction

Founder of Chaos Theory Discusses Long-Term Predictability

by James L. Ulrich

Climate is what you expect; weather is what you get." With this aphorism, Dr. Edward Lorenz, renowned meteorologist and a founder of chaos theory, began his talk on the feasibility of climate prediction. Held September 30th at Columbia University, it helped inaugurate this year's International Research Institute and Columbia Earth Institute lecture series on climate-related issues.

Lorenz offered a more detailed explanation of climate, observing that it is "not what you expect tomorrow, but what you would expect some time further in the future than the time for which weather prediction is possible." Chaos theory — the study of systems that "aren't random, but look random" — suggests that such predictability has an upper limit of two weeks. In more concrete terms, Lorenz described climate as a system consisting of three components: the atmosphere, including clouds and pollutants; the oceans, including both sea and sea ice; and the rest of the Earth itself, including glaciers, rivers, saltwater, and vegetation. For each component he drew a distinction between internal conditions, which are integral parts of the climate system (sea temperature, for example), and external conditions, such as volcanic activity, which, while affecting climate, are not considered to be features of the climate itself.

Lorenz cautioned that it is not an easy thing to define exactly what climate is, offering in evidence four mathematical models, each describing the climate differently, and each having advantages and disadvantages in terms of its ability to describe long-term climate change.

First, he offered the example of a deterministic model, one in which all future states of the model are known once the starting state is known. This determinism permits climate to be represented as average values for certain properties, temperature, for instance, computed infinitely far into the future. But because this approach describes climate as a single, immutable "average state," it holds little interest for those who wish to predict climate change.

A related model of climate might instead

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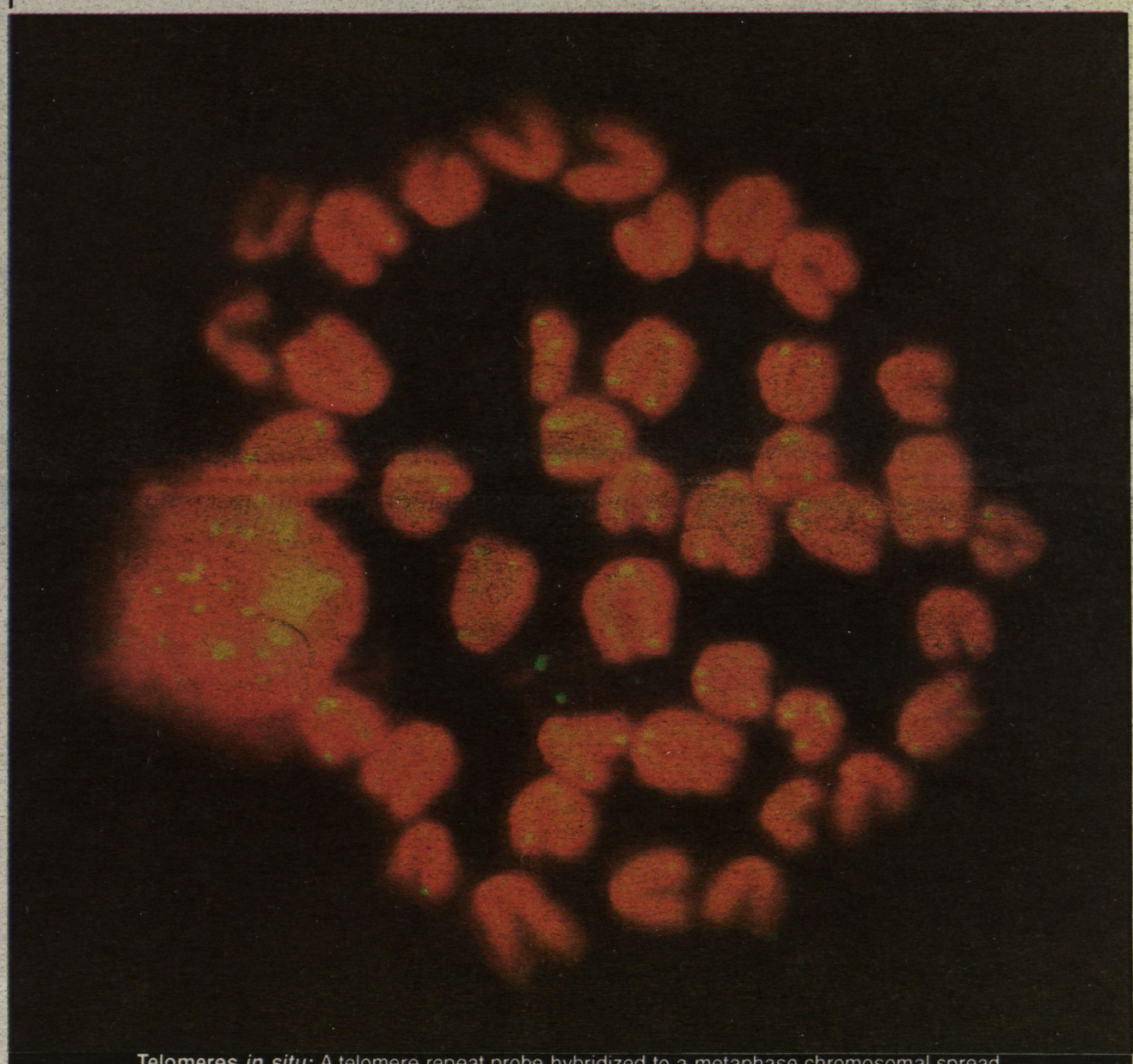
Telomerase, Cell Immortality, and Cancer

Series of New Studies Test the "Telomere Hypothesis" With Mixed and Intriguing Results

by Jeremy Kay, *ASN&R* Staff Writer

It's a seemingly nonsensical pattern of nucleotides — six base pairs repeated over and over, forming a DNA strand that could hardly encode any kind of gene. And yet it has managed to wind up at the center of one of the hottest areas of investigation in cell biology, capturing the imagination of many in the field and sending pharmaceutical watchers on Wall Street into a tizzy. Why should anyone care about this chain of apparent genetic gibberish? Because, according to a recent hypothesis, this DNA might hold a message vital to the phenomena of aging and cancer — encoded not in its base pairs, but in its physical length.



Telomeres *in situ:* A telomere repeat probe hybridized to a metaphase chromosomal spread.

These six-base-pair repeats are found at the very ends of the chromosomes, and comprise a structure known as the telomere. The telomere is a long DNA chain that appears to act as a sort of protective cap for the chromosome, guarding against various sorts of chromosomal damage and loss. From the time that telomeres were first identified, more than 60 years ago, scientists have thought of them simply as chromosome stabilizers. They were not considered very interesting until recently, when a provocative hypothesis emerged implicating them in cellular senescence — the aging process by which a cell becomes unable to divide — and in cancer.

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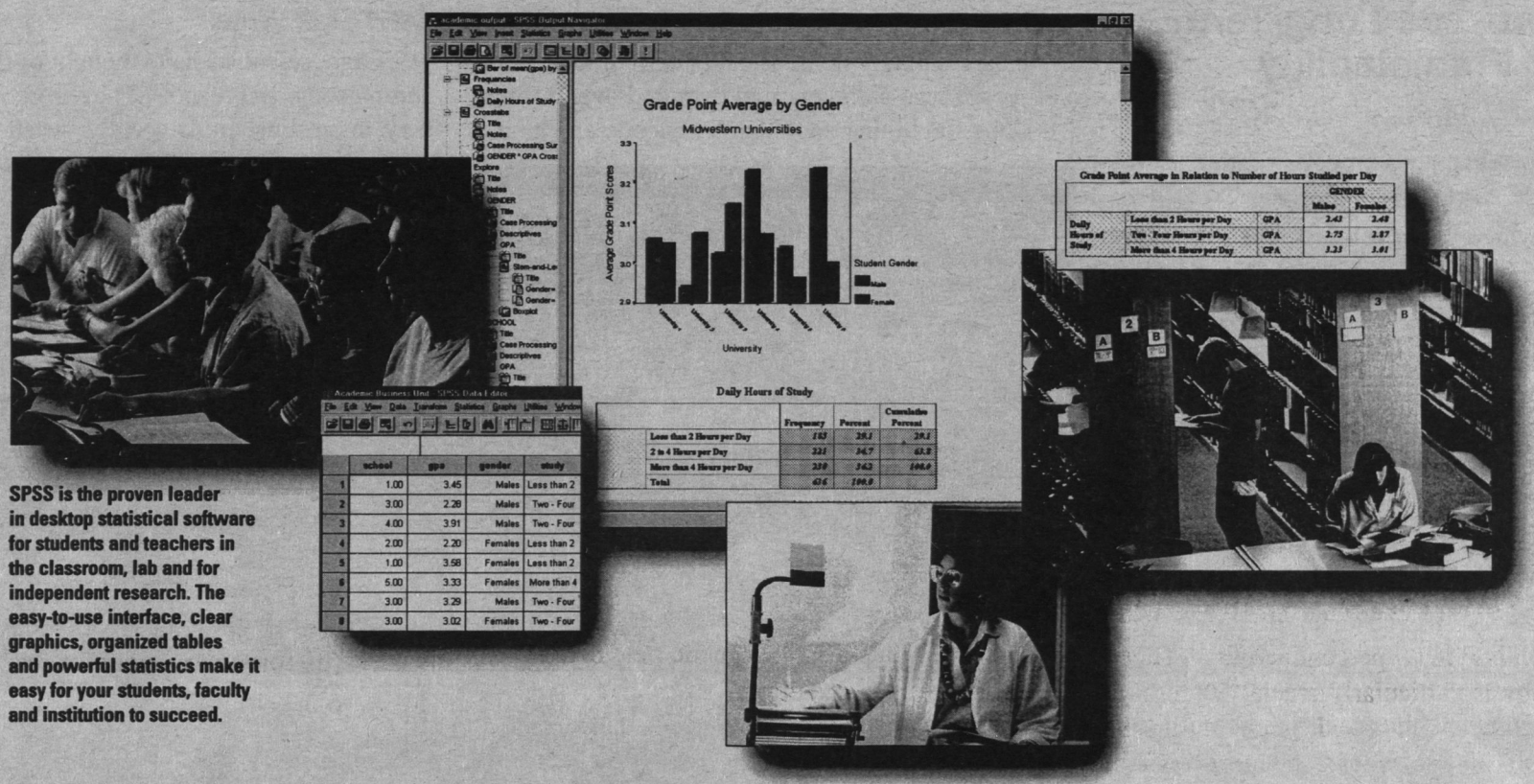

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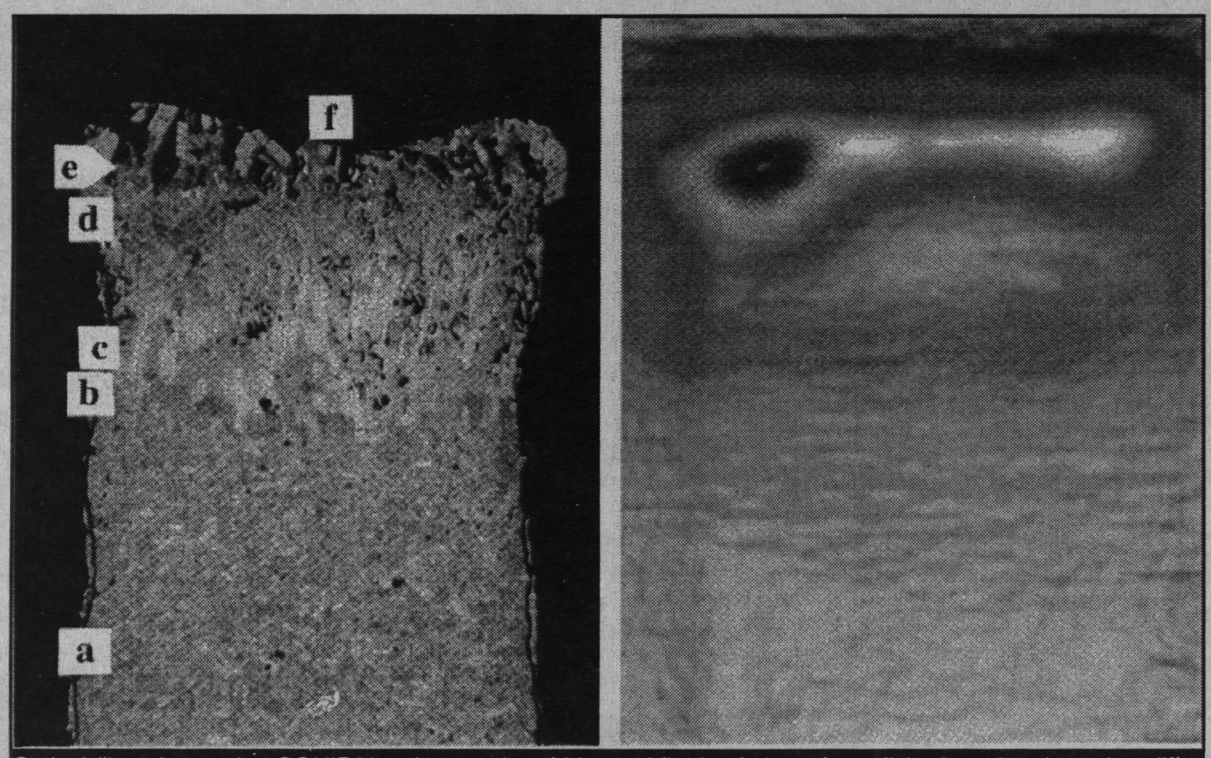
A Superconducting Needle in a Haystack

Combining SQUID With Petrology Methods Promises to Open New Windows in Superconductor Research

by Ilana Harrus, Ph.D., *ASN&R* Staff Writer

In the Sept. 11 issue of *Nature,* researchers from the IBM T.J. Watson Research Center and Columbia University reported the development of a new technique to isolate tiny quantities of superconducting material hidden in a mixture of ordinary matter, and solved a long-standing problem for researchers in superconductivity. This new methodology is particularly crucial for research in high-temperature superconductivity because test materials are produced at very high pressure, and only a tiny fraction in the mixture may exhibit superconductivity. Using the new method developed by Dr. Bruce Scott and collaborators, it is now possible to detect concentrations of superconducting material as small as one part per million. The new method uses a SQUIDs measurements coupled to existing techniques borrowed from petrology, a branch of geology dealing with the structure and origin of rocks.



Optical (l) and scanning SQUID(r) micrographs of identical fields of view of a polished section through a diffusion-couple experiment processed at 60 kbar and 950C for 3h. The scanning SQUID micrograph shows magnetic flux exclusion only in the reaction zone (e).

SQUIDs (Superconducting Quantum Interference Devices) are magnetic field detectors invented almost 35 years ago. Their use, at first cumbersome and restricted, has become widespread. Largely due to the discovery of high-temperature superconductivity, it is now possible to operate such a device at "warm" temperature of -196 degrees Celsius. This may not be your average beach temperature, but it is much warmer than the nearly -273 degree Celsius previously needed. More importantly, the warmer temperature can be obtained using liquid nitrogen and no longer requires the use of liquid helium, more expensive and more difficult to handle. SQUIDs can detect magnetic fields 250,000 times weaker than that of the Earth, and are used in experiments ranging from epilepsy diagnostics to tests of general relativity.

A very schematic view of a SQUID defines it as a superconducting ring with two Josephson junctions. These junctions, named after their discoverer, Dr. Josephson, consist of a layer of isolating material sandwiched between two superconductors. Josephson showed that, under certain circumstances, a current could flow through the junction, which then behaves like a superconductor. In this simplified view of a SQUID, the ring, "tuned" to have a current flowing across the two Josephson junctions, is put through the magnetic field to be measured. The magnetic field alters the current already present, and this variation is used to determine the value of the magnetic field needed to produce the measured effect.

Once the SQUID microscope has detected the location of the superconductor in the mixture, the investigators used imaging and measurement techniques borrowed from the field of petrology (members of the research group include scientists from the Lamont-Doherty Earth Observatory). Although SQUIDs had been used before to detect superconducting material, now coupled with petrographic techniques, this is the first time it has become possible to detect, image and measure the properties of the superconductor.

In the paper published in *Nature,* the researchers describe how they isolate the superconducting property of a system which had heretofore been studied without promising results. The methodology developed has a large number of applications. As Dr Scott said: "The method can be used whenever the superconductor comprises a small fraction of a heterogeneous mixture." One of the important applications, as noted earlier, is in high-temperature superconductivity research, where trial samples are created using high-pressure methods. This relatively new method is not yet optimized, and the number of possible problems is large compared to those seen at atmospheric pressure. In this case, Dr Scott said, "SQUID petrology is important for unraveling these problems and determining exactly what is going on."

For the moment, the procedure remains quite complicated, with the three different phases of the work —detection, imaging, and measurement — still separated. The next step will be to simplify and integrate the method. "We would like to develop a single tool that both images and identifies a superconductor compound in a complex mixture," Dr. Scott said.■

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compute an average of values taken over a finite period of time. Climate change could then be represented by the differences resulting from varying the time interval over which averages are taken. However, this approach begs the question of just what one should regard as "change." For example, should the coming and going of El Nino be regarded as two distinct changes in climate, or simply as a feature of the climate appearing every four years or so?

To avoid this question, one can resort to a third model in which climate is once again presented in terms of infinite averages, but with certain external conditions, such as carbon dioxide levels, held fixed. By selecting different values at which to fix the external conditions, one can model overall climate change. However, this approach fails to model changes in the internal features of the climate.

A fourth model of the climate, which Lorenz dubbed the "ensemble" approach, averages together all those climate changes, internal and external, which might reasonably be expected to occur over a period of time, thereby describing climate in terms of a representative outcome.

Having established the types of systems that might be used to model the climate, Lorenz proceeded to speak about weather prediction. He

(l) Antonio Divino Moura, Director, Int'l Research Inst. for Climate Prediction at Columbia Univ.; (r) Edward N. Lorenz, MIT.

referred to weather prediction as an "initial value problem," in which data describing the weather at a given point in time are fed into a model (typically a computer program) based on some set of physical laws which describe how weather patterns evolve. Given the weather today, the model computes what the weather will be tomorrow, or a week from now. Theoretically, one could extend a weather forecast to a climate forecast by asking the model to calculate the evolution of weather patterns not over a week, but over a year, or even a decade. Lorenz observes that, in practice, this doesn't work because "our atmosphere is a chaotic system."

In a chaotic system, small differences in starting conditions may lead to great differences in the overall behavior of the system over time. Since it is not possible to capture every single detail of the weather conditions at a given time, any weather data fed into a forecasting model will deviate slightly from the conditions that actually exist. For example, one might take humidity readings in New York and Philadelphia on a summer afternoon when both these cities are warm and dry, although a thunderstorm is passing through Trenton. The average humidity in the sample data for the northeast will then deviate slightly from the actual average humidity. Because the climate

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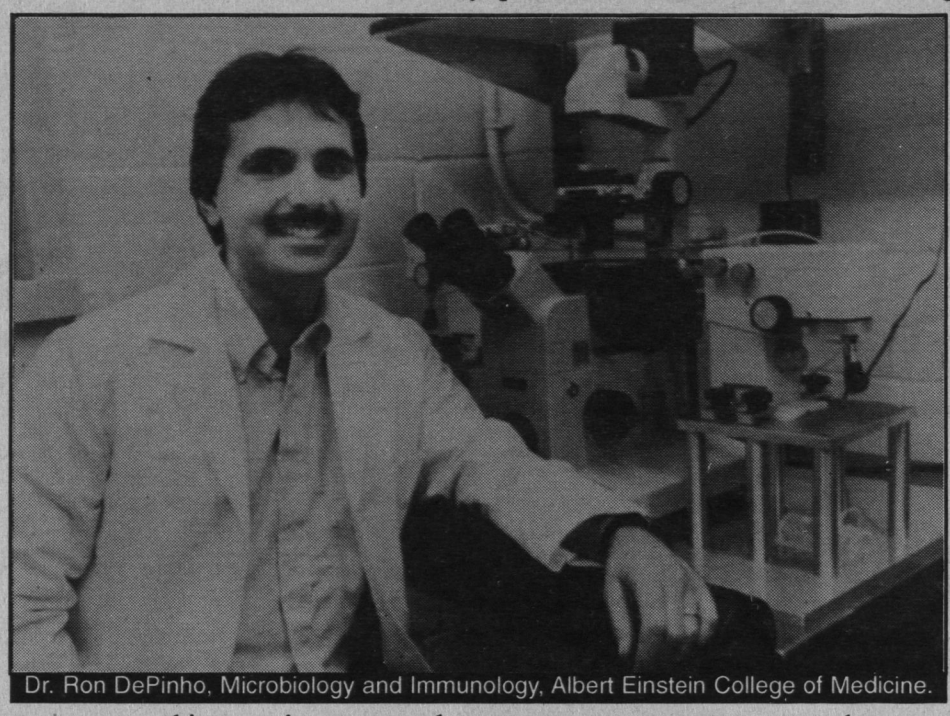
Telomeres...Continued from Page 1

According to this hypothesis, a key step in the transformation of a normal cell into a cancerous one is the activation of an enzyme called telomerase, which is capable of lengthening a cell's telomeres. Most normal cells in the adult do not express telomerase, but over 90% of human cancers do. If the hypothesis is correct and telomerase is in fact necessary for the maintenance of cancerous cells, inhibiting telomerase could be a way of treating a wide variety of cancers.

Although no drugs yet exist that can act as telomerase blockers, pharmaceutical companies have rushed to develop them, while the popular press has trumpeted them as the next potential "magic bullet" that could cure cancer. With only preliminary data so far, indicating telomerase can affect cell division, many cell biologists studying cancer and sensecence are eager to begin examining the enzyme's role in these processes.

Now, however, a new set of experiments, published in the October 3 issue of *Cell*, appear to dash some of the excitement that has been building around telomerase. Researchers at Cold Spring Harbor Laboratories and at Albert Einstein College of Medicine collaborated on the first study to test the effects of manipulating telomerase in mammals. Along with colleagues from Canada and Spain, they created a line of transgenic mice missing the gene coding for part of the telomerase enzyme, effectively "knocking out" all telomerase activity in these mice. They found that, even without telomerase, cells from these knockout mice were still capable of forming tumors. Dr. Ronald DePinho, Professor of Microbiology, Immunology, and Medicine at Albert Einstein, and a principal investigator in the study, is quick to point out that this is not the end of all hope that telomerase could be a point of attack against cancer. However, he noted: "The issue of whether telomerase inhibition is a 'magic bullet' should be seriously questioned" as a result of his group's recent work.



Dr. Ron DePinho, Microbiology and Immunology, Albert Einstein College of Medicine.

The Telomere Hypothesis

Why would anyone think that telomerase, an enzyme that adds onto the barren ends of DNA molecules, far from the fertile ground of gene transcription, might be an Achilles' heel for cancer? The reason lies in a new conception of the role of telomeres that has emerged in the last few years, which suggests that telomeres may do more than simply guard the chromosome against damage. According to this hypothesis, the length of a cell's telomeres is a key signal controlling the cell's ability to divide.

The hypothesis is based on the observation that, every time a cell divides, it loses a tiny bit of DNA from the telomeric region at the end of each chromosome. In order to divide, a cell must replicate its DNA so that both daughter cells will have a copy of all the original genetic material. Due to a quirk in the enzymes that make up the cell's DNA replication machinery, it is physically impossible for the cell to copy the very end of a DNA strand. Thus, in the absence of outside influences, each generation of cells produced by mitosis will have slightly shorter telomeres than did the generation before. This end-replication problem afflicts all eukaryotic organisms, from protozoa to humans; bacteria get around the problem with tricks like having circular DNA.

What prevents the telomeres from shrinking away to nothing over the course of generations, leaving the chromosome vulnerable to damage? In 1985, Drs. Carol W. Greider and Elizabeth H. Blackburn identified a specialized enzyme that could lengthen telomeric DNA. The enzyme became known as telomerase, and Dr. Greider, who was until recently at the Cold Spring Harbor Laboratory, and who was one of the principal investigators in the recent *Cell* paper, became one of the leading experts on how telomerase works and what it does.

One of the key properties of telomerase is that it is not active in most adult human tissues. This means that most cells probably do undergo telomere shortening when they divide, and that they are most likely limited in the number of times they can divide

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New Study Will Examine Plant-Derived Preventative Therapies for Colon Cancer

Rockefeller Team to Investigate Three Compounds Commonly Found in Fruits and Vegetables

by Dan Coulter, *ASN&R* Staff Writer

Dr. Steven J. Shiff, a researcher at the Rockefeller University Hospital in Manhattan was recently awarded a grant to investigate the potential preventative properties of three plant-based compounds for colorectal cancer. The Rockefeller University Hospital, established in 1910, was the first hospital in the United States solely devoted to patient-oriented biomedical research, linking laboratory investigations with bedside observations to provide a scientific basis for disease detection, prevention and treatment.

Every year, approximately 100,000 new cases of colorectal cancer are diagnosed and 55,000-60,000 people die from the disease. Dr. Shiff, the principal investigator in the new research, will study the effects of curcumin, rutin and quercetin on the lining of the colon in volunteers with a history of colon polyps, pre-malignant benign colon tumors, to determine their potential as chemopreventatives for colorectal cancer.

Many, if not all colorectal cancers begin as non-cancerous growths called polyps. A polyp becomes cancerous through progressive genetic mutations in genes that are important for the regulation of cell growth and death. Specifically, the polyps develop when the normal routine of cell division and apoptosis, a type of programmed cell death, go awry — probably because of genetic mutations that accumulate in these cells due to prolonged or repeated environmental insults, such as a diet rich in fatty foods. When apoptosis is disabled, tissues no longer can properly regulate their cell populations. Cell growth goes unchecked, and cancer may ensue. Individuals at risk for colon cancer may have colon cells that possess a reduced ability to undergo apoptosis.

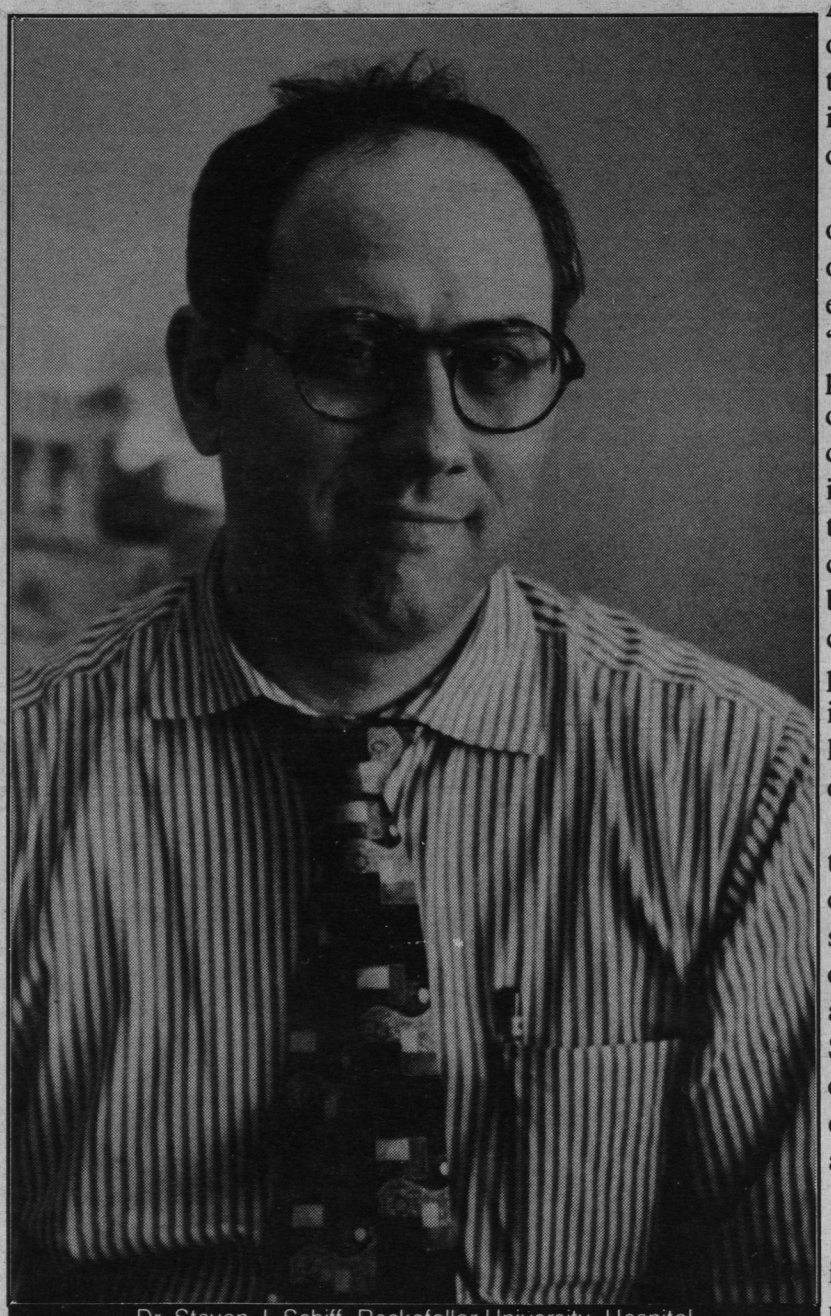
WHAT DO BROCCOLI, TOMATOES AND MUSTARD HAVE IN COMMON?

Three plant-derived compounds, curcumin, rutin and quercetin, were selected by Dr. Shiff as primary targets for study because all three possess anti-inflammatory properties. "Curcumin," said Dr. Shiff, "has been used by natural healers and folk medicine for centuries as anti-inflammatory agents." The compound gives the yellow color to the seasoning curry, and to mustard. It is the major ingredient of tumeric, the powdered form of the root of Curcuma longa Linn. Rutin and quercetin can be found naturally in many fruits and vegetables such as tomatoes, broccoli, cranberries, and onions, as well as in tea. Rutin breaks down into quercetin after being digested in the colon.

Dr. Shiff speculates that these compounds may prove safer and better tolerated than other cancer-thwarting nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, and aspirin-like drugs such as sulindac. NSAIDs in general have been shown to prevent colorectal cancer, and to reduce related deaths by up to half. However, many NSAIDs can cause unwanted side effects, such as irritation of the stomach lining or kidney damage. Dr. Shiff and his team have set out to determine if these plant-based preventative therapies are at least as effective as conventional NSAIDs, and to see if they are better tolerated by most patients.

CELL DEATH TO PREVENT COLON CANCER

The NSAID sulindac works to thwart cancer by prompting cells to "turn on" a program of regulated cell death. In this new study, Dr. Shiff and his colleagues will compare the three plant-derived compounds to sulindac, and determine whether these naturally occurring substances can affect cells in a similar manner. "Ideally, we would like to find the lowest optimal dose of each of the three plant compounds that would safely inhibit the development of colorectal cancer," explains Shiff.



Dr. Steven J. Schiff, Rockefeller University Hospital

In a recent study, Dr. Bert Vogelstein of Johns Hopkins and his team noted: "The inactivation of the p53 gene in a large proportion of human cancers has inspired an intense search for the encoded protein's physiological and biological properties. Expression of p53 induces either a stable growth-arrest or programmed cell death (apoptosis). In human colorectal cancers, the growth-arrest is dependent on the transcriptional induction of the protein p21, but the mechanisms underlying the development of p53-dependent apoptosis are largely unknown."

Dr. Shiff notes: "The gene p53 is probably important for making a polyp change into a cancer. There are also other genes that Vogelstein has shown that, when mutated, can cause normal mucosa to form a polyp. So we conceptualize colon cancer forming through the progressive development of genetic mutations in cells, which permit them to stick to the bowel wall and to proliferate. As this proliferation continues, the cells develop even more mutations that allow them to spread beyond the wall of the colon and invade the rest of the body. At this point the cancer becomes life threatening."

As stated earlier, poor diet is felt to be one of the major contributors to the development of colon cancer. Diets rich in fruits and vegetables appear to prevent colon cancer. "That's why these plant-based therapies will probably play some role in the prevention of colon cancer," comments Dr. Shiff. "These compounds, when taken orally, will either inhibit the acquisition of progressive mutations or they might inhibit the fixation of cells that are destined to form cancer into the bowel wall. We are trying to look at the precise mechanisms through which these drugs prevent colon cancer. We can do this by looking at things like the rate at which cells proliferate in the colon lining as well as the death and maturation process of these cells."

With regard to the possible application of these compounds to treat other forms of cancer, Dr. Shiff noted that there is already strong evidence that other gastrointestinal cancers, particularly esophageal cancer, are affected by aspirin and aspirin-like drugs. Shiff's team will focus on cancer of the colon, however, because of the strong evidence that has established these compounds as capable of preventing colon cancer.

ANY VOLUNTEERS ?

Dr. Shiff is looking for volunteers to participate in this study who have had polyps removed but who do not have cancer. The ten-week study should provide clues to the prevention of colorectal cancer by these plant-derived agents. Although it takes about ten years for a tumor to develop from a polyp, Dr. Shiff points out that the effects of these agents should be evident within ten weeks. Since the lining of the colon largely replaces itself every 3 to 5 days, Dr. Shiff says that measures such as cell proliferation, cell death, and cell differentiation should be influenced quickly by the agents, permitting predictions to be made about subsequent tumor formation.

The research team will recruit men and women aged 18 years and older who have a history of colon polyps. Participants must be non-smokers, and should be generally healthy. People interested in enrolling as participants should call Dawn Stoddard, M.S., F.N.P., at 1-212-327-7458 or write to stoddad@rockvax.rockefeller.edu. All participants will receive a stipend as compensation for their contribution to the study.■

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without producing unstable, telomere-deficient chromosomes. For scientists looking to explain a phenomenon known as replicative senescence, the idea that cell division might have an absolute limit imposed by telomere length was intriguing.

Senescence occurs in all cell cultures made from human somatic cells. Cells taken from a kidney, liver, skin, cartilage, or almost any human organ system can grow in culture if treated with the proper chemicals and growth factors. The cultured cells will continue to divide for a certain number of division cycles — the numer of divisions is determined by the type of tissue from which the culture is derived. Eventually, however, the cells will become senescent — they will stop dividing and just sit there in the bottom of the petri dish. Adding additional growth-stimulating factors cannot prevent senescence — it seems to be an inescapable fact of life for cultured human cells.

How do the cells know to stop dividing? Since human somatic cells lack telomerase and their telomeres shorten with every division cycle, it is tempting to conclude that the cell can detect when its telomeres have reached a critically short length. Perhaps short telomeres somehow activate a biochemical pathway that inhibits cell division. In support of this notion are several experiments done with a type of cell known as fibroblasts, taken from humans and grown in culture. Apparently, fibroblasts from older donors have shorter telomeres, and reach senescence faster than cells taken from younger donors. In addition, fibroblast telomeres were found to shorten over the course of being cultured into senescence. These results seem to suggest that a link between telomere length and the prevention of cell division might, in fact, exist.

Even more striking evidence that telomere length can regulate cell division comes from studies with cells that do posess active telomerase. The telomere hypothesis predicts that tissues in which a lot of cell proliferation occurs should express telomerase in order to evade the short-telomere senescence signal. It turns out that this is exactly what happens — in humans, telomerase is normally expressed only in cells that need to divide rapidly and extensively, such as the developing embryo and the germline cells that give rise to sperm and eggs. Telomerase is also expressed in a type of cell that divides when it is not supposed to —cancerous cells. In cancer, a variety of glitches in the machinery controlling cell division causes cells to give up cooperating with the rest of the body, establishing instead their own private colonies. These glitches help cancerous cells bypass various intracellular safety mechanisms designed to halt unwanted proliferation. As a result, they become "immortal" — they can go on dividing forever, both in the body and in cell culture. In other words, they do not undergo senescence as normal somatic cells do. The discovery that almost all human cancers express telomerase suggested that telomerase activation might be one important way in which cancerous cells immortalize. Perhaps, without telomerase to refresh the telomeric DNA strands, cancer cells would be halted in their tracks as their rapid proliferation triggers the short-telomere senescence signal.

There has been much debate since this hypothesis first emerged over whether telomerase actually does confer immortality on cancer cells. In favor of the hypothesis is the extremely strong correlation between telomerase expression and immortality — most immortal cell lines, whether of cancerous origin or not, do express telomerase. Other evidence comes from experiments showing a correlation between shorter telomeres and senescence in cultured human fibroblasts.

So far, however, no one has been able to go beyond correlations and show a causal link between telomerase and immortality, or between shortened telomeres and senescence. No cancerous cell line has been definitively shown to require telomerase for propagation, although some inconclusive evidence does exist. Moreover, there are some types of cancer which appear to get along quite nicely without telomerase. It remains entirely possible that the presence of telomerase in cancer cells is simply a coincidence. The experiment performed by the laboratories of Drs. DePinho and Greider was an effort to find out whether telomerase is required for the immortalization of cells and the formation of tumors, and thus to determine whether the relation is, in fact, causal.

Dr. Carol Greider, Johns Hopkins (formerly of Cold Spring Harbor Laboratory)

Life Without Telomerase

Dr. DePinho said in an interview that he became involved in the telomerase question because of his long-standing interest in immortalization. His lab has been studying various molecular pathways that regulate the conversion of senescent cells to immortal ones, pathways that include tumor suppressor genes like p53, Myc, and the retinoblastoma genes, as well as telomerase. One particularly important technique his lab has used to understand immortalization is to make mouse "knockouts" that lack various genes involved in cancerous transformation, to see how the absense of these genes affects the ability of cells to immortalize. Dr. Greider, having isolated the gene for one component of the telomerase enzyme, was interested in doing a knockout experiment on this gene, Dr. DePinho said, and proposed a collaboration with him because of his experience in studying mouse models of cancer and generating knockout mice.

The knockout experiment was exciting, Dr. DePinho said, because it provided the first opportunity to test many of the most basic assumptions of the telomere hypothesis. It was assumed, for example, that mice without telomerase would have shorter telomeres, but nobody knew for sure. Similarly, nobody had ever been able to study directly the effects of telomere loss in an organism more complicated than yeast. The pioneering molecular biologist Barbara McClintock, one of the first to study telomeres, looked at the chromosomes of maize plants in 1941 and built a strong but circumstantial case that telomeres were required for chromosome stability. More recently, researchers developed a strain of yeast lacking telomerase and found that, after a sufficient number of cell divisions, chromosomal abnormalities began to appear and nearly all the cells died. But the question remained — in the environment of a multicellular organism, would cells with short telomeres actually suffer chromosome damage and death?

After the long, arduous process of generating a knockout mouse line. Drs. Greider, DePinho, and their collaborators were finally able to answer questions like these. "When we analyzed the telomerase-deficient mice," Dr. DePinho said, "what emerged initially was really quite satisfying: The telomeres did get shorter." To measure the shortening of telomeres, the researchers needed to breed their telomerase-deficient mice for several generations — presumably, the founding generation of the knockout strain has normal-length telomeres. After breeding six generations of knockout mice, the researchers collected cells from every other generation and used a technique called fluorescent *in situ* hybridization (FISH) to measure the amount of telomeric DNA on the chromosomes of these cells. A DNA probe consisting of nucleotides complementary to the telomeric six-base-pair repeat was synthesized, and labeled with a fluorescent marker. When the mouse cells were exposed to this probe, the telomeric regions of their chromosomes bound the DNA probe and became fluorescent. Longer telomeres bind more probe and thus appear more intensely fluorescent than shorter telomeres.

The authors found that FISH-labeled intensity decreased over the course of six generations in the telomerase-deficient mice, and that, in 5% of cells from the sixth generation, no telomeric DNA could be detected at all. The authors estimate that cells from sixth generation knockout mice have probably undergone more than 300 divisions without telomerase. Apparently, over the course of 300 telomerase-less divisions, the telomeres can shrink dramatically. Do the cells with little or no telomeric DNA have the predicted chromosomal abnormalities? Apparently so. The researchers found that the number of end-to-end chromosomal fusions increased in cells from later generations of telomerase-deficient mice, as did the number of cells with missing chromosomes. "It's exactly what Barbara McClintock predicted 60 years ago," Dr. DePinho said. "In the absence of telomeres, you get chromosomal loss and fusion."

The knockout experiment, then, confirms the most widely accepted tenets of telomerase theory — that telomeres shorten in the absence of telomerase, and that critically short telomeres can destabilize chromosomes.

On the other hand, the more controversial aspects of the telomere hypothesis — the assertion of a causal link betweeen telomerase and immortalization, or between telomere shortening and senescence — do not receive much support from the telomerase knockout experiments. Although the data on chromosome instability are interesting, Dr. DePinho said, the biggest and most exciting questions raised by this experiment have to do with cancer. "We wanted to know, in the face of telomerase deficiency, can [cells] become immortal?" To find out, the researchers isolated fibroblasts from knockout mice and grew them to senescence. Unlike human somatic cells, which never immortalize unless a cancer-causing gene is somehow added to their DNA, mouse fibroblasts have a greater ability to overcome senescence. At a rate of approximately 2 per million, senescent mouse fibroblasts spontaneously begin dividing again and go on to establish an immortal cell line.

The researchers used this property of mouse cells to test the effects of telomerase and shortened

Continued on Next Page

Telomeres... Continued from Previous Page

telomeres on immortalization. If telomerase is necessary for immortalization, then cells from the knockout mice should be unable to form permanent colonies, or should at least show a reduced rate of colony formation compared to cells from normal mice. This was not the case, however — cells taken from knockout mice of all six generations immortalized just as easily as control cells. Moreover, the cultures remain immortal through up to 200 rounds of cell division.

These experiments seem to show that telomerase is not required for immortalization and indefinite proliferation, at least in mice. In trying to make sense of these results, Dr. DePinho said, "you have to consider that the regulation of immortality in mouse cells seems to be different than in humans," given that human somatic cells never immortalize while mouse cells do so readily. "Mice have a higher rate of cancer. It's likely that human cells have an extra level of regulation that makes it harder for them to immortalize." The possibility remains, then, that telomerase is more tightly linked to immortalization pathways in humans than in mice, in which case the loss of telomerase function might shut down an immortal human cell line more easily than an immortal mouse line.

After looking at the question of immortalization, the researchers sought to determine whether cells lacking telomerase could become cancerous. They took cells from knockout mice of all six generations, introduced various viral oncogenes, and then transplanted the transformed cells into recipient mice. Tumors formed quite normally. "We used a somewhat artificial model of cancer," Dr. DePinho said, "but it does show that you can generate a tumor even in the face of telomerase deficiency and significant telomere erosion and genomic [i.e. chromosomal] instability."

If sixth generation knockout mice have very short telomeres and a high incidence of chromosomal abnormalities, it seems odd that telomerase-null tumor cells, or immortalized cell lines made from knockouts, or from highly proliferative tissues like sex cells, should be able to divide so many times without dying. Why don't they suffer the same fate as yeast cells lacking telomeres — death due to excessive chromosome damage? One possibility is that, even after six generations, telomeres are long enough to protect most chromosomes. To test this possibility, Dr. DePinho is now examining later-generation knockout mice for evidence of damage to tissues that normally express telomerase. Another plausible explanation is that some other mechanism is able to take over for telomerase when it is absent. "In yeast lacking telomerase, 99% of cells die. But some survivor cells do pull through," Dr. DePinho said. This survival has been shown to be the result of chance DNA recombination events that lengthen the telomeres. It is quite possible, Dr. DePinho said, that recombination could be a routine mechanism of telomere maintenance in mice. It could be part of the mechanism that allows mouse fibroblasts to overcome senescence. Also, recombination has been implicated as a mechanism of telomere maintenance in some cancers that do not express telomerase.

Waiting for Telomerase Blockers

Clearly, the results of these experiments cast serious doubt on the notion that cancers rely heavily on telomerase for immortalization and protection from senescence. Dr. DePinho still believes, however, that there is more to learn about the link between telomerase and cancer. Because of the somewhat unsubtle way that the telomerase-negative cells were made cancerous, he said, it is possible that, following insertion of the viral oncogene, an alternate telomere maintenance pathway became active that would not ordinarily function in a naturally-occurring cancer. He and his coworkers plan to crossbreed the telomerase-deficient mice with another strain created in the laboratory several years ago, in which a tumor-suppressor gene called p16 is knocked out. These mice have a spontaneous cancer rate much higher than normal mice. "It will be interesting to see whether, if you cross these two strains, you will have the same high rate of cancer" in mice without both telomerase and p16, he said.

Although it now appears that telomerase inhibitors will not be the cancer-fighting panacea that some had hoped for, they could still turn out to be a valuable weapon in the oncologist's arsenal. "If, as in yeast, you could kill 99% of the cells by inhibiting telomerase, that would be pretty good," Dr. DePinho said. In combination with other cancer-fighting drugs that could wipe out the survivors, telomerase inhibitors might be very effective. They would also probably have the advantage of causing very few side effects, since most cells do not possess telomerase and would therefore obviously not be disturbed by its inhibition.

Of course, before anyone can get too excited about telomerase inhibitors, they need to be invented. Various pharmaceutical companies are working to develop them, and now that the catalytic domain of the telomerase enzyme has been cloned, pharmacologists will be able to apply "rational" drug design methods to the problem. It seems we may have to wait until these drugs exist before any definitive answers emerge to the question of whether telomerase causes, or is merely correlated with, cancer. Only then will it be possible to test, in human cancer cells, whether telomerase is required for survival.■

CONVERGENT TOTAL SYNTHESIS OF A TUMOUR-ASSOCIATED MUCIN MOTIF

Sames D. Chen XT. Danishefsky SJ.

Nature. 389(6651):587-591, 1997 Oct 9.

Synthetic glycoconjugates that mimic cell-surface tumour antigens (glycolipids or glycoproteins with unusual carbohydrate structural motifs) have been shown to trigger humoral responses in murine and human immune systems(1-3). This raises the exciting possibility of inducing active immunity with fully synthetic carbohydrate vaccines, particularly if vaccine compounds can be synthesized that resemble the surface environment of transformed cells even more closely. Glycopeptides seem particularly suitable for this purpose. In contrast to most glycolipids and the carbohydrates themselves, glycopeptides bind to major histocompatibility complex molecules, and, in favourable cases, can stimulate T cells and lead to the expression of receptors that recognize the carbohydrate part of a glycopeptide with high specificity(4-8). The preparation of glycopeptides and glycoproteins remains, however, a difficult challenge(9-12): earlier synthesis methods have been inefficient, and established cloning approaches that allow engineering of global glycopatterns produce only heterogeneous glycoproteins(13). Here we report an efficient strategy of the synthesis of tumour-associated mucin glycopeptides with clustered trisaccharide glycodomains corresponding to the (2,6)-sialyl T-antigen. Our approach involves construction of the complete glycodomain in the first stage, followed by convergent coupling to amino acid residues and subsequent incorporation of the glycosyl amino acid units into a peptide chain. This general strategy allows the assembly of molecules in which selected glycoforms can be incorporated at any desired position of the peptide chain. The resultant fully synthetic O-linked glycopeptide clusters are the closest homogeneous mimics of cell-surface mucins at present available, and so are promising compounds for the development of anticancer vaccines.

SPIN-GAP PROXIMITY EFFECT MECHANISM OF HIGH-TEMPERATURE SUPERCONDUCTIVITY [Review]

Emery VJ. Kivelson SA. Zachar O.

Physical Review B-Condensed Matter. 56(10):6120-6147, 1997 Sep 1.

When holes an doped into an antiferromagnetic insulator they form a slowly fluctuating array of "topological defects" (metallic stripes) in which the motion of the holes exhibits a self-organized quasi-one-dimensional electronic character. The accompanying lateral confinement of the intervening Mott-insulating regions induces a spin gap or pseudogap in the environment of the stripes. We present a theory of underdoped high-temperature superconductors and show that there is a local separation of spin and charge and that the mobile holes on an individual stripe acquire a spin gap via pair hopping between the stripe and its environment, i.e., via a magnetic analog of the usual superconducting proximity effect. In this way a high pairing scale without a large mass renormalization is established despite the strong Coulomb repulsion between the holes. Thus the mechanism of pairing is the generation of a spin gap in spatially confined Mott-insulating regions of the material in the proximity of the metallic stripes. At nonvanishing stripe densities, Josephson coupling between stripes produces a dimensional crossover to a state with long-range superconducting phase coherence. This picture is established by obtaining exact and well-controlled approximate solutions of a model of a one-dimensional electron gas in an active environment. An extended discussion of the experimental evidence supporting the relevance of these results to the cuprate superconductors is given.

THE GLUR2 (GLUR-B) HYPOTHESIS - CA2+-PERMEABLE AMPA RECEPTORS IN NEUROLOGICAL DISORDERS [Review]

Pellegrinigiampietro DE. Gorter JA. Bennett MVL. Zukin RS.

Trends in Neurosciences. 20(10):464-470, 1997 Oct.

The abnormal influx of Ca2+ through glutamate receptor channels is thought to contribute to the loss of neurons associated with a number of brain disorders. Until recently, the NMDA receptor was the only glutamate receptor known to be Ca2+-permeable. It is now well established that AM PA receptors exist not only in Ca2+-impermeable but also in Ca2+-permeable forms. AMPA receptors are encoded by four genes designated gluRI (gluR-A) through gluR4 (gluR-D). The presence of the gloR2 subunit renders heteromeric AMPA receptor assemblies Ca2+-impermeable, Recent studies involving animal models of transient forebrain ischemia and epilepsy show that gluR2 mRNA is downregulated in vulnerable neurons. These observations suggest that downregulation of gluR2 gene expression may serve as a 'molecular switch' leading to the formation of Ca2+-permeable AMPA receptors and enhanced toxicity of endogenous glutamate following a neurological insult.

THE CONVERGENCE OF THE SOLUTIONS OF THE NAVIER-STOKES EQUATIONS TO THAT OF THE EULER EQUATIONS

Temam R. Wang X.

Applied Mathematics Letters. 10(5):29-33, 1997 Sep.

In this article, we establish partial results concerning the convergence of the solutions of the Navier-Stokes equations to that of the Euler equations. Convergence is proved in space dimension two under a physically reasonable assumption, namely that the gradient of the pressure remains bounded at the boundary as the Reynolds number converges to infinity.

MUTATIONS IN GSF1 AND GSF2 ALTER GLUCOSE SIGNALING IN SACCHAROMYCES CEREVISIAE

Sherwood PW. Carlson M.

Genetics. 147(2):557-566, 1997 Oct.

One function of the Saccharomyces cerecvisiae Snf1 protein kinase is to relieve glucose repression of SUC, GAL, and other genes in response to glucose depletion. To identify genes that regulate Snf1 kinase activity, we have selected mutants that inappropriately express a SUC2promoter::HIS3 gene fusion when grown in glucose and that require Snf1 function for this phenotype. Mutations representing two new complementation groups (gsf1 and gsf2) were isolated. gsf1 mutations affect two distinct responses to glucose: the Snf1-regulated glucose repression of SUC2 and GAL10 transcription and the Snf1-independent induction by glucose of HXT1 transcription. gsf2 mutations relieve glucose repression of SUC2 and GAL10 transcription and, in combination with snf1 Delta, cause an extreme slow growth phenotype. The GSF2 gene was cloned by complementation of the gsf2-1 snf1 Delta slow growth phenotype and encodes a previously uncharacterized 46 kD protein.

ARBORESCENT GRAFT POLYBUTADIENES

Hempenius MA. Michelberger W. Moller M.

Macromolecules. 30(19):5602-5605, 1997 Sep 22.

Cascade-branched, "graft on graft" polybutadienes, denoted arborescent graft polymers, were prepared by hydrosilylation of polybutadiene vinyl groups with chlorodimethylsilane, followed by grafting with living polybutadiene chains. Repeated hydrosilylation-anionic grafting cycles led to a treelike outward growth, yielding well-defined, spherically shaped macromolecules. The molecular weight of the materials increased dramatically with each grafting cycle, since polymer chains rather than small molecules were used as building blocks. The materials were characterized by means of gel permeation chromatography, static light scattering measurements, and viscosimetry.

DECREASED HDL CHOLESTEROL LEVELS BUT NORMAL LIPID ABSORPTION, GROWTH, AND FEEDING BEHAVIOR IN APOLIPOPROTEIN A-IV KNOCKOUT MICE

Weinstock PH. Bisgaier CL. Hayek T. Aaltosetala K. Sehayek E. Wu L. Sheiffele P. Merkel M. Essenburg AD. Breslow JL.

Journal of Lipid Research. 38(9):1782-1794, 1997 Sep

To determine the physiological role of apolipoprotein (ape) A-IV, knockout mice were created by gene targeting in embryonic stem cells. In apoA-IV knockout mice, plasma cholesterol and triglyceride levels were reduced 25% and 44%, respectively, compared with controls. These changes were accounted for by decreased high density (HDL) and very low density lipoprotein (VLDL) levels, respectively, and metabolic studies indicated increased HDL-cholesteryl ester (CE) fractional catabolic rate (FCR) and reduced VLDL transport rate (TR), respectively. ApoA-IV knockout mice had greater than 70% reductions in both hepatic and intestinal apoC-III RNA levels and a similar reduction in the plasma apoC-III level. Complementation analysis, via crossbreeding of a mouse apoC-III transgene onto both the normal and apoA-IV knockout backgrounds, clearly demonstrated that the low triglyceride (VLDL) level in the apoA-IV knockout mice was due to alterations in apoC-III and not apoA-IV. ApoA-IV knockout mice had normal growth, feeding behavior, and lipid absorption, except male mice showed increased food intake in the 2 h after an 18-h fast, suggesting that under some circumstances apoA-IV might serve as a satiety factor. In summary, studies in apoA-IV-induced mutant mice have demonstrated a role for apoA-IV in increasing HDL cholesterol by inhibiting HDL cholesteryl ester FCR

yet argue against the apolipoprotein as an overall important mediator of lipid absorption/metabolism.

CALCIUM-MEDIATED INTRACELLULAR MESSENGERS MODULATE THE SEROTONERGIC EFFECTS ON AXONAL EXCITABILITY

Saruhashi Y. Young W. Hassan AZ.

Neuroscience. 81(4):959-965, 1997 Dec.

We carried out experiments to investigate the mechanisms of serotonin-induced axonal excitability changes using isolated dorsal columns from young (seven to 11-day-old) Long-Evan's hooded rats. Conducting action potentials were activated by submaximal (50%) and supramaximal constant current electrical stimuli and recorded with glass micropipette electrodes. In experiment 1, to study Ca2+-mediated mechanisms, we superfused the preparations with Ringer solutions containing varying Ca2+ concentrations. Following superfusion with Ca2+-free Ringer solution for 4 h, we tested initial responses to serotonin agonists. Studies then were repeated after preparations had been washed for 1h with Ringer solution containing 1.5 mM Ca2+ and 1.5 mM Mg2+. After 4 h superfusion of Ca2+-free Ringer solution, quipazine (a serotonin(2A) agonist, 100 mu M) did not induce significant axonal excitability changes (amplitude change of 1.4+/-1.3, percentage of predrug control level, +/-S.D., n=6). A 100 mu M concentration of 8-hydroxy-dipropylaminotetralin (a serotonin(1A) agonist) reduced response amplitudes by 36.3+/-4.2% (+/-S.D., P<0.0005, n=7) and prolonged latencies by 22.3+/-4.3% (+/- S.D., P<0.0005, n=7). Application of serotonin (100 mu M) decreased amplitudes by 6.6+/-5.0% (+/-S.D., P<0.05, n=6). Extracellular calcium concentration ([Ca2+](e)) was measured al various depths in the dorsal column with ion-selective microelectrodes. Four hours' superfusion with Ca2+-free Ringer solution reduced [Ca2+](e) to less than 0.1 mM in dorsal columns. In 1.5 mM Ca2+ Ringer solution, quipazine increased the amplitudes by 38.3+/-5.8% (P<0.0005, n=6). Likewise, serotonin increased the amplitudes by 13.8+/-4.9% (P<0.005, n=6). In contrast however, 8-hydroxy-dipropylaminotetralin still reduced amplitudes by 35.0+/-6.4% (P<0.0005, n=7) and prolonged latencies by 24.1+/-4.5% (P<0.0005, n=7). In experiment 2, we investigated calcium-dependent and cAMP-mediated protein kinase signalling pathways to evaluate their role as intracellular messengers for serotonin(2A) receptor activation. Two protein kinase inhibitors, 50 mu M H7 (an inhibitor of protein kinase C and c-AMP dependent protein kinase) and 100 mu M D-sphingosine (an inhibitor of protein kinase A and C) effectively eliminated the excitatory effects of the serotonin(2A) agonist. 100 mu M cadmium (a Ca2+ channel blocker) also blocked the effects of quipazine. Neither these protein kinase inhibitors nor cadmium alone affected action potential amplitudes. These results suggest that replacing Ca2+ with Mg2+ blocks the excitatory effects of quipazine but does not prevent the inhibitory effects of 8-hydroxy-dipropylaminotetralin, and calcium-mediated protein kinase mechanisms modulate axonal excitability changes induced by serotonin and its agonist.

THE DELAYED FORMATION OF DWARF GALAXIES

Kepner JV. Babul A. Spergel DN.

Astrophysical Journal. 487(1 Part 1):61-68, 1997 Sep 20.

One of the largest uncertainties in understanding the effect of a background UV field on galaxy formation is the intensity and evolution of the radiation field with redshift. This work attempts to shed light on this issue by computing the quasi-hydrostatic equilibrium states of gas in spherically symmetric dark matter halos (roughly corresponding to dwarf galaxies) as a function of the amplitude of the background UV held. We integrate the full equations of radiative transfer, heating, cooling, and nonequilibrium chemistry for nine species: H, H+, H-, H-2, H-2(+), He, He+, He++, and e(-). As the amplitude of the UV background is decreased, the gas in the core of the dwarf goes through three stages characterized by the predominance of ionized (H+), neutral (H), and molecular (H-2) hydrogen. Characterizing the gas state of a dwarf galaxy with the radiation held allows us to estimate its behavior for a variety of models of the background UV flux. Our results indicate that a typical radiation field can easily delay the collapse of gas in halos corresponding to 1 sigma cold dark matter perturbations with circular velocities of less than 30 km s(-1).

A THIRD NEUROFIBROMATOSIS TYPE 1 (NF1) PSEUDOGENE AT CHROMOSOME 15Q11.2

Kehrersawatzki H. Schwickardt T. Assum G. Rocchi M. Krone W.

Human Genetics. 100(5-6):595-600, 1997 Oct.

Sequences related to the neurofibromatosis type 1 (NF1) gene have been identified on several human chromosomes. In the centromeric region of chromosomes 14 and 15, two NF1 pseudogenes have been described. Sequence comparison between NF1-related exons amplified from two yeast artificial chromosome clones hybridizing to chromosomal region 15q11.2 and published NF1-related sequences localized at 15q11.2 suggested that a third NF1 pseudogene resides in this chromosomal region. The previous localization of an NF1-related locus to the telomeric part of chromosome 15 could not be confirmed by us. Our findings further support pericentromeric spreading of partial NF1 gene copies at chromosome 15q11.2 during evolution.

GROUND-STATE ENTROPY OF POTTS ANTIFERROMAGNETS - BOUNDS, SERIES, AND MONTE CARLO MEASUREMENTS

Shrock R. Tsai SH.

Physical Review A. 56(3 Part A):2733-2737, 1997 Sep.

We report several results concerning W(Lambda,q)=exp(S-O/k(B)), the exponent of the ground-state entropy of the Potts antiferromagnet on a lattice h. First, we improve our previous rigorous lower bound on W(hc,q) for the honeycomb (he) lattice and find that it is extremely accurate; it agrees to the first 11 terms with the large-q series for W(hc,q). Second, we investigate the heteropolygonal Archimedean 4.8(2) lattice, derive a rigorous lower bound, on W(4.8(2),q), and calculate the large-q series for this function to O(y(12)) where y=1/(q-1). Remarkably, these agree exactly to all 13 terms calculated. We also report Monte Carlo measurements, and find that these are very close to our lower bound and series. Third, we study the effect of non-nearest-neighbor couplings, focusing on the square lattice with next-nearest-neighbor bonds.

DEFICITS IN GRAY MATTER VOLUME ARE PRESENT IN SCHIZOPHRENIA BUT NOT BIPOLAR DISORDER

Zipursky RB. Seeman MV. Bury A. Langevin R. Wortzman G. Katz R.

Schizophrenia Research. 26(2-3):85-92, 1997 Aug 29.

Studies using magnetic resonance (MR) imaging have provided strong evidence that patients with schizophrenia as a group have structural brain abnormalities, including enlarged ventricles and sulci as well as smaller cortical gray matter volumes. This study was undertaken to investigate whether the brain abnormalities found in schizophrenia could be distinguished from those seen in bipolar disorder. The MR scans of 23 patients with schizophrenia were compared to those of 17 healthy community volunteers and 14 patients with bipolar disorder. Images were processed using computer-based image processing techniques to generate quantitative measures of cerebrospinal fluid (CSF), gray matter and white matter volumes. Compared to the community volunteers, the schizophrenia group had larger total CSF volumes while the bipolar group had larger lateral ventricles. Smaller cortical gray matter volumes were found in the schizophrenia group, but not in the bipolar group. The schizophrenia group had regional deficits in gray matter volumes in comparison with both the community volunteers and tile bipolar group. These findings suggest that the brain tissue abnormalities found in schizophrenia and bipolar disorder may be distinguishable using MR imaging.

TEMPORAL STABILITY OF POLYDIPSIA-HYPONATREMIA

Schnur DB. Frick S. Smith S.

Schizophrenia Research. 26(2-3):199-202, 1997 Aug 29.

We evaluated temporal stability and outcome predictors associated with polydipsia-hyponatremia (PH). Severity of PH was measured on two occasions separated by al least 1 year in 25 chronic psychiatric inpatients (24 with schizophrenia). Three-quarters of the sample had clinically evident PH on follow-up. Follow-up PH severity was significantly related to intake severity and hospitalization length. Our findings suggest that PH may be a persistent condition with specific outcome predictors.

A STRATEGY FOR RAPID, HIGH CONFIDENCE PROTEIN IDENTIFICATION

Qin J. Fenyo D. Zhao YM. Hall WW. Chao DM. Wilson CJ. Young RA. Chait BT.

Analytical Chemistry. 69(19):3995-4001, 1997 Oct 1.

A procedure is described for rapid, high-confidence identification of proteins using matrix-assisted laser desorption/ionization tandem ion trap mass spectrometry in conjunction with a genome database searching strategy. The procedure involves excision

NEW YORK REGIONAL CALENDAR OF

NOV 5-7

Nov 5: "Geostrophic Manifold and Slow Manifold," Prof. Han-Ru Cho, Univ. of Toronoto, 12-1,Inst. For Terrestrial & Planetary Atmospheres, Rm. 120, Endeavor Hall, SUNY Stony Brook

5: "The Evolution of Chemical Diversity," Dr. Clive G. Jones, Inst. for Ecosystem Studies,3:30, R. 038, Ecology & Evolution Dept., Life Sciences Building, SUNY Stony Brook

5: "Stormy Weather: Instability in the Midatlantic Atmosphere," Dr. David Muraki, Courant Inst., NYU, 4:30, Applied Mathematics Colloquia, Rm. 214, SW Mudd, Columbia Univ.

5: "The Ground-State Permeability of the Red Blood Cell Membrane for K+ and Na+: An Electroneutral Exchange Prcess," Dr. Ingold Bernhardt, Inst. Biology, Humbolt Univ., Germany, 12:00, Physiology&Celluar Biophysics, Rover Physiology Conference Room , P&S 11-505, Columbia Univ.

6: "A Novel Map Kinase Mediates Inhibition of Calcium Currents by the Neuropeptide Bradykinin," Dr. Francesco Belardetti, GlaxoWellcome, S.p.A. Medicine Research Ctr., Italy, 12:00, Neubiology&Behavior, Neurological Inst. Alumni Auditorium, 710 West 168th St., Columbia Univ. P&S

6: "Mechanisms theat Guide Motor Axons to Their Targets in Drosophila," Dr. David Can Vactor, Harvard Med. School, 4:00, Biochemistry & Cell Biology Dept., Rm. 038, Life Sciences Building, SUNY Stony Brook

6: "Boron Isotopic Composition of Foraminifera as A Paleo-pH Tool and its implication for Glacial-Ocean Chemistry," Dr. Abhijit Sanyal, Alfred Wegner Inst. for Polar and Marine Research, Germany, 4:00, Geosciences Dept., Rm. 123, ESS Building, SUNY Stony Brook

7: "The Fe202 Diamond Core: Its Role in Oxygen by Methane Monooxygenases and Related Enzymes," Dr. Larry Que, Univ. of Minnesota, 4:00, Chemistry Dept., Rm. 116 Old Chemistry Building, SUNY Stony Brook

7: "Nitrogen Requirements for High-Temperature Tolerance: The Paradox of the Temperate Algae," Dr. Valrie Gerald, Marine Sciences Res. Center, 12:30, Rm. 120, Endeavor Hall, South Campus, SUNY Stony Brook

NOV 7-13

7: "Medical Magnetic Resonance Imaging with Laser-Polaized He-3 and Xe-129," Dr. William Happ, Princeton Univ., 2:00, Physics, Rm. 428, Pupin Hall, Columbia

7: "Understanding the Chemistry of Electronic Materials: Thin Film Growth and Surface Reactivity," Dr. Stacey Bent , NYU, 3:00, Chemistry Dept., Rm. 1003, Main Building, 100 Washington Sq. E., NYU

7: "Translational Regulation and Control of Drosophila Body Pattern," Dr. Robin Wharton, Dept. of Genetics, Duke Univ.,12:00-1:15, Physiology Dept., Rm. 92, 21th Floor Annenberg Building, (100th st. & Madison av.) Mt. Sinai School of Medicine

10: "Structure, Scope, and Mechanism of an Antibody Aldolase: Programming Covalent Catalysis," Dr. Carlos F. Barbas, Dept. of Molecular Biology, Scripps Research Inst., 4:00, Chemistry Dept., Rm. 412, Chemistry Building, SUNY Stony Brook

10: "Genes, Synapses, and Long-Term Memory," Eric Kandel, Columbia Univ., 12:00, CTR for Neural Science, Rm. 809, 5 Wash. Pl., NYU

11: "Everything You Always Wanted to Know About the Sex Lives of Anabolic Steroid Using Rats," Dr. Ann S. Clark, Dartmouth College, 4:00, Dept. of Neurobiology and Behavior, Rm. 038, Life Sciences Building, SUNY Stony Brook

11: " ATP-Senitive K+ Channels, What are They Good For?", Dr. Joe Bryan, Dept. Cell Biology, Baylor College of Medicine, 12:00, Physiology, P&S 11-505, 630 W. 168th st., Columbia Univ.

12: "Vortex Pairs on a Rotating Sphere," Dr. Mark DiBattista, NYU, 3:30-5:00, Courant Inst. of Mathematical Sciences, Rm. 1302, Warren Weaver Hall, 251 Mercer St., NYU

12: "Evolution of eye development in the cave fish *Astynax,*" Dr. William Jeffery, Biology Dept., Pennsylvania State Univ., 3:30, Rm. 038 Life Scicnces Bldg., SUNY Stony Brook

13: "The Cellular Basis of Coordination Between Behaviorally-Related Neuronal Circuits," Dr. Michael Nusbaum, Dept. Neuroscience, 12:00, Neurology & Behavior, Neurological Inst. Alumni Auditorium, 710 West 168th St. Columbia Univ. P&S

NOV 13-18

13: "TBA," Dr. Catherine Forster, Anatomical Science, SUNY Stony Brook, 4:00, Geosciences Dept., Rm. 123, ESS Building, SUNY Stony Brook

13: "Centrosome and Microtubule Nucleation," Dr. Yixian Zheng, Carnegie Inst., 4:00, Biochemistry & Cell Biology Dept.,Rm. 038, Life Sciences Building, SUNY Stony Brook

14: "Biochemistry of VDJ Recombination," Dr. Eugenia Spanopoulou, Ruttenberg Cancer Ctr, 12:00, Rm. 92, 21st Floor Annenberg Building, Mt. Sinai Medical Center.

14: "Marine Reserve Development,' Dr. WIlliam Ballantine, Leigh Marine Lab., Auckland Univer., 12:30, Rm.. 120, Endeavor Hall, South Campus, SUNY Stony Brook (not yet confirmed)

14: "Heavy Ion Researh at RHIC," Dr. Barbara Jacak, SUNY, 2:00, Physics, Rm. 428, Pupin Hall, Coumbia Univ.

17: "TBA" DR. Jean Baum, Rutgers Univ., 4:00, Chemistry Dept., Rm. 412, Chemistry Building SUNY Stony Brook

17: "Celluar Mechanismsof Cerebellar Long-Term Potentiation and Depression," David J. Linden, John Hopkins Univ., 12:00,Rm. 809, Ctr. for Neural Science, 4 Wash. Pl., NYU

17: "Tautomycin, a Flexible Bioactive Substance," Dr. Makoto Ubukata, Toyama Prefectural Univer, Kosugi, Japan, 2:00, Chemistry dept., Rm. 140, 8th Floor, Basic Science Tower, HSC, SUNY Stony Brook

18: "Intraepithelial Lymphocytes (IEL): Natural Born Fas-Mediated Killlers," Dr. Tesu LIn, La Jolla Inst. of Allergy & Immunology, 12:00, Physiology & Cellular Biophysics, Rover Conference Room -P&S 11-505,

18: "Organization and Regulation of Sexually Dimorphic Forebarin Pathways," Dr. Richard B. Simerly, Oregon Region Primates Res. Center, 4:00, Dept. of Neurobiology and Behavior, Rm. 038, Life Sciences Builing, SUNY Stony Brook

SEMINARS & EVENTS

NOV 18-21

18: "Fas, Intestinal Intraepithelial Lymphocytes and Graft-Versus-Host Diseasse," Dr. Tesu Lin, 12:00, Physiology,Ctr for Molecular Recognition, P&S 11-505 Building, 630 W. 168th St., Columbia Univ.

19: "A New View of the Ocean's Thermohaline Circulation," R. Hallberg, GRDL, Princeton Univer., 3:30-5:00, Courant Inst. of Mathematical Sciences, Rm. 13092, Warren Weaver Hall, 251 Mercer St., NYU

19; "Timing is Everything: Evolution of Flowering Time in Plants," Dr. Gordan Fox, Dept. of Biology, Univ. of Cali-San Diego, 3:30, Ecology & Evolution, Rm. 038, Life Sciences Building, SUNY Stony Brook

19: " The Einstein Postdocoral Experience; Honoring our Past - Shaping our Future," The Belfer Inst. for Advanced Postdoctoral Studies of theAlebert Einstein Schoolof Medicine Presents a symposium, Speakers include Drs. Ellie Ehrenfel (NIH), Sherie Morrsion (UCLA), Carol Prives (Columbia Univ), Larry Squire (UCSD School of Medicine). 1:00, Robbins AUditorium, Albert Einstein Colege of Medicine

20: "Can We See Fly Thinking - An Approach of Genetic Electrophysiological, and Optic Imaging Analysis of Drosophila Learning," Dr. Yi Zhong, Cold Spring Harbor Lab, 12:00, Neurobiology&Behavior, Neurological Inst. Alumni Auditorium, 710 West 168th St., Columbia Univ P&S

20: "Relationships among Natural Radioactvities in a Podasol Formed on Conway Granite,NH," Gar Harbottle, Brookhaven National Lab., 4:00, Geosciences Dept., ESS Building, SUNY Stony Brook

20: "The Golgi Apparatus in Fission Yeast," Dr. Thomas G. Camppell, Univ. College London, 4:00, Rm. 038, Life Sciences Building, Biochemsitry & Cell Biology, SUNY Stony Brook

21: "Recruitment of Infauna: Negative Cues," Dr. Sally Woodin, Bio. Dept., Univer. of South Carolina, 12:30 Marine Sciences Research Center, 12:30, Rm. 120, Endeavor Hall, South Campus, SUNY Stony Brook

21: "Science in Crisis: Fact or Fiction?", Dr. Mike Lubell, CUNY, 2:00, Physics, Rm. 428 Pupin Hall, Columbia Univ.

NOV 21-25

21: " Asymmetric Synthesis of Anti-HIV and Anti-Hepatitis B Nucleosides Using Carbohydrate Chiral Templates,"Dr. David C.K. CHu, Univ. of Georgia, 3:00, Chemistry Dept., Rm. 1003 Main Building, 100 Washington Sq. E., NYU

21: "The Role of Water in Biological Macromolecules," Dr. Helen Berman, Chemistry Dept., Rutgers Univ., 12:00-1:15, Physiology & Biophysics Dept., Rm. 92, 21th Floor Annenberg Building, Mt. Sinai School of Medicine

21: "The Value and Future of the Chemistry Ph.D.," Panelists: Ronald Breslow, Sally Chapman, Madeleine Jacobs, Edouardo Macagno, Janet Osteryoung, Edel Wasserman, 4:30, Rm. 309, Havemeyer Hall, Columbia Univ. (Further Info: email cccc@chem.columbia.edu)

22: "Ice Clouds and the Atmospheric General Circulation," Dr. Leo Donner, GFDL, 12-1, Inst. for Terrestrial & Planetary Atmospheres, Rm. 120, Endeavor Hall, SUNY Stony Brook

24: "New Chemical Approaches to Tracing Cellular Signal Transduction Cascasdes," Dr. Kevan Shokat, Princeton Univ., 4:00, Rm. 412, Chemistry Building, SUNY Stony Brook

24: "Assembly of Receotive Fields in Cat Visual Cortex, David Ferster, NW Univ., 12:00 Ctr for Neural Science, Rm. 809, 4 Wash. Pl., NYU

25: "AGEs and Rage: Implications for the Pathogenesis of Complications in Diabetes and Beyond,: Dr. Ann Marie Schmidt, Dept. Medicine, Columbia Univ., 12:00, Physiology & Celllulad Biophysics, Rover Physiology Conference Room P&S 11-505, Columbia Univ.

of copper-stained bands or spots from electrophoretic gels, in-gel trypsin digestion of the proteins, single-stage mass spectrometric analysis of the resultant mixture of tryptic peptides, followed by tandem ion trap mass spectrometric analysis of selected individual peptides, and database searching of the relevant genomic database using the program PepFrag. The scheme provides sensitive, real-time protein identification as well. As facile identification of modifications, A single operator can unambiguously identify 5-10 proteins/day from an organism whose genome is known at a level of >0.5 pmol of protein loaded on a gel. The utility of the technique was demonstrated by the identification and characterization of a band from a human HTLV-I preparation and 11 different proteins from a yeast RNA polymerase II C-terminal repeat domain-affinity preparation. The technology has great potential for postgenome biological science, where it promises to facilitate the dissection and anatomy of macromolecular assemblages, the definition of disease state markers, and the investigation of protein targets in biological processes such as the cell cycle and signal transduction.

THE MECHANISM OF CELL DEATH IN LISTERIA MONOCYTOGENES-INFECTED MURINE MACROPHAGES IS DISTINCT FROM APOPTOSIS

Barsig J. Kaufmann SHE.

Infection & Immunity. 65(10):4075-4081, 1997 Oct.

Various pathogenic bacteria with the capacity to live within eukaryotic cells activate an apoptotic program in infected host cells, Induction of apoptosis by Listeria monocytogenes in murine dendritic cells and hepatocytes has been described, Here we address the questions of whether and how the pathogen kills macrophages, its most important habitat, Employing several complementary techniques aimed at discriminating between apoptosis and necrosis, we show that murine bone marrow-derived macrophages (BMM) undergo delayed necrosis but not apoptosis when infected with listeriolysin (Hly)-producing L. monocytogenes, This pathogen failed to elicit apoptotic morphology, DNA fragmentation, and surface annexin V binding of macrophages, in contrast to Shigella flexneri infection or gliotoxin treatment, which were used as positive controls, Furthermore, macrophages infected with L. monocytogenes released lower quantities of interleukin-1 beta (IL-1 beta) than did Shigella flexneri-infected ones, indicating diminished or even absent activation of IL-1-converting enzyme in macrophages harboring L. monocytogenes, We conclude that murine BMM die by necrosis after several hours of cytoplasmic replication of L. monocytogenes, The pathogen may benefit from this feature by the possibility of taking advantage of cells of "pseudo-healthy" appearance, thus avoiding rapid elimination by other phagocytes.

DAMPED LY-ALPHA ABSORPTION ASSOCIATED WITH AN EARLY-TYPE GALAXY AT REDSHIFT Z=0.16377

Lanzetta KM. Wolfe AM. Altan H. Barcons X. Chen HW. Fernandezsoto A. Meyer DM. Ortizgil A. Savaglio S. Webb JK. Yahata N.

Astronomical Journal. 114(4):1337-1344, 1997 Oct.

We report new HST and ground-based observations of a damped Ly alpha absorption system toward the QSO 0850+4400. The redshift of the absorption system is z = 0.163770+/-0.000054 and the neutral hydrogen column density of the absorption system is log N = 19.81+/-0.04 cm(-2). The absorption system is by far the lowest redshift confirmed damped Ly alpha absorption system yet identified, which provides an unprecedented opportunity to examine the nature, impact geometry, and kinematics of the absorbing galaxy in great detail. The observations indicate that the absorption system is remarkable in three respects: First. the absorption system is characterized by weak metal absorption lines and a low metal abundance, possibly less than 4% of the solar metal abundance. This cannot be explained as a consequence of obscuration by dust, because the neutral hydrogen column density of the absorption system is far too low for obscuration by dust to introduce any significant selection effects. Second, the absorption system is associated with a moderate-luminosity early-type S0 galaxy, although the absorption may actually arise in one of several very faint galaxies detected very close to the QSO line of sight. Third, the absorbing material moves counter to the rotating galaxy disk, which rules out the possibility that the absorption arises in a thin or thick co-rotating gaseous disk. These results run contrary to the expectation that low-redshift damped Ly alpha absorption systems generally arise in the gas-and metal-rich inner parts of late-type spiral galaxies. We suggest instead that mounting evidence indicates that low-redshift galaxies of a variety of morphological types may contain significant quantities of low metal abundance pas at large galactocentric distances.

CHARACTERIZATION OF CHANGES IN GENE EXPRESSION ASSOCIATED WITH MALIGNANT TRANSFORMATION BY THE NF-KAPPA-B FAMILY MEMBER, V-REL

Petrenko O. Ischenko I. Enrietto PJ.

Oncogene. 15(14):1671-1680, 1997 Oct 2.

In this study, alterations in gene expression patterns have been examined in v-Rel-transformed avian bone marrow cells, Using a conditional v-Rel estrogen receptor chimera (v-RelER) which transforms cells in an estrogen-dependent manner, we constructed subtraction cDNA libraries from v-RelER-transformed bone marrow cells, Several different sequences were identified whose expression was altered upon hormone activation of v-RelER. These include two genes related to the MIP-I chemokine family (mip-1 beta and a tca3 homologue), a cell surface antigen sca-2 and the transcription factor nfkb1. The expression of each gene was assayed in a number of wild-type and mutant v-Rel-expressing fibroblast and hematopoietic cells, All v-Rel-transformed hematopoietic cells tested express high levels of nfkb1 and sca-2. In fibroblasts, wild-type v-Rel induced expression of mip-1 beta and nfkb1, while nontransforming mutants of v-Rel failed to do so, suggesting a role for these two genes in v-Rel mediated transformation, Finally, these genes are expressed at high levels in cells overexpressing wild-type and truncated forms of c-Rel, implying that v-Rel transforms, in part, by induction of c-Rel target genes.

PLASMA CONFINEMENT IN A LEVITATED MAGNETIC DIPOLE

Kesner J. Mauel M.

Plasma Physics Reports. 23(9):742-750, 1997 Sep.

Plasma confinement in the field of a levitated dipole offers many advantages for magnetic fusion. MHD stability is obtained from compressibility which utilizes the large flux tube expansion of a dipole field. Such a device could be high beta, steady state, and exhibit good confinement properties. The large flux expansion will ease the difficulty of the divertor design. The configuration is ideal for electron cyclotron heating and controlled convective flow patterns may provide a mechanism for fueling and ash removal.

INTERACTION OF WW DOMAINS WITH HEMATOPOIETIC TRANSCRIPTION FACTOR P45/NF-E2 AND RNA POLYMERASE II

Gavva NR. Gavva R. Ermekova K. Sudol M. Shen CKJ.

Journal of Biological Chemistry. 272(39):24105-24108, 1997 Sep 26.

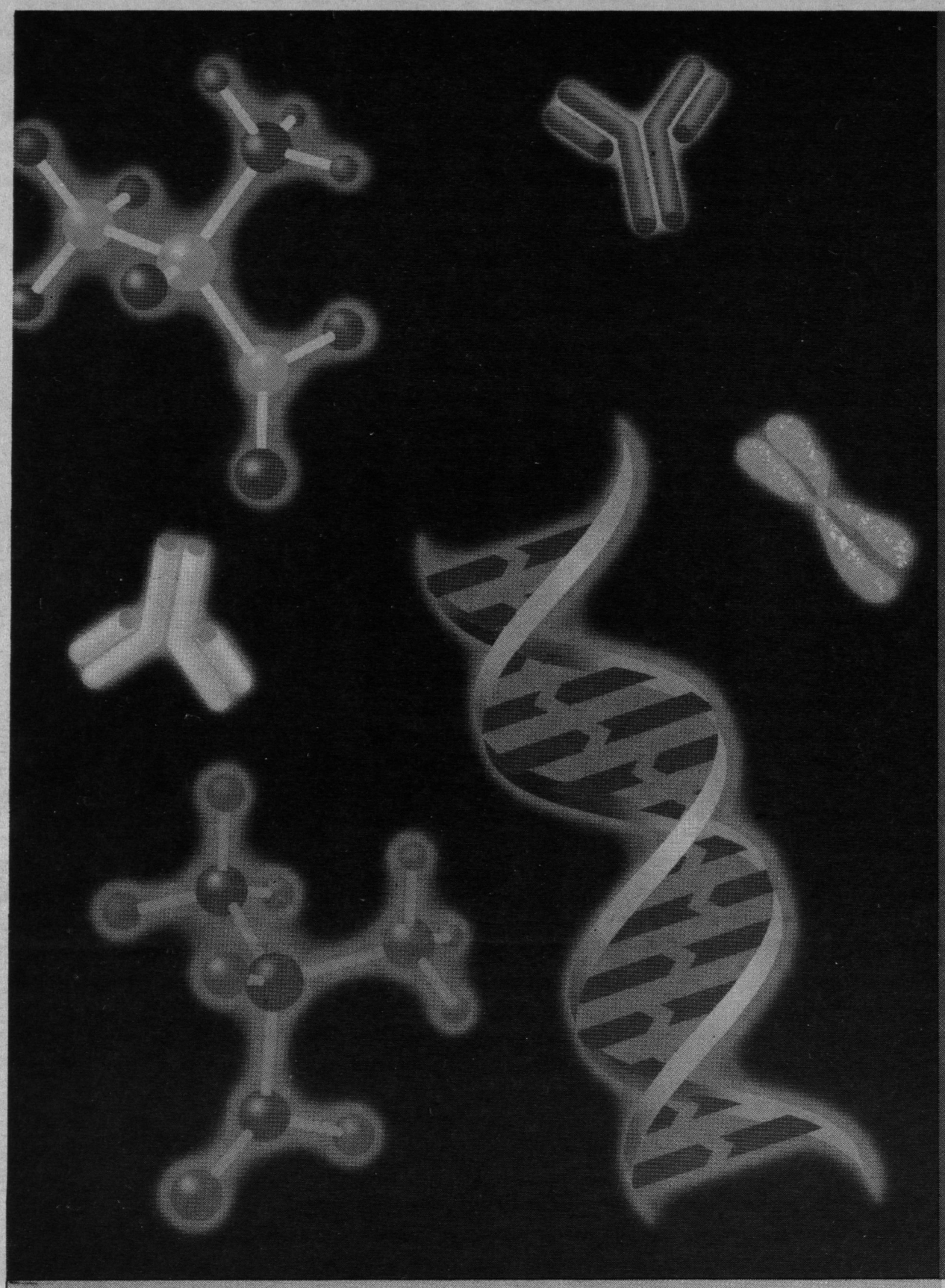
NF-E2 is an erythroid-specific transcription factor required for expression of several erythroid-specific genes. By Far-Western blotting and yeast two-hybrid assay, we demonstrate that p45, the large subunit of NF-ES, is capable of binding to a specific set of WW domain containing proteins, including the ubiquitin ligase hRPF1. This binding is mediated through the interaction between the WW domains and a PY motif located within the amino-terminal region of p45. Interestingly, the carboxyl-terminal domain of mammalian RNA polymerase II binds a similar set of WW domains to which p45 interacts with. We discuss the data in terms of possible new pathways through which the processes of transcriptional regulation by NF-EB could be regulated in erythroid and megakaryote cells.

ON THE INTEGRABLE GEOMETRY OF SOLITON EQUATIONS AND N=2 SUPERSYMMETRIC GAUGE THEORIES

Krichever IM. Phong DH.

Journal of Differential Geometry. 45(2):349-389, 1997 Feb.

We provide a unified construction of the symplectic forms which arise in the solution of both N=2 supersymmetric Yang-Mills theories and soliton equations. Their phase spaces are Jacobian-type bundles over the leaves of a foliation in a universal configuration space. On one hand, imbedded into finite-gap solutions of soliton equations, these symplectic forms assume explicit expressions in terms of the auxiliary Lax pair, expressions which generalize the well-known Gardner-Faddeev-Zakharov bracket for KdV to a vast class of 2D integrable models; on the other hand, they determine completely the effective Lagrangian and BPS spectrum when the leaves are identified with the moduli space of vacua of an N=2 supersymmetric gauge theory. For SU(N-c) with N-f less than or equal to N-c + 1 flavors, the spectral curves we obtain this way agree with the ones derived by Hanany and Oz and others from physical considerations.



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Selected Funding Updates

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

NASA/Goddard Space Flight Center: New Millenium Mars Microprobe Science Team

The National Aeronautics and Space Administration, Office of Space Science is releasing a NASA Announcement of Opportunity (AO 97-OSS-05) entitled New Millennium Mars Microprobe Science Team which solicits proposals for science team members for the New Millennium Mars Microprobe Mission. Participation is open to all categories of organizations, domestic and foreign, including industry, educational institutions, nonprofit organizations, NASA centers, and other Government agencies. This solicitation will be open through January 27,1998. The full text of the AO and all appendices will be available electronically from the World Wide Web by selecting "Research Opportunities" at: http://www.hq.nasa.gov/office/oss/>.

Information and hard copies can be obtained from: Dr. Michael A. Meyer, Research Program Management Division, Code SR, NASA Headquarters, Washington, DC 20546-0001; Phone: 202-358-0307; FAX: 202-358-3097; E-mail: michael .meyer@hq.nasa.gov.

NSF: Computational Biology

The Computational Biology Activity (CBA) was created to support studies developing or requiring computational techniques outside the normal scope of the various disciplinary programs of the NSF. For purposes of this announcement, computational biology is defined as the development and application of computational methods, including their theoretical, mathematical, and engineering bases, to biology. Computational biology is inherently interdisciplinary, and many important biological problems will require fundamental advances in computer science and mathematics. Moreover, the application of biological ideas and materials to problems from computer science and engineering is likely to yield significant biological insight.

The Computational Biology Activity supports the development and use of computational tools, algorithms, and related research that will enhance both the underlying biology and the associated computational infrastructure. Projects are expected to have a broad impact on biology. To meet these objectives, CBA will consider appropriate projects involving both single investigators and teams of researchers. Collaborations among biological, computational, mathematical, and other scientists as appropriate are encouraged. CBA supports formal and informal training of investigators at all levels to develop and use these techniques.

Inquiries regarding the Computational Biology Activity should be directed to: Computational Biology Activity; E-Mail: cba@nsf.gov; Tel: 703-306-1469; FAX: 703-306-0356. (Ref: NSF 98-7) Deadline: 10 January.

EPA/NSF: Star Partnership for Environmental Research - Decision-Making and Valuation for Environmental Policy

The Environmental Protection Agency (EPA) and the National Science Foundation (NSF) announce their intent to support a special awards competition in Fiscal Year (FY) 1998. This EPA/NSF competition has been developed based on a Memorandum of Understanding between the agencies which establishes a partnership emphasizing the support and merit review of fundamental, extramural environmental research. NSF and EPA's Office of Research and Development are continuing their cooperation in this extramural grants program in FY 1998. This year's EPA/NSF Partnership competitions will include the following four research areas:

- Water and Watersheds
- Technology for a Sustainable Environment
- Decision-making and Valuation for Environmental Policy
- Environmental Statistics

This announcement solicits applications for Decision-making and Valuation for Environmental Policy. Awards made through this competition are dependent upon responsiveness of the proposals to the announcement, the quality of the proposed research, and the availability of funds. Under this announcement, EPA and NSF anticipate awarding:

Approximately $2 million for Decision-making and Valuation for Environmental Policy, with a projected award range from $60,000 to $125,000 per award per year, and an approximate duration of 2 to 3 years. Field experiments, survey research, and multi-investigator projects may be considered for a higher funding level. Proposals in response to this announcement must be received by **January 15, 1998.** It is anticipated that awards will be made by Fall 1998. Copies of this announcement may be obtained by calling Peter Saal at ext. 2-9033.

Environmental Protection Agency: Science to Achieve Results Research Grants

The EPA's Office of Research and Development (ORD), invites research grant applications in the following areas of special interest to its mission:

- Ecological Indicators - proposals due **February 26**
- Drinking Water - proposals due **February 26**
  - Disinfection Byproducts
  - Emerging Contaminants from the Contaminant Candidate list
- Air Pollution Chemistry and Physics - proposals due **January 29**
- Urban Air Toxics - proposals due **February 12**
- Health Effects and Exposures to Particulate Matter and Associated Air Pollutants - proposals due **January 29**

Additional general information on the grants program, forms used for applications, etc., may be obtained by exploring the EPA Web page at http://www.epa.gov/ncerqa. Information not available on the Internet may be obtained by contacting: U.S. Environmental Protection Agency, National Center for Environmental Research and Quality Assurance (8703R), 401 M Street, SW, Washington DC 20460. Phone: 1-800-490-9194.

Contact persons for each topic are: **Ecological Indicators** - Barbara Levinson, 202-564-6911; **Drinking Water** - William Stelz 202-564-6834; **Air Pollution Chemistry and Physics** - Deran Pashayan, 202-564-6913; **Urban Air Toxics** - Deran Pashayan, 202-564-6913; **Health Effects and Exposures to Particulate Matter and Associated Air Pollutants** - Deran Pashayan, 202-564-6913. A complete copy of this annopuncement may be obtained by calling Peter Saal at ext. 2-9033.

NATO Scientific & Environmental Affairs: Science for Peace

The Science for Peace Programme is the most recent initiative of the NATO Science Committee. It aims at assisting Partner countries in their transition towards a market- oriented and environmentally sound economy. The Programme will give a new dimension to the Science Committee's ongoing cooperative activities by enabling Partner scientists to engage in applied R&D projects jointly with NATO counterparts. In helping to strengthen the socioeconomic infrastructure of the Partner countries, it is expected that the programme will contribute to overall stability and peace.

The objectives of the Programme are: (1) To support applied science and technology projects that relate to industrial, environmental or security related problems; and (2) To help Partner scientists to increase contacts in the NATO science community, while building a stronger science infrastructure in their home countries.

SfP projects will be of a cooperative nature, jointly carried out among NATO and Partner countries. Projects involving more than one Partner country will be encouraged. Projects will have a duration of three to five years. Science for Peace projects will have as essential characteristics:

- High quality applied science and technology with a potential for commercialization in the case of industry-oriented projects.
- Ability to contribute to the solution of problems of long term significance dealing with industrial or environmental issues or security-related issues with multilateral ramifications.
- Ability to promote collaboration among scientists, industry and end-users.
- Good prospects for promoting the integration of the country's scientists into the international Research and Development community.
- Encourage the participation of younger scientists.

NATO funding to participants in research institutions in Partner countries as well as in Greece and Turkey will be provided for experts, scientific equipment computers, software, travel, training of project personnel and project-specific consumables. NATO funds will not be provided to pay for salaries or for overhead costs, such as the construction of buildings, the maintenance of premises and the supply of consumables including electricity and heating oil. NATO funds will also not be provided for office equipment, copiers and fax machines. For all projects, NATO funds for Partners must be complemented with a national contribution which will, as a minimum, include salaries of personnel working on the project.

Proposals should be submitted to the NATO SfP Programme Office on a four page standard application form and will be evaluated by the SfP Steering Group. Deadlines for submitting proposals are:15th January 1998 and 15th May 1998. Applications procedures for the Science for Peace Programme are described in detail

Continued on Page 20

Blaming It On the Sun

Dispute About the Nature and Size of the "Greenhouse Effect"

by Ilana Harrus, Ph.D., *ASN&R* Staff Writer

In an article published in the Sept 26. issue of *Science,* Dr. Richard C. Willson of the Columbia Center for Climate Systems Research (judiciously located in California), reported the measurement of a small increase in the energy received by the Earth from the sun. Despite the small magnitude of the effect, the announcement raised questions about a possible correlation between this effect and the global warming problem.

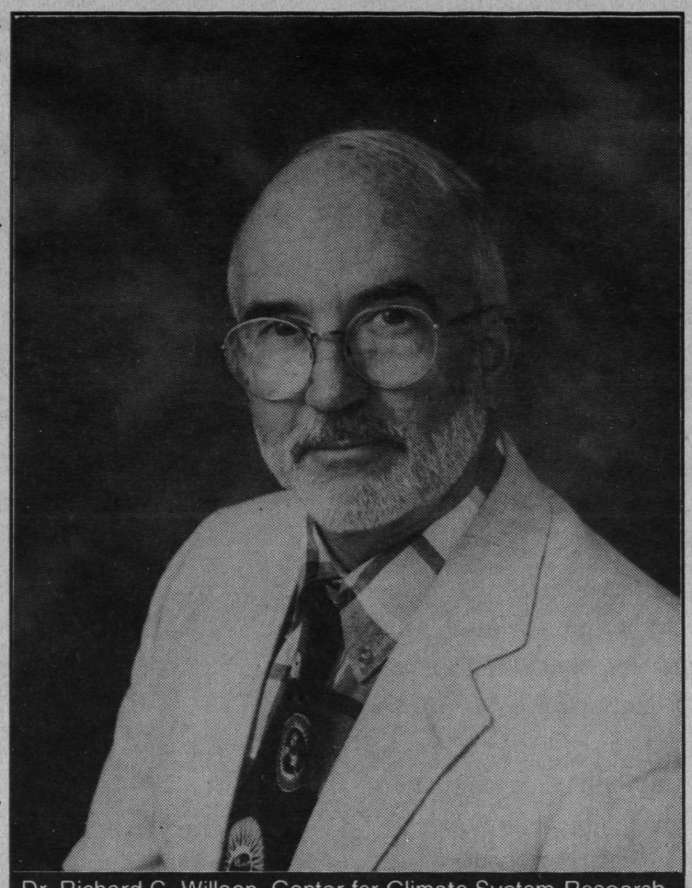
When sunlight reaches the Earth, much of the radiation received is re-emitted at lower energy in the infra-red range. This essential radiation would escape without the presence in the atmosphere of gases which trap most of the infra-red emission and send it back toward the surface of the Earth. This is the so-called "greenhouse" effect, because, just as in a greenhouse, the temperature achieved inside is higher than that expected from incoming radiation alone. Without this greenhouse gas (composed mainly of water vapor, carbon dioxide, ozone and small quantities of other gases) Earth's temperature would be on average 33 degrees Celsius lower, and life, at least as we know it, would not be possible.

Since the beginning of this century, industrial byproducts have slowly modified the composition of the atmosphere's greenhouse gases. This is believed to have induced a more efficient greenhouse effect, and thus contributed to an increase of the earth's surface temperature. This increase has been measured and amounts to an average of 0.5 degrees Celsius since the last century. To understand this number, and to be able to predict future changes, different models were developed. By taking into account factors like the interactions of the atmosphere with the oceans and with the Earth's surface atmosphere, as well as with the amount of man-made greenhouse gases added to the atmosphere, these models predict a further increase in average temperature ranging anywhere from 1.5 to 4.5 degrees Celsius.

It may seem too small a number to worry about, but one has to realize that during the period known as the "Little Ice Age" (1450-1890), temperatures were, on average, only 0.5 to 1 degree Celsius lower than today. In addition, during the last major Ice Age which peaked about 18,000 years ago, the mean temperature-difference was about the same order of magnitude as that now predicted, albeit in the reverse direction (i.e., 3 to 4 degree Celsius lower than that of today). At that time, polar ice covered most of North America as far south as the Great Lakes, year-round. Thus, if the amplitude of the increase is correct, it is something to worry about.

It is true that, with or without human intervention, the climate of the Earth is continually changing (after all there were not many cars around 18,000 years ago). The novelty of the changes observed and those predicted, is the speed at which they are occurring. While the previous changes in the Earth's climate spanned thousands of years, those due to industry-induced modification of the greenhouse gases are forecast for a near future (50 to 100 years). All that is bad news; the good news is that the bad news is still very uncertain.

While it is now accepted by all but the most vociferous anti-environmentalists that some increase in temperature has taken place, there is no real agreement on the consequences of this increase, or on its long-term effects. For a start, the increase measured is less than half the amount it should have been if the models used were completely accurate. The cause of this discrepancy is not clear. There is in fact no shortage of uncertainties in all the theories and models involved here. First, no one really knows the size of what global-warming aficionados call "positive feedback". This process characterizes the way in which even a small temperature increase due, for example, to the further addition of carbon dioxide to the atmosphere, would be amplified and lead to even larger increases in temperature. Evidence seems to point to a positive feedback relationship, but its amplitude is not known accurately. Some, like Dr. Richard Lindzen of the Massachusetts Institute of Technology, have suggested that the effect could be a "negative feedback" system leading to a stable self-correcting system. In addition, we must now add another source of uncertainty here, this time dealing with the activity of the sun itself.



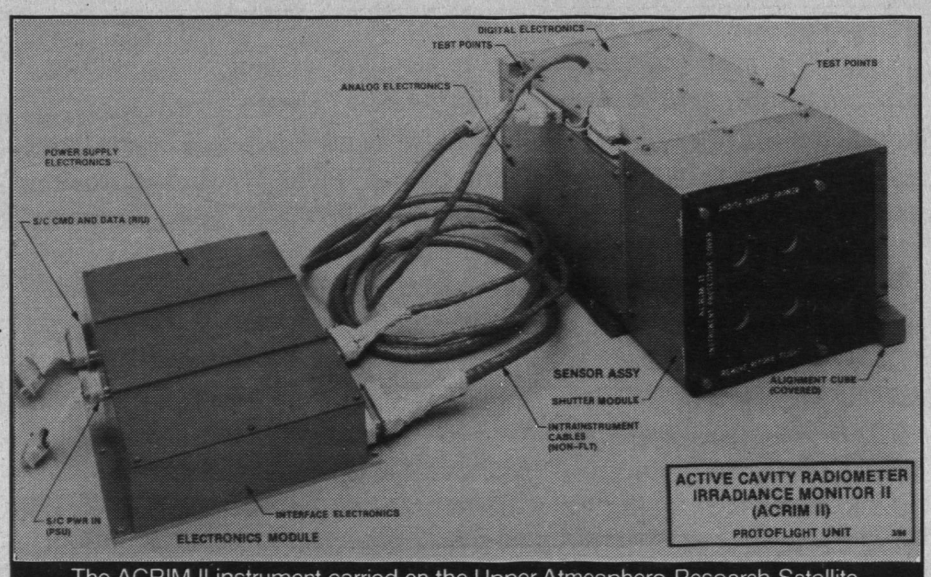
Dr. Richard C. Willson, Center for Climate System Research, Columbia University.

It is obvious that the sun plays an important role in the variation of the Earth's temperature. One remarkable characteristic of the sun's energy output has been its apparent stability. Scientists used to call the total amount of energy received from the sun "the solar constant". This is now seen to be a misnomer.

Since the late 1970s, a series of satellites has been launched to monitor precisely total solar-irradiance (TSI), a measure of the power received by the Earth from the sun. In the first of those missions (one called ACRIM I), it was shown that variations existed in solar activity during a solar cycle directly linked to variations in the measure of TSI. This result was confirmed by a second space-based measurement.

One problem with the data used in this monitoring enterprise was that only two of the instruments flown had the capability to correct for degradation of their on-board sensors. In addition, there was no simultaneous coverage by the two ACRIM instruments. ACRIM I stopped functioning at the end 1989, and ACRIM II started only in 1991, making precise calibration difficult. This imposed a "three-way-comparison" in the analysis of the data. Data from the ACRIM experiments were compared to that of a less sophisticated instrument (it lacked the capability to correct for its own performance degradations) in orbit from 1978 to 1993, overlapping both ACRIMs. A precise ratio of ACRIM I to ACRIM II results was thereby derived.

It is the result of this somewhat complicated procedure that is at the basis of the results reported by Dr. Willson. The two ACRIM experiments covered part of two 11-year long solar cycles. According to Dr. Willson, the value of the TSI minimum increased significantly from one cycle to the other. The increase found is small (0.036%), and must be sustained for a long period of time to have any effect on the Earth's average temperature. If the effect measured by Dr Willson is indeed long-term, the expected increase in temperature in the next century will be around 0.4 degree Celsius, not negligible when compared to the expected 1.5 to 4.5 degrees Celsius effect previously mentioned.



The ACRIM II instrument carried on the Upper Atmosphere Research Satellite.

To learn more about the effect of the sun's radiation on global warming in particular, and on Earth's climate in general, another TSI monitoring experiment is planned. This will begin in late 1999 with the launch of another ACRIM satellite experiment as part of the Earth Observation System (EOS/ACRIM III).

In early December in Kyoto, there will be an international meeting in which the U.S. is expected to sign a revised version of the 1992 United Nations Convention on Climate Change (known as the "Rio Treaty"). This treaty should help implement the regulations needed to reverse the effects of overdeveloped industries on our planet. In the meantime, and before blaming unusual (and frequent) meteorological catastrophes on our star, it is probably still a good idea to help reduce the amount of carbon dioxide and other greenhouse gases injected into the atmosphere.■

Lorenz.. Continued from Page 4

is chaotic, this small deviation may result, with even a good model, in a marked difference between the weather the model predicts and the weather that actually develops.

Nonetheless, Lorenz believes that, in certain cases at least, long-range climate prediction is still possible. For even though climate may behave chaotically in one way, it can behave quite predictably in others. As an example, Lorenz presented a set of east-west wind speed readings taken biannually over Singapore from 1965 to 1986. While the specific speed tended to fluctuate randomly, the overall measurements revealed certain predictable features: the wind typically comes out of the west in one half of the year, and out of the east in the other, and is usually within a certain range of values. Hence, one can predict, to a certain degree, the wind speed and direction over Singapore in any given year.

Lorenz believes that one type of chaotic system, said to have "weak coupling between different intensities of chaos," offers particularly good opportunities for long-term forecasting. In this weakly-coupled system, chaotic behavior in one part of the system may take a long time to influence behavior in another part of the system. Lorenz gave as an example a thunderstorm moving through the Ohio basin. Though that thunderstorm could affect weather over Europe, if the effects take over a month to make their way across the Atlantic the Ohio thunderstorm could be safely ignored when making a three-week forecast of the weather in Paris.

Lorenz cautioned, however, that the climate may be forecast only to the extent that it behaves according to rules, even chaotic ones, on which one can construct a model. He wondered further if there were indeed "some set of quantities which we might justifiably call 'climate,' which do not undergo the day-to-day fluctuations that characterize weather, and whose future is almost completely determined by its past? At present, we do not know," though he suspects the answer is 'yes' for some phenomena, and 'no' for others. Notably, he feels that the long-term consequences of the greenhouse effect fall into the category of things that, in principle, can be computed, though he acknowledged that "we have yet to master the techniques for doing so."■

Continued from Page 16

in the "Guidelines for Project Proposals for the SfP Programme". Application forms and Guidelines for SfP Project Proposals are available from: Science for Peace Programme Office, Scientific Affairs Division, NATO, B-1110 Brussels, Belgium. Telephone: (32-2) 707 4619; Fax: (32-2) 707 4232; E-mail: science.sfp@hq.nato.int. Application guidelines are posted on the WWW at: http://www.nato.int/science

NASA: Computational Nanotechnology

NASA/ARC plans to release a NASA Research Announcement NRA2-36829 entitled Computational Nanotechnology. Research topics of interest include, but are not limited to: fullerene nanotechnology, diamonoid mechanosynthesis, self assembly, biological analogues, simulation (quantum, molecular mechanics, meso-scale, finite element, integration, etc.) molecular CAD, component design, etc. For more information see the following URLS:

http://science.nas.nasa.gov/Groups/Nanotechnology/grants or
http://www.nas.nasa.gov/nanotechnology

Participation is open to all categories of organizations, foreign and domestic, including industry, educational institutions, profit and nonprofit organization, NASA centers, and other Government agencies. The NRA will be open through December 30, 1997, proposals may be submitted throughout this period. All responsible sources may submit an offer which shall be considered by the agency. The anticipated release date of the NRA is on or about September 30, 1997, with an anticipated offer due date of on or about December 30, 1997.

The NRA and any documents related to this procurement will be available over the Internet. These documents will be in ASCII or RTF format and will reside on a World-Wide Web server, which may be accessed using a WWW browser application. The WWW address, or URL, of the NASA/ARC Business Opportunities home page is http://procurement.nasa.gov/EPS/ARC/class.html

NSF/EHR: Advanced Technological Education

This program promotes exemplary improvement in advanced technological education within associate degree-granting institutions in collaboration with 4-year institutions, secondary schools, and industry. Support is given for curriculum development and program improvement for science and engineering technicians who are being educated for the high-performance workplace. Support may be provided for a variety of projects and a few centers. Preliminary Proposals for Centers and Projects due by April 15, 1998. (NSF 97-20 and NSF 97-29.) Formal proposals are due October 15, 1998. Contact the Division of Undergraduate Education at 703-306-1668.

NSF: Collaboratives for Excellence in Teacher Preparation

This program seeks to promote comprehensive change in the undergraduate science, mathematics, engineering, and technological education of future teachers. All (or a subset) of the components of teacher preparation can be addressed. Projects are encouraged that support collaborative efforts among institutions and among the faculties in the departments of mathematics, the sciences, engineering, and education. Projects range from those addressing a single component to projects encompassing all aspects of the complex process of teacher preparation. Contact the Division of Undergraduate Education at 703-306-1666. Deadline: May 1, 1998.

NSF: Summer Programs in Japan and Korea

Program for U.S. science and engineering graduate students to intern at Japanese and Korean research labs and receive language instruction. Contact the Division of International Programs by phone, 703-306-1701, or by e-mail, jkpinfo@nsf.gov (NSF 96-151) Annual Deadline: December 1, 1997.

NSF/INT: U.S.-Egypt Collaborative Research in Science and Technology

Awards are limited to international travel, living expenses, and research costs by visiting researchers (up to $50,000) and will not cover researchers' salaries in either country. Activities should encourage industry participation or identify future benefits to industry or the private sector in Egypt. Applications must be submitted jointly by a U.S. researcher and by an Egyptian counterpart or counterparts. Deadline: December 1, 1997. For further information, contact Dr. Osman Shinaishin in the Division of International Programs by phone, 703-306-1707, or by e-mail, oshinais@nsf.gov

PA-97-106: Feline Immunodeficiency Virus - A Potential Model of AIDS

The Division of AIDS, NIAID, solicits applications on the molecular biology, immunology, and host factors involved in feline immunodeficiency virus (FIV) infection of cats. The overall goal of these studies is to advance the understanding of the virus/host infection process in this model and to determine the potential use and/or validate the application of the FIV/cat model for testing potential therapeutics, topical microbicides, and novel mucosal-targeted vaccine designs against HIV. Applicants proposing studies focusing solely on FIV pathogenesis are encouraged to apply under PA-96-072 "Mechanisms of AIDS Pathogenesis". Traditional research project grants (R01), small grants (R03), and First Independent Research Support and Transition (FIRST) awards (R29) may be submitted in response to this program announcement.

DK-98-003: The Cell Biology of the Pancreatic Beta Cell

The National Institute of Diabetes and Digestive and Kidney Diseases invites investigator-initiated research grant applications to elucidate the pathways and factors responsible for the development and maintenance of beta cells in the pancreas. Current evidence suggests that the endocrine pancreas is derived from progenitor cells in the ducts of the exocrine portion of the pancreas. An expanded knowledge of the precise location and nature of these putative progenitor cells, the factor(s) responsible for differentiation into endocrine cells, the lineage dependent factors responsible for development of alpha, beta and delta cells, the trans-acting factors which subsequently regulate expression of the genes for the hormones themselves, and the local growth factors which comprise the milieu of the endocrine islet is crucial to the development of strategies for islet and/or B cell regeneration.

This solicitation is intended to stimulate the application of advances in cell biology and molecular biology to the study of the cell biology of the pancreatic beta cell. Collaborative efforts that link expertise in cell biology to expertise in diabetes are strongly encouraged. Also, two-year pilot and feasibility applications are available within this solicitation. It is anticipated that results obtained by studies supported by this solicitation will aid in the development of improved therapies for the treatment of diabetes mellitus.

Support of this program will be through the NIH research project grant (R01) award, the FIRST (R29) award, or the exploratory/developmental award (R21). Letter of Intent due: February 19, 1998; Application Receipt Date: March 19, 1998

PA-97-107: Prevention of Recurrent Disease After Liver Transplantation

To encourage experienced and new investigators to submit small grants (R03s) to plan multicenter clinical trials or to submit research project grants (R01s) to conduct full-scale multicenter clinical trials on methods for preventing the recurrence of disease after liver transplantation. Of major relevance are studies on preventing the recurrence of alcoholic liver disease, and preventing the recurrence of hepatitis B and C virus infection after liver transplantation. Specific interventions should be compared. It is of interest to learn about the natural history of these diseases in patients undergoing standard therapy. Letter of Intent due: December 9, 1997; Application Receipt Date: January 9, 1998.

PA-97-111: Respiratory Pathogens - Specific Research Needs

The National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute, and the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, invite applications for research issues of importance, opportunity and need in understanding selected respiratory pathogens and host responses to these pathogens. The purpose of this omnibus solicitation is to alert the extramural research community to areas of need and importance to the mission of the Respiratory Diseases Branch, NIAID, the Division of Lung Diseases, NHLBI, and the Division of Human Communication, NIDCD. Projects aimed at stimulating basic and applied research that may lead to more effective and accepted prophylactic and therapeutic approaches for controlling severe respiratory infections will be considered. Applications on measles will not be considered responsive to this PA since other NIAID initiatives have been issued recently to support research in this area.

Traditional research project grant (R01) and FIRST award (R29) applications may be submitted in response to this program announcement. Applications for R01 grants may request up to five years of support; applications for R29 grants must request five years of support.

RFA: OD-98-003: Centers for Complementary and Alternative Medicine Research

The mission of the OAM is to encourage and support the investigation of complementary and alternative medicine (CAM) practices, with the ultimate goal of integrating validated alternative medical practices into health and medical care. The OAM also is charged with training investigators who can help fulfill this mission.

The demographics, prevalence, and patterns of use of alternative unconventional medicine in the United States have been described (Eisenberg et al., New England J. Med. 328: 246-352, 1993). The most relevant findings are the following: a) most people use CAM therapies for chronic rather than life-threatening medical conditions; b) users of alternative therapies do not inform their primary care physicians; c) extrapolation to the population of the United States suggests that Americans made approximately 425 million visits to providers of CAM therapy during 1990; and d) expenditures associated with CAM therapies appear similar to non-reimbursed expenses incurred for all hospitalizations in the United States. These findings indicate that alternative medicine modalities occupy a larger role in the health care of U.S. citizens than previously understood. The goal of this RFA initiative is to encourage research of CAM by establishing Centers for CAM Research. Such Centers will make the resources necessary for the conduct of high quality research available to investigators interested in CAM.

The expressed purpose of this RFA is to provide a mechanism to examine the potential efficacy, effectiveness, safety and validity of CAM therapies, and to provide scientific/technical assistance to investigators as they develop their research projects. The establishment and support of Centers for CAM Research, under the auspices of the OAM, will meet these objectives. The Centers will support a multidisciplinary group of researchers and clinicians to perform basic, preclinical, clinical, epidemiologic and health services research of CAM in one of four research theme areas. The Centers will provide many of the resources necessary for the conduct of high quality research, including an environment for training future scientists. Finally, the Centers will encourage collaboration between basic and clinical scientists, and

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Mutated Gene Causes Neuronal Death

Identification of First Glutamate Receptor Linked with Neurodegeneration

by RU News Services

A gene responsible for the degeneration and death of certain nerve cells in the brain has been cloned, yielding information that may be useful for further studies of such neurodegenerative diseases as Alzheimer's and Parkinson's, investigators from the Howard Hughes Medical Institute at The Rockefeller University and from The Johns Hopkins School of Medicine report in the Aug. 21 *Nature*.

The gene carries instructions to make a receptor for chemicals called neurotransmitters, which nerve cells use to communicate. The discovery, from mouse studies, marks the first time scientists have identified and directly linked a mutant gene in the glutamate receptor family to the death of brain cells. Because of the mutation, the resulting faulty receptor acts as if a neurotransmitter always is present -- even when none of the chemical is there. This false detection causes the nerve cells to die.

"The mutations in the d2 glutamate receptor gene may play a role in changing the metabolism of the adult nerve cells to reactivate a program of cell death that normally occurs only during natal development. If we can reveal more about this process and understand it, it may be possible to slow the process down or stop it and preserve the neuron," explains Nathaniel Heintz, Ph.D., professor and head of the Laboratory of Molecular Biology at Rockefeller and an investigator at Howard Hughes.

During fetal development, programmed cell death is used to sculpt the final number of cells in the mature brain. About twice as many cells begin the process of developing into brain nerves than are needed in an adult brain. Consequently, many of the cells activate a biochemical program to commit suicide, known as an apoptotic death, because they receive certain chemical signals.

"We think that the surveillance mechanisms that monitor the normal metabolism of neurons are much like those monitoring the cell-division cycle in other types of cells. In neurodegenerative diseases, these mechanisms may activate the apoptotic cell death pathway as a normal response to the severe dysfunction of neurons. Our discovery of the d2 glutamate receptor gene mutation helps us to understand how this gene functions in normal neurons, but the $64,000 question remains: 'How does its altered function trigger cell death?'" says Heintz.

Heintz and his colleagues would like to pursue studies of two possible explanations related to the mutant receptor's function and the initiation of cell death. The glutamate receptor is part of a biochemical relay system that transports signals between cells. When glutamate binds to the receptor, located in the outer membrane of the neuron, the receptor allows charged molecules, usually calcium ions, to enter the cell and pass the signal along.

The first possibility of how the mutation causes cell suicide is simply that death ensues from the direct action of the receptor increasing the amount of ions coming into the cell. Other studies have shown that unusually high levels of calcium ions can enter the cell in response to increased activation of glutamate receptors, as occurs in stroke. These ions are critical in causing cell death. However, no direct pathway linking calcium ions to programmed death has yet been discovered. The second possibility is that the mutation alters the signaling properties of the receptor, and that the resulting aberrant signals are critical in the initiation of cell death.

The receptor mutation occurs because of the substitution of two of the four nucleic acids used to build the gene, located on chromosome 6 of lurcher (Lc) mice. This switch changes the instructions carried by the gene and consequently, the receptor protein it makes. The mutation causes the death of Purkinje neurons in the cerebellum, the brain structure that controls all aspects of coordination and fine motor control in mature animals.

Heintz's coauthors included Jian Zuo, Philip L. De Jager, Weining Jiang, Ph.D., at Rockefeller, and Kanji A. Takahashi and David J. Linden, Ph.D., at Johns Hopkins. The National Institute for General Medical Sciences, part of the federal government's National Institutes of Health, funded the research, with support from the National Institute of Mental Health, the McKnight Foundation, the Derelbiss Fund and the National Alliance for Research on Schizophrenia and Depression.■

Continued from Page 20

between the CAM and conventional medical communities.

Specific objectives for the current Center applications include: (a) Performing research related to CAM treatments in one of four research theme areas: cardiovascular disease, drug abuse, HIV/AIDS, or pediatric disorders; (b) Establishing an advisory committee to provide program direction and advice to the principal investigator of the Center, including prioritization of research protocols and utilization of core facilities; (c) Developing a mechanism for scientific/technical merit review of proposed studies from investigators; (d) Developing workshops, seminars, etc. for training purposes; (e) Establishing a system to identify and support junior investigators in their career development; (f) Investigating basic mechanisms of CAM therapeutic and diagnostic interventions; (g) Conducting controlled trials of sufficiently developed CAM interventions or pilot trials for the purpose of developing controlled trials; and (h) Acting as an institutional focus for training in research methodology, bioethics, biostatistics, clinical trial design, epidemiological studies, health services studies and basic laboratory methods as they relate to CAM. Letter of Intent due: December 1, 1997; Application Receipt Date: January 13, 1998.

PA-98-003: Clinical Use of Medications to Treat Alcoholism

The National Institute on Alcohol Abuse and Alcoholism is seeking research grant applications on the clinical use of medications to treat alcohol abuse and alcoholism. Relevant topics include investigation of drugs to treat various aspects of alcoholism, particularly acute and protracted alcohol withdrawal, post-treatment relapse, alcohol craving, psychiatric comorbidity, alcohol-induced cognitive dysfunction, intoxication, and alcohol-induced organ damage. This program announcement also solicits research on behavioral issues surrounding use of medications in alcoholism treatment, such as compliance to the medicational regimen. In this program announcement, the research is to be conducted in humans. For animal studies, see the program announcements "Neurobiology of Ethanol-Related Behaviors" (PA-94-77) and "Alcohol, Hormones, and Medical Complications" (PA-97-062). This program announcement replaces the announcement "Research on Promising Pharmacotherapies for Alcoholism" issued February 1990.

Research support may be obtained through applications for a regular research project grant (R01) or First Independent Research Support and Transition (FIRST) Award (R29). Applicants may also submit Investigator-Initiated Interactive Research Project Grants (IRPG) under this program announcement.

RFA: HL-97-016: New Approaches to Improve the Viability and Function of Transfused Platelets

The Transfusion Medicine Scientific Research Group, Division of Blood Diseases and Resources, National Heart, Lung, and Blood Institute (NHLBI), announces the availability of a Request for Applications on the above subject. The purpose of this initiative is to encourage the conduct of research on the alterations produced in blood platelets during collection/processing and storage, on the development of detection techniques for monitoring viability and function of platelets after collection/processing and during storage, and on the prevention of defects responsible for loss of function. The recent availability of sophisticated tools and analytical techniques to study the platelet surface components, evidence that platelet storage and viability can probably be improved, and need to make maximum use of blood products, make it possible and timely to pursue such questions in an important area of hematologic research and national health need. Thus, the intent of this solicitation is to: (a) encourage established investigators with available tools to devote resources to this area; (b) attract new scientific expertise such as cell biology, biochemistry, molecular biology, into studies of platelet viability and function; and (c) promote inter-disciplinary collaborative research in helping to solve a fundamental question in hematology; i.e., what biologic events result in loss of platelet viability and/or function after collection/processing and during storage and how can these events be prevented. The ultimate goal will be to define the conditions which will provide better hemostatic function as a result of platelet transfusions to thrombocytopenic patients. Letter of Intent Receipt Date: November 28,1997; Application Receipt Date: January 22, 1998.

NIAID Award Policy: Competing Renewal RO1 Grants

Based on recommendations of its National Advisory Council, the National Institute of Allergy and Infectious Diseases (NIAID) is announcing a revised award policy for competitive renewal investigator-initiated research project (R01) grants.

For the past three years, NIAID has limited the increase in direct costs awarded to 10 percent over the last noncompeting year of the grant (see NIAID AWARD AND APPLICATION POLICIES, NIH GUIDE, Volume 23, Number 40, November 18, 1994). After assessing the effects of that policy and the budget outlook of the Institute, NIAID is revising that policy.

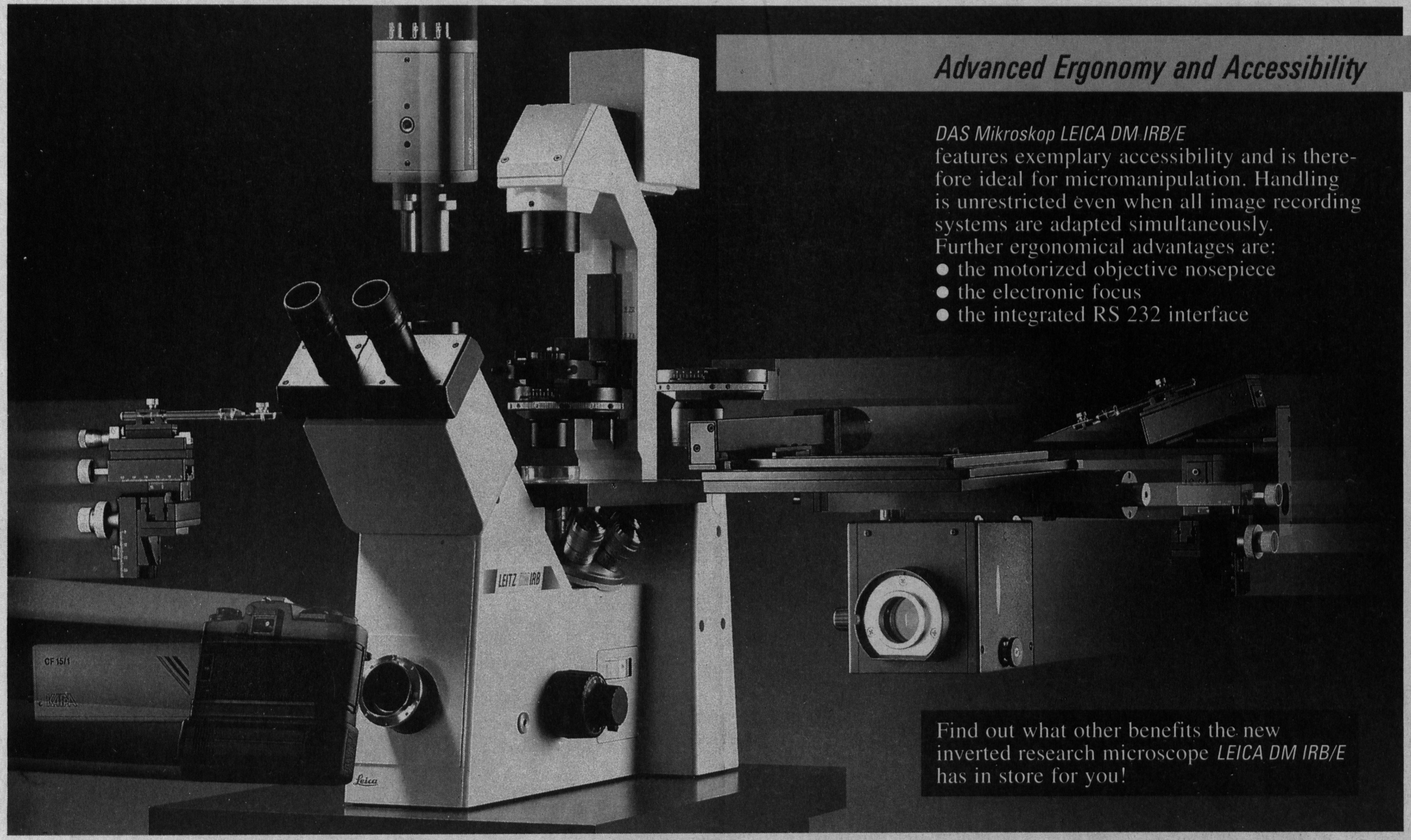
Beginning with awards for fiscal year 1998, the direct costs awarded in the first year to a research project grant (R01) resulting from a competing renewal application will be limited to no more than a 20 percent increase over the direct costs awarded in the last non-competing year of that grant.

PAS-98-002: Polycystic Kidney Disease - Mechanisms, Model Systems, Interventions

The National Institute of Diabetes and Digestive and Kidney Diseases through its Division of Kidney, Urologic and Hematologic Diseases invites experienced and new investigators to submit research grant applications to pursue basic and applied investigations in order to better understand the etiology and pathogenesis of Polycystic Kidney Disease (PKD), both dominant and recessive; the genetic determinants, and cellular and molecular mechanisms which disrupt normal kidney function; mechanisms of cyst formation and growth; development of experimental model systems; development of imaging methods to assess cyst growth and provide markers of disease progression; and the identification of innovative therapeutic interventions and gene targeted strategies to prevent progressive renal insufficiency due to this disorder. The intent of the Program Announcement (PA) is to intensify investigator-initiated research, to attract new investigators to the field, and to increase interdisciplinary research. The ultimate aim is to encourage and facilitate PKD-related research studies where progress already attained offers new opportunities to increase the pace with which knowledge is accrued.

RFA: DK-98-002: Effect of Diabetes on the Urinary Bladder and Erectile Function

The National Institute of Diabetes and Digestive and Kidney Diseases through its Division of Kidney, Urologic and Hematologic Diseases invites investigators to submit research grant applications which will increase the basic knowledge of the effects of diabetes mellitus on the lower urinary tract. Specifically, this request addresses studies of urothelial cell, vascular, neurological and smooth muscle functions and interactions in the normal urinary bladder and in penile erectile function and the changes which occur with diabetes mellitus. The overall scientific goal of this initiative is to enhance the understanding of the molecular and cellular changes which occur in the urinary bladder and penile erectile function of the person with diabetes. The intent of this Request for Applications (RFA) is to intensify investigator-initiated research, to attract new investigators to the field, and to increase interdisciplinary research to enhance the scope and effectiveness of research in this area. Letter of Intent Receipt Date: December 9, 1997; Application Receipt Date: January 9, 1998.■



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