FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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NCHGR's Intramural Genetics Hub Gets Rolling

by Celia Hooper

Ask Francis Collins, Director of the National Center for Human Genome Research (NCHGR). Ask Jeff Trent, recently designated Scientific Director of NCHGR's new intramural program. Or ask almost any one of the scientists now moving into NCHGR's research facilities on the fourth floor of building 49 ... Independently, each is likely to tell you the same thing about NCHGR's new intramural research program: "We don't want to become this little walled-off part of NIH," says Collins. "Our major goal is not to be an island unto ourselves, but to interact with others on campus," says Trent.

In interviews with *The NIH Catalyst*, the expansive Collins and the more reserved Trent said that they see tremendous opportunities for collaboration on campus. "What we want to do is set up a hub of genetics...with many spokes reaching out to the other institutes for the expertise we lack," says Collins.

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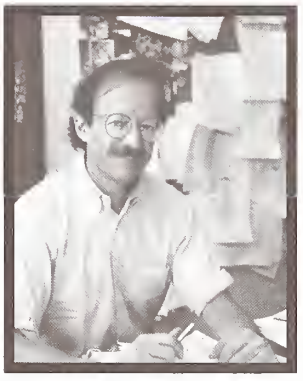
NCHGR Director Francis Collins.

NIH Director-Designate Addresses Senate Committee at Confirmation Hearing

The confirmation hearing for NIH Director-Designate, Harold Varmus, was held on November 3. Speaking before the Senate Committee on Labor and Human Resources, Varmus gave the following statement.

Senator Kennedy, Senator Kassebaum, and members of the Committee:

I am honored to appear before you today as President Clinton's nominee to direct one of our country's greatest assets, the National Institutes of Health.



Harold E. Varmus, M.D.

My preparation for this job has been unusual. For most of my adult life, I have been an academic scientist, studying retroviruses and cancer genes, teaching graduate and medical students, and training postdoctoral fellows at the University of California, San Francisco (UCSF). Given this background, I would like to explain why I want to take on the responsibilities of running an immense institution, why I believe I am prepared to do it, and what I hope to achieve.

I grew up in an atmosphere that encouraged public service in the health professions. My mother was a psychiatric social worker, active in community affairs in my home town, Freeport, New York. My father was a family doctor who also served as the Jones Beach State Park physician for 30 years. In this climate, it was natural that I would consider a career in medicine. But as a pre-medical student at Amherst College, I developed a love of literature that I set aside only after a year of graduate studies.

My indecision about careers did not end there. I began Columbia Medical School fascinated with the brain, intending to practice neurology or psychiatry; a new interest in tropical health brought me to a mission hospital in India; by the time of my residency, I thought I had settled on the practice of internal medicine.

The NIH then pointed me in a new direction, when I served as a Public Health Service officer at the NIH campus in Bethesda. My mentor, Ira Pastan, showed me how to use a simple model organism — the bacterium, *Escherichia coli* — to understand a complex phenomenon, hormone action. This experience converted me to an enthusiastic bench scientist, so I sought further research training and then work as a professor in a basic science department of the medical school at UCSF. In this new setting, I used another kind of simple microbe, a retro-

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Roundtable Wrap-Up

Lance A. Liotta

Over the past year, the office of the DDIR has conducted a series of roundtable workshops aimed at improving communication and gathering ideas for improving the quality of scientific life in the intramural programs of the NIH. Participating scientists were drawn from all levels: Fellows, tenure track and tenured investigators, Section Chiefs, and Lab Chiefs. Separate discussion groups focused on the special problems of clinical research. The ideas generated in these brainstorming sessions have proven invaluable for the new policies that have been implemented.

As expected, there was no shortage of opinions, complaints, and suggestions. But there was also an outpouring of devotion to the basic premise of the Intramural Research Program (IRP): creative freedom for individual investigators under a broad institute mission. Viewpoints varied widely on almost all topics. Nevertheless, there were two areas of unanimity. The first was that retrospective review by the Boards of Scientific Counselors was the best way to ensure quality control, in view of the unpredictable nature of scientific progress, the need to have freedom to strike out in bold new directions, and the duty to respond rapidly to emerging opportunities and challenges. The second point of unanimity was the essential nature of the Clinical Center as the heart of intramural NIH.

Most scientists felt that despite FTE and fiscal restrictions, their work had never gone better, and they operated with a strong sense of excitement about the rapid growth of fundamental knowledge in their field. The biggest problems, they felt, centered around bureaucratic barriers, imposed delays, and constraints that produced frustrating missed opportunities. If these problems were addressed, they could do so much more!

Here are few examples of complaints and suggestions that reflect recurring themes.

Oversight and bureaucracy:

"People making the rules in the past didn't understand what NIH scientists do, and the goal has become [creating] an administrative structure rather than a scientific structure."

"There has been a 'reversal of accountability.' We believe this problem has been created by a shift in emphasis at NIH from scientific achievement to an all-consuming concern about personal behavior."

"The scientific personnel in Laboratories and Branches should have more responsibility for review of administrative support personnel."

"Many independent investigators need more information about their own budget and how they can share resources to reduce expenditures."

"If there is going to be a faculty council, there should also be a general council (with elected representatives) for tenured scientists and ... Laboratory and Branch Chiefs"

Clinical Research

"There have been improvements in recruiting clinical fellows to NIH, but it needs to move much faster."

"Many laboratory scientists have innovative proposals for new treatments or clinical research experiments but can't get their ideas translated into clinical trials. We need more workshops to help laboratory-based and clinical researchers combine their knowledge."

"In most areas, current clinical trials are very creative (such as [those for] gene therapy and novel drugs), but in some pockets, we are just combining conventional treatment a little differently."

I recommend strongly that the DDIR roundtable workshops be continued. However, this decision will be up to the new DDIR since I am stepping down on Nov. 8 to allow the new NIH Director to choose his own DDIR. During the past 15 months, I have been very proud to be part of numerous positive changes in the IRP. These changes have expanded career development and outside activities, enhanced clinical research and communication, and led to accreditation of our animal-care and -use facilities, for example. Nevertheless, I look forward to returning full time to the Laboratory of Pathology.

While a search for the new DDIR is under way, Michael Gottesman has been appointed Acting DDIR. Gottesman received his M.D. in 1970 from Harvard Medical School. His research training began at Harvard in the laboratories of William Beck and Bert Valle, and continued in the laboratory of Martin Gellert at NIH from 1971 to 1974. Gottesman joined the permanent staff of NCI in 1976 and became Chief of the Molecular Cell Genetics Section of the Laboratory of Molecular Biology in 1980. He has been the Chief of the Laboratory of Cell Biology since 1990, Acting Director for the National Center For Human Genome Research from 1992 to 1993, and until recently was the Acting Scientific Director of the NCHGR. His research interests at NIH have ranged from how DNA is replicated in bacteria to how cancer cells elude chemotherapy. During the past eight years, in close collaboration with Ira Pastan, Gottesman has identified a human multidrug resistance gene that enables some cancer cells to evade many of the most common anti-cancer drugs. This gene encodes a protein that acts to pump anti-cancer drugs out of drug-resistant tumor cells. Gottesman has received wide recognition for his scientific accomplishments. I stand ready to assist and fully support him into the future. ■

—Lance A. Liotta
Deputy Director for Intramural Research

Structural Biology is Focus of New DCRT Lab

Four previously separate DCRT groups have joined forces to form a new Laboratory of Structural Biology (LSB), offering intramural scientists expanded expertise in applying cutting-edge computational techniques to structural biology.

"DCRT scientists have been pioneers in the measurement of intermolecular forces, and in molecular graphics, molecular dynamics, and computer simulations," says DCRT Director David Rodbard. "This realignment will create a new critical mass and a cohesive and cooperative nucleus for interactions with other scientists at DCRT, at NIH, and throughout the world."

Adrian Parsegian, who has pioneered the use of experimental, theoretical and computational approaches to understand intermolecular forces, heads the new lab. The LSB's three units, the Section on Molecular Forces (SMF), the Molecular Graphics and Simulation Section (MGS), and the Analytical Biostatistics Section (ABS), will provide the following research resources to NIH scientists:

- research collaboration and support
- molecular simulation, modeling, and graphics
- software development and support; such as application of the program CHARMM
- evaluation of hardware for specific biomedical applications
- lecture series, courses, and journal clubs.

Lab Chief Parsegian will also head the Section on Molecular Forces. "There's an enormous interest here at NIH in learning how to measure intermolecular forces and learning how to use force measurement techniques to understand the conformations of proteins," says Parsegian. Current computer programs are not set up to incorporate intermolecular forces, says Parsegian. One of LSB's goals is to incorporate measured forces into computer programs, improving their power to predict accurately what happens when a drug approaches a large molecular surface, or how two pieces of protein will find each other and bind together, for example.

According to Parsegian, modeling of intermolecular forces will provide new opportunities for rational drug design and more effective ways to address diseases involving pathological interaction between molecules or unwanted precipitation of molecules, such as the "gelation" or aggregation that occurs in sickle cell disease.

Sergey Leiken, a Visiting Scientist in SMF, recently collaborated with NIAMS scientists to study the forces involved in the packing of collagen triple helices. And NIDDK/DCRT collaborators Parsegian, Donald Rau, Sergey Bezrukov, Nina Sidorova, and others are using the "osmotic stress technique" developed by Parsegian and colleagues for direct force measurement on all classes of biological material. This collaboration has delineated a new kind of interaction called the "hydration force." SMF is now learning to use the osmotic stress technique on individual molecules, for example, to monitor the opening and closing of ionic channels or to change solvation of heme proteins.

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Woman Scientist Advisors Appointed

A few months ago, the Task Force on the Status of Women at NIH proposed several recommendations to the Deputy Director for Intramural Research and the NIH Director to improve the NIH environment for women scientists. One recommendation was the appointment of Women Scientists Advisors to the Scientific Directors. These advisors have now been appointed. Women scientists or others with questions or concerns may contact the Women Scientist Advisors for their home Institute, Center, or Division. A list of these advisors, along with their phone and fax numbers, is published below.

Name	Institute	Phone	FAX
B. J. Fowlkes	NIAID	496-5530	496-0877
Joan Schwartz	NINDS	496-4049	402-0117
Susan Swedo	NIMH(basic)	496-6081	402-0296
Nancy Ostrowski	NIMH(Clin)	496-0514	496-4103
Maura Kibbey	NIDR	496-8251	402-0897
Indu Ambudkar	NIDR	496-4278	402-1228
Cecilia Snowden	NIDR EODPP	496-7716	402-3420
Linda Kaste	NIDR EODPP	496-7716	402-3420
Sandra Smith-Gill	NCI/DCBDC	496-2202	402-1031
Susan Shoaf	NIAAA	493-4936	402-2365
Megan Adamson	NIAAA	443-4101	443-5880
Amy Newman	NIDA	8-(410)-550-1455	8-(410)-550-1648
Michelle Evans	NIA	402-8162	402-8157
Amy Rosenberg	CBER(PSA)	496-1236	496-1659
Susan Sieber	DCE(NCI)	496-5946	496-1297
Elizabeth Murphy	NIEHS	8-(919)-541-3873	8-(919)-541-7880
Carol Thiele	NCI/DCT(Clin)	496-5505	402-0575
Susan Bates	NCI/DCT(basic)	496-0785	402-0172
Caroline Tolstoshev	NCBI/NLM	496-2475	480-9241
Grace Yeh	DCPC/NCI NCI-FCRDC	8-(301)-846-5369	8-(301)-846-6093
Donita Garland	NEI	496-6999	496-1759
Peng Loh	NICHD	496-3239	496-9938
Barbara Sonies	CCRMD	496-4733	402-0663
Leepo Yu	NIAMS	496-5880	402-0009
Ann Dean	NIDDK	496-6068	496-5239
Arlyn Garcia-Perez	NHLBI	496-1559	402-1443
Elise Feingold	NCHGR	496-7531	480-2770
Marlene Cole	NCRR	496-2522	402-0352
Christy Ludlow	NIDCD	496-9365	480-0803
Bonnie Douglas	DCRT	496-2847	402-0007

In Future Issues. . .

- Harold Varmus and the future of intramural research
- Faculty groups at NIH
- NIH Science Education Efforts

Intramural Scientists Sound Off on *Science* Articles

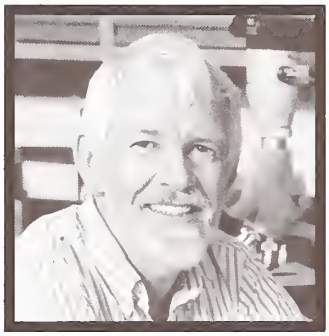
by Seema Kumar

Can we talk? In August and September this year, *Science* ran a two-part series examining the organization and management of the NIH Intramural Research Program (IRP) and its relationship to the extramural program. Author Jon Cohen asserts that the IRP is at a crossroads and that the new leadership faces a tough decision about what direction the IRP should take. Cohen cites four IRP problem areas in the first article: uneven quality of research; top-down management that is rigid and confining; presence of European-style "Herr Professor" hierarchy within some laboratories; and difficulties in recruiting and retaining top notch scientists at all levels. The series concludes that deep ambiguities exist in NIH's mission and "strenuous efforts must be made if excellence is to be sustained."

In keeping with our role as a forum for intramural scientists, we invited a cross-section of our readers to vent their reactions to Cohen's charges. We got an earful! Of 20 scientists and administrators selected at random from our mailing list, most who had read the article had a strong opinion and wanted to talk ... and talk. Below, we bring you excerpts from eight of these interviews. These responses reflect the opinions and sentiments of the respondents and not those of the Office of Intramural Research or *The NIH Catalyst* board and staff. Do you want to talk about the Cohen piece? Air your opinions on the FAX BACK page!

Gary Boorman, Branch Chief, NIEHS

My reaction is that [we at] NIH do have a responsibility to reexamine our priorities and our differences and the way we do business. The



Gary Boorman

strength of the article is that it — and other articles like it — keep us on our toes. But the weakness of the article is that it is based on generalizations...

I think there is always a variation in the quality of research programs, whether intramural or extramural, and it is true of any organization that you never have a uniform distribution of excellent labs — you probably have good labs and excellent labs.

Rosemarie Hunziker, Senior Staff Fellow, NIAID

At NIH, some areas are more outstanding than others. Overall I think it is pretty high quality, but I don't think many of the researchers at NIH do high-risk research. I agree that the research that goes on at intramural NIH is not necessarily different from research that goes on elsewhere. It is high quality because the people in it are good, but it is not stuff that wouldn't happen in a university. The possible exception is that there are some who are doing very-long-term experiments that might not lead to papers immediately, and these people need the protective environment of the intramural program.

In talking to colleagues in other institutes, I know that the "Herr Professor" labs are a very big problem, but I personally have very little experience with that. The only place we usually see [the lab chief wielding power] is in allocating lab space, and that is just something that is going to happen no matter where you are. ... Somebody has to decide who is going to get space. But in terms of stifling research or having any overpowering contribution to which direction an investigator should go, absolutely not! At least not in our lab!

In immunology, the field I know, the quality of intramural research is not slipping, but overall, I can see that there are some areas that are not where they [ought to be].

Anonymous Extramural Administrator

I spent several years at the intramural program and am familiar with what goes on. I agree completely with the contention that although there are a few stellar labs at NIH, a lot of them are quite mediocre. I also agree with the point that "Herr Professor" labs and top-down [management is stifling young researchers]. I also agree that the quality of research [at NIH] is not as good as it should be, considering that NIH scientists don't have to compete for grants, and therefore have more time and could be doing creative, risky research. However, [both quality and management style] probably vary from lab to lab and so it is very difficult to extrapolate based on personal experience. It is also difficult to get much of a feeling for [how NIH is doing overall]. There are very few data or statistics ...

How the intramural labs are reviewed is a very serious problem. A rigorous-enough and objective-enough review is not carried out. In some institutes, in one day, at least 30 people were reviewed — [the Board of Scientific Counselors] came for one day and had other back-up documents they had read [before they came], and people gave talks ... but very little appeared to change as a result of it, and certainly there were people [reviewed] there who, under other conditions, should have or would have [been subject to changes in the resources made available to them].

It is true that other places might be more attractive to people than NIH and recently, [there has been] no [recruitment of] top-flight [senior] scientists. However, there is a real effort to change that. Now, we have Francis Collins and Harold Varmus; these are the kind of people to get to attract more good people. ...

Jaswant Bhorjee, Program Director in the Extramural Program, NCI

In parts, what the *Science* article said was correct. In some basic science efforts at NIH, there is a great degree of overlap with what goes on outside — in the univer-

Jaswant Bhorjee

sities. ... In clinical research, I think that there are some very strong features at NIH. They have more opportunities for doing things that cannot be easily done outside, like, for example, innovative clinical trials.

The contention that the quality of intramural research is not uniform can be said for the university research enterprise also ... The top 100, or even the top 50, universities have the same kind of distribution in quality: there are a few top-flight researchers, and the rest are just coasting along, doing repetitive science. This, I think, happens everywhere ...

There is something to say for competing for grants. It challenges the extramural scientists to think loudly, to think clearly, to think new, and to be competitive, whereas that challenge perhaps does not exist at NIH because intramural scientists don't have to compete for shrinking funds... The opposite side of the coin is that this very feature must allow NIH scientists the luxury of taking risks in science that outside scientists cannot ... The leaders at NIH should challenge intramural scientists to take risks because that is what can be attempted here ...

Recruitment and retention problems exist because of the salary structure. Some star scientists who make $50,000—60,000 a year — which is peanuts — can command upwards of $100,000 outside NIH. I don't think that the NIH system is itself bad, but the salary structure is very poor for bright and creative young people. If NIH cannot keep its bright young cadre, it is not the fault of NIH; it is the fault of the government salary structure.

Mark Levine, Senior Investigator, NIDDK

The problems that I saw with the article were that first, the IRP has to be different; it was meant to be dif-

Mark Levine

ferent, and you can't judge it by the same criteria that you [use to] judge work that competes for grants. I can't prove it for every scientist, but I can say for myself and for the people that I know that there is no place that I could be doing what I am doing, especially clinically, anywhere else in the world. Period. Second, the sampling source is biased, consisting in part of outside people who might be jealous of the intramural program ... They have a vested interest in trying to get some of IRP's money.

In terms of retention [of staff], NIH was never designed to keep lots of people. It was designed to train people and then to send them out. I stayed here because I knew that the work that I wanted to do could not be done anywhere else. This place to my mind is unique — it's special, and it should not be tampered with.

Some of the things said about the top-down style of management were true. The scientific directors (SDs) do have a tremendous amount of power. Decisions by the SDs can be arbitrary, and it really depends on the personality of the SD. In all fairness, the system was designed to be very flexible so that there is a minimum of bureaucracy. If scientists want something, they ask the SD and get a yes or no answer. I would still dispute calling the system top-down management ... I would call it a benevolent autocracy. Top-down management implies that SDs are telling people what to do, and I don't think that it is true, at least from my experience. What they do control — tightly — are resources, space, and positions ... I don't know how to fix their tight control when disputes arise. This is a particularly difficult problem when there are disagreements based on subjective opinions about science rather than on objective evidence.

There is no question that the salary I earn here is less than the salary I could earn on the outside. I can't get industry money easily, and I don't have the perks of honoraria and painless arrangements for foreign travel. I trade these and other things because at NIH I can take very high scientific risks. If some of them don't work, I am not suddenly high and dry. And if high risks pay off, as they sometimes do, many people will benefit.

Pradman K. Qasba, Indepeudent Investigator, NCI

I think the point raised about NIH's mission and Congress' priority is a pertinent one. It is Congress' function to set

Pradman K. Quasba

the priorities for basic research. I firmly believe that the mission of NIH should be given serious consideration. Congress sees things differently, but I believe that the mission of NIH should not be targeted only to curing diseases but conducting basic science that will lead to cures as we understand diseases better. Cure does not come immediately, and the history of medical science has shown us that cures for specific diseases do not come by targeted research. They come from the understanding of the basic chemical and biological reasons underlying the disease. Other agencies and companies are not interested in building basic sci-

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MRIPS: The Imaging-Magician's Toolbox

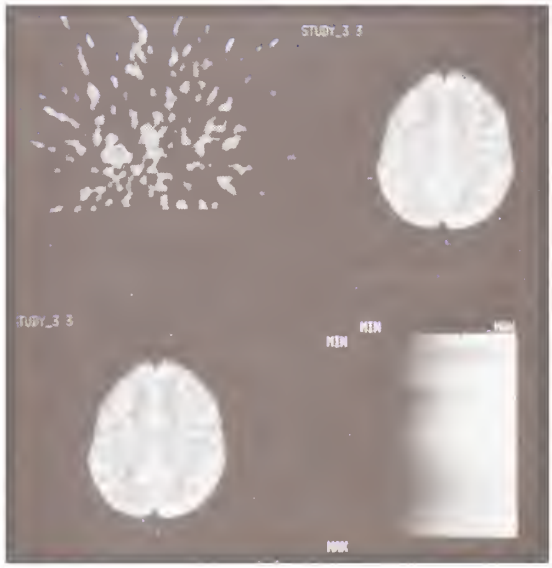
by Celia Hooper

NIH scientists are now cracking open the lid of a powerful new image-handling toolbox, a customized, integrated assemblage of computer workstations, data-serving routines, and software packages that will allow researchers to perform near-magic on virtually any type of visual information.

Currently in its second round of testing and trouble-shooting, the toolbox is called the Multimodality Radiological Image Processing System (MRIPS). Joseph Frank, who heads OD's Laboratory for Diagnostic Radiology Research (LDRR), says the $1.2 million MRIPS system was designed to handle extremely sophisticated image-handling tasks — such as combining data from a variety of different radiological imaging techniques — but will ultimately be useful "for anything where you need to analyze images, from gels to electron microscopy, from histology to molecular structures." Collaborating with LDRR on the MRIPS project are NCRR's Biomedical Engineering and Instrumentation Program (BEIP) and several parts of Division of Computer Research and Technology (DCRT).

BEIP's Ronald Levin, acting chief of LDRR's MRIPS section, says the system was originally conceived as a replacement for the "helter-skelter sneaker-net," an antiquated, widely scattered hodgepodge of noncompatible, non-interfacing computer routines for two-dimensional data generated by techniques such as computerized tomography (CT), magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET). In some instances, it was virtually impossible for researchers to obtain computerized records of radiological images or analyze the data in any way. A 14-member MRIPS steering committee, composed of researchers from many different institutes that will ultimately use the system, quickly developed a wish list of features that took the system well beyond just the three-dimensional upgrade, making MRIPS potentially useful to a much wider spectrum of scientists.

Multiple views of surface-rendered magnetic resonance scan.



Multimodality imaging of one axial slice of brain activity as a human subject performs repetitive-hand-movement task: PET image (upper left), magnetic resonance image (upper right), superposition of scans (lower left). Superposition required "warping"— reorientation and resizing of images. [Courtesy Thomas Zeffiro, LNS, NIA.]

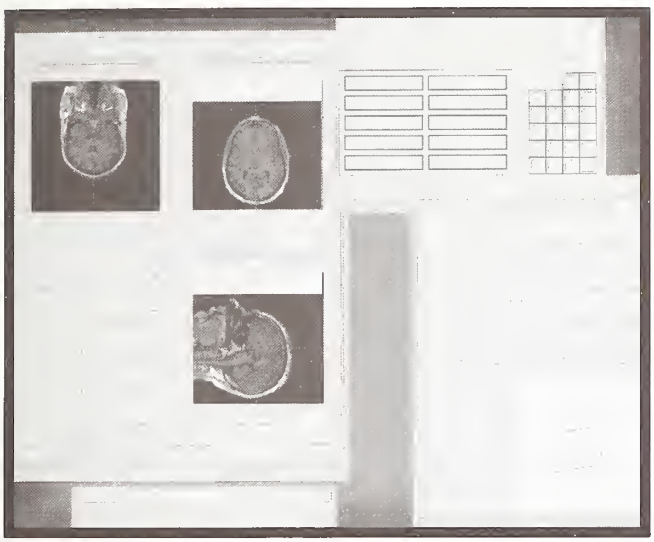
Frank says the steering committee sought to make the system "forward compatible" — capable of performing tasks that researchers may dream up in the future. "We have the source code," or basic programming, of MRIPS, Frank says. "So the system can be improved and advanced. This makes it much more robust for meeting the needs of intramural scientists ... As the science progresses, MRIPS can grow with it." Bonnie Douglas, a DCRT systems analyst and acting deputy chief of LDRR's MRIPS section, stresses that MRIPS users will be able to make many modifications and customized adaptations of the system by themselves. "Unlike previous systems, with MRIPS, the researcher can add functions and modify functions, features, and menus. You don't need a computer whiz," Douglas says.

One potential forward compatibility is virtual-reality surgery. Levin says that if NIH surgeons want it—and if someone funds it—MRIPS could potentially be adapted to allow surgeons to practice delicate experimental surgery on the computer before cutting into a patient. With 3-D goggles or a neurosurgical microscope field projecting a reconstruction of the patient's tissues based on CT and other images, the surgeon would use computerized surgical instruments to practice the operation on the image. After the surgeon had perfected the technique, he or she could then use the computer to guide the actual surgery on the patient.

Frank says an important feature of MRIPS is that it will serve as a data highway, allowing researchers to share and move digital images much more freely among a variety of workstations (including Digital Equipment Corporation, SUN Microsystems, Hewlett-Packard, and Silicon Graphics Inc.). He sees MRIPS as a boon to intramural collaboration, allowing all researchers on a project to call up, construct, reorient, and analyze an image or series of images from any computer workstation on campus. Levin notes that safeguards on the confidentiality of patient records have been built into the system. Frank says fiber-optic data transmission will be a key to greater speed in MRIPS' ability to move images.

The statistical powers of MRIPS will also be evolving over the next few years. Initially, says Douglas, the system will compute angles, flows, oxygen uptakes, time-series analyses, distances, areas, volumes, and other measurements and will calculate the means, standard deviations, and other simple statistics on these data. Within a couple years, however, MRIPS will perform a variety of correlational and multivariate statistical analyses.

Frank expects that the most compelling immediate use of MRIPS will be in combining structural images of the brain or heart—such as those generated



Sample MRIPS screen showing some image-manipulation and visualization capabilities. Functions can be customized according to individual researchers' preferences.

by MRI—with functional images generated by PET, for example. "This really opens up the whole world of function and metabolism at a fine level," says Frank. He also expects that structural biologists will quickly embrace MRIPS to combine images of macromolecules based on X-ray crystallography, electron microscopy, and MRS. MRIPS will allow researchers to superimpose the 3-D molecular images for greater resolution and to manipulate the combined image to analyze spatial and functional relationships within and between molecules.

"There is a lot of demand for MRIPS," says Levin. Although the complete system will not be available for use until January, he has given a handful of desperate scientists access to parts of the system during its debugging phase. "There are some people who have been waiting five years to read their data tapes," says Levin. "We've opened up bits and pieces to those people, but right now, this is still a test environment."

Douglas and Levin say they are cautiously optimistic—and just a tad nervous—about MRIPS' debut. Analogous systems, such as MIRAGe or ANALYZE from the Mayo clinic, have evolved and added functions gradually over a decade. "Our system has to have all the MIRAGe functions from day one," says Douglas. "And all the functions have to be working and debugged from day one." The task of debugging the system is complicated by the fact that MRIPS must run flawlessly on four different types of workstations. "We've got to find all the 'gotchas' so they don't burn the researchers," Douglas says.

Levin compares MRIPS to a flashy new model of sportscar. "We can't come out with a Pinto," says Levin. "All the bells and whistles have to be in place. We can't have the chrome falling off when you close the door."

Douglas says that scientists who want to get their hands on MRIPS as soon as possible can sign up for a two-day training session in December. Other researchers can register for beginning, intermediate, and advanced MRIPS classes offered in early spring.

Ultimately, Frank says, MRIPS is limited only by the imagination of NIH's scientists. "We're trying to make the system as versatile as possible. It is a toolbox. Given the tools and hardware, it is up to researchers to be creative and change or invent new science" with MRIPS. ■

The MRIPS Steering Committee

Member	*Institutional affiliation*
Stephen Bacharach	CC, DCRT
Richard Carson	NM/CC
Richard Coppola	NIMH
Charles DeCarli	NINDS
Margaret Douglas	DCRT
Joseph Frank	DR/CC, OD
James Haxby	NIMH
Earl Henderson	NLM
Dennis LeBihan	DR/CC
Ronald Levin	NCRR
Robert Phillips	NIDA
Scott Selbie	NIDCD
Daniel Rio	NIAAA
Urs Ruttimann	NIAAA
Geoffrey Sobering	NCRR
Robert Turner	NHLBI
Thomas Zeffiro	NIA
Sandra Zink	NCI ■

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ence knowledge, and this is where NIH has to play a vital role. Building basic scientific knowledge should be the responsibility of the society, and government (NIH) is representative of the society.

Many scientific discoveries that have developed into hot areas today were initiated here at NIH without any noise or publicity. Think about the polyoma virus ... or retroviruses, which were discovered here, or immunoglobulin research. Later development of these areas may have taken place outside of NIH, but the fundamental work was developed here at NIH. The reason for this is that intramural scientists had and continue to have the freedom to work on obscure things that nobody dares to tackle. What is being done at NIH at this time may seem very basic and primitive at times, but it does lay a sound base for any medical breakthroughs that follow for the society as a whole and the world at large.

Jeff Hoeg, Section Chief, NHLBI

My overall impression was that even though there was an attempt to make the article evenhanded, its overall tenor was biased against the NIH system. That argument that NIH is slipping in quality is a gross generalization ... and personally, I don't think it is true at all. There are certain individuals who have very high profiles and have very good ideas. The vast majority do very-high-quality work, and there are always going to be a few labs, in an institution this size, that are not going to come up to snuff. But I think those are rare here at NIH.

That selective cutting rather than across-the-board cutting must be done is a legitimate issue. There are labs that are

continued on page 23.

Recently Tenured

Dimiter S. Dimitrov *came to NIH in 1990 from the Holland Laboratory of Biomedical Research, American Red Cross. He is a Visiting Scientist in the Laboratory of Mathematical Biology, NCI.**

Why do many candidate drugs and antibodies inhibit HIV-1 infection efficiently in vitro but fail to significantly affect virus pathogenesis in vivo? To answer this and other questions, I have quantitatively analyzed HIV-1-infection kinetics to discover mathematical relationships between several critical variables associated with HIV-1 infections, such as the number of infected cells, the time needed to complete a single cycle of infection, and the rate of transmission to uninfected cells. I began with "simple" in vitro cell culture systems but intend to examine a much more complex issue — the progression of HIV-1 disease. In collaboration with M. Martin, R. Willey, and G. Englund from NIAID and R. Blumenthal, who heads our section at NCI, I have developed a novel approach for quantifying HIV-1 infection. We demonstrated that the most critical variable of HIV-1 infection in tissue cultures is the number of *infecting* virions released from infected cells and transmitted to uninfected cells *during* the spread of the virus. This number is very high for cells in contact with each other and varies widely with the virus isolate and cell type. This may explain why neutralizing antibodies and soluble CD4-receptor molecules may not be efficient in blocking cell-to-cell spread of HIV-1, which is probably the dominant mode of virus transmission in vivo.

I am also interested in studying how enveloped viruses fuse with cells and what determines their tropism. I have developed fusion assays, using fluorescent dyes and videomicroscopy, that allow quantification of membrane fusion mediated by the HIV-1 envelope glycoprotein. In collaboration with H. Golding from FDA and R. Blumenthal, I demonstrated that cell membrane fusion does not necessarily result in formation of syncytia — a commonly used indicator of cell fusion — and that the membrane-proximal domains of CD4 are critical for the fusion kinetics. In collaboration with C. Broder and E. Berger from NIAID, I found that in addition to the CD4 receptor, other human cellular components are required for fusion. The identification of such cellular fusion cofactors, which may lead to the development of novel types of antiviral drugs, will be of highest priority in my future research.

Scientists tenured August 1993 to date

Murali K. Cherukuri, NCI*	Elizabeth Snyderwine, NCI
Edward Chu, NCI	Serge Beaucage, CBER/FDA
David C. Kaslow, NIAID	Ann E. Dean, NIDDK

Neal Epstein *came to NIH in 1983 as a Clinical Associate in NHLBI. Recently, he became the Codirector of the newly formed Section of Inherited Cardiac Diseases in the institute's Cardiology Branch.*

Hypertrophic cardiomyopathy (HCM) is an inherited heart disease characterized by an increase in ventricular wall thickness in the absence of

another cause for the hypertrophy. It is the most common cause of sudden death in otherwise healthy, young individuals. I have been working with Lameh Fananapazir to integrate the molecular biology of the disease with the clinical management of patients.

My laboratory has demonstrated both allelic and nonallelic heterogeneity of HCM. We found that the disease is caused by missense mutations in the cardiac beta-myosin heavy chain gene in 10% to 30% of affected families, and we have identified 13 distinct point mutations in the gene. We used these mutations to show that the slow myosin in skeletal muscle is transcribed from the cardiac myosin heavy chain gene. This has allowed the study, in collaboration with other labs, of the abnormal function of this myosin in a variety of assays and led to the description of a rare myopathy in the skeletal muscle of these patients. We are currently looking for other disease genes that cause HCM and are studying the variable expression of the disease within kindreds with the same mutation. We are also studying the molecular consequences of therapeutic interventions in HCM.

Lee Helman *came to NIH in 1983 from Washington University in St. Louis. He now heads the Molecular Oncology Section for NCI's Pediatric Branch.*

My research effort has focused on the role of insulin-like growth factors (IGFs) in pediatric sarcomas — specifically, rhabdomyosarcoma (RMS) and osteogenic sarcoma. We have identified IGF-II as an autocrine growth and motility factor in human RMS and have demonstrated overexpression of this growth factor in virtually all RMS tumors evaluated. We also established that the mitogenic action of IGF-II is mediated through the type-I IGF receptor, whereas the motility response appears to be mediated through the type-II IGF receptor. We recently demonstrated that blocking this IGF pathway can inhibit the growth of RMS tumors in nude-mouse xenografts. Our efforts are now aimed at elucidating the mechanism of IGF-II overexpression in RMS and identifying novel, clinically useful agents that may interfere with this pathway.

We have also been studying the role of IGF-I in human osteosarcomas and have found that in vitro growth of these cells is dependent on the presence of IGF-I. These tumors occur during adolescence, when circulating IGF-I concentrations reach their lifetime peak. Other investigators have observed that removal of the anterior pituitary inhibits

the growth and metastasis of this tumor in rodent models. Because growth hormone is produced in the anterior pituitary and regulates IGF-I production, this inhibition presumably works by blocking the growth hormone/IGF-I axis. In light of this evidence, we initiated a multicenter, phase I study using a somatostatin analog to inhibit growth hormone secretion. The goal of the study is to define a dose that maximally inhibits the growth hormone/IGF-I axis. Once this dose is defined, we hope to test directly whether such inhibition will improve the prognosis of patients with osteosarcoma.

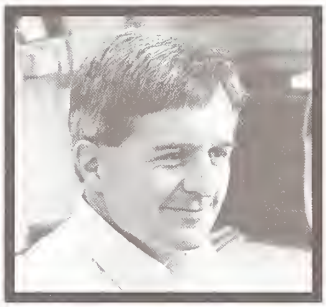
Judy Kassis *came to NIH in 1987 from the University of California at San Francisco. She is now a Scientist at the Division of Cellular and Gene Therapy, Center for Biologics Evaluation and Research.*

The goal of our laboratory is to understand how gene expression is controlled during development. We are studying the *Drosophila engrailed (en)* gene, which has an exquisitely regulated expression pattern and is crucial for proper segmentation of the *Drosophila* embryo and for proper formation of adult cuticle.

Spatially and temporally regulated transcription relies on positive and negative cis-acting sequences called enhancers and silencers. At least for transcriptional enhancers, these sequences can be located many tens of kilobases (kb) away on the DNA. At the *en* locus, sequences located up to 40 kb upstream and 20 kb downstream of the promoter are thought to regulate transcription. How such distantly located regulatory elements influence transcription remains largely unanswered. One model posits that proteins bound near the promoter interact with proteins bound to the enhancer and cause a looping of intervening DNA. At *en*, this model requires the interaction of proteins bound to sites separated by large linear distances. One might imagine that the same proteins could mediate an interaction between noncontiguous pieces of DNA. Two years ago we identified *en* regulatory DNA, and we postulate that it has the ability to do just that: first, it promotes interactions between transposons (P elements) located on homologous chromosomes, and second, it directs P elements to particular regions of the *Drosophila* genome.

During the past year, we identified three sites in *en* DNA (called pairing-sensitive, or PS,) sites that mediate interactions between transposons present on homologous chromosomes. We also identified PS sites within other *Drosophila* genomic DNA. In transgenic flies, an interaction between transposon-encoded and genomic-encoded PS sites is important for the pattern of expression of the transposon-encoded gene. Our studies provide insight into mechanisms that govern expression of exogenously added genes in transgenic organisms. The study of gene expression in transgenic animals helps us understand the expression of foreign genes in human gene therapy.

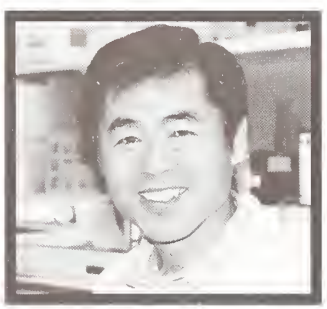
Seldon Morris, *a Public Health Service Scientist at the FDA's Center for Biologics Evaluation and Research, came to CBER from The Johns Hopkins University in 1986.*



My laboratory has concentrated on studies designed to better understand the biology of mycobacteria and the pathogenesis of mycobacterial diseases. One area of interest has been the identification and characterization of mycobacterial proteins that evoke immune responses in infected individuals. We have demonstrated that lipoproteins are among the most immunogenic mycobacterial antigens. By creating a series of overlapping synthetic peptides from mycobacterial lipoproteins, we have identified species-specific epitopes that are recognized by T cells. These peptides could form the basis for immunodiagnostic reagents or components of a multivalent mycobacterial vaccine.

Recently, we have also focused on the molecular mechanisms of drug resistance in *Mycobacterium tuberculosis*. We showed that resistance to streptomycin (SM) is associated with mutations in the gene encoding the ribosomal S-12 protein. Studies of isoniazid (INH) resistance in our laboratory have demonstrated that deletions or specific mutations in the catalase-peroxidase gene confer reduced sensitivity to INH. Using these genetic markers of SM and INH resistance, we found that multiple-drug resistance in some *M. tuberculosis* strains results from an accumulation of independent mutational events. However, because other resistant strains lack the defined mutations, multiple-drug resistance in these organisms must result from different genetic mechanisms. Our laboratory is currently working on defining these alternative mechanisms of multiple-drug resistance.

Sanai Sato *came to NEI in 1984 as a Guest Researcher. He is now a Visiting Scientist at that institute.**



In diabetes, the increased flux of glucose into the polyol pathway results in the accumulation of polyol, or sorbitol, which has a link to the onset of diabetic complications. This has spurred worldwide interest in developing aldose reductase inhibitors as new pharmacological treatments for diabetic complications. All inhibitors now undergoing clinical trials also inhibit another enzyme that is also dependent on NADPH, namely, aldehyde reductase. Our research focuses on distinguishing between the effects of aldehyde and aldose reductases.

In the kidney, aldehyde reductase predominates in the cortex, the site of pathological changes associated with diabetes. Despite the extremely low level of aldose reductase, polyols accumulate in the cortex of both diabetic and galactosemic animals. The generation of aldehyde reductase

continued on page 23.

The Office of Human Subjects Research: Questions and Answers

by Alison Wichman, Director of Education, OHSR

The NIH Intramural Research Program (IRP) has a long and distinguished history of rapidly transferring basic scientific discoveries from the laboratory to the bedside. NIH has an equally long history of establishing ethical safeguards in the conduct of research involving human subjects. In fact, NIH created one of the earliest policies for this research when it opened the Clinical Center 40 years ago. As we celebrate the Clinical Center's anniversary, it is appropriate to acknowledge IRP's guiding principle, that progress in science and medicine must never be achieved by compromising the fundamental rights and welfare of individual research subjects.

The Office of Human Subjects Research (OHSR) was established in 1991 to help develop, coordinate, and oversee IRP's policies and procedures for the protection of human subjects research, consistent with sound ethical standards and regulatory requirements (45 Code of Federal Regulations, or CFR, Part 46, Protection of Human Subjects). Recently, OHSR issued a new brochure that provides information on ethical principles and Federal regulatory requirements for protecting human subjects involved in research and guidelines on NIH policies for intramural investigators. (Brochure available through OHSR; phone: 2-3444.)

Below are some of the most frequently asked questions about OHSR and its policies and procedures.

1. What is the difference between the Office of Human Subjects Research (OHSR) and the Office for Protection from Research Risks (OPRR)?

OHSR is an office within the Office of the Deputy Director for Intramural Research (DDIR), which helps investigators in the IRP understand and comply with ethical guidelines and regulatory requirements for research involving human beings. A major difference between OHSR and OPRR is that OHSR's activities and responsibilities are limited to the IRP, NIH, whereas OPRR is responsible for implementing 45 CFR 46 and for educational activities in all domestic or foreign sites in which DHHS funds are used to conduct research involving human subjects. OPRR is organizationally located within the Office of Extramural Research, NIH.

2. What is the NIH Multiple Project Assurance (MPA)?

The MPA is the IRP's assurance to OPRR that the IRP will conduct all its research activities involving human subjects in accord with the ethical principles of The Belmont Report — Ethical Principles and Guidelines for the Protection of Human Subjects, and of 45 CFR 46. Responsibility for implementing the MPA rests with the DDIR. However, others share this responsibility, including NIH Institute, Center, and Division (ICD) officials; NIH Institutional Review Boards (IRBs); Laboratory, Branch, and Section Chiefs; research investigators, and other research personnel. Each is expected to be familiar with the NIH MPA, which contains the IRP's policies and procedures for the conduct of research with human subjects. For example, the MPA describes the responsibilities of investigators who design and conduct the research, as well as the responsibilities of the NIH's IRBs for its review and approval. Copies of the MPA can be obtained by calling the OHSR.

3. What is the primary responsibility of NIH's IRBs?

The mandate of the IRBs is to protect the rights and safeguard the welfare of human research subjects. IRBs are generally composed of members whose expertise in science and ethics and other nonscientific areas enables them to review protocols from diverse perspectives. NIH has 14 IRBs, including two in the National Cancer Institute and one formed recently at the National Institute of Drug Abuse's Addiction Research Center in Baltimore. IRP investigators conducting or collaborating in research involving humans at NIH or at other domestic or foreign sites must receive approval by an IRB before they begin their research activities.

4. What is an "exemption" from the requirements of the NIH MPA, and what does an investigator need to do to get an exemption?

Six categories of research are exempt from the requirements of the NIH MPA, although they involve human subjects. The rationale behind these exemptions is that although the research involves human subjects, it does not expose them to physical, social, or psychological risks. An example of such research is the study or collection, in certain circumstances, of existing data, documents, records, and pathological or diagnostic specimens. Only OHSR is authorized to determine whether a research activity is exempt from the requirements of the MPA. To find out whether a research activity fits into one of the exempt categories, fill out a form provided by OHSR. OHSR will respond in writing.

5. What responsibilities do investigators have if they plan to collaborate in research that enrolls human subjects at other domestic or international sites?

Collaboration among intramural researchers and others in the United States and abroad is an important activity that NIH supports and promotes. Because such collaborative research activities are subject to the requirements of the NIH MPA, intramural investigators need to be aware of what constitutes "collaboration," and IRB Chairs or OHSR staff will help determine this in unclear cases. Briefly, collaboration exists if the IRP investigator expects "something in return" as a result of having participated in a research activity. "Something in return" could include data, samples, or even patent rights. NIH views authorship as prima facie evidence of collaboration. Other examples of possible collaborative research activities include visits to institutions to perform research or clinical work, exchange of research data containing personal identifiers, and substantive intellectual contributions to research techniques, protocol design, or interpretation of data.

OHSR has Information Sheets on the following subjects. For a copy, call OHSR at 402-3440

Information Sheet #1	Responsibilities of the Office of Human Subjects Research
Information Sheet #2	Institutional Review Board Leadership
Information Sheet #3	Criteria for IRB Approval of Research Involving Human Subjects
Information Sheet #4	Single Project Assurances
Information Sheet #5	Guidelines for Writing Research Protocols
Information Sheet #6	Informed Consent
Information Sheet #7	Research Involving Cognitively Impaired Subjects: A Review of Some Ethical Considerations
Information Sheet #8	Answers to Questions Frequently Asked of NIH's OHSR
Information Sheet #9	Continuing Review of Research Involving Human Subjects
Information Sheet #10	Research Involving Children
Information Sheet #11	Interim Guidance on Research Involving Women and Minorities

6. What is a Single Project Assurance (SPA)?

The requirements of the NIH MPA apply when an intramural investigator collaborates in research activities in which subjects are enrolled at non-NIH sites. If the collaborating institution or site does not have its own MPA, negotiation of an OPRR-approved SPA is necessary to certify review and approval by an on-site IRB. The local IRB review is important, particularly in foreign countries, because institutions often draw from culturally dissimilar subject populations, or are located in places with varying ethical, legal, or regulatory requirements for the protection of human subjects. Guidance on how to negotiate an SPA is available from NIH IRB Chairs or the OHSR.

7. Currently, which issues concerning the conduct of research involving humans are being given special attention in the IRP?

Genetics research raises several ethical considerations, including confidentiality, the publication of pedigrees, and presymptomatic testing for genetic diseases. Another issue receiving special attention at IRP is the inclusion of women and minorities in protocols. The NIH Revitalization Act of 1993 mandates the inclusion of woman and minorities in clinical research, unless their inclusion is inappropriate to their health or the purpose of the research. Guidance on the inclusion of women and minorities in research will be provided to both the intramural and extramural communities in early 1994.

8. What educational activities and materials are available about research with human subjects?

OHSR has Information Sheets on various subjects and has recently released the booklet *Guidelines for the Conduct of Research Involving Human Subjects at the National Institutes of Health*. The Information Sheets and booklet are available upon request from OHSR. Also, members of the OHSR staff are available to conduct or participate in educational activities for groups or individuals. OSHR now designing a self-instructional, computer-based program for IRP staff that should be helpful orienting new research investigators.

If you have any ideas or comments about how OHSR can be more helpful and responsive to your educational and research needs, please contact us by phone at 301-402-3444, by FAX at 301-402-3443, or use the FAXBACK provided in *The Catalyst*. ■

DCRT LAB

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The Molecular Graphics and Simulation Section uses computationally intensive techniques such as molecular dynamics, molecular mechanics/quantum mechanics, and molecular modeling and graphics to study biologically significant problems. Much of MGS's efforts is focused on developing and evaluating new theoretical methods. According to Section Chief Bernie Brooks, "It is clear that the simulation and modeling methods that will be used in the next two decades for solving problems in structural biology and rational drug design do not yet exist in a productive form."

Section Chief Brooks and his coworkers have made significant contributions to the understanding of protein hydration/solvation, the motion of proteins such as Interleukin 1-β, and the structure and function of HIV-1 protease. The group is now beginning studies on another HIV protein, reverse transcriptase.

MGS members also conduct collaborative and independent research on basic phenomena such as the temperature dependence of protein behavior and the dynamic properties of different lipid phases. They support and encourage the use of scientific computing as a research tool and offer courses and a seminar series. Resources for macromolecular simulation, modeling, movie making, generation of publication-quality molecular graphics, and physical models are provided by the section. For example, MGS offers a version of CHARMM that can be run on a cluster of inexpensive Hewlett-Packard workstations, using the algorithms previously developed for the Intel supercomputer. CHARMM is widely used on campus for modeling molecular structures and analyzing equilibrium and dynamic properties of macromolecular systems.

Peter Munson, chief of the Analytical Biostatistics Section, has devoted his career to making mathematical modeling understandable and accessible to the bench scientist. An outgrowth of many of these method-development projects has been a series of computer programs for bench scientists. Notable among

continued on page 23.

FIVE DAYS AT THE 1993 NIH RESEARCH FESTIVAL

by Seema Kumar

Anyone who came to NIH's Bethesda campus during the week of September 20 could not have helped but sense that something different was happening here that week. For one, finding a parking space was even more difficult than usual — if that is possible — but more, the air was thick with excitement as groups of researchers shuttled across campus to take in lectures, attend workshops, and browse through aisles of posters.

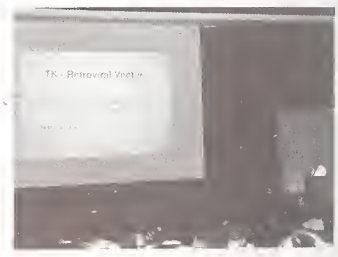
It was time, once again, for the annual NIH Research Festival — a week celebrating scientific exchange and collaboration, a time to bring out the research goods and show them off to campus colleagues. The 1993 organizing committee, chaired by NINDS Scientific Director Irwin Kopin, selected molecular medicine as the theme for this year's festival. Also this year, for the first time in the festival's 7-year history, 29 researchers received awards for their posters: $500 for travel to the scientific meeting of their choice (see box).

We attempted to capture the spirit of the festival with our Olympus, and in the spread below, we bring you some of the highlights.

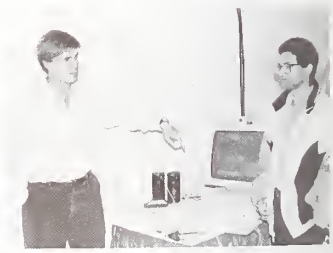
The 1993 research festival was kicked off on Monday, Sep. 20, by the NIDDK Distinguished Alumni Symposium, "Contributions of Basic Science to Biomedical Research." Several ex-NIDDK scientists, including Nobelist Arthur Kornberg of the Stanford University School of Medicine in Stanford, Calif., presented their research. Elizabeth Neufeld of the University of California at Los Angeles School of Medicine received the Distinguished Alumna Award for her contributions to understanding Hurler syndrome.

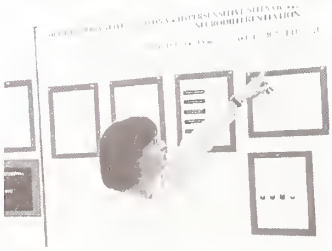
Above, NIDDK Director Phillip Gorden presents the award to Neufeld. "To receive an award from one's own institution ... is much better than many other awards," said Neufeld.

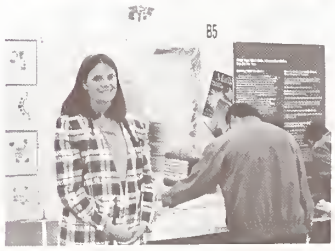
It was hard to get into the packed Masur Auditorium for Monday afternoon's session on "Clinical Applications of Gene Therapy," co-chaired by Deputy Director for Intramural Research Lance Liotta and Kopin. NCHGR Director Francis Collins could not speak as scheduled at 2:30 p.m. because of an NCHGR Advisory Council Meeting but did appear at 5:00. "Everything except trauma has a genetic basis," said Collins, stressing the importance of gene therapy in disease prevention and control. The crowd, gathered to listen to Collins' presentation, instead heard Melissa Rosenfeld discuss gene therapy for cystic fibrosis, followed by NHLBI's Cynthia Dunbar, NINDS's Edward Oldfield, and NCI's Craig Mullen and Steve Rosenberg.

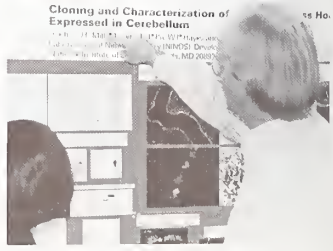


On Monday and Tuesday, intramural scientists, including postdoctoral fellows (M.Y. Degtyarev, NIDDK, top left; Roberta Carbone, NICHD, bottom left), fellows of the Office of Education's Clinical Residents Research Program (top center), and research support groups, such as the NIH information office (Constance Raab, NIAMS, bottom center) and DCRT (top right), presented posters and demonstrations under the festival tents in parking lot 10-D. Bottom right, Bill Hayes, who won one of the $500 poster awards, explains "Cloning and Characterization of a Rat LIM-Class Homeobox Gene Expressed in Cerebellum."









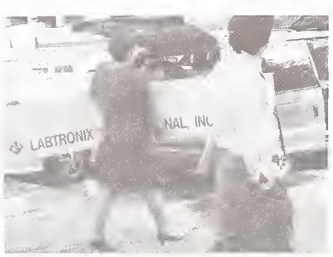
On Tuesday, the symposia continued with the morning session at Masur, "Transcriptional Control," and the afternoon session at Lipsett, "Cellular and Functional Imaging." Also on Tuesday afternoon and throughout Wednesday, 46 workshops at various locations on campus featured topics ranging from apoptosis to genome-mapping and -sequencing, free radicals, and transgenic systems.

Above, Nitin Gogate of NINDS presents his work on pre-oligodendrocytes and oligodendrocytes in human brain at the "Glial Cells" workshop, chaired by Joan Schwartz, NINDS, and Vittorio Gallo, NICHD.

Above, Scheherazade Sadegh-Nasseri of NIAID talks about her work on kinetic and structural analysis of how the major histocompatibility complex (MHC) class II molecules work at the "Peptides and MHC molecules" workshop chaired by William Biddison, NINDS, and David Margulies, NIAID.

On Thursday and Friday, Sep. 23 and 24, the final two days of the festival, the Technical Sales Association (TSA) put on its scientific-equipment show, also under the tents in parking lot 10-D. Some 300 different companies from the United States and Canada showed off their latest wares, including a broad selection of reagents, instruments and products. The show is the largest on-site exhibit sponsored for the biomedical research community in the U.S. The event has raised more than $80,000 for the Children's Inn at NIH over the past four years.

The 1993 Research Festival concluded Friday afternoon. By 4:00 p.m., the presenters at the TSA equipment show had packed up their goods and left NIH ... 'til next year.



First Research Festival Fellows' Awards Make A Surprise Debut

by Celia Hooper

After their posters came down and the tents were folded up, 29 NIH Fellows got an unexpected reward: $500 in travel money to attend the scientific conference of their choice.

The Fellows were recipients of the first Research Festival Fellows' Awards. The windfall prizes took everyone by surprise—including members of the Office of Intramural Research who proposed the awards.

Last spring, OIR requested money from the Office of the Director to fund prizes for outstanding work presented at the Research Festival. Suddenly, at the very end of fiscal year 1993—just days before the Research Festival—the money became available. With no time to publicize the awards or arrange for an elaborate jury system for judging the Fellows' work, Lance Liotta, Deputy Director for Intramural Research, made a quick deal with NIH's Scientific Directors: The SDs would nominate three to four of their best Fellows presenting posters in the festival. Liotta rounded up a handful of senior scientists on the days of the festival to rank the nominated posters. The Fellows who authored the top 29 posters will have $500 deposited in their research accounts to cover travel sometime before next year's festival.

Fogarty Visiting Fellow Colin Hodgkinson won a prize for coauthoring the poster, "The microphthalmus locus encodes a novel basic helix-loop-helix leucine zipper protein related to the MYC supergene family." Hodgkinson says the unanticipated money will definitely be useful. "I didn't know there were any prizes," Hodgkinson says. The NINDS Fellow says he and his colleagues are just pushing into a new phase of their research and he hasn't had time yet to figure out what conference he will attend with the money.

Liotta hopes funding for the awards will be continued in the years ahead—preferably with a little more time for planning and advertising. "From the feedback I've gotten, these awards were a smashing success," says Liotta. "At a time of fiscal restraint, they allow us to recognize our talented Fellows—they're the future of biomedical research. I'm glad we could do it." ■

Winners of the 1993 NIH Research Festival Fellows Award

Name	Title and Nominator
Y. Kim	Transcriptional activation domain of the *Drosophila* NK-1 homeodomain protein. [Korn]
Y. Kim	NKX-1, a mouse homeobox gene expressed in part of the nervous system and mesoderm. [Korn]
W. Hayes	Certain forebrain nuclei may arise from pre-patterns of LIM-class homeobox gene expression in *Xenopus* neurulae and tailbud embryos. [Guroff (Acting SD, NICHD)]
M. Morasso	Homeoboxes in *Xenopus* epidermis. [Guroff (Acting SD, NICHD)]
B. Peters	A silencer upstream of the epsilon globin gene mediates positive and negative regulation of epsilon globin gene expression. [Multiple authors; nominated by Spiegel]
M. Kim	Functional cooperation between the pituitary-specific factor Pit-1 and an AP-1 (-like) factor for the induction of the human thyrotropin beta gene expression. [Multiple authors; nominated by Spiegel]
J. Bishop	Alternate 5' exons of the rat BDNF gene: Brain region-specific patterns of expression. [Multiple authors; nominated by Kopin]
O. Studitskaia	A rapid method for cloning mutagenic DNA repair genes. [Guroff (Acting SD, NICHD)]
S. Kyostio	Negative regulation of adeno-associated virus p5 and p19 expression by Rep78 and Rep68 proteins. [Multiple authors; nominated by Spiegel]
M. Eckhaus	Ultrastructural pathology of nephropathy in transgenic mice containing a partial HIV-1 genome. [Vaitukaitis]
C. Hodgkinson	The microphthalmis locus encodes a novel basic helix-loop-helix leucine zipper protein related to the MYC supergene family. [Multiple authors; nominated by Kopin]
C. Hollander	DNA damage responsiveness and sequence conservation of the mammalian gadd45 gene. [Chabner]
S. Zullo	Fluorescent in-situ hybridization (FISH) analysis of microsatellite repeats in the human genome. [Kirch]
C. Felder	Anandamide, an endogenous canabinoid, binds to the cloned human cannabinoid receptor and stimulates receptor-mediated signal transduction. [Pickens]
W. Devane	Metabolic studies of anandamide, an endogenous cannabinoid ligand. [Kirch]
V. Gordon	Characterization of multiple proteases that activate bacterial toxins in wild-type and protease-deficient CHO cells. [Mergenhagen]
T. Lockwich	Ca2+ entry in parotid acinar cells. [Mergenhagen]
K. Isaacs	Colocalization of calretinin, calbindin and tyrosine hydroxylase in the substantia nigra. [Kirch]
C. Wiese	Structural characterization of murine MyTI, a zinc finger gene expressed in the oligodendrocyte lineage. [Multiple authors nominated by Kopin]
D. Dichek	Localized in vivo adenoviral-mediated gene transfer via a catheter-based system. [Korn]
C. Kappel	Human osteosarcomas depend upon the insulin-like growth factor-I receptor for growth. [Chabner]
A. Fujimori	DNA topoisomerase I mutation at the enzyme catalytic site in a human leukemia cell line resistant to camptothecin. [Chabner]
P. Fleming	Synthetic studies directed towards 18F labeled CP 55,244, a potential ligand for imaging cannabinoid receptors. [Pickens]
S-L. Lin	An efficient computer-vision based technique for protein structural comparisons and biomolecular recognition. [Rabson]
S-Y. Le	RNA structural motifs and mediation of translational control. [Rabson]
S. Leikin	Assembly of collagen fibers. [Rodbard]
Y. Wang	Regulation of insulin, hexokinase-1, and glut-1 mRNA levels in insulin secreting cells (Rin 1046-38) by GLP-1. [Martin]
H. Steiner	Dynorphin regulates c-fos and zif268 gene induction by cocaine in striatal neurons. [Pickens]
G. Westergaard	The use and modification of stone tools by capuchin monkeys *(Cebus apella)*. [Guroff (Acting SD, NICHD)] ■

FAES MAY GAIN NEW LIFE THROUGH MERGER WITH NFBR

by Seema Kumar

For 35 years, the Foundation for Advanced Education in the Sciences (FAES) has stood by as NIH's avuncular friend — a nonprofit organization that receives nongovernmental money and uses it to fund fellowships, grants, awards, and educational programs at NIH. On June 30, President Clinton signed legislation that may allow FAES to become a more official part of the NIH family.

Lois Kochanski is the Executive Director of FAES.

The new act broadened the mission of the National Foundation for Biomedical Research (NFBR), a nonprofit corporation to support the NIH mission "and to advance collaboration with biomedical researchers from universities, industry, and nonprofit organizations." Previously, NFBR's only designed function was to administer endowed positions, although it never became operational. Now, NFBR could absorb all of FAES' traditional and current activities, including its graduate programs, bookstore, lectureships, fellowships, and grants. Under the aegis of NFBR, FAES' historic activities could be on sound statutory ground and operate free of potential conflicts of interest for NIH scientists involved in these activities. If and when the merger is completed, NFBR will subsume FAES.

"It is very exciting that [we have] an opportunity to restore some of our activity ... and the vitality we had known in the past," says Lois Kochanski, Executive Director of FAES. "We are hoping ... that with this legislation, [FAES and NFBR] can join forces and move forward together in the best interest of the scientific community, both in accomplishing the main objective of [NFBR] — the endowed chairs — and all of [FAES'] activities."

In particular, FAES hopes to restructure its currently inactive grants program, used to support intramural research at NIH. Among NFBR's plans are several endowed chairs, designed to attract and retain top biomedical researchers at NIH.

FAES has a long history at NIH. It was organized in the early 1950s by a group of NIH scientists who saw an FAES curriculum as a way to supplement laboratory training with advanced coursework. The program grew rapidly and prompted the creation of an extragovernmental framework to administer the courses and other activities. In 1959, FAES was incorporated as a nonprofit organization "to foster and encourage scientific research and education, and to facilitate communication among scientists."

In the ensuing years, FAES' list of services grew to include academic programs, community and minority educational programs, cooperative Ph.D. programs with local universities, cultural programs, a bookstore, fellowships, grants, awards, lectureships, and a health insurance program. NIH scientists were closely involved in many activities, serving on boards and as contacts for outside grants administered by FAES.

But two years ago, HHS lawyers became concerned that some of FAES' activities created at least the appearance of conflicts of interest for NIH employees involved in these activities and that some of the activities might be inconsistent with Federal statutes and regulations. They questioned whether NIH employees should serve as officers or directors of FAES; whether there could be contacts between NIH scientists and potential FAES donors whose money might ultimately support NIH research activities; FAES' role as a fiscal agent for grants from private donors to support research in NIH laboratories; FAES' eligibility for obtaining small-business privileges and concessions, including operating a bookstore on NIH premises for the benefit of NIH and its employees; and certain fundraising activities.

"When the conflict-of-interest matter was brought up, some of our programs [were] cut back, ... FAES [suffered] a loss of morale, and we felt that our standing was tarnished at NIH," says Kochanski. FAES and NIH staff agreed that legislation was needed.

The new legislation came in the form of an amendment to the statutes enacted in 1990 NIH Amendments that originally established NFBR to solicit and administer outside funds for endowed chairs. NFBR, as contemplated in the 1990 legislation, has remained dormant. The 1993 amendment revives NFBR's original goal but also

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Possible Programs and Activities of the new NFBR, Including Current FAES Programs

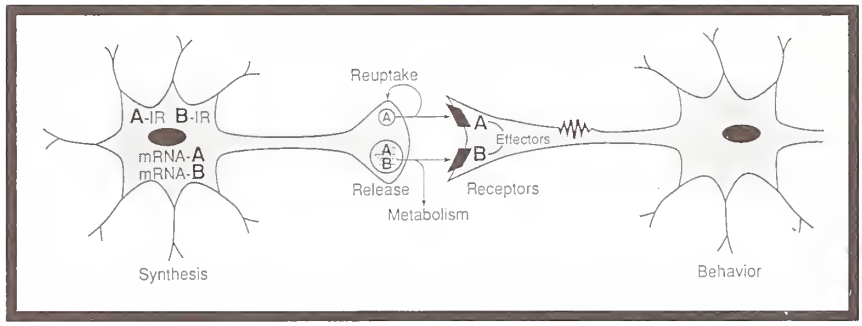
- An endowed-chairs program that will solicit and administer outside funds to support research ventures at NIH.
- Academic programs, including daytime biotechnology courses and laboratory instruction and evening classes on topics ranging from recombinant DNA technology and biochemistry to statistics. Many of the programs are accredited and allow students to obtain continuing medical education credits (Category I of the Physician's Recognition Award of the American Medical Association) and college credits.
- Community and minority science education programs including biotechnology courses for students and teachers from historically black universities throughout the United States.
- Cooperative Ph.D. programs with Johns Hopkins University and the University of Maryland in biochemistry, physics, and chemical physics.
- Cultural programs including a chamber music series and display of an art collection throughout NIH.
- A bookstore, located in Building 10, Room B1-L101, that supplies textbooks for FAES courses and other biomedical science publications .
- A fellowship program that solicits and administers funds from private donors to support intramural research at NIH.
- Awards, memorial funds, and a lecture series covering a broad range of cultural, historical, and philosophical subjects of relevance to the NIH community.
- A health insurance program to provide health coverage for the large number of visiting fellows and guest workers at NIH who are not eligible for federal benefits.
- A Social and Academic Center, located at the corner of Cedar Lane and Old Georgetown Road, designed to serve as a center for scientific and social interaction. Kochanski says the center is currently underutilized, except during the holiday season, when scheduling gets very tight. ■

Coexistence of Neuropeptides with Classical Neurotransmitters

Jacqueline N. Crawley, Ph.D., Chief, Section on Behavioral Neuropharmacology, Experimental Therapeutics Branch, NIMH

Neurotransmitters mediate synaptic transmission in the nervous system. As classically described, neurotransmitters are synthesized in a neuron, stored in synaptic vesicles at the axon terminal, and released into the synaptic cleft by depolarizing stimuli, where they activate a receptor on a second neuron, initiating a postsynaptic physiological event. Until the 1970s, only a small number of neurotransmitters were known, including acetylcholine, glutamate, γ-amino butyric acid, norepinephrine, epinephrine, dopamine, and serotonin. With the advent of highly specific radioimmunoassays and immunocytochemistry 20 years ago, a new class of neurotransmitters, the neuropeptides, was discovered in the mammalian central nervous system. From two to 60 amino acids long, these peptides — which now number at least 50 — appear to satisfy many of the classic criteria for neurotransmitters.

Most remarkable was the discovery of coexistence, the occurrence of a neuropeptide within the same neuron as a "classical" neurotransmitter (Fig. 1). Immunohistochemical mapping using double-labeling techniques demonstrated peptides within the same cell bodies and axons, and electron microscopy demonstrated peptides within the same large, dense-core synaptic vesicles, that bear the well-known transmitters. The great Swedish neuroanatomist Tomas Hökfelt, describing the phenomenon of coexistence as a new principle in neuroscience, finds that two or more transmitters per neuron is the rule, rather than the exception (1).



Classical neurotransmitter A and neuropeptide B, coexisting in a neuronal pathway.

If two, three, or more chemicals are released from the same neuron, each with its own postsynaptic receptor, the question becomes, who is in charge? Is the classical transmitter the primary synaptic signaler, with the coexisting neuropeptide serving a minor modulatory function? Or is the peptide also a primary transmitter, acting independently at its own receptor? Is the neuropeptide released only under unusual circumstances, thereby conveying unique information? Could the peptide serve another type of function, perhaps regulating neuronal development or recovery from injury? As the anatomical picture develops, there is a growing need for functional studies of neuropeptides in action.

Our laboratory investigates the behavioral actions of neuropeptides, particularly where they coexist with neurotransmitters in brain pathways relevant to neuropsychiatric disorders. We use simple animal behavior paradigms, well-characterized for the effects of the classical transmitter in the pathway, to determine whether the coexisting peptide mimics, inhibits, or modulates the action of the classical transmitter. Two examples illustrate some of the ways in which coexisting neuropeptides act in vivo.

Cholecystokinin and Dopamine

Dopamine (DA) is a catecholamine found in the mammalian midbrain in two parallel systems: the nigrostriatal pathway, which degenerates in Parkinson's disease, and the mesocorticolimbic pathway, thought to be involved in schizophrenia. Cholecystokinin (CCK) is a peptide eight amino acids long, known as a gastrointestinal hormone. CCK coexists with dopamine in ventral tegmental neurons of the mesocorticolimbic pathway — specifically, in axons projecting to the medial posterior nucleus accumbens (2), an anatomical subdivision termed the shell of the accumbens.

We started our functional studies of the CCK-DA coexistence by using a standard behavioral paradigm, DA-induced hyperlocomotion. Exploratory locomotion of rats, measured in an automated photocell-equipped open field, is increased by microinjection of dopamine into the nucleus accumbens or by systemic administration of dopaminergic agonists, amphetamine, or cocaine. When microinjected into the shell of the accumbens, CCK alone has no effect on exploratory locomotion, over a wide dose range (3). But when microinjected into this region with DA, picogram doses of CCK potentiate DA-induced hyperlocomotion (3). When microinjected into the anterior nucleus accumbens or into the caudate nucleus — regions that contain CCK but not DA — CCK has no effect alone or in combination with DA, and it has no effect on inhibited, DA-induced hyperlocomotion (4).

CCK potentiates the release of DA in the shell of the accumbens, but inhibits DA release in the anterior nucleus accumbens (7). Researchers in other laboratories who are using two other dopamine-mediated behaviors —amphetamine-induced hyperlocomotion and self-stimulation of the ventral tegmentum — have also found that CCK again induces opposite effects in the anterior and medial posterior nucleus accumbens (5,6). These findings indicate that CCK is a facilitative modulator of DA in the mesolimbic terminal field in which CCK and DA coexist.

Two subtypes of CCK receptors are known in the brain (8). Using recently developed CCK antagonists that are selective for the two subtypes of the CCK receptor, behavioral and physiological experiments confirmed that the facilitative actions of CCK in the posterior medial nucleus accumbens are mediated by the CCK-A receptor subtype, whereas the inhibitory actions of CCK in the anterior nucleus accumbens are mediated by the CCK-B receptor subtype (7,9). We are now studying these potent, selective, nonpeptide CCK antagonists, which cross the blood-brain barrier, as potential candidates for the treatment of neuropsychiatric disorders, such as schizophrenia, that result from dysfunctions of the mesolimbic dopamine pathway.

Galanin and Acetylcholine

In the mammalian basal forebrain, acetylcholine (ACH) is the transmitter found in the nucleus basalis of Meynert neurons, which project throughout the cerebral cortex, and in the medial septum and diagonal-band neurons, which project to the hippocampus. Neurons in these pathways are involved in learning and memory, and they degenerate early in the progression of

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Tissue Inhibitor of Metalloproteinases-2 (TIMP-2): A Multifunctional Inhibitor of Tumor Invasion and Angiogenesis

by William G. Stetler-Stevenson, M.D., Ph.D.
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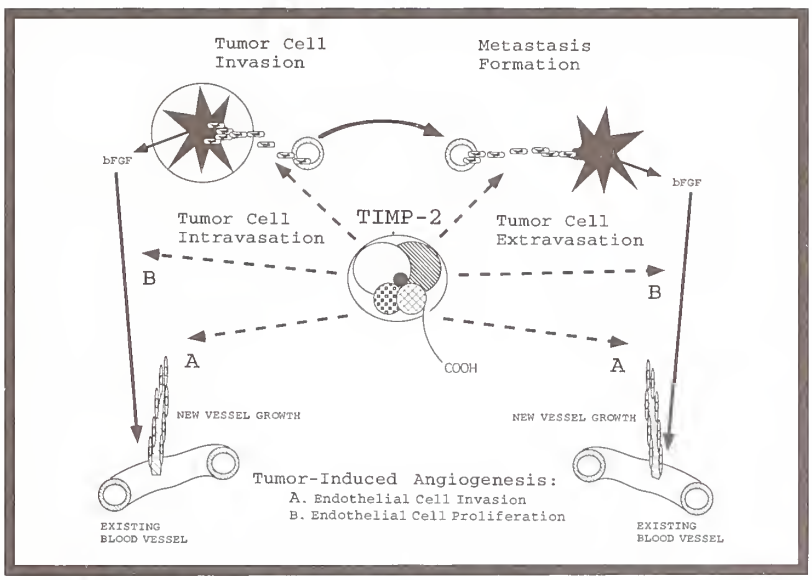
The remodeling of extracellular matrix (ECM) occurs during many biological processes, both physiological and pathological. Matrix turnover associated with physiological processes—such as ovulation, oocyte fertilization, and placental development—tends to be highly regulated, and a functional extracellular matrix with intact and well-defined matrix boundaries is retained during physiological processes. In contrast, remodeling in many pathological conditions impairs matrix function or organization and damages matrix boundaries. Examples of such pathological conditions include inflammatory collagen vascular diseases, such as rheumatoid arthritis, and a variety of other conditions ranging from granuloma formation to neoplastic cell invasion.

The spectrum of extracellular-matrix remodeling may also be viewed in terms of the spatial extent and the nature of the remodeling process. For example, in some processes, there is extensive tissue destruction and reorganization. This may occur in both physiological and pathological circumstances, such as postpartum uterine remodeling and osteoarthritis. In other conditions, such as neurite outgrowth or tumor-cell invasion, degradation of the extracellular matrix occurs only in the immediate pericellular milieu and is coupled with cell migration to produce an invasive cellular phenotype. Excessive matrix degradation would inhibit these processes by interfering with the matrix attachment needed for traction during cellular migration. Thus, the matrix remodeling and turnover associated with cell invasion have spatial and temporal constraints that differ from those governing processes with more-extensive matrix destruction. The objective of our lab is to understand how matrix degradation is regulated in these various processes. This understanding may allow selective disruption of destructive pathological conditions while normal physiologic functions are preserved.



Many biological processes involving ECM turnover have been linked with expression of matrix metalloproteinase enzymes. The matrix metalloproteinases are a family of zinc - atom - dependent endopeptidases with specific and selective activities against many components of the extracellular matrix (1,2). This family currently consists of nine enzymes, which are secreted as zymogens that must be activated extracellularly and which are separated into three subgroups based on substrate preference: the interstitial collagenases, stromelysins, and gelatinases (type IV collagenases).

The matrix metalloproteinase family of enzymes is further defined by the fact that all members are inhibited by a group of related endogenous inhibitors known as the tissue inhibitors of metalloproteinases (TIMPs) (1,2). TIMP-1 and TIMP-2 have been isolated, cloned, and characterized from several species. Comparison of the human TIMP-1 and TIMP-2 amino acid sequences shows 66% homology. However, both inhibitors are highly conserved (greater than 95% identity) across several species. TIMP-3 has been cloned from chick embryo fibroblasts transformed by rous sarcoma virus (3), but the sequence for mammalian TIMP-3 has not yet been reported. These inhibitors each have 12 cysteine residues that are highly conserved and internally bonded to form six disulfide loops (4). The matrix metalloproteinase inhibitory activity of both TIMP-1 and TIMP-2 is dependent on intact disulfide loops and appears to reside within the three N-terminal loops in both inhibitors. Inhibition occurs through formation of 1:1 stoichiometric complexes between the TIMPs and activated matrix metalloproteinases.

The role of matrix metalloproteinases in ECM degradation can be regulated at many stages, including gene activation and transcription, mRNA stability, translation and secretion of latent proenzymes, binding of proenzymes to cell membranes and/or ECM components, proenzyme activation, inactivation by endogenous inhibitors, and degradation or removal of active or inactive enzyme species. Although transcriptional activation of these protease genes may be a requirement for ECM turnover in some conditions, current evidence suggests that this is not sufficient. Activation of proenzyme forms of these proteases is required for initiation of matrix degradation, and the balance of activated proteases and endogenous inhibitors is crucial for determining the extent of ECM turnover (1,2). We have focused on the regulation of matrix metalloproteinase activity during the invasive processes of neoplastic cell infiltration and angiogenesis. Ultimately, we wish to determine whether manipulation of the critical balance between active proteases and TIMPs might be exploited therapeutically to block tumor-cell invasion, metastasis, and the tumor-associated neoangiogenesis that fosters tumor growth and metastasis.

Tumor-cell invasion and angiogenesis share several functional similarities. Initiation of cellular invasion in both processes requires attachment to a basement membrane, followed by creation of a proteolytic defect in the basement membrane and migration through this defect. After the invading cell crosses this connective-tissue barrier, cell proliferation and continued invasive behavior result in production of either a new vessel lumen or metastatic foci.

In addition to sharing these functional similarities, angiogenesis and tumorigenesis may be mutually stimulatory. Formation of new blood vessels is permissive for expansion of tumor foci in three dimensions (5). Before vascularization, tumor foci exist as small asymptomatic lesions restricted by the limitation of passive oxygen and nutrient diffusion. After vascularization, the tumor

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NEUROPEPTIDES

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Alzheimer's disease. Galanin (GAL) is a 29-amino acid peptide that coexists with ACH in the basal forebrain neurons in primates (10). In rats, the GAL-ACH coexistence is seen in the septohippocampal pathway (11), which is essential for performance of the spatial memory tasks at which rats excel. Functional studies of the GAL-ACH coexistence performed by our lab and others demonstrate that GAL impairs working memory when administered into the lateral ventricles, medial septum, or hippocampus (12-15). These functional studies of the rat's spatial memory include the delayed-alternation T-maze, the Morris water maze, the sunburst maze, and the delayed nonmatching-to-sample operant task. We also found that lower doses of GAL induce performance deficits when cholinergic transmission is compromised, as occurs during treatment with scopolamine (an antagonist of the muscarinic ACH receptor), or after basal forebrain lesions that model the neuronal loss characteristic of Alzheimer's disease (16,17). Biochemical analyses show that GAL inhibits the release of ACH (18), and that GAL inhibits phosphatidyl inositol hydrolysis stimulated by the cholinergic agonist, carbachol (19). These data indicate that GAL is an inhibitory modulator of ACH in the septohippocampal pathway. Post-mortem studies report that GAL is present in higher concentrations in the region of the nucleus basalis of Meynert of Alzheimer's victims than it is in age-matched controls or in people who have died with Down's syndrome (20). The first GAL receptor antagonists — chimeric peptides based on the active N-terminal amino acids of GAL — have been developed by Tamas Bartfai and coworkers at the University of Stockholm (21), and are now being studied in our rodent-memory paradigms. If a GAL antagonist improves performance or ameliorates the memory deficits induced by lesions of the cholinergic pathways in the animal studies, then a GAL antagonist alone or in combination with a cholinergic agonist might be a treatment for symptoms of Alzheimer's disease.

Future Directions

Neuroscientists are also discovering direct actions of endogenous neuropeptides in current experiments with new peptide-receptor antagonists. These studies have revealed primary roles for substance P in pain transmission (22), for corticotropin-releasing factor in stress responses (23), and for neuropeptide Y in feeding (24). Coexistences, therefore, appear to come in many flavors, with some peptides acting alone, while others modulate, potentiate, or inhibit classical neurotransmitters. Functional studies on each coexistence are required to determine the physiological and behavioral roles of the endogenous peptide. Right now, neuropeptide transmitters appear to be second-order modulators that may "fine-tune" the function of neural networks and may provide a novel avenue for the development of psychotherapeutic drugs. ■

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TISSUE INHIBATOR
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foci undergo rapid local expansion and acquire enhanced metastatic potential that correlates directly with the degree of vascularization of the primary tumor (6). Thus, tumor invasion and metastasis formation are closely linked to tumor-induced neoangiogenesis.

Abundant evidence, both correlative and direct, implicates matrix metalloproteinases in the creation of the proteolytic defect in basement-membrane type IV collagen that is essential for cellular invasion (2). This evidence strongly supports a specific role for gelatinase A in most human tumors studied. Numerous studies correlate low TIMP expression with enhanced invasive and metastatic properties in several murine and human tumor-cell lines.

Direct demonstration of the role of matrix metalloproteinases comes from studies in which we have used both TIMP-2 and antibodies to gelatinase A to neutralize invasion across reconstituted basement membranes in vitro (7). Unpublished studies from our laboratory demonstrate that nanomolar concentrations of TIMP-2 will block the angiogenic response to basic fibroblast growth factor (bFGF), a principal angiogenic cytokine produced by vascularized human tumors, in the chick chorioallantoic-membrane assay. TIMP-1 has also been shown to inhibit angiogenesis in vitro.

Recently, in collaboration with Schnapper et al. (8), we demonstrated the critical nature of the balance of matrix metalloproteinases and TIMPs in an in vitro model of angiogenesis. These experiments show that addition of exogenous TIMPs inhibits the formation of endothelial cell tubes on the reconstituted basement-membrane matrix. This effect was mimicked by the addition of antibodies that neutralized gelatinase A. Up to a certain point, increasing concentrations of exogenous gelatinase A result in an enhancement of tube formation that is inhibited by addition of TIMP-2. However, the addition of excess activated gelatinase A beyond a critical concentration resulted in a decrease in tube formation that was reversed by addition of TIMP-2. These results suggest that the early stages of endothelial-tube formation are dependent on a critical balance of active protease, gelatinase A, and inhibitor, TIMP-2. Excess protease activity, although initially stimulatory, becomes inhibitory at higher concentrations, and the protease inhibitor, TIMP-2, can reverse this effect.

These results demonstrate the critical nature of the balance between active protease and protease inhibitor, and they show that the balance can be altered by addition of exogenous protease inhibitors to block both endothelial-cell invasion in angiogenesis and tumor-cell invasion in metastasis. This suggests that matrix metalloproteinase inhibitors, particularly gelatinase A-specific inhibitors, may have dual potential for clinical prevention of tumor-cell dissemination and tumor-associated neovascularization.

Although the mechanism for TIMP-mediated inhibition of tumor invasion and angiogenesis appears, at least in part, to be through inhibition of protease activity required for cellular invasion, recent observations suggest that TIMPs affect another distinct group of biological activities through mechanisms other than metalloproteinase inhibition. These include biological activities required for angiogenesis and tumor-cell invasion. In fact, TIMP-1 was independently identified and cloned as the agent responsible for erythroid-potentiating activity (EPA) (9). TIMP-1/EPA augments the formation of red blood cell colonies by erythroid precursors (CFU-E and BFU-E), and TIMP-2 was shown to have similar activity (10). The growth-stimulatory activity in these assays is thought to be due to a direct cellular effect mediated by a cell-surface receptor and not through inhibition of metalloproteinase activity, although the precise mechanism is not yet known. Recently, several labs reported growth-stimulatory effects of TIMPs on several cell lines in vitro (11, 12). Again, the mechanism of these effects and the requirement for metalloprotease inhibitory activity are unknown.

We recently demonstrated a novel growth-inhibiting activity of TIMP-2 that is unique to this inhibitor and independent of its metalloproteinase-inhibiting activity. A cartilage-derived inhibitor (CDI) of angiogenesis inhibits angiogenesis in the chick chorioallantoic-membrane assay. However, CDI also inhibits in vitro endothelial-cell proliferation and migration (14). The amino acid sequence of this inhibitor identifies it as a TIMP-like protein (14) and suggests that TIMPs may block angiogenesis by mechanisms other than direct inhibition of matrix degradation. We recently studied the ability of TIMP-1 and TIMP-2 to inhibit endothelial cell growth in vitro, and we found that TIMP-2—but not TIMP-1—specifically inhibits the proliferation of human microvascular endothelial cells stimulated with bFGF (13). Also, a synthetic metalloproteinase inhibitor, BB94, effective at nanomolar concentrations, did not mimic the inhibitory effect of TIMP-2 on endothelial-cell proliferation. Thus, the ability of TIMP-2 to block bFGF-stimulated microvascular endothelial-cell growth is apparently not due to inhibition of matrix metalloproteinase activity. This is the first demonstration that TIMP-2 has growth-inhibitory properties that are unrelated to protease-inhibitory activity.

Our recent findings suggest that, in addition to directly blocking tumor-cell and endothelial-cell invasion, TIMP-2 can also block bFGF-stimulated endothelial-cell growth. This further suggests that TIMP-2 may have several activities that could be exploited in the oncology clinic: blocking primary tumor growth through inhibition of bFGF-stimulated angiogenesis, as well as preventing matrix degradation necessary for cellular invasion, thus blocking infiltration of the primary tumor mass by new blood vessels and tumor-cell dissemination. Preliminary studies have identified specific and saturable TIMP-2 binding to cells in culture (M. Buck, H. Emmonard, and W. Stetler-Stevenson, unpublished observations). Isolation and further characterization of this receptor will indicate whether the TIMP-2 receptor is similar to the previously characterized EPA/TIMP-1 receptor (15). Preparation and expression of chimeric and mutant TIMP molecules as well as mutagenesis experiments should reveal the domains responsible for TIMP metalloproteinase-inhibiting activity and whether or not these are also involved in endothelial-growth inhibition or erythroid-potentiating activity. The nature of the differential response of various cell lines to free TIMP-1 and TIMP-2 is also of interest.

We are investigating the effects of TIMPs on other processes related to cellular invasion, including cell attachment and cell migration. Preclinical investigations of the in vivo effects of TIMPs and high-potency, synthetic matrix metalloproteinase inhibitors on ECM turnover during angiogenesis and tumor-cell-invasion are under way. Preliminary findings suggest that TIMP-2 may block the angiogenic response induced by media conditioned

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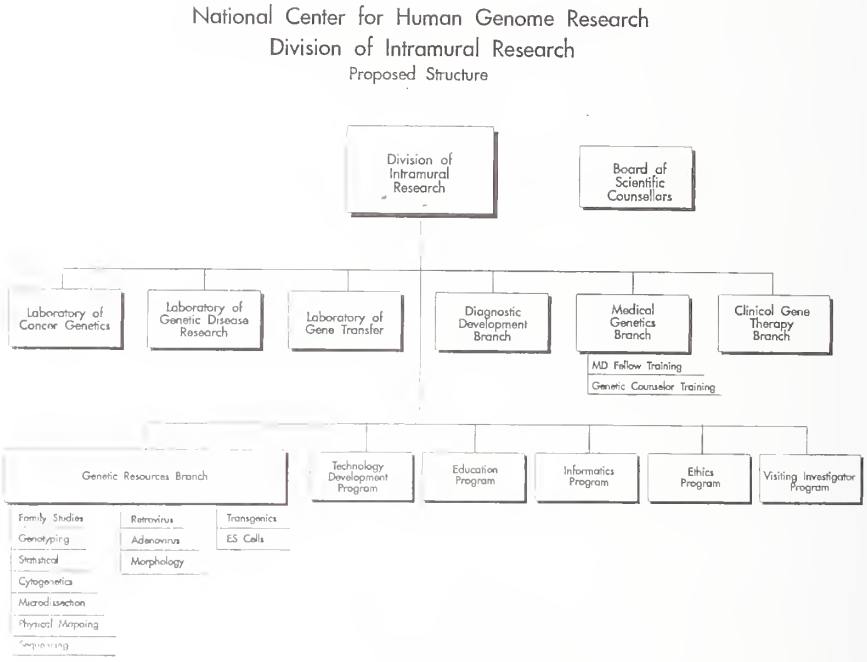
NCHGR'S INTRAMURAL GENETICS
continued from page 1.

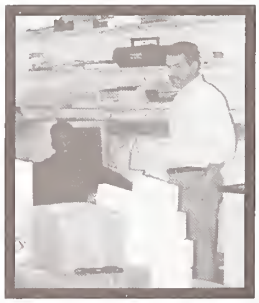
"Our people come from academic backgrounds where collaborative research is the rule—they have a cross-disciplinary mentality. I would like to see genetics at NIH become blind to institutional affiliation."

In keeping with the goal of making NCHGR a hub of collaborative efforts, a primary emphasis in the structure and staffing of the new institute has been on techniques. Collins says that historically, "genetics has been strongly represented here [at NIH], but the things [that the NCHGR's intramural program is] doing have not been available before." NCHGR's young staff brings to the intramural program "approaches involving large units of DNA, such as YACs [yeast artificial chromosomes], and micromanipulation of chromosomal regions contributing to diseases," says Collins.

"Working with these techniques is labor-intensive and pretty daunting for a single investigator without some help. We want to provide that help," says Collins. He and Trent designed one of NCHGR's four branches, the Genetic Resources Branch, as a collection of 12 core facilities, each specializing in one of the labor-intensive techniques. The cytogenetics core, for example, will perform fluorescent in situ hybridization (FISH), a technique that pins brightly colored fluorescent dots to particular DNA sequences for which a researcher is "fishing." The physical-mapping core will be home to NCHGR's YAC pack. Scientists in the retrovirus and adenovirus cores will develop gene-transfer vectors that could be used in gene therapy, while their colleagues in the embryonic-stem-cells core will create "knockout" mice in which the function of selected genes is eliminated. Trent says he expects that all the core facilities will be up and running by the end of the year. He and Collins envision several types of possible arrangements for collaboration with intramural researchers, ranging from conducting on-site techniques tutorials and lab visits to enlisting NCHGR core scientists to perform the new techniques as part of a cooperative study, to bringing other intramural scientists into an NCHGR study for expert advice.



One of NCHGR's five programs, the Technology Development Program, will take aim at the next generation of genetic techniques. Nic Dracopoli, who was snagged from the Massachusetts Institute of Technology in Cambridge, heads the program and says his first big technology project is devising a method for determining large numbers of genotypes as quickly and economically as possible. Dracopoli says that currently, determining genotypes needed to map even the simplest hereditary disease can take a good technician two years, assuming that he or she does nothing but run gels and assuming that the lab is equipped with the fastest machines and methods of today. The time required to analyze DNA fragments for polygenic or other complex genetic diseases can be prohibitive. Dracopoli hopes within two or three years to devise refinements on current gel-based techniques or—possibly—a mass-spectrometry-based technique to speed up massive genotyping projects. "We would like to make it possible to take on whole genome mapping as a trivial problem," says Dracopoli. "It would be nice to be able to attack a new genetic disease without a huge gear-up of equipment and people ... to make large problems accessible that aren't at the moment."



NCHGR Scientific Director Jeff Trent and graduate student Rodney Wiltshire survey unopened boxes in the Laboratory of Cancer Genetics.

In addition to technology development, Dracopoli will continue to pursue epidemiological genetics in ongoing and new studies with longstanding intramural collaborators Peggy Tucker, Chief of the Family Studies Branch of NCI; Alisa Goldstein, a Senior Staff Fellow in the Genetic Epidemiology Branch of NCI; and Sherri Bale, Acting Chief of the Genetic Studies Section in NIAMS' Laboratory of Skin Biology. "One attraction of coming here is the opportunity to build collaborative projects with researchers in the Clinical Center and elsewhere," says Dracopoli. "That is very exciting."

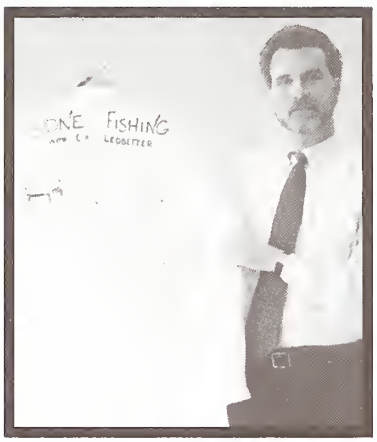
Scientific Director Trent, who will also head NCHGR's Laboratory of Cancer Genetics, says that the first wave of staffing for NCHGR labs, mostly located on the second, third, and fourth floors of the Conte Building, is just about complete, with scientists arriving from more than 20

different major universities across the country. "Five weeks ago, there was one person on 4A. Now there are 50 people." To avoid antagonizing and disrupting other research groups on campus, Collins largely steered clear of recruiting on campus. "But we have taken on three junior investigators who were being heavily recruited by institutions outside NIH," Collins says. All three of the junior scientists are pursuing gene-therapy or related bone marrow stem-cell research and were situated in labs that had lost a Senior Investigator in recent years. One Senior Scientist who was being heavily recruited by labs outside NIH is expected to move from NCI to head NCHGR's Clinical Gene Therapy Branch.

Collins lured David Ledbetter from Baylor College of Medicine in Houston to head NCHGR's Diagnostic Development Branch. Ledbetter, an expert in molecular cytogenetics, including FISH, says, "Our mission is to do research in technological development and to take advantage of new techniques emerging from the Human Genome Project and elsewhere, and to apply them in the development of diagnostics for...cytogenetic diseases, as well as Mendelian [genetic] diseases."

Nic Dracopoli heads NCHGR's Technology Development Program.

Ledbetter uses FISH and polymerase chain reaction techniques to define chromosomal and genetic defects leading to mental retardation and other disorders. One important discovery was of a microdeletion on chromosome 17 that leads to Miller-Dieker lissencephaly, a developmental disorder in which neuronal precursor cells fail to migrate correctly, resulting in a smooth, massively undeveloped brain cortex and complete, irreversible impairment of cognitive development. Ledbetter also used the techniques to sort out more complex genetic anomalies underlying two other types of mental retardation—Prader-Willi Syndrome and Angelman Syndrome. Both result from deletion of a small region on chromosome 15, but whereas deletion of the father's DNA leads to Prader-Willi Syndrome in his child, deletion of the mother's DNA leads to Angleman Syndrome. These chromosome 15 deletion syndromes have become the classic examples of genomic imprinting in human genetic diseases.



David Ledbetter head at NCHGR's Diagnostic Development Branch, displays prized lab coat given to him by families of patients.

Trent, recruited from the University of Michigan in Ann Arbor, will be using chromosome microdissection and FISH. Working with Paul Melzer, also from Michigan, who will head NCHGR's Molecular Cytogenetics Section, Trent says he will be using the techniques to pursue genes that are disregulated due to chromosome deletions, rearrangements, and duplications, particularly in cancer cells. Collins is excited about the potential applications of FISH and chromosome microdissection. "Gene mapping using FISH is an extremely powerful way to put any piece of DNA on the map," says Collins. "And the microdissection technique is especially good for getting a lot of pieces of DNA from one region." Collins describes Trent and Melzer as the world's leading practitioners of chromosome microdissection, a technique for physically isolating pieces of a chromosome as small as five megabases. Trent says these tiny pieces of DNA may hold as few as 50 genes. "It's one way to subdivide the genome and focus a gene search very quickly," Trent says. "You can develop band-specific probes and libraries very rapidly by amplifying just one section from one chromosome." The genes that Trent and Melzer study somehow become amplified in malignant cells, duplicating up to several hundred copies of the gene per cell.

Collins is also hoping to use NCHGR's intramural program as a base for collaborating with extramural investigators. The Visiting Investigator Program will allow non-NIH investigators to come to Bethesda on a temporary basis to learn a new technique or collaborate on a research project with NCHGR scientists.

Overall, Collins says he is impressed by what he has seen of the research environment surrounding NCHGR. He finds the IRP to be "incredibly rich. People are doing very interesting things, and I think it's going to take me a couple years to get a sense of all that is going on. For almost any question you could ask, there's an expert here." He also senses a climate change in Bethesda. "The atmosphere here is sort of charged," says Collins. "There is a sense of excitement with the new Director—a great sense of anticipation of the future of the intramural institutes. There are a lot of very talented young scientists here, and there is a sense that NIH can compete for the very best people from the outside. ...I'm really tickled to be here," says Collins. "A year and a half ago, I could not have imagined leaving the University of Michigan, but the opportunities here are truly wonderful."

At the moment, Trent's enthusiasm for the NCHGR's intramural program is tempered by the magnitude of his responsibilities in assembling an unprecedented program and by immediate logistical concerns—such as learning how to circumvent bureaucratic obstacles rarely encountered in the academic environment that he formerly called home. Borrowing good ideas from extramural institutions he has been affiliated with and from other NIH Scientific Directors, Trent hopes to cre-

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NIH Director-Designate

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virus, to study the genetic basis of cancer and the way genes behave in animal cells.

Although I left Bethesda in 1970, I did not leave the NIH. As a new faculty member, a large part of my salary was paid by an NIH Career Development Award, and for over 20 years, most of my laboratory's work — like that of most university labs — has been financed by grants from the NIH. I have been fortunate. With NIH funding, I have worked unimpeded by anything other than my own limitations. I have known the joys of discovery, nurtured brilliant students, and received public accolades for work that was largely an act of love. The indebtedness I feel towards the NIH is one of the reasons I am sitting before you today.

In 1989, my colleague, Mike Bishop, and I shared the Nobel Prize in Physiology or Medicine for our discovery that viral cancer genes are derived from cellular genes. One unexpected consequence of this honor was a sudden and widespread interest in my views. As a result, I have spoken out or taken action on many topics — the funding of young investigators; indirect cost reimbursements; the training of new scientists; and science education for the public. I have been especially concerned about the need to explain why fundamental research in biology and chemistry is essential to progress against cancer, AIDS, and other diseases — and why it is essential to the success of our biotechnology and pharmaceutical industries.

These new activities have helped to make me a candidate for the NIH Directorship. But what qualities and aspirations would I bring to the job?

- As a working scientist, I will bring to discussions of science policy an intimate knowledge of how science is done and a firm commitment to scientific excellence.
- As an investigator who has seen the pursuit of an obscure chicken virus create a new vision of human cancer, I will defend open-ended basic science against the calls for restricted applications of what is already known.
- As a fair-minded citizen concerned with the role of science in our society, I will try to improve science education at all levels and to promote the careers of women and minority scientists.
- And as a medically-trained custodian of federal funds, I will encourage NIH investigators to extend their biological discoveries to clinical settings.

These are large challenges, especially in a time of fiscal constraint. But it is also a time of remarkable exuberance in biology, when our understanding of living forms is reaching heights that could not have been imagined 50 or even 20 years ago. We are learning the instructions written into our genes; the way our cells divide and our organs develop; and the precise damage to molecules that causes disease.

I welcome the stewardship of NIH, for the NIH remains the world's best hope for sustaining this progress and for realizing its dividends for human health. ■

FAES Gains New Life

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expands the scope of NFBR to cover all of FAES' historic activities. FAES' legal team is now busy drawing up the proposed agreements, the articles of incorporation, and the bylaws that would allow the merger of FAES' programs and assets into NFBR if an agreement can be reached with the NFBR Board.

If and when the merger is completed, the Foundation will have flexible powers to administer endowed positions, fellowships, and grants. Specifically, the legislation says "such fellowships and grants may include stipends, travel, health insurance benefits and other appropriate expenses." A 11-member, non-NIH Board of Directors will oversee the NFBR. For more information call Lois Kochanski at 496-7976. ■

Call for Cartoonists/Illustrators

The NIH Catalyst is searching for NIH employees who have hidden talents as cartoonists or illustrators. If you are interested in volunteering your services to *The Catalyst*, please call us at 402-1449 or 402-4274. ■

Tissue Inhibator

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by Kaposi's sarcoma cells. We are now analyzing the mechanism and potential clinical utility of this effect. ■

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SOUND OFF
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run efficiently ... but there are other labs that are run inefficiently. By doing an across-the-board cut, the labs that are inflated and bloated won't be hurt, yet a lab that is running close to the bone, but efficiently, is going to be very severely hurt.

Anonymous Intramural Administrator

Even if the issues raised in the articles are not true, if it propagates a [negative] perception, then talented young investigators may not want to come here — after all, they are trying to learn and build up their credentials. If the [negative] perception prevails, you basically get into a downward spiral; people would be scared away from coming here, and the place would not be as good as it was. ... Part of the problem is that you can't argue with perception. It has a tendency to be self-fulfilling — and that is scary. ■

NCHGR's INTRAMURAL GENETICS
continued from page 21.

ate in NCHGR "an atmosphere where science can thrive with as little bureaucratic and administrative headache as possible." Trent says he is excited at the vertical integration of research that is possible at NIH, carrying ideas from basic lab discovery to the patient's bedside. "We hope to affect the outcome of some human genetic diseases, as well as understand their biology," says Trent. "At this point, we are a bit overwhelmed. A year from now, maybe I'll have a feeling for the great individual accomplishments that may come out of NCHGR. But right now, we're more at the level of unpacking boxes ...There is a great deal of excitement...and a great deal of work." ■

Empty boxes are a sign of the times as scientists move into NCHGR's labs on the fourth floor of Bldg. 49.

DCRT LAB
continued from page 11

these are LIGAND, a Macintosh- and PC-based program for analysis of receptor binding studies; ALLFIT, for dose-response curve analysis; and PULSEFIT, for analysis of pulsatility in hormone time series. These programs are available for use by biomedical investigators at NIH and throughout the world.

Scientists already have abundant data on gene sequences, according to Munson, but they continue to need reliable mathematical modeling routines to help them identify structures in macromolecules for possible manipulation of their function. ABS member Valentina Di Francesco, a postdoctoral mathematician, is studying mathematical statistical approaches to protein structure description and prediction. She is concentrating on the residue contact map as a means of understanding the large available database of protein structures. George Hutchinson, a mathematician, is studying the applications of symbolic computation with the program Mathematical. He is currently adapting the ALLFIT program to this system, and is coordinating the NIH-wide neural networks journal club that meets alternate Fridays at DCRT. ■

RECENTLY TENURED
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polyols in in vitro studies and the accumulation of polyol in the cortex are inhibited more effectively by nonspecific inhibitors than by aldose reductase-specific inhibitors. Microalbuminuria, an early sign of diabetic nephropathy, is also reduced more effectively by nonspecific inhibitors than by specific inhibitors. To date, the first step of the polyol pathway — the reduction of glucose to sorbitol — is believed to be catalyzed solely by the enzyme aldose reductase. Our observations suggest, however, that aldehyde reductase also contributes to the formation of polyols in certain tissues, and thus may play a central role in the onset of diabetic complications. ■

** NIH Scientific Directors have granted to Murali Cherukuri, Dimiter Dimitrov, and Sanai Sato "intent for tenure" status that guarantee them full tenure if and when they receive their U.S. citizenship.*

New Cell Biology Interest Group Forming at NIH

A Cell Biology Interest Group is being organized at NIH. Its purpose is to provide a framework for communication and interaction among the many NIH scientists working in the diverse fields of cell biology. At a Nov. 5 organizational meeting, about 80 NIH scientists expressed great enthusiasm for the interest groups and decided its activities and projects will include: (1) A monthly workshop to be held in Wilson Hall from 3-5 p.m. one Wednesday each month where three NIH scientists will present their work. The first meeting will be announced in the NIH Calendar of Events. (2) A monthly NIH Lectureship/Visiting Professorship in Cell Biology to bring visitors to the NIH campus; and (3) A Directory for Cell Biology at NIH.

If you would like to be included in Cell Biology Interest Group Activities, please send your name, laboratory and institute, two sentences describing your research interests, your telephone number, FAX number, e-mail address, and mailing address to Rick Klausner, Building 18, Room 101, FAX number 402-0078. The initial organizing committee members coordinating these activities are Juan Bonifacino, Harris Bernstein, Diana Blithe, Sam Cushman, Monique Dubois-Dalcq, Peter Fishman, Rick Klausner, and Ed Korn. ■

The NIH Catalyst Publication Schedule Changes

The winds of administrative change have blown the publication schedule of *The NIH Catalyst* slightly off course. Starting this Nov. issue we will be coming out every other month with distribution on the 15 of each month. Our next issue is scheduled to appear Jan. 15. ■

FAX-BACK

In this issue we are asking for your opinions on four areas: your reaction to the recent *Science* articles, and your opinions on *The NIH Catalyst*, clinical research at NIH, and on whether there exist administrative or organizational impediments to conducting quality research at NIH. Fax your responses to 402-4303 or mail it to us at Building 1, Room 134.

1) What was your reaction to Jon Cohen's articles in *Science* that raised concerns about the intramural research program?

2) Are there specific administrative or organizational impediments at NIH to the conduct of the highest quality of scientific research?

3) What do you see as the most important issues that should be addressed to maintain the quality of the Clinical Center's staff and research? How can NIH expedite the translation of basic research into innovative clinical science?

4) In December, *The NIH Catalyst* will have completed one year as a pilot publication. What are your opinions about *The NIH Catalyst* and how can we improve?

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 134, NIH, Bethesda, MD 20892. Ph: (301) 402-1449.

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