FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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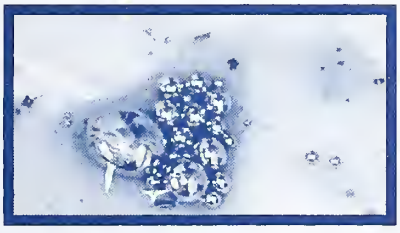
HI-YO, QUICKSILVER —AWAY . . . !



courtesy of the Division of Environmental Protection, NIH and Scott Neese, 3D EnviroLogics LLC

Mercury beads from an abandoned sanitary line in a wall

Though you might have played with mercury as a child, this doesn't make it safe. Mercury toxicity can affect multiple organ systems, including the central and peripheral nerves, lungs, kidneys, skin, and eyes. It is also mutagenic and affects the immune response. Other mercurial facts follow.

- Acute exposure to high air concentrations can cause severe respiratory damage.
- Long-term, low-level exposure can lead to tremors, depression, delirium, irritability, memory loss, and other cognitive problems.
- Lewis Carroll immortalized the neurological syndrome arising from chronic occupational mercury poisoning, madness, with his character the Mad Hatter in *Alice's Adventures in Wonderland.*
- Hatters routinely used mercury compounds in conditioning felt for hats, although the connection between mercury and madness wasn't understood until mid-20th century, nearly 100 years after Lewis' novel.
- Mercury is not toxic in insoluble forms such as cinnabar (mercuric sulfide), and deposits exist worldwide. Soluble forms such as mercuric chloride or methylmercury are poisonous.

—*C.W.*

MERCURY FALLING . . . AND SPILLING —BUT THERE'S A PLAN FOR A MERCURY-FREE NIH

by Christopher Wanjek

Sandwiched between gold and thallium on the periodic table—and, unfortunately between the carpets and floors and in drawers, plumbing, and vacuum lines in many NIH labs—lies mercury, a well-studied neurotoxin.

Research at NIH in the 1940s confirmed the occupational hazard that mercury posed, which led to a ban on its use in hat making. It is with a twist of irony, then, that mercury spills remain one of the most common HAZMAT response calls from NIH facilities.

Many NIH labs, unnecessarily, still use mercury-containing instruments, such as thermometers, thermostats, and switches. Some older buildings have years' worth of mercury accumulation; some new buildings are heading down the same path.

Highly toxic and persistent in the environment, mercury—atomic number 80 and public enemy number one for the ORF Division of Environmental Protection (DEP)—is readily dispersed when dropped and can be very expensive to clean up.

Mercury from spills and from disposal of mercury-contaminated chemicals such as bleach that enter the sewage system can ultimately result in pollution of waterways. Indoors, spills pose acute inhalation and dermal contact hazards and may add to body burdens of the element.

Even in a fanciful world of no spills, the general use and disposal of mercury is still a problem because it cannot be destroyed, only extracted and recycled.

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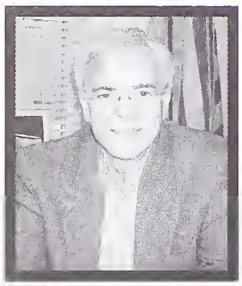


Michael Gottesman

To guarantee public access to NIH-supported research, Congress included language in its 2008 NIH appropriations legislation that mandates the deposit of published NIH-supported peer-reviewed articles into the public database known as PubMed Central, which is maintained by the National Library of Medicine.

This legal requirement follows several years of discussion about the best way to accomplish the goal of making NIH-funded research available without charge to anyone who wants to read peer-reviewed research papers and reviews, the most visible product of the research of biomedical researchers.

All papers reporting research supported by NIH funds with acceptance dates of April 7, 2008, or later must be submitted to PubMed Central upon acceptance for publication. PubMed Central will post these articles within 12 months of the print publication date.

Anyone supported through an NIH grant or contract, receiving an NIH salary, or working at NIH using NIH funds to support his or her research is covered by this new legal requirement, even if co-authors are not NIH-supported.

ALL PAPERS REPORTING RESEARCH SUPPORTED BY NIH FUNDS WITH ACCEPTANCE DATES OF APRIL 7, 2008, OR LATER MUST BE SUBMITTED TO PUBMED CENTRAL UPON ACCEPTANCE FOR PUBLICATION. PUBMED CENTRAL WILL POST THESE ARTICLES WITHIN 12 MONTHS OF THE PRINT PUBLICATION DATE.
ANYONE SUPPORTED THROUGH AN NIH GRANT OR CONTRACT, RECEIVING AN NIH SALARY, OR WORKING AT NIH USING NIH FUNDS TO SUPPORT HIS OR HER RESEARCH IS COVERED BY THIS NEW LEGAL REQUIREMENT . . . .

For intramural scientists, many of whom have been submitting papers to PubMedCentral voluntarily, this requirement involves minimal additional burden. We have already told intramural scientists how to access the NLM PubMed Central site—

<http://pubmedcentral.gov>

—and over the next month or so will provide you with additional detailed information in a user-friendly format.

The Copyright Issue

For intramural scientists, copyright should not be a major issue because government employees may not claim U.S. copyright in their publications and hence cannot transfer copyright.

Many journals will submit papers to PubMed Central for you—for an overview, see

<http://publicaccess.nih.gov>.

However, if they do not, the specific journal format of the article (that is, the copyedited form of the article in its specific journal format) may be protected. Therefore, without specific journal permission to use the published form of the article, it should be the accepted version submitted by the authors to the journal that would also be submitted to PubMed Central.

Does this result in the literature containing two versions of the same paper? In theory, it might, if the copyedited version is very different; but the author is free to send scientific changes to PubMed Central to harmonize the two versions. Ideally, journal publishers would provide PubMed Central with the published article, there-by ensuring there is only a single version.

A Win-Win Policy

The advantages of this new requirement to the public are obvious. As already noted, for NIH scientists, enabling public access to our scientific papers will broaden the exposure of our research, with a resulting increase in citations and impact on the scientific literature.

PubMed Central links to other data resources referred to in the papers, resulting in a richer understanding of scientific content..

Because Congress has mandated this new requirement, we will be held accountable for any failure to fully comply. The NIH intramural program can be expected to be under special scrutiny with respect to this new mandate. Thus, I seek your enthusiastic embrace of this new outlet for our scientific work and will be developing with the scientific directors a system to be sure that all papers are submitted as specified. Initially, the system will involve frequent reminders as we become familiar with the requirements.

Any constructive ideas about how best to achieve full compliance will be appreciated.

—Michael Gottesman
Deputy Director for Intramural Research

Moving Ahead with GWAS

by Jerry Menikoff
Director, Office of Human Subjects Research

A new year seems the appropriate time to discuss one of the newest and most promising areas of genetic research: genome-wide association studies (GWAS).

In each of these studies, hundreds of thousands of single-nucleotide polymorphisms (SNPs) are evaluated in hundreds of specimens, with the lofty goal of discovering the genetic changes that play a role in many common diseases.

In this piece, I will try to briefly describe some of the NIH procedures that apply to NIH researchers working in the GWAS arena. I will highlight considerations related to the consent of the people whose genomes are being analyzed—among our chief concerns in the Office of Human Subjects Research.

Because the relevant issues are somewhat different for researchers who produce new genomic data and those who use data that have been produced by others, each topic will be addressed separately.

For Researchers Who Produce GWAS Data

If you intend to produce data by analyzing genomes—either from specimens collected here at NIH or from specimens collected by collaborators outside NIH—you should become familiar with the NIH GWAS rules. OER maintains a website at

<http://grants.nih.gov/grants/gwas>

that provides a wealth of information about these rules, including specific information for NIH researchers.

Although the rules formally apply to NIH research approved on or after January 25, 2008, many aspects of those rules will apply to your work even if you received approval prior to that date.

NIH does not want the applicable protections to vary substantially merely because a study received approval a few weeks before the official effective date. Analyzing hundreds of thousands of SNPs in a person's genome, and putting those results in a databank, is an activity that requires appropriate oversight, regardless of the starting date.

The new NIH rules are designed, in part, to maximize the public benefit from the production of GWAS data. Thus, for example, they generally require you to gather and present your data in a way that allows them to be included in the central NIH database for GWAS data, dbGaP.

Richard G. Wyatt

What's Past is Prologue: *OHSR Director Jerry Menikoff beside a poster from a 1998 NIH symposium on "Medical Research Ethics at the End of the 20th Century: What Have We Learned?"*

Appropriate confidentiality protections will have to be in place; in particular, there are special rules relating to informed consent, among them that there must be IRB review of the consent process. Depending on the specific aspects of the study, the IRB could be at NIH or elsewhere.

Also with regard to consent, different considerations apply depending on whether the samples are collected prospectively or already exist.

If you are collecting samples prospectively, then the consent process, including the consent forms, should adequately discuss the special issues relating to GWAS.

Subjects should be made aware of how their genome will be analyzed, what will be done with the results of that analysis (including the fact that the information generated will be put in a database to be broadly shared with other researchers), and of the privacy and other risks relating to those activities.

In designing the consent aspects of your study, you might benefit from looking at the "Points to Consider" document, which was written by NIH to give guidance to IRBs and institutions on consent issues. A link to that document is on the first page of the OER GWAS website mentioned above.

If your study involves genomic analysis of previously collected specimens, there is a good chance that such an analysis was not contemplated at the time of collection. Thus, the original consent forms are unlikely to provide the types of specific information that would be expected in a prospective study.

It will ultimately be up to the IRB to determine whether the original consents are adequate to allow the study to proceed, or whether it might be necessary to renew the consent of the people whose specimens are being used.

For Researchers Who Use GWAS Data Produced by Others

If you want to use data stored in dbGaP for your own research, you will need to go through two steps. First, you need to obtain a one-time approval from your IC that authorizes you to gain access to data in that repository. Once that has been secured, you must then submit requests for the specific sets of data in dbGaP that you want to access.

Those requests will be reviewed by the data access committee (DAC) that has responsibility for the oversight of those datasets. In particular, the DAC will make sure that your proposed use does not violate any use limitations included in the original consent forms.

GWAS research has tremendous potential, but it is complex, and NIH is still in the process of working out the details of implementing these new rules. So, be on the lookout for additional guidance, which should be coming out in the near future. Questions can be sent to

<GWAS@mail.nih.gov>.

And if you have specific questions related to protecting the interests of the people whose specimens are being used, don't hesitate to contact the Office of Human Subjects Research by phone at 301-402-3444, fax at 301-402-3443, or e-mail at

<ohsr.nih.ddir@mail.nih.gov>.

From the Director, Office of Intramural Training and Education

Widening the Horizons—and the Smiles—of NIH Trainees

"Great work comes from happy trainees. Happy trainees work at NIH."

This spin on an old ad campaign (about certain dairy products) is supported by empirical data. According to the Sigma Xi Postdoctoral Survey, postdoctoral fellows who participate in career and professional development activities are more productive and experience less conflict during their postdoctoral experience.

Catalyst photo

Sharon Milgram

To help you make sure our trainees are productive and happy, we at the OITE have revamped our services and our style. The OITE complex now incorporates the Career Counseling Center (see page 5), open to all trainees, and three other units: the Graduate Partnerships Program (GPP), Postbac and Summer Research Programs, and the Office of Postdoctoral Services.

The recently created Career Counseling Center and Office of Postdoctoral Services (OPS) will work together to promote career development for our largest group—the postdocs.

In the coming year, we will focus on creating new programming, including courses in lab management, effective communication, leadership, and grantsmanship. We will also keeps tabs on national postdoctoral programs to ensure that NIH is out front in attracting, retaining, and providing services for fellows.

Another initiative in the OITE is to provide more diverse and comprehensive training, incuding programs to help guide trainees through tricky work-related situations, such as interactions in large multicultural teams and handling conflict.

We are creating teaching initiatives, including a new course—"Scientists Teaching Science"—and programs for trainees to visit local liberal arts colleges to get a first-hand look at what faculty positions at such institutions are like.

We are also expanding our ESL offerings and will soon provide workshops for supervisors who want to mentor and train students more effectively at all educational levels.

A priority is to give all NIH trainees access to OITE services. We are routinely traveling to other campuses, improving our videoconferencing capabilities, and clustering activities so that when off-campus trainees attend our events, they have a full day of useful workshops, discussions, and presentations to make it worth their while.

Two such "clustered" events are the **First Annual Career Symposium on April 9**, which will provide 15 discussion panels on a variety of biomedical careers, including science writing, undergraduate teaching, science policy, and research-intensive careers in all sectors. Panelists with varied educational experiences and backgrounds were invited to this inaugural event organized by the Fellows Committee, the Graduate Student Council, OITE, and other NIH offices.

We are also holding a **graduate and medical school fair in July**. We plan to offer workshops to help our summer interns and postbacs prepare strong applications for graduate and professional schools, and we will welcome representatives from up to 80 institutions who are coming to recruit our students and learn about our excellent training programs. Please visit our website at

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

for updates on our events and encourage your trainees to stop by the OITE to get acquainted with our staff and services. If you have ideas you'd like to share, call me at 301-594-2053 or e-mail **<milgrams@mail.nih.gov>**.

Lift-Off! Fellows Committee Launches New Website

After many months of planning and design by members of the Webpage Subcommittee and the NIH Center for Information Technology (CIT), FelCom has gone live with a new website.

The old site had no IT support and was difficult to update. The new one, spearheaded by FelCom NINDS representative Michele Rankin, is CIT supported, easier to keep current given the turnover of FelCom members, and—most important—a great resource for all NIH fellows.

Fellows can find:

- Names and contact information of FelCom representatives
- Subcommittee descriptions
- Synopses on roles of FelCom liaisons
- Upcoming activities
- FelCom meeting minutes
- Links to the NIH handbook for postdocs, Fellow-L (the fellows list serve), and the ever-popular Fellows Merchandise and Exchange Board.

A link to the ClinFelCom portal can also be found here. Designed by clinical fellows Hemant Sarin (NIBIB/CC), Kathy Calvo (NCI), and Melissa Meredith (NHGRI), with the assistance of the Office of Clinical Research Training and Medical Education, the portal offers access to many items of particular interest to clinical fellows, including:

- The history of Clinical FelCom
- Supplemental courses
- Grant-writing resources
- Links to the Accreditation Council for Graduate Medical Education, local medical boards, the NIH Clinical Research Information System and the Picture Archiving and Communication System

Other highlights of interest include the list of upcoming offerings from the Career Development Subcommittee, as well as links to archived seminars.

Information about FelCom's annual FARE competition (FARE 2009 is coming soon in March!) is also available. There is also a link for the Visiting Fellows Subcommittee, a particularly active committee composed of and serving postdoctoral visiting fellows and recently made a part of FelCom.

Find out what other NIH fellows are doing and how and where you can meet more fellows—such as at monthly FelCom Fridays (sometimes held on Thursday or Wednesday), hosted by the Social Subcommittee.

The Webpage Subcommittee welcomes comments or suggestions for improvement, which can be sent via the "Contact us" link in the upper right-hand corner of the home page.

Funded by the Office of Intramural Training and Education and implemented by the Division of Enterprise and Custom Applications branch of CIT, the new FelCom website can be accessed at

<http://felcom.od.nih.gov/>.

—Michele Rankin
Hemant Sarin

Career Counseling for NIH Trainees Gets a Dedicated Space and Staff

by Caroline Small
OITE communications intern

The Office of Intramural Training and Education (OITE) has opened a Career Counseling Center in Building 2, the first at NIH focused on meeting the needs of the nearly 5,000 trainees, from postbacs to postdocs, who came to NIH to expand their research universe and launch their careers.

OITE Director Sharon Milgram identified the need for trainee-oriented career counseling as her top priority when she arrived at NIH in early 2007. Trainees expressed feeling lost in their careers had often sought information on career opportunities both at and away from the bench. The OITE staff had addressed these needs by acting as career advisors and assisting with CV and résumé development.

With the advent of the Career Counseling Center, four dedicated certified counselors were hired to handle the large number of trainees requesting these and other services. The counselors' schedules filled almost immediately—about 200 trainees have taken advantage of the service since the center's inception in October. The center will celebrate its grand opening in April.

Counselors assist with self-assessment, understanding career options, and developing the means to meet career goals. They also offer mock interviews and help trainees apply to graduate and professional school and for jobs in all fields. Upon request and at no charge, they administer the Strong Inventory, which helps identify an individual's specific career interest, and the Myers-Briggs Type Indicator, which helps analyze an individual's working style and personality type.

The four certified career counselors currently on staff are Melanie Sinche, who developed the plan for the center; Elaine Diggs and Anne Kirchgessner, who travel regularly to the NIH campuses in Baltimore, Frederick, and Research Triangle Park, N.C.; and Denise Saunders, a licensed psychologist, who is stationed in Durham, N.C., and travels to Bethesda. In addition, William Higgins, a professor of biology at the University of Maryland, College Park, advises on graduate and professional school.

The OITE staff anticipates additional hiring, including an employer development specialist to connect trainees with worldwide employment opportunities.

The center holds workshops on topics including résumé and cover-letter writing, improving networking skills, and career options for scientists. It also hosts discussions with professionals from different scientific fields, creates employer connections via on-campus visits, and hosts career fairs.

"This is just the beginning," says Pat Sokolove, OITE deputy director.

The next major event is the Career Symposium on **April 9, 2008**. Sponsored by the NIH Fellows Committee, the Graduate Student Council, OITE, and the Career Counseling Center, it will bring representatives from a range of fields, including nonprofits, law firms, and foundations. The full-day symposium will include panels, speakers, and skill-building workshops.

The Career Counseling Center is open to all trainees. To sign up for an appointment with a counselor, check the OITE website

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

under "Opportunities for Current Trainees." ■

CME Continues at NIH with a New Partner

by Lori Bibb

Beginning in March, the NIH continuing medical education (CME) program will have a new partner—the Johns Hopkins University School of Medicine Office of Continuing Medical Education (JHU CME), based in Baltimore.

Before its recent restructuring, the NIH Office of Education had managed CME and, with the Foundation for Advanced Education in the Sciences (FAES), maintained accreditation through the Accreditation Council for Continuing Medical Education (ACCME). Reorganization as well as employee attrition led to the JHU partnership to ensure continuation of CME at NIH.

The NIH CME office has been transferred to the Clinical Center's Office of Clinical Research Training and Medical Education, under the leadership of Fred Ognibene. Linda Wisniewski in the office will become the NIH CME liaison between the NIH staff and the JHU CME office.

The partnership is expected to revitalize the CME program and improve the handling of registration, attestation for credit, and program evaluation.

Last year, NIH offered 45 CME-accredited activities, such as the Wednesday Afternoon Lecture Series, the Clinical Center Grand Rounds, and other seminars and courses. In years past, however, there were many more offerings—484 in the four-year period from 2003 to 2006, including 136 regularly scheduled conferences, 150 journal article readings, 86 FAES courses, and 47 enduring materials (non-live CME-accredited activities such as viewing a video or CD-ROM).

During this four-year period, 80,535 physicians and 92,053 nonphysicians participated in 9,329 hours of CME instruction at NIH. CME is considered a critical activity for medical professionals to maintain basic skills as well as licensure. In the United States, all states require CME for practicing physicians as a condition of continuing licensure, although the number of credits required varies by state.

Joan Schwartz, assistant director for intramural research, expects that CME activities that were discontinued because of a lack of staff, such as enduring materials, will be reinstated. She also anticipates that the new partnership will yield an increasing number of NIH CME offerings, partly because NIH staff will be able to participate in JHU activities as well. The JHU CME office sponsors more than 300 CME-accredited activities for the university each year.

The ACCME determines what types of programs can be considered CME, taking into account the content of the presentation or materials, the design of the materials, and any conflicts of interest of the presenter(s). Materials can include live lectures, written publications, online programs; they can be audio or video.

The transition to the partnership will be transparent, says Schwartz. On the horizon are the use of the JHU Office of CME website, the possibility of the use of a card reader to track attendance, and the means to do evaluations electronically. These changes will be detailed at

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

Mercury Falling . . .

continued from page 1

Reprocessing and final containment is expensive, and there are few environmentally friendly disposal options.

While Congress has proposed legislation to establish secure repositories and ban exports, much of the recovered mercury is currently sold for reuse, often in developing countries.

The NIH Clinical Center established a program in the late 1990s to remove mercury-containing products. The Mayo Clinic and many other leading biomedical research facilities also have gone mercury-free.

Ed Rau, a DEP environmental health officer in charge of mercury cleanup, and DEP Director Kenny Floyd want to make the rest of NIH mercury-free. They have proposed to the Office of Intramural Research and the NIH Scientific Directors a plan to ban the procurement of mercury-containing devices by the end of 2008 and to eliminate all uses of mercury in labs by the end of 2009.

"For virtually all laboratory needs, there are mercury-free alternatives," said Rau. There are costs associated with purchasing replacements, but these are minuscule compared with the potential costs of spill cleanup, he observed.

Rau added that as the largest biomedical research facility in the world, "we should use our buying power to drive the market to develop better, less toxic products, which would benefit both science and the environment."

Legacies of Past Use

Floyd's team assesses levels of mercury and other hazardous substances in NIH labs and buildings as part of a decommissioning protocol carried out before renovations or demolition.

Mercury is detected by combination of visual observations (looking for telltale silvery droplets under flooring and in sink traps), analysis of solid residues (from pipes and soil, for example), and air sampling (using a highly sensitive portable atomic absorption spectrophotometer).

courtesy of the Division of Environmental Protection, NIH and Scott Neese, 3D EnviroLogics LLC

Mercury droplets

Air readings in laboratories with active ventilation systems are well below the permissible exposure level of 100,000 ng/m^3 set by OSHA years ago. Because of mercury's tendency to bioaccumulate, however, more recent guidelines developed by the Agency for Toxic Substances and Disease Registry and EPA have set no-health-effect levels for the general population far lower, from 200 to 300 ng/m^3.

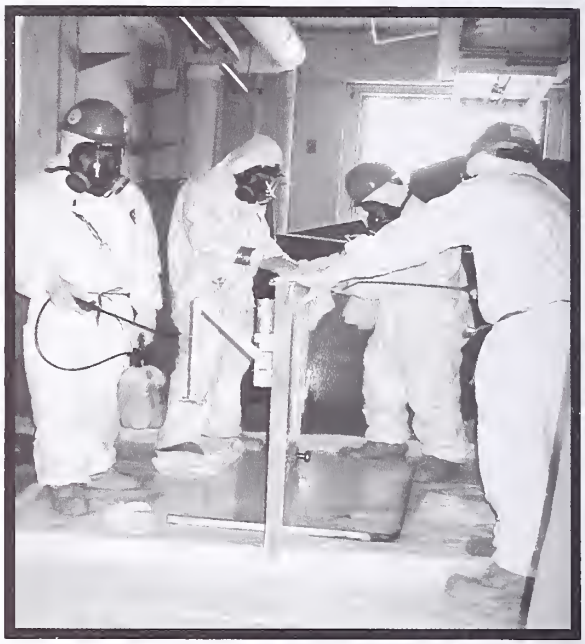
Surveys of spaces in Building 3 in 2002 revealed that about a third of the labs had air mercury concentrations over 250 ng/m^3, over 10 times the building background level.

Using the mercury meter, Floyd said they were able to follow trails of mercury contamination from one lab where spills were evident into restrooms, cold rooms, and offices, suggesting tracking underfoot and the potential to bring home contamination on shoes and clothes. Floyd is also worried about carrying bad habits into the newer NIH facilities.

"If we bring mercury into the new buildings, we can only surmise we'll have problems down the road," he said. Spills already have occurred in two of our newest buildings, 33 and 35.

Paramount among problems presented by spills is the cleanup cost. Demolition debris containing as little as 200 micrograms of mercury per liter of extract must be disposed of as hazardous waste.

A very small volume of mercury can contaminate tons of material. Removal of hazardous substances and contamination in Building 3 was approximately $1 million; about 75 percent of the total cost was mercury decontamination and disposal. Initial studies began in the spring of 2002, and the actual decontamination began in December 2002 and was fully complete by late February 2004.



photos courtesy of the Division of Environmental Protection, NIH and Scott Neese, 3D EnviroLogics LLC

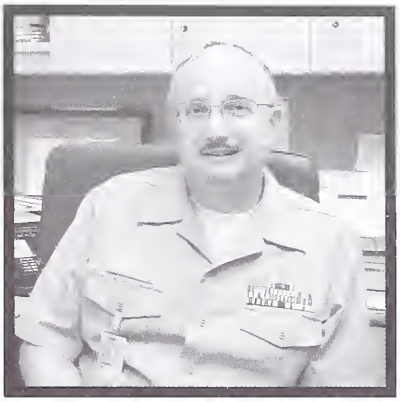
Building 3 decontamination team

Mercury is indeed the top toxic concern as NIH renovates old labs, Rau said. Lead and asbestos are relatively easy to locate and remove. Mercury moves and spreads, as the name quicksilver implies.

Cleanup in active labs, in response to spills, is especially problematic. When mercury gets behind casework or under floor tiles, cleanup usually requires removal of these items, shutting down the lab and disrupting science for weeks.

Other Effects on Research

While the neurotoxic effects of mercury exposure are well established, there are lesser known, more insidious effects that could compromise research conducted in contaminated laboratories.



Christopher Wanjek

Ed Rau

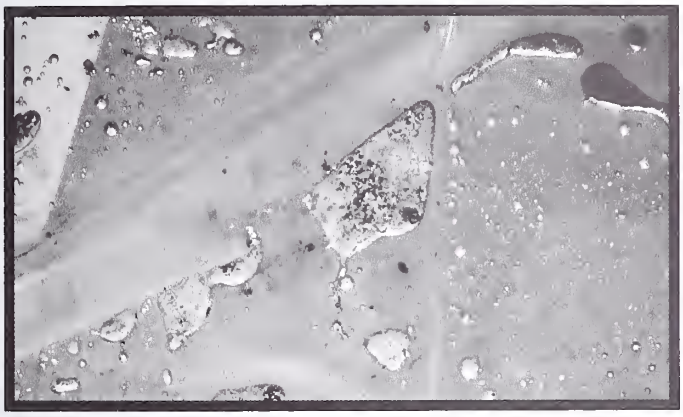
Christopher Wanjek

Kenny Floyd

Rau suggests that low levels of mercury contamination in facilities could affect responses of laboratory animals. He notes that mercury is a potent immunomodulator that's been found to affect the immune response of animals at very low levels of exposure, as low as 0.4 mg/kg body weight. This can result in hypersensitivity reactions and alterations in the host response to infectious agents.

Additionally, the presence of low levels of mercury in an environment has been shown repeatedly to favor development of antibiotic-resistant bacteria.

Bacterial resistance to mercury toxicity, probably developed since primordial times to cope with naturally occurring mercury, is located on the mercury-resistance locus (mer). This locus and the antibiotic-resistance integron In2 are both carried on the same transposon (T21).



courtesy of the Division of Environmental Protection, NIH and Scott Neese, 3D EnviroLogics LLC

Mercury spill from lab building (6) vacuum line

Thus, mercury-contaminated environments select and enrich for populations with multiple antibiotic resistance—unwanted guests in clinical and biomedical research facilities.

A Mercury-free NIH

At first, Floyd said he'd like to pick what he calls the low-hanging fruit, the easily replaceable thermometers and reagents in the proposed mercury ban. Floyd said his office remains sensitive to the needs of scientists to obtain precision measurements and to continue ongoing research using the same instrumentation. Mercury-free models should be selected when the instrumentation is replaced.

For the mercury ban to work, however, Floyd said he needs to hear from the intramural research community to understand the extent of unavoidable uses of mercury.

The DEP has a proposed waiver process for research with no mercury-free alternatives. But the fact that the Clinical Center has gone mercury-free is evidence, he said, that world-class research need not be affected by the switch.

Standing exceptions to the ban would include energy-saving lighting. Although fluorescent bulbs contain a few milligrams of mercury, the energy saved by using them in place of incandescent bulbs results in far less mercury released into the environment as a result of coal-burning power generation.

Wheels in Motion

The DEP extended the Clinical Center's voluntary mercury reduction program in 2001 to all NIH labs and facilities as an initiative called the "Mad as a Hatter? Campaign for a Mercury-Free NIH."

Rau is the self-declared NIH Mad Hatter, sometimes donning an alternate uniform—a big purple hat and bowtie—for publicity events. Mad, in this case, means angry about pollution and spills that don't need to happen, especially in brand new lab buildings at NIH, Rau said.

Floyd sees the procurement ban and subsequent replacement of mercury-containing instruments as an extension of laws already in place but not strictly enforced.

Maryland is among several states that prohibit the sale of mercury thermometers and certain other mercury devices. And the DHHS Affirmative Procurement Plan of July 2006 prohibits use of mercury in aneroid manometers and temperature-measuring devices, electronic thermostats, mechanical switches, and ultrasonic and photoelectric sensors.

A more challenging but necessary part of procurement controls will be restrictions on purchases of chemicals such as certain brands of bleach that contain significant levels of mercury as an unintended contaminant arising from manufacturing processes.

Mercury Exposé

Mercury is ubiquitous, and researchers might not know they are using products containing mercury. To access a link to a list of procedures and products that involve or contain mercury, as well as links to a growing list of alternatives, visit **<http://orf.od.nih.gov/Environmental+Protection/Mercury+Free/Alternatives.htm>**.

Rau, an expert on management of hazardous substances, said he knows that reluctance to change boils down to lab culture.

One idea that could help, he said, would be for scientists to state in their published papers that the work was performed mercury-free, to improve awareness of mercury hazards and encourage the entire scientific community to make the switch to mercury-free alternatives. He would also welcome greater participation by scientists in establishing cleanup levels for mercury and other hazardous contaminants in laboratories.

"These problems originate at the lab-bench level and so must the solutions," Rau said. ■

For more information and to confer with DEP on mercury use and alternatives in your lab, Ed Rau may be contacted at 310-496-7775 or **<raue@ors.od.nih.gov>**.

NIEHS "Sister" and "Two Sister" Studies Probe the Mix Of Genes and Environment that Underlie Breast Cancer

by Eddy Ball
NIEHS

For the past three years, scientists in the NIEHS Epidemiology Branch have championed a nationwide campaign to recruit sisters of women with breast cancer for what they believe is the largest effort of its kind ever attempted—a study involving a cohort of more than 50,000 sisters who will be followed prospectively for 10 years or more.

What the study promises other investigators at NIH and elsewhere is a mother lode for data mining in future explorations of breast cancer and other diseases.

Launched in October 2004 and known as the Sister Study, the study has already recruited more than 46,000 women, but it still needs to increase the number of participants from targeted demographic groups (see "Recruitment Call . . . ," page 9).

The investigation is being led by NIEHS Epidemiology Branch Chief and Principal Investigator Dale Sandler in partnership with Biostatistics Branch Chief and Co-Investigator Clarice Weinberg.

The researchers view the effort as their "life's work" and characterize the Sister Study as a pioneering initiative that "in many ways feeds into the [NIH] Roadmap for multidisciplinary studies and encourages collaborations across divisions."

The project is a prospective study of the etiology of breast cancer using a risk-based sampling approach. In a recent paper,* Weinberg and Sandler described the strategy as one offering investigators several significant benefits, including "a sizable increase in the rate of accrual of newly incident cases, enrichment for risk factors that are known or even unknown, and a high level of motivation among participants."

"Basically, the idea is to enrich for genes that are related to risk and to also enrich for exposures. The same kind of strategy could be followed in studying something like autism," Weinberg elaborated.

"One of the things about the Sister Study, like other prospective studies, such as the Nurses' Health Study," Sandler explained, "is that what we've built is a resource for the future. . . . We are already designing into the study opportunities to look at . . . respiratory disease, osteoporosis, and a host of other conditions."

Steve McCaw

Sister Researchers: *Clarice Weinberg (left), co-investigator, and Dale Sandler, principal investigator, in studies to plumb the underpinnings of breast cancer*

The study aims to uncover the links between genetics and the environment in the development of breast cancer using epidemiological analysis and biochemical investigations of a cohort with about twice the risk of other women for developing breast cancer. The volunteers are at increased risk because they have a sister with the disease.

Laboratory data from samples now being archived will be analyzed, along with information collected at enrollment and during annual interviews to track the volunteers' ongoing medical histories and everyday lives. The investigators will search for correlations between outcomes and the genetic makeup, diet, and environmental exposures of the volunteers.

The Sister Study is a massive undertaking, with banked samples of whole blood, cryopreserved lymphocytes, plasma, serum, urine, toenail clippings, buccal cells, and household dust.

Should a woman develop breast cancer—or any other cancer—"down the road," Sandler added, tumor tissue will be requested and then added to the sample bank.

The study's prospective design allows investigators to assess exposures before the onset of disease and to avoid biases common to retrospective studies, while creating a framework for testing new hypotheses.

Sandler and Weinberg anticipate about 1,500 cases of incident breast cancer to develop in the cohort during the next five years. Beyond that, as the volunteers age, there may be as many as 3,000 new cases to analyze, Weinberg said.

The Two Sister Study: Targeting Young-Onset and Survival Issues

In an effort to glean additional insights from the Sister Study cohort, Sandler and Weinberg have secured a commitment for three years of funding from the Susan G. Komen for the Cure foundation for a family-based study.

Called the Two Sister Study, its aim is to investigate the genetic and environmental factors that influence young-onset breast cancer—breast cancer developed before age 50.

The study will include about 2,000 of the 50,000 women with breast cancer whose sisters enrolled in the Sister Study, along with their unaffected sister and genetic data from any parents who are still living.

According to Weinberg, criteria for enrollment in the Two Sister Study include the development of breast cancer before the age of 50 and during the past three years. Participants will provide saliva and household dust samples, information about family and lifestyle, and

* C. R. Weinberg, D. L. Shore, D. M. Umbach, and D. P. Sandler, "Using risk-based sampling to enrich cohorts for endpoints, genes,and exposures," *Am. J. Epidemiol.* **166**. 447 (2007).

Recruitment Call for Sisters from Underrepresented Groups

The Sister Study has been on track in meeting enrollment goals in terms of total numbers. However, co-investigators Dale Sandler and Clarice Weinberg are still striving to build a cohort that reflects the diversity of American and Puerto Rican women in terms of age and geographic distribution, race and ethnic background, and education and occupation.

Cohort diversity is particularly important, they say, in light of the fact that different populations of women may experience the disease very differently.

African American women, for example, are 10 percent less likely to be diagnosed with breast cancer, but 35 percent more likely to die from it—a statistic that underscores the need for the study to be as inclusive as possible.

The investigators seek to double the number of women enrolled from several target groups, including:

- Racial and ethnic minorities
- Women aged 65 to 74
- Women with less than a college education
- Women in underrepresented occupations, especially in trades and industry

Visit the bilingual (Spanish and English) Sister Study website:

<http://www.sisterstudy.org/English/index1.htm>

Recruiters may be contacted by e-mail or called toll free at 1-877-474-7837 (1-866-889-4747 for deaf or hard of hearing).

The Sister Study is funded by NIEHS and has received additional financial support from a sister IC, the National Center on Minority Health and Health Disparities, for targeted recruitment of minorities.

The study has also received nonfinancial support from the American Cancer Society, the Susan G. Komen for the Cure foundation, the Intercultural Cancer Council, the Sisters Network, and the Y-ME National Breast Cancer Organization.

The women in the study themselves have also provided additional support, Sandler said. "They really care about the research and about their sisters. . . . They even help us recruit."

—Eddy Ball

details of their breast cancer diagnosis and treatment.

The affected sisters will also be asked to give permission for release of medical records and tumor tissue blocks.

If they have living parents who are willing to provide saliva samples for extraction of DNA, their parents will also be included.

The plan is to genotype more than 1,500 markers on about 150 candidate genes to identify genetic variants that tend to be transmitted to offspring who develop breast cancer.

Looking to the future, Weinberg said, "I'm hoping that we'll be able to afford to do a genome-wide association study for Two Sisters, where we look at maybe 500,000 SNP markers across the genome."

The archived DNA will serve as a resource for future tests of new candidate genes uncovered in ongoing whole-genome scans and could potentially be employed in studies of gene-gene interactions and epigenetic modifications.

Exposures related to risk will be identifiable from the comparison of the affected and unaffected sisters. The family structure will then provide a powerful basis for characterizing the combined effects of genetic and nongenetic risk factors.

The young-onset cases enrolled in the Two Sister Study will be merged with the incident cases diagnosed in the larger Sister Study during follow-up. Together, they will form a cohort of cancer survivors.

The investigators hope to secure funding to follow these survivors for up to 10 years to identify factors that influence prognosis following treatment. ■

Reminder: Application Deadline for NIH-Duke Clinical Research Training

Applications are being accepted for the 2008–2009 NIH-Duke Training Program in Clinical Research. The deadline for applying is **March 1, 2008**.

Designed primarily for physicians and dentists who desire formal training in the quantitative and methodological principles of clinical research, the program calls for part-time study, allowing students to integrate their academic with their clinical training.

Courses are offered at the NIH Clinical Center via videoconference. Credit earned may be applied toward satisfying the degree requirement for a Master of Health Sciences in Clinical Research from Duke University School of Medicine in Durham, N.C.

The degree requires 24 credits of graded course work, plus a research project for which 12 units of credit are given.

Applications are available in the Office of Clinical Research Training and Medical Education, Building 10, Room B1L403. Additional information on coursework and tuition costs can be found at

<http://tpcr.mc.duke.edu>.

Interested individuals should check with their institute or center regarding funding for participation in this program. E-mail queries regarding the program may be addressed to

<tpcr@mc.duke.edu>.

On Tenure Track

by Julie Wallace

Julie Wallace

Chris Buck

Virologist **Chris Buck** recently joined the Laboratory of Cellular Oncology (LCO) at NCI as an investigator, but he is a familiar face in Building 37. Buck did his postdoctoral training there, working under mentors John Schiller and Doug Lowy, and he is elated to be staying. "This is the best place in the world to do science," he says.

Buck's interest in virology goes back to his graduate work on HIV with Robert Siciliano at the Johns Hopkins School of Medicine in Baltimore. His studies at NIH focus on human papillomaviruses (HPVs), a diverse family of more than 100 small DNA viruses that are tissue specific, living on epithelial surfaces like skin and mucous membranes.

These viruses are specially adapted to live in the relatively immune-privileged environment of the outer layers of the skin and are released by normal cell death at the skin surface.

Although some HPV types can cause skin warts, others are nearly commensal, causing either no symptoms or very benign symptoms. In a minority of cases, infection with some HPV types can progress to cancer, most notably cervical cancer.

A group of about a dozen "high-risk" HPV types cause nearly all cases of cervical cancer. Recently developed prophylactic HPV vaccines can protect against two of these types, which together cause about 75 percent of cervical cancer cases.

The diversity of the HPV family of viruses appears to be driven by their ability to escape from neutralizing antibodies raised against the capsid of another HPV type. However, the fact that diverse HPVs live in similar epithelial environments and appear to enter cells by similar pathways tells scientists like Buck that, despite the differences in the antibody recognition of these viruses, there are molecular patterns that all HPVs share—hidden structures on the surfaces of these viruses that are common to all HPVs. If an antibody response could be mounted against a conserved HPV antigen, then a broad range of HPV types could be neutralized.

Toward this goal, Buck is now studying the basic features of the virion structure. HPV is a nonenveloped virus; its capsid coat is a naked protein shell made of L1 proteins that are folded into an icosahedral structure.

Virologists now view viral entry into a cell as a dynamic process, says Buck. During entry, parts of the virus are coming and going as the virion twists and molds itself. At each step, conformational changes in the proteinaceous capsid structure reveal highly conserved motifs that are identical among a broad range of HPVs.

To begin his studies, Buck will use mass spectrometry to generate a basic "parts list" of cellular proteins that are incorporated into the HPV virion. Buck also hopes to use advanced mass spectrometric methods to reveal the motifs that may be exposed to the environment only transiently and to see the dynamic changes of the virion structure.

In addition to studying the infection processes, Buck is also interested in the assembly process, particularly in understanding how the viral DNA is captured and packaged in the capsid.

A tool Buck developed during his postdoc years aids all these studies: an HPV-based gene delivery vector that generates high yields of infectious virions. This technology mimics the entry and assembly pathways of HPV, allowing Buck to evaluate what proteins and conformational changes are required at each step in the pathways.

Other projects include collaborating with Barney Graham at NIAID's Vaccine Research Center in pursuit of the possibility of using HPV-based vectors for genetic vaccination against other pathogens and helping to develop a clinical trial evaluating the ability of a common gelling agent found in vaginal lubricants, carrageenan, to protect against HPVs. ■

Gottesman to Give First Roberts Lecture of 2008

Susan Gottesman, chief of the Biochemical Genetics Section, Laboratory of Molecular Biology, NCI, will give the first Anita B. Roberts Lecture of 2008—"Stress Adaptation via Regulatory RNAs," **March 4**, in Lipsett Amphitheather, Building 10, at 1:30 p.m.

The Anita B. Roberts Lecture series is sponsored by the NIH Women Scientists Advisors Committee and the Office of Research on Women's Health. The lecture is open to the public, and sign-language interpreters are provided on request.

Individuals with disabilities who need reasonable accommodation to participate should contact Dierdre Andrews, 301-496-3891, or Federal Relay, 1-800-877-8339, five days before the lecture.

New Special Interest Group: Pediatric Clinical Research and Outcomes

The Pediatric Clinical Research and Outcomes SIG is a forum for harmonizing and advancing the design and implementation of pediatric clinical research with a particular emphasis on age and developmentally appropriate and interpretable outcome measures that may extend across diseases or conditions.

Pediatric clinical research differs from general clinical research in the diversity and longitudinally dynamic nature of the patient populations.

Outcome measures, biomarker development, methodology, and even the study questions themselves can be unique for a particular subpopulation and different among the various pediatric subpopulations and general clinical research.

Moreover, particular ethical issues, reflected in the additional regulations that apply specifically to pediatric research, require planning, procedures, and study conduct that differ from the general paradigms.

This SIG is recruiting members. Contact Steven Hirschfeld at **<hirschfs@mail.nih.gov>**.

ON TENURE TRACK

King Kwong joined the Thoracic Oncology Section of the Surgery Branch, NCI, in September 2007. A cardiothoracic surgeon, Kwong was recruited from the University of Maryland School of Medicine (Baltimore) faculty, where he was active in both clinical and translational research of thoracic cancers. He will continue these activities at NIH, seeking to bring the results of his bench research to the care of clinical patients.

Yvonne Evrard

King Kwong

Most current modalities of cancer treatment, Kwong says, have not been able to capitalize on differences, such as those between normal cells and cancer cells, between different subtypes of the same cancer, or even between the same type of cancer in different patients. Molecular profiles of tumors from two patients with lung cancer, for example, may reveal widely disparate genetic or proteomic profiles.

Kwong's laboratory is exploring targeted molecular therapies that focus on the changes that occur within apoptotic pathways that permit a normal cell to become a cancer cell. This research is an extension of work done in Kwong's previous laboratory at the University of Maryland, where he and his research team had identified notable differences in the regulation of proteins involved in the apoptotic pathways of normal and lung cancer cells. As he explains, apoptosis pathways are highly conserved intracellular mechanisms found in all cells, including cancerous ones.

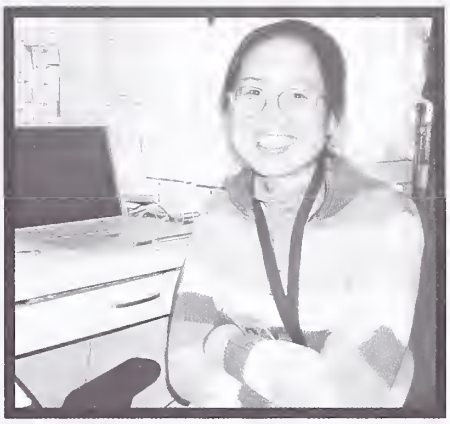
Here at NCI, Kwong's group is pursuing experiments to determine how apoptosis is abnormally regulated in thoracic cancers. In addition, his laboratory is trying to determine whether inhibition of a group of proteins called IAPs (inhibitors of apoptosis) can either eliminate lung cancer cells outright or better sensitize them to other modes of cancer treatment.

A better understanding of the role of apoptosis in the establishment of lung cancer, Kwong believes, will guide the development of novel agents that manipulate the apoptotic pathway in favor of the cancer patient. These treatments might eliminate the cancer cells or render them more vulnerable to chemotherapy, radiation, or other existing molecular-targeted cancer treatments. Kwong hypothesizes that a multipronged molecular approach could, theoretically, convert even terminal metastatic disease into a chronic disease state in select cancer patients.

Basically, Kwong hopes to establish a more systematic understanding of lung cancer and other thoracic malignancies and to actively contribute—both at the bench and in the clinic—to improving the standards of clinical care, optimizing current therapies, and developing new ones.

—Yvonne Evrard

Helen Su is an NIAID tenure-track clinical investigator, having participated in NIAID's new Clinical Research Transition Program, an initiative providing opportunities for physicians to gain clinical and translational research experience in association with an NIAID laboratory.



Christopher Wanjek

Helen Su

She studies the human immune system, primarily through a protocol she developed involving patients with poorly characterized autoimmune disease and immunodeficiencies.

From 2002 until late 2006, Su worked first as a clinical fellow in allergy and immunology and later as an assistant clinical investigator under the mentorship of Michael Lenardo in the section on molecular development of the immune system in the Laboratory of Immunology, NIAID.

Su has a medical degree and doctorate from Brown University in Providence, R.I., where her research focused on host-virus interactions.

She became interested in the relationship between immunodeficiency and autoimmunity during her pediatric residency at St. Louis Children's Hospital, where she saw what appeared to be healthy children suddenly consumed and killed by a hyperactive yet ineffectual immune response to normally innocuous pathogens.

As a clinical fellow at NIH, she studied patients with a variant of autoimmune lymphoproliferative syndrome called caspase-8 deficiency state (CEDS).

CEDS is characterized by autoimmunity and lymphocyte accumulation due to genetic mutations that interfere with the cell-death mechanism, as well as a profound immunodeficiency whose mechanism was previously unexplained.

In a 2005 *Science* article on which she was lead author, she and her colleagues reported how caspase-8, known to trigger apoptosis, also activates immune system cells via the gene transcription factor NF-κB (*Science* **307**:1465–1468, 2005).

Su wants to understand the molecular mechanisms that regulate the human immune system and how their derangements cause disease.

The Clinical Center, she says, offers unparalleled access to a diverse patient population with similar immune disorders, as well as the resources to apply multiple methods—genetic, biochemical, and clinical—to plumb the causes of immune dysregulation.

—Christopher Wanjek

People

Recently Tenured

Mirit Aladjem *received her Ph.D. from Tel Aviv University in Israel in 1991 and performed her postdoctoral studies at the Salk Institute in La Jolla, Calif. She joined the Laboratory of Molecular Pharmacology, NCI, as head of the DNA replication group in October 1999. She is now a senior investigator in that lab.*

My group studies the regulation of DNA replication in mammalian cells. We ask how cell-cycle signaling pathways regulate DNA replication and how replication coordinates with gene expression and chromatin condensation.

Fran Pollner

Mirit Aladjem

During the S-phase of the eukaryotic cell cycle, particular sections of the genome replicate at different times, yet it is striking that replication of the entire genome is coordinated such that each and every genomic locus replicates exactly once.

To achieve the high precision of DNA replication, cell-cycle regulators must interact with chromatin to ensure that replication starts at the correct location and the exact time. The cell-cycle machinery must also receive signals from replicating chromatin to detect and respond to replication errors.

We use a genetic approach to identify DNA sequences that determine where and when replication starts and then use those sequences to find proteins that bind them. Such proteins are likely to signal from the cell-cycle network to chromatin and back, facilitating proper cell-cycle progression and ensuring genomic integrity.

We have identified DNA sequences—termed "replicators"—that determine the location of replication initiation events. We have also identified DNA sequences that dictate the timing of DNA replication—these are termed "replication timers." Interestingly, some sequences can act as both replicators and replication timers, whereas others affect the timing but not the location of DNA replication.

We have dissected the sequence requirements for replicators and replication timers and shown that these genetic elements also affect epigenetic modifications on chromatin. Importantly, replicator sequences can prevent gene silencing, suggesting that replicators might be used to improve the expression of gene-therapy vectors.

Current studies aim to identify proteins that bind replicators and replication timers. Such proteins likely dictate the time and location of initiation of DNA replication and play a role in coordinating replication with other processes that occur concomitantly on chromatin, such as transcription.

We are also asking how cells respond to perturbation of DNA replication—an important question because the sensitivity of cells to anticancer drugs often depends on cell-cycle checkpoint pathways that are activated when DNA replication is perturbed. We tracked replication patterns on single DNA fibers to examine how cells recover from a mild drug-induced disruption of DNA replication.

We found that cells can convert perturbed replication forks into DNA breaks. The conversion process requires a nuclease (Mus81) and a helicase (Bloom's syndrome helicase). The DNA breaks are transient; a recombination process (nonhomologous end-joining) repairs them and restores DNA replication.

Cells that cannot form transient DNA breaks, or cells that form breaks but cannot repair them, are very susceptible to drugs that inhibit DNA replication. These observations suggest that the pathway that forms and repairs transient DNA breaks is essential for cellular adaptation to varying rates of DNA replication.

Fran Pollner

Jeffrey Diamond

As we continue to identify proteins that interact with chromatin, we need to create tools that will help scientists understand how those interactions integrate into a network that affects cell-cycle progression.

In collaboration with Kurt Kohn, Yves Pommier, and John Weinstein from the LMP, we organize current knowledge about cell-cycle regulation using the molecular interaction map (MIM) notation first proposed by Kohn. Our electronic MIMs are available at

<http://discover.nci.nih.gov/mim/index.jsp>

and allow easy navigation within pathways as well as links to pertinent additional data in the form of annotations and references. In collaboration with Jeff McFadden from NIST, we use MIMs to guide simulation-based studies of the control principles underlying bioregulatory networks.

Jeffrey Diamond *received his Ph.D. from the University of California, San Francisco, in 1994. He completed a postdoctoral fellowship at the Vollum Institute of the Oregon Health & Science University, Portland, before joining NINDS as an investigator in 1999. He is currently senior investigator in the Synaptic Physiology Unit, NINDS.*

My lab explores how neurons communicate at synapses. At most synapses, the presynaptic cell releases a diffusible neurotransmitter that activates receptors on the postsynaptic cell. Our studies are designed to explore which features of synapses affect their strength, reliability, and, ultimately, their function within neural circuits.

We are studying how synaptic communication in the hippocampus depends on the diffusion dynamics of the neurotransmitter glutamate and how glutamate transporters regulate this process. Transporters in glial astrocyte membranes take up most synaptically released glutamate and maintain glutamate at low levels outside of cells, preventing glutamate-induced neurototoxicity.

The synaptic physiology field focuses primarily on glutamate's actions within the synaptic cleft, but we also know that synaptically released glutamate can diffuse beyond the cleft to activate targets outside the synapse, a phenomenon referred to as "spillover."

We do not yet understand the effect of spillover on synaptic communication in the brain. The extent to which spillover occurs depends on how long glutamate is permitted to diffuse after its synaptic release. We measure this by recording electrophysiological signals associated with the transport process from glial cells in brain slices. In addition, we can record the time course of synaptic and extrasynaptic receptor activation tracking similar signals from neurons. We have found that glial transporters remove synaptically released glutamate very quickly—within a millisecond of release—but that receptors are still activated by spillover.

Specific roles for neuronal transporters are less clear, but we have shown that they protect NMDA receptors in the

hippocampus from glutamate spillover, thereby aiding the learning and memory functions of these receptors. We also have shown that neuronal transporters contribute to inhibitory synaptic transmission by providing substrate for the synthesis of the inhibitory neurotransmitter GABA.

By limiting glutamate spillover and enhancing inhibition, neuronal transporters may constitute an endogenous safeguard against hyperexcitability leading to seizure activity in epilepsy—an idea we plan to test in the future.

Our work on the retina focuses on specialized synapses that shape the time course of the visual signal in the inner retina. Bipolar cells, which receive input from photoreceptors, convey graded "analog" synaptic signals to amacrine and ganglion cells.

Synaptic feedback inhibition from amacrine cells to bipolar cell synaptic terminals confers temporal precision required for more complex visual processing.

We are examining the synaptic and cellular mechanisms that regulate the feed-forward analog signals and the inhibitory feedback. We are also studying synaptic activation of ganglion cells, the neurons that form the output signal that is transmitted from the retina through the optic nerve to the rest of the brain.

We are particularly interested in the role of NMDA receptors in ganglion cell activation and have shown that NMDA receptors on some ganglion cells are excluded from the synaptic cleft and activated only during stronger synaptic stimulation. This exclusion may serve to extend the range over which ganglion cells can encode changes in light-stimulus intensity.

In addition, we think that calcium that enters the cell through NMDA receptor channels may contribute differently during different components of the visual signal, and we are designing experiments to elucidate this process. Overall, we aim to understand how synapses are optimized to perform specific tasks required by the surrounding neural circuitry.

John Isaac *received his Ph.D. from the University of Southampton in the United Kingdom in 1994. He completed his postdoctoral training at the University of California, San Francisco, before returning to the United Kingdom to start an independent laboratory at the University of Bristol in 1997. He returned to the United States in 2004 to join NINDS as a tenure track investigator. He is currently senior investigator and chief of the Developmental Synaptic Plasticity Section, NINDS.*

Fran Pollner

John Isaac

During early postnatal development, neuronal circuits in the mammalian brain self-organize into functional networks able to efficiently process information and produce appropriate output. Dysfunction of this critical process is thought to contribute to several neurological disorders including autism and schizophrenia.

Our laboratory investigates the molecular and cellular mechanisms underlying development of neuronal circuits. The primary focus is to understand how long-lasting changes in the strength of synaptic connections between neurons produce functional circuitry.

We use electrophysiology in brain slices combined with live imaging and molecular manipulations to study the mechanisms regulating synaptic function during development.

Using the somatosensory system of the rodent we investigate the mechanisms by which sensory experience causes long-lasting changes in synaptic strength of excitatory and inhibitory networks in layer 4 of neocortex. Layer 4 is the input layer of primary sensory neocortex, receiving the majority of ascending sensory input from the periphery.

Our somatosensory cortex studies have revealed a critical developmental window when the balance of inhibitory-excitatory drive in the layer 4 circuit is established. In the mouse, feed-forward inhibitory circuitry—which is driven by ascending sensory input from the thalamus—is dormant in the first postnatal week but is rapidly recruited during a two- to three-day period at the start of the second postnatal week.

This surprisingly rapid development of the inhibitory network suggests that sensory experience may play a role in shaping the inhibitory network at a very precise developmental time. We are now investigating the mechanisms driving the recruitment of feed-forward inhibition.

In work on mechanisms of synaptic plasticity at hippocampal CA1 synapses, we have found that PICK1, a protein that directly interacts with AMPA-type glutamate receptors, is an essential part of the expression mechanism for long-term potentiation (LTP) and long-term depression. Moreover, we find that PICK1 rapidly regulates the calcium permeability of AMPA receptors during LTP. This intriguing novel mechanism provides a potential therapeutic target to prevent excitotoxicity mediated by calcium-permeable AMPA receptors that occurs during cerebral ischemia.

We are also developing novel approaches to analyze circuit function in brain slices. We have devised a method to use two-photon laser uncaging of glutamate to activate individual neurons in layer 4 of somatosensory cortex. This enables us to probe the connectivity and synaptic properties of the layer 4 circuit with high spatial and temporal precision.

In addition, we are using virally transfected channel rhodopsin 2, a light-activated ion channel, to selectively activate specific inputs using light. We have succeeded in labeling thalamic inputs to neocortex and are using this technology, combined with calcium imaging, to map thalamic-recipient spines in layer 5 pyramidal neurons.

Such optical technologies combined with electrophysiology are now enabling us to analyze neocortical circuits and will facilitate high-resolution probing of developmental and experience-dependent changes in circuit function.

Michael Otto *received a Ph.D. degree in microbiology from the University of Tübingen, Germany, in 1998. He joined the Laboratory of Human Bacterial Pathogenesis at NIAID's Rocky Mountain Laboratories in Hamilton, Mont., in 2001. He is now a senior investigator in that lab and head of the Pathogen Molecular Genetics Section.*

Originally a biochemist with continuing education in microbiology, I am especially interested in the pathogenesis of staphylococcal infections. During my graduate and postdoctoral time at the University of Tübingen, under the supervision of Friedrich Götz, I studied *Staphylococcus epidermidis*, the most common cause of nosocomial infections.

My initial studies focused on a bacteriocin produced by *S. epidermidis*, and I later became interested in the pathogenetic mechanisms of this bacterium,

Recently Tenured

most notably the process of biofilm formation.

Joining the Laboratory of Human Bacterial Pathogenesis expanded my opportunities for first-rate scientific interchanges. Work with neutrophil immunologist Frank DeLeo, especially, involving analysis of host-pathogen interactions led to enhanced understanding of the mechanisms underlying the success of *S. epidermidis* in nosocomial infections. More recently, in response to the epidemic outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA), my laboratory has started studying *S. aureus*, the more virulent cousin of *S. epidermidis*.

Michael Otto

We have identified several novel mechanisms by which *S. epidermidis* evades human innate host defense. Most notably, we have conducted a detailed investigation of the structural factors and gene regulatory processes involved in biofilm development.

Interestingly, we found that a polysaccharide secreted by staphylococci as a biofilm matrix component plays a crucial role in immune evasion. We also discovered that *S. epidermidis* makes use of the same substance as *Bacillus anthracis*—poly-γ-glutamic acid—to evade neutrophil phagocytosis and antimicrobial peptides. Further, global analysis of gene expression in biofilms yielded important insights into the physiological basis of biofilm resistance to antimicrobials and innate host defense.

Often, my research has revolved around bioactive peptides. In analyzing the mechanism of quorum sensing, or cell density–dependent gene expression, in staphylococci, we found that staphylococci signal cell density by means of a post-translationally modified peptide containing a thiolactone structure.

Much of my current research is focused on phenol-soluble modulins (PSMs), proinflammatory and leukocidal peptides that contribute to the exceptional virulence of community-associated MRSA. In addition, we believe that a different subclass of the PSMs contributes to structuring processes in a biofilm, and we continue investigating this putative double role of the PSMs in staphylococcal pathogenesis.

Finally, we recently identified the system that staphylococci (and likely many other Gram-positive bacteria) use to sense the presence of human antimicrobial peptides and trigger the expression of counteractive measures against this key part of innate host defense on the human skin.

While we have continued interest in *S. epidermidis* and biofilm development, we will concentrate on investigating the PSMs.

Much needs to be learned about these key virulence factors of *S. aureus* in terms of specific receptor interactions, structure-function relationships, and evolution. We hope these studies will contribute to the identification of targets for anti-staphylococcal drug and vaccine development.

Ling-Gang Wu received his Ph.D. in neuroscience in 1994 from Baylor College of Medicine in Houston, Texas. He did postdoctoral work at the University of Colorado, Denver, and the Max-Planck Institute for Medical Research, Heidelberg, Germany, from 1994 to 1999. He was an assistant professor at Washington University in St. Louis in 1999 before joining NINDS as an investigator in 2003. He is currently a senior investigator in the Synaptic Transmission Unit, NINDS.

Fran Pollner

Ling-Gang Wu

Neurons communicate with each other mostly via synaptic transmission. Regulation of the strength of synaptic transmission plays essential roles in many physiological and pathological processes, such as control of neuronal network outputs, neuronal development, learning and memory, and neurological diseases.

Consequently, it is essential to understand how synaptic strength is determined, maintained, and regulated.

During the past eight years, we have studied endocytosis, which is essential to the maintenance of synaptic strength because it retrieves and thus recycles vesicles at the nerve terminal.

How endocytosis is mediated and regulated is poorly understood. We developed a system that enables measurement of both rapid and slow endocytosis, applying a high time-resolution technique—called capacitance-measurement technique—to a large central synapse, the calyx of Held in the auditory brainstem.

At this central synapse, we provided a systematic view of the time course of endocytosis in various stimulation conditions. We found that rapid endocytosis is activated by calcium during strong nerve activity, which may speed up the vesicle recycling needed to maintain synaptic transmission during intensive nerve activity.

We have identified three modes of endocytosis that may give rise to different time courses: a rapid kiss-and-run mode that allows for rapid-fusion pore opening and closure; a slow mode; and a rapid bulk endocytosis, which retrieves a piece of membrane much larger than a single vesicle. These findings contribute to a current debate and challenge a generally accepted view.

We provided the most direct evidence to date to support the existence of the kiss-and-run form at synapses, about which there has been much debate. Regarding bulk endocytosis, we countered the generally held opinion that this is a very slow form, with a time course of minutes.

Using the capacitance-measurement technique, which provides a high time resolution, we showed that bulk endocytosis may take only a few seconds after stimulation. Thus, bulk endocytosis may also provide a mechanism to speed up endocytosis.

In summary, we have shown how different modes of endocytosis participate to retrieve fused vesicles. Regulation of these different modes may therefore provide a mechanism to generate synaptic plasticity during various patterns of nerve activity.

In addition to the research on fusion and retrieval, we also studied short-term synaptic plasticity, which is involved in controlling the output of the synapse and the neuronal circuit. In particular, we worked on short-term depression (STD) of synaptic transmission that can be caused by repetitive firing at many synapses.

We found that a calcium-calmodulin–mediated inactivation of calcium channels in the nerve terminal contributes significantly to the generation of STD—a finding that overthrows the long-held view that STD is mainly caused by depletion of a readily releasable pool of vesicles.

Our findings contribute to our understanding of how synaptic strength and the output of neuronal circuits are controlled and regulated. ■

Cartoon

by Fatima Husain

Evolution of a Protocol

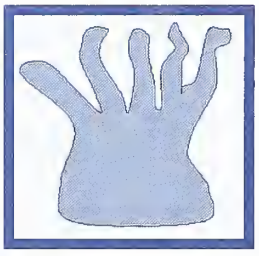
Shiny new idea in your mind

amoeba

Your supervisor has other ideas

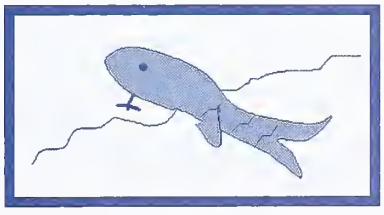
algae

Scientific review committee: many heads



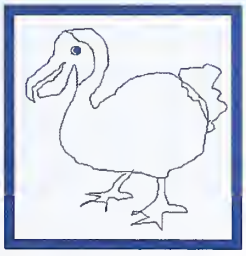
hydra

IRB review committee: promised land

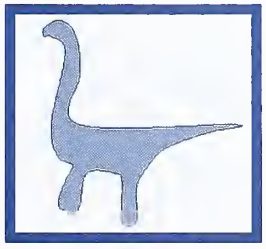


Amphibian

Data collection: alas, some protocols become extinct for one reason or another



dodo



apatosaurus

But the fittest survive – and then there's data analysis and writing: "The Scream"

human

CATALYTIC REACTIONS?

If you have a photo or other graphic that reflects an aspect of life at NIH (including laboratory life) or a quotation that scientists might appreciate that would be fit to print in the space to the right, why not **send it to us via e-mail: catalyst@nih.gov>; fax: 402-4303; or mail: Building 2, Room 2E26.**

Also, we welcome "letters to the editor" for publication and your reactions to anything on the *Catalyst* pages.

In Future Issues...

- Inside the Doors Of Building 33
- Dual-Use Technology
- Research Roundup

Kids' Catalyst —The Joys of Amateur Radio

International radio symbol

Driver's license . . . ah, freedom! But you have to wait until you're old enough, and then you are still limited in where you can go and how fast you can get there, and you have responsibility for tires, gas, insurance, etc. It's not all fun.

But there's another kind of license. . . one that will allow you to go to the other side of the country or overseas. Or to the moon or a space station—and you'll be going at the speed of light!

What's more, even if the power goes out—and you have no computer, no video games, no TV, no phone service—you could still be talking to people all over the world and you could also be helping with emergency assistance during something like a power outage.

Welcome to the world of amateur radio. There are people at their own radio stations all over the world, with radios, big and small, who aren't limited to listening to that little section on the FM dial. With their receiver and transmitter (and license), they can listen *and* talk to people as far away as the space station—and beyond, once there are people beyond the space station. And you can, too.

The catch? Just as with a driver's license, you have to take a test (so you have to be able to read) to get your amateur radio license, but it's a test on information you'll be excited to learn because it will allow you to operate a radio and to know what you're doing.

There are lots of people who can help you get started, such as NIMH's Andy Mitz (call signWA3LTJ) of W3NIH, our very own radio club—the NIH Radio Amateur Club **<http://nihrac.od.nih.gov>**.

The radio club operates the Emergency Communications Center at NIH; it's housed on the third floor of Building 11, the power plant. And that's where the group meets the first Saturday of each month.

Steve Saletta (NINDS) operates one of the Emergency Communications Center radios

Andy can be reached by phone at 301-402-5573 or e-mail at **<arm@nih.gov>**.

Information on how to apply for and get an amateur radio license can be found at the Federal Communications Commission website **<http://wireless.fcc.gov/services/index.htm?job=licensing&id=amateur>**.

And the best site for information, according to Andy, is the American Radio Relay League, at **<http://arrl.org>**.

—Jennifer White
call sign KB3QFD

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