FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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BIRKEDAL-HANSEN MOVES IN AS NIDR'S SCIENTIFIC DIRECTOR

by Celia Hooper

After a sometimes contentious year of waiting and—as *Science* put it last spring—looking "down in the mouth," NIDR is welcoming a new Scientific Director: Henning Birkedal-Hansen, previously Assistant Dean for Research and Graduate Affairs at the University of Alabama's School of Dentistry in Birmingham. Birkedal-Hansen, who started work at NIDR on Feb. 16, also held positions as Chairman of the Department of Oral Biology and Director of the Research Center in Oral Biology at Alabama before coming to NIH.

"What appealed to me about the job was the opportunity to influence basic science related to oral health," Birkedal-Hansen says. "The program has a great reputation for its scientific excellence, and its location on the NIH campus provides a collection of highly competent scientists [for potential collaboration]. It is the perfect environment for research, and you won't find it anywhere else in the world," says Birkedal-Hansen. "I haven't doubted for a second that this is the best job in the world."

Henning Birkedal-Hansen

Birkedal-Hansen says he plans to analyze the strengths and weaknesses of the dental institute before he launches any drastic transforma-

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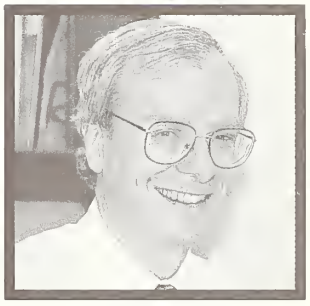
REVAMPING THE INTRAMURAL WORKFORCE:

ROUGH MARCHING ORDERS AND CREATIVE MOVES

by Celia Hooper

At the Scientific Directors' meeting in mid-January, the Clinton administration's toughlove approach to budget and bureaucracy finally hit home. Yes, Virginia (and Maryland and D.C.), they really *do* plan to excise 252,000 jobs from the federal government by 1999, and NIH's Intramural Research Program will not be exempt from these cuts.



Jack Mahoney

In this issue of *The NIH Catalyst*, we give the bad news and the good news. First, in this article, is the bad news about the expected cuts. Then, in the three related articles (pages 4, 5, and 6) that follow, we soften the blow with some good news about a new type of training position that could bring much-needed help to NIH labs (without consuming precious full-time equivalents, or FTEs) and about two innovative programs for tapping senior expertise and free off-campus space and resources.

NIH's Deputy Director for Management, Jack Mahoney, gave the Scientific Directors the bad news about the cuts on Jan. 19: to meet the 1994 employment ceilings imposed by the Office of Management and Budget (OMB) and HHS, NIH must lose approximately 300 FTEs. The 1995 target calls for dropping roughly another 400 FTEs. Michael Gottesman, Acting Deputy Director for Intramural Research, says that the far more dire news is that unless the rules are changed, 10 percent of these cuts must come from grade levels GS-14 and above.

Mahoney says NIH is "on a track to accomplish our 1994 reduction targets" through attrition, and he believes outright layoffs, or reductions-in-force (RIFs), are highly unlikely—and highly disfavored by NIH's leadership. At present, many institutes, and NIH as a whole, are, in fact, below their FTE ceilings and could proceed to hire or replace some people, if it weren't for another obstacle: since late last year, NIH has been under a temporary PHS-wide employment freeze. "No one ever defined what length of time was 'temporary,'" says Mahoney.

NIH Director Harold Varmus has been seeking relief through all possible channels. Other parts of HHS—

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SIX THOUSAND POINTS OF LIGHT

Michael Gottesman

One of the virtues of the current review of the NIH Intramural Programs by a committee of External Advisors is the opportunity "to see ourselves as others see us" and to use this information to improve the quality of our lives and work at NIH. Although our External Advisors are assembling their report for presentation to Dr. Varmus this month, we have already begun to benefit from the self-scrutiny that has accompanied their efforts. One fact that I learned is that there are approximately 6,000 working scientists in the Intramural Research Program (IRP) at NIH, of whom close to 2,500 are scientists-in-training.

In searching for what is best and what is in need of remediation in the IRP, I have had the opportunity to talk with many of you. Others have taken time to write to me and to the External Advisors. Although it is premature to talk about policies and procedures that we may want to change at NIH, it seems clear that some of our problems are self-imposed and can only be solved if we all pitch in and help. Some of these problems may seem trivial in the greater scheme of things, but they all conspire to affect our work environment, and I would like to use this opportunity to bring them to your attention.

SOME OF OUR PROBLEMS ARE SELF-IMPOSED AND CAN ONLY BE SOLVED IF WE ALL PITCH IN AND HELP.

Consider, for example, the mentoring that we provide to IRP scientists-in-training. As teachers, our senior scientists are responsible for fostering the careers of these 2,500 individuals. Do we sit down on a regular basis and discuss their futures? Should they consider jobs in industry, government, or academia? Do they have a chance at a tenure-track position at NIH? Should they consider medical practice, teaching, law school, or business? Once a career direction has been defined, do we provide appropriate training experiences? Do trainees have the opportunity to develop their ideas independently and to present their work in both informal and formal settings? Are senior scientists acting truly as mentors, or simply as passive observers of students? No records are kept of what happens to scientists trained at NIH, and this should surely change.

On another front, do our trainees take advantage of the wealth of educational experiences available at NIH? Do they take full advantage of seminars and journal clubs inside and outside of their own areas of interest? Dr. Varmus and I have been encouraging the establishment of seminar series that will broaden NIH's educational offerings, and we hope that senior scientists and fellows will use these opportunities to learn about exciting new developments in biology. The NIH Director's Seminar Series — lectures of general interest presented by tenured and tenure-track IRP scientists (see page 3 for a list of speakers) — offers a potpourri of exciting new science, and complements the six established NIH Lectures (including the Mider and Dyer Lectures). With support from the NIH Director's discretionary fund, each of the major special-interest groups (Cell Biology, Genetics, Immunology, Structural Biology, and Neurosciences) will have several outstanding speakers each year giving talks of general interest, and some of the smaller special-interest groups will also be sponsoring NIH-wide talks. We expect to average one major NIH-wide seminar per week. Watch for them on posters and on the yellow sheet. Don't miss them.

Consider, too, the immediate physical environment in NIH labs. Has anyone else noticed that our laboratories are overpopulated, cramped, and sometimes downright unpleasant to work in? The "critical mass" for explosive science may have been exceeded in some laboratories, which may be headed for a black hole from which no useful information can possibly escape. Crowded conditions can lead to safety hazards, and it may be time to "just say no" to that extra person if there is no room to work in a safe and pleasant environment.

Finally, consider the broader environment in which we live and work. You may have read in the local press of concerns about NIH's incinerators. Have you thought about why NIH burns so much medical-pathological waste? In a few months, when the incinerators are completely shut down, NIH will have to truck this waste to some distant site for disposal. Not everything that is burned is truly medical-pathological waste (MPW); in some cases, MPW containers may be used for general waste as well. Paper and other recyclable materials that are not MPW should be in other waste containers. Tissue-culture material and glass may be autoclaved or treated with bleach and then pulverized. Beyond these possible first steps, NIHers need to come up with some creative solutions to the problem of waste disposal. We are now establishing an NIH-wideworking group to suggest ecologically sound, cost-efficient, simple alternatives to the current disposal system with the aim of reducing the amount of MPW processed. If you have any ideas, FAX them to *The NIH Catalyst* (see page 20), or send them directly to me. Also, let me know if you wish to volunteer for the task force.

These are but a few of the opportunities we have to improve the quality of our lives at NIH. None of these issues can be resolved without the creative input and cooperation of NIH's 6,000 scientists ... including you.

Michael Gottesman
Acting Deputy Director for
Intramural Research

FAX-BACK Feedback

Below is a sample of the FAX-BACK comments we received for each topic raised in the January issue.

On concerns about clinical research in the wake of the FIAU episode:

"One wonders whether FIAU was as exhaustively tested in preclinical trials for toxicity as FIAC, which was abandoned because of excessive toxic side effects. This is not clear in your article." — *Anonymous.*

"The NIH leadership will have to work very hard to prevent the NIH Clinical Program from being hit with even more burdensome regulations." — *Steve Tronick, NCI.*

On techniques you would like to see covered in the "Hot Methods Clinic:"

"In situ PCR analysis of fixed tissue." — *Anonymous.*

"Gene Knockout Techniques." — *Steve Tronick, NCI.*

On starting a new feature on the merits and demerits of scientific products:

"Such a feature is not a good idea — we don't need more 'info-mercials' for proprietary products and equipment. Let's keep *The Catalyst* for news and opinion and leave the product reviews for other publications such as the *Journal of NIH Research*." — *J.M. Sayer, NIDDK.*

"DNA and protein synthesizers. Any instruments or systems over $15,000 since we usually are given little time to make intelligent decisions about expensive equipment (e.g., centrifuges, spectrophotometers, etc.). b) PCR sequencing and cloning kits; cDNA libraries. This will be a great feature!" — *Steve Tronick, NCI*

Suggestions to NIH Director Harold Varmus to improve the intellectual atmosphere on campus:

"Scientists here sometimes get tunnel vision. We could combat this by starting a program of "internal sabbaticals" in which investigators spend six months or a year in another lab/institute on campus, learning and doing something new." — *J.M. Sayer, NIDDK.*

"Promote greater inter- and intra-institute scientific exchange among the intramural scientists by supporting bimonthly poster sessions on a rotating basis using the NIH Research Festival as a format." — *Anonymous.*

"Develop programs (i.e. poster sessions, an office for technical support) to encourage and better utilize the contributions of technical support. Lack of a Ph.D. or M.D. degree should not cause us to overlook the potential of these valuable members of the NIH family." — *Kathy Higinbotham, NCI-FCRDC.*

"Implement a graduate program and require NIH senior scientists to teach at least one course per semester. Harold Varmus' ideas are great ones. Make sure he and Mike Gottesman read *The Catalyst* carefully! Keep up the gook work. *The Catalyst* is a terrific publication." — *Steve Tronick, NCI.* ■

Association For Women In Science Opens Bethesda Chapter

The Association for Women in Science (AWIS), a national organization that supports the advancement of women in scientific fields, has launched a new Bethesda chapter.

Meeting for the first time in October, the group elected NINDS researcher Joan Schwartz as its president. Deborah Henken, also of NINDS, became the president-elect, and Carol Colton of Georgetown University Medical School is the organization's first secretary. The group has attracted members from the Uniformed Services University of the Health Sciences, the Armed Forces Radiobiological Research Institute, and Georgetown, as well as extramural and intramural sections of NIH. "This is a great chance to meet not just NIH women, but other women scientists in the area," says Schwartz. "It's a way to set up a young women's network." Schwartz says that historically, leaders in scientific fields have tapped into an old boys' network when they needed help or had jobs to offer. "Lack of networking has been a huge problem for women scientists" who weren't included, Schwartz says.

Schwartz says that typical meetings begin with 45 minutes of visiting, networking, socializing, refreshments, and time to post and read notices of jobs, postdoctoral fellowships, and other opportunities available or sought. The remainder of the meeting features a speaker and discussion of topics of interest for chapter members.

Catherine Didion, Executive Director of the chapter's parent organization, which is located in Washington, D.C., spoke at the initial assembly. At a meeting in December, Bernice Sandler, a Senior Associate at the Center for Women Policy Studies in Washington, D.C., discussed mentoring. Sandler is the author of a chapter on the myths, realities, dangers, and responsibilities of mentoring published by AWIS in it recent book, *A Hand Up—Women Mentoring Women in Science*.

Sandler says all women can profit from groups such as AWIS. "It's a way to meet lots of people, get information, and learn what's going on," Sandler says. "Women are often isolated from

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Speakers Invited for the First Half of the 1994 NIH Director's Seminar Series

NIH Director Harold Varmus has invited the following speakers to present their work during the first half of the 1994 NIH Director's seminar series. Launched in February, the new seminar series features tenure-track and tenured intramural scientists discussing exciting new findings of general interest to NIH researchers.

3/14	3p.m.	Ward Odenwald, NINDS	Probing the *Drosophila* Genome for CNS Developmental Genes; and the Serendipitous Discovery of the *white* Gene's Role in Homosexual Behavior
4/19	Noon	Jennifer Lippincott-Schwartz, NICHD	Membrane Traffic and Compartmentalization within Eukaryotic Cells.
5/17	Noon	Cynthia Dunbar, NHLBI	Gene Transfer and Transgenic-Mouse-Model Approaches to Understanding Hematopoiesis.
6/14	Noon	David Nielson, NIAAA	Tryptophan Hydroxylase: Regulation of Gene Expression, Association with Serotonin Metabolism, and Suicidal Behavior. ■

THE NEW IRTAs: NIH TRAINING AUTHORITY WIDENED TO ATTRACT NEW BRAINPOWER

by Celia Hooper

On Feb. 10, the Directors of NIH's Institutes, Centers, and Divisions approved two new extensions of NIH's Intramural Research Training Awards (IRTA) program. The Division of Personnel Management (DPM) is now dotting the i's and crossing the t's, and expects the first trainees to enter the program in the next few months.

Mimi Blitz

The point of the new extensions is to bring some desirable new groups of students to NIH to boost their credentials and to train them in the conduct of research. But because the students in these new programs come as trainees—not government employees—they will not draw down the dwindling supply of full-time equivalent (FTE) positions, an advantage that will certainly not be lost on any Lab Chiefs who are feeling the pinch of lowered FTE ceilings (see related article, page 1).

Under one of the extensions, the **General IRTA Fellowship Program**, predoctoral or postdoctoral scholars who qualify for IRTAs and who have won grants or fellowships from non-U.S. government sources, can receive funds from NIH to bring their total funding up to the level of traditional IRTAs with comparable experience and training. Mimi Blitz, a personnel specialist in DPM, says that until now, NIH was missing a golden opportunity to recruit trainees—some with very prestigious (but not very lucrative) fellowships from universities and foundations—because there was no way to combine external and intramural fellowship funding. Potential trainees were forced to choose between outside fellowships and NIH IRTAs. The new program also provides health insurance to trainees whose external fellowships do not cover it.

IRTA General Fellows must be U.S. citizens or permanent residents, have approved fellowships from an outside organization, not be employees of the outside sponsor, be postdoctoral scholars (with five or fewer years of postdoctoral research experience at the time of entry) or graduate students enrolled in Ph.D., M.D., D.D.S., D.M.D., D.V.M. or equivalent degree programs for which NIH training is an approved and integral part, and be receiving less money from their outside fellowship than is provided by a traditional IRTA. For example, if a postdoc fresh out of graduate school was receiving less than $25,000-$30,000 from an outside fellowship, the intramural program supporting the student would contribute funds to bring his or her total support up to the $25,000-$30,000 IRTA entry level. Levels of support depend on the type and extent of schooling and work experience that an IRTA brings to NIH. Awards are for one year or less, but may be renewed one year at a time over the life of the IRTA's outside fellowship up to a maximum of three years for predoctoral students and five years for postdocs. IRTA General Fellows coming to the end of their external grants may be considered for transfer to regular pre- or postdoctoral IRTAs, but cannot extend their maximum years of IRTA support (three or five years) through such transfers.

The second program extends NIH's predoctoral training in two ways. Through the **IRTA Student Support Fellowship Program**, institutes can provide financial support and research experience to disabled and economically disadvantaged high-school and undergraduate students, with particular emphasis on recruitment of female and minority students. Although some aspects of this new program—such as schedules, eligibility, recruitment, and selection of students—will parallel provisions of the Stay-In-School Program, Blitz stresses that there is an important difference. Whereas Stay-In-School students, who now occupy FTEs, are at NIH to perform routine work, the new IRTA Student Fellows will be coming here to receive meaningful training

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Summer Help Available!

The NIH Office of Education (OE) has received over 2,400 applications from talented high-school, college, medical, and graduate students who wish to work in NIH intramural laboratories this summer. These students have identified three institutes and three research areas that they are interested in. Their applications, which include a statement of interest, a resume, letters of recommendation from science faculty, and transcripts, are now in the hands of the institutes' summer program coordinators listed below. Interested scientists may contact the appropriate summer coordinator. Students may be supported through the Intramural Research Training Awards mechanism, but funding must be provided by the institutes. Questions? Call Deborah Cohen at 402-2176.

1994 Intramural Summer Coordinators

CC	Cathy Richardson, 10/1N312, 496-6924
DCRT	Helen Madigan-Sedor, 12A/3013, 496-6951
NCHGR	Patricia Stewart, 49/4A06, 402-4575
NCI/DCE	Judy Schwadron, 31/11A11, 496-6556
NCI/DCPC	Mike Genua, 31/10A50, 496-9606
NCI/DCT	Kathleen Peters, 31/3A44, 496-5964
NCI/DCBDC	Carol Howes, 31/3A05, 496-3381
NCRR	Henry Eden, 13/3W13, 496-5771
NEI	Micki Risley, 31/6A23, 496-4274
NHLBI	Doug Price, 10/7N220, 496-3483
NIA/GRC	Ronda Thornton, GRC/1D09, (410)558-8116
NIA/NEURO	Karen Turner, 10/6C103, 496-8970
NIAAA	Marcia Hammer, DANAC, 443-1073
NIAID	Phil Baker, Twinbrook/106, 496-1220
NIAMS	Lynn Eyre, 6/408, 402-1375
NICHD	Gordon Guroff, 49/5A68, 496-4751
NIDCD	Gail Mundell, 31/3C11, 402-0508
NIDDK	Mary Daniels, 10/9N208, 496-3225
NIDR	Paul Kolenbrander, 30/310, 496-1497
NIMH	Jean Barr, 10/4C101, 496-5337
NINDS	Levon Parker, 31/8A19, 496-5332 ■

TAPPING "SENIOR" EXPERTISE — A GOLDEN RESOURCE

by Seema Kumar

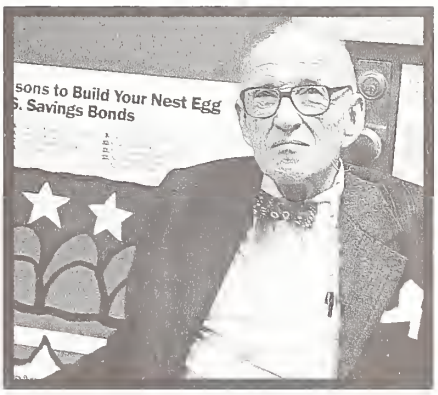
For the past 20 years, eminent immunochemist Elvin Kabat has made significant contributions to the scientific and intellectual milieu at NIH, but unlike most 20-year veterans of NIH, Kabat is not a full-time NIH employee. Kabat, 79, and his Columbia University colleague Harold Ginsberg, 77, belong to a growing pool of "senior" scientists who bring valuable expertise to intramural labs without using up precious full-time equivalent (FTE) slots. With future FTE cutbacks, NIH may rely more on this pool of expertise, and according to Kabat and Ginsberg, that would not be such a bad idea.

"I have enjoyed working here at NIH, interacting with the scientists ... and have had many fruitful collaborations," says Kabat. During his two decades at NIH, Kabat has held various non-FTE positions including Fogarty International Scholar and Guest Researcher. He has worked in five different institutes and collaborated with top NIH scientists. Ginsberg, on the other hand, is a relative newcomer, here as a Fogarty International Scholar. But already, Ginsberg has had productive collaborations and is soon to be appointed as an expert scientist at NIAID. Ginsberg says he is "very pleased to have an opportunity to concentrate on research without worrying about funding, supervising, or teaching."

WITH FUTURE FTE CUTBACKS, NIH MAY RELY MORE ON "SENIOR SCIENTISTS" AND ACCORDING TO KABAT AND GINSBERG, THAT WOULD NOT BE SUCH A BAD IDEA.

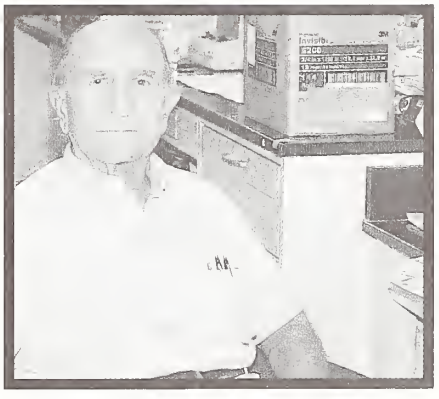
Both Ginsberg and Kabat hold emeritus faculty positions at Columbia University, in New York. Ginsberg has moved to Bethesda but retains a lab at Columbia which he frequently visits. Kabat, on the other hand, commutes from New York for two days each week — a schedule that he has followed since his first NIH appointment as a Fogarty Scholar in 1974. Throughout this period, Kabat has divided his time and scientific energies between Columbia and NIH, juggling a tough schedule of teaching, research, and writing. But Kabat, known for his workaholic ways, does not mind the inevitable delays and hassles of commuting as long as "I get to do what I want."

Kabat's long-term relationship with NIH is in some respects ironic. In the McCarthy era, PHS canceled his grant for studying allergic encephalomyelitis in monkeys when he was blacklisted as a suspected communist sympathizer. Kabat protested this label by refusing further NIH funding for nine years, relying instead on funds from the Office of Naval Research and the National Science Foundation. He had had a previous political run-in when he published a paper on biological warfare after World War II and was accused of undermining national security. But the politics of NIH grants did not sidetrack Kabat's scientific career. In 1991, President Bush bestowed the National Medal of Science on him in the Rose Garden. Kabat, who will turn 80 this September, plans to continue coming to NIH as long as he is allowed to and plans to "work till he drops." During his visits to the Bethesda campus, Kabat works on his *Sequences of Proteins of Immunological Interest*, a three-volume compilation of amino acid and nucleotide sequences of immunological proteins, including T lymphocyte receptors, major histocompatibility complex antigens, complement, and integrins. The volumes are now available on Gopher and the data bank is being expanded and kept up-to-date by Tai Te Wu of Northwestern University and computer science student George Johnson using Gopher. At Columbia, where he is now Higgins Professor Emeritus of Microbiology, Kabat conducts research on antibodies to dextran and, until two years ago, supervised the work of two Ph.D. students.



Elvin Kabat, a Columbia University Emeritus Professor, spends two days a week at NIH

Ginsberg, the Eugene Higgins Professor of Medicine and Microbiology, Emeritus, at the College of Physicians and Surgeons of Columbia University, first came to NIH as a Fogarty Scholar in 1992-1993. Ginsberg, a leading expert in molecular virology and infectious diseases, collaborated with Robert Chanock of NIAID's Laboratory of Infectious Diseases. To continue this fruitful collaboration, Chanock and NIAID Scientific Director John Gallin offered Ginsberg a five-year appointment as an expert to stay on at NIAID's Twinbrook facility to pursue further work on the pathogenesis of adenovirus and simian immunodeficiency virus (SIV) infections.



Harold Ginsberg, a Fogarty Scholar, will soon be appointed as an expert at NIAID.

Ginsberg, who works in a lab with many younger colleagues, says that age is seldom a factor in his relationship with his lab mates and that he does not feel self-conscious about his "senior" status.

A physician by training, Ginsberg's research is now focused on unravelling the molecular mechanisms involved in the pathogenesis of diseases produced by adenoviruses and SIV. ■

Where Intramural Meets Extramural: The Fruitful Interface

by Seema Kumar

At a time when it seems that intramural and extramural programs might be pitted against each other for a piece of the dwindling NIH budget, cooperation between the two camps seems far-fetched. But ask Tom Quinn and Brian Murphy of NIAID, and they will tell you that not only do many collaborations and exchange programs exist between intramural and extramural groups, but they represent an innovative way to deal with limitations in personnel and resources.

Collaborations and exchange programs between intramural and extramural groups represent an innovative way to deal with limitations in personnel and resources.

"Many intramural [scientists] are based off the main NIH campus, [including] the NCI scientists at the Frederick Cancer Research Facility and NIA and NIDA scientists at the Francis Scott Key Medical Center at Baltimore, and these scientists interact almost daily with extramural colleagues," says Quinn. "The major benefit overall for both sides is the steady flow of ideas and concepts and the sharing of resources and data that ... culminate in collaborative research that is beneficial to both parties."

Quinn and Murphy speak from personal experience: For the past 13 years, Quinn, an intramural researcher at NIAID, has conducted much of his groundbreaking work on AIDS and other sexually transmitted diseases at The Johns Hopkins University School of Medicine, where he has lab space and direct access to a rich resource not available to him at the Clinical Center: large numbers of patients at high risk for HIV and other sexually transmitted diseases (STDs) who come to the two Baltimore City-run STD clinics managed by Hopkins' infectious-disease division.

"My research has really benefited from being so close to this critical resource," says Quinn. "I am only two blocks from the clinic, and specimens come to our laboratory within an hour after they have been taken from the patients, and in some cases, this is critical for our research. ... You can't always do that in Montgomery County."

What Quinn can do at NIH's Bethesda campus in Montgomery County, where he spends roughly half his time, is "keep up with the cutting-edge basic research and be at the forefront of developments in basic research in AIDS." As part of a 10-year mega-project funded by intramural and extramural NIAID, Quinn led a U.S. government team that traveled to Haiti, Cuba, and Zaire during the early years of the AIDS epidemic and initiated some of the early work on the epidemiology, virology, immunology, and clinical aspects of the disease. More recently, Quinn has set up similar intramural projects in India and Brazil and along with the Fogarty International Center, in Mexico.

Quinn's research at Johns Hopkins, including his early work on heterosexual transmission of HIV, complemented his research in the international arena and yielded important insight into the similarities and differences in the epidemiological and clinical features of the disease. From 1986 to 1988, Quinn and his colleagues published a series of papers in *Science*, the *Journal of the American Medical Association*, and the *New England Journal of Medicine* reporting the changing profile of the HIV-infected population in the Baltimore STD clinics — from a predominantly male population to one equally distributed between men and women. Initially, the spread of HIV to women was linked to intravenous drug use, but Quinn and his extramural colleagues soon observed a change to co-infection with syphilis that was independent of intravenous drug use. Quinn and his intramural colleagues had observed a similar profile in Africa during the early AIDS epidemic. In other studies, Quinn and his colleagues found that "heterosexual men and women who were not intravenous drug users and who had acquired syphilis, herpes, or chlamydia were acquiring HIV at a significantly higher rate. Co-infection with other STDs was facilitating heterosexual transmission of HIV."

Tom Quinn, an intramural researcher at NIAID, spends roughly half his time at Johns Hopkins University

At Hopkins, Quinn is close to another rich resource: the emergency department, where poor, inner city patients with HIV are most likely to come for medical care and treatment. Quinn and his collaborators have been monitoring the trends in HIV infection in ER patients and are also looking for patients with the acute retroviral syndrome — the transitory illness accompanying the early stage of HIV infection before patients develop antibodies to the virus. HIV multiplies at its highest rate at this stage, and NIAID Director Anthony Fauci and his colleagues in Bethesda need samples from such patients to better understand the immunopathogenesis of HIV.

For its part in the cooperative arrangement for Quinn, Hopkins dedicated space to NIAID — free of charge — and gets in exchange the benefit of interactions with Quinn and NIAID clinical staff fellows who spend at least six months per year in Hopkins' infectious-diseases consultative service. One of Quinn's responsibilities in his assignment to Hopkins is to facilitate the clinical training of NIAID Clinical Staff Fellows who are interested in infectious diseases. The Johns Hopkins Hospital, a 1,000-bed acute-care facility, provides a rich resource for this training.

Developing Vaccines

For the past two decades, NIAID's Laboratory of Infectious Diseases (LID) has led a comprehensive effort to develop vaccines for three major respiratory viruses — an undertaking that is beyond the personnel and space capabilities of the tiny intramural lab. LID scientists attribute their successes in developing and evaluating candidate vaccines for the respiratory syncitial virus (RSV),

parainfluenza virus-type 3 (PIV-3), and the influenza-A virus to a unique ar-rangement for drawing on outside resources.

LID employs three contractors: Program Resources Incorporated (PRI), a Rockville-based vaccine-manufacturing plant that makes 1,000-5,000 doses of experimental vaccines for clinical trials; BioQual, another small company in Rockville that tests NIAID's experimental vaccines in animal models; and The Johns Hopkins University School of Medicine, which conducts human studies.

Brian Murphy, an NIAID intramural scientist, uses outside resources to support his research on vaccines for respiratory diseases.

The contracts themselves are not the key to the unique system's success, says Murphy. The real key is that "extramural researchers in the United States who are developing vaccines for these three viruses can plug into this system. It is these plug-ins that represent a unique way for intramural and extramural scientists to interact," says Murphy.

For example, since the 1970s, intramural scientists have led a systematic effort to evaluate the usefulness of a cold-adapted influenza-A virus vaccine developed in the late 1960s by John Maassab at the University of Michigan School of Public Health in Ann Arbor. PRI makes the variants, which are then tested not only by intramural NIAID at the clinical center and at Johns Hopkins, but also at extramural Vaccine Evaluation Units (VEUs) located at four different universities across the United States. Results from these various studies provide a basis for further vaccine development. "Our own capabilities within the intramural facility really rest with phase 1 and early phase 2 trials; Phase 2 and 3 and some Phase 1 are done by the extramural community VEUs," says Murphy. This coordinated partitioning of the work helps avoid unnecessary repetition, says Murphy.

"Yet another type of intramural-extramural interaction comes into play when vaccines are developed within an NIH intramural laboratory, like, for example, the experimental RSV vaccines made in our section, or the experimental rotavirus vaccines made by Albert Kapikian [of LID]," says Murphy. "Once the basic characterizations of these candidates are completed in our contract facility at Johns Hopkins, these are extensively tested in the other VEUs."

With NIH's tremendous restrictions on space and lack of large manufacturing facilities that meet FDA standards, using such contracts for extramural expertise and facilities is essential, says Murphy. In addition, he says, the 1986 Technology Transfer Act is prompting NIH project leaders to identify at an early phase of vaccine development industrial sponsors to support the research and perform some of the preclinical and clinical studies.

"For example, currently we have a CRADA with Wyeth Laboratories to develop RSV vaccines. We will do some of the studies in our intramural vaccine facility at Johns Hopkins, Wyeth will independently contract out to do the studies at another center, and we will coordinate the efforts. This helps us bring products to completion faster because the more work that an industrial sponsor can do at an early phase, the more they can use that information for their licensure application," says Murphy.

Murphy is taking FTE cutbacks at NIH in stride — and not just because his contracts with extramural scientists buffer the impact of the cuts on his research. "Having been here 23 years, I find it remarkable how intramural scientists and the NIH in general are able to find ways of dealing with FTE restrictions," says Murphy. "Necessity is always the mother of invention, and I can't imagine a situation where the occupiable space available at NIH won't be filled by one mechanism or the other."

Murphy concedes that "cutting back FTEs will impact on the continuity of our programs — especially long-term projects. But projects that are good will survive and things will work out." ■

Honoraria-Ban Update

The Justice Department has asked the U.S. Supreme Court to rule on the honoraria ban, which prohibits federal workers from receiving payments for speeches, articles, or appearances. But the good news for federal workers is that, in the interim, until the high court makes a decision, the Justice Department will not prosecute people for accepting honoraria or withdrawing money from escrow accounts in which they are holding honoraria.

Last year, two lower courts ruled that the honoraria ban is so broad that it violates the First Amendment rights of employees; nevertheless, the Justice Department decided in January to appeal these decisions. In a letter to the U.S. Office of Government Ethics, Assistant Attorney General Frank Hunger stated that the Justice Department will not punish any worker receiving payments for speeches or articles between Sept. 28, 1993, and the date on which the Supreme Court rules. The high court is expected to decide this spring whether or not to hear the case and to rule by July 1995 if it elects to review the honoraria-ban case. Hunger emphasizes that it remains illegal for employees to accept outside payments for job-related appearances or writing—defined by some researchers as presentation of work less than a year old.

Meanwhile, the U.S. House of Representatives is considering a bill (HR 1095) that would restore the rights of federal employees to accept honoraria. The bill, sponsored by Rep. Barney Frank, D-Mass., and co-sponsored by Rep. Steny Hoyer, D-Md., and Rep. Connie Morella, R-Md., among others, permits federal employees making less than $108,000 annually to accept payment for articles or speeches unrelated to their jobs. Senior-level employees (GS-15 and above) would be required to notify their ethics office before they could accept more than $200 in honoraria from one source in a year. Payment for work-related activities would continue to be banned for all employees. — *C.H.* ■

GENBANK AT NIH: DATABASE GROWS BY 1,000 SEQUENCES PER WEEK

by Jim Fleshman, Ph.D., Barbara Rapp, Ph.D., and Dennis Benson, Ph.D., NLM

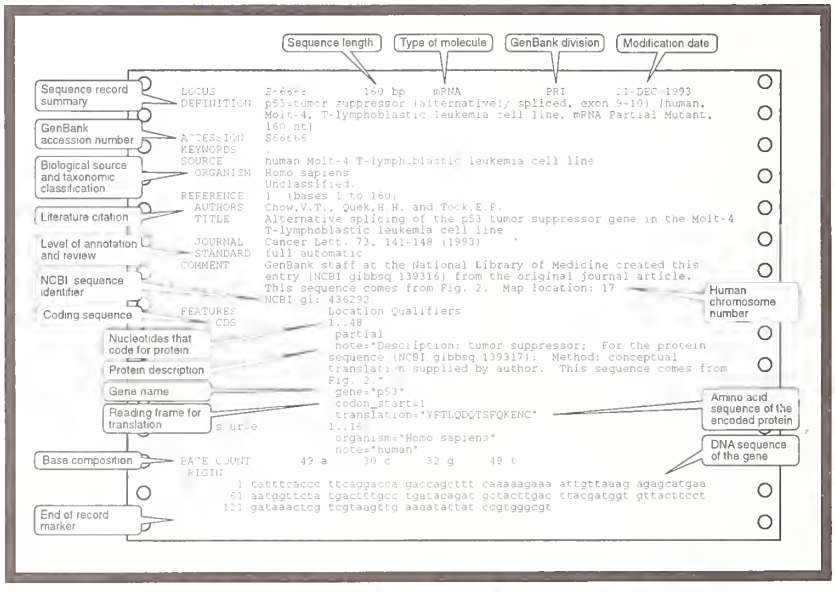
GenBank is one of the oldest and largest of the DNA-sequence databases and is an essential resource for biologists worldwide engaged in gene discovery and other aspects of molecular genetics. Since October 1992, GenBank has been based at the National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine (NLM) located on NIH's Bethesda campus. GenBank has grown at an astonishing rate since then: more than half of the sequences currently in the database have been added in the past 18 months. As the Human Genome Project and related genome efforts continue to increase the rate at which genes are identified and sequenced, and as greater biological and medical understanding of sequence data is acquired, GenBank and NCBI will play an increasingly important role in capturing this new knowledge and making it accessible to the research community.

GenBank has always been supported by NIH, but it has not always been part of the Intramural Research Program. From 1982 to 1992, contractors established and distributed the database, and subcontracted the design and data entry work to Los Alamos National Laboratory in Los Alamos, N. M. GenBank's new home, NCBI, was created by legislation on Nov. 4, 1988, with the mission to develop automated information systems to support biotechnology and molecular biology and to conduct basic research in computational molecular biology. As a component of the NIH Intramural Program, NCBI scientists pursue research in bioinformatics, molecular-structure modeling and prediction, and mathematical methods for sequence analysis. Other staff and contractors design and develop database software and provide support for NCBI's computing systems and thousands of users of GenBank and NCBI's other databases and services.

NCBI's Director, David Lipman, says that locating the center within NLM created the ideal environment for GenBank. NLM's extensive experience in producing biomedical databases can be combined with the knowledge and skills of NCBI staff who understand the basic science of molecular biology and the special requirements of molecular-sequence databases. In fact, NLM is one of the key sources of new sequence data. Nine NLM indexers with backgrounds in molecular biology scan 3,300 MEDLINE journals to capture published sequences as new GenBank records.

A Proliferation of Sequences and Services

As of last month, GenBank comprised more than 173 million nucleotides from more than 160,000 DNA and RNA sequences. Each GenBank entry (see figure) includes a concise description of the sequence, the scientific name and taxonomy of the source organism, and a table of features that identifies coding regions and other sites of biological significance, such as transcription units, sites of mutations or modifications, and repeats.



Example of a GenBank printout and what it means.

Protein translations of coding regions are included in the feature table. Each GenBank record corresponds to a continuous piece of DNA, and the largest entry now is yeast chromosome III, with 315,338 bases. Although human entries predominate, constituting 30% of the total, more than 8,000 species are represented.

GenBank users typically want one of two things from the database: 1) to retrieve records based on a set of search criteria, such as gene or protein name, author, organism, and accession number, or 2) to search the database for sequences similar to a sequence of interest. NCBI provides several services and programs to use in accomplishing these tasks: Internet e-mail services for record retrieval and for BLAST-sequence-similarity searches; an interactive on-line system called GenInfo; interactive network client-server programs; or self-contained CD-ROM databases and retrieval software (see box on page 9). The growth in the use of NCBI search services has increased even more rapidly than GenBank itself. NCBI computers now conduct more than 2,000 text searches and 2,500 similarity searches every day, and more than 2,000 users have purchased annual subscriptions for the Entrez CD-ROM. Entrez is a graphical point-and-click database-retrieval system for Macintosh, PCs with Windows, and Unix users. It is now also available at no charge via Internet.

Steve Tronick, Acting Chief of NCI's Laboratory of Cellular and Molecular Biology, is a frequent and enthusiastic user of NCBI services. "All the services I've used are fantastic," says Tronick. "We use Entrez and the BLAST server extensively, and GenInfo, with its daily updates, is very helpful. Whenever we get a new sequence, the first thing we do is log into NCBI. I think the BLAST server is as important to our research as the PCR [polymerase chain reaction] technique."

GenBank relies on individual scientists to help make the database as comprehensive, current, and accurate as possible. NCBI can assist authors who have new data to submit to GenBank or who wish to provide additional information and corrections to existing entries. Pending completion of a new data-submission program this summer, the best way to submit data to GenBank is to use the Authorin program, which is available upon request at no charge. Mac and PC versions are available. Authorin output files may be submitted electronically via e-mail to gb-sub@ncbi.nlm.nih.gov or by mailing a diskette with the output file to GenBank Data Submissions, NCBI/NLM, Building 38A, Room 8N/803.

The central role that molecular genetics has assumed in biomedical science is illustrated by the fact that many journals now require authors to submit new sequences to GenBank and obtain accession numbers prior to publication. NCBI staff can usually assign an accession number within one working day for sequences submitted via e-mail. This accession number serves as confirmation that the sequence has been submitted, and it allows readers of journal articles to retrieve the data about the sequences. Direct submissions are processed by NCBI and NLM staff and contractors. After the GenBank submissions staff completes a systematic quality assurance review, with assistance from NCBI Basic Research Branch scientists, a draft of the GenBank record is sent to the submitter for approval. GenBank

exchanges new data and updates daily with the two other major international sequence databases, the European Molecular Biology Laboratory Databank (EMBL) and the DNA Database of Japan (DDBJ), obviating the need for multiple submissions.

NCBI also depends on the community of GenBank users to keep the database as up-to-date and accurate as possible. Although only the submitting scientist is permitted to modify sequence data or annotations, NCBI encourages all GenBank users to inform the staff of possible errors or omissions, provide updated publication information, or request the release of data that have been published. Such updates may be sent via e-mail to update@ncbi.nlm.nih.gov.

Making GenBank Better

GenBank continues to evolve. The explosive growth in sequencing efforts has challenged NCBI database and software designers to improve methods for data representation and searching.

One major challenge has been reducing redundancy in the database: more than 5% of the entries have duplicate sequences, and another 5% have close matches. Many records contain coding sequences with no features, translations, or protein-product names. A current project, called "GenBank Select," will reduce redundancy and will standardize feature annotation. Another challenge has been to improve the taxonomic classification of sequences. Because taxonomy can provide an essential key to database organization, searching, and analysis, NCBI's Scott Federhen, in collaboration with representatives of the other leading sequence databases, has undertaken a comprehensive review of GenBank taxonomic data to correct errors, identify inconsistencies, and incorporate new scientific findings. The fruits of this effort will appear in the April release of Entrez (network and CD-ROM versions). A third major challenge arose from the fact that GenBank data fields were not comprehensive and did not readily lend themselves to processing by standard software tools. Jim Ostell, Chief of NCBI's Information Engineering Branch, has created a rich and extensible sequence and mapping data specification using the ISO standard Abstract Syntax Notation 1 data description language. This new specification preserves all of the existing information while enabling GenBank to gracefully accommodate new knowledge.

The introduction of new GenBank-related services and the improvements in the design and implementation of the database are very much in the spirit of current government-wide quality- improvement initiatives, according to Lipman. He notes that the final year of the old GenBank contract cost NIH $4.8 million. Today, 18 months after assuming responsibility for GenBank, NCBI's annual cost to produce the database is approximately $2.8 million. "We're delivering more services and higher-quality services at lower cost, and 10 times more people are using those services. That's what reinventing government is all about," says Lipman. ■

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Note: GenBank and MEDLINE are registered trademarks of the Department of Health and Human Services and the National Library of Medicine, respectively.

GenBank: Easy Deposits, Unlimited Withdrawals, High Interest

It's easy — and free — for NIH intramural scientists to contribute sequences to GenBank and to search the database. The table below summarizes the different services available from NCBI.

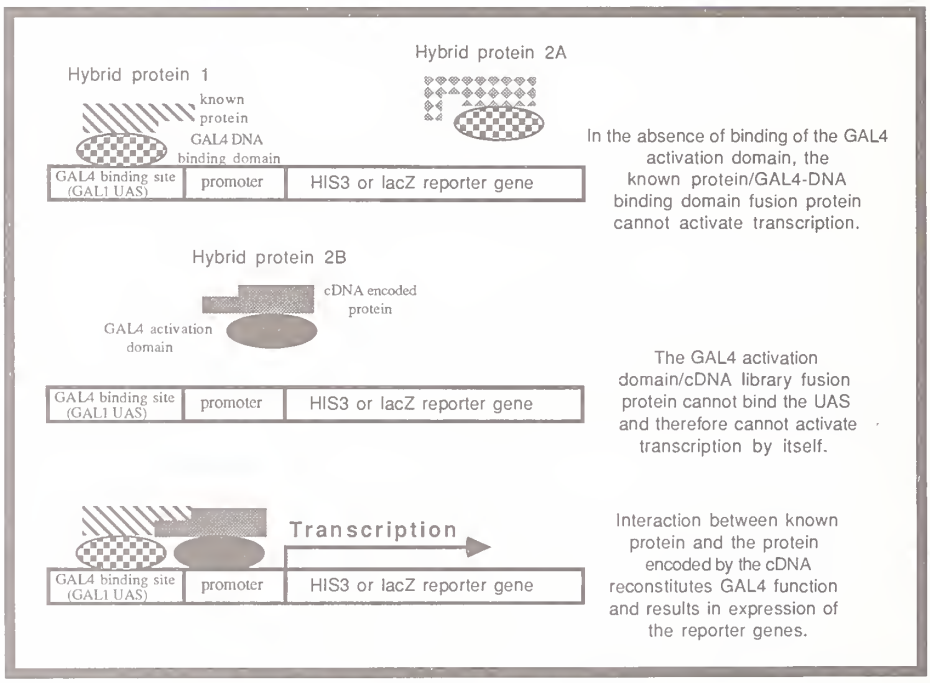
Service	Purpose	How to use or to get help
GenBank submissions	For submitting new sequences to GenBank.	To send a new submission by e-mail, use : gb-sub@ncbi.nlm.nih.gov.
GenBank updates	For correcting or updating an existing sequence; for requesting release of hold-until-published data.	To send an update by e-mail, use: update@ncbi.nlm.nih.gov.
Automated e-mail services, by access code		
retrieve@ncbi.nlm.nih.gov	For Retrieving GenBank and other sequence records based on any text term, including accession number, author name, and locus or gene name.	To receive documentation, send a message containing only the word **help** in the body of the message. To receive assistance with a problem or question, send e-mail to: retrieve-help@ncbi.nlm.nih.gov.
blast@ncbi.nlm.nih.gov	For performing a sequence-similarity search by using the BLAST algorithm.	To receive documentation, send a message containing only the word **help** in the body of the message.
est_report@ncbi.nlm.nih.gov	For retrieving reports from the dbEST database. dbEST is a database of "single-- Sequence Tags," also known as transcribed sequence fragments or putatively transcribed partial sequences).	To receive documentation, send a message containing only the word **help** in the body of the message. EST data are also contained in the databases searched by the retrieve and blast e-mail services.
GenInfo	For providing an interactive on-line search service for NIH users; search capabilities are similar to the retrieve e-mail service.	To apply for a GenInfo account, call the Service Desk at 6-2475.
Network applications	For providing "client-server" programs, in which the client program on the local PC, Macintosh orUnix workstation queries the NCBI server.	To use NCBI network applications, Internet access and locally installed TCP/IP software are required.
Network Entrez	For searching sequence databases and a sequence-related subset of MEDLINE. Using an intuitive point-and-click retrieval system.	To receive information send e-mail to: net-info@ncbi.nlm.nih.gov.
Network BLAST	For interactive BLAST similarity searching for Windows, Macintosh, and Unix users.	To receive information, send e-mail to: blast-help@ncbi.nlm.nih.gov.
NCBI Home Page on World-Wide Web/Mosaic	For providing hyper-text-like access to NCBI databases and search services and to information about NCBI software, services, and research activities.	To access, use: URL http://www.ncbi.nlm. nih.gov. Requires access to Internet "browsing" software, such as Mosaic.
CD-ROMs	For annual CD-ROM subscriptions to Entrez and GenBank.	To receive infomation, send e-mail to: info@ncbi.nlm.nih.gov. Available through GPO for $76 and $49 respectively.

HOT METHODS CLINIC: THE TWO-HYBRID SYSTEM

by Nicholas MacDonald, Ph.D., and Lance Liotta, M.D., Ph.D., NCI

Many scientists have experienced the ecstasy of discovering a new gene or protein, only to be faced with the agony of trying to elucidate its function and interaction with other proteins. Most proteins exert their effects by binding to other proteins; thus, the quest for function becomes a search for proteins that bind a new target molecule. Unfortunately, even if one finds a candidate binding protein by immunoprecipitation or solid phase blotting, these methods often do not yield sufficient quantities of the binding protein to completely characterize it. Affinity columns also require large quantities of target protein, and sometimes researchers have only a cDNA clone.

That is why many investigators are hoping that the exciting "two-hybrid" system, first described in 1989, is not "two" good to be true. The two-hybrid system is a method for directly cloning genes that encode a protein that binds to the protein of interest. The method was developed by Fields and Song (1), and, with recent refinements (2-4), is proving to be a powerful tool.



The Yeast Two-Hybrid System

How the Method Works

This **yeast-based two-hybrid genetic assay** gets its name from the two hybrid proteins that are constructed for the assay. One hybrid consists of the DNA-binding domain of the yeast transcription factor GAL4 (amino acids 1-147) fused to the known protein. The second hybrid protein is the product of a GAL4 activation domain (amino acids 768-881) cDNA library fusion. When the two hybrid proteins are introduced into yeast, any cDNA in the second hybrid that encodes a protein that binds to the known protein will cause the DNA binding domain of GAL4 to localize in proximity with the activation domain. This reconstitutes GAL4 function, and thus activates transcription of reporter genes downstream of GAL1 UAS (the GAL4 binding site). Because the yeast two-hybrid assay uses a strain of yeast that is auxotrophic for histidine and carries HIS3 and LacZ genes under the control of GAL1 UAS, clones with interacting proteins will confer histidine prototrophy and ß-galactosidase activity on transformants, making them readily detectable by their blue color.

Once identified, promising cDNAs should be cloned into the GAL4 -DNA binding domain fusion vector and checked to see if they are still able to activate transcription from GAL1 UAS alone. Without this check, false positives are a frequent and frustrating outcome of the two-hybrid screen. Clones that pass the second test (i.e., GAL4-cDNA library fusions that are not able to activate transcription from GAL1-HIS3 or GAL1-lacZ in the absence of the "target" protein) should be characterized and the binding of the known protein to the cloned protein confirmed by a separate in-vitro test.

Protocol for the Yeast Two-Hybrid Technique

(The following was adapted from protocols supplied by S.E. Elledge, Baylor College of Medicine, Houston, Texas. Mention of specific products does not constitute an endorsement.)

After subcloning the gene of interest into a GAL4 DNA-binding domain fusion vector, it is transformed into Y190 (or similar strain) using the lithium acetate protocol described in *Current Protocols in Molecular Biology*. Transformants should be selected for on complete minimal medium lacking Trp (CM-Trp) plates. The resulting strain (Y190/GBD) should be checked for its growth properties on CM-His plates containing differing concentrations of 3-aminotriazole (3-AT; Sigma A8056) and for its ability to activate the LacZ reporter. Usually 3-AT concentrations of 25-50 mM are sufficient to select against clones that are unable to activate transcription on their own. Constructs that activate transcription alone, for whatever reason, cannot be used in this assay.

Inoculate 200 ml of CM-Trp media with yeast from an overnight culture or with a single Y190-GBD colony. Grow the yeast overnight at 30 °C with shaking. Take an optical density reading (OD A_{600}) of the culture and inoculate 500 ml of yeast extract peptone dextrose media (YEPD) such that in ~2 generations (3-4 hours) the A_{600} is 0.5-0.8. Harvest the cells by spinning them down at 4,000g for 10 minutes, wash once in 100 ml of distilled water, resuspend in 50 ml LiSORB (100 mM lithium acetate [LiOAC], 10 mM Tris pH8, 1 mM EDTA, 1 M sorbitol) and incubate at 30°C for 15-30 minutes. Re-pellet the cells by centrifuging as above and resuspend in 625 µl LiSORB. Store on ice.

Boil 200 µl of 20 mg/ml sheared salmon-sperm-DNA for 7-10 minutes, add 800 µl LiSORB and mix by pipeting up and down. Cool to room temperature (ice may be used, but if the temperature drops below room temperature, the mixture will gel, ruining assay). Add 40 µg of library cDNA.

To 100 µl of the DNA-LiSORB mixture, add 100 µl of cell suspension and incubate at 30 °C for 30 minutes. Then, to 100 µl of cell/DNA solution add 900 µl of 40% PEG3350 in 100 mM LiOAc/TE (100 mM LiOAC, 10 mM Tris pH8, 1mM EDTA) and

incubate at 30 °C for 30 minutes. Heat-shock at 42 °C for 7 minutes (plate 5 µl of cells on CM-Leu, Trp [complete medium lacking leucine and tryptophan] to test transformation efficiency; efficiency should be ~5x10⁴-10⁵ colonies/µg cDNA library). Pool cells and add to 100 ml CM-His, Leu, Trp media, shake at 30 °C for 1-3 hours, harvest cells and resuspend in 6 ml of CM-His, Leu, Trp liquid media and plate, using 300 µl for each 150 mm plate containing CM-His, Leu, Trp + 3-AT plate. (Cells frozen in 10% DMSO at -70 °C at this stage lose less than half their viability). Colonies that grow after 3 to 5 days should be tested for ß-galactosidase activity using the X-Gal colony filter assay (5). Blue colonies are taken for further analysis.

Troubleshooting Tips

"It is important to add adenine to the YEPD since strain Y190 is an *ade2* mutant. There is enough adenine for the strain to grow but it is clearly limiting in the YEPD that we purchase, and the strain grows slowing without additional adenine. I supplement with adenine to a final concentration of 0.6mM (0.3mM is probably sufficient)."

"The transformation efficiency has been somewhat variable, but never more than 2x10⁴ colonies/µg."—*Matt Marton, NICHD.*

"In my experience, a transformation efficiency of 10⁵-10⁶/µg of cDNA library is more realistically obtained. Consequently, ~200µg of cDNA library is required to represent ~106 independent transformants."

"When growing up the yeast, an OD_{600} of 0.5-0.8 should be taken as a rough guide only. For the best transformation efficiencies, growth of each strain should be optimized." — *Jian-Xin Lin, NHLBI.*

Two-Hybrid Contacts

The researchers listed here are still learning the Two-Hybrid Technique. They are not experts (yet), but will do their best to help others grappling with the methods.

Matt Marton 496-1442 NICHD	(Has tested the Two-Hybrid Technique with two known proteins)
Jian-Xin Lin 496-0098 NHLBI	(Presently optimizing the library transfection step)
Henry Levin lab 402-4281 NICHD	(Now working their way through the protocol)
Gary Leong 496-6153 NICHD	(Currently testing interactions between different proteins)
Nicholas MacDonald 496-9753 NCI ■	(Now working his way through the protocol)

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NIH Director To Fund Inter-Institute Speakers

NIH Director Harold Varmus will be providing money from his Discretionary Fund to bring in speakers presenting topics of broad interest to NIH scientists. Inter-Institute interest groups should nominate speakers before June 1. Group leaders may contact Celia Hooper (402-4274) for further details. ■

Symposium on History and Science of Opiates and Opioids

The NIH DeWitt Stetten, Jr., Museum of Medical Research and NIDDK will sponsor a symposium, "Synthetic Opiates and Opioids: Drugs as Medicines, Drugs as Research Tools," on March 29, 1994, in the Lipsett Amphitheater, Building 10, from 2:00 to 4:00 p.m., to celebrate the opening of a Stetten Museum exhibit of the same title. The symposium will feature historical and scientific discussions of the work of the Laboratory of Medicinal Chemistry (LMC), NIDDK. Speakers include Caroline Jean Acker, Ph.D., Stetten Memorial Fellow in the Historical Office, Kenner C. Rice, Ph.D., Chief of the LMC, and Louis S. Harris, Ph.D., of the Department of Pharmacology, Medical College of Virginia in Charlottesville. ■

More on Interest Groups...

The NIH Inter-Institute DNA Repair Group is organized by Vilhelm Bohr of the Laboratory of Molecular Genetics, NIA in the Gerontology Research Center, Baltimore; phone (410)-558-8162; fax: (410)-558-8157; and Kenneth Kraemer, Laboratory of Molecular Carcinogenesis, NCI, Building 37, Room 3D06; phone 496-9033; fax: 496-8419. The group holds monthly seminars by invited speakers generally on the third Tuesday at 1:30 p.m., in Building 37, Room 1A19. For the schedule of seminars, or to add your name to the group's mailing list, call Kraemer.

The NIH-Inter-Institute Glycobiology Interest Group, with members from NIH, the FDA, and academic institutions and biotechnology companies in the Washington-Frederick-Baltimore area, was formed about six years ago by Gil Ashwell and Vince Hascall. They brought together researchers from many disciplines interested in the diverse, emerging field of glycobiology — the study of the synthesis, degradation, structure, function, and clinical applications of monosaccharides, complex carbohydrates, and glycoconjugates. The interest group has satellite glycobiology interest groups in the local area, and has grown to about 300 members.

Today, the group is a rich source of expertise for problem solving and information exchange on current research and new glycobiology technology. The group meets monthly on a Thursday afternoon and sponsors seminars and poster sessions by members and occasional outside speakers. Informal discussions and refreshments usually follow the meetings. Joint meetings are held annually with the Georgetown and Johns Hopkins groups as a half- or full-day symposium; a combined meeting will be in held in Annapolis this June. For more information, call Gerry Dienel at 402-3123. ■

Birkedal-Hansen Moves

continued from page 1.

tions. "I don't expect to make major program changes in the short run. Over the long run—maybe—but I don't come in with an agenda to overhaul the place," Birkedal-Hansen says. He sees NIDR as home to "very good scientists with a good track record."

Last year, NIDR was caught up in divisive acrimony after Institute Director Harald Loe shuffled leadership and created a blue-ribbon panel to review and develop long-range plans for the intramural program. Creation of the special panel, as well as its recommendations, sparked controversy that found its way to the pages of *Science*. But with the passage of time and the selection of Birkedal-Hansen, who was never involved in the fray, these troubles receded and institute personnel have united in support of the new Scientific Director.

Birkedal-Hansen sees one element of last year's debate—whether NIDR should emphasize applied or basic research—as "a pseudoproblem." In his view, NIDR has two constituencies that it must serve: the taxpayers and the scientific communities inside and outside of NIH. "It is important to me that we do science that is as good or better than any other outfit on campus," says Birkedal-Hansen. "And we need to be aware that there is a dental-research community out there whose interest we serve. We are not competing with what they do, but we want to be in the avant garde of what they do—breaking new ground, trying the impossible, setting the research agenda that will spread [through the extramural community] in the decade ahead, leading the charge....In a well-managed program, I don't see that there is any conflict between applied and basic research."

NIDR Director Loe is enthusiastic about Birkedal-Hansen's appointment. "Dr. Birkedal-Hansen will provide dynamic leadership for our Intramural Research Program," says Loe. "We are delighted to have him join our institute."

In his own lab at NIH, Birkedal-Hansen will continue studies of matrix metalloproteinases—enzymes that he describes as "instrumental in all remodeling of human tissues, whether it be in embryonic development, the growth of tumors, or inflammatory diseases" (see Research Commentary, page 17, *The NIH Catalyst*, November 1993). Birkedal-Hansen says the metalloproteinases and their inhibitors can be used "like a toolbox" by researchers who wish to study the regulation of remodeling and growth "and why it goes wrong and why it goes right."

Birkedal-Hansen's research focuses on the role that matrix metalloproteinases play in human periodontal, or gum, disease, one of the most prevalent threats to oral health. He is sorting out how the enzymes mediate cellular mechanisms and microbial process that lead to inflammatory destruction of gum tissue. Birkedal-Hansen notes that periodontal disease provides a highly accessible clinical system for researchers. "There are so many parameters that can be measured, unlike the situation with many other inflammatory diseases. This could become a prototype for attempts to intervene in these diseases," Birkedal-Hansen says. He is already planning collaborations with NCI scientists through his wife, Bente Birkedal-Hansen, who will be working in Lance Liotta's Laboratory of Pathology with William Stetler-Stevenson.

Birkedal-Hansen hopes two distinctive programs at NIDR—its pain and bone research—will evolve as trans-NIH collaborative centers. "The pain program takes neurophysiology from the basic science labs through to pain management in the clinic," Birkedal-Hansen says. "This is a model for what we want to consider in the future" for the transfer of basic research into clinical results, he says. Similarly, he says, NIDR "has had a very strong bone group. We hope this group can work with all interested parties on campus to create a basic-science-to-clinical-bone-science outfit." Birkedal-Hansen says that at this time, he is not sure how an expanded bone science unit would be structured or placed within NIH, "but this is a unique opportunity where we would like to take a leadership role."

Birkedal-Hansen received his degree as a dentist from the Royal Dental College in Copenhagen in 1969. He earned the Danish equivalent of a Ph.D. in 1977 and has been at Birmingham since 1979. He says his only regret in joining NIH is leaving behind good friends and colleagues in Alabama. Even the prospect of Maryland's hot summers, icy winters, and bureaucratic hassles haven't fazed Birkedal-Hansen. "I realize that the government [and academia work] in different ways , but I am also aware that every position has its own set of problems. You never really solve your problems," says the philosophic Dane, "you just trade them in for a new set. I am prepared to work within the system to see how that can be done."

Birkedal-Hansen also waxes philosophic when asked how he feels about assuming a position as a Scientific Director after NIH's other Scientific Directors were criticized in a news article in *Science* last August. "The Scientific Director is like a coach" of a sports team, he says. "The fact that not all people think the coach is doing a good job is not reflected by whether the team is winning or not....The most important issue is whether the team is winning. We are here to do science—not to feel good about ourselves. That's great if we do, but we have a job to do: high-quality science that improves the quality of health." ■

Women In Science

continued from page 3.

other people on the job, where men tend to talk with men, and women tend to talk with women. Because there are fewer women [in the scientific workplace], women have fewer people to talk with who are comfortable with them."

The Bethesda chapter's third meeting, slated for March 2, was to feature three women scientists from industry presenting the pros and cons of working in the private sector. The Bethesda group was in the process of selecting its May topic as *The NIH Catalyst* went to press.

"People have been incredibly enthusiastic" about AWIS' new chapter, says Schwartz, who says future meetings will follow the interests of chapter members. "The people who have come say it's a fantastic way to meet others, talk....It's also a way to get information on specific subjects and jobs." Along these lines, Schwartz says, she is assembling a file drawer of useful information on jobs, fellowships, AWIS publications, mentors, and other resources that NIH scientists can peruse at their leisure in the Building 10 library.

AWIS membership and meetings are open to all interested scientists—including men. Those wishing to join the new chapter may contact Regina Armstrong at (301) 295-3205. ■

Recently Tenured

Alan Breier *received his M.D. from the University of Cincinnati in 1980 and completed his psychiatry residency at Yale University in New Haven, Conn., in 1984. After a three-year fellowship at NIMH and an associate professorship at the University of Maryland at College Park, he returned to NIMH in 1993 and is now Chief of the Unit of Pathophysiology and Treatment, Experimental Therapeutics Branch.*

Schizophrenia is a severe, debilitating brain disorder that poses enormous public- health challenges to the nation. The etiology of this illness is not known, and there are currently no treatments that cure or reverse the disease process. The goals of my research are to identify brain regions and neurochemical systems involved in the pathophysiology of schizophrenia, and to understand how pharmacotherapeutic agents work to correct the pathophysiologic deficits.

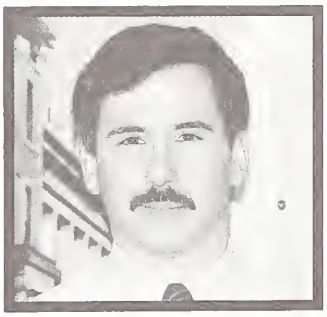
Our early in vivo imaging studies identified three morphologically abnormal brain structures in patients with schizophrenia: prefrontal cortex, superior temporal gyrus, and hippocampus. This was of interest because these three regions function together in neural circuits responsible for some of the most sophisticated human mental processes. We found that two primary symptoms of schizophrenia, auditory hallucinations and disconnected verbal expression, were related to volumetric reductions in parts of the superior temporal gyrus that play roles in auditory association and language generation, respectively. Moreover, we found morphologic abnormalities in regions of cortical white matter that form connections between these three regions. Taken together, these data suggested to us that a dysfunction in cortical-cortical circuitry may give rise to the core behavioral manifestations of schizophrenia. Because glutamate plays an important role in prefrontal-temporal-hippocampal connections, we are using positron emission tomography (PET) to examine the effects of glutamatergic antagonism on local glucose utilization in these three regions. In preliminary studies, we found that glutamatergic antagonism exacerbated auditory hallucinations and verbal expressiveness of schizophrenic patients and altered metabolic activity in frontal and temporal cortical brain regions.

Traditional neuroleptic drugs, introduced over 40 years ago, have been the mainstay of schizophrenia treatment. Clozapine, a new antipsychotic agent, is the first drug to demonstrate clinical superiority to traditional neuroleptics in the most severely ill schizophrenic patients. My group was the first to establish that clozapine's clinical superiority extended beyond the small subgroup of the most severely ill patients to the largest group of more typical patients. Rodent studies have suggested that clozapine has unique actions in cortical regions. We have undertaken a series of clinical investigations to determine whether clozapine's clinical superiority is related to its effects in the frontal cortex, superior temporal gyrus, and hippocampus. Thus far, we have found that clozapine alters metabolic activity in frontal and temporal cortices and that its symptom-reducing effects are related to morphologic characteristics of the prefrontal cortex. We are currently working on a new imaging method that uses special characteristics of PET tracers to quantify synaptic neurotransmitter concentrations in vivo. The results will help us better understand the neurochemical basis of schizophrenia and the mechanism of action of new antipsychotic agents.

Scientists tenured November 1993 to date

Lev G. Goldfarb, NINDS David W. Hackstadt, NIMH
Christina T. Teng, NIEHS

Douglas Laske *received his M.D. from the College of Physicians and Surgeons of Columbia University in New York in 1985. He joined the Surgical Neurology Branch of NINDS as a Clinical Associate in 1990 and is now a Staff Surgeon.*



My research efforts have focused on the pharmacokinetics of regional drug delivery to the central nervous system (CNS) and on targeted toxin therapies for treating malignant brain tumors. Regional drug-delivery methods currently used to treat certain brain tumors use a variety of methods (direct injection, slow-release, biodegradable implants) to administer anticancer agents directly to the tumor site. However, simple diffusion is often insufficient to spread the agent widely enough to infiltrated adjacent brain. Our laboratory has developed a new method of regional drug delivery to the CNS that achieves greater distribution of macromolecules in brain than do methods that depend on diffusion alone. This high-flow microinfusion technique may allow for more extensive distribution of a variety of compounds including antibodies, neurotrophic factors, enzymes, and genetic vectors.

We have applied this microinfusion technique to enhance the distribution of targeted protein toxin conjugates for brain-tumor therapy. After preclinical testing, we conducted a clinical trial in which patients with recurrent malignant brain tumors were treated with microinfusion of the targeted protein toxin transferrin-CRM107. The targeted toxin — first produced in our laboratory — is a conjugate of human transferrin (Tf) coupled to a diphtheria toxin with a point mutation (CRM107) that eliminates nonspecific binding. Tf-CRM107 binds to the transferrin receptor, which is highly expressed by tumor, but not by normal neurons or glia. Early results have been encouraging and we are continuing to explore the clinical utility of Tf-CRM107 and to investigate new cell-type- specific toxins. ■

Commentary

Laminin and Amyloid Precursor Protein in Neural Development and Repair and in Alzheimer's Disease

Maura C. Kibbey, Ph.D., Cell Biology Section, Laboratory of Developmental Biology, NIDR

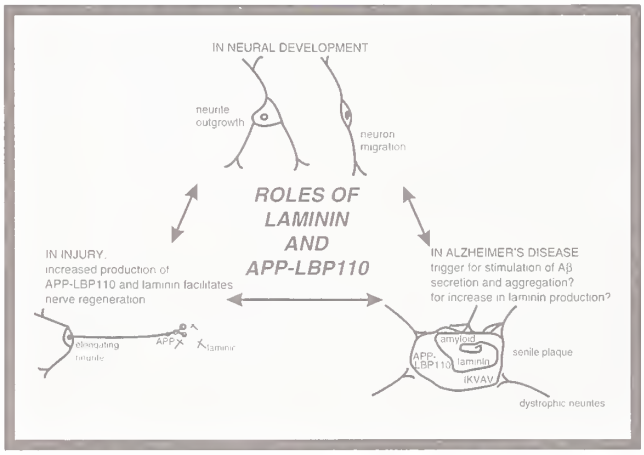
One of the delights of basic research is the unpredictability of its destination. In the course of pursuing research on the role of laminin and its receptors in the brain in NIDR's Laboratory of Developmental Biology, I ended up studying amyloid precursor protein (APP), a molecule central to Alzheimer's disease (also see related article on page 15). Through this work, I have recently arrived at an answer to a question that has long troubled Alzheimer's researchers: what is the normal function of APP?

Only in the past 10 to 15 years have scientists begun to appreciate the importance of extracellular-matrix molecules in the central nervous system. Because these proteins are rare in the adult brain (except in the basement membrane surrounding blood vessels, ependymal cells, and the meninges), earlier workers questioned their importance. Now we know that many matrix proteins, particularly laminin and proteoglycans, are abundantly expressed, but only at discrete times during the proliferation, migration, and differentiation of neurons and glia (for reviews, *see refs.1 - 3*). Our laboratory is primarily interested in the role of laminin in promoting these biological activities.

Laminin is an 800-KDa glycoprotein composed of three chains, A, B1, and B2, in a cruciform shape. In vitro studies have shown that primary neural cells survive and elaborate processes when grown on laminin (4,5). The laminin domain responsible for neurite outgrowth proved to be within an elastase-generated fragment of the long arm of the laminin A chain (6). Synthetic-peptide mapping pinpointed the biologically active site to the amino acid sequence isoleucine-lysine-valine-alanine-valine (IKVAV) (7).

Three years ago, scientists in our lab used affinity chromatography to isolate a specific IKVAV-binding cell surface membrane protein of 110 kDa (LBP110) (8). It is this protein that led us into Alzheimer's disease research. Like APP, LBP110 can be localized to both cell membrane and intracellular compartments of migrating and mature neural cells (9 - 12). Expression of LBP110 is up-regulated in glia in response to ischemic and mechanical injury (11), suggesting that it may have a role in repair.

We recently published results that showed that LBP110 and APP share antigenic epitopes and that both bind IKVAV-containing peptides and not another biologically active laminin peptide (13), and we now believe that LBP110 is an APP. APP is actually a family of alternatively spliced proteins, with representatives present in tissues throughout the body, including brain tissue; however, some isoforms have a more restricted distribution [e.g., APP695 in the nervous system (14)]. The widespread expression of APP in normal embryonic and in adult tissues has led scientists to conclude that this family of proteins must have nonpathologic functions. The proteolytic processing of APP to form amyloid ß-peptide (Aß) appears to be critical in the development of senile plaques, a pathologic hallmark of Alzheimer's disease (15).



Hypothesis for the roles of laminin and APP-LBP110 in neural development, injury, and Alzheimer's disease.

We recently proposed an answer to the long-standing mystery of APP's nonpathologic function: at least one of APP's nonpathologic roles may be in neurite formation (13). Rat PC12 pheochromocytoma cells (a neural crest - derived tumor) stably transfected with APP antisense cDNA exhibited similar patterns of reduced APP and LBP110 protein and, interestingly, the antisense transfectants were rendered unable to form neurites when plated on either laminin or IKVAV-containing peptide. Normally, PC12 cells primed with NGF and cultured on either laminin or IKVAV-containing peptide adhere rapidly and form long neurites (7). These experimental results suggest that APP-LBP110 may have a normal function in neural development.

Like LBP110, APPs are up-regulated in response to central nervous system injury (9). Because laminin expression is increased in many models of nervous system injury (16,17) and because exogenous addition of laminin improves peripheral-nerve regeneration (18), researchers suspect that laminin plays a direct role in nerve repair. We hypothesize that as a laminin receptor, APP-LBP110 is thus also important in neurite outgrowth in repair as well as in development. It is possible that in Alzheimer's disease, the laminin present in the senile plaques (19,20) facilitates the aberrant neuronal sprouting that researchers observe in neurons growing near plaques. Another layer of complexity was recently added to this possible mechanism when Aß peptide added to laminin-coated dishes was found to increase neurite outgrowth of rat embryonic dorsal root ganglia cultures (21). Aß alone had no effect on neurite outgrowth. Other laboratories have reported that Aß forms insoluble aggregates in culture (as in plaques) that are toxic to neural cells (see, for example, ref. 22), suggesting that regulation of local concentrations of Aß may be critical in the control of disease progression.

As we continue our research on APP-LBP110, it will be important to define which domains of APP bind to laminin and to IKVAV-containing fragments in order to understand these interactions further. To understand the involvement of laminin and APP in the pathology of Alzheimer's disease, it will be important to identify the types of laminin present in the plaques vs. in the normal brain parenchyma. This way, it should be possible to determine whether the laminin is in an altered form, or is degraded, or whether only some of the three laminin chains are present.

In addition to neurite outgrowth, the IKVAV site has also been shown to stimulate protease activity and cell migration (23, 24), activities important in neural development, repair, and disease. Disruption of the delicate balance of proteases, APP, APP's breakdown products, and laminin in the brain could thus rapidly result in pathologic growth. Future studies examining these molecules, as well as others, should advance the understanding of neural development, repair, and Alzheimer's disease.

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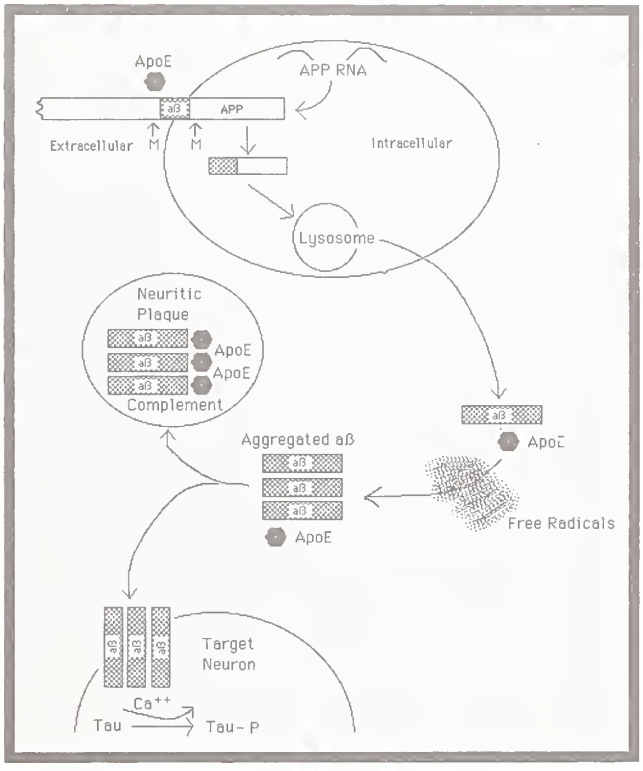
COMMENTARY

THE MAKINGS OF A PLAQUE

Benjamin Wolozin, M.D., Ph.D.,
Section of Geriatric Psychiatry, NIMH

Alzheimer's disease is one of the major illnesses affecting the burgeoning geriatric population in America. There are approximately 4 million cases of Alzheimer's disease in the United States, costing $90 billion annually. In the past decade, dramatic advances in the field have greatly increased our understanding of the illness, and researchers have now identified many of the building blocks and biochemical interactions in neuritic plaques and neurofibrillary tangles—the lesions present in the brains of Alzheimer's patients. In this paper, I discuss the rapidly evolving picture of how neuritic plaques develop.

Neuritic plaques contain a 4-kDa, 40 - 42-residue peptide, termed beta-amyloid, or aß, whereas neurofibrillary tangles contain a hyperphosphorylated form of the microtubule-associated protein, tau (1-3). The aß peptide derives from a parent protein, termed amyloid precursor protein (APP), that is membrane-bound and present in all cells in the human body (4,5). The aß domain spans the junction region between the cell membrane and the extracellular domain of APP (see figure). Investigators initially assumed that elevated levels of aß production would be responsible for the accumulation of neuritic plaques in the brains of Alzheimer's patients. However, studies show that the aß peptide is constitutively produced and secreted as part of APP metabolism, and the concentration of aß in blood does not appear to differ between Alzheimer's and control subjects (6). Moreover, transgenic mice that overproduced APP or aß do not develop neuritic plaques or neurofibrillary tangles, which strengthens the argument that aß is not harmful by itself. Conditions that increase aß production through physiologic mechanisms do not appear to cause plaque formation either. For instance, using a rat model, Bill Wallace at NIMH has found that lesioning the nucleus basalis of Meynert, a locus of cholinergic neurons in the central nervous system, increases APP and aß but does not produce neuritic plaques (7). Thus, under normal physiologic conditions, aß does not appear to generate neuritic plaques.



Pathway for Plaque Formation. Following synthesis and membrane insertion, a small amount of amyloid precursor protein (APP) is processed into aß, which is then secreted. As a result of abnormal processing or interactions with extracellular molecules important to Alzheimer's disease, aß may aggregate into potentially toxic calcium channels and also form neuritic plaques.

Altered Processing of APP in Alzheimer's Disease

Why, then, does aß accumulate in neuritic plaques in the Alzheimer's brain? Two possibilities appear likely: either the processing of APP is altered or the environment surrounding the aß peptide is changed. Studies of cell biology and genetics indicate that the processing of APP is altered in the tissues of people with Alzheimer's disease. Many studies have shown that the metabolism of cells from these patients is abnormal, and based on work from my laboratory, it is reasonable to infer that these changes result in disease-related alterations in APP processing.

We have been examining the metabolism of APP in primary cultures of olfactory neuroblasts generated from biopsies of epithelium from the superior portion of the nasal cavity of Alzheimer's and age-matched control donors (10). Like fibroblasts, these cells divide in culture but have the advantage of expressing many neuronal proteins, including neurofilament protein, neuron-specific enolase, and Trk, a nerve-growth-factor receptor (10). Our work has focused on the C-terminal fragment of APP that is generated after cleavage of APP at the plasma membrane. Cleavage of APP results in the secretion of the extracellular portion of APP and the internalization of the C-terminal fragment (see figure) (11,12). Though the cleavage generally occurs in the aß domain, the site of cleavage is variable, and some fragments that contain the entire aß domain are generated. These larger fragments are the precursor of the aß peptide (13). Even under basal conditions, the olfactory neuroblasts derived from Alzheimer's patients show a small but noticeable increase in the amount of the C-terminal fragment they produce. After blockade of lysosomal action with the weak base chloroquine, disease-related differences in APP are even more evident with this precursor showing sevenfold higher concentrations in Alzheimer's compared with control cells (9). Although we haven't yet detected a corresponding increase in the secreted portion of APP, studies of blood serum from Alzheimer's patients do show a 50% increase in the amount of a 130-kDa secreted form of APP (14). Thus, the processing of APP is different in cells of people with Alzheimer's disease, and such changes could alter the fate of aß.

Further evidence that changes in APP metabolism contribute to Alzheimer's disease comes from genetic data. In several pedigrees, mutations at residues 670, 693, or 717 of APP770 correlate with the presence of an early-onset form of Alzheimer's disease (15). The mutation at position 670 is of particular interest because it results in production of increased amounts of aß, suggesting that increased aß can be deleterious (16). Although we do not yet understand how the other mutations affect APP metabolism, Steve Younkin at Case Western Reserve University in Cleveland suggests that these mutations may alter the processing of APP to yield a slightly longer form of aß—42 versus 40 residues. This 42- residue

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form is more hydrophobic and may have a greater tendency to polymerize into neuritic plaques.

Extracellular Factors Contributing to Plaque Formation

Equally strong evidence suggests that factors other than the processing and amount of aß are critical for plaque formation. One such factor that has received a great deal of attention lately is apolipoprotein E (apoE). ApoE is important in lipid metabolism and is one of the proteins found in high- and low-density lipoproteins. It is also important to nerve regeneration and is synthesized by glial cells and taken up by neurons in large quantities after neuronal injury.

In humans, there are three alleles for apoE: *apoE-e2, apoE-e3, and apoE-e4.* They differ in the presence of cysteines or arginines at residues at position 112 or 158. Data from Alan Roses' group at Duke University in Durham, N.C., indicate that apoE alleles are important in Alzheimer's disease (17). *ApoE-e4,* the dominant allele found in 31% of control populations, is present in 64% of the late-onset sporadic cases and 80% of the early-onset familial cases of Alzheimer's disease. In certain families, the chances of developing Alzheimer's disease rise to 90% for individuals who are homozygous for the *apoE-e4* allele (17). Thus, the presence of the *apoE-e4* allele is an important risk factor for the illness.

An emerging association among genetics, biochemistry, and pathology has propelled the apoE story out of the realm of genetics and into the forefront of Alzheimer research. Studies of brains from Alzheimer's patients show apoE associated with neuritic plaques, and, at autopsy, the brains of patients who carried the *apoE-e4* allele have larger plaques (18). The increased plaque size may occur because apoE, as well as other apolipoproteins, binds to the aß peptide. apoE4 has an increased avidity for aß compared to apoE2 or 3 (19). Once bound, apoE may promote plaque formation through some unidentified mechanism (see figure). A weakness in this story is that the affinity of apoE for aß is in the millimolar range—below physiologically relevant concentrations. However, we find that addition of nanomolar concentrations of apoE into cells grown in serum-free culture medium downregulates APP levels, suggesting that apoE associates with APP at a much higher, physiologically relevant affinity than is the case for the aß (unpublished observations). Taken as a whole, the evidence suggests that apoE acts as an important chaperone to APP that, in some forms, promotes formation of neuritic plaques.

Other molecules may also promote the formation of neuritic plaques. For instance, complement C3 and other downstream complements can all be found associated with neuritic plaques. In fact, the presence of C3 may distinguish between neuritic plaques present in people who have died with Alzheimer's disease and the occasional plaque found in the brains of elderly people who have died with no signs of Alzheimer's (10). If complement is important to plaque formation, this might explain why transgenic mice, which are generally deficient in complement activity, do not develop lesions when APP or aß is overexpressed. Similarly, although aß fails to form neuritic plaques when injected into murine brains by itself, co-injection with proteoglycans results in rapid formation of neuritic plaques (H. Fillit, personal communication). Finally, pedigree studies show that a genetic locus on chromosome 14 is also associated with early-onset Alzheimer's disease (21). The identification of this gene may highlight another important agent in plaque formation.

Aß Toxicity

Behind the interest in the mechanism of plaque formation lies an assumption that aß is somehow harmful to the brain. The information presented above indicates that the issue is complex. We know that neuritic plaques accumulate in the brains of Alzheimer's patients. We also know that particular mutations in the APP gene are strongly associated with Alzheimer's disease. This genetic information provides clear evidence that changes in APP physiology can be harmful. The strongest data indicating that aß can be harmful comes from in vitro data in which Bruce Yankner at Harvard University in Cambridge, Mass., showed that aß is toxic when applied directly to hippocampal neurons (22). But other evidence suggests that aß is not toxic by itself: in vivo, transgenic animals, animals microinjected with aß, and lesioned animals—all of which have increased levels of aß— do not develop neuritic plaques, neurofibrillary tangles, or noticeable cognitive deficits.

The answer to this contradiction may come from a synthesis of intracellular and extracellular events. Although aß may not be toxic in isolation, it may become toxic under some conditions. Harvey Pollard of NINDS has shown that aß can aggregate to form calcium channels in membranes (23); however, many factors affect the tendency of aß to form these channels. For instance, neutral phospholipids, such as phosphatidyl choline, a lipid found on the external side of the plasma membrane, inhibit aggregation of aß into calcium channels, whereas acidic phospholipids and free radicals greatly facilitate aß polymerization (H. Pollard, personal communication) (24).

A conceptual framework for interpreting the complex interactions affecting aß toxicity emerges when we consider that aß exists in equilibrium between monomeric and polymeric forms. In vivo, under normal physiologic conditions, equilibrium favors monomeric over potentially toxic polymeric forms of aß. Changes occurring in Alzheimer's patients, or as the consequence of aging, may disturb this equilibrium in favor of polymerization. Factors that shift the equilibrium may include changes in lipid-membrane composition, in aß length, or in the interaction of aß with other molecules, including proteoglycans, complement, and apoE.

New Directions

The aß peptide appears to be harmless as a monomeric peptide, but it can easily become toxic due to its tendency to aggregate and possibly form calcium channels. The pathway that leads from aß production to plaque formation involves a series of biochemical steps and molecules. Presumably, an alteration in any of the critical molecules in this pathway can tip the scale, causing aß to aggregate and form neuritic plaques. The molecular interactions involved in the pathway leading to plaque formation are now being elucidated. As new transgenic and in vitro models incorporate the complexity of these multiple factors, they may yield a better understanding of the pathophysiology of Alzheimer's disease and an accurate model for testing potential therapeutic agents.

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REVAMPING THE INTRAMURAL WORKFORCE

continued from page 1.

including the Food and Drug Administration—have managed to win exemption from the hiring freeze, but as of mid-February, NIH still hadn't.

Gottesman believes that winning some easing or modification of the requirement that 10 percent of the cuts come from grade levels GS-14 and above is especially crucial for NIH. The goal behind the rule was to reduce the ranks of midlevel government managers and supervisors, but in the Intramural Research Program, most of the people at the 14 level are laboratory or clinical scientists with few managerial or supervisory responsibilities. In an appeal to the PHS and HHS, NIH is requesting a reduction in the percentage of cuts that must come from the ranks of independent scientists at the GS-14 level. If NIH does not win its appeal, hiring at the higher levels could continue to be frozen for the remainder of the year and perhaps beyond—even making the questionable assumption that the rate of attrition holds steady. Mahoney says attrition is expected to slow while some people wait for retirement buyouts and while others, who would normally be leaving NIH for other government jobs, bump into FTE ceilings elsewhere.

PHS and NIH have established procedures for individual exemptions to the 14-and-above freeze. Full-time patient-care positions are exempt from the freeze, but thus far, no other exceptions have been acted upon by PHS. The exemption process starts when Institute Directors nominate exceptional candidates to a subcommittee of NIH's Resource Allocation Group (RAG), chaired by Duane Alexander. The subcommittee reviews the nominations and has recommended to Varmus and PHS leaders that about half of the applications be approved, with preference given to minorities, women, and disabled people who have been underrepresented in the higher GS echelons at NIH. In the meantime, Gottesman has urged the Scientific Directors to find other ways to placate outstanding candidates for GS-14s—and to keep them at NIH. These include retention bonuses, where appropriate, and pay-step increases within the rank of GS-13.

Mahoney doesn't expect that the buyout authority that was being ironed out by Congress in February would be useful to NIH if enacted late in the fiscal year because it would cost, rather than save, additional funds. The buyout packages—of up to $25,000—only save an institution money if they are accepted early in the fiscal year, before employees have earned a large portion of their yearly salaries.

Mahoney says it is conceivable that the long-range 1999 FTE ceilings may not be as low as projections made on the basis of the 18 percent reductions taken through 1995. This worst-case scenario envisions NIH losing about 3,000 of the 17,520 FTEs that it possessed in fiscal 1992. Although the Clinton administration's government-wide FTE reduction target and HHS's overall target is a 12 percent cut in the work force, some parts of HHS—such as the Social Security Administration—have been spared thus far, forcing other parts—such as NIH—to take larger cuts. Mahoney hopes targets in subsequent years will even things out, softening the blow to NIH, but he notes, "There is some concern that the best predictor of the future is the past."

Even if efforts to ease the cutbacks pay off, the conclusion that NIH's intramural program will be downsizing is inescapable. Mahoney notes that Alexander's working group is examining creative ways for NIH to reduce its staff. "Our success in the long term will depend on how innovative we are in examining solutions in this downsizing," says Mahoney.

Gottesman also sees creative, new proposals as a key to coping with the cuts and is hopeful that recommendations from the External Advisory Committee, now preparing its final report, will provide both constructive strategies and political ammunition for accomplishing the pruning in the least painful, least damaging way. If approved by HHS, another new NIH project—a bid to make intramural NIH a "laboratory" or demonstration project for applying the principles of reinventing government—might alter administrative procedures, and ultimately, provide the flexibility needed to cut red tape, thereby easing and speeding the transition to a leaner, keener intramural program ■

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continued from page 16.

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DCRT Announces 30th Anniversary Symposium

This year marks the 30th anniversary of the founding of DCRT. To commemorate this event, DCRT will sponsor a symposium in Masur Auditorium on Monday, May 2, featuring a talk by Russell Doolittle of the University of California San Diego, on "The Computer as Biology's Telescope."

More details will be available in April through the DCRT Information Office at 496-6203. ■

THE NEW IRTAS

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that will encourage and advance nascent careers in science. Blitz notes that some promising Stay-In-School students with an interest in research may be considered for an IRTA award as their work evolves from performance of routine chores to the conduct of research.

IRTA Student Fellows must be U.S. citizens or resident aliens who are accepted for enrollment or are already enrolled and in good standing as full-time students at an accredited high school, college, or university. They must be disabled or demonstrate financial need as defined by government standards, be at least 16 years old, and have the approval of their schools. Sons and daughters of NIH employees may not work in their parents' laboratories. Student Fellows can schedule up to 20 hours per week in the lab during the school year, and may participate full-time during holidays, vacations, and summers. Awards are for one year, but may be renewed yearly, provided that the student continues to meet financial and scholastic eligibility criteria. Upon graduation, students may be granted a four-month extension of their fellowships or, if eligible, may transfer to another IRTA program. Stipends for IRTA Student Fellows are comparable to those provided by the Summer IRTA Program. Students are expected to have health insurance through their schools or families, but if they do not, institutes may help students purchase policies through the Foundation for Advanced Education in the Sciences (FAES).

In another modification of its current Predoctoral IRTA Program, NIH has extended the provision that grants fellowships to students who have been accepted into but have not yet started medical school or doctoral programs. The new extension, aimed particularly at women, minority, and disabled students, allows participants to come to NIH up to one year after they have received their baccalaureate degree but before they have been accepted into doctoral programs. The interim fellowships are for one year, but may be renewed for additional years on a case-by-case basis if the recipient is making satisfactory progress toward entrance into an accredited graduate or medical school. Blitz says that the emphasis in the interim fellowship program is to win students to research careers who might not otherwise consider the possibility and to bolster the credentials of students as they apply to graduate programs. Again, under-represented minorities, women, and disabled persons will be given priority in this program. Each of the interim fellowships must be approved by the Deputy Director for Intramural Research or the Associate Director for Intramural Affairs.

Although the primary beneficiaries of all the new IRTA programs will, by design, be the students themselves, Philip Chen, Associate Director for Intramural Affairs, expects that NIH labs will also profit from the presence of the new IRTAs. Chen notes that with the new IRTAs, "NIH intramural scientists will now be able to seize upon opportunities, otherwise lost, to attract a cadre of excellent young trainees of diverse backgrounds into biomedical research careers." ■

Now Hear This...Conference Services are Available for the Asking

When Elvin Kabat of NIAID recently attended a lecture at Masur Auditorium, he was disappointed. The content of the lecture may have been fine, but it was hard to tell: Masur was too big for the lecture, the sound system was unsatisfactory and only members of the audience who were seated closest to the speaker could hear the talk. Kabat says that his dissatisfaction with the lecture services were not limited to this one instance.

"Often, I found that the rooms in which lectures were held were not equipped with good sound amplification systems...and there did not seem to be a relationship between the size of the room and the degree of interest expected in the topic," says Kabat. "Some of the biggest auditoriums seemed to have talks that attracted only about 20 people...a clique that did not pay any attention to whether the sound system was properly set up or not."

So Kabat decided to write NIH-Director Harold Varmus and ask him to do something to make the audiovisual/conference services at NIH better. Varmus passed Kabat's request along to Marion Buckman in his office who sent it to audiovisual services expert Gene Colville and to Steve Ficca, Director of the Office of Research Services (ORS) whose Conference Services Branch (CSB) provides expertise and support to all aspects of conference services. According to Ficca's office,"conference and audiovisual services are available for the asking," and "highly trained staff are available to provide set-up, operational support, and hands-on training in the use of equipment such as the microphones and overhead projectors." Their tip to prevent audience loss: remind speakers always to use their microphone.

Ficca says that many scientists at NIH may not be taking advantage of the vast array of conference services that are available to them in the major auditoriums in Building 1, 31, and 10 and also in individual ICD meeting rooms. Contact CSB for more information on audiovisual services or to reserve equipment. They are listed in the NIH Telephone Directory in the Yellow Pages under the Conference and Audiovisual Services (sections 10 and 38). —*S.K.* ■

NIH Earns AAALAC Accreditation

On Nov. 29, the Council on Accreditation of the American Association for Accreditation of Laboratory Animal Care (AAALAC) issued the long-awaited news: the NIH Intramural Research Program has won Full Accreditation from the NIH Animal Care and Use Program.

Achievement of accreditation "has been eight years in the making. We were elated to get this news," says James Taylor, Head of the Office of Animal Care and Use, which led NIH down the home stretch in its drive to accreditation. "NIH has now been recognized by our peers for having a responsible animal-care and use program that meets the principles of the 'Guide For the Care and Use of Laboratory Animals,'" he says.

James Taylor and Rosemary Riggs

AAALAC commended "NIH's exceptional effort to develop a high quality animal care and use program" and underscored excellence in sanitation; planning; the development and communication of policies; training; occupational safety programs; prompt, creative responses to problems; and extension of environmental-enrichment programs to new species.

Richard Wyatt, Assistant Director for Intramural Affairs, cautions that no one associated with animal care or use should rest on NIH's new laurels, however. "We have to recognize the need for ongoing efforts to maintain the high standards of a fully accredited facility," says Wyatt. "This effort involves a broad spectrum of people—not only the veterinarians, but also NIH scientists, program directors, engineers, and many others." —*C.H.* ■

NIH Mail Service Bottoms Out

It was neither snow, nor rain, nor heat, nor gloom of night, but by December, almost everything else that could stay NIH's couriers from the swift completion of their appointed rounds was working against them, and the campus mail service almost ground to a halt. November's *NIH Catalyst* took more than a month to reach most readers, and test mailings from Building 10 showed that this snail's pace was not atypical.

But Steve Ficca, Director of Research Services, says several unusual circumstances conspired to trip up the mail at the end of last year, and service should now be improving.

UNUSUAL CIRCUMSTANCES CONSPIRED TO TRIP UP THE MAIL AT THE END OF LAST YEAR, AND SERVICE SHOULD NOW BE IMPROVING.

The problems started when the Division of Support Services, which includes the Mail Services Branch, moved off campus to a new facility in Rockville. The move cost the mail service two days. More seriously, automated-sorting equipment could not be installed immediately and, in fact, is still not on-line. Building-maintenance problems cost another day, and five holidays over a three-month period, combined with mail service employees' extensive use of leave due to the severe weather, created a serious backlog.

These delays came just as severe winter weather was setting in and NIH was deluged with end-of-year and holiday mail from vendors and others.

Ficca says on top of these temporary crises were ongoing problems: a shortage of staff exacerbated by the current hiring freeze and lowered FTE ceilings; low pay and the resulting problems in attracting motivated employees; and a critical lack of supervisors and drivers.

Research Services has implemented some short-term measures to deal with the backlog, including adding an extra shift at the mail facility and contracting out for mail-truck drivers. They are also examining several other options to speed the mail, including direct delivery of U.S. mail to large buildings (such as Buildings 10 and 31 and the Natcher complex), which would have their own zip codes and mail-handling centers. Other ideas may emerge from a study of the mail functions now being carried out by an outside consulting firm, including a survey of mail-user needs to be completed this spring. Ficca says he may also contract out the mail service itself if problems pile up again. At least one small institute is investigating the possibility of renting a post office box.

In the meantime, here are some suggestions to help speed the mail to your hands:

—Urge people who are mailing information to you NOT to send it to NIH via the U.S. Postal Service's express mail. Even this priority mail is delivered to the NIH central mail-handling facility and must wend its way through the system. The extra money paid for overnight delivery is wasted.

—Change the address you list with professional societies to your home address and have all your scientific journals sent there.

—Use fax and e-mail as much as possible and distribute your fax and e-mail addresses widely to your colleagues. —*C.H.* ■

APRIL SEMINAR TO EXPLORE SILLIER SIDE OF SCIENCE

Who says science or scientists can't be silly? Certainly not Mark Abrahams, editor of *The Journal of Irreproducible Results*, a non-peer reviewed publication featuring "inconclusive investigations and obscure nonfindings." For nearly four decades, the journal, which claims to be the "only scientific journal with a sense of humor," has published strictly scientific papers on wacky topics by Nobel Laureates, doctors, biologists, mathematicians, astrophysicists, clinical psychologists, and other scientists from such prestigious institutions as Harvard, MIT, Stanford, and NIH.

Abrahams recently published a compilation of these papers and plans to share some of the irreproducible results with NIH scientists at 12:30 on Thursday, April 14 in the Masur Auditorium. Topics coming under scientific scrutiny include "Survival Strategies among Animal Crackers," "Patterns of Limb Retention in Hellenic Statuary," "Feline Reactions to Bearded Men," (which makes the startling discovery that 26% of cats exposed to a photograph of Supreme Court Justice nominee Robert Bork's beard suffered paralysis) and "Baldness and Hydrofriction," which shows that baldness is caused not by genes but by water impacting upon hair during showers.

Former and present employees of NIH who contributed to the magazine will assist Abrahams as he presents some of the irreproducible data. For more information, call Scott Finley at 496-7946. —*S.K.* ■

This Just In...

The DDIR's Electronic Bulletin Board: Michael Gottesman, acting Deputy Director for Intramural Research, is hitting the information superhighway. Beginning in late March, NIH computer users on the Bethesda campus can access the DDIR's Bulletin Board through Gopher for the latest news and chitchat from Bldg. 1. Access for other campuses is being devised.

Clinical Center To Get New Chief: Saul Rosen, acting Director of the Clinical Center will be retiring as of May 1. John Gallin, NIAID's Scientific Director, has been proposed as NIH's Associate Director for Clinical Research as well as Director of the Clinical Center. Also, William Paul of NIAID has been selected to head the Office of AIDS Research.

NIDCD Begins Search for New SD: David Lim, Scientific Director of NIDCD has announced that he is stepping down. Jay Moskowitz, Deputy Director of NIDCD, will be acting SD as the institute searches for a new SD. ■

ALZHEIMER'S DISEASE

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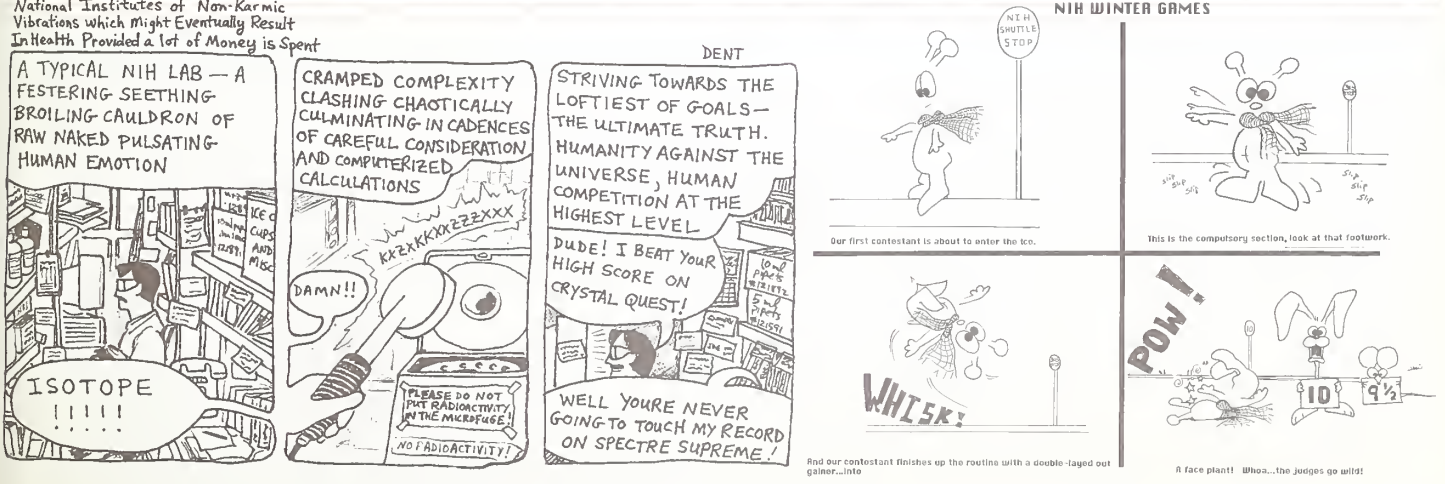

FAX-BACK

In this issue we are asking for your feedback in four areas: creative suggestions for waste disposal; your consumer complaints or raves about scientific products (reagents, kits, equipment, instruments, etc.); tips and suggestions for our Hot Methods Clinic; and your opinion on the new distribution system for *The NIH Catalyst*.

In Future Issues. . .

- Recommendations from the Report of the Extramural Advisory Committee
- Task Force Report on The Status of Minority Scientists
- Computational Bioscience and Engineering Laboratory's New Parallel Computing Power

1) An NIH-wide working group is being established to find ecologically sound, cost-efficient, and simple alternatives to current medical-pathological waster disposal systems. Do you have any ideas to share with this group? Would you be interested in volunteering to serve on the task force?

2) We are still considering starting a new feature in which we discuss the merits and demerits of scientific products but need more feedback. As a "consumer" of scientific gear, have you had particular problems with a reagent, kit, or piece of equipment? Has a particular product worked especially well for you? What products would you most like to see reviewed?

3) Do you have any tips or comments about the yeast two-hybrid system featured in this issue's Hot Methods Clinic? Do you have any tips for our next Hot Methods Clinic feature: In situ PCR. What techniques would you like to see covered in future issues?

4) With this issue of *The NIH Catalyst*, we are testing out a new distribution system to reach scientists who have not been receiving the publication regularly. In addition to sending copies to our mailing list, we are placing copies of *The Catalyst* outside the cafeterias in Building 1, 10, 31, and 37. Does this system work better? Should we discontinue mailing altogether?

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