FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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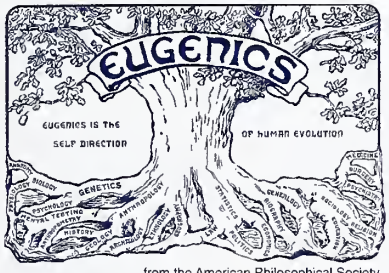
Cold Spring Harbor Archives

AMERICAN EUGENICS: NOT A PRETTY STORY

by Fran Pollner

It's unlikely that Gregor Mendel expected that his obscure life's work would be rediscovered after his death and recognized as an extraordinary addition to the understanding of biological organisms.

It is even less likely that he could have foreseen that his painstaking counts of peas of different colors and shapes—the basis of the science of genetics—would spawn a eugenics movement led by scientists who posited a single-gene causation of lunacy, pauperism, criminality, sloth, epilepsy, and other traits they deemed loathsome.



from the American Philosophical Society and the Eugenics Archives

"Eugenics is the self-direction of human evolution"—the philosophy of a movement in American history now the subject of a website from Cold Spring Harbor Laboratory, where a workshop was recently held examining possible parallels between past and present

But, indeed, Mendelian genetics, born in the second half of the 19th century, was used in the first half of the 20th as an allegedly scientific springboard for laws that imposed constraints on immigration, marriage, and reproduction in the United States. Not only did some scientists promote eugenics—the science of being well-born—those who did not did little to oppose it.

One hundred years later, on the

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RESEARCH COMMUNITY AT HALF-MAST

by Celia Hooper

Fran Pollner

As *The NIH Catalyst* went to press, the United States had just witnessed the worst peacetime attack in history—the September 11 terrorist attack on the towers of the World Trade Center and the Pentagon. NIHers quickly rose to do their part in recovery efforts.

With central coordination from the DHHS Office of Emergency Preparedness, the Public Health Service deployed 41 officers PHS-wide. NIH staff expected to assist with forensic pathology and to backfill at the Navy Medical Center, replacing staff deployed to New York aboard the Navy's medical ship *Comfort*. Fifty nurses and 50 doctors added their names to the lists of volunteers prepared to help with victims from New York or the Pentagon.

HHS dispatched five disaster medical teams to New York and three in the Washington metropolitan area. Each team had approximately 35 physicians, nurses, and emergency medical technicians trained to handle traumatic injuries. In addition, four disaster mortuary operational response teams were sent to New York and three to the Washington area.

The NIH Blood Bank collected an astonishing 404 units of blood in 36 hours—about 60 percent of the blood was drawn from NIHers and others on campus. The bank quickly shipped off 70 units of blood it had in store to Fairfax INOVA hospital for victims expected from the Pentagon crash. Named a regional collection center, the NIH Blood Bank stayed open until 8:00 p.m. collecting, typing, and testing almost eight times the number of donations it usually handles in a day.

"If there's anything we can do to help, we want to do it—we wish we could do more," was what donors told Susan Leitman of the Clinical Center's Department of Transfusion Medicine. Leitman was amazed by the nonstop efforts of blood bank staff and the patience of donors, from whom she heard not a single complaint, despite waits of up to 2 to 3 hours. "It was extraordinary," Leitman says.

Harvey Klein, chief of the transfusion medicine department, urged people to call the Blood Bank to make appointments to donate blood in upcoming weeks. "We are concerned that there will once again be a real shortage after the acute period has passed," Klein wrote in an NIH-wide message.

Security on the Bethesda campus was intensified, with all but four or five entrances to the campus closed. NIH police posted at the street entrances and some buildings checked for parking permits, ID cards, and other evidence that people coming in had a good reason to enter. It was not clear how long the intensified security would be in effect. ■

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Guest Editorial from the Assistant Director, OIR

Ten Years and Counting: Have NIH Women Scientists Advanced since the Task Force Report?

Joan P. Schwartz

Half the doctoral degrees awarded in the biomedical sciences these days are going to women. Similar diversity ought to be reflected in the ranks of the NIH workplace.

A recent talk on "The Advancement of Women Scientists" by Dr. Virginia Valian, professor of psychology at Hunter College in New York, stimulated me to think hard about the representation of intramural women scientists at all levels of NIH. Valian opened by noting that although women now enjoy smoother entry into the biomedical work world, they still encounter obstacles to advancement once there—not just in science but across all fields. Is this also true at NIH?

Prologue

Ten years ago, then-NIH Director Bernadine Healy established a Task Force on the Status of NIH Intramural Women Scientists. Its charge was to:

- Assess the career development and status of intramural women scientists with regard to recruitment, retention, compensation, and reentry into the work force.
- Determine whether there were impediments to the career development of women scientists at NIH.
- Recommend to the deputy director for intramural research (DDIR) and the NIH director administrative and structural changes to correct any identified problems.

The task force identified problem areas and recommended actions to remedy them (see *The NIH Catalyst*, June 1993, for a summary of the report). I would like to discuss each in turn in terms of what we have accomplished since that time and where improvement is still needed.

If NIH wants to increase the representation of women, it has to determine why fewer women are being selected for tenure-track positions than are represented in the postdoc pool

- ***To address the need to better inform women scientists about NIH policies and procedures***, the task force concluded that each IC ought to have a woman scientist advisor (WSA) who would serve as a liaison between the IC's female cohort and the administration, particularly the scientific director (SD). The WSAs now comprise a committee that meets every six to eight weeks to discuss ongoing issues relevant to women scientists. A subcommittee meets on a regular basis with the DDIR to discuss how best to implement changes that the WSAs have identified as necessary.
- ***To ensure equal compensation for equal work***, a process was undertaken in 1994 whereby each WSA, together with her SD, compared the pay of tenured male and female scientists in the IC. Subsequently, in concert with the DDIR, they came up with a list of scientists who needed pay adjustments. A one-time agreement with the Department of Health and Human Services allowed NIH to correct the pay of 49 women (1/4 of the total) and four men, including adjusting for two years' worth of back pay and benefits.

As a result of the expanded use of Title 42, with its potentially higher pay scales, in the appointment of tenured scientists, a similar analysis is needed now to ensure that women scientists of equal accomplishments have not fallen behind in compensation. At the same time, women need to become informed about and request Title 42 appointments. An Office of Intramural Research (OIR) database that includes all tenured scientists, tenure-track investigators, and staff scientists and clinicians is close to completion. That database will be used to assess pay across the ICs over the next two months. If significant disparities are found, the appropriate SD will be asked to review the data and make corrections as needed.

- ***To enhance the visibility of women scientists of all racial and ethnic groups***, the task force advised that care be taken to ensure their proportionate inclusion as speakers in all NIH-sponsored meetings, symposia, and seminar series. The most dramatic step taken was to name one of the most prestigious of the NIH Lectures after Dr. Margaret Pittman, the first woman laboratory chief at NIH. Seven distinguished women scientists have now presented the Pittman lecture. In addition, the percentage of speakers who are women has increased dramatically in all the lecture series.

However, vigilant women scientists still spot symposia or meetings with a negligible number of women speakers. Obviously, more work needs to be done.

- ***The need for flexibility in child-rearing and other family-related issues*** was addressed governmentwide by the passage of the Family and Medical Leave Act of 1998 and by the agreement of the SDs that comparable benefits should be provided to our trainees even though they are not government employees. Availability of sufficient high-quality childcare, at a price that our trainees and employees can afford, remains a problem, although NIH is expanding its own facilities with the opening of the new POPI (Parents of Pre-Schoolers, Inc.) in September 2001 and with a new daycare center on the drawing board.
- Finally, ***establishment of uniform tenure and promotion plans to enable women to compete more equally*** has occurred, and OIR has been tracking numbers of women in tenured and tenure-track positions ever since. Since the tenure-track plan was put into place in 1994, na-

tional searches are required for all new positions, tenured or tenure-track, and WSAs or their representatives are on every search committee.

The percentage of women on tenure-track has ranged from 21 to 29 percent and is currently 25 percent. This is lower than the percent of women who are postdoctoral fellows (which we guesstimate to be about 40 percent), but higher than the number of tenured women, which has remained constant at 18 percent over the past 10 years. In contrast, women comprise 34 percent of our staff scientists and staff clinicians.

Thus, NIH has taken positive steps to promote the advancement of women scientists in the intramural program, and this has resulted in improvements in some areas but not all. If NIH wants to increase the representation of women, it has to determine why fewer women are being selected for tenure-track positions than are represented in the postdoc pool. Do they apply and not get selected, or do they never apply?

Removable Obstacles

Valian described two impediments to the advancement of women—*gender schema* and *accumulation of advantage*.

Gender schema refers to a set of gender biases harbored by most people, consciously or otherwise: We perceive men as task-oriented and capable of independent action; we perceive women as feeling and nurturing. In a study by Heilman et al. (*J Appl Psychol* **74**:935, 1989), groups of managers were asked to rate other managers by means of listed adjectives.

"Even successful women managers were perceived as having less leadership ability than successful men managers. Furthermore, women managers were seen as having negative qualities that men managers did not have, such as being bitter, quarrelsome, and selfish."

Accumulation of advantage refers to the molehills of disadvantage that add up to a mountain. A computer simulation of promotion practices at a hypothetical company (Martell et al., *Am. Psychol.* **51**:157, 1996) showed the effect of a 1 percent bias against the promotion of women. The company had eight levels, with equal numbers of men and women eligible for promotion at each level.

After repeated promotions, the highest level had become 65 percent male and 35 percent female. "Operating at a minute disadvantage," Valian observed, "can have substantial long-term effects."

We have seen what may be a similar phenomenon at NIH. We are currently analyzing tenure-track dropouts, and the data suggest that a higher percentage of women leave the tenure track. If that means they're getting fabulous job offers elsewhere, great! But preliminary analyses suggest a small bias that favors men on the tenure track with more space, larger budgets, and higher salaries.

That small bias implies the possibility that women are not receiving the support they need to succeed in the tenure track. If so, this is indeed an example of accumulation of advantage, and the NIH must correct it. And men need to understand the subtle and not-so-subtle disadvantages women have in science and not contribute to this problem.

The same dynamic applies to tenured women. If they have fewer resources—which, again, some analyses indicate is the case—they will not do as well and therefore will not get promoted as quickly or receive the higher salaries.

Self-Promotion

What to do? I often tell women we need to take assertiveness training. Valian would say we must learn to negotiate from a position of strength, which means we need a greater sense of entitlement.

Working hard and being an excellent scientist are not enough—self-promotion is required. There is general agreement that even women in leadership positions must work twice as hard for the same recognition. According to Dr. Alice Huang, of the California Institute of Technology in Pasadena, we need to understand power and how to gain it in our own right. We must become aware of what is available and ask for it.

One thing that would help is an increase in the number of women in leadership positions in the intramural program. The change from no women SDs to four has meant a voice for women at the highest level. The number of female lab and branch chiefs increased from 4 percent to 10 percent after a concerted effort in 1994–1995 but has hardly changed since then.

One take-home message is that opening the doors for equal opportunity is not enough. We have to take very positive steps to encourage women to apply for those available positions, and we have to offer a supportive, equally endowed environment. And we have to acknowledge women's accomplishments at every stage.

Finally, those of us who have achieved leadership positions need to be mindful of our obligation to serve as a role model for those coming onto the scene. In the words of Mary Bunting, a past president of Radcliffe College in cambridge, Mass.: "Once you are in a position of power, do not forget that you are still a woman."

—Joan P. Schwartz, Assistant Director
Office of Intramural Research

Getting Oriented to NIH

For a concise and complete grasp of the plethora of professional and personal services available to NIH trainees and employees, stop by the second annual NIH Orientation Fair, **Tuesday, September 25, from 10:00 a.m. to 1:00 p.m.** in the exhibit area in front of the Visitor Information Center on the B-1 level of Building 10.

Sponsored by the Office of Education, the Office of Research Services, and the Work and Family Life Center, the fair will house more than 50 booths representing such entities as the NIH Library, the Office of Animal Care, the Credit Union, Parking and Police, Occupational Safety, and dozens more. Attendees can sign up for ListServes, pick up giveaways, and get their questions answered. The theme of the fair is "Ask me about the NIH."

Sign language interpretation is available upon request. Individuals who require this or other accommodations should call the NIH Office of Education at (301) 496-2427. ■

'Faces and Phases' Fall Schedule Online

The NIH Work and Family Life Center and the Employee Assistance Program are holding the fourth annual "Faces and Phases of Life" personal and professional development seminar series.

For a full fall schedule, descriptions of the seminars, and information on how to register, please visit **<http://wflc.od.nih.gov/faces.html>** or call 301-435-1619. ■

Eugenics: Not a Pretty Story

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cusp of a new century, the mapping of the human genome opened another door to gene-based strategies to improve human health. Today, however, many eyes are also open—to the potential for abuse.

Facing the Past

Among the vigilant are scientists at Cold Spring Harbor Laboratory (CSHL) in New York, perhaps more attuned than other researchers to how science can veer off course because of the checkered history of CSHL.

Now a world-class enclave of research and teaching in the biological sciences, CSHL was in its early decades the focal point of the American eugenics movement. Its officers produced and disseminated the movement's newsletter and from 1910 to 1940 ran the Eugenics Record Office (ERO), the repository of the movement's scientific papers, monographs, and family pedigrees gathered by fieldworkers trained at CSHL.

The ERO gave scientific weight to the prejudices that drove the enactment in 1924 of the U.S. Immigration Restriction Act and Virginia's Racial Integrity Act. It also crafted a model law used by 32 states to allow the compulsory sterilization of America's "unfit." This model was later adopted in Nazi Germany and earned Harry Laughlin—ERO director and the model's chief architect—an honorary degree from Heidelberg University in 1936, a year after its Jewish faculty had been expelled.

The rise and rationale of the American eugenics movement is now exposed in words and images at a CSHL website—

<http://vector.cshl.org/eugenics>.

—with funds from a grant from NHGRI's ELSI (Ethical, Legal, and Social Implications of Human Genetics Research) program.

The Image Archive on the American Eugenics Movement is co-directed by Jan Witkowski, director of the CSHL Banbury Center, and David Micklos, director of the CSHL Dolan DNA Learning Center. Its aim is that history not repeat itself. To that end, CSHL hosted a workshop on "American Eugenics and the New Biology: Perspectives and Parallels." The workshop was attended by scientists, legislators, ethicists, judges, and some journalists and was designed to cast the issues and the archives as widely as possible into the public arena.

Garland Allen, a biology professor at Washington University in St. Louis who wrote two of the archive essays—on the social origins of eugenics and its research flaws—tracked the ascendancy of the stitched-together science of eugenics into public policy.

Fran Pollner

David Micklos: *He and co-principal investigator Jan Witkowski decided to shine a giant beam onto what Micklos terms a "dark and relatively cloistered part of American history."*

What began in some scientific circles as excitement over the principles of Mendelian inheritance—that a "unit character" passed from parent to offspring produces a phenotype that could explain the inheritance of such traits as hemophilia—was molded into a movement that championed the science of human improvement through better breeding—an extension of agricultural and animal breeding principals to humans.

Eugenics was not the pet of the lunatic fringe; its intellectual leader, Charles Davenport, had taught at Harvard for 10 years and was a member of the National Academy of Sciences when he prevailed upon the Carnegie Institution of Washington to fund a research station at Cold Spring Harbor to study evolution by breeding farm animals and crops. Soon after, he secured funds for the ERO, which existed from 1910 to 1940 and boasted a board of distinguished scientific advisors. Laughlin, the ERO director, was appointed the eugenics expert to the House Committee on Immigration and Naturalization, where he presented charts on the prevalence of criminal behavior among those "biologically incapable of adapting to a complex society" and other proof of the inferiority of newer immigrants to America.

In the Name of Science

Other "scientific" findings of the American eugenics movement included:

- "Degeneracy" statistics showing that the birthrates of the "pathological"—criminals, the insane, deaf-mutes, the tubercular—were swamping those of "normal stock." The former reportedly had an average of six children; the latter, such as British intellectuals and Harvard graduates, had an average of 1.5 and 2 children, respectively.
- Anecdotal evidence that marriages ought to be made in the eugenics clinic, such as the case of one well-born man who had dallied with a "feeble-minded tavern girl" and then married a "worthy Quakeress." The first union formed a "line of hereditary defectives"; the second produced only "pillars of society."
- Pedigree charts purporting to demonstrate the passage of a trait—such as manic-depression, pauperism, and pellagra—through the generations. One Yale scholar concluded that scholarship was a sex-linked trait since it showed up only among the male members of families he'd tracked.

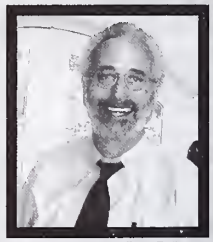
Ten thousand family histories were accumulated by CSH fieldworkers, said Elof Carlson, a geneticist and science historian at the State University of New York, Stony Brook. These were used to advise individuals regarding the eugenical fitness of proposed marriages. The ERO produced a Classification of Human Stock that defined "the fit" (those with genius, special skills, intelligence, courage, unselfishness) and "the unfit" (those who were socially inadequate, feeble-minded, paupers, epileptic, deformed, and "cacaesthenic," or ugly). Genetics was proffered as the sole source of fitness. Claiming that their findings conformed to Mendelian principles, scientists presented studies of the offspring of "retarded" individuals that yielded re-

Blue Ribbons for 'Fitter Families'

Steve Selden, of the University of Maryland, College Park, and author of *Inheriting Shame: The Story of Eugenics and Racism in America*, presented a slice of American life from 1911 through the 1920s—the Fitter Families Contests that, like judging livestock, became a staple of state fairs all over the country.

Under the eye of health-care professionals, contestants were assessed in examining rooms covered with posters illustrating how "some people are born to be a burden to the rest."

One poster declared that a person of poor hereditary stock is born every 16 seconds and "costs us $100" every 15 seconds, while a child with a high IQ is born only once every seven minutes.

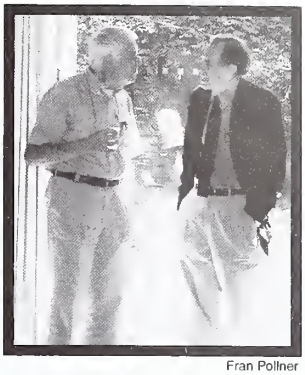


Fran Pollner

Steve Seldin

These contests were fostered by the Race Betterment Foundation, funded by the J. H. Kellogg fortune, encouraged by the *Women's Home Companion*, and legitimized by the eugenics movement.

CSHL workshop participants compared such propaganda to the Nazi rationale for murdering people whose care would exact too high a price from hard-working Aryans. And some were moved to sound cautionary notes about carrying modern prenatal diagnosis and managed care to extremes. ■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Gar Allen (left) and Neil Holtzman

tardation rates greatly exceeding any that would be predicted by Mendelian genetics.

But, Carlson noted, other geneticists—even those who were not eugenicists—did not challenge these papers. And the few demurrals that eventually were published appeared, unheralded, in obscure specialty journals not read by the general public or even most scientists. They were modest, polite, and did nothing to counter the laws and public policies based on eugenics.

It would have taken just three hours of research in books available at the time to refute every argument made by eugenicists, observed Paul Lombardo, a historian and lawyer who teaches bioethics and health law at the University of Virginia, Charlottesville.


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Paul Lombardo

Arguments that should have been made were not, he said.

"We have an obligation to remember this politeness of our forebears. We must critique our colleagues—not just subtly and in small footnotes behind closed doors. The science community and the media have an obligation," he said, noting that the atrocities that achieved the status of law in this country in the 1920s remained in effect for more than four decades. Immigration restrictions against Italians, Russians, Turks, and others were operative until the 1960s; it was not until 1967 that the racial integrity (anti-miscegenation) law was overturned; and under the authority of the eugenical sterilization law (adopted by 32 states after the Supreme Court found, in the words of Justice Oliver Wendell Holmes, Jr., that "three generations of imbeciles are enough" in the notorious *Buck* v. *Bell* case), 66,000 people were sterilized by 1963. The last documented forced sterilization occurred in Virginia in 1979.

In the Light of Today

According to his definition of eugenics—interference with individuals' procreative choices in order to attain a societal goal—eugenics lingers in our society, perhaps more dangerous because it is not so obvious, cautioned Neil Holtzman, professor of pediatrics at the Johns Hopkins Medical Institutions in Baltimore.

Eugenics may lurk under the masks of compassion and cost savings. At the dawn of prenatal diagnosis, he said, some scientists maintained that:

- Carriers of recessive hereditary defects should be warned against or prohibited from having children.
- Parents have a duty to abort if a severe birth defect is detected.
- Parents should feel guilty if they continue to reproduce kids with cystic fibrosis.

Society needs to be alert to the abuse potential of genetic advances, he emphasized—lest such occurrences as these turn out to be modern landmarks along a slippery slide to the past. Some more recent concerns:

- The implied obligation to screen for carriers of such conditions as sickle cell anemia or Tay-Sachs.
- A recent survey of managers of newborn screening programs in which 19 percent included as an important goal of newborn screening to "identify children who might be unsuitable for genetic reasons to reproduce."
- Surveys of genetics professionals and primary-care physicians that show a proclivity to encourage prenatal diagnosis for such conditions as spina bifida, Down syndrome, cystic fibrosis, sickle cell anemia, achondroplasia, and Klinefelter's syndrome.

Holtzman urged that any remaining sterilization laws be repealed; that the stigma attached to those with genetic disabilities be eliminated; that full care for all infants born with prenatally detectable conditions be guaranteed; and that genetic counselors be trained to be nondirective.


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Dean Hamer

"To use eugenics around sexual orientation is a real live threat," said NCI's Dean Hamer, whose reported findings that gay brothers shared DNA markers on the X chromosome more often than expected suggested a genetic component to male sexual orientation. They also suggested that sexual orientation is not all genetics, he said. Nonetheless, as soon as his and other limited, preliminary data were reported, there was talk of prenatal screening for the "gay gene"—with prominent individuals suggesting that selection on that basis is acceptable.

The public, he said, and especially judges—who make and overturn laws—need to learn, at the least, how to identify and thwart such misuse of science. ■

NIH Library Resources

The NIH Library offers classes, one-on-one tutorials, and web-based tutorials on how to use electronic resources: to access full-text journals, search databases, create instant bibliographies, order and receive articles via e-mail, set up a literature alert service, use the new NLM Gateway, conduct a Web of Science cited reference search, set up a Porpoise profile, and order documents through PubMed. For more information, go to

<http://nihlibrary.nih.gov/training.htm>

or call 301-496-1080. This training is free and for NIH staff only. ■

Hispanic Scientists Day

The second NIH Hispanic Scientists Day will be held Monday, **October 1**, 2001, 10:30 a.m.–1:00 p.m., in Building 10's Lipsett Amphitheater. A one-hour seminar will be followed by poster presentations by Hispanic scientists, postdoctoral fellows, and postbaccalaureate trainees. The event is sponsored by the NIH Hispanic Employee Organization. For more information, contact Marta Leon-Monzon at 301-435-7693, 301-496-4564, or **<ml7w@nih.gov>**.

Bioethics Course

The Department of Clinical Bioethics is again offering the seven-week course on Ethical and Regulatory Aspects of Human Subjects Research.

Beginning October 31, the course will meet Wednesday mornings, 8:30 to 11:30 a.m. in the Lipsett Auditorium.

To register and make arrangements for any special needs, contact Terri Jacobs at 301-496-3822 or at **<tjacobs@cc.nih.gov>**.

A limited number of course notebooks will be available in Building 10, Room 1C118, on the Bethesda campus the week before the first class. ■

Research Fest

The 15th annual NIH Research Festival—a showcase for the NIH intramural research program—will be held **October 2–5** in the Natcher Conference Center. This year's Research Festival Organizing Committee is co-chaired by Peter Lipsky, NIAMS, and J. Carl Barrett, NCI. For a schedule of events, see **<http://festival01.nih.gov>**.

For more information, contact Paula Cohen at 6-1776 or e-mail **<pc68v@nih.gov>**.

Proud of Its Résumé: Office of Education Celebrates Its 10th with 11 Candles and a Video

by Fran Pollner

They seem to have been woven into the fabric of NIH from the beginning—subspecialty accreditation for medical fellows, the poster day for summer students (see "Dreams on Display," page 10), the annual postdoc Job Fair, the Clinical Research Training Program (CRTP), the FARE (Fellows Award for Research Excellence) competition.

But they weren't.

None of these NIH "institutions" had their origins before the creation of the NIH Office of Education (OE), which, much like the Internet, seems to have always been here but, in fact, was not even an entity on paper until 1990. The OE celebrated its 10th anniversary only last spring—actually a year beyond its 10th.

"A 10th anniversary is worth waiting for," quips OE Acting Director Brenda Hanning, explaining the delayed celebration. Part of that extra year, she said, was spent producing an OE video—"The Investigators at NIH"—to commemorate the anniversary and convey the accomplishments of the OE through the exhilarated narratives of young clinical and basic research trainees and their NIH mentors.

Outer ring *(left to right): Steve Alves, Education Program coordinator; Vicki Malick, then assistant director for clinical training, now with NIDDK; Jim Alexander, deputy director; Ione Lagasse, program coordinator, Continuing Medical Education;* ***center row****: LaShawn Drew, acting director, NIH Academy; Sylvia Scherr, executive director, Continuing Medical Education; Shirley Forehand, assistant director for administrative services; Brenda Hanning, acting director; Donna Stewart, administrative assistant; Kenny Williams, Education Program coordinator;* ***front row****: Valerie McCaffrey, NIH Academy program coordinator, NIH Academy; and Debbie Cohen, Education Programs officer;* ***not shown****: Marian McDonald, web assistant*

Central Casting

OE was originally the brainchild of NIH scientific directors (SDs) looking for an answer to concerns raised in a 1988 Institute of Medicine report (see "Where Have All the Fellows Gone?" below) that cited a "troublesome trend in recruitment into NIH training programs in what had become the post-Vietnam era," recalls OE Deputy Director Jim Alexander.

"The intent behind creating OE was to reverse that trend, and the SDs felt that centralized recruitment would serve NIH well," said Alexander, who, like a lawyer taking his clients with him, brought to the new OE office a briefcase of programs he had run as chief of the Clinical Center's special programs—recruiting clinical associates and administering the clinical electives and summer research programs for medical students. Responsibility for CME (continuing medical education) and GME (graduate medical education) program accreditation also moved from the Clinical Center to OE.

From day one, when OE began with three on the staff, to the present, nothing has remained static. Staff and programs have grown apace. Though there was no "barometer of superior quality that could withstand close scrutiny," OE set out to quell concerns that the quality of trainees attracted to NIH might be declining by devising means to enhance competition for NIH slots and to inspire the best efforts of those selected.

Learning Curves

There was an early emphasis on student programs—to develop an IRP pipeline from undergraduate to postbac to doctoral candidates—but that did not detract from the drive to advance the abilities of NIH's physician researchers and postdocs.

A Resident Awards program that offered $2,000 for the best abstract was an early attempt to attract the most academically gifted to NIH for subspecialty and fellowship training. It was discontinued after two years. The FARE competition, on the other hand—launched in collaboration with the NIH Fellows Committee—has persisted and thrived, generating increasing numbers of participants, winners, and outstanding research efforts since its inception in 1994. The FARE travel awards to present winning research papers at scientific meetings have boosted both the fellows and NIH.

A drive to enhance NIH's GME status began in 1991, with OE's securing accreditation of six internal medicine subspecialty training programs: critical care medicine, endocrinology-metabolism, hematology, medical oncology, infectious diseases, and rheumatology.

Today, notes Hanning, that number has tripled, with additions not only in inter-

Where Have All the Fellows Gone?

In 1988, an Institute of Medicine (IOM) panel issued a report and recommendations on "strategies to strengthen the scientific excellence" of the NIH intramural research program (IRP). The study was "prompted by a concern [that the IRP] is experiencing difficulties in attracting and retaining basic scientists and clinical investigators." The committee cited intensified competition from universities and industry and the end of the doctor draft as possible explanations for what was perceived by some as a decline in the caliber of NIH trainees in the 1980s compared with the '60s and '70s, when placement in Bethesda was also an alternative to assignment in Saigon.

Creating a central Office of Education was an NIH response to the IOM report. Its mission was to oversee and advance the recruiting and retention of outstanding trainees into all IRP training programs. ■

nal medicine but also pediatric subspecialties, bloodbanking and transfusion medicine, clinical and laboratory immunology, cytopathology, hematopathology, and medical genetics. There is also residency training in anatomic pathology, dermatology, and psychiatry. More accredited subspecialty programs are anticipated, Hanning notes, adding that on the GME horizon is a project to establish outcome measures of physician competencies—part of a national initiative that will be phased into the accreditation process in 2002.

By all accounts, among the most valuable OE projects are those that equip NIH trainees for the world beyond NIH—where the large majority of postdocs who do not travel the NIH tenure track are headed. Among these are the annual Job Fair, which OE began in 1996, and the series of workshops and seminars variously cohosted by the Office of Research on Women's Health and the Fellows Committe to impart such survival skills as grant writing, debt management, and public speaking.

"Our office is a catalyst for students," says Hanning, pointing with pride to the NIH Academy (the newest of the NIH student programs, geared to postbacs with an interest in eliminating health disparities; see *The NIH Catalyst*, January-February 2001, page 8) and OE's programmatic support and individual counseling services for all of NIH's postbacs.

Winning Line-ups

Alexander counts the centralized recruitment mechanism built by OE among the office's greatest gift to NIH. "If we have done anything for NIH, it's to put this system into place," he says, clicking onto the NIH "training" website:

<http://www.training.nih.gov>.

He calls it a "work in progress." It's a work that has made a good deal of progress.

The website, notes Hanning, had more than 1.5 million hits in January, typically a peak month. It boasts 11 online application systems, including those for the CRTP, FARE, summer programs, and the NIH Academy.

"You can see the value in this kind of system," Alexander observes. "Investigators all over NIH can go in and find just the candidate they want by clicking. It's all there: the major, the GPA, the cover letter, the résumé, the interests, reference letters. The investigator gets a snapshot."

The website also posts tenure-track ads and postdoc vacancies (437 posted in 2000–2001). People interested in doing research at NIH can scroll through a list of openings at NIH labs.

It also provides a tally of applicants and positions available in certain NIH training programs. Ratios of late resemble more those of the golden years the IOM panel sought to restore than the situation that prompted its 1988 report. For instance, the 2001 summer internship programs to further careers in biomedical research among high school, college, and graduate level students had 3,296 applicants—of whom 818 were offered and accepted positions. The only cohort of summer students whose numbers have not increased are medical and dental students.

Similar competition exists for postbac slots at NIH. In the last six months, 398 individuals applied for these positions; 85 new postbacs are now on campus. A look at the postbac roster reveals considerable diversity among the institutions of origin—from small liberal arts colleges to large state schools to the Ivy League. What the trainees have in common, almost universally, is superb GPAs.

"I'm not certain that the standardization of recruitment procedures in 1990 was viewed by everyone as the way to go. NIH is, after all, a confederation of disparate entities (the ICs) with significant autonomy," Alexander remarks.

Today, old and new recruitment methods coexist, but Hanning is aiming to further democratize the system by working in concert with the institutes to create the equivalent of an admissions committee to "make sure that no excellent candidate goes unnoticed" and that the best and brightest students converge on the NIH campus from every part of the country.

Hanning anticipates that such a committee will be in place in time to process summer 2002 applicants. Also on her wish list—to make a summer here a bit more feasible for out-of-towners with scarce resources—is a "patron saint of housing."

Credit Galore

Just as the applicant pool for fellowship positions has swelled, so has attendance by NIH denizens at CME activities. Indeed, OE's CME program is a rising star.

In 1998, 6,459 physicians and 7,669 nonphysicians availed themselves of OE's CME offerings. In 2000, those numbers rose to 34,802 and 15,573, respectively.

Sylvia Scherr, who stepped into the position of CME executive director two years ago in August 1999, credits NIH's FAES/CME Committee with fostering the growing respect of NIH physicians for CME programs—once considered either a "nuisance" or a "rubber-stamp"—and for the excellence of the CME programs, which reflect the increasingly stringent standards of the accrediting councils.

The programs also meet the real professional needs of physicians, Scherr says, citing as an example the Great Teacher series (see *The NIH Catalyst*, July–August 2001, page 15), designed to fill the gaps in clinical expertise that NIH physicians pinpointed in a survey.

Another newcomer, sought by NIMH and OE, is approved sponsorship of continuing education credit in psychology.

A CME website, launched last fall and expected to be glitch-free by this fall's end—(**<http://www.cme.nih.gov>**)—provides a comprehensive list of available CME programs and a system whereby physicians can keep track of their own CME records.

Forward Thinking

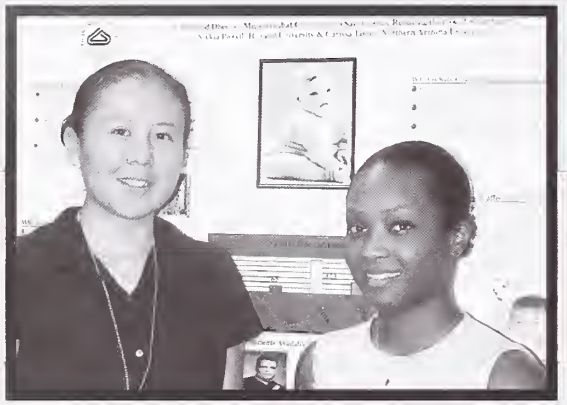
Hanning, who arrived in January 1999—just in time to see the OE through its first site visit in 20 years for reaccreditation of the CME program—reserves a special place in her heart for GME, which, she says, has flourished in the past two years under the guidance of the NIH GME Committee. She characterizes its members as "an extraordinary group of physician-scientists" committed to directing training programs as well as pursuing their own research and serving in the clinics and on the wards.

High on Hanning's agenda is increasing awareness of NIH as a "unique training site with a unique patient population—a natural fit for physicians interested in academic medicine." In her opinion, there is no better place than NIH for training in clinical research. "The more people we attract into our graduate medical programs," she maintains, "the better it will be for clinical research nationally." ■

Dreams on Display: Summer Students Bring Fresh Air to a Dog Day in August

text and photos by Celia Hooper

On August 9, more than 400 students left their summer homes in labs across the NIH campus to expose their research projects to the light of Poster Day and the inquiring minds of their colleagues. Nine of them captured by the Catalyst *camera represent the gamut of students who summer in an NIH lab—from high school and college students to college grads and graduate students.*

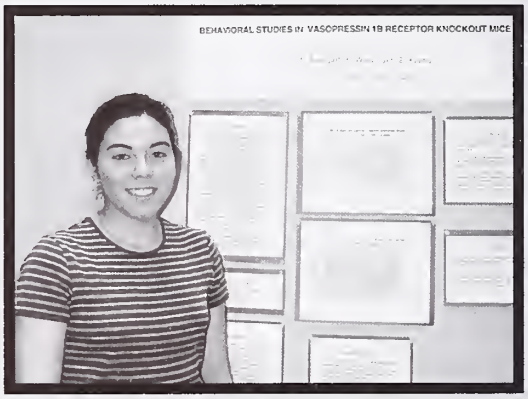


Nikkia Powell *(right), a junior at Howard University in Washington, D.C., and* ***Carissa James****, a junior at Northern Arizona University in Flagstaff, collaborated on their project on "Childhood Obesity: Measures that Contribute to Satiety while Reducing the Risk of Weight Gain" with preceptors Janice Yates and Barb Corey, CC Nursing Department. A Bowie, Md., native, Powell hopes to go to graduate school after she earns a nursing degree and would like to become a nurse-etbicist. James comes from Tuba City, Ariz., and is a member of the Navajo Nation. She would like to pursue nursing through the Indian Health Service after graduating from nursing school. "I learned a lot on the [CC] Alcohol Unit," James says. "You hear what patients have gone through. I can take that back to the reservation. You also learn about the research here. I would recommend the research experience to other students."*

Andrew Louie *is a second-year medical student at George Washington University in Washington, D.C., who worked on "Characterization of Alanine Aminotransferase Elevation in Volunteer Whole Blood Donors" with preceptors Cathy Conry-Cantilena and Harvey Alter in the CC Department of Transfusion Medicine. Originally from Los Angeles, Louie will be the second generation of biomedical investigators in his family. He says his father was here some years ago, which may explain a certain familial partiality toward NIH. "I knew this was the mecca of research and wanted to see what it was like. I've had a very enjoyable time with excellent mentoring. . . . [it was] a wonderful way to learn, not just about my project but also about other health issues [presented at lectures for students]."*

Christopher Brewer *(right), a junior at Abraham Lincoln High School in Philadelphia, discusses his poster on the "Regulation of MITF, a Transcription Factor Involved in Pigmentary/ Deafness Syndromes, by Phosphorylation: Initial Purification of Phospho-MITF-specific Antibodies" with NIDDK postdoc Kagnew Gebreyesus. Brewer's preceptor was Keren Bismuth in the NINDS lab of Heinz Arnheiter.*

"It's been great here—a totally new experience," he says. "I can't wait to come back next year. I learned so much!" He hopes to go to college and some day become a neurosurgeon.



Joanna Sweigart *is a postbac who attended Smith College in Northampton, Mass. The Houston, Texas, native worked in Scott Young's NIMH lab with preceptor Scott Wersinger on "Behavioral Studies in Vasopressin 1B Receptor Knockout Mice." She expects to spend the next year working in Houston and studying for the MCATs. She dreams of pursuing internal medicine or geriatrics, but says that if things don't come through on medical school applications next year, she's thinking about doing a pre-IRTA year at NIH—an option she might have pursued this year if she hadn't already made job commitments in Houston.*

"I'm amazed how many high school kids are here. I didn't know anything about this when I was in high school. The only thing I knew about NIH was from the [children's book] 'Rats of NIMH'!"

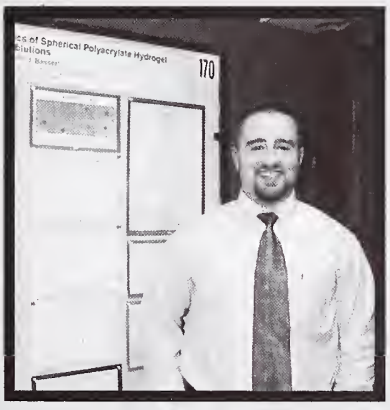
Sweigart's discovery of the training opportunities at NIH came when an NIH scientist gave a lecture at Smith and tossed off the line, "If anyone wants to come and help with this research, I'm the only one doing it, and I'll be glad to have you." Sweigart spoke to him after the lecture and said she'd be interested. "It was very lucky," she concludes.

***Erin Reese**, a Virginia Commonwealth University School of Engineering (Richmond) senior, was in the Biomedical Engineering Summer Internship Program. Originally from Fredericksburg Va., Reese plans to continue with biomedical engineering in graduate school. She worked with preceptor Aneta Petkova in the NIDDK lab of Robert Tycko on the "Synthesis and Purification of Human Amylin for Structural Analysis by Solid State NMR."*

"This program," she says, "showed me what the research process is like. . . . it was an excellent experience, and I would recommend something like this for someone else."

***Curtis Henry**, a junior at Florida A & M in Tallahassee, worked in Roscoe Brady's lab in the NINDS Developmental and Metabolic Neurology Branch, where with preceptor Gary Murray he pursued the "Purification and Properties of Mutant Glucocerebrosidase Expressed in 293 Cells."*

Henry says "this was a life-changing experience. It affirmed my goals to become an immunologist and pursue a Ph.D. I would love to come back to NIH to finish this research—or go on to something else."



***Keegan Haselkorn**, a St. Louis University senior, was in the Biomedical Engineering Summer Internship Program and worked with Ferenc Horkay in Peter Basser's NICHD lab. His project was on the "Swelling and Shrinking Kinetics of Spherical Polyacrylate Hydrogels in Physiological Salt Solutions." Haselkorn is now applying to graduate schools and hopes to pursue a doctorate in biomedical engineering. The summer program, he says, helped him decide what specialties he might enjoy. "NIH has a great learning atmosphere. You get to do research, but you have the mentors there to help you along. The most surprising thing was that I was able to get results and produce something publishable in 10 weeks. I didn't think it was possible to be very productive in such a short time!"*

***Ethan Bromberg-Martin**, who just graduated from George C. Marshall high school in Falls Church, Va., will be attending Brown University in Providence, R.I., in the fall. He worked under preceptor Brian Mozer in the NHLBI Laboratory of Biochemical Genetics of Marshall Nirenberg to complete his project on "The Molecular Genetics of Neural Development in Drosophila."*

"The most interesting thing," he says, was working in a lab and seeing what genetics research is like." Bromberg-Martin is not sure what he'll pick for his major but is thinking about biology, philosophy, and computers. He says one factor inspiring his interest in genetics was his complex medical history, starting with neuroblastoma in the first weeks of life and followed by the ongoing medical consequences of treatment.

Poster Day Brochures

Poster Day is an annual event sponsored by the NIH Office of Education (see story, page 8). A limited number of brochures listing the titles of the 407 posters, with the names of the students and preceptors, is available from Education Program officer Debbie Cohen at **<dec@helix.nih.gov>**

Clinical Center Unveils New Training Program

The Clinical Center is now collaborating with the University of Pittsburgh in a clinical research training program that will lead to one of two possible degrees in clinical research from the University of Pittsburgh.

Similar to the NIH-Duke Masters Program in Clinical Research, initiated in 1998, this new venture is aimed at filling the void in the community of formally trained clinical investigators. It will be open to a wider audience than the CC-Duke program—PhDs and doctorally prepared pharmacists and nurses, as well as physicians and dentists.

The training consists of a core curriculum, offered in an intensive eight-week summer session at the University of Pittsburgh, followed by a nine-month methodology seminar, held via videoconferencing at the Clinical Center.

The core courses include clinical research methods, biostatistics, introduction to clinical trials, and measurement in clinical research.

Trainees can choose from four specialty concentration areas: effectiveness and outcomes, clinical therapeutics, health and behavior, and epidemiology. Either a Certificate in Clinical Research (15 credits) or a Master of Science in Clinical Research (30 credits) can be earned.

The next session begins July 2002. ICs can provide information on the official training nomination procedure. For more info, visit

<www.pitt.edu/~crtp/>

or e-mail **<crtp@imap.pitt.edu>**.

Recently Tenured

Patricia Becerra *received her Ph.D. from the University of Navarra, Spain, in 1979. She did postdoctoral work at NCI and NIAID and then worked at Georgetown University in Washington before returning to NCI. She joined NEI as a visiting scientist in 1991 and became an investigator there in 1994. She is now a senior investigator in the Laboratory of Retinal Cell and Molecular Biology (LRCMB), NEI.*

Fran Pollner

Patricia Becerra

My interests are in the area of protein structure as it relates to function, with a focus on the interactions of components involved in cell differentiation and survival. My research at NEI has applied these interests to relevant systems in the retina.

My lab group has been studying pigment epithelium–derived factor (PEDF), a protein that acts in neuronal differentiation and survival in cells derived from the retina and CNS. PEDF inhibits angiogenesis, and its expression is downregulated over the replicative lifespan of mammalian cells.

This interesting factor is secreted by retinal pigment epithelial cells into the interphotoreceptor matrix, where it acts on photoreceptor cells. Its importance in the development, maintenance, and function of the retina and CNS is evident in animal models for inherited and light-induced retinal degeneration, as well as for degeneration of spinal cord motor neurons.

When I joined the LRCMB, little was known of PEDF's structure, biochemistry, and mechanism of action. Much of our progress in understanding PEDF relied on our development of overexpression systems that yielded recombinant proteins as functionally active neurotrophic factors identical to the native protein and ideal for biochemical, biophysical, and biological studies.

The cDNA sequence for PEDF predicts a unique protein with strong homology to members of the serine protease inhibitor (serpin) superfamily. For this reason, we first studied PEDF as a serpin. We established that PEDF belongs with the subgroup of noninhibitory serpins and that it has characteristics of a substrate rather than an inhibitor of serine proteases. Moreover, a region from its amino-terminus confers the neurotrophic activity to the PEDF polypeptide, not requiring the serpin reactive loop (the structural determinant for serpin inhibition).

We concluded that PEDF's neurotrophic activity must be mediated by a mechanism independent of serine protease inhibition, and we proposed that during evolution this serpin might have lost its inhibitory activity and gained its neurotrophic function. These findings provided an example of the separation of inhibitory and other activities in a serpin.

Our investigations were next directed toward the hypothesis that PEDF's neurotrophic activity is mediated by interactions with cell surfaces. Focusing on retinoblastoma and cerebellar granule cells, we prospected for PEDF receptors and found evidence for 1) a saturable, specific, and high-affinity class of receptors on the surface of both cells, with characteristics of an 80-kDa plasma membrane protein, and 2) the amino-terminal region in PEDF that interacts with the receptor. Our work demonstrated that the first step in the biological activity of PEDF is the binding to receptors on the surface of target cells, a significant advance in the elucidation of PEDF's mechanism of action.

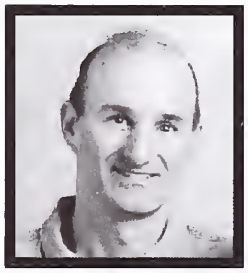
We hope our PEDF research lays the groundwork for the development of therapies for diseases involving defective neuronal differentiation or cell survival, such as retinitis pigmentosa, age-related macular degeneration, and amyotrophic lateral sclerosis.

The reported antiangiogenic effects of PEDF suggest it may also be useful in treating diseases in which new blood vessel formation plays a role, such as diabetic retinopathy, age-related macular degeneration, tumor growth, and rheumatoid arthritis.

The role of a cell-surface receptor in the mechanisms of action of PEDF represents a key aspect of regulation. Along these lines, our first priority is the identification of the PEDF receptor protein, and we are investigating cell-surface receptors in the normal and diseased retina. Consistent with our goal of elucidating the mechanisms of action of PEDF, we are interested in signal transduction and the expression of genes affected by PEDF's stimuli.

Future work will also explore the development of sustained delivery systems for PEDF in animal models of retinal and CNS diseases.

Bill Copeland *received his Ph.D. from the University of Texas at Austin in 1988 and did his postdoctoral work at Stanford (Calif.) University before joining the Laboratory of Molecular Genetics of NIEHS in 1993. He is now a senior investigator in the Laboratory of Molecular Genetics, NIEHS.*



Bill Copeland

My major research interest at NIEHS is mitochondrial DNA (mt-DNA) replication and how the structure of replication proteins relates to mt-DNA stability and drug sensitivity. Mitochondria, the subcellular site of energy production, are unique organelles in that they possess a circular chromosome of 16,569 bp coding for 13 polypeptides, 22 tRNAs, and 2 ribosomal RNAs.

Mammalian mt-DNA is 16 times as prone to oxidative damage and evolves 10 to 20 times as fast as nuclear DNA. Point mutations and DNA deletions in the mt-DNA give rise to a wide range of severe diseases. These mutations can occur during DNA replication. DNA polymerase γ is responsible for replicating mt-DNA and is composed of a 140-kDa subunit containing catalytic activity and a 55-kDa accessory subunit.

We were the first to clone, overproduce, and characterize the human DNA polymerase γ catalytic subunit, p140, and p55 accessory subunit. We discovered that, in addition to its polymerase and exonuclease activities, the human DNA polymerase γ catalytic subunit also has dRP lyase activity. This activity is required for base excision repair. This key activity and the fact that DNA polymerase γ is the only DNA polymerase in animal cell mitochondria mean that it is necessary in both DNA replication and repair.

We were also the first to determine that the 55-kDa accessory subunit increases the length of DNA synthesized by enhancing the binding of the polymerase to DNA. We are now determining the role of the mt-DNA polymerase with and without the accessory subunit in mt-DNA mutation by studying the fidelity of DNA replication and determining the mutation spectrum produced in vivo.

DNA polymerase γ is unique among the cellular replicative DNA polymerases in that it is highly sensitive to anti-HIV nucleoside analogs, such as AZT, dideoxynucleotide, and other nucleoside analogs. These drugs can cause mitochondrial toxicity by producing mitochondrial myopathies such as ragged-red fiber disease in AIDS patients. We are determining what structural elements in polymerase γ make this cellular polymerase sensitive to antiviral nucleoside analogs. To accomplish this goal, we are studying the inhibition of DNA polymerase γ and several mutant polymerases by antiviral AIDS drugs. We showed that a single tyrosine residue is responsible for the sensitivity of mt-DNA polymerase to dideoxynucleoside analogs.

Accessory proteins are also required for initiation, elongation, and maturation of mt-DNA replication. To understand their role as well as the overall mechanism of replication, we have cloned and overproduced the single-stranded DNA binding protein and helicase. My group is now examining the assembly and communication of these proteins with the DNA polymerase.

We are also studying a nuclear DNA polymerase involved in repair of interstrand crosslinks. Damaging agents such as cisplatin, nitrogen mustard, and other bifunctional alkylating agents cause interstrand crosslinks in DNA that present a difficult problem for replication and must be repaired for faithful replication and viability of the

cell. We have cloned and overproduced a DNA polymerase involved in this crosslink repair and named it DNA polymerase θ. Human DNA polymerase θ is 198 kDa and is homologous to the Drosophila *mus308* protein product, a DNA polymerase-helicase involved in repair of interstrand crosslinks.

To fully understand this new human DNA polymerase, the full-length cDNA has been functionally overexpressed in insect cells by a recombinant baculovirus and the active protein purified and characterized. Future work will explore the role of this polymerase in DNA repair and, specifically, how it acts on DNA-containing bulky adducts or crosslinks.

Frank Gherardini *received his Ph.D. from the University of Illinois, Urbana-Champaign, in 1987 and did a postdoctoral fellowship in the laboratory of Philip Bassford at the University of North Carolina, Chapel Hill. In 1991, he joined the faculty at the University of Georgia, Athens, where he was an associate professor of microbiology before joining the Laboratory of Human Bacterial Pathogenesis at NIAID's Rocky Mountain Labs in Hamilton, Mont., in July 2001.*

Frank Gherardini

My research group focuses on the physiology, biochemistry, gene regulation, and pathogenesis of *Borrelia burgdorferi*, the causative agent of Lyme disease in humans. The bacterium is transmitted to humans by ticks of the genus Ixoides, and a chronic inflammatory condition develops, causing pathological manifestations in neurologic, cardiac, rheumatologic, and dermatologic tissues. The disease is characterized by early and late stages similar to the disease course in syphilis.

B. burgdorferi faces several environmental and immunological challenges during its infective cycle and must alter (regulate) gene expression to adapt successfully to these conditions. Analysis of the *B. burgdorferi* genome sequence has revealed that there are very few known regulatory proteins in this bacterium. Conspicuously absent are global regulatory proteins such as CRP, LexA, Fnr, IHF, OxyR, Lrp, and the σ factors involved in the heat shock response, σ^{32} and σ^{24}. This suggests that compared with other well-characterized pathogenic bacterial systems, the global regulatory systems operating in *B. burgdorferi* are relatively simple. Clearly, these systems are required for *B. burgdorferi* to adapt as it encounters very different environments during transfer from an animal reservoir to the tick and then to a human host.

Our research efforts have focused on three important regulatory proteins, PerR, F^{54}, and F^{S}, which control the expression of genes that are critical to the pathogenesis of Lyme disease.

(1) PerR-dependent regulation in *B. burgdorferi*. Analysis of the genome of *B. burgdorferi* identified an open reading frame that has 54.3 percent similarity to a protein encoded by *perR* from *Bacillus subtilis*. PerR, which requires a metal ion as a cofactor, has been shown to regulate *dps*, *hemA*, *katA*, and *mrgA*, some of which are involved in an oxidative stress response and response to Mn limitation. Because of the function of PerR from *B. subtilis*, we have begun to analyze a putative oxidative stress response in *B. burgdorferi*. *B. burgdorferi* contains genes encoding an Mn-dependent superoxide dismutase (*sodA*), a putative flavin-dependent NADH peroxidase (*npx*) (designated as *nox* in the *B. burgdorferi* genome database), and a neutrophil-activating protein (*napA*) that complements an alkyl-hydroperoxide reductase mutant of *E. coli*. Our working hypothesis is that *B. burgdorferi* cells are using these three proteins to convert toxic O^{2-} to H_2O_2, and then to H_2O, in a two-step process that is regulated by PerR. Because this system would promote the in vivo survival of *B. burgdorferi* cells when challenged by O^{2-} and H_2O_2 from host cells, we are particularly interested in this process and how it is regulated.

Fran Pollner

Pu Paul Liu

(2) Regulation of gene expression by F^{54} and F^{S}. Regulation of gene expression by F^{S}, a member of the F^{70} family, is responsible for the transcription of a variety of genes encoding virulence factors in *Salmonella* sp. Salmonella plasmid virulence genes, *spvR* and *spvABCD*, are carried on large (50- to 100-kb) plasmids in a variety of Salmonella species, including *S. typhimurium*, *S. choleraesuis*, and *S. dublin*. Loss of these plasmids, of SpvR, SpvC, and SpvD, or of F^{S}, results in loss of virulence and the ability of the cells to multiply in the reticuloendothelial system in mouse models. *B. burgdorferi* contains *rpoS* (encoding F^{S}), and our preliminary data indicate that expression of *rpoS* regulates several plasmid-encoded genes that may be important in the virulence of the bacterium.

We have mapped one transcriptional start site of *rpoS* from *B. burgdorferi* to a potential F^{54}-dependent promoter. Furthermore, analysis of the transcription of *rpoS* in a *B. burgdorferi* F^{54}-mutant indicates that F^{S} is regulated by F^{54} during different stages of the infective cycle. Thus F^{54}-holoenzyme is required for F^{S} expression, and both proteins play key roles in the pathogenesis of Lyme disease. We hope that continued elucidation of these genetic and biochemical processes will lead to more effective diagnosis and treatment of Lyme disease.

Pu Paul Liu *received his medical degree from Beijing Second Medical College in 1982 and his Ph.D. from the University of Texas M.D. Anderson Cancer Center in Houston in 1991. He did his postdoctoral work at the University of Michigan, Ann Arbor, before joining the Laboratory of Gene Transfer of the then-National Center for Human Genome Research in 1993. He is now a senior investigator and head of the Oncogenesis and Development Section in NHGRI.*

The main focus of my research is the genetic control in hematopoiesis and the development of leukemia. Leukemia affects 26,000 Americans each year and represents a significant burden on the health-care system. Hematopoiesis is the process of terminal differentiation of mature blood cells from stem cells, a process controlled by a complex network of proteins regulating cell proliferation and differentiation. Leukemia, a tumor of white blood cells, is an example of abnormal hematopoiesis. In addition, many hematological diseases, such as certain forms of anemia and neutropenia (decreased white blood cells), result from defects in hematopoiesis.

Chromosome 16 inversion is one of the most common chromosome abnormalities in human acute myeloid leukemia (AML). During my postdoctoral training, I found that a fusion gene between *CBFB* and *MYH11* is generated by this inversion. After joining NIH, my lab demonstrated that this *CBFB-MYH11* fusion gene, through its encoded fusion protein CBFb-SMMHC, suppresses the normal function of the transcriptional heterodimer CBF (composed of CBFb and AML1) and blocks normal hematopoiesis in transgenic mice.

We showed that this suppression of CBF function by CBFb-SMMHC could be explained by the ability of CBFb-SMMHC to sequester AML1 in the cytoplasm, away from the nucleus, where normally AML1 is located and involved in the regulation of gene expression. Using transgenic mouse models, we demonstrated recently that *CBFB-MYH11* is necessary but not sufficient for the development of leukemia and that additional genetic changes are needed for full leukemic transformation. Since this discovery, we have identified such cooperating genetic changes using a retroviral insertional mutagenesis approach in mice.

CBF genes encode transcription factors that associate with other nuclear proteins and regulate expression of target genes. We are now working to identify downstream target genes of CBF oncoproteins, which will lead to better understanding of the process of leukemogenesis and, potentially, to the discovery of new diagnostic and therapeutic

Recently Tenured

targets. In addition, we will test the hypothesis that the other subunit of CBF, *AML1*, is a leukemia suppressor in transgenic mice. Finally, we will test new therapeutic approaches for AML that specifically counteract the function of *CBFB-MYH11* in our established murine leukemia model.

Knowledge of normal hematopoiesis will enhance our understanding of leukemogenic process. To understand the role of *Cbfb* in hematopoiesis and other developmental processes, we have generated mice with a *Cbfb-GFP* knock-in fusion. In parallel studies, we are isolating zebrafish mutants defective in their ability to differentiate white blood cells. Our methods include chemical mutagenesis and screening for loss of expression of myeloid-specific markers in fish embryos. We will identify the genes altered in these mutants by genetic mapping and positional/candidate gene cloning. We hope this will yield new insight into the control of myelopoiesis.

Alan Perantoni *received his Ph.D. from the Catholic University of America, Washington, D.C., in 1983, after having conducted his dissertation research at NCI. He was an assistant professor in the Pathology Department, University of Colorado Medical School in Denver, before returning to NCI in 1992 as a senior staff fellow. He is now a senior investigator in the Developmental Biology Working Group of the Laboratory of Comparative Carcinogenesis, NCI.*

Alan Perantoni

My interests are in the area of cell specification and inductive signaling and how they relate to the neoplastic process. I am particularly interested in the mechanisms responsible for the accumulation of aberrant stem cells found in embryonal neoplasms such as the pediatric Wilms' tumor, which caricatures metanephric development.

Accordingly, I have focused on the characterization of factors that mediate normal metanephric stem cell commitment, that is, the inductive signaling ligands that cause specification; the signaling pathways that direct the differentiation; and the downstream events that regulate and execute morphogenesis—all in an effort to define possible targets of carcinogenesis.

Metanephric development is driven by reciprocal inductive interactions between the epithelial ureteric bud, which is derived from the mesonephric duct and serves as the progenitor of the collecting duct system, and the metanephric mesenchyme (MM), which originates in the adjacent nephrogenic cord, converts to a polarized epithelium under the influence of the ureteric bud, and forms the epithelia of the nephron. I am most interested in this signature event of morphogenesis—epithelial conversion—since it appears to be the point at which differentiation is severely inhibited in the Wilms' tumor.

The nature of the inductive ligands has remained an enigma for more than 70 years, despite the efforts of several groups to define them. To accomplish this, I established a rat cell line from the natural inductor, the ureteric bud, and purified factors from cell culture medium conditioned by these cells. As a result of such studies, I have identified three growth factors or cytokines that function in combination to induce epithelial conversion with kinetics comparable to those in vivo: fibroblast growth factor–2, leukemia inhibitory factor, and transforming growth factor–β_2.

Fran Pollner

Nick Ryba

Although these factors can function somewhat independently of one another, causing epithelial tubule formation after several days, they are most effective in combination, yielding tubules in two to three days, as in vivo. Because the factors we identified implicate specific signaling pathways, I am now interested in determining how signaling from these pathways integrates to produce a more profound and accelerated inductive response. To address this question, my group has focused on establishing a stem cell line from rat MM.

In addition, we have developed a model for identification of molecular events specifically associated with epithelial conversion using differential display. This approach has revealed a large series of known and novel sequences that are differentially transcribed with morphogenesis. The list includes transcription (co)factors, cell-cycle regulatory proteins, cell adhesion molecules, and signaling proteins. Of these, CITED1, a CBP/p300-binding transcriptional coactivator, is especially intriguing. It is expressed in the metanephros only in blastemal and stem cells and in blastemal populations of Wilms' tumors and is downregulated with epithelial conversion. We are currently investigating the possibility that it functions as a gatekeeper for this morphogenetic event.

We hope that these studies lead to a better understanding of the mechanisms responsible for Wilms' tumor formation and the resulting expansion of metanephric stem cells. But beyond this, we hope the work may help define other blocks in the terminal differentiation of renal cells, such as in renal carcinoma, which originates in tubular epithelia. Furthermore, a comprehensive understanding of the regulation of stem cells responsible for renal tubular and glomerular development may eventually lead to therapies that could invoke mechanisms of tissue regeneration in the treatment of the numerous disorders that damage the tissues of the kidney.

Nicholas Ryba *received his D.Phil. from the University of Oxford in 1985 and did postdoctoral work at the MPI for Biophysical Chemistry in Göttingen, Germany, and at Leeds University, England, before joining the Laboratory of Immunology, NIDR, in 1991. He is now a senior investigator in the Oral Infection and Immunity Branch, NIDCR.*

I have always been interested in the biology of sensory perception and since coming to NIH have used molecular approaches to study olfaction, pheromone detection, and taste. Over the last few years, my group has concentrated primarily on understanding the physiological basis of taste sensation and discrimination. This work on taste has involved a wonderful wide-ranging collaboration with Charles Zuker's group at the University of California in San Diego.

Our sense of taste allows us to distinguish the sweetness of honey from the bitterness of tonic water and the sourness of unripe fruit from the saltiness of seawater. Although taste perception involves many steps, it begins at the surface of taste receptor cells with the recognition of the tastant molecules by taste receptors. This means that the identification of functionally defined taste receptors generates powerful molecular tools to begin to dissect not only the cellular basis of tastant recognition, but also the logic of taste coding. For example, defining the size and diversity of the receptor repertoire provides evidence for how a large number of chemosensory ligands may be recognized, and analysis of the patterns of receptor expression contributes to our understanding of chemosensory discrimination and coding.

Recently, we isolated two novel families of G-protein coupled receptors expressed in subsets of taste receptor cells of the tongue and palate (T1Rs and T2Rs). One of these, the T2Rs, is a family of about 30 different genes that include several functionally validated mammalian bitter taste receptors. Nearly all of the T2R genes are clustered in regions of the genome that have been genetically implicated in controlling responses to diverse bitter tastants in humans and mice, consistent with a role as bitter taste receptors.

Notably, we found that most T2Rs are coexpressed in the same subset of taste receptor cells, suggesting that these cells are capable of responding to a broad array of bitter compounds but not of discriminating between them. This is consistent with what we know about bitter taste, which serves as an important warning of the presence of many

chemically unrelated noxious substances.

In contrast to bitter taste, the number of biologically relevant sweet tastants is modest. Thus, it is generally believed that the sweet-receptor family is likely to be quite small. Genetic studies of sweet tasting have identified a single principal locus in mice (*Sac*) that influences responses to several sweet substances. Very recently, we used transgenic mice to show that the *Sac* locus encodes a T1R-family receptor and we developed a cell-based reporter system to prove that T1Rs encode functional sweet taste receptors. Intriguingly, we found a complete cellular segregation of T1R and T2R receptors, strongly suggesting that sweet and bitter tastes are encoded by activation of different subsets of taste receptor cells (as might be expected for modalities that influence such opposite behaviors).

In the future we hope to extend these studies to define the logic of taste coding by examining the physiology and connectivity pathways of T1R- and T2R-expressing cells in the various tastebuds and by investigating the effect of genetic ablation, or knockouts, of the different cells and receptor combinations.

Nico Tjandra *received his Ph.D. in physics from the Carnegie Mellon University, Pittsburgh, in 1993 and did postdoctoral work at the Laboratory of Chemical Physics in NIDDK. He joined the Laboratory of Biophysical Chemistry in NHLBI as a tenure-track scientist in 1997 and is now a senior investigator in that lab.*

My interests are in the area of protein structure and dynamics and how they define biological function. We are focusing on proteins in cell signaling and apoptosis. We use high-resolution nuclear magnetic resonance (NMR) to elucidate the structures and dynamics of these proteins.

Fran Pollner

Nico Tjandra

The interaction between GTP-binding proteins, their receptors, and their effectors are well characterized in the plasma membrane. In contrast, the specific interaction and function of these proteins in the Golgi membranes is still not clear. Human G_α interacting protein (GAIP) is a major component in the regulation of G_α signaling in the Golgi by interacting specifically with the $G_{\alpha i3}$. We used NMR to find the structure of parts of the GAIP, including the solution structure of the "Regulation of the G_α signaling" (RGS) domain of GAIP. We used NMR for a backbone dynamics study of human GAIP. The dynamics data revealed flexible regions within this protein. Comparison between the NMR structure of GAIP and the X-ray structure of the RGS4-$G_{\alpha i3}$ complex identified the conformational changes that result from GAIP interaction with the G_α protein that are also consistent with our dynamics data.

We concluded that the overall structure of the whole class of RGS domains has very little variation and that the sequences flanking the RGS domains of these proteins determine what type of signals they will regulate as well as where they are localized.

Bax is a member of the Bcl-2 family of proteins that regulates apoptosis, or cell death. In collaboration with Richard Youle's laboratory at NINDS, we have determined the solution structure of human Bax by NMR spectroscopy. Our structure identifies an elegant mechanism in which two crucial steps in Bax's control of apoptosis—dimer formation and insertion into the mitochondrial membrane—are simultaneously regulated.

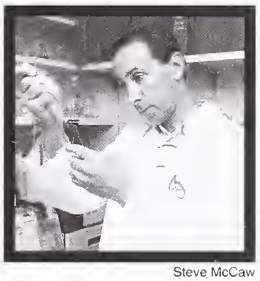
Our structure also shows that the packing of the COOH-terminal helix of Bax plays an important role in its function. When this helix is packed against the hydrophobic BH3-binding pocket, it eliminates the possibility for dimer formation. The packing of this helix also hinders its exposure, thus inhibiting Bax insertion into the mitochondria membrane. Based on our structure, regulation of Bax in apoptosis must include displacement of the COOH-terminal helix from the hydrophobic pocket.

What is even more surprising is that the structure of Bax, a pro-apoptotic protein, is essentially identical to Bcl-x_L, an anti-apoptotic protein, even though they share only 20 percent sequence homology. We found just three flexible regions that substantially differ in the two structures. Identification of these regions would not have been possible without Bax structure. Interestingly, some of these loops that distinguish the two proteins were thought to have no significance in Bax function; therefore, no extensive biological data are available about them.

The high degree of similarity between the two structures has at least two consequences. First, functional models that have been proposed for Bcl-x_L might also be applicable to Bax. Second, perhaps other components in the apoptosis pathways or differences in structure of these proteins after insertion into mitochondria membranes might be important in differentiating their functional roles. We believe that our structure will have a great influence on how future experiments in the apoptosis field will be designed and will give us a better understanding of how this important biological process is regulated.

Looking ahead, we hope to examine structures of other protein components that make up the cell signaling of the Golgi as well as the mitochondrial apoptosis pathway to better understand these complex and yet basic cell functions.

Darryl Zeldin *received his M.D. degree from Indiana University in Indianapolis in 1986, and completed a residency in internal medicine at Duke University in Durham, N.C., and a fellowship in pulmonary/critical care medicine at Vanderbilt University before joining the Laboratory of Pulmonary Pathobiology of NIEHS in 1994. He is now a senior investigator and head of the Clinical Studies Section at NIEHS.*



Steve McCaw

Darryl Zeldin

My research interests are in eicosanoids, with an emphasis on how they function in the heart, kidney, and lung. This work in this area has been driven by three main hypotheses: (1) P450 cytochromes metabolize arachidonic acid to eicosanoids that play critical roles in modulating fundamental biological processes such as cardiac contractile function and vascular tone; (2) environmental or genetic factors that lead to aberrant P450 activity cause altered production of bioactive eicosanoids and result in heart disease and hypertension; and (3) environmental or genetic factors that affect cyclooxygenase (COX) activity lead to altered prostaglandin production and result in lung dysfunction and asthma.

My lab was the first to clone CYP2J2, a human P450 that is abundant in the heart and active in the metabolism of arachidonic acid to epoxyeicosatrienoic acids (EETs). Subsequent studies from our group demonstrated that EETs improve heart contractile function after ischemia, inhibit cardiac L-type calcium channel activity, and beneficially affect cardiac electrical and mechanical properties.

In further work with CYP2J2, we created transgenic mice in which we overexpressed CYP2J2 in heart myocytes. These mice exhibit improved postischemic cardiac function, a shortened cardiac action potential, and, interestingly, enhanced responsiveness to β-adrenergic receptor agonists. These mice are the first in vivo animal model to permit evaluation of P450 functions in heart.

My colleagues and I also demonstrated that CYP2J2-derived eicosanoids decrease cytokine-induced endothelial adhesion molecule expression, an important component in the development of vascular inflammation and arteriosclerosis. This occurs via inhibition of the transcription factor NF-κB. We showed that exposure of endothelial cells to hypoxia and reoxygenation, such as occurs during heart attack and stroke, decreases CYP2J2 expression, but that maintenance of CYP2J2 protein concentrations attenuate hy-

poxia-reoxygenation–induced cell death. Moreover, we demonstrated that CYP2J2-derived EETs increase tissue plasminogen activator expression and fibrinolytic activity, actions that reduce the formation of intravascular clots. Together, these studies demonstrate that CYP2J2 and its eicosanoid products play critical roles in normal cardiac myocyte and endothelial function and may be involved in limiting damage such as vascular inflammation, hemostasis, and cardiac dysfunction after ischemia.

In 1999, my laboratory reported cloning CYP2J5, a new mouse P450 that is primarily expressed in the kidney, active in the metabolism of arachidonic acid to EETs, and localized to proximal tubules and collecting ducts—sites where EETs are known to affect renal fluid and electrolyte transport and mediate the actions of several hormones, including angiotensin II and arginine vasopressin. We observed that maximal CYP2J5 expression occurs at a critical time during postnatal renal development when abnormalities in renal function are demonstrable in animals that subsequently develop hypertension.

Evidence to support the hypothesis that CYP2J products are involved in the development and/or maintenance of hypertension comes from recent studies in our lab showing upregulation of a CYP2J immunoreactive protein and increased EET biosynthesis in kidneys of spontaneously hypertensive rats. We mapped the *Cyp2j* locus to a chromosomal area that co-segregates with the hypertensive phenotype in Dahl salt-sensitive rats. Our recently developed *Cyp2j5* knockout mice have systemic hypertension de novo and will be instrumental in evaluating the role of this P450 in kidney function, renal eicosanoid metabolism, and blood pressure regulation.

Our combined work on human and mouse CYP2Js has led to a better understanding of the role of cytochromes P450 in the metabolism of arachidonic acid into compounds that modulate critical cardiovascular functions. The opportunities for translational research in this area include development of new drugs for blood pressure control, vascular inflammation, atherosclerosis, and ischemic heart disease. The identification of individuals at increased risk for these disorders due to P450 genetic variation may also lead to new approaches to disease prevention. We hope to pursue some of these areas in the years ahead.

More recently, we have gone on to examine the role of COXs in lung function. Our work in this area is based on the hypothesis that COX-derived eicosanoids are important modulators of the lung immune response to environmental agents and that COX-deficient mice provide a novel model system to study basic immunologic mechanisms in inflammatory lung disease.

My group was the first to report that allergic lung responses are increased in COX-deficient mice. More recently, we have examined the effects of disruption of *COX* genes on pulmonary responses to inhaled bacterial lipopolysaccharide (LPS). Interestingly, although COX-deficient mice had increased bronchoconstriction after LPS exposure, there were no differences in inflammatory indices between the genotypes. This finding indicates that COX enzymes are important in regulating physiologic but not inflammatory responses to inhaled LPS.

We hope ongoing studies on the effect of COX-derived eicosanoids on pulmonary immune response to environmental agents will lead to opportunities for further mechanistic and translational research. ■

SHARED RESOURCES: FREDERICK

The July-August 2001 issue of The NIH Catalyst *included charts of NIH's shared resources for the intramural community. Not listed were the resources available to all NIH scientists (and often to others) that are housed at the NCI-Frederick campus on the grounds of Fort Detrick in Frederick, Md., 37 miles from the NIH Bethesda campus. Here's a partial list.*

■ **Advanced Biomedical Computing Center:** Includes sequence analysis, databases, molecular modeling and visualization, crystallography. To establish an account or get info on technical support and training seminars, contact the ABCC Helpdesk at 301-846-5555 or <**helpuser@ncifcrf.gov**>. ABCC Director Stan Burt can be reached at 301-846-5763 or <**burt@mail.ncifcrf.gov**>.

■ **cDNA Clones Database:** Contains referral information for obtaining cDNA clones from microarray experimentation: <**http://web.ncifcrf.gov/researchresources/clonedb/**>.

■ **Biological Resources Branch Preclinical Repository:** Stores and distributes bulk cytokines, monoclonal antibodies, and cytokine standards. Check <**http://web.ncifcrf.gov/research/brb/preclin**> for other NIH repositories as well and contact Craig Reynolds at <**reynolds@mail.ncifcrf.gov**> with questions or comments.

■ **Mouse Models of Human Cancers Consortium Repository** (<**http://web.ncifcrf.gov/researchresources/mmhc/**>; program director John Sharp <**jsharp@ncifcrf.gov**>): An NCI-funded repository and distribution center for mouse cancer models and associated strains.

■ **Laboratory Animal Production Program** <**http://web.ncifcrf.gov/apa/**>; project officer Clarence Reeder <reeder@mail.ncifcrf.gov>): Provides animals for use in scientific research: inbred and athymic mice and rats; hybrid mice; surgical services.

■ **Molecular Diagnostic Services for HIV and SIV** (<**http://resresources.nci.nih.gov/database.cfm?id=306**>; contact Jeffrey Lifson, <**lifson@avpaxp1.ncifcrf.gov**>, AIDS Vaccine Program, SAIC-Frederick): Measurement of viral loads from SIV-infected monkey plasma and determination of HIV RNA concentrations in human plasma.

■ **Biological Products Laboratory Repository–HIV reagents** (<**http://resresources.nci.nih.gov/database.cfm?id=381**>; contact Jeffrey Lifson, see above): Reagents for use in AIDS vaccines, including HIV p7 and p24 capture-assay kits, large-volume production and purification of retroviruses, monoclonal antibodies, and antisera to SIV and HIV.

■ **Research Technology Program:** Includes an array of resources available to NCI investigators and accessible to other ICD on a space-available basis, through special arrangement with the NCI Project Office (contact David Goldstein at 301-846-1108 or <**goldsted@mail.ncifcrf.gov**>). These are:

—**Laboratory of Molecular Technology** (<**http://web.ncifcrf.gov/rtp/lmt.asp**>), which provides standard and high-throughput core sequencing, microarray, molecular diagnostics, and specialized oligonucleotide synthesis.

—**Image Analysis Laboratory** (<**http://web.ncifcrf.gov/rtp/labs/IAL/cml/default.asp**>, which provides electron and confocal microscopy services.

—**Protein Chemistry Laboratory** (<**http://web.ncifcrf.gov/rtp/PCL.asp**>), which provides amino acid sequencing, protein digestion, and separation of resultant peptides by HPLC, MALDI-TOF mass spectrometry, and macromolecular interactions using surface plasmon resonance spectroscopy (BIAcore analysis).

—**NMR Spectroscopy** (<**http://web.ncifcrf.gov/rtp/labs/ACL/NMR/default.asp**>), which provides determination of molecular structures in solution using an NMR paradigm developed in-house.

—**Veterinary Pathology and Histotechnology Services** (<**http://web.ncifcrf.gov/rtp/labs/lasp/phl/**>), which offer a full range of services, including animal necropsies, routine and special histological preparations, histopathologic evaluation, and assistance in experimental design.

For general information about NCI-Frederick research support services and cost estimates, contact Marjorie Strobel <**strobel@ncifcrf.gov**> or David Goldstein <**goldsted@mail.ncifcrf.gov**> at 301-846-1108.

Other resources available through the Developmental Therapeutics Program (directed by NCI's Edward Sausville), including pilot and clinical grade production of biologicals, screens for antitumor and antiviral compounds, and generation of animal tumor models, can be found at <**http://resresources.nci.nih.gov/**>. ■

Win-Win Situation: New Fogarty Scholar Brings Transporting Research and New FAES Course to NIH

Come the spring, postdocs interested in improving their understanding of the clinical and pathological aspects of their work will have a new course in pathobiology to round out their FAES selections, thanks to the anticipated work of Irwin (Win) Arias, professor and chair of physiology at Tufts University School of Medicine, Boston.

Win Arias

On October 1, Arias begins a nine-month stay here as a Fogarty Scholar, and a major part of his agenda is to establish an intramural course on pathobiology for PhD students and postdocs that will "demystify medicine" and bridge what has become a widening gap between advances in biology and their application to human disease.

The course has been taught for 16 years at Tufts, where Arias also pursues his pioneering research in the pathobiology of ATP-binding casette transporters—including members of the families of multidrug-resistance proteins—in the bile canalicular domain of the plasma membrane of hepatocytes.

During his Fogarty tenure, Arias intends to collaborate with the NICHD lab of Jennifer Lippincott-Schwartz, intensifying the focus on intracellular trafficking pathways within hepatic cells using high-resolution cell imaging to track the delivery of fluorescent GFP-tagged chimeras to the apical membranes of hepatic cells and assess the effects of mutants and other perturbants.

With John Hanover's NIDDK Laboratory of Cell Biology, he will explore new techniques of energy transfer, wth a focus on the movement of cholesterol within cells and the regulation of cholesterol synthesis.

And with Michael Gottesman's NCI Laboratory of Cell Biology, he will carry out further work on the biology of anticancer drug resistance mechanisms.

Arias also expects to explore the imaging technologies of NHLBI's Robert Balaban and their applications in the study of mutant mice. ■

Thumbs Up: Dealing with Repetitive Stress Injuries

by Fatima Husain, NIDCD

It started simply enough last fall with a twinge in my right thumb. A week later, the twinge had escalated to a painful throb. I switched from the trackball (which I had just started using) back to my trusted mouse. Despite the intervening winter holidays, the pain persisted over the next two months. Simple tasks like zipping my jacket, brushing my teeth, or twisting doorknobs became fraught with sharp pains.

Finally, at the recommendation of my supervisor, I visited the Occupational Medical Services (OMS) on the 6th floor of Building 10. I was diagnosed with tendonitis (inflammation of the tendons) of my right thumb, one of the many repetitive stress injuries (RSI) you may encounter in the workplace.

RSIs are disorders of the musculoskeletal system caused by the cumulative effects of tiny amounts of damage. They occur over a period of time when muscles or joints are stressed, tendons are inflamed, nerves are pinched, and the flow of blood is restricted.

The most famous of the RSIs is carpal tunnel syndrome, caused by a pinched nerve at the wrist. Early intervention in RSI is important, partly to avoid unnecessary pain and partly to prevent more permanent damage.

At NIH, we have a number of resources to combat RSI. The first line of defense is online information: a guide to ergonomics at **<http://www.niehs.nih.gov/odhsb/ergoguid/home.htm>**, which details RSI causes and prevention strategies, and another guide at **<http://www.nih.gov/od/ors/ds/ergonomics/index.html>**, that includes a chart to help evaluate your symptoms and a series of simple illustrated exercises to combat RSI. You can also visit **<http://www.zdnet.com/anchordesk/story/story_1958.html>** to download timekeeper-type shareware software that reminds you to take breaks at your desktop.

Jeff Rechler

Fatima Husain

If you'd like an evaluation by medical personnel, you can make an appointment with OMS at 6-4411. After a nurse has determined that your symptoms appear to be work-related, you will be evaluated by a physician or a physician assistant. Generally the treatment is to reduce inflammation, rest the injured area, strengthen the muscles around the area, and take suggested steps to prevent such injuries in the future. An OMS physical therapist is also available should such continuing service be needed.

When warranted, OMS will recommend that you continue treatment with a specialist outside NIH. OMS may also recommend an ergonomic evaluation of your workspace by an Occupational Safety and Health Branch specialist.

In my own case, after five visits with the OMS physical therapist (about two months after my original diagnosis), the inflammation in my right thumb had gone down significantly and most of the pain had vanished.

Today, months later. I sense no inflammation or pain in my thumb. To prevent future inflammation, I often use my left hand for gross motor skills like manipulating the mouse. I also practice simple exercises to strengthen the muscles of my right hand and take frequent breaks at work. ■

Acknowledgments

M'Lou Stevens, PA-C, OMS
Terry Black, Physical Therapist, OMS

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: NIH response to terrorism, preventing the misuse of science, improving the representation of women at NIH, and new activities for the Office of Education

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 2, Room 2W23.

In Future Issues...

- Facilitating NIH's First Crack At Human Embryonic Stem Cells
- Research Festival
- Mouse Imaging Facility Opens

1) What are your reactions to NIH's responses to the terrorist acts of September 11?

2) What do you think scientists ought to do to prevent the misuse of scientific advances?

3) What are your suggestions for improving the representation of women at all levels at NIH?

4) Are there new activities for the Office of Education that you would like to see?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2W23, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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