FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 5, ISSUE 1 ■ JANUARY–FEBRUARY 1997

HALL EFFECT IMAGING MAY GIVE MEDICINE A NEW SENSE

by David Ehrenstein

Those physicists have done it again. Doctors had barely heard of gamma radiation, beta decay, and nuclear magnetic resonance before they found themselves applying the concepts in X-rays, positron emission tomography, and magnetic resonance imaging of the human body. The next addition to the list of obscure physics topics to sweep clinicians off their feet could well be the Hall effect, which may some day allow painless diagnoses of tumors, kidney function, and fetal health in the womb, along with major improvements in conventional ultrasound imaging.

Han Wen, of the Lab of Cardiac Energetics, NHLBI, is the inventor of Hall effect imaging (HEI), and he got the idea partly from artifacts his group and others observed in the electrocardiograms (EKGs) taken of patients while they were simultaneously undergoing magnetic resonance imaging (MRI). Wen and his colleagues saw extra peaks that were synchronized with the heartbeat, he says. "After a lot of attempts to rearrange hardware and [doing] all kinds of other things to get rid of these peaks, we just realized that they're always there; they're inherent." About three years ago, several

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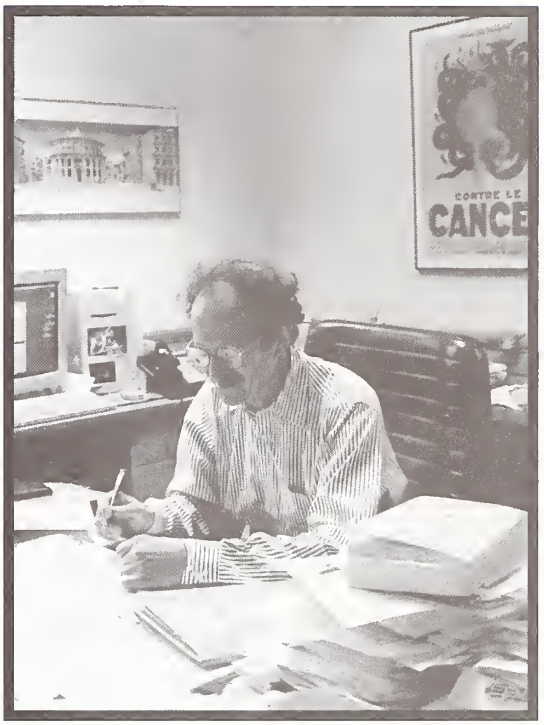
BEYOND POLITICS: VARMUS SETS SIGHTS FOR SELF AND SCIENCE

by Fran Pollner and Celia Hooper



Celia Hooper

Harold Varmus, the first Nobel laureate to serve as the director of NIH—and the first scientist-director of NIH to run his own research lab on campus—has had what he deems an "exhilarating" time of it thus far: not only has the pace of scientific discovery been accelerating during the three years he's been in Bethesda but he has managed to steer NIH clear of the fiscal icebergs that have cut into, if not capsized, other federal agencies.

And he expects no less during his remaining three years—his estimated time of departure.

In an interview with *The NIH Catalyst,* Varmus reflected on his accomplishments at what he designated the "middle of my term," citing among them changes in institute leadership and the ascendancy of the collaborative attitude. An eloquent advocate of basic research, he also took pride in the elevation of the status of clinical research confirmed in the blueprints for a new Clinical Research Center here.

Among his goals for the future are establishing a clinical research training program for medical and dental students and a Ph.D.-granting program with a clinical research component. Another is to sharpen the boundaries between science and politics, including disconnecting the selection of the NIH director from U.S. presidential elections. In summing up some of the scientific winds of change in the aftermath of the 1996 elections, Varmus

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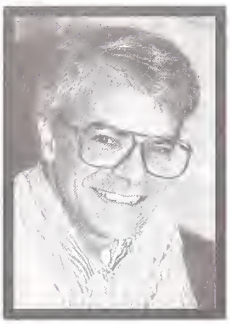
Improving the Climate For Clinical Research at NIH



Michael Gottesman

Despite significant advances in understanding basic human disease pathogenesis—and the public's rightful demand for translation of these basic findings into improved diagnosis and treatment of disease—economic factors are making it tough to conduct clinical research in the United States. At NIH, we've witnessed declining morale among our clinical researchers and an increasing concern over how this affects our ability to recruit beginning researchers to dedicate their careers to this goal. What can we do to reverse these trends?

We are currently witnessing a whirlwind of activity at NIH devoted to improving the climate for doing clinical research here: we want to recruit and retain more dedicated clinical researchers. Most of these activities are in the fact-finding stage—thus the plethora of committees. But some concrete actions have already been taken.

The most obvious problem affecting morale and retention of our NIH clinical researchers is that salaries simply do not reach the level accorded equivalent work in the private sector—indeed, they may be falling further behind. This inequity is being addressed through Title 38, a means of supplementing the salaries of physician-researchers who spend a substantial portion of their time (more than 10 %) in direct patient contact. As of this writing, 115 clinical researchers at NIH have benefited from salary increases under this authority. And we recently succeeded in extending Title 38 salary supplements to NIH physicians who have medical responsibility for large-scale interventional clinical trials. Through this mechanism, we have been able to secure salaries comparable to midlevel pay scales for academic clinicians, as tabulated by the American Association of Medical Colleges.

A second obvious obstacle to recruitment is the burden of debt that limits career choices for many medical students. NIH currently has three loan repayment programs (LRPs) to overcome this obstacle: an AIDS research LRP, which has supported 96 researchers; a clinical research LRP, designed specifically for disadvantaged clinicians, supporting 32 researchers; and a new LRP for research generally, which currently supports 22 researchers, half of whom do substantial clinical work. Contact Marc Horowitz at the Office of Loan Repayment and Scholarship for guidance (402-5666).

We are currently witnessing a whirlwind of activity . . .

The decision to build a new Clinical Research Center to replace our aging and inefficient infrastructure represents perhaps the most direct and far-reaching step to support clinical research at NIH. Among recommendations for the new center's operations, offered by the NIH Options Team, are that a "Board of Governors" oversee the Clinical Research Center's financial management and that the budget for the center be as stable as the NIH intramural budget itself (a recommendation recently translated into a three-year pilot plan to shape a budget process).

Another committee addressing the issue of clinical research is the NIH director's Clinical Research Panel, chaired by David Nathan, president of the Dana Farber Cancer Institute, and including representatives from major U.S. medical centers and private industry. We have already acted on the panel's suggestion that NIH pilot an intramural Clinical Research Training Program (CRTP), modeled after the basic science training offered to medical students by the HHMI (Howard Hughes Medical Institution) Research Scholars Program. To this end, my office has established the Board of Tutors, chaired by John Gallin and consisting of senior clinical researchers. We have devised a one-to-two-year program that will include the core curriculum in clinical research, already available at the Clinical Center, and individualized instruction in managing research patients and using the relevant laboratory tools. A package soliciting applications and describing the program has been sent to all U.S. medical and dental schools for distribution to third-year medical students. For more information about the CRTP, visit our web site at <http://helix.nih.gov:8001/oe/student/crtp/> or contact Audrey Boyle in my office for an information package (496-1921).

The dejection of our clinical researchers, however, may reflect deeper problems than money, new facilities, or more training opportunities can eliminate. One of the issues of which I recently became aware is a sense among clinical researchers that there is a "double standard" for evaluation and review of clinical research. Some of this feeling derives from the very complex rules established to protect human subjects in the conduct of clinical research, as well as from my recent urging that there be significant pre-IRB review of clinical research protocols. To define and address this perception and other similarly difficult problems, I have asked Steve Straus, of NIAID, to chair a Committee on Recruitment and Career Development of Clinical Researchers at NIH. This committtee will evaluate the current status of our researchers, including the various personnel mechanisms for their support and the extent of clinical research activities on campus.

We're also determined that the public be reminded every so often of the high quality and public health importance of our clinical research programs, and we are planning a series of events that will serve this objective. The first of these—Clinical Research Day, on February 10, 1997—celebrates the past, present, and future triumphs of clinical research at NIH, showcasing the plans for the new Mark O. Hatfield Clinical Research Center, current research activities, and projections into the next century. In the fall of 1997, we will have a glorious ground-breaking celebration for the new Clinical Research Center, also with a view toward letting the public know the scope and promise of the clinical research conducted on this campus.

I do not know that these ongoing activities will solve all of the problems of our clinical researchers, but I do know that we all need to work together to ensure that clinical research continues to be a vigorous, intellectually stimulating, and effective component of our intramural program. I welcome your thoughts about these issues, which can be sent to me or to *The NIH Catalyst* in response to the "Call for Catalytic Reactions" on the back page of this issue.

Michael Gottesman
Deputy Director for Intramural Research

CATALYTIC REACTIONS

Below are comments we received in response to questions posed or issues raised in the November-December issue.

On Daycare and Parenting at NIH

I would like to offer my perspective on the NIH daycare facilities. My son attended the POPI preschool from age 3 to 5 and then went to Ayrlawn (now Executive Child Development Center) from age 5 to 12.

These facilities were central in our lives for 10 years, and I cannot overstate their importance. They were far more than a convenient source of daycare and after-school care. Over the years, the staff, other children, and their parents became a wonderful extended family—providing warm friendship day to day and support in times of crisis. Stephen (who is now 16) even went back to do his high-school community service requirement at ECDC.

The location of the preschool on campus was particularly important when I was in the lab because it enabled me to pick up Stephen and then go back to the lab if something needed finishing up. It was also reassuring to be nearby in case of snow, illness, or emergency. Especially during my five years as a single parent, this proximity was crucial, as was the support and "backup" provided by friends and staff at both centers.

I certainly believe that an investment in enhanced childcare facilities is worthwhile to sustain NIH as an institution that encourages parents. The sizes of the waiting lists for POPI and ECDC speak to the importance of these resources and suggest that some expansion is warranted. The concept of providing temporary backup care when regular daycare arrangements fall through responds to a tremendous need, but it would have to be carefully thought through, so that it didn't disrupt the quality of care and the sense of community among the regular daycare children.

One partial source of funding that should be explored is contributions from families whose children attended POPI and ECDC/Arylawn in the past. Many of us recognize our debt to those institutions and would welcome the chance to return the favor, but we haven't been asked! You might be surprised at the magnitude of the response if an e-mail or other communication went out to parent alumni asking for help in sustaining the daycare system at NIH.

Thanks for this opportunity to comment.

—Barbara Harrison, NIDDK

One would expect that the reputed "premier health research institution in the world" (I am not convinced) should be setting an example for the rest of the country by providing the best state-of-the-art childcare facilities on site. . . . I was particularly surprised to see the comments by Paul Horton concerning the dismal condition of the POPI facility. . .

My advice to NIH fellows, many of whom are no doubt doubled-up in mad laughter at that silly list of elitist schools on page 12, is to go with good, registered home care or get a live-in nanny. I would suspect that the nice rosy picture of a few lucky couples advancing through the ranks decades ago does not quite cut it with the majority of fellows today. Poor childcare combined with poor parking, poor mentoring, pay inequality, and rather dismal chances of job advancement (read tenure) will ensure continued mediocrity.

—R. Dwayne Lunsford, NIDR

Just a note to compliment you on your incredibly sensitive and comprehensive treatment of parenting among NIH scientists and administrators. I hope that this article is read by everyone—not just those who have preschoolers and after-school daycare needs. Well done!!!

—Jan Hedetniemi, OD

One thing that I hope will emerge from the Catalyst *"parenting" issue is a listserv list for NIH parents. I haven't found anyone willing to run this yet, but I think it could be useful, especially to single parents, in establishing a network. It would be great if we could share information and maybe even exchange babysitting.*

—Celia Hooper

Regarding question 2. What would you recommend to improve NIH work life?

Better exercise facilities and better daycare/emergency-care provisions.

Regarding question 4: Are NIH daycare facilities important? Is the investment worthwhile? Should the NIH investment in on-site daycare be larger?

I believe that the daycare facilities are very important and should be highly prioritized for renovation and expansion. The need for the funds for "scientific" purposes is an infinite sink and should not prevent this critical function from being attended to. I support the commitment to substantially expand the daycare effort to accommodate many of those on the waiting list and to provide occasional care and emergency care for infants and children (when schools close during the work week for weather problems, for example). An immediate effort should be made. In the longer term, the construction budget of the new clinical center should absorb these costs.

—Norman Salem, Jr., NIAAA

Great issue of the *Catalyst*. Humanity, at last. In public yet! Thanks.

—Adrian Parsegian, DCRT

Reality Check

Congratulations on a lovely job!! The article ["The Jugglers: How NIH Scientists Balance Careers and Families"] was nicely balanced, and well-researched, and gave an upbeat but "room for improvement" view of the entire situation (although last time I checked, I had two sons, but wouldn't mind a daughter in the future. . . .) ■

—Helene Rosenberg, NIAID

Fran Pollner

Helene Rosenberg, in relaxed mode at home, with sons Joshua, 6, standing tall, and Michael, 18 months

NIH Gets an Ombudsman

By Joan P. Schwartz, NINDS

Lorna Heartley

Joan P. Schwartz

What do you do when you believe that your lab chief should just be thanked in the acknowledgments of your paper, but he or she insists on inclusion as a co-author? Or what do you do if a former postdoctoral fellow leaves the laboratory and takes reagents needed to advance a project, refusing to share them with incoming fellows? Or suppose you believe that a review committee being constituted to give advice on your potential tenure does not have the expertise needed to evaluate your science? Until now, such problems—which fall into categories such as mentorship, authorship, reagent sharing, data management, and career advancement—have fermented at the local level, often with no resolution or a delayed resolution that aggravates the problem.

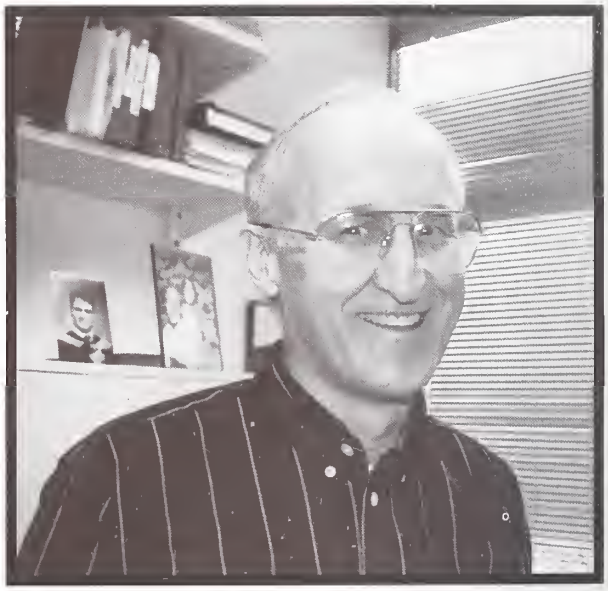
Several offices at NIH are about to launch a pilot project that we hope will help people deal with these issues and disputes. Working together, members of the Office of Equal Opportunity, the Office of Human Resources Management, the Office of Intramural Research, and the NIH Committee on Scientific Conduct and Ethics are now establishing a Cooperative Resolution Center, to be headed by an NIH ombudsman. The center will serve as a neutral site for resolving work-related conflicts.

> **... IT WILL PROVIDE A CONFIDENTIAL SETTING FOR CONFLICT RESOLUTION....THE CENTER SHOULD ALLOW RESOLUTION OF DISPUTES AT AN EARLY STAGE, BEFORE THEY HAVE BECOME INTRACTABLE.**

We see three advantages deriving from the center. First, it will provide a confidential setting for conflict resolution, independent of the institute structure. Anyone may use the office. Second, the process should be fast because specific time limits will be set for resolution of problems. Third, and most importantly, having the center should allow resolution of disputes at an early stage, before they have become intractable. At the same time, participants in this process do not give up their rights to file a grievance or an EEO complaint, should these become necessary.

David Lee Robinson, chief of the Section on Visual Behavior, National Eye Institute, and a 25-year veteran of NIH, has agreed to pilot the role of ombudsman and get the Cooperative Resolution Center started. An advisory committee, consisting of scientists on the NIH Committee on Scientific Conduct and Ethics, will assist Robinson in determining how best to run the center and to evaluate its success during the pilot period. We see this as an experiment in the best sense of the word—finding out what procedures work best in resolving NIH's unique workplace conflicts.

An ombudsman is by definition someone who maintains absolute confidentiality regarding any case, is independent of both management and personnel, serves as an informal information resource, handles complaints, and assists in resolving disputes. The ombudsman is a facilitator, not a decision maker. When a person who thinks he or she might want the ombudsman's help first visits his office, the ombudsman will listen, discuss different options, and make informal suggestions for resolution of the problem. Ultimately, once the issues have been clarified and all parties to the dispute are willing to try the alternative dispute-resolution process, the ombudsman will recommend one of the various forms of alternative dispute resolution (ADR) available, depending on the facts of the case.



Fran Pollner

NIH's first ombudsman: David Lee Robinson

The Cooperative Resolution Center will initially offer mediation, early neutral evaluation, and peer panel evaluation. Mediation involves the use of an impartial third party who serves as a catalyst to help the parties improve communication and thereby reach a mutually acceptable agreement. Mediators are trained in negotiating, building trust and consensus, and interest-based problem solving. If both sides reach an agreement, that agreement is usually written down. If no agreement is reached, the parties may elect to pursue another ADR process or exercise their rights in another arena.

Early neutral evalulation uses a neutral third party to provide an objective evaluation of the strengths and weaknesses of each party's position. This could be useful when there is a scientific basis to the dispute. The "early neutral evaluator" would be a subject-matter expert who would produce a written report and a set of recommendations, based on the presentations by all parties.

A peer panel evaluation uses a group (generally three) of early neutral evaluators, or scientific experts. Each party to the dispute would choose one expert, and the ombudsman would appoint the third. The panel would produce a written report based on presentations by each party. Such a mechanism might be particularly appropriate when the dispute involves a "community standard"—for example, determining what contributions in a given work merit authorship in that discipline.

We believe that the availability of the ombudsman, the Cooperative Resolution Center, and a successful ADR program will benefit NIH. The process will be easily accessible and will provide a diversity of options for resolving conflicts through cooperation and problem solving, as an alternative to litigation or administrative proceedings. We're launching the ombudsman with a five-ICD pilot project, including NIDA, NIAID, NIEHS, NHLBI, and OD. For the rest of you: stay tuned! Final details concerning space, communications, and finances are being considered and will be reported in the next issue of *The NIH Catalyst*. ■

JUST ASK!

Dear Just Ask:
How can one identify research groups within the NIH intramural program that are interested and/or working on a family of proteins termed serpins (serine protease inhibitors)? The molecular weight of a serpin protein is around 50,000 Da. Many serpins inhibit serine proteases, but some do not have demonstrable inhibitory activities (e.g., ovalbumin, angiotensinogen, pigment epithelium-derived factor [PEDF], and maspin). Thank you.

—Pat Becerra, NEI-LRCMB

Dear Pat:
Your question offers us the opportunity to outline the somewhat haphazard ways in which intramural scientists, in general, can identify potential collaborators on campus.

Our first step in an attempt to track down intramural serpin experts was to search the CRISP database. We usually do this via the Community of Science Web Page at this Uniform Resource Locator (URL): <http://cos.gdb.org/>. After selecting their "Federally Funded," then their "NIH" menu choices, we first restricted our search to "Maryland" and were able to find research in your lab and one other that you are already in touch with by searching under the name of specific serpins (rather than the generic term "serpin," which yielded nothing). The nationwide search for "serpin*" (using the asterisk as a wildcard that covers both "serpin" and "serpins") turned up everyone with grant proposals that included the word serpin or serpins, but none of these folks are here at NIH.


Lorna Heartley

Celia Hooper

Our next move was to try the search engine on the NIH home page at this URL: <http://search.info.nih.gov/>. Searching under "serpin*" turned up some useless junk, but searching under the names of specific serpins yielded your 1995 Research Festival poster abstract and some lengthy reference documents—but no collaborators.

Unstymied, we forged ahead and contacted the heads of various relevant interinstitute interest groups on campus to see whether they could think of anyone. We followed up on several vague leads ("I think there's someone up at Frederick working on serpins. . ."), but none panned out. Finally we tried sending queries to the subscribers to the DDIR's Bulletin Board and to the Fellow-L list. (Since Yours Truly keeps the DDIR's Bulletin Board list, I just put on another hat and did this. Other folks who need help finding collaborators this way would send a message to <hooper@box-h.nih.gov>. To post a message on the fellows' list, send it via e-mail to <felcom@helix.nih.gov>, and the volunteers who keep that list will post it for you.) This had no immediate payoffs.

Things were looking grim until last year's Research Festival when, on your own, you found a fellow serpin researcher, J. H. Lee, who presented a poster in collaboration with Mark Brantly (NHLBI) entitled "A Conformational Change in the Reactive Site Loop of α-1-antitrypsin Associated with Rapid Intracellular Degradation."

A month and a half later, my various list queries paid off when Kee Lee, a new postdoc in the Lab of Cellular and Molecular Immunology, NIAID, contacted me. Lee did his doctoral dissertation on antitrypsin and has identified several temperature-stable antitrypsin mutants and characterized structural and functional aspects of these proteins. Lee is wondering about their in vivo functions. Happy collaborating! ■

—C.H.

NCI Launches Independent Intramural Review Office

NCI has established a new office with oversight responsibility for the scientific review of the research of intramural principal investigators and laboratory and branch leaders. The new Office of Advisory Activities (OAA) also coordinates the recruitment and orientation of the ad hoc site visit teams, the site-visits themselves, the compilation of the site-visit reports, and, as needed, the clarification of those reports at Board of Scientific Counselors (BSC) meetings. The new office was created with an eye toward complying with the precepts put forth in 1995 by a blue ribbon panel (the Bishop-Calabresi committee), which called for a mechanism to ensure objectivity in the review of the NCI intramural program.

The OAA is located within the NCI Division of Extramural Activities (DEA) and will coordinate its intramural review with its external advisory functions, including facilitating operations of the extramural oversight Board of Scientific Advisors and numerous ad hoc working groups and staff task forces that review NCI operations. The OAA will also work with the presidentially appointed National Cancer Advisory Board and with the DEA director to coordinate the activities of that board with all of the other NCI advisory bodies. It will also work directly with the Intramural Advisory Board (IAB), which represents NCI intramural scientists across a broad range of issues involving intramural operations and principles. One focus of the IAB is the intramural review process from the principal investigators' perspective, reviewing the review process and bringing forward recommendations for changes in the process. Very minor changes that are within the scope of the existing guidelines may be incorporated quickly by the OAA and without clearance from other advisory groups. However, substantive changes in the review process will not be made without consultation with all relevant advisory groups, including the NCI Executive Committee and the BSC.

The OAA is led by Robert Hammond, who headed the NIDDK Review Branch since 1989 and has served in senior review capacities at different institutes, including NCI, since his arrival at NIH in 1980. Before that, he held appointments at the U.S. Army Research Institute for Environmental Medicine, in Natick, Mass., Ripon (Wisc.) College, and George Mason University, Fairfax, Va., where his efforts focused on comparative physiology and endocrinology. He received his Ph.D. in biology from Tulane University, in New Orleans, and completed a postdoctoral fellowship in animal physiology at Liverpool University in England.

Senior staff from across NIH have been recruited to the OAA, including Florence Farber, of the NCI Grants Review Branch, and Judy Mietz, formerly with the NHLBI Laboratory of Molecular Immunology, who will serve as executive secretaries for the intramural research review, and Susan Feldman, former NIH committee management officer, who will serve as resident expert on pertinent federal laws, regulations, and policies. ■

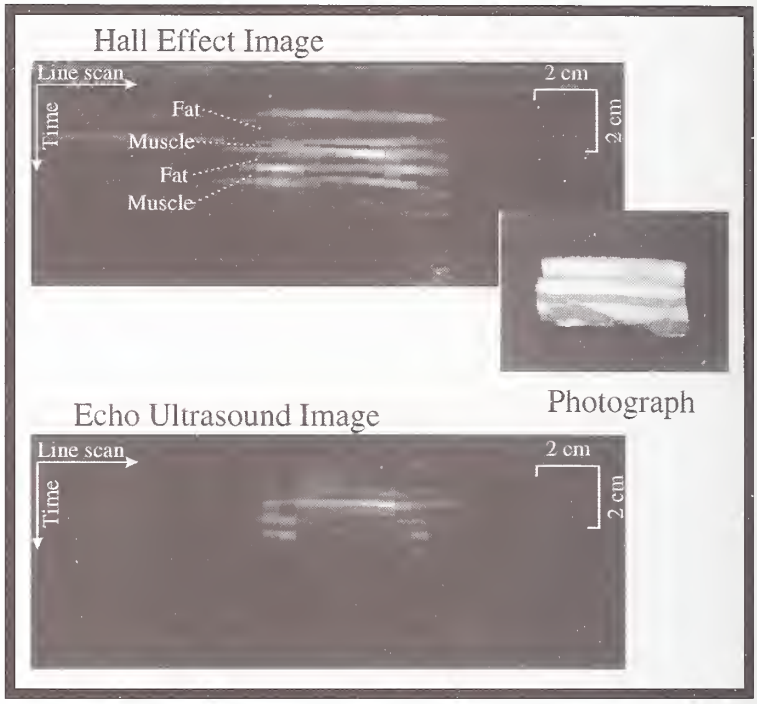
—Cynthia Morgan

Hall Effect Imaging
continued from page 1

labs, including his, realized the cause: as blood was pumped rapidly out of the heart, the electrolytes and any other electrically charged constituents of the blood would follow curved paths because of the magnetic field, with opposite charges curving in opposite directions. Such a separation of positive and negative charges caused by a magnetic field is known as the Hall effect (named after E. H. Hall, who reported the result in 1879). The charge separation generates the Hall voltage, which in this case was contaminating the EKG signal.

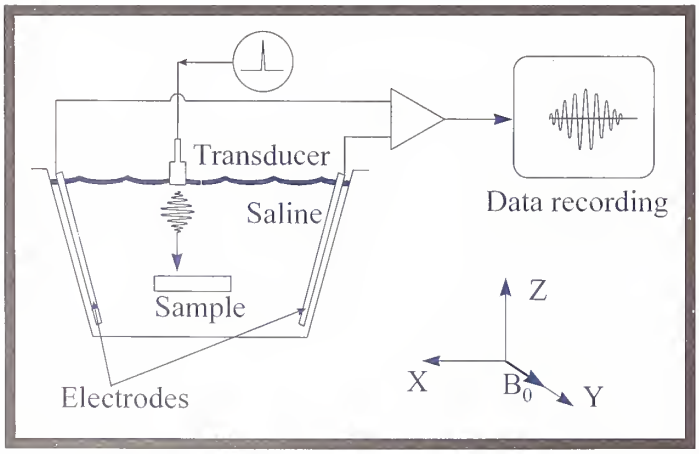
Wen realized that the effect was closely related to the blood's electrical conductivity, a property that happened to be of interest in a variety of body tissues because of its other effects on certain MRI data. He reasoned that the Hall effect could be used to map conductivity in the body—as long as some motion of the tissue could be generated that would play the role of blood flow through the heart in the EKGs. The motion also had to be spatially confined so that signals originating from different locations in the body could be distinguished. Fitting these requirements, ultrasound proved to be a good source of motion.

In ultrasound imaging, pulses of high-frequency sound are sent into the body, and the time of arrival of the echoes indicates the distances to the various sound-reflecting tissues. Because the sound penetration and reflection are mainly determined by tissue density, ultrasound is essentially a density probe. In HEI, the ultrasound pulses are applied to tissue within a magnetic field and jiggle it just enough to generate a Hall voltage, which is detected with electrodes; thus, HEI measures the electrical conductivity of the tissues, rather than their density. Although this was the original concept, Wen discovered in the lab that the HEI signal's noise level could be drastically reduced by running it in "reverse mode," that is, by using the electrodes to apply voltage pulses and measuring the resulting ultrasound signal. In the reverse mode, the combined effects of the voltage pulse and the magnetic field on the tissue's charges cause an ultrasound vibration. Either way, the output measures tissue conductivity.



Han Wen

Bringing home the bacon: Hall effect image (top) provides better definition of the muscle and fat layers of the bacon slice (photograph in middle) than that achieved with echo ultrasound (bottom).



Han Wen

Schematic of the experimental set-up for HEI in reverse mode. The sample is submerged in saline, and voltage pulses are applied across the electrodes. The combination of the electric field pulses and the presence of a large magnetic field (perpendicular to the page, not shown) causes ultrasound vibrations, which are detected by the transducer.

The beauty of Wen's technique is that it should be able to give high-resolution pictures of tissue conductivity, which, unlike density, varies quite a bit from one tissue to another. That should yield images with far better contrast than conventional ultrasound and permit a new kind of tissue characterization based on conductivity. Wen cites an example from intravascular ultrasound imaging, where a "bulge" might be seen on the wall of a blood vessel. "It's very hard to tell whether that bulge is just a bulge of the muscle lining of the artery, or [whether] it's actually a fatty plaque. Now, potentially, you could use this technique [to identify the nature of the bulge], because it's conductivity-sensitive. There's a big difference in conductivity between fat and [muscle]."

Robert Balaban, a collaborator and head of the lab, says the same principle might apply to tumor diagnosis. "Then an [HEI] exam of the breast *may*, and I want to emphasize *may*, provide another way of characterizing a tumor versus a cyst, which is a big part of tissue characterization." There is also evidence that conductivity varies with physiological state, so that ischemic (oxygen-deprived) tissue—for example, in a heart attack patient—would look different from normal, or the stages of tumor development could be observed.

Wen and Balaban can imagine other possible applications

that might allow patients to avoid invasive diagnostic procedures. A kidney that isn't properly concentrating electrolytes in the urine, for example, ought to have a clearly different conductivity from a healthy kidney, so HEI could save the trouble of catheterizing the individual kidneys for diagnosis. The cerebrospinal fluid in a developing fetus is sometimes tested for signs of proper development, and, according to Wen, "the conductivity is one of the standard test parameters. And if you can do that noninvasively, it's going to be much less painful for the mother and for the baby."

Although quite promising, the HEI technology has not yet been tested on an animal. The most complicated sample so far was a piece of bacon. "I thought bacon was just too bizarre," Wen recalls. But Balaban explained that bacon is animal tissue with interlaced fat and muscle, which ought to have distinctly contrasting conductivities. After Balaban purchased the sample at a Bethesda grocery store, Wen observed the expected result: the layers of the bacon showed up much more clearly in the HEI image than with conventional ultrasound.

Before imaging an animal, a few engineering problems must be solved, the largest of which is to design a new, nonmetal ultrasound detector. Balaban explains that it's needed to defeat the largest source of noise in the current system. "If you put any metal in the magnet and it [vibrates] at ultrasound frequencies, it generates a Hall voltage, and that's an interference. Han and I have suffered through that in these initial studies. It's a new class of [sound] detectors that we have to come up with." Fortunately, they have found collaborators at the Naval Research Lab, in Washington, who are already experts on such detectors, which rely on interferometry and coiled fiber optics to give high sensitivity without the use of any metal parts. The main problem is to adapt these detectors for use at ultrasound frequencies.

Some other challenges, which appear less difficult, include designing a good way to deliver electric pulses to the body and adapting conventional ultrasound electronics and data processing. But despite these hurdles, Balaban is optimistic. He foresees experiments on humans within a year and a clinical device three to five years after that. "The reason I'm that positive about it is because basically we know a lot about ultrasound as a clinical tool already. What we're doing is adding the magnetic field, which is also now a commercial device." And Wen points out that expensive MRI magnets aren't needed for HEI; fairly cheap ones will suffice—magnets "that they use in junkyards to pull up cars and things like that. That's good enough for us." He adds that an HEI magnet could be much smaller than one from a junkyard.

Balaban stresses that the best applications of this technology may not yet have been imagined. Conductivity has not been observed so directly in the past, and new HEI data may reveal new physiological information and new directions for basic research. He draws a parallel with MRI, which yielded much unexpected information after researchers began experimenting with it. "We're going to look around a little bit with this new technology. We have a few ideas, but the real thing is now to explore the body with this new 'sense' and really see what comes out of it." ■

New Center To Tackle Inherited Disease

Born of the joint efforts of seven NIH institutes and one center, a new Center for Inherited Disease Research (CIDR) has materialized at the Bayview, Md., campus of the Johns Hopkins School of Medicine. Its main purpose in life is the identification of the genetic loci and allelic variants that play important roles in multifactorial human disease, including, but not limited to, cardiovascular and pulmonary disease, cancer, psychiatric disorders, hearing and language disorders, neurological disease, diabetes, and autoimmune diseases.

To achieve that end, CIDR will utilize high-throughput genotyping in support of relevant research involving human populations and families and, possibly, pertinent animal models. Access to CIDR is open to all investigators on a competitive basis. Intramural scientists should get approval of their scientific directors first.

CIDR will carry out genome-wide genotyping scans on samples provided by principal investigators whose proposals have been accepted. A variety of different mapping approaches may be supported by genotyping within CIDR, including affected-pedigree-member methods, transmission-disequilibrium testing, and linkage analysis in pedigrees. Investigators may also consult with CIDR researchers about study design and statistical analysis. Once CIDR has completed its studies, the data and results of the analyses will be returned to the principal investigator for further research.

Proposals from extramural investigators will undergo the customary NIH review for scientific merit. Additionally, all proposals, whether of intramural or extramural origin, will be examined by a chartered CIDR Access Advisory Committee for compliance with criteria, including suitability of the project for the high-throughput genotyping capabilities of CIDR, feasibility of study design for detecting genetic contribution to disease, the likely impact of the study on biomedical research and, for intramural studies, the scientific merit of the proposal. A Board of Governors, the policy-setting body for CIDR, will review the recommendations of the Access Advisory Committee, determine what resources are available, and then advise the center director regarding when the most highly rated projects can be initiated. The board will be made up of the directors of the eight participating institutes and centers (or their designees). This scrutiny by the CIDR Access Advisory Committee is not expected to lengthen the review process beyond what is normally required for extramural grant submission and review.

CIDR's lead agent and manager is the National Center for Human Genome Research; its seven other sires are the National Cancer Institute, the National Institute of Child Health and Human Development, the National Institute on Deafness and Communication Disorders, the National Institute on Drug Abuse, the National Institute of Environmental Health Sciences, the National Institute of Mental Health, and the National Institute of Neurological Disorders and Stroke.

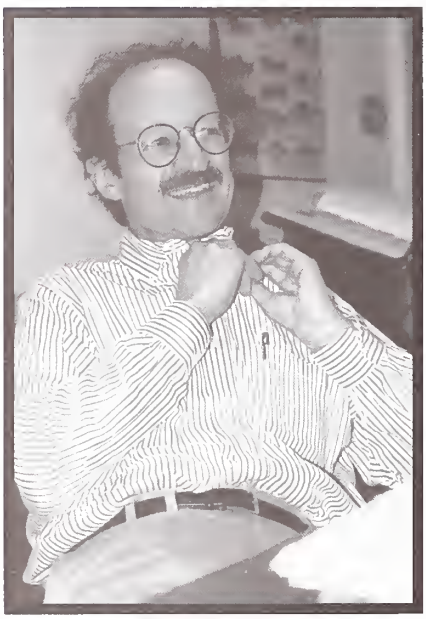
A description of CIDR will soon be available at the NCHGR homepage on the World Wide Web at <http://www.nchgr.nih.gov/home.html>. If you want more information about CIDR or are interested in using its services and facilities, contact Jerry Roberts, scientific review administrator and chief of staff, CIDR Board of Governors, in the NCHGR Office of Scientific Review, 496-0838. ■

BEYOND POLITICS
continued from page 1

informed his advisory committee at its year-end meeting that "my resignation has not been requested, nor do I have any intention of submitting it." A week later, *The NIH Catalyst* began its interview with a question that tied the presidential election to the NIH director's agenda. Varmus rejected the premise upon which the question was based.

Q: With the 1996 elections now over, what are your plans for *your* "second term" as NIH director?

Varmus: I see myself as unlinked to the electoral process. I don't believe the NIH directorship should be as politicized as it's been the past eight years or so. I didn't come in with the election—I came in some months later after it became clear that Dr. Healy and the administration were on divergent tracks—and my expectation is that I'll probably leave the position before the second administration is over, which would give the president a chance to name someone else who'd also [span] the electoral events and would disconnect the NIH nomination process from the electoral process.


Celia Hooper

Q: But you could decide to stay over.

Varmus: Well, it's subject to correction, but I think of myself as somewhere near the middle of my term as director. I think the appropriate length of time here is probably about six years. You can do a lot of things in six years, but beyond that you probably start to get stale. It's good to have change in this job because people bring in new ideas, new ways of doing things, and change is so healthy. It's the nature of the scientific—and the educational—enterprise.

Q: Would you consider staying at NIH to continue doing research here?

Varmus: I'd consider that.

Q: What do you consider your accomplishments thus far, and what do you hope to have accomplished by the time you leave?

Varmus: Several things have already been done. I see the changes in leadership as achievements—and some of those institute directors and scientific directors are likely to be in place considerably longer than I am. It's not only that I've brought in specific strikingly accomplished and energetic people; it's also that the way people think about the institutes is radically changed. There's a great deal more interaction among the institutes, a greater sense that NIH is a single unit. The leadership retreats we've had have helped people understand that although I'm determined to ensure that the institute directors retain a good deal of autonomy, it's also extremely important that the institutes work together in a way that both expedites the science and improves our political and economic prospects.

The second achievement involves the clinical center and clinical research in general. There's no doubt that the new Clinical Research Center is going to be built and that it will have tremendous impact on life at NIH and on clinical research generally. In addition, I put together a very strong panel from the clinical research community, headed by David Nathan [president of the Dana Farber Cancer Institute in Boston], that made several recommendations about the way we train, recruit, finance, and otherwise provide an infrastructure for individuals doing clinical research. This is amazingly important as many of the basic sciences have matured to the point where clinical applications of laboratory discoveries are closer and closer to reality.

Some of the recommendations are already in place—for example, more loan-repayment programs. We've done that for clinical research here, and we're trying to extend that to investigators on the outside. Some of the training suggestions, too, have been put in place locally, and we'd like to see them in place more broadly. We're looking very carefully at recommendations regarding the GCRCs [General Clinical Research Centers].

[Another goal for NIH] is to achieve sufficient [budgetary] support so we at least keep ahead of inflation. We can no longer expect to get 10 and 20% increases, as sometimes occurred in the past. We're not going to be opening new institutes. Instead, what I'd like to see is steady growth and prompt attention to seizing new opportunities in science, identifying areas of emphasis, getting people to work together and share resources, and effectively interacting with the industrial sector, the private sector, making sure the money goes as far as possible.

We've had very good budgets in the past two years. Given the way the rest of the government fared, they were remarkable. I don't consider that a personal triumph so much as a triumph for the directors, who made extremely effective presentations; for the scientific community and other constituents of NIH, who were very strong advocates for our budget; for the remarkable leadership in Congress by John Porter [R–Ill.] and Mark Hatfield [R–Ore.] and many others; and for our supporters in the Department [of Health and Human Services], especially Donna Shalala, and in the White House. There are constraints, but we work as a team. If the institute directors continue as they have to advance the cause of NIH, we'll all rise with the incoming tide.

Q: Do you expect any changes from the incoming tide? Are there any salient changes in Congress that would affect NIH?

Varmus: Sure. There are some. Mark Hatfield is no longer in Congress. But I don't want to make predictions. We'll go forward with as strong a budget proposal from the president for FY 1998 as possible. We're in negotiations now with the White House, and we hope that Congress will act in our behalf with its usual bipartisan support.

Q: Have you learned anything in the time you've been here about dealing with Congress and the White House that you might apply in the remaining three years?

Varmus: I'm not sure if "learning" is the right gerund, but I'm better acquainted

with a lot of people and have a good relationship with our Appropriations Subcommittee chairmen, Congressman Porter and Senator Specter [Arlen Specter, R–Pa.]. Those relationships *are* important, so from that point of view, being around for a while is a good thing. On the other hand, the longer you're here, the more likely you are to have some major screw-up. I've been fairly lucky so far to have avoided major potholes, and I think my credibility is pretty good. I'm not prone to backslapping, but I think people respect my speaking frankly and and trying to advance the cause of research and public health.

Q: What realms of science do you think most benefit from the collaborative approach at NIH?

Varmus: I think they all do. Particularly dramatic, though, is an area like neuroscience, where there's been a tradition of competition and a tendency for one institute to claim a domain that is obviously a shared domain. So many institutes are involved in neuroscience; so much is going on. Fundamental discoveries in genetics, various aspects of cell growth, signaling molecules, and cell death have had profound effects on every single disorder of the nervous system. Imaging devices have had an impact on our perceptions of the nervous system.

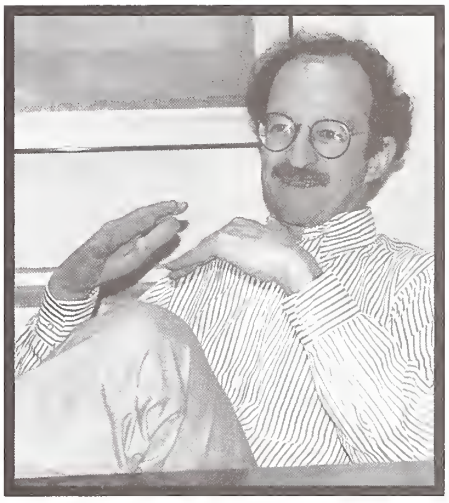
Another important realm is the unravelling of the components of the genomes—in the plural, because the human genome is not the only important genome; this work is profoundly influencing every sphere of medical research. Genes become the glue to bind institutes together. We've seen institutes collaborate in the sense that matters most, that is, they've contributed money to a common pot to generate a center for the study of complex genetic traits, cooperatively run now in Baltimore [see story, page 7]. And everyone's paying attention to information as it arrives in GenBank, through the work of the Library of Medicine. It's a beehive.

Q: Do you see the Intramural Research Program undergoing any more major changes?

Varmus: There are still things we're thinking about, such as the need to pay attention to how the intramural program is different from the extramural program. Are there ways we can be more responsive to acute public health needs in such areas as emerging infections, vaccine production, possibly some aspects of genetics? I think it's incumbent upon us [to be more responsive] because of the different nature of the activity here, the way it's financed, and the mass of scientists we have on hand. One way is to make greater use of the Clinical Center in training students. Michael [Gottesman, director of the Intramural Research Program] and I are pushing hard to develop a program, in the next year, we hope, that will bring medical students to the campus to learn clinical research, much the way the Howard Hughes Medical Scholars program brings medical students here to do laboratory work. We hope to have a significant cohort of students in that program next year. [See "From the DDIR," page 2.]

I've also been interested for a long time in developing a graduate program here. A Ph.D. program oriented around clinical problems is particularly appealing to me—not that one has to do clinical research to get a Ph.D., but every graduate student would have some time in the Clinical Center learning firsthand about some clinical problem. They could use that experience with disease as an informational backdrop and inspiration for doing high-quality laboratory research.

My advisory committee last week also suggested a program for people who had just gotten their Ph.D. to come here for one year before they go out as postdocs to do laboratory work. In that one year, they would get exposed to clinical problems. Another possibility would be to have Ph.D. students at other institutions around the country come to NIH for one year of exposure to clinical problems and then go back to [the home institution]. These are all worth thinking about, but the most fully developed of these ideas would be to have a Ph.D.-granting program in which the focus would be human physiology, with research programs built on intimate acquaintance with a clinical situation in the Clinical Center. The Clinical Center is a remarkable re-source for teaching. Every time I go over there, I'm amazed at what nature has presented us.



Celia Hooper

Q: Would this cost a lot of money?

Varmus: Small potatoes compared with the overall budget of NIH. To set up a program of fairly modest size to bring medical students to campus for exposure to clinical research would not cost much money. But if we wanted, for example, to house these students in a manner that resembles what is done for the Howard Hughes students staying at the Cloisters, we might eventually have to build a dormitory, which would cost a few million dollars. We might need to turn to the new National Foundation for Biomedical Research (sometimes known as the Foundation for the NIH) to help raise money.

Q: Regarding the reorganization on the NIH campus: NCI has undergone a major review, and there are others in the works. Do you expect cataclysms?

Varmus: NCI was in particularly difficult straits and clearly needed a very deep overhaul. The spectacular success there is due to [NCI Director] Rick Klausner's leadership and the willingness of people at NCI to pitch in and make very needed and important changes. Other institutes are undergoing reviews of their intramural programs. The NIMH review will be done in January; there are four others going on [NIAMS, NIA, NIDA, and NIAAA]; and there will be additional ones later. I don't expect changes as dramatic as those at the cancer institute, but I do expect significant differences in research emphases and changes in program content and the way the programs interface with extramural activities.

There's another type of review going on that people may not know about yet: I'm assembling small groups to provide independent advice to institute directors about their performance. I was surprised when I realized that institute directors can serve for a very, very long time without getting an independent review. Institute directors are unlikely to be criticized by their grantees due to the risk of reprisal. In general, we hesitate to criticize the person who is in charge of the treasury. But we all need corrective

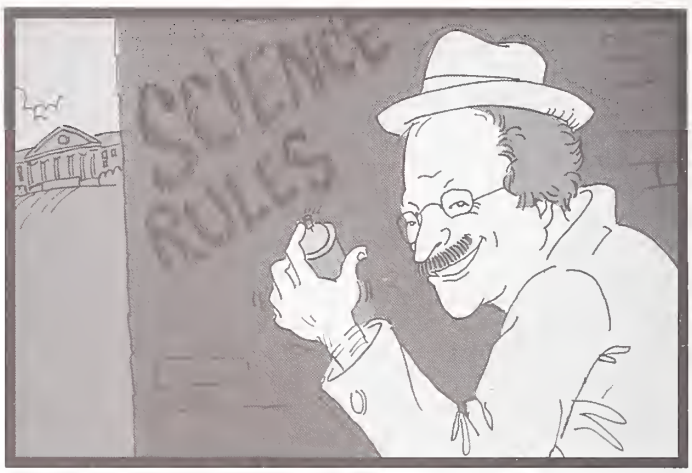
advice. I try to get it at least once a year by asking Tony Fauci [NIAID director] to run a principals-only, closed meeting of institute directors to elicit their frank opinions and come back to me with a list of the comments made—with no attribution. One of the dangers of my position is that the only person above me whom I see regularly is Donna Shalala [HHS secretary], but she doesn't know [day in and day out] what I do.

Q: Does it work?
Varmus: It's been useful. Yes. Happily, I have not received a lot of devastating criticism, but I have gotten a few useful suggestions.

Q: Can you give us any examples?
Varmus: No. The advice was given in confidence, and I think I'll just keep it confidential.

Q: Who will constitute the groups that will be giving advice to the institute directors?
Varmus: I make the final selections, but I get advice from several people, including the institute directors themselves. Each institute has advocates, scientists, patients, and people in Congress interested in how they manage, how they lead, how they make scientific decisions. Institute directors have a harder job than I do, and they're accountable to a lot of people. My objective here is to get an informal report on where the directors have been successful and where corrective action ought to be taken. The intention is certainly not to decide who gets another number of years of service, but to make suggestions that will be received in the spirit in which they are given.

Q: Do you anticipate gene therapy research and AIDS research proceeding any differently as a result of the reconstitution of the RAC [Recombinant DNA Advisory Committee] and last year's report of the NIH AIDS Research Program Evaluation Task Force [chaired by Arnold Levine, chairman of the Molecular Biology Department at Princeton University]?
Varmus: AIDS is closer to the surface right now and the issues are somewhat clearer. We've had a massive review of the AIDS program and an incredibly valuable report. We've moved quite quickly on a lot of fronts, increasing the amount of money on RO1 grants, putting together a prevention initiative, and, most importantly, seizing what is clearly the most underexploited goal of the research endeavor: to develop a vaccine. I'm quite optimistic that the leadership we're trying to provide in AIDS vaccine development is going to have a very stimulatory effect on investigators everywhere to think more seriously about the prospects of a vaccine, about doing more work in immunology. I have had the good fortune to be able to recruit, with the assistance of the institute directors and Bill Paul [director, Office of AIDS Research], one of the world's great scientists—David Baltimore [professor of molecular biology and immunology at the Massachusetts Institute of Technology]—to chair the AIDS Vaccine Research Committee.



At a December "celebration of leadership" at NIH, which happened to coincide with his birthday, Harold Varmus received many irreverent tributes from people in high places—like the cartoon above (a product of NCI creative genius), depicting how the NIH director integrates art and science after hours.

We're also all very much inspired by the discovery of the co-receptors [for HIV], actually a series of discoveries catalyzed by the fundamental discovery made in the intramural program by Ed Berger [NIAID] and colleagues, which really set this whole new field moving. This is one of those examples where a dramatic scientific discovery fertilizes a scientific field so that a whole crop of new investigators seems to have grown up instantly. And there's a lot to exploit in terms of treatment and prevention.

Q: What have been some of the high and low points since you've been here?
Varmus: There have been a lot of high points. I get a thrill when a major discovery is announced; I've been exhilarated by our budgetary success.

As for the lows, we're very frustrated by our difficulties in human embryo research. Mistakes were made in the very beginning in the way this work was described to the public and Congress—partly my fault, partly not—and I've been frustrated by the real difficulty in moving this very important new field of work ahead. This includes new contraceptive methods, understanding fertilization well enough to improve in vitro fertilization procedures, prospects for developing human embryonic stem cells that could have a tremendous role in transplantation in the future.

Q: Do you see any way to counter misapprehensions about this research?
Varmus: It's going to be hard. I don't want to lay out a strategy at this point, but I hope that public education . . . will allow us to get there eventually.

Q: What about your own research? Do you like being an intramural researcher?
Varmus: I think it's going reasonably well. I try to get to my lab every day. And, yes, I enjoy it. I don't want to extrapolate [about the experience of typical scientists at NIH] from what's obviously an unusual situation. While I try not to take advantage of my position, I think inevitably it's going to help me out. Obviously, people are not going to place obstacles in my way, and I probably get minor renovations more quickly than others do. So I don't think I always get a totally fair view of what's going on. But having a lab certainly has acquainted me with the difficulties in parking, which I hear about every day. I'm worried about that, and I'm working hard to try to develop a parking plan that will solve this problem.

I also hear about the difficulty in

working in locked labs [due to strict radiation security rules imposed last year]. . . . I never carry keys around. I hate it when I can't get into my own lab because the doors have to be locked because there's a low-level radioactive filter on a bench top. Having a lab puts me in touch with some of these realities.

I've also very much enjoyed my collaborations on campus. I've had the good fortune to tap into a lot of the richness of the intramural research program. It's been wonderful.

Q: Is it hard to balance your lab and administrative activities?
Varmus: Well, let's face facts. I don't spend as much time in the lab as I wish I did. I don't spend as much time reading the journals as I wish I did. But I do try to make it [to the lab] every day and hold long lab meetings once a week. I'm accessible to my group, I come in occasionally on Saturdays or Sundays or stay late in the day during the week. We do get a measure of productivity in papers published, and I don't think the rate is so different from what it was in San Francisco [University of California at San Francisco]. I have a much smaller lab, but I'm fortunate to have postdoctoral fellows who are independent and bright, and we do quite well. In addition, I'm very lucky to have Suzanne Ortiz, who managed my lab in San Francisco and who shields me from some of the administrative problems.

Q: Is there anything else you'd like to say to *The Catalyst*'s readers?
Varmus: You tell me. What are people worried about?

Q: Postdocs are worried about getting jobs. . . .
Varmus: Well, everyone in the world is worried about getting jobs. There's a shortage of jobs. But there are jobs, and everybody I've seen look for one has always ended up getting something, maybe in the industrial sector rather than in academia and not always laboratory positions, but people do find jobs. There are many reasons to be optimistic about maintaining a career in which one's training has been in the biological sciences. But I think NIH investigators have got to become better mentors; we need to know our trainees well and to provide a realistic sense of where the jobs are and what each trainee is best suited to do. ■

Interest Group Gazette

We ring in another year with three new interest groups added to our ever-growing list of interest groups. There has also been a personnel change in the **Genetics Interest Group:** Robert Nussbaum (NCHGR) has stepped down as organizational head, and Elliot Gershon, NIMH, and Lynn Hudson, NINDS, have taken hold of the reins. The group meets the last Tuesday of each month from 4:00 to 5:30 p.m. in Building 49, Conference rooms A and B. For further information, contact Gershon at 496-3465 or <elliotg@helix.nih.gov>, or Hudson at 496-9660 or <hudson@helix.nih.gov>.

The **Molecular Psychiatry Interest Group** held its first meeting on January 30. The purpose of the group is to bring together investigators from various clinical and basic science backgrounds—molecular genetics, neurobiology, physiology, pharmacology, and imaging—to explore common interests related to the fundamental biological mechanisms of psychiatric disorders. For more information, contact: Julio Licinio, Clinical Neuroendocrinology Branch, NIMH, at 496-6885; fax: 402-1561; or e-mail: <licinio@codon.nih.gov>.

The **NIH Reactive Oxygen Species Interest Group** (NIH ROS Interest Group) was organized at the last monthly meeting last year of the Oxygen Club of Greater Washington, D.C., Inc. The co-organizers are Chuang Chiueh, NIMH, and Daniel Gilbert, NINDS. All members of the Oxygen Club who are NIH scientists are automatically members of the NIH ROS Interest Group. Oxygen Club members pay no dues to join the new group. All NIH scientists interested in the biological effects of reactive oxygen species are encouraged to join. Reactive oxygen species include the superoxide radical anion, peroxyl radicals, hydrogen peroxide, lipid hydroperoxides, hydroxyl radical, alkoxyl radicals, thiyl radicals, ozone, singlet oxygen, and the nitrogen free radicals (i.e., nitric oxide and nitrogen dioxide). The Oxygen Club was formed at NIH in 1987 and has sponsored two international symposia.

Meetings are held the second Friday of each month (September through May) at 4:00 p.m. in Building 49, Conference Rooms A and B. The NIH Oxygen Club web site is <http://rsb.info.nih.gov/o2-club/> and will also serve as the web site for the NIH ROS Interest Group. The next scheduled meetings are February 14, with Mordechai Chevion, Hebrew University–Hadassah Medical School, Jerusalem, discussing transition metals that promote oxidation; and March 14, with Ingeborg Hanbauer, NIH, discussing the toxic effect of lead mediated through oxygen free radicals.

Last but not least on the list of new interest groups is the **Calcium Interest Group**, which held its first business meeting (and official launching) January 14. The envisioned scope of the group includes stimulus-secretion coupling in neurons and endocrine cells, stimulus-contraction coupling in muscle, the role of calcium in cell proliferation, interactions among calcium stores and calcium entry pathways, and spatiotemporal aspects of signaling. Some techniques to be highlighted are calcium imaging and mathematical modeling. A standing meeting date, time, and location have not yet been determined. Contact these individuals for information:

- Indu Ambudkar, 496-1478; <ambudkar@yoda.nidr.nih.gov>
- James Russell, 496-5493; <james@helix.nih.gov>
- Arthur Sherman, 496-4325; <asherman@nih.gov>
- Stanko Stojilkovic, 496-1638; <stankos@helix.nih.gov> ■

—Bev Stuart

RECENTLY TENURED

Eugene Koonin *received his Ph.D. from Moscow State University in the former Soviet Union in 1983 and subsequently worked as a research scientist and laboratory chief at the Institute of Microbiology, Russian Academy of Sciences, in Moscow. In 1991, he joined the National Center for Biotechnology Information (NCBI), where he is now a senior investigator in the Computational Biology Branch.*

My work in computational biology at NIH has been dedicated to four main activities: exploring the evolution of viruses, detecting conserved motifs in proteins, predicting new protein functions and characterizing protein families and superfamilies, and undertaking the comparative analysis of complete bacterial genomes.

Fran Pollner

Eugene Koonin

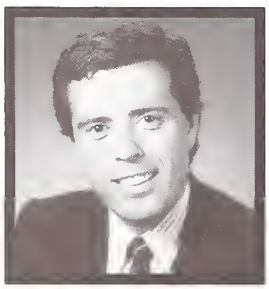
In 1994, my NCBI colleagues Roman Tatusov and Stephen Altschul and I developed a new program called MoST (Motif Search Tool) for detecting conserved and potentially functionally important motifs in protein sequences. This new method, combined with existing approaches, helped us and others to discover several new motifs in proteins, which led to important functional predictions. These include, for example, a novel nucleotide-binding motif shared by eukaryotic translation initiation factor eIF-2B and a variety of nucleotidyltransferases, and another motif that is conserved in splice-junctions of self-splicing proteins and in the hedgehog family of development regulators.

Lately, we have been concentrating on proteins implicated in human disease or development. Many of these proteins have multiple domains and are primarily regulatory rather than enzymatic. They contain motifs that define critical protein-protein interactions that are subtle and hard to detect yet are likely to provide important clues to the proteins' mechanisms of action. An example of a recent discovery in this area is a domain shared by BRCA1, the product of the breast and ovarian cancer susceptibility gene, and proteins involved in cellular DNA's damage-responsive checkpoints. Experimental pursuit of this lead may advance our understanding of BRCA1's involvement in cell-cycle control and malignant transformation. Very recently, my colleagues Arcady Mushegian and Mark Boguski and I completed a detailed analysis of the protein sequence encoded by all positionally cloned human disease genes.

A major achievement in the past two years in genome research has been the sequencing of the first complete genomes of single-celled species. By the end of 1996, complete genome sequences were available for four bacteria, one archaea (*Methanococcus jannaschii*), and one eukaryote (the yeast *Saccharomyces cerevisiae*). Comparative analyses of these sequences opens up a whole new area of research and may eventually result in the reconstruction of the list of specific genes that must have been present in the last common ancestor of bacteria, eukaryotes, and archaea. So far, our computer analyses have resulted in the prediction of several new gene functions and the reconstruction of biochemical pathways in bacterial and archaeal species that have not been extensively characterized experimentally (e.g., *Haemophilus influenzae* and *M. jannaschii*). Mushegian and I have proposed the deduction of a theoretical minimal gene set for cellular life that could be derived by comparing genomes of distantly related species, detecting conserved genes, and supplementing the conserved genes with unrelated genes that perform the same essential functions in each of the bacteria. By comparing the genomes of *H. influenzae* and *Mycoplasma genitalium*, we converged on a set of about 250 genes that may present a reasonable approximation of the minimal gene repertoire required for a cell to function. We are now working simultaneously on the detailed comparison of bacterial, archaeal, and eukaryotic genomes and the development of an automated system for genome analysis.

Computational biology obviously has been on the rise in the 1990s, but the real excitement lies in the near future, when multiple genome sequences of model organisms and the human genome become available. The approaches and tools we are developing now will prepare us intellectually and technically to begin mining the wealth of information about life encoded by these sequences.

Julio Panza *received his M.D. from the National University of Rosario, Argentina, in 1981 and trained in internal medicine and cardiology at the Italian Hospital of Buenos Aires from 1982 to 1986. He joined NHLBI's Cardiology Branch as a clinical research fellow in 1986 and became head of the Echocardiography Laboratory in 1990. He has also directed the Clinical Vascular Physiology Laboratory since 1991.*



Julio Panza

My principal research interest has been the investigation of the dynamic mechanisms mediating vascular-function abnormalities that may have pathophysiological and clinical implications. In particular, my lab's studies center on endothelial function in patients with essential hypertension and patients with hypercholesterolemia, a focus informed by the observation that the contractile state of vascular smooth muscle is dependent on the presence and integrity of endothelial cells.

We have performed intra-arterial infusion of drugs into the brachial artery with noninvasive measurement of the response of the forearm vasculature and found that both hypertensive and hypercholesterolemic patients have impaired endothelial function. In both sets of patients, impaired function is due to decreased activity of nitric oxide, a small molecule released by endothelial cells during resting conditions and in response to a variety of physiological and pharmacological stimuli. Although we do not yet understand the precise mechanisms accounting for this abnormality, we have observed important differences between hypertensive and hypercholesterolemic patients, suggesting that distinct pathophysiological pathways underlie the endothelial dysfunction in these two conditions.

Endothelium-derived nitric oxide plays a central role in vascular homeostasis by regulating not only vascular tone but also other important processes, such as thrombus formation, lipid transport, and oxidation of lipid molecules. Therefore, a defect in nitric oxide activity might constitute a link between risk factors and the development of atherosclerosis. Our goal is to further characterize the precise mechanisms that regulate endothelial function and that contribute to endothelial dysfunction. This research may lead to a more rational and specific approach to the prevention and treatment of atherosclerosis.

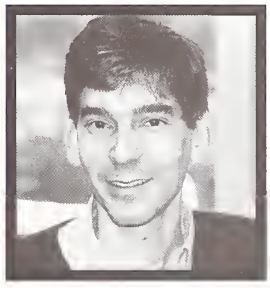
In addition to my research in vascular physiology, I have directed the clinical and research activities of the Echocardiography Laboratory of NHLBI since 1990. This laboratory is responsible for the performance and interpretation of approximately 2,000 studies per year. Over the

past few years, we have focused on using cardiac ultrasound imaging to study coronary artery disease. Routine transthoracic echocardiographic examination can identify the pattern of myocardial contraction at rest, during inotropic stimulation to increase cardiac muscle contraction, and during stress, but there is significant attenuation of the ultrasound signal due to the density of the fat, muscle, and bone of the chest wall. Transesophageal echocardiography overcomes the limitations of the transthoracic examination by obtaining heart images through a transducer positioned within the esophagus. We initially reported on the accuracy of transesophageal dobutamine stress echocardiography for the identification of obstructive coronary artery disease in patients undergoing coronary angiography. More recently, we have focused on the study of the myocardial response to dobutamine (a positive inotropic agent) to unmask viable myocardium in patients with left ventricular systolic dysfunction.

Future research directions include the use of novel methodologies, including myocardial contrast echocardiography and three- and four-dimensional imaging, that we anticipate will expand the usefulness of echocardiography as a tool for the clinical investigation of heart disease.

Philip Rosenberg *received his Ph.D. in biostatistics from Yale University in 1988. He joined NCI that year as a staff fellow and is currently a biostatistician in the Division of Cancer Etiology and Genetics.*

My research has focused on two fundamental questions that turn out to be closely related. First, given that there are limited direct data about human immunodeficiency virus (HIV) infection rates, how does one track its spread in the United States? Second, how does one model the incubation period of the disease?



Fran Pollner

Philip Rosenberg

When I began my research in 1988, 83,000 AIDS cases had been reported to the Centers for Disease Control. That figure now stands at more than half a million. To get a handle on the extent of HIV infection, both diagnosed and unsuspected, I helped to develop what is now known as the "back-calculation" method, whereby one works backwards, on the basis of the AIDS incubation period, to learn how many people must have been infected over time to account for the subsequent numbers of diagnosed AIDS cases.

This so-called back-calculation method has become a major approach worldwide to estimating the size of the AIDS epidemic. In collaboration with epidemiologists at the CDC, I have used these techniques to help make official Public Health Service estimates of HIV prevalence. On the basis of the concordance of back-calculation with other data, the estimate of about 1 million HIV-infected people in the United States was revised downward to 630,0000 to 900,000 Americans living with HIV or AIDS in 1992. A careful look at the numbers underlying this total, however, cautions against complacency. People living with AIDS today are typically in their late 30s, but my research indicates that the majority of newly infected individuals are in their teens and 20s. Thus, the "stability" of HIV prevalence in the United States is misleading: typically, people become infected in their 20s, progress to AIDS in their 30s, and are dead by age 40. Clearly, prevention efforts need to focus on teenagers and young adults.

The calculations of national infection rates are made in light of careful assessment of the natural history of the disease. As chief statistician for the NCI Multicenter Hemophilia Cohort Study (MHCS), I have helped to monitor the experience of more than 1,200 HIV-positive people with hemophilia. Our results suggest that HIV-positive hemophiliacs infected as children progress to AIDS more slowly than hemophiliacs infected as adults (or any other group, for that matter). By exploiting the extensive database of clinical, immunologic, and virologic outcomes in the MHCS, we are working to zero in on the biological mechanisms that account for the protective effect of younger age at infection.

The scientific environment of NIH has allowed me to work at the interface of statistics and epidemiology. The software I developed for back-calculation has evolved into a general-purpose "toolbox" for statistical deconvolution. To estimate the incubation period for AIDS, I developed new methods to obtain smooth estimates of the hazard function from survival data that are directly applicable in cancer and other diseases. My current investigative focus is on identifying those groups at highest risk of HIV infection in the 1990s. Preliminary results point to young homosexual men and young women exposed to heterosexual contact with at-risk individuals as most vulnerable. Minorities within those two groups are at especially high risk.

Jürgen Wess *joined the NIMH Laboratory of Cell Biology as a visiting fellow in 1988 and became a principal investigator in the NINDS Laboratory of Molecular Biology in 1991. Since 1993, he has headed the molecular biology research unit at the NIDDK Laboratory of Bioorganic Chemistry. Wess received his Ph.D. in pharmacology in 1987 from the University of Frankfurt, Germany.*

Fran Pollner

Jürgen Wess

The activity of virtually every cell in the body is regulated by extracellular signals (e.g, neurotransmitters, hormones, and sensory stimuli) that are transmitted into the cell via distinct plasma membrane receptors, most of which are members of the superfamily of G protein-coupled receptors (GPCRs). By using different muscarinic acetylcholine receptors (m1–m5) and various members of the vasopressin peptide receptor family (V1a and V2) as model systems, my group has addressed the following fundamental questions regarding the structure and function of GPCRs: How are GPCRs arranged (assembled) in the lipid bilayer? How do GPCRs bind ligands? Which structural elements determine the specificity of receptor–G protein interactions? What conformational changes do activating ligands induce in the receptor protein?

Given the lack of high-resolution structural information on any GPCR, we have used a molecular genetic strategy (involving the functional rescue of misfolded mutant muscarinic receptors by complementary mutations) to gain insight into GPCR structure. We have identified specific contact sites between individual transmembrane helices, thus providing insight into the molecular architecture of the transmembrane receptor core.

We recently found that GPCRs can be assembled from multiple independently stable building blocks. We have shown that coexpression of muscarinic or vasopressin receptor fragments—obtained by splitting the wild-type receptors in various intracellular and extracellular loops—results in functional receptor complexes. Immunocytochemical studies revealed that the individual receptor fragments (even when expressed alone) were stably insert-

ed, with proper orientation, into lipid bilayers. Moreover, we have demonstrated that truncated V2 vasopressin receptors known to be responsible for X-linked nephrogenic diabetes insipidus can be functionally rescued (in cultured cells) by coexpression with a C-terminal V2 receptor fragment missing in the mutant receptors. Such findings have potential therapeutic relevance.

We were among the first to comprehensively map the ligand-binding domain of a GPCR (m3 muscarinic receptor). The amino acids forming the acetylcholine binding site were identified by site-directed mutagenesis, and a molecular model of the acetylcholine–receptor complex was delineated. We also showed that the binding site for muscarinic antagonists is distinct from the acetylcholine binding domain, although some amino acids are shared by both sites.

Characteristically, each GPCR can activate only a limited set of the many structurally similar G proteins expressed within a cell. Using different muscarinic and vasopressin receptor subtypes as model systems, we could identify distinct intracellular receptor segments (as well as single amino acids contained within these regions) that are sufficient to dictate receptor–G protein coupling selectivity. On the basis of these findings, we proposed a structural model of the receptor surface critical for G protein recognition.

A major focus of our current work is identifying specific regions on the G protein(s) that are contacted by the different, functionally critical receptor sites. To address this issue, we developed a new experimental approach involving the coexpression of hybrid GPCRs with hybrid G protein α subunits. Using this approach, we identified a functionally critical contact site between a short segment of the m2 muscarinic receptor and a short sequence on $G\alpha_i$.

The molecular nature of the ligand-induced structural changes in GPCRs (resulting in receptor activation) is as yet unknown and represents a major focus of our future work. Interestingly, we recently identified a series of mutant m2 muscarinic receptors that can activate the proper G proteins even in the absence of ligands. The predicted structural characteristics of these constitutively active mutant receptors suggest that ligand-induced receptor activation involves a translational and/or rotational movement of one of the transmembrane helices.

Since all GPCRs, as well as all heterotrimeric G proteins, share a high degree of structural homology, our findings should be of great general relevance. A better understanding of the molecular basis of ligand–receptor–G protein interactions should pave the way for the development of novel therapeutic strategies.

Scott Whitcup *joined NEI's Laboratory of Immunology in 1990 and joined the Clinical Branch in 1993. He was appointed NEI clinical director in 1994 and branch chief in 1995. Whitcup received his M.D. from Cornell University Medical College in 1984 and completed residencies in internal medicine (at UCLA Medical Center) and ophthalmology (at the Massachusetts Eye and Ear Infirmary, Harvard Medical School).*

Fran Pollner

Scott Whitcup

My laboratory focuses on the role of cell-adhesion-molecules and cytokines in the pathogenesis of ocular inflammation. Initial studies in two experimental models—autoimmune uveoretinitis and endotoxin-induced uveitis—demonstrated that the expression of E-selectin, ICAM-1, and VCAM-1 is upregulated in the eye before the influx of inflammatory cells. We then showed that monoclonal antibodies against several cell adhesion molecules, including ICAM-1, LFA-1, Mac-1, VLA-4, E-selectin, and P-selectin, could inhibit both autoimmune and endotoxin-induced ocular inflammation. We subsequently treated ragweed-induced allergic conjunctivitis in mice by blocking ICAM-1 and LFA-1 with monoclonal antibodies or the selectins with a small molecule inhibitor.

More recently, we investigated changes in cell adhesion molecule expression on lymphocytes during cell activation. These studies involved transgenic animals that express hen egg lysozyme (HEL) in the lens. Transgenic mice develop severe ocular inflammation only if injected with *in vitro*-activated splenocytes taken from wild-type animals immunized with HEL; nonactivated cells cause no ocular disease. Fluorescence-activated cell sorting (FACS) analysis showed that activation is associated with upregulation of VLA-4 on the cell surface, and anti-VLA-4 antibody inhibited the adoptive transfer of disease. We have also demonstrated upregulation of adhesion molecule expression in the retina and choroid of patients with uveitis, as well as in human corneas undergoing allograft rejection. Our work led to the granting of the U.S. patent for treating uveitis by blocking cell adhesion molecules with monoclonal antibodies; studies in patients with sight-threatening uveitis are planned.

Our research on the involvement of cytokines in uveitis yielded the interesting observation that two pro-inflammatory cytokines, TNF-α and IL-12, paradoxically ameliorate ocular inflammation while provoking systemic inflammation or even death. This observation underscores the uniqueness of the ocular environment and supports the hypothesis that cytokines can have varying effects, depending on the type of inflammation, time course of the disease, and other cytokines present. Our ongoing studies use knockout mice deficient in ICAM-1, LFA-1, and IL-6 to further define the role of adhesion molecules and cytokines in uveitis. We also plan to investigate what effects blocking CD40 ligand may have on ocular inflammation.

In addition to my laboratory research, I am involved in clinical studies on the pathogenesis, diagnosis, and treatment of uveitis. In recent clinical trials, we have investigated the safety and efficacy of the carbonic anhydrase inhibitor, acetazolamide, for cystoid macular edema, a major cause of vision loss in patients with uveitis, and the combination of prednisone and cyclosporine for ocular Behçet's disease.

Intraocular lymphoma is a disease that frequently masquerades as an idiopathic uveitis. We have shown that elevated ratios of IL-10 to IL-6 in the vitreous or the cerebral spinal fluid are associated with the presence of malignant cells, which can be extremely difficult to recognize by cytopathology. Also, in collaboration with investigators at NCI, we are conducting a Phase I/II trial of combination chemotherapy for lymphoma of the central nervous system or eye.

I am also studying the ocular complications of AIDS. We were the first to recognize retinal toxicity associated with the antiretroviral agent didanosine (ddI). Histopathological examination revealed destruction of the retinal pigment epithelium and overlying neural retina; electron micrography showed a membranous cytoplasmic inclusion consistent with a metabolic storage abnormality. Finally, we are involved in investigating new therapies for cytomegalovirus retinitis and are currently studying whether increases in CD4+ T-cell counts that are induced by anti-HIV medication will prevent progression of this disease.

Roger Woodgate *received his Ph.D. in biology from the University of Sussex, Brighton, England, in 1986 and joined NICHD's Section on Viruses and Cellular Biology as a senior staff fellow in 1989, shortly after completing his postdoctoral fellowship in the laboratory of the late Hatch Echols at Berkeley. He currently heads the unit on DNA mutagenesis in the Section on DNA Replication, Repair, and Mutagenesis.*

Fran Fisher

Roger Woodgate

Most living organisms are continually subjected to a variety of chemicals, both synthetic and natural, that damage their DNA. Although many organisms have evolved elaborate repair processes to deal with this damage, under certain conditions not all of the damage can be processed by error-free repair mechanisms. As a result, the DNA is replicated with a much lower fidelity than normal. My laboratory focuses on trying to understand the molecular mechanisms of this mutagenic process. To date, most of our efforts have focused on *Escherichia coli*, but we are now using *Saccharomyces cerevisiae* and *Xenopus laevis* as model systems in our investigations of similar processes in eukaryotic cells.

Genetic experiments with *E. coli* indicate that DNA polymerase III holoenzyme (the main replicative enzyme), RecA, and the UmuDC-like mutagenesis proteins—all of which are induced as part of the cell's multigene so-called "SOS" response to DNA damage—are directly required for the mutagenic process. In the mid 1980s, Bryn Bridges and I proposed a two-step model to explain UmuDC and RecA activities. We suggested that the RecA protein might act to influence the incorporation of incorrect nucleotides opposite DNA lesions, and the Umu proteins might act at a later stage by promoting continued DNA synthesis from the incorrectly paired primer.

In an attempt to test this hypothesis, we overproduced and purified the UmuD and UmuC proteins and demonstrated that UmuD undergoes a RecA-mediated post-translational cleavage reaction that generates a shorter, but active, UmuD' protein. We also discovered that UmuD' exists as a dimer in solution and that it interacts with a monomer of UmuC to form a mutagenically active UmuD'C complex. Indeed, using these purified proteins together with RecA and DNA polymerase III, we were able to reconstitute the mutagenic process in vitro and demonstrate translesion DNA synthesis. Experiments undertaken by Ekaterina Frank in my laboratory revealed that UmuD' physically interacts with RecA protein and that this protein-protein interaction provides a means by which Umu proteins can target DNA lesions.

Recently, in collaboration with Wayne Hendrickson at Columbia University in New York, we were able to crystallize the UmuD' protein. The structure was refined to 2.5 Å and elucidated the self-cleavage process UmuD undergoes during its conversion to UmuD'. In addition, we discovered that whereas UmuD forms a molecular dimer with itself, the extended amino and carboxyl terminals of one UmuD' protomer can interact with a protomer from another dimer to form an extended polymeric structure that we believe is essential for mutagenic activity.

We have also investigated the in vivo stability of the Umu proteins in *E. coli*. Because relatively few molecules of active UmuD'C complex are required to promote mutagenesis, *E. coli* has evolved an exquisite mechanism to reduce the cellular concentration of UmuD': instead of forming a homodimer with itself, UmuD' preferentially forms a heterodimer with the intact UmuD protein. This heterodimeric complex is specifically recognized by the ClpXP serine protease, and the UmuD' protein is therefore rapidly degraded. We are now performing experiments aimed at elucidating the signals that allow ClpXP to recognize the heterodimeric UmuD-UmuD' complex but not the homodimeric UmuD' protein.

A major goal of our work is to identify similar processes in eukaryotic cells. As part of a collaborative study with Eric Ackerman (NIDDK), we have shown that whereas *X. laevis* oocytes can efficiently replicate undamaged single-stranded DNA, they are unable to replicate DNA that contains adducts. Interestingly, this replication arrest was alleviated in progesterone-matured oocytes and in oocytes microinjected with mRNAs encoding the prokaryotic UmuD' and UmuC mutagenesis proteins. This finding strongly suggests that the basic mechanisms contributing to mutagenesis are conserved between prokaryotic and eukaryotic cells. Indeed, both structural and functional homologs to UmuC that have been identified in *S. cerevisiae*, mice, and human cells are now under investigation. ■

New Listserv Address

The **Pain Interest Group** recently announced its own listserv address: <paingroupl@list.nih.gov>.Anyone at NIH can subscribe to the list. Monthly get-togethers are held the second Monday of the month at 3 p.m. For further information, M.A. Ruda can be reached by phone at 402-4980, or fax at 402-0667, or e-mail at <ruda@yoda.nidr.nih.gov>. ■

It's Elementary!

Want to spark the scientific interest of kids about 8 to 10 years old? A science teacher is seeking scientists to lead 25 students (grades 3, 4, and 5) through simple science activities or experiments during an afterschool club.

The Science Club meets on Thursdays from 3:45 to 4:30 p.m. at North Chevy Chase Elementary School, 3700 Jones Bridge Rd. Openings to help out are available February through April 1997. If interested, e-mail Amy Chang at <achang@asmusa.org> or call her at 493-8657 in the evenings. ■

Not For Biologists Only

It may be called the NICHD Biologist Forum, but this monthly information exchange and technical skills update often offers pearls of wisdom to more than its current members—who toil in the NICHD laboratories of molecular genetics, eukaryotic gene regulation, and mammalian genes and development.

Monthly forum topics have included primers on conducting DNA mutagenesis or purification, protein stabilization, sequencing, and PCR reactions, as well as training on the use of available computer hardware and software.

The forum meets the second Monday of each month, from 4 to 5 p.m., in the second floor library of Building 6B. February's featured speaker is biologist Belinda Jackson, who will discuss her research in the Lab of Eukaryotic Gene Regulation. ■

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: how best to improve the climate for clinical research at NIH; how to maximize the value of the new ombudsman office; your advice to Harold Varmus on how an NIH director might satisfy public, scientific, and one's own research interests in equal—or near-equal—measure; and the vacationing Hot Methods Clinic (yes, this last item is a repeat from last issue's "call"; you're getting a second chance). **Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@od1em1.od.nih.gov>; fax: 594-3592; or mail: Building 1, Room 334.**

In Future Issues...

- How NIH Scientists Spend Their Summer
- What's Going On At Frederick
- Research Sources In Cyberspace

1) What do you think of the efforts under way to enhance the appeal and feasibility of clinical research as a focus for NIH scientists? Are they sufficient? Are they necessary?

2) What issues would best be handled by an ombudsman? Are there ways to ensure that the office is truly accessible to everyone without its becoming overburdened? How could instructive dispute resolutions be publicized without violating confidentiality?

3) What do you see as priorities for the NIH director, in general and in the next three years specifically?

4) The Hot Methods Clinic is returning next issue. What updates can you provide on previous Hot Methods? What techniques would you like to see covered in the future?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 334, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; e-mail: <catalyst@od1em1.od.nih.gov>

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