FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ FEBRUARY 1993

FROM THE EDITORS

Welcome to the first issue of *The NIH Catalyst*, a publication that we have designed for you, the intramural scientists at NIH.

In each issue, this bimonthly newsletter will showcase the excellent scientific research being conducted here at NIH and serve as an interactive communication mechanism where ideas are exchanged, opinions voiced, and issues examined. The purpose is to create a forum that both allows scientists at all levels to advise policy development and promotes cross-fertilization of research insights and collaboration across institutes. Our goal: **Extend the spirit of the NIH Research Festival throughout the year.**

The newsletter contains news and feature articles on research, policy and related topics, reports and mini-reviews by intramural scientists, a regular column by the Deputy Director for Intramural Research, information on special topics such as education, computer resources, parking, and awards, and a section introducing recently tenured staff and their work. Future issues will feature debate, commentary and essays by NIH intramural scientists, and such useful and interesting items as technology tips, hot citations, and patents. We welcome ideas on topics for these and other sections, and we invite scientists to submit articles. For information on where to send them, call 402-1449.

In designing the publication, we have tried to anticipate your information needs and hope that we are meeting most of them. If you have any suggestions or comments on the newsletter or its contents, write us. *The NIH Catalyst* will evolve to reflect your input, interests and needs. ■

SDs' FIRST CAREER DEVELOPMENT RETREAT BRINGS TENURE-Track Policy to NIH

Draft Plan to Be Circulated to Intramural Scientists for Input

For the first time in its history, NIH will employ a formal tenure-track policy to recognize potential for independence and excellence in intramural scientists. When implemented, the policy will offer both the institution and scientists a much-needed definition and elucidation of the tenure process.

According to the Scientific Directors, the new tenure-track policy will combine the procedural aspects of academic tenure-track systems, such as written policy and regular review, with the benefits provided by NIH's existing informal system — guaranteed salary, personnel, and research resources. The new tenure-track policy is part of an entire career development plan drafted at a day-long Scientific Directors' retreat held January 15. The career development plan also addresses issues of concern to women and minority scientists and proposes changes in position titles to reflect those in academia. The Scientific Directors will circulate the draft to intramural scientists for their comments.

> WE HOPE THE NEW POLICY WILL IMPROVE NIH'S SUPPORT FOR YOUNG SCIENTISTS.

At the retreat, the Scientific Directors also endorsed the appointment of a Woman Scientist Advisor in each Institute, Center, and Division (ICD). The appointee will serve as a liaison between women scientists and their Laboratory or Branch Chiefs and Scientific Directors. The Scientific Directors also implemented other recommendations made by the Task Force on the Status of Women Scientists at NIH, including measures to ensure equal pay, improved visibility, and flexibility in granting leave for family responsibilities. The task force had also recommended establishing a formal tenure-track policy as a way to improve the representation of women scientists at NIH.

Several groups at NIH, including the Scientific Directors, the Task Force on the Status of Women Scientists at NIH, and the Task Force on the Intramural Research Program (which prepared the Klausner Report), had felt that the lack of concrete guidelines resulted in misunderstandings, unrealistic expectations, and inconsistencies among the various ICDs and had made recommendations to Lance A. Liotta, Deputy Director for Intramural Research, on these and other issues.

The new policy, Liotta hopes, will address many of these recommendations and improve NIH's support for young scientists. ■

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FROM THE DEPUTY DIRECTOR FOR INTRAMURAL RESEARCH

OFFICE OF INTRAMURAL RESEARCH IMPLEMENTS NEW PROGRAMS AND POLICY

Dr. Lance Liotta

Welcome to the first issue of *The NIH Catalyst*. I am Lance Liotta, the new Deputy Director for Intramural Research at NIH, and in this regularly featured column, I will update you on policy and new programs being developed by the Office of Intramural Research. In this issue, I want to share with you the mission and philosophy that guide the Intramural Research Program (IRP) and inform you about some of the new programs that are already in place.

Mission and Philosophy

Lewis Thomas characterized NIH as the "century's finest invention," and scientists and policy makers alike have hailed the NIH intramural program as the crown jewel of the U.S. government's biomedical research enterprise. Throughout its history, intramural NIH has lived up to this acclaim with such fine, cutting-edge accomplishments as the breaking of the genetic code that led to the current revolution in molecular biology, discovery of slow viruses causing neurologic disease, pioneering work on oncogenes and cellular signaling, development of the diagnostic test for the HIV infection, and development of the only drugs approved for treatment of AIDS—AZT, ddI, and ddC. In the last four years alone, NIH intramural discoveries totaled 200!

As Deputy Director for Intramural Research, my overall mission is to ensure NIH's preeminence by sustaining and enhancing its four important elements:

- A critical mass of scientists conducting highly creative fundamental research
- Rapid transfer of innovative basic research to the patient bedside
- Mentorship and training of the scientific leaders of the future
- Partnership with extramural scientists in academia and the biotechnology industry

Our most important commodity is creative freedom in science, and our investment in the future comes from supporting the career development and independence of young scientists. My career at the NIH mirrors that of many scientists who were spawned and nurtured within the intramural program. Here we have the privilege of stable laboratory resources that enable us to wake up with a new idea and start the first experiment right after our morning coffee. Here we are reviewed on the basis of our accomplishments, and these determine retention, promotion, and space allocation.

In a recent editorial in *Science,* Nobelist Arthur Kornberg of Stanford University reflected on the nature of scientific endeavor. Kornberg pointed out the flaw in the philosophy that demands justification and a charted path of discovery for each scientific project. He noted that truly great discoveries, such as x-rays, penicillin, and recombinant DNA, resulted from a pursuit of curiosity that had no apparent relevance to medicine. He noted that scientists must rely on intuition, serendipity, and capacity to move quickly into new directions and that the most cost-effective route to discoveries is through creative and intellectual freedom. He also maintained that "Scientists, as is true of athletes and artists, should be awarded contracts on the basis of what they have achieved rather than for what they promise to do." His view echoes the philosophy of the intramural program, and the environment we strive to maintain exemplifies this recommendation for the optimal way to conduct science.

OUR MOST IMPORTANT COMMODITY IS CREATIVE FREEDOM IN SCIENCE, AND OUR INVESTMENT IN THE FUTURE COMES FROM SUPPORTING THE CAREER DEVELOPMENT AND INDEPENDENCE OF YOUNG SCIENTISTS.

Four Crucial Elements

A critical mass — the right size, depth, and breadth of scientific expertise — is crucial to recruit, train, and retain world-class scientific leaders and represents an essential component of IRP's eminence. It affords the necessary flexibility to combat public health emergencies and challenges, to take innovative laboratory findings to the bedside with speed, and to provide inspiring mentorship for young scientists. The intramural program has reached a critical mass and stability of resources to serve the nation's health needs and the scientific enterprise.

We remain dedicated to the mentorship of each generation of scientific leaders; 50,000 scientists, including 11 Nobel Prize winners, have worked at NIH, and many fondly remember NIH as a place where they conducted some of their early innovative work. Here basic and clinical scientists work side by side in a critical mass of expertise and ideas — a haven for creative science.

The IRP remains unmatched in the speed at which it can rush a laboratory discovery to the bedside. The intramural program can move discoveries three times faster than comparable outside institutions.

Interaction between intramural and extramural investigators takes place constantly and at many

levels. The interaction begins with the seeding of trained investigators and continues through the cross-fertilization across different disciplines and institutions. Stimulated by the Federal Technology Transfer Act of 1986, our collaborations with industry based on NIH inventions have steadily increased as well.

The IRP remains one of the most productive and prestigious biomedical research institution in the world. The impact of intramural publications remains at the highest level in the nation. NIH intramural scientists are cited more than many other scientists; they stand in the top one-hundredth of one percent in terms of citations in the past decade, according to the Science Citation Index. However, Intramural NIH has suffered from a declining morale stemming from regulatory burdens, barriers to recruitment, retention, and career development, severe space constraints, and a deteriorating physical infrastructure. I am dedicated to a revitalization and renewal of Intramural NIH.

New Programs

Let me now tell you about some of the new programs instituted or under development:

- We have instituted **an enhanced IRTA fellowship** to train American postdoctoral fellows and foreign citizens that does not use the FTE slot. The new fellowship allows M.D. or Ph.D. scientists to start their NIH experience as late as five years (seven years for foreign citizens) after they receive their degree and to remain in the program for five years. A new pay scale provides a higher level of incremental pay raises that total up to $5,000 more than was previously possible. The longer training period is designed to maximize the opportunity and mentorship time and allows fellows to achieve their maximum potential.

- For the first time in the history of NIH, the Scientific Directors have initiated **a formal tenure track.** The tenure track system, which will identify scientists who have high potential for early independence and excellence, is part of an entire career development plan we developed at a Scientific Directors' retreat on January 15. *[See story on p. 1]* A draft plan will be circulated to intramural scientists for their input and comments.

- On the basis of a fact-finding mission by two committees — a Women Scientists Committee *[see committee report on p.4]* and a Minority Scientists Committee — we are developing and implementing strategies to strengthen recruitment, retention, and promotion of women scientists and scientists from minority, and underserved and underrepresented populations. Our hope is to **increase representation of women and minority scientists** at the levels of tenured scientists, section chief, lab chief and above. We are also attempting to reach high school and college students to steer them into careers in science. These efforts to support the scientific intellectual capital are being spearheaded by Michael Fordis in our Office of Education.

- To increase **collaboration across the NIH campus and across institutes,** we will expand the length of the yearly research festival, a celebration of NIH research. The event will include poster awards, poster discussion sessions, and expanded social activities. In addition, we hope that this newsletter will extend the spirit of Research Day all year through.

- Our new Office of Human Subject Research, headed by Alan Sandler, and our IRB chairs have implemented a new program to **reduce the time for protocol approval,** to achieve a uniform review for monitoring the progress and quality of the protocols, and to identify protocols that might have special public interest.

- Our **new database system,** which lists intramural scientific accomplishments, including fundamental discoveries, citation performance, and rate of IND filings, became operational in December 1992 *(see story on page 14).* NIH scientists can search for information by investigator name or by scientific topic. The database is on-line and accessible by modem from anywhere in the world. For more information on how to access the database, call the Office of Education at 496-2427.

I could tell you about our plans to ensure uniform, high quality scientific peer review, a new policy for reagent material and transfer, a new Technology Transfer Board, new guidelines for animal research, and our NIH Master Plan to refurbish the aging infrastructure of the NIH campus, but I will reserve that for the next issue and instead end with our most pressing problem: the hiring freeze and the salary barrier for recruitment and retention of mid-and senior-level scientists. We love our work, but like everyone else, we have bills to pay and children to educate. Data from the Association of Medical Colleges indicate that our senior-level physicians could double their salaries if they took positions at medical schools. Although the SBRS hiring system has been enacted into law, the OMB has not actualized this authority. Some of our most prominent scientists are planning to leave NIH simply because they cannot keep waiting for the SBRS. We don't have direct control over the SBRS or the honorarium ban. But we do have control over consulting and outside activities guidelines.

Therefore, we have implemented **new guidelines for consulting and outside medical practice.** Senior-level physicians can now apply for outside practice, and our scientists can consult for academia with no dollar limit. A consulting scientist may accept up to $25,000 per year from a company with no limit on the number of companies, only a limit on the number of hours spent on all outside activities. This limit is 500 hours per year including weekends and holidays.

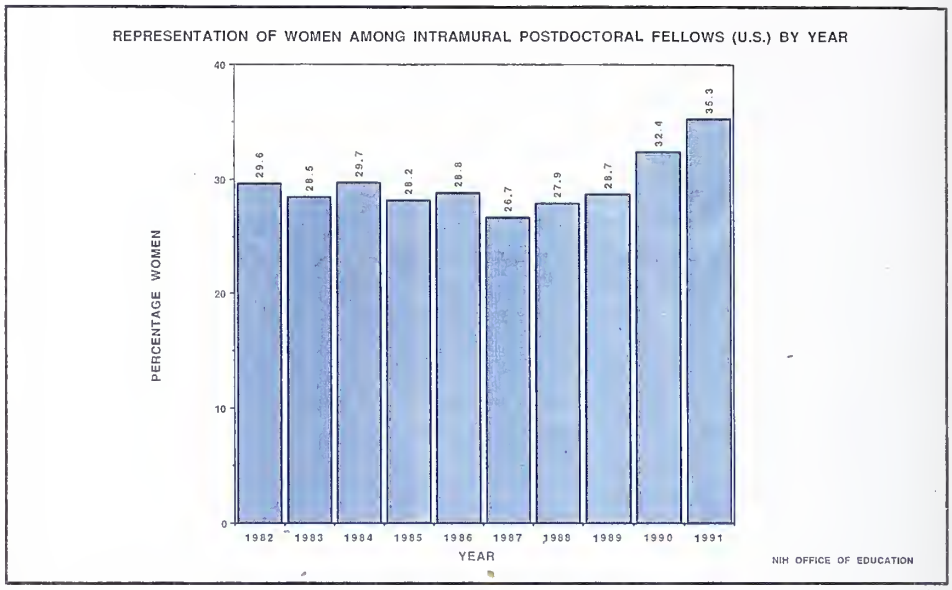
Finally, I welcome your comments and value your input because the theme for the DDIR office is policy based on grass roots input from NIH scientists and the collective wisdom by advisors from all levels of the scientific community. ■

Lance A. Liotta, M.D., Ph.D.
Deputy Director for Intramural Research

REPORT

COMMUNICATION, VISIBILITY, FAMILY LEAVE WILL IMPROVE WOMEN SCIENTISTS' STANDING

At the end of a year-long fact-finding mission, the task force on the status of women scientists at NIH concluded that increased communication, a tenure-track plan, equal pay, improved visibility, and a flexible family leave plan will help improve the NIH environment for women. Hynda Kleinman of NIDR, who currently heads the task force, reports:



Despite efforts to improve their standing, women scientists remain greatly underrepresented in the NIH intramural program at the levels of tenured senior investigator, section chief, lab chief, and above. To address the problem, the Office of Intramural Research (OIR) initiated a fact-finding mission that would guide the development of programs to better recruit, retain, and promote women scientists and increase their visibility.

A 26-member task force was formed in November 1991 to identify real and perceived impediments to women scientists at NIH and, to make recommendations on the basis of these data to the Director and the Deputy Director for Intramural Research on what can be done to rectify them. The task force, composed of tenured and nontenured scientists and administrators from most of the institutes and the Office of the Director, began by collecting data on the present status of women at NIH.

Michael Fordis, Director of the Office of Education and a task force member, collected and analyzed data on recruitment, tenure, pay, promotion, awards, and lectureships. In addition, other task force members, including Joan Schwartz of NINDS, organized four public forums to obtain the NIH community's perspective on these issues.

The data indicated that NIH has successfully recruited women to postdoctoral positions. Over the last decade, the percentage of women in postdoctoral positions averaged 29.5%. In the last two years, the percentage of women in postdoctoral positions has risen to 35.1% and is now equivalent to the percentage of women nationwide who are completing a Ph.D. program in the life sciences.

However, the task force saw many problems with the standing of women scientists at intramural NIH. The group found, for example, that women represent only 18% of all the tenured scientists and only 4% of the lab chiefs. Further, the task force noted that many meetings and lectures held at NIH still lack a representative number of women speakers.

Based on these findings, the task force made specific recommendations to improve the NIH environment for women. The recommendations include increased communication, appointment of a career development coordinator, a tenure-track plan, equal pay, improved visibility, and a flexible family leave plan. The changes will benefit all NIH employees.

The task force will continue to collect data regarding the status of NIH women. Fordis, for example, is planning a survey of women who have left NIH to determine what, if any, obstacles exist for the retention of women in the intramural program.

The Scientific Directors have unanimously endorsed the appointment of a Woman Scientist Advisor for each Institute, Center, and Division. The appointee will attend lab chiefs' meetings and provide information from these meetings to the women of the Institute. The Woman Scientist Advisor will also convey the concerns of women scientists to lab chiefs and to their Scientific Directors. The advisor should increase communication, promote understanding, and improve the status of women scientists.

An annual lecture series will feature a talk by a well-known non-NIH woman scientist. In addition, OIR plans to establish a lecture series in which the NIH nominee for the Women in Science and Engineering (WISE) award will speak.

In summary, the task force has identified issues and made recommendations that when implemented will improve the environment for intramural NIH women scientists. We welcome additional comments. Comments can be sent to Building 30, Room 407. ■

FEATURE

BUILDING 41-T TO BE UPGRADED FOR HIGH-CONTAINMENT TB RESEARCH

by Seema Kumar

Even as the nation struggles to rebuild its almost-extinct tuberculosis research community, a scarcity of resources is hampering its effort to combat the disease's resurgence. This shortage is requiring a rebuilding of a very different kind — construction of safe and contained facilities in which to study the highly contagious, drug-resistant organism.

According to TB experts, very few operating facilities in the United States have the levels of biosafety needed to conduct state-of-the-art research of highly contagious, airborne organisms such as *Mycobacterium tuberculosis*. This is further complicated by the existence and spread of drug resistant strains. In addition, personnel appropriately trained to operate and work in such facilities are lacking. Further, academic institutions have, as a rule, avoided such efforts because of the difficulty in arranging insurance, thus contributing to the paucity of such facilities in the country.

In an attempt to provide the much-needed infrastructure for TB research, NIH has approved NIAID's request to renovate Building 41-T into a high-containment facility for research on multi-drug-resistant (MDR) TB. The facility (to be built using special funds allocated by the Director from NIH royalty funds) will allow researchers to work safely with hazardous, MDR-TB strains, house infected animals, and handle isolates from patients suspected of having MDR-TB. Since extramural researchers are also hampered by the lack of such facilities, the fully equipped Building 41-T will be available to both the extramural and the intramural communities. NIAID will serve as the lead institute and oversee the renovated 41-T facility.

"To develop better diagnostics, research, and treatment for TB and MDR-TB, we need a rapid, coordinated basic research effort involving both extramural and intramural scientists," says John Gallin, Director of Intramural Research for NIAID. "Such a research agenda will require handling of TB-infected animals and infectious and drug-resistant *M. tuberculosis* organisms. This in turn will require a facility with higher levels of biosafety." When renovated, Building 41-T could serve as a national resource for both intramural and extramural scientists, Gallin adds.

After a century of decline, tuberculosis is reemerging as a significant public health problem in the United States. Several interrelated factors, including the emergence of drug-resistant strains, the HIV/AIDS epidemic, increase in numbers of immigrants from countries where TB is endemic, poverty, intravenous drug use, and the increasingly crowded environments of prisons and homeless shelters, are contributing to the resurgence of TB.

In particular, there is an alarming rise in MDR-TB, strains that are resistant to two or more antibiotics. Poor compliance with treatment regimens and treatment with too few drugs or inadequate doses have contributed to MDR-TB. Even with treatment, the mortality rate for MDR-TB is 40% to 60%—the same as for TB left untreated. Moreover, in persons coinfected with HIV, mortality rises to 80%.

As Barry Bloom of the Albert Einstein College of Medicine in New York City and Christopher Murray of the Harvard School of Public Health in Cambridge, Mass., predicted recently in *Science,* if TB cases continue to rise at the rate measured between 1985 and 1991, the nation may have more than 86,000 cases resulting from active transmission before the end of the decade. Further, Bloom and Murray predict that the direct treatment costs for these cases will amount to $2.2 billion and indirect costs will total an additional $1.9 billion.

While TB has reemerged in new and dangerous forms, treatment regimens and diagnostic tools to combat the disease have remained decades old. TB research and technology began to wane when, after the advent of antibiotics, the disease was thought to be conquered. Not only did the decline create a shortage of scientists and physicians actively working on TB, but it almost brought

TB causes more deaths worldwide than any other infectious disease. Spread through the air, the disease usually affects the lungs, although other organs are sometimes involved. Some 1.7 billion people—one-third of the world's population—are infected with *Mycobacterium tuberculosis*. Each year, 8 million people worldwide develop active TB and 3 million die. In the United States, a total of 26,283 active TB cases, in all 50 states, were reported to the Centers for Disease Control, an increase of 18% since 1985. In addition, an estimated 15 million Americans may have latent TB and may develop active disease at some point in their lives.

Early symptoms include weight loss, fever, night sweats and loss of appetite. As the disease advances, patients experience chest pain, cough and, when a blood vessel is eroded, bloody sputum. TB is diagnosed using the tuberculin skin test, or the Mantoux test in which a purified protein derivative (PPD) from the bacterium is injected under the skin of the forearm and examined 48 to 72 hours later. If a red welt forms around the site, the person may be infected but doesn't necessarily have active disease.

The drug isoniazid (INH) prevents the disease in most persons in close contact with infected persons or who are infected with the tubercle bacilli but do not have active TB. Taken for 6 to 12 months, the treatment prevents drug resistant strains from emerging, provided the regimen is strictly followed. Adverse reactions to INH are rare, although a small percentage of patients, especially those over 35, suffer INH-related hepatitis. Rifampin is recommended for persons with close contact with patients with INH-resistant TB.

NIH recommends a yearly PPD test of all NIH personnel. ■

drug development for the disease to a grinding halt.

However, with the resurgence of TB and the continued increase in MDR-TB, public health experts say TB research must be revived and must reach a level necessary to face today's health problem. "We know how to cure and prevent conventional TB; we must quickly develop the capacity to prevent the spread of drug-resistant TB," Bloom and Murray warn. "If we do not learn from the current epidemic of TB and if we do not develop new scientific tools to diagnose, prevent, and treat the disease, the tragedy unfolding in New York City could repeat in any city in America that has homeless people, AIDS, prisons, hospitals, and nursing homes."

Currently, confirmed diagnosis for active TB by positive bacteriologic culture takes four to six weeks, and determination of drug sensitivity requires an additional two to three weeks. Patients may have already spread the disease or succumbed to it before drug resistance is determined.

"We need better diagnostic tests for TB that can shorten the time before infectious patients are placed on appropriate antimycobacterial therapy," says Gallin. "We also need improved tests to determine infection in immunocompromised individuals who do not test positive to the presently used tuberculin test, and assays to quickly evaluate the drug sensitivity."

In addition, new and improved vaccines are needed to stem the spread of TB and MDR-TB. The only available vaccine, BCG, now used in infants in developing countries, prevents the spread of the *M. tuberculosis* within the body but does not prevent initial infection. In adults, the effectiveness of the vaccine has shown varied results in large trials. Those vaccinated also test positive to the purified protein derivative (PPD) test, thus rendering this skin test less useful.

Researchers say that basic research is needed to understand the pathogenic mechanisms of TB infection and to determine the mechanisms of drug resistance. In addition, animal models for TB are needed for the evaluation of therapies and vaccines against TB. The few models that exist are inadequate.

Such coordinated basic research will need a facility with higher biosafety levels (BL-3/4), says Gallin, and Building 41-T, an existing high-containment structure in the Bethesda Campus, will be renovated for this purpose. The building has 1,000 square feet of usable work space for BL-3 research, of which 400 square feet offer BL-4 conditions. However, while the building is well designed, it is relatively small and obsolete, says Gallin. For instance, the high-containment glove box area is not functional, and the HVAC system is not functional at a BL-4 level. Further, there are numerous structural problems, an inadequate laboratory facility, and inadequate autoclaves. Thus, the building will need to be renovated before it can be used. The renovation is expected to begin soon.

According to Gallin, the renovated facility will also be used for other types of research that require higher levels of biosafety, including hazardous viral agents such as dengue and tick-borne encephalitis. ■

NIAID Research Agenda for Tuberculosis

NIAID, the lead institute for tuberculosis research at NIH, supports 49 research projects related to TB. Another six NIAID TB projects are funded through the National Vaccine Program. In FY 1993, NIAID will devote an estimated $14.7 million to TB research, an increase of almost 1,000% since 1984. The institute recently formulated a research agenda with plans to increase support for

- Basic research into the biology of TB
- Development of new diagnostic tools
- Development of new drugs and drug delivery systems
- Clinical trials of anti-TB therapies
- Development of new vaccines
- Training to increase the number of TB researchers
- Prevention education for health care workers and the public

Advertising Strategy to Recruit Postdoctoral Fellows Proves Effective

The Office of Education (OE) reports that its two-year pilot advertising program proved successful in increasing the visibility of postdoctoral training positions at NIH while using each advertising dollar more efficiently. In addition, says the OE, the new advertisements yielded better responses than before, and scientists who used the ad placement service found it easier to use and felt that the service should be continued.

"We hope to continue offering the advertising service and expand and improve on the existing program," says Michael Fordis, Director of the Office of Education. "During 1993, we plan to increase the number of advertisements appearing in *Cell* and expand the number of advertisements in which all listed positions fall within a closely related discipline such as developmental biology, structural biology, or neuroscience."

Before 1990, NIH lacked a centralized and coordinated advertising system for recruiting applicants to postdoctoral positions. Generally, individual ICDs recruited postdoctoral fellows using their own methods. In Fall 1990, the OE launched a pilot advertising program to centralize and coordinate the recruiting efforts of the ICDs. The program, in which all ICDs participated, sought to determine if such a service could increase the visibility of postdoctoral training positions and stabilize

FEATURE

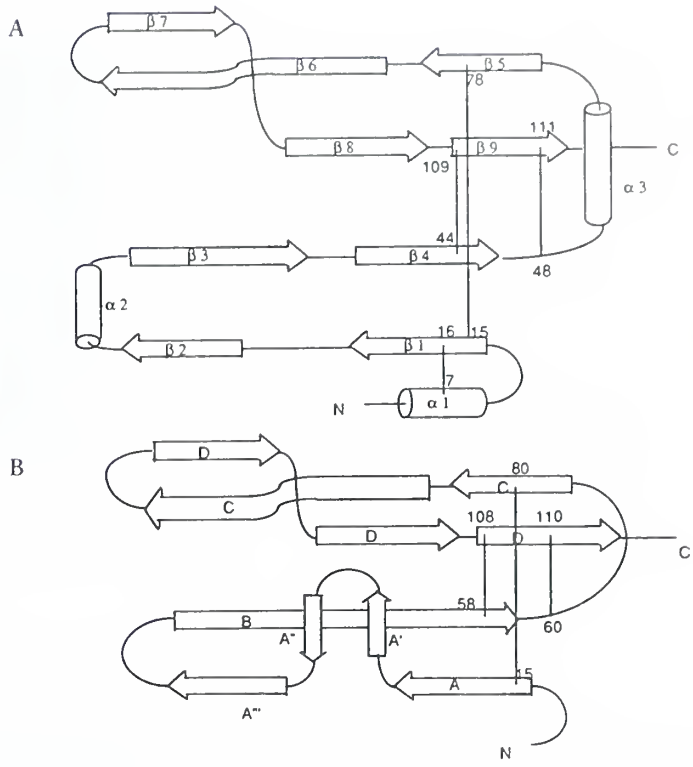
3-D STRUCTURE OF TGF-β REVEALS UNSUSPECTED RELATIONSHIP TO NGF AND PDGF

by Seema Kumar

When David Davies of NIDDK and colleagues reported the crystal structure of transforming growth factor-β2 (TGF-β2) last July, they surprised themselves and other structural biologists with a molecule whose folding pattern departs from the norm. Six months and five papers later, this hitherto unique fold is turning out to be the norm — a significant new folding motif — for disulfide-rich growth and developmental factors.

The TGF-β fold, which looks like an outstretched hand with slightly curved fingers, is characterized by disulfide bridges at the base of the palm and two pairs of looping, antiparallel β-*strands* that form the fingers. The fold is unusual in that it lacks the characteristic hydrophobic core found in compact globular proteins. Four months after this unusual fold was discovered, two independent groups, Mark Swindells at the Protein Engineering Research Institute in Japan and the NIDDK group, reported that they found a similarity between the TGF-β structure and the structure of another important cytokine, nerve growth factor (NGF).

By itself, this similarity came as a surprise to researchers because of low sequence homology between the two and because these molecules form dimers in very different ways. However, an even bigger surprise lay in store for researchers: In the November, 1992 issue of the *EMBO Journal,* a Swiss group at Hoffman La Roche reported that the structure of platelet-derived growth factor (PDGF) was similar to NGF and, therefore, to TGF-β. According to researchers, PDGF dimerizes in yet a third way, quite different from that of the other two cytokines.



Schematic representation of (A) TGF-β and (B) NGF highlight the topological similarities between the two structures. The cylinders represent the α helices, the arrows the β strands, and the lines represent the disulphide bonds.

Together, say NIDDK scientists, these results from various institutions suggest that this unusual folding pattern may in fact be a significant new motif that could be used as a building block for other cystine-rich growth factors. They also suggest that the members of these families descended from a common ancestor.

"Just from looking at the sequence alone we could not have guessed that the structures could be related," says Davies. "However, once you determine the three-dimensional structure,

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costs at the same time.

Multiple postdoctoral openings were listed in full-page advertisements in *Science* or *Cell.* Clinical positions were advertised in the *New England Journal of Medicine* or in subspecialty journals. Every opening was also listed in an electronic database, and readers of the journal advertisements were referred to this service if they wished to review all available openings. The print and electronic services were available to all investigators at no direct cost to the individual laboratories.

An analysis of the advertising experience over the last two years revealed that nearly 80% of scientists using the piloted service described ad placement as either easier or much easier than before, and a like percentage felt that the visibility of their postdoctoral advertisements was increased. Of those with previous experience in recruiting postdoctoral fellows to NIH, over three-quarters described the response to the advertisements as either increased or significantly increased over responses to previous advertisements. Nearly 90% felt that the service should be continued. On average, approximately 16 applications have been received per position listed. In the last year more than 1,800 accessions to the electronic database of postdoctoral positions have

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many of these similarities seem obvious."

"Proteins with similar sequences are clearly related, but proteins can also evolve to a point where the sequences of their descendants lack any significant similarity," say researchers Alexey Murzin and Cyrus Chothia of the MRC Laboratory of Molecular Biology and the Cambridge Centre for Protein Engineering in Cambridge, UK, in a recent article in *Current Opinions in Structural Biology*. "In these cases, relationships can only be inferred from the similarities in structure and function that are seen in the three-dimensional structures produced by x-ray crystallography and multidimensional NMR."

This story's first piece came last July when two groups of researchers — Sun Daopin, Karl Piez, and David Davies of NIH and Yashushi Ogawa of Celtrix Pharmaceuticals in California, and a

David Davies heads the Molecular Structure Section of the Laboratory of Molecular Biology, NIDDK.

group from Ciba Geigy in Switzerland — determined the structure of TGF-β2. Both groups reported that the structure was common to all 18 members of the TGF-β superfamily. Important regulators of development and cell growth, this family of versatile cytokines both inhibits and stimulates cell growth, and their repertoire of activities includes promotion of wound healing and bone reformation. Scientists had long wondered about the basis of TGF-β's versatility, and when researchers Michael Sporn, Anita Roberts, and colleagues at NCI discovered TGF-β, there was interest in determining its structure. Some of this interest stemmed from its potential as a target for therapeutic drugs. For instance, TGF-β malfunction has been implicated in some cancers, and drugs that mimic its growth inhibitory effects may be useful in cancer therapy. Mimicking TGF-β's wound healing and bone reformation properties would have use for therapy as well.

"THE PDGF STRUCTURE HAS THE THREE DISULFIDE BRIDGES THAT ARE ALMOST CERTAINLY THE SAME AS IN TGF AND NGF."

So when the TGF-β structure was determined, it sparked interest among researchers and its unusual fold was duly noted. Then in November, Swindells of Japan and Daopin, Gerson Cohen, and Davies of NIDDK noted the similarities between TGF-β and NGF. NGF, originally crystallized by Alex Wlodawer at FRCF, belongs to a family of neurotropic factors that control development and survival of neuronal populations in the peripheral and central nervous system. Determining the structure-function relationship of NGF, say researchers, will shed light on its potential for use in Alzheimer's and Parkinson's disease. Tom Blundell from Birkbeck College in London, Wlodawer, and colleagues published their findings on the structure of NGF in the December 1991 issue of *Nature*.

Davies and his team had conducted a more detailed analysis of the two structures using the program ALIGN and confirmed what Swindells and Chotia and Murzin had observed.

"When you superimpose the two structures and align their sequences, it turns out that only eight amino acids out of 112 are the same in both structures, and so the sequence homology is very low," says Davies. "And of those eight amino acids, six are cystines, and they form three disulfide bridges that superimose in NGF and TGF-β. So the three disulfide bridges are obviously the clue to these structures, and they probably come from some ancestral disulfide-rich protein that had this structure."

While both TGF-β2 and NGF exist as dimers, they assemble their parts in different ways: In the TGF-β2 dimer, hydrophobic patches at the base of one hand lie on patches in the fingertips of the other. Thus the palms form the dimer interface. However, in NGF, the base and the fingers are parallel to each other but curved away such that the back of the hands are touching each other and the two pairs of fingers are pointed in the same direction.

The final piece indicating a new general motif came in November 1992 when a Swiss team reported in the *EMBO Journal* that they had determined the structure of PDGF and noted that its structure too was similar to that of nerve growth factor.

"The PDGF structure has the three disulfide bridges that are almost certainly the same as in TGF and NGF. As far as we can tell, the dimer in this case is formed in yet a third way," says Davies. Shaped like a shallow trough, the PDGF dimer's main body is formed by β strands and two ends are formed by the N-terminals.

The Swiss group is now comparing the coordinates of TGF-β and PDGF to confirm and examine this similarity in detail. The next step, says Davies, is to find the receptors and the signal transduction pathways activated by these cytokines. NCI researchers Sporn, Roberts, and colleagues, in collaboration with the NIDDK group, have already located the receptor binding site on the back of the "hand" in TGF-β. Knowing the structure of the cytokines has provided researchers with the first step toward their goal. ■

FEATURE

INDIAN "HUNTING MAGIC" TURNS UP POTENTIAL BIOTECH MAGIC

by Seema Kumar

John Daly's lab has an international reputation in the natural products field, and not without cause. Ever since he joined NIH in 1958, Daly has been working on biologically active compounds from natural sources, and during this time his lab has discovered more than 200 compounds from frog skins, most not found anywhere else in nature.

So when Katharine Milton, an anthropologist studying food-gathering habits of Amazonian Indians, brought back a frog secretion that the Indians use as part of their hunting ritual, the job of finding the active ingredients in this "hunting magic" naturally found its way to Daly's lab.

Milton had observed that in a ritual called "taking frog," Matses Indians in western Amazonia first collect mucus secretions from a large frog on flat little sticks, dry them, and store them for later use. A few days before a group decides to go hunting, members burn themselves, moisten the sticks with their saliva, and rub the secretion into their burns. What follows would dissuade most people from taking frog. The hunters get violently ill — nauseated, incontinent, and near delirium — and then go into a very listless state that lasts for about a day. Peter Gorman, a writer who tried this ritual, described an agony so great he prayed he would die. What makes this ritual worthwhile for the Indians is that when they come out of the listlessness, their perceptions are heightened and they feel ready to hunt—in Gorman's words, "God-like."

ADENOREGULIN HAS NO EFFECT ON THE SYSTEM BY ITSELF BUT SEEMS TO AUGMENT THE EFFECT OF THE NORMAL ENDOGENOUS ADENOSINE

Now Daly, Janet Caceres, Roger Moni, and Fabian Gusovsky of NIDDK and collaborating FDA colleagues have identified in this brew a new peptide of 33 amino acids that enhances binding of agonists to adenosine receptors. The researchers have named the peptide adenoregulin, referring to its ability to regulate the A1 adenosine receptor. The findings are published in the November 1992 issue of *Proceedings of the National Academy of Sciences*.

While a wide range of clinical uses for adenosine analogs have been proposed — they are protective against certain types of kidney failures, stroke, and certain heart abnormalities — adenosine itself is the only compound being used clinically in cardiac abnormalities. A major limitation to clinical use of adenosine compounds has been their ability to affect multiple systems. Thus, while they may prove useful in slowing the heart rate, analogs also will likely cause vasodilatation and a drop in blood pressures. Conversely, their use in vasodilatation to improve blood flow to an organ may also slow down the heart rate.

John Daly, chief of the Laboratory of Bioorganic Chemistry at NIDDK, directs and conducts research on biologically active agents.

"The tempting part of adenoregulin is that it has no effect on the system by itself but seems to augment the effect of the normal endogenous adenosine," Daly speculates. "So in a system that is trying to compensate by increasing adenosine, the end effect may be augmented by adenoregulin." Animal studies are needed to confirm the speculation, he adds.

In the *PNAS* paper, the NIDDK group, biologist Charles Myers from the American Museum of Natural History, and colleagues identify the frog as *Phyllomedusa bicolor*, a large green frog that inhabits the

continued on page 12.

Mini-Review

Treatment of Severe Beta-Globin Disorders

by Griffin P. Rodgers, Chief, Molecular Hematology Unit, Laboratory of Chemical Biology, NIDDK

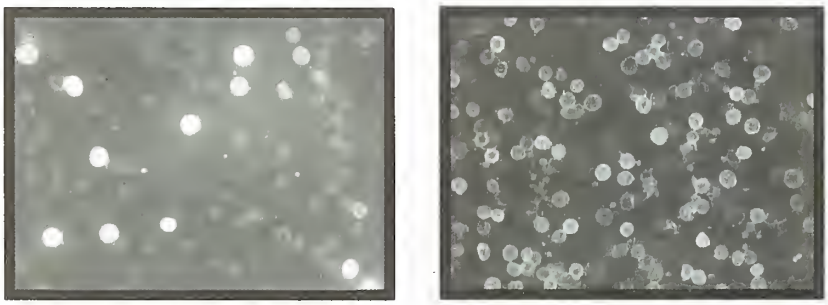
Numerous epidemiological and experimental studies support the view that increased levels of fetal hemoglobin (HbF) may improve the symptoms of patients with sickle cell anemia and beta-thalassemia. Prior to birth, HbF is the predominant form of oxygen-carrying molecules in red blood cells. After birth, however, HbF is reduced to 1-2 percent and adult hemoglobin takes over. In sickle cell anemia, a genetic defect in the adult hemoglobin gene causes the molecules to polymerize and form sickle shaped cells, and in beta-thalassemia, the defect results in inadequate red blood cells.

Hydroxyurea (HU), a cell-cycle specific agent that blocks DNA synthesis, has been shown to increase HbF production in most nonhuman primates and patients with sickle cell anemia (SS). However, the levels of HbF achieved so far in our studies of SS patients at NIH (LCB, NIDDK, Clinical Hematology Branch, NHLBI), and in studies at Harvard and Johns Hopkins, have only averaged 10%-15%, whereas epidemiological and biophysical studies suggest that a 20%-25% level of HbF in a pancellular distribution will be required before unambiguous clinical benefit occurs in SS patients.

To achieve the required increase in HbF levels and greater proportions of erythrocytes containing fetal hemoglobin (F-cells), several animal studies and small, pilot clinical trials are exploring higher doses of HU administered over longer periods and combination therapies of HU and growth factors as alternatives.

HU-Erythropoietin Combination for SS

Our studies on the treatment of SS have focused on the use of recombinant human erythropoietin (Epo), shown to significantly increase F-cell production in a baboon model and, more recently, to act synergistically with HU to increase F-cell numbers and HbF in the Rhesus monkey. In collaboration with Arthur W. Nienhuis of the CHB, NHLBI, and George J. Dover of The Johns Hopkins University School of Medicine, Constance T. Noguchi, Alan N. Schechter, and I recently treated four SS patients with HU administered for four consecutive days in an alternating fashion with escalating doses of Epo (and oral iron sulfate). The combination therapy was associated with a 40% increase in a subgroup of reticulocytes containing fetal hemoglobin (F-reticulocytes) and a 48% increase in HbF over the maximum values previously achieved using HU alone. Stimulation of F-reticulocytes occurred within days after Epo administration, while HbF augmentation occurred over several weeks but persisted for many weeks after cessation of Epo. The combination therapy was also associated with a further significant decline in total reticulocyte count and in the indirect bilirubin level, suggesting additional improvement in the rate of hemolysis. We are now coordinating a Phase II clinical trial comparing HU and Epo (with iron) to daily HU given at the maximum tolerable dose in several university hospitals and in the Clinical Center to determine which regimen is less myelotoxic, more effective in increasing HbF levels, and associated with greater clinical benefit.



Example of the change in peripheral F-cell numbers, as determined by immunofluoresence microscopy, in a patient before (left) and during (right) treatment with hydroxyurea/erythropoietin.

Concurrently, studies are under way at other centers to modulate the expression of HbF. They include: a multicenter, blinded, controlled clinical trial of HU; a Phase I trial of butyric acid in SS and beta-thalassemia patients; and a Phase I trial of phenylbutyrate in SS patients. Since butyrate compounds may act through a different mechanism than HU, these compounds could eventually be used in combination.

HU Treatment for Beta-Thalassemia

We have also expanded the application of HU treatment strategy to treat several severely affected patients with homozygous beta-thalassemia and beta-thalassemia intermedia, in collaboration with Yi-Tao Zeng and Shu-Zhen Huang at the Shanghai Institute of Medical Genetics. Preliminary data indicate that HU is effective in stimulating HbF production and F-cell numbers in some patients, thereby lengthening their transfusion intervals. Unexpectedly, in other patients, we have found such treatment to augment primarily beta-globin biosynthesis, corresponding to an increase in appropriate-size beta-mRNA transcripts in peripheral blood erythroid cells, and associated with an improvement in the effectiveness of erythropoiesis and an abolishment of the transfusion requirements. For these reasons, there is cautious optimism that a useful, effective treatment regimen of selected SS and beta-thalassemia patients is emerging on the basis of altering gene expression. Molecular studies are currently under way to determine the basis of the HU effect, specifically whether there are alterations in chromatin structure or transcriptional factor binding in the gamma and beta-globin gene promoters. ■

SYDENHAM'S CHOREA AS A MODEL FOR OBSESSIVE COMPULSIVE DISORDERS

by Susan E. Swedo
Child Psychiatry Branch
NIMH

Childhood-onset obsessive-compulsive disorder (OCD) is a psychiatric disorder characterized by recurrent, intrusive thoughts (obsessions) and unwelcome repetitive, ritualized behaviors (compulsions). Although its biologic basis has been recognized, the etiology of OCD is not known and a number of different perspectives have been suggested to date.

Since 1986, under the direction of Judith L. Rapoport, Henrietta Leonard, a child psychiatrist at NIMH, and I have studied several different patient populations with OCDs, using a variety of clinical research strategies. Clinical examination of children with this disorder first led to the recognition of genetic and neuroendocrine influences on OCD, and later led to several PET studies and to the largest cerebrospinal fluid study ever reported for a psychiatric disorder. Further, unique clinical observations in children with this disorder suggested the existence of an obsessive-compulsive spectrum of disorders and led to the first systematic study of trichotillomania or compulsive hair-pulling (Swedo et al., N Engl J Med 1989, 321:497-501). More recently, our research has focused on the similarities of a known medical illness—Sydenham's chorea—and OCDs. The research suggests that Sydenham's chorea may serve as a useful model to study the etiology and biochemical origins of OCDs.

OUR RESEARCH SUGGESTS THAT SYDENHAM'S CHOREA MAY SERVE AS A USEFUL MODEL TO STUDY THE ETIOLOGY AND BIOCHEMICAL ORIGINS OF OCDs

Sydenham's Chorea

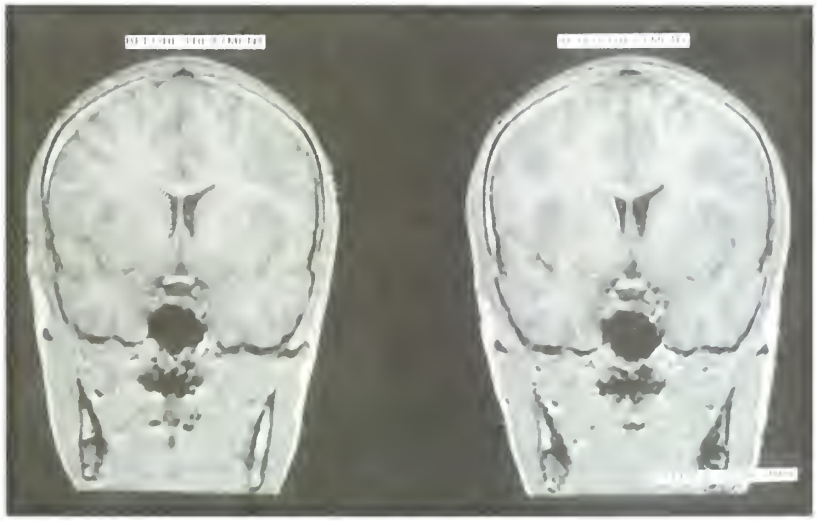
Sydenham's chorea is a variant of rheumatic fever in which antibodies directed against Group A beta-hemolytic streptococci cross-react with neuronal cell components, particularly within the basal ganglia. These antibodies induce an inflammatory reaction that manifests as abnormal movements (chorea) and psychological changes, including emotional lability and irritability. We have found that over 70% of children with Sydenham's chorea have an abrupt onset of obsessive-compulsive symptoms concomitant with their motor symptoms. This obsessionality appears to be identical to that of OCD, including contamination fears, fears of harm coming to oneself or to others, and cleaning, checking or repeating behaviors.

An Ideal Model

If the clinically similar Sydenham's obsessionality results from the same CNS dysfunction as OCD, then the subacute course of Sydenham's chorea will provide an ideal model in which to study not only regional localization and biochemical disruptions but also etiologic models. Intriguing preliminary evidence for such an association comes from MRI-documented disruptions of the blood-brain barrier in the basal ganglia in Sydenham's chorea and caudate enlargement in acute exacerbations of OCD. The well-known "rheumatogenic" families of Sydenham's chorea may be utilized as genetic models for OCD (and possibly Tourette's syndrome), while determination of the specific nature of the antineuronal antibodies may direct us to the antigenic components and thus, the dysfunctional receptors in OCD.

Plasmapheresis

A controlled treatment trial of plasmapheresis, intravenous immunoglobulin, and prednisone is under way to examine the responsivity of OCD, Sydenham's chorea and Tourette's syndrome to each of these modalities. Plasmapheresis, which removes 95% of circulating antibodies, should be the most effective regimen and may provide relief to a subgroup of the thousands of children suffering from OCD. ■



MRI scan of patient with abrupt onset of obsessive compulsive symptoms and movement disorder. Patient was treated with plasmapheresis, and caudate size returned to normal range. Symptoms decreased in severity concomitantly with caudate regression.

BIOTECH MAGIC
continued from page 9.

canopy of the rain forest. When Daly saw the frog, he realized that it was the same frog from which Italian scientist Vittorio Erspamer had isolated more than a dozen biologically active peptides. However, the vasoactive and even the opioid peptides identified by Erspamer did not explain the pharmacological effects experienced by the Indians.

With the sticks provided by Milton and a half stick provided by Gorman, researchers at Daly's lab, including MARC student Caceres, began to look for other substances. The team first looked for known hallucinogens found in some frog secretions, but found none. The researchers then injected the extract into mice and found that the mice entered a very listless state similar to those experienced by the Matses Indians. The listlessness reminded Daly of the effects of another class of compounds, typified by adenosine, that his lab studies. The mice behaved as though they had received an adenosine analog. So Daly and Gusovsky set up a binding assay to determine if hunting magic contained an ingredient that affects adenosine receptors. It did.

Researchers then separated the components of the skin extract using high-pressure liquid chromatography and found three significant fractions. Of these, two inhibited the binding of agonists to the adenosine receptor. One fraction, however, stimulated it. When researchers isolated the three fractions, they found the stimulatory one to be highly pure. They then determined the amino acid sequence of the peptide and named it adenoregulin. The researchers are continuing their efforts to characterize the other two peptides.

"We are now primarily interested in understanding what adenoregulin does and in studying its effects in functional systems in animals," says Daly. Scientists plan to use an existing mouse model of ischemia to explore the potential of adenoregulin to protect against stroke as adenosine analogs do.

Daly's main problem now is the lack of material. While these frogs are not rare, they are difficult to collect because of their inaccessible habitat, high in the rainforest canopy. Indians manage to catch them only when they accidentally fall from the trees or during a very brief breeding season.

Fortunately, though, the frogs are easy to raise and have been successfully bred in France. Daly and his colleagues are also exploring the possibility that other species of *Phyllomedusa* may contain adenoregulin in their skin secretions. In fact, Daly has learned that the Baltimore Aquarium is raising a different species of *Phyllomedusa.* If this species contains adenoregulin, a potential source of the compound may turn out to be closer to home than previously believed. ■

RUBBISH!

Pitohui! That's what New Guineans say about eating the Pitohui bird — spit it out.

Natives consider the Pitohui a "rubbish bird," not worth eating unless skinned because it contains a poison. The poison is potent enough that if one handles the bird and then rubs one's mouth, burning and numbness result, as University of Chicago graduate student Jack Dumbacher found out during a field trip to New Guinea a year ago. He suspected that the bird had a toxin in its feathers and contacted Daly's lab.

Daly and NIDDK colleagues Thomas Spande and H. Martin Garraffo discovered that the bird's feathers and skin contained the same toxin as that found in frogs used to poison blow darts in South America — frogs that Daly first worked with some 30 years ago. The poison, the first to be reported in a bird, is called homobatrachotoxin (one of the batrachotoxins discovered in the frogs) and is the only other occurrence in nature outside this group of frogs. The researchers reported their discovery in the October 30 issue of *Science.*

What does this mean? According to the NIDDK group, either the bird and the frog have independently developed the biosynthetic machinery to make the toxin or both of them have developed an ability to concentrate it from something they eat or from some symbiotic microorganism. The diet argument seems tempting because when they are raised in captivity, the frogs do not produce any batrachotoxin. Dumbacher, Daly, and colleagues plan to study the birds' diet — mostly insects and seeds — to determine if it provides the toxin that presumably protects them from predators.

Another interesting question that is turning up some pharmacologically enticing prospects is how the bird protects itself from its own toxin — one of the most poisonous substances known. Scientists know that the frogs have evolutionarily developed a different sodium channel — the site of action of the toxin — such that it does not interact with the toxin.

Although researchers don't yet know how the bird protects itself, they suspect that a new class of local anesthetic-type compounds may provide the answers. Preliminary evidence based on muscle extracts from this bird indicates that it can shift the toxicity of the poison. When injected into mice, these muscle extracts reduce the toxicity of batrachotoxin. The NIDDK group plans to isolate the substance and determine what it is. ■

Suggestions? Submissions? Questions?

The NIH Catalyst welcomes ideas or suggestions from intramural scientists to improve any aspect of this publication or to increase its utility. We also invite scientists to submit articles or call us with story ideas.

The NIH Catalyst is particularly interested in submissions for the following categories:

- *Hot Citations:* Citations and abstracts of recently published, exciting papers and listing of texts and other books by intramural scientists.
- Mini-reviews: Short review of an exciting area of intramural research, clinical or basic.
- *Debate and Discussion:* Topics you would like to see covered under this category or would be interested in writing about or suggestions on someone you know who might be interested in participating.
- *Commentary:* Commentary on science, policy or related issues of local and national interest.
- *Essays or Opinion:* Brief opinion or essay on an issue of interest to the intramural community.
- *Letters to the DDIR:* Asking the DDIR a question or expressing views to the DDIR.

Please direct questions, suggestions or ideas to the editor, *The NIH Catalyst,* Bldg. 1, Room 134; or call 402-1449.

Recently Tenured

Scientists tenured October 1992 to Date

Steven Akiyama, NIDR
Susan Bates, NCI
J. Silvio Gutkind, NIDR
Kathleen Kelly, NCI
Glenn Merlino, NCI
Richard Rothman, NIDA
Patricia Steeg, NCI

Steven Ken Akiyama, Ph.D.

Steven Akiyama's research at NIDR's Laboratory of Developmental Biology focuses on bioadhesion and cell behavior. Since he first joined NCI as a guest researcher in 1981, Akiyama has been interested in cell adhesion and migration. In his career as an assistant professor and an associate director for basic research at Howard University Cancer Center in Washington, D.C., Akiyama has made significant contributions to the understanding of these processes and their role in development and disease. In particular, his research has focused on the structure and function of fibronectin and integrin adhesion receptors.

In 1990, Akiyama became a Senior Staff Fellow in the Laboratory of Developmental Biology, NIDR. Recently, his research has focused on the role of integrins and fibronectin in migration and in signal transduction.

Cell-substrate adhesion plays an important role in proliferation, migration, differentiation, and regulation of morphology in animal cells. These functions in turn play prominent roles in normal physiological processes such as embryonic development, wound healing, and maintenance of tissue organization. Extracellular adhesive proteins such as collagens, fibronectin, vitronectin, and laminin can modulate cell behavior by binding to cell surface adhesion receptors, the integrins.

Using novel monoclonal antibodies that he developed, Akiyama demonstrated that integrins play crucial roles in cell adhesion and migration, cytoskeleton and extracellular matrix assembly, and tumor cell metastasis. The antibodies have since been used by numerous laboratories around the world. Akiyama also characterized the intracellular processing of integrins, showing altered processing by malignant cells. He was the first to show that maturation of asparagine-linked carbohydrates is important for the fibronectin-binding activity of integrins and in the activation of keratinocytes during wound healing. His results have improved understanding of the biological role of carbohydrates and integrins.

Recently, Akiyama has begun to characterize signal transduction events that accompany cell adhesion. He is finding that tyrosine phosphorylation of the 120 kd focal contact-associated kinase (FAK) can occur as a result of cell adhesion to a variety of extracellular matrix proteins. Furthermore, he is exploring the use of anti-integrin monoclonal antibodies as anti metastasis agents and the use of recombinant fibronectin fragments to accelerate the process of wound healing. Akiyama received his M.S. from Yale University in New Haven, Connecticut, and an M.S. and a Ph.D. from Cornell University in Ithaca, New York.

Richard B. Rothman, M.D., Ph.D.

Richard Rothman heads the Clinical Psychopharmacology Section at NIDA's Addiction Research Center in Baltimore. The section conducts both preclinical and clinical studies into the mechanisms of action of drugs of abuse, with a major focus on cocaine and opiates. Several projects under way in the preclinical program attempt to delineate the existence of opioid receptor subtypes and determine their functions. Another major interest of the section is learning the role that antiopiate peptides play in the development of tolerance and dependence to opioids.

In collaboration with medicinal chemists at NIDDK, Rothman and his team in the Clinical Psychopharmacology Section are attempting to synthesize and evaluate putative cocaine antagonists using various techniques, including quantitative ligand binding methods, in vivo microdialysis, radioimmunoassay, and various in vitro assay systems. Clinical studies under way will test the dopamine hypothesis of cocaine's addictive actions, as well as the antiopiate model of tolerance and dependence.

Rothman received his Bachelor's degree in chemistry from Swarthmore College in Pennsylvania, and his M.D. and Ph.D. in pharmacology from the University of Virginia, Charlottesville. Rothman then worked in pharmacology research at NIMH and became the chief of the unit on receptor studies in the Laboratory of Medicinal Chemistry, NIDDK. Two years ago, he became the permanent chief of the Clinical Psychopharmacology Section at NIDA.

Rothman has won several awards and scientific recognition, including the Joseph Cochin Young Investigator Award in 1991 and the Scientific Achievement Award in Biological Sciences in 1989, both for contributions in the field of opioid pharmacology. In 1989, Rothman also won the A.E. Bennett award (basic science) for a paper on opiate receptor subtypes ■

This regular feature will list the names and affiliations of recently tenured scientists. A brief description of scientists' works will be featured, with their approval.

NIH-GWU to offer Graduate Program in Genetics

■ Beginning Fall 1993, NIH and George Washington University will offer a new, formal graduate program in genetics in which students will complete their Ph.D. coursework at GWU and conduct their dissertation at NIH intramural laboratories.

The program, established after months of negotiation between the Office of Education (OE) and the George Washington University School of Arts and Sciences, is different from most other programs at NIH, says Michael Fordis, Director of the (OE).

"While students have previously come to NIH to do their doctoral work, the arrangement came about mostly on an ad hoc basis and was often initiated by a student," says Fordis, "However the new program formalizes the advantages of such an arrangement."

Students admitted to this program will receive a full tuition waiver for four years from GWU and will receive support through Predoctoral Intramural Research Training Awards from ICDs that accept students.

The program will allow students a choice among projects in basic molecular genetics as well as prevention, diagnosis, therapy, and cure of human genetic diseases. During the first semester of study, students will identify an appropriate laboratory at NIH by completing six months of laboratory rotations. NIH scientists from the selected laboratories will then serve as the students' research directors.

Applications are currently being accepted for the first class that will enter in the fall of 1993. According to Fordis, GWU has agreed to waive the four-year tuition for five students entering during each of the next four years so that by 1996, 20 graduate students will be participating in the program on the NIH campus. Fordis anticipates that the numbers will increase as the program becomes established.

NIH scientists interested in serving as dissertation advisors can receive additional information by contacting Jeffrey Sich at 402-2177. ■

Mentors Sought for Students and Teachers

■ The Office of Education would like to hear from intramural scientists interested in serving as research mentors for students and teachers seeking research internships at NIH over the next year. The interns are fully supported. Students' educational levels range from high school to college, and most teachers are currently responsible for instruction in high school biology or chemistry. Many high school students and teachers will have received initial training in recombinant DNA technology before entering the intramural laboratories. Interested intramural scientists can inform the OE by returning forms recently distributed across campus or can contact Deborah Cohen directly at 402-2176. ■

Scientists Needed for NIH Education Network

■ The Office of Education has a number of opportunities for scientists to participate in efforts to improve the quality of science education in the surrounding communities. Scientists can determine their own level of involvement and time commitment. Opportunities range from speaking to classes as a member of the NIH Speakers Bureau to responding to questions posted by students on NIH Ednet, an electronic bulletin board. OE is eager to identify postdoctoral fellows as well as tenured faculty who wish to participate. Scientists interested in further information should contact Mary McCormick at 402-1914 or Deborah Cohen at 402-2176. ■

1993 Catalog Of Intramural Research Projects On-Line

■ The 1993 Postdoctoral Research Fellowship Opportunities Catalog is now available on-line over Internet as well as over the local NIH network. The second edition of the catalog describing research projects in the various ICDs has been updated and expanded to include additional descriptions of individual research projects and representative citations. Potential postdoctoral fellows around the world can use this database to identify projects and preceptors in their areas of interest.

The database will also enable intramural scientists to more easily identify NIH colleagues with like interests. The catalog provides the means for browsing and for rapid searching and retrieval of information using any terms. A search using a particular term brings up the names of all scientists associated with the term along with their ICD and laboratory/branch affiliations. Research description and key references for each individual may then be retrieved by selecting an individual's name.

The OE plans to provide a mechanism by which the descriptions can be continually updated. Future plans also include developing a similar database of specialized research techniques and reagents with individual descriptions to provide NIH scientists access to their colleagues' expertise. For information on how to access the catalog on-line, contact the OE at 496-2427. ■

Parking Update

The Office of Research Services (ORS) reports that the parking status at NIH has stabilized since early October, with the total number of parking spaces, including those provided by temporary lots, continuing to remain at 8,900. According to the ORS, when the multilevel parking garage is completed this summer, 1,500 spaces lost to various construction projects will be restored, and as planned, certain temporary lots will be returned to grass.

Meanwhile, the ORS has launched a campaign urging commuters to use alternate arrangements, including satellite lots and TRANSHARE program (TRANSHARE offers incentives to employees using public transporation). More and more commuters are using the satellite lots (Garage 57 and Mid Pike Plaza) and the related shuttle services daily. Some 700 NIH personnel are now participating in TRANSHARE, and close to 100 are using the Shady Grove lot.

The ORS also reports that Federal law under Title 45 CFR and Maryland Transportation Regulations require that full-time, dedicated spaces, marked with handicap signs, are to be used only by disabled employees or those driving disabled employees displaying a handicap permit or handicap license plate. These spaces are placed at locations that provide a direct, barrier free access route to specific buildings and are continually reviewed, monitored, and adjusted to meet employment needs. To ensure that the 150 or so handicap spaces are available, handicap regulations are strictly enforced at all times. Ticketing on all other spaces during the night or on weekends is minimal. ■

DCRT Team Wins BOSS Award

A team of computer scientists and engineers from the Division of Computer Research and Technology (DCRT) recently received the prestigious "BOSS" (Best of Open Systems Solutions) award for implementing the Advanced Laboratory Workstation (ALW) system on the NIH campus.

The team, headed by Keith Gorlen of DCRT's Computer Systems Laboratory, and Perry Plexico and John W. Dickson of the Computer Center Branch, received the honor under the "Innovation in Hardware, Software, and Networking Approaches" category. The winners were honored at a special luncheon and showcased the ALW system during the Federal Computer Conference's OpenNet '92 demonstration at the Washington Convention Center, December 8-10.

David J. Lim (left), Director of the Division of Intramural Research for NIDCD, recently received the 1992 Shambaugh Prize in Cairo, Egypt, from M. Nasser Kotby (right), President, Collegium Otorhinolaryngologicum Amicitae Sacrum (ORLAS). Lim received the award for his outstanding contributions in auditory neurobiology and otology. The Shambaugh Prize, established in 1949 in honor of the prominent American otolaryngologist George E. Shambaugh, Sr., is awarded once every two years. ■

The Federal Computer Conference grants the BOSS awards once a year to recognize government agencies that have best applied open systems towardsbecoming more efficient and cost effective. The DCRT team developed the ALW system by integrating and enhancing Transarc's Andrew File System® with other software developed at Carnegie Mellon University in Pittsburgh, PA, and the Massachusetts Institute of Technology in Cambridge, MA. The innovative design emphasizes reliable daily backup of user files, centralized software management, high availability, and provision for customized configuration of user workstations.

The ALW system, which currently supports 150 workstations and more than 300 registered users, gives biomedical researchers "plug and play" capability for UNIX® workstations made by Sun, Digital Equipment Corporation, and Hewlett-Packard. The system provides ALW users at NIH access to more than 115GB of managed disk storage, applications software, software maintenance services, electronic mail and news, computation and database servers, and an international distributed file system.

ALWs are particularly suitable for scientific applications that require high-performance graphics or computation, or access to large amounts of data. The most popular applications include medical image processing, DNA and protein sequencing and searching, statistical analysis, and molecular graphics and modeling.

DCRT's workstation loaner program allows NIH scientists to evaluate the features of ALW before investing in their own workstations. If you are interested in a loaner machine or additional information about the ALW system, call 496-1111. ■

DCRT Offers Courses, Seminars on Scientific Computing

The Division of Computer Research and Technology offers a varied program of short courses and seminars of interest to the NIH research community. All classes are held at the NIH main campus and are free. The spring 1993 term runs from late January to the end of May, and additional students are welcome as long as the classes are not full. For more information or to request a brochure detailing the program, call the DCRT Training Unit at 496-2339, or stop by the office, Building 12A, Room 1023.

In collaboration with DCRT, the NIH Training Center offers a full spectrum of hands-on PC and Macintosh computer classes for a variety of commercial software packages. Call the NIH Training Center at 496-6211 for their most recent quarterly catalog. A partial list of the spring term classes follows:

Introduction to Diffusion Theory	2/23
Network Services	2/24
Bibliographic Manager Programs for the Macintosh	2/24
New Tools for Genome Sequence Analysis	2/25
Introduction to Image Processing	3/2, 3/4, 3/9, 3/11
Introduction to Parallel Computing	3/10
Molecular Modeling with Quanta	3/22, 3/26
Usage of Applications of Molecular Quantum Mechanical Programs	3/29, 4/5, 4/12, 4/26, 5/3, 5/10, 5/17
Comparing Macintosh Sequence Analysis Programs	3/31
Computer Data Structures	4/5, 4/7, 4/12, 4/14
LISTSERV Electronic Mailing Lists	4/8
Physical Models of Cell Locomotion	4/13
Mainframe Services at NIH	4/15
Networks for the Scientific Community	4/20
Topics in Flow Cytometry	4/20, 4/27
Image Processing on the Macintosh	4/21
Experimental Data Analysis	4/22, 4/27, 4/29, 5/4
Inside Image	4/27
GCG Sequence Analysis on the Convex	5/4-5/6
Recurrent Problems in Data Analysis	5/10-5/12
Analysis of Ligand Binding Data Using the LIGAND Program	5/11
Introduction to Molecular Modeling	5/13
Modeling Protein Folding	5/18

Advertising Strategy

(continued from page 5)

been recorded from individuals at universities all over the world. These accomplishments have been achieved concomitant with a much greater efficiency in the use of each advertising dollar.

Says Fordis, scientists who know they will need to recruit fellows during the next calendar year and wish to be included in such ads should contact the OE at their earliest convenience. For more information on the advertising service, scientists should contact Shirley Forehand at 496-2427. ■

Gopher It!

Free, computerized access to Current Contents, GenBank, and Protein Data Bank is now amazingly easy, thanks to Gopher, the information search and retrieval tool implemented on the NIH Convex computer system. Based on a "client-server" model, this system allows you access to data on remote computers from software running on your own PC, Mac, or Unix workstation.

The best way to discover what is available is to run Gopher and explore! Convex users can start by typing "gopher." Gopher is quick, simple-to-use, and can "tunnel" to other Gopher servers around the world without effort by the user.

If you are on the NIH Convex (Helix), here are some of the databases you can search:

- Current Contents
- Current Index to Statistics
- GenBank
- Protein Identification Resource (PIR)
- Protein Data Bank (PDB)
- NIH Phone Book
- DCRT Technical Publications
- INTERFACE Technical Notes
- The Internet Resource Guide

Searches with Gopher are very fast, generally taking a few seconds to generate a list of matches for the keyword entered. Once a list of matches is returned, a given entry can be displayed in its entirety and then saved as a file or printed.

Gopher has access to a large variety of network services locally and worldwide. Services include the NIH Card Catalog, weather reports, and access to university directories, to name a few. To find out more about using Gopher from your own computer, or to express what you would like to see in this system, call the Convex staff at 496-4823.

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In the Next Issue...

- Francis Collins Comes to NIH
- Draft of Career Development Policy
- New Clinical Center Master Plans
- Tech-Transfer

and more!

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An editorial board comprising representative members of the intramural community is being formed and will be announced in the next issue.

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