FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 13, ISSUE 5 ■ SEPTEMBER–OCTOBER 2005

AIMING FOR THE CALM AFTER THE STORM: YOGA AT THE CRC

by Geoff Spencer

Intellectual flexibility has been a hallmark of Kate Berg's NHGRI career.

Director of the Special Populations Research Program in the Medical Genetics Branch, Berg has searched for genes involved in attention deficit hyperactivity disorder, chromosomal sites linked to hereditary prostate cancer, mutations related to holoprosencephaly, and, in particular, better ways to understand the genetic-environmental underpinnings of conditions affecting minorities and isolated populations.

Maggie Bartlett

Kate Berg

But for one hour each Tuesday over the past two years, dozens of Clinical Center patients, family members, and NIH employees have benefited from a different yet equally flexible side of this intramural researcher: Kate the Yoga Instructor.

Relying on a few strategically placed mats and many positive minds to convert a no-nonsense con-

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NHGRI HOSTS 'GEEK-FEST' TO START THE BALL ROLLING

STEP 1: SEQUENCING THE HUMAN GENOME — STEP 2: INTERPRETING IT — ENTER ENCODE

by Jim Swyers

Eric Green

Brainstorm: *More than 100 genomic scientists from three continents met in Rockville for three days in July to plumb the depths of the human genome sequence*

In 2000, a small group of computer scientists working in relative isolation at the University of California, Santa Cruz, developed a fairly simple yet powerful software tool to assemble the almost-complete human genome sequence.

Now, five years after the completion of an initial draft of the human genome sequence, it is no longer possible for any single group of individuals—or scientific discipline for that matter—to make sense of all the data that have been amassed about the human genome.

Rather, deciphering the information embedded in the 3-billion–base human genome sequence requires the combined intellect and talents of multidisciplinary teams of scientists working collaboratively worldwide.

An initial surprise about the human genome is that instead of the expected 100,000 or so genes, it appears to contain only about 20,000 to 25,000 genes. Moreover, most of the estimated 5 percent of the human genome sequence believed to be functionally important based on evolutionary conservation does not encode protein.

Establishing functions of these conserved noncoding sequences (as well as other functional regions that are not evolutionarily conserved) represents a high-priority goal of genomics programs

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Responding to Hurricane Katrina: NIHers Swiftly Volunteer their Services As NIH Leaders Coordinate Disaster Relief Actions

Richard Wyatt

The story of Hurricane Katrina and NIH's role in disaster relief will be unfolding for months to come, but it is clear that the NIH community responded (and continues to respond) with compassion, energy, and professionalism to meet medical and public health needs.

In short order, NIH staffed a field hospital, created a national consultation service, and prepared the NIH Clinical Center (CC) to receive storm victims and their families. Soon after, the Intramural Research Program started arranging housing for displaced scientists from the storm-ravaged areas.

To catalogue the NIH response is useful, but it is also important to recognize the outstanding leadership and spirit that characterized the early response. NIH Director Elias Zerhouni, Deputy Director Raynard Kington, CC Director John Gallin, CC Deputy Director for Clinical Care David Henderson, and, indeed, the entire NIH leadership mustered efficiently to plan, assess, and coordinate to make NIH resources available and do the right thing in the face of the disaster.

For the first time in my memory, the NIH Director clearly asked the NIH biomedical research organization to "set aside business as usual in this unusual time." This call to action was heard by myriad NIHers—more than could serve at once—who stepped up to help. There was even frustration in the voices of some who wanted to serve but for whom there was no immediate role. For many, their service is continuing to support and conduct outstanding biomedical research at the NIH and waiting to see whether additional appropriate active response roles emerge.

NIHers have responded directly through deployments to the affected region to offer assistance. One of the first of five commissioned officers from NIH to arrive was Captain Charles McGarvey, Clinical Center Department of Rehabilitation Medicine, who was the team leader for a field hospital in Baton Rouge, La. Others followed quickly, and within days, some 40 officers and approximately 60 civilian health professionals and support personnel had been deployed to sites in the affected areas to meet medical, nursing, mental health, and even veterinary needs.

Our administrative staff and our clinical staff worked together to mobilize a coordinated response. Through an unprecedented call to medical school deans with the assistance of the Association of American Medical Colleges (AAMC), Dr. Zerhouni spoke with our academic partners, some of whom (such as the staff at Duke University in Durham, N.C.) joined directly and others of whom catalogued resources that could be deployed as needed. As of this writing, more than 1,250 volunteers (intramural and AAMC partners) have offered their support. More than 75 additional NIH officers remain prepared, ready, and willing to go at a moment's notice to serve where needed.

Many NIHers—including the Director's immediate office staff and CC staff—have served long hours in situ to organize, facilitate, and communicate so that others could go out efficiently and serve.

Additional details of some NIH efforts include:

- Making available up to 100 beds in the Clinical Center without perturbing our research mission should the need arise to transfer select patients here from the disaster area. Housing for families in the old Clinical Center, Safra Family Lodge, and the NIH Children's Inn has also been made available.
- Establishing a 24/7 consultation call center for various specialty medical areas—including infectious diseases, environmental/toxic concerns, and oncology—to aid primary care providers in the affected region and link them to health advice around the country
- Mustering a team of more than 150 specialized medical and support personnel to staff a field hospital in Meridian, Miss., or to supplement wherever needed. The team was led by CC staff, including Dr. Pierre Noel, Captain Elaine Ayres, and Captain Laura Chisholm, as well as NIEHS Director David Schwartz. Many traveled to Mississippi and stood ready to assist, although, as the situation evolved, this facility was not needed.
- Providing DNA identification of remains and match-up of DNA samples from relatives, if needed, through NHGRI
- Providing intramural research laboratories and local housing to displaced graduate students, postdocs, and senior scientists who lost their laboratories and resources, mainly in New Orleans

This is a time to recognize with pride the substantial contributions of NIH staff whenever called upon to help with disaster relief, as well as the commitment and talent of NIH leadership who have responded so effectively in this crisis. We need to remember for the next time how we can pull together in such a crisis to serve others beyond this creative research environment in which we are privileged to work.

—Richard Wyatt
Executive Director, Office of Intramural Research

For extensive information on the NIH response to Hurricane Katrina, visit
<http://www.nih.gov/about/director/hurricanekatrina/>

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worldwide.

In an effort to identify all the functional elements in the human genome, NHGRI recently launched the ENCODE (Encyclopedia of DNA Elements) project. ENCODE involves the large-scale generation of experimental and computational data and the rigorous integration and analyses of the results.

In the initial phase, an international group of investigators—the ENCODE Consortium—is focused on analyzing the same set of 44 genomic regions that together account for 1 percent (~30 million bases) of the human genome.

Eric Green

Gerps and targs, anyone?: *One of the five analysis groups work in real time during smaller group breakout sessions*

Informing the ENCODE Project

To establish how best to analyze the large amount of data already generated by ENCODE, NHGRI's extramural and intramural research divisions, along with the NIH Intramural Sequencing Center (NISC), a major participant in ENCODE, jointly sponsored an intensive three-day workshop for more than 100 ENCODE consortium scientists from leading public and private genomic research organizations in the U.S., Canada, Europe, Japan, and Singapore.

The objective of the workshop was to begin the detailed analysis required to evaluate and compare the effectiveness of the many different technologies currently being used to find functional elements in the human genome.

"All we ask," NHGRI Scientific Director and NISC Director Eric Green told the assembled group at the workshop onset, "is that you be flexible, spontaneous, and productive."

The proceedings—affectionately dubbed the "Rockville Geek-fest" by NHGRI Director Francis Collins in tribute to the fact that most participants were bioinformaticians and computer scientists—were designed to catalyze the rigorous analysis of ENCODE data and to help assess progress in interpreting the targeted 1 percent of the human genome with respect to functional sequences.

"Your job is to compare all of the different methods used to date in studying this 1 percent of the human genome, establish what you have and have not learned, and speculate about which approaches are ready to be used in analyzing the entire human genome," Collins said.

Ewan Birney, a senior scientist at the European Molecular Biology Laboratory–European Bioinformatics Institute and coordinator of ENCODE data analyses, said that the ultimate goal of the workshop was to solidify the functioning of five distinctive but collaborative groups that would eventually lead the ENCODE Consortium in writing "high-impact" research papers about the areas of study addressed by ENCODE.

The five analysis groups—formed before the workshop and composed of consortium members—were assigned to study

- Sequence alignments and conservation
- Genes and transcripts
- Transcriptional regulation
- Chromatin structure and replication
- Sequence variation.

The goal is for each to submit a major paper for publication within the next year.

A Casual But High-Stakes Affair

Over the course of the three days, participants alternated between meeting in their separate groups and massing for presentations and question-and-answer sessions.

Clad in shorts and tee shirts, and continuously consuming high-carbohydrate snacks and soft drinks, participants spent much of their group sessions staring intensely at their laptop screens, occasionally breaking their concentration to ask other group members about a particular sequence alignment or how a particular piece of data was derived.

Words like "transfrags," "cagetags," "ditags," "gerps," "targs," "bincons," and "phastcons" were the major lexicon, and "USB thumb drives" were the major currency.

Although the typical 16-hour days at the workshop were grueling for many participants, most said it was well worth the sacrifice because they were getting the opportunity to work side-by-side with collaborators they had never before met in person. Many also said that the stakes were too high not to be involved firsthand in the proceedings.

Garry Cutting, professor of pediatrics at the Johns Hopkins University School of Medicine in Baltimore, for instance, was thinking about his cystic fibrosis (CF) patients when he emphasized the need to understand better the genetic regulation of the CF gene, which resides in one of the ENCODE target regions.

"Even though the cystic fibrosis gene was discovered 16 years ago," Cutting said to his workshop colleagues, "we still do not understand what sequence elements regulate its expression. If we did, we might be able to use those elements in designing treatments for patients."

He noted that although many mutations have been identified, "we also have patients whose mutations have escaped detection. Their mutations must exist somewhere other than where we are looking."

In the realm of his particular primary interest, then, he expects that ongoing gatherings will yield nothing less than "discovering the location of all the elements that regulate transcription of the CF gene."

The Wave of the Future

Workshop organizers were similarly optimistic at the conclusion of what was considered a quite productive experience, agreeing that collaborations and large-group interactions are the wave of the future in genomics research.

"The human genome is so complex that its full interpretation will require the hard work of large, diverse teams of energetic investigators. This just can't be done by isolated groups any longer," observed Elise Feingold, NHGRI extramural program director and co-coordinator of ENCODE.

"We see this as only the beginning of an extraordinarily important set of collaborations—I am tingling with excitement about all of the positive outcomes of this meeting," Birney said. Collins agreed that there would be much to expand upon for years to come "when all the dust from this workshop settles."

For more information about the ENCODE project, see **<genome.gov/ENCODE>**.

Stopgap Prohibitions Eased in Final NIH Ethics Rules; Ban on Outside Consulting for Industry Unchanged

by Fran Pollner

Final conflict-of-interest (COI) rules for NIH employees took effect August 31, 2005, well within the one-year time limit for re-evaluation set in the interim final rules issued in early February.

The final rules recast the stopgap prohibitions related to financial interests in pharmaceutical and biotech companies and other "substantially affected organizations" (SAOs) such that automatic divestiture is required only of senior-level NIH employees—approximately 200 NIH employees (see the summary of the rules, page 5).

They also maintain the blanket ban on outside consulting and other activities with SAOs, NIH-supported research institutions, and health-care providers and insurers. But they restore—with prior approval—the ability of NIH scientists to pursue those intellectual interactions and other activities with professional scientific organizations that are generally deemed to be crucial to advancing biomedical research and the NIH public health mission.

On August 25, NIH Director Elias Zerhouni announced the imminent release of the final rules, first in an e-mail to the NIH community and two hours later in a press telebriefing, which was attended by reporters from major daily newspapers and scientific publications.

The final rules, he said, achieve the "right balance [in] protecting the agency's integrity without imposing burdens" on NIH scientists. The proscriptions in the interim final rules were "too broad," he said, noting, however, that "the ban on outside consulting with industry will remain in force." He did not rule out revisiting the consulting issue should more sophisticated safeguards against the actual and perceived risks of such connections be developed.

HHS and the Office of Government Ethics, in consultation with NIH leadership, considered more than 1,300 comments from NIH scientists and others in crafting final regulations that would

- Protect the integrity of NIH science
- Maintain the public's trust that NIH science is untainted by conflicts of interest
- Not impose unfair and unnecessary hardships on NIH scientists and other employees
- Not jeopardize NIH's ability to recruit and retain the best scientific minds or, consequently, the NIH public health mission.

Many of the revisions embraced in the final rules reflect the criticisms and cautionary concerns emanating from the NIH community regarding the interim final rules (see *The NIH Catalyst,* Special Reference Issue, February 22, 2005).

Linking divestiture of financial holdings in SAOs to the level of decision-making responsibility and removing "impediments to normal academic interactions" were oft-voiced suggestions with which NIH leadership agreed.

Zerhouni observed that 12,000 of the 18,000 NIH employees are now relieved of blanket disclosure requirements but must still be alert to a potential conflict arising from a new responsibility or a new acquisition.

In addition to the reporting and divestiture rules that apply to the 200 or so senior employees, about 6,000 NIHers will be required to report their financial holdings in SAOs. This cohort includes individuals who file either confidential or public financial disclosure reports and also clinical investigators involved in IRB-approved NIH clinical research protocols.

Zerhouni emphasized the wisdom of the case-by-case approach to recognizing and managing potential conflict of

interest among these 6,000, as opposed to the broad-brush divestiture requirements in the interim final rule.

Asked whether the rules were subject to further revisions, Zerhouni responded that though these rules are final, "we are always reviewing; the issues are always evolving." ■

Note: The deadline for public and confidential filers and clinical investigators to report their holdings in SAOs is October 31, 2005.

The deadline for divestiture for senior employees is January 30, 2006.

The rules and a lengthy explanatory preamble appear in the August 31, 2005, edition of the *Federal Register* and can be viewed at **<http://www.nih.gov/about/ethics/08252005supplementalfinancialdisclosure.pdf>**.

Assembly of Scientists Welcomes Revisions in Rules

The NIH Assembly of Scientists (AOS), which had issued a statement quite critical of the interim final rules (see *The NIH Catalyst,* Special Reference Edition, February 22, 2005), registered its satisfaction with the modified regulations, "especially [those] easing the restrictions on interactions and holding leadership positions with professional societies."

In a statement issued after the NIH director's announcement, the organization also applauded the lifting—"for all but the most senior NIH employees"—of the requirement to "divest financial holdings in medical or pharmaceutical companies by employees and their families when no conflict of interest exists with their professional duties at the NIH."

"We are gratified that, as the preamble to the regulations notes, the revisions proposed by the AOS, and NIH scientists more generally, were influential in shaping these regulations," the group stated.

The AOS anticipates collaborating with NIH leadership in implementing the regulations "in a way that minimizes the paperwork burden on scientists"—and in any future process to revisit the "blanket prohibitions on consulting and almost all other outside activities with medical and pharmaceutical companies." It also intends to work with NIH leadership in "addressing the other major challenges that affect morale of NIH employees."

AOS To Hold Elections

The current Interim Executive Committee of the NIH Assembly of Scientists will be replaced by a more formal AOS Council to be elected in October of 2005.

Twelve of the 24 seats on the Council will be up for election this year, and the other 12 in the fall of 2006; each member will serve a two-year term. The members will represent at least 12 different Institutes and Centers and will include at least one tenure-track Investigator, at least one staff clinician, and at least one staff scientist. The Council will select six of its members to also serve a one-year term on the Assembly's Executive Committee.

To nominate oneself or a colleague for election in October to a seat on the AOS Council, e-mail Cynthia Dunbar at **<dunbarc@nhlbi.nih.gov>**.

No one will be placed on the ballot without his or her consent. ■

Conflict-of-Interest Regulations For NIH Employees Finalized

by Celia Hooper

In an electronic memo to all NIH employees August 25, NIH Director Elias Zerhouni announced the release of final regulations governing conflict-of-interest (COI) for NIH empoyees, including stock ownership (and other financial interests), outside consulting (and other outside activities), and acceptance of gifts associated with awards.

Highlighted below are some of the most significant changes from the interim final rules issued in February 2005 (see *The NIH Catalyst*, Special Reference Edition, February 22, 2005).

Additional COI information can be found at the NIH Ethics website and includes a summary of the final regulations **<http://www.nih.gov/about/ethics/summary_amendments_08252005.htm>** and a Q & A for NIH employees **<http://www.nih.gov/about/ethics/<QandA_for_employees_08252005.htm>**.

The Changes

The following is adapted from the DDIR Bulletin Board, August 2005.

Divestiture of Financial Interests in Substantially Affected Organizations: The interim final rules called for some 6,000 NIHers, their spouses, and minor children—staff who file disclosure forms—to divest all stocks in pharmaceutical, biotech, medical device, and other companies interested in or affected by the work of by NIH, known technically as "substantially affected organizations," or SAOs. All other NIH staff had to divest these stocks if their holdings in any one such company were in excess of $15,000, which is also the government-wide "de minimis" standard.

The new rule requires only that about 200 of the most senior NIH leaders (IC directors, their deputies, scientific directors, clinical directors, extramural staff who report directly to an IC director, and the NIH director and those who report directly to him) or the NIH director)—and their spouses and minor children— divest their aggregate SAO holdings down to (and maintain them at or below) the "de minimis" $15,000 for any one company. Also, those same employees may hold a total of $50,000 in pharmaceutical, biotechnology, and healthcare-related sector funds.

The roughly 6,000 staff members who are not "senior" but who file confidential or public disclosure forms, and also those investigators who do not file either disclosure report but who are listed on clinical protocols, will be required to report the amount of each of their SAO holdings, but divestiture will only be required when this is the appropriate way to manage a conflict between a holding and what the employee does in his or her job.

Accepting Prizes: Awards offered to senior employees will be considered under the same standard applied to all other employees since the interim rule. That is, all employees may be approved to accept both bona fide awards and associated gifts provided that the group awarding the prize cannot be affected by the employee's duties or those of his or her subordinates. The NIH Ethics Office maintains a growing list of bona fide awards posted at **<http://ethics.od.nih.gov/topics/awards-list.htm>**.

Each nomination for a prize must be reviewed and approved to assure that the group awarding the prize is not affected by the duties of the prize recipient or his or her subordinates.

Outside Activities: As before, outside activities such as consulting for SAOs, grantees, and contractors and health-care providers and insurers are prohibited. Significantly, however, outside activities with professional organizations can now be allowed with prior approval. This change would permit NIH scientists to serve as an officer or board member for a professional society.

Activities unrelated to NIH's mission, such as hobbies, arts, sports, manual labor, child care, and secretarial work, even if compensated, are allowed, and do not need to be pre-approved unless the work is for a prohibited source, such as a pharmaceutical company or grantee.

Of course, longstanding rules precluding outside activities that conflict with duties or misuse of official time and other resources continue to apply, as do special provisions surrounding religious and political activities.

Other changes in the rules permit giving a single general lecture in a regularly scheduled university course (as well as multiple lectures) or a Grand Rounds lecture, even at a grantee institution. These activities must be approved in advance.

Compensation for teaching, speaking, or writing may be allowed if the subject matter is within one's area of expertise but not the subject of one's current research or recent work and is approved in advance, and if any funds from SAOs (or supported research institutions or health-care providers or insurers) to support these activities are unrestricted.

The rules also allow compensated outside service on a non-NIH scientific review committee or data and safety monitoring board, as long as an SAO, such as a pharmaceutical or biotech company, does not select or pay the board members and the program is not NIH- or HHS-funded.

Outside medical practice is still allowed, as is writing or editing for peer-reviewed journals or textbooks, again subject to prior approval, and provided any SAO financial contribution is unrestricted.

Official Duties: As always, there is a wide range of activities that may be allowed within the scope of one's official duties, with permission in advance from one's supervisor. ■

Nanotechnology Seminar Series

Ruth Duncan, professor of cell biology and drug delivery and director of the Centre for Polymer Therapeutics, Welsh School of Pharmacy, Cardiff University, Wales, will present the next lecture in NCI Nanotechnology Seminar Series, Tuesday, **September 27, 2005**, 3:00–4:00 p.m., in the Natcher Conference Center, Room E1/E2. The event will be webcast at **<http://videocast.nih.gov>**. For more information, visit **<http://nano.cancer.gov>**.

NIH Research Festival
October 18–21:
<http://researchfestival.nih.gov>

Very Interesting

Inadvertently omitted from the Interest Group Directory in the July-August *Catalyst.*

Neural Cell Function Interest Group
Meeting time: 3rd Friday, 2:30 p.m.
Meeting place: Building 49, Room 1A51A/B
Contact 1: Lee Eiden
Phone: 301-496-4110
E-mail: <eidenl@mail.nih.gov>
Contact 2: Harold Gainer
Phone: 301-496-6719
E-mail: <gainerh@ninds.nih.gov>
http://tango01.cit.nih.gov/sig/home.taf?_function=main&SIGInfo_SIGID=142

The Calm after the Storm

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ference room in the Hatfield Clinical Research Center into a calming yoga studio, Berg volunteers her time to teach people how to use yoga to focus on their minds and bodies—their selves—instead of worrying about treatment schedules, homesickness, and other elements beyond their control. Her class is among the activities made available by the Recreational Therapy service of the CC Department of Rehabilitation Medicine.

"The patients and families who come to my class are under a lot of stress. Maybe they're a parent of a child with cancer or the brother of someone with a spinal cord injury; almost none have had yoga, but they hear that it's stress reducing," says Berg. "Yoga is not going to cure them, but it will give them another tool for coping with disease in themselves or their family."

Accessible

The average in-patient stay in the Clinical Center is seven to eight days. Berg doesn't often see patients more than once, but their reaction is nearly always the same. They come to her class claiming they're not flexible enough to do yoga, and leave proclaiming they haven't been so relaxed since coming to NIH. Often, they ask Berg where they can find a yoga instructor when they go home.

One secret to Berg's success is that she makes her class accessible to everyone. At the beginning of each class, she asks each person if they have any health problems or physical limitations. She then picks yoga exercises based on the individual needs of her students. She provides props like blocks and straps for those who need additional support to get into some of the poses.

While there is little risk involved in yoga, people with certain medical conditions, such as detached retinas or high blood pressure, should not attempt certain yoga poses. Headstand, Berg observes, would not be wise for people who get migraine headaches. She cautions that anyone with a health condition should consult with his or her doctor before trying yoga.

"The class is safe for almost everyone because we can work around any physical issues," Berg says, adding that her students have ranged from age 9 to age 80-plus.

George Patrick, recreational therapy chief, is among Berg's fans, often taking part in her yoga sessions. "Kate has a good calmness about her and she figured out that she needs to keep it simple. When patients are there, she's very attentive to their [physical] needs and makes it easy enough for them to succeed," he says.

Different Kinds of Therapy

The yoga class is just one of many recreational therapies offered to CC patients and their families. Recreational therapists run programs to assist patients in adjusting to their disease, treatment, and hospitalization. Patients often have symptoms of boredom, depression, and anxiety.

Based on a patient's individual needs, recreational therapists recommend they participate in activities, such as arts and crafts, music therapy, animal-assisted therapy, Tai Chi, or personal fitness.

According to Patrick, the classes are open to NIH staff as well as patients and their families. "The more the merrier. It really helps our patients to be part of a group. We have a few volunteers who teach classes and we encourage our own staff to participate as well so that patients know they are just ordinary people."

The names of the patients who attend the yoga class are given to their assigned recreational therapist, who can then follow up with the patient to see how the session went and to record the benefits they got from doing yoga.

Patrick says it is also a chance to encourage patients to continue an activity that is relaxing, peaceful, and focus driven.

"Yoga is really beneficial for rehabilitation by promoting posture, flexibility, and range of motion," says Patrick. "The key is getting patients to focus on taking care of themselves, and not thinking about anything else for at least 60 minutes, practicing a series of exercises to make them aware of right-to-left differences in their bodies. The body needs to be flexible; otherwise you're more prone to injury and falls."

Without calling yoga a cure-all, Patrick sees it as a healing practice that has particularly beneficial effects on illness-related secondary symptoms, regardless of what the primary diagnosis is. Improved mood—related to reduced pain, tension, headache, or fatigue—is perhaps the most clearly observable effect for many patients.

Lessons from Patients

Berg has many stories about the patients she's worked with and what they've been able to teach her. For ex-

ample, about a year ago, she had a patient with very limited physical mobility who had taken yoga classes regularly and was glad to have a chance to continue them at NIH. She showed Berg some adaptations to the shoulder stand and bridge poses that were so effective that Berg now teaches them to all her students, whether or not they have limited mobility. "I think of her every time I do either of those poses," Berg says.

Another time, two cancer patients under treatment at the Clinical Center joined the class at the same time. The woman was wearing a wig; the man, a hat. As soon as they got into the class, they pulled off their head coverings. The woman, completely bald, was exquisitely beautiful—much more so without the wig, according to Berg. She had done yoga before her illness, and Berg watched over the weeks as she gained back her strength and was able to go deeper into the poses.

The man was very ill. He could only sit quietly and breathe with difficulty, but he stayed in the class until it ended and came back several more times. What particularly touched Berg was that each time these patients came they removed their head coverings for class and then carefully put them back on before leaving. They clearly felt comfortable in the class.

Perhaps what makes people feel most welcome is Berg's gentle reminder at the start of each class that "it's not a competition"—everyone has options, and no one needs to do every pose.

The Path to Yoga's Paths

Berg's affinity for yoga dates back to her childhood. Before she'd even heard of yoga, she'd naturally assume yoga-like poses, such as sitting with her legs folded in the lotus position or reading lying on her back in a supported shoulder stand. Berg began actively studying yoga while in college, and about 10 years ago, she started practicing it every day and reading yoga texts.

Eventually, she spent a yearlong apprenticeship under a yoga instructor so she could teach yoga to others.

Berg is trained in a style of yoga called "Sivananda," which includes meditation, yoga poses called "asanas," and breathing exercises called "pranayama." It is named after Swami Sivananda, a yoga master from India who lived from 1887 to 1963 and whose teachings have influenced practitioners of yoga all over the world.

Sivananda teaches four paths of yoga, one known as "karma" yoga. Karma yoga is the practice of selflessness, without thoughts of gaining something in return. It is this path of yoga that led Berg to volunteer to teach the yoga class at the Clinical Center.

She has dubbed her particular brand of yoga instruction there a "Sivananda hybrid," a modification of classic Sivananda that avoids certain poses that might be too taxing and is especially careful to accommodate limitations.

At the end of this year, Berg will retire from NIH and will no longer teach the yoga class at the Clinical Center. However, she will continue to offer classes at the yoga studio she has created in her Silver Spring home and plans on doing some writing about the health aspects of yoga and meditation.

She and Patrick are looking around for someone to replace her at the CC yoga "studio." Berg feels she will be leaving the next instructor a gift.

"I get so much out of [teaching this yoga class]," says Berg, "so much satisfaction." ■

—Photos by Maggie Bartlett

Hispanic Heritage

As part of the 2005 Hispanic Heritage Month Celebrations—and in honor of the 10-year anniversary of the NIH Hispanic Employee Organization—the NIH-HEO is sponsoring three fall events.

- **Health disparities panel discussion** (HIV/AIDS, diabetes, public health, obesity), **September 21**, 9:00–10:30 a.m., Lipsett Auditorium, Building 10
- **WALS Lecture** on reducing disparities through health services research, **October 5**, 3:00 p.m., Masur Auditorium, Building 10
- The **Sixth NIH Hispanic Scientist Day**, Wednesday, **October 12,** 1:30-4:30 p.m., Lipsett Auditorium (keynote on "AIDS vs. Cancer, Antiretrovirals and Their Consequences," other talks, poster session, and reception)

For more information, contact Maria Hessie at 301-435-1680 or 301-496-3981. ■

NIH History Day

The third annual **NIH History Day** will be held Thursday, **September 22**, beginning at 11:00 a.m. in the Lipsett Amphitheater, Building 10, and will feature NIH historian Victoria Harden, director of the Office of NIH History, speaking on "An Indescribable Experience: NIH Researchers and the AIDS Epidemic, 1981–1990."

Harden is hoping that all the intramural investigators involved in AIDS research at the time will be the audience—to stand and be recognized (and photographed for the archives).

NIAID Director Anthony Fauci and Michael Gottesman, deputy director for intramural research, will deliver welcoming remarks.

Two panels from the now-historic AIDS Memorial Quilt will be displayed.

Harden has co-edited two AIDS history books—*AIDS and the Historian* (NIH, 1989) and *AIDS and the Public Debate: Historical and Contemporary Perspectives* (OS Press, 1995).

For more info, visit **<http://history.nih.gov/NIH_HistoryDay05.html>**.

If It's August, It Must Be Poster Day

by Karen Ross

For one day each August, NIH summer trainees—who run the gamut in educational level from high school through postgraduate schools—fill large common areas of the Clinical Center with hundreds of posters that tell the stories of the research they have been conducting with their NIH preceptors. For many, this research experience marks the beginning of a lifelong pursuit.

Macular Degeneration and a Two-Faced Immune System

Vanessa Montalvo, Howard University, Washington, D.C.
Immune Mediators' Involvement in Retinal Damage: the Good and the Bad
Preceptor: Igal Gery, Laboratory of Immunology, NEI

Age-related macular degeneration (AMD) is the leading cause of blindness in Americans over the age of 55. People with AMD suffer from blind spots and distorted vision due to deterioration of the central part of the retina.

Although the cause of AMD is not known, one possibility is that decades of minor assaults on the retina from inflammation and light exposure may eventually cause the permanent damage characteristic of AMD.

Montalvo and her colleagues are investigating how the immune system both protects the retina from the types of injuries that may presage AMD ("the good immune system") and, conversely, contributes to these injuries ("the bad immune system").

CCL2, a chemical that recruits immune cells known as macrophages, also provides protection against cytotoxic processes and appears to belong in the "good" column.

Karen Ross

Vanessa Montalvo

Montalvo and her co-workers exposed normal mice and mice lacking the *CCL2* gene to intense light and looked at the effect on their retinas. Normal retinas tolerated the light exposure to some degree, but in the retinas that lacked CCL2, the photoreceptor cells were almost completely obliterated.

On the other hand, C3, a member of the complement cascade, which is normally responsible for attacking and destroying invading bacteria and viruses, may have a negative effect on the retina.

Montalvo found C3 in retinas that were inflamed due to the transgenic expression of the immune molecule IL-7 and in retinas that were exposed to intense light.

Normal, undamaged retinas did not contain any C3.

Experiments to determine whether C3 is recruited to the retina after other kinds of damage are under way.

—Karen Ross

More Insights on AMD

A new discovery that has excited us all has established the major role of complement in AMD. The discovery, published in three different papers in a Science *issue (Volume 308, Issue 5720, April 15, 2005), is that an unusually strong correlation exists between AMD occurrence and a polymorphic variant of the gene for complement factor H (CFH).*

The function of CFH is to block the activation of complement, and individuals who carry this variant have low CFH activity and, as a result, high levels of complement activation.

In addition, it has been known for several years that complement deposition is a common finding in retinas of AMD patients. Activated complement components initiate pathological processes, including recruitment of inflammatory cells and neovascularization, the major problem in AMD. It is assumed, therefore, that complement activation and deposition in the retina plays a major pathogenic role in AMD.

Montalvo's study in mice is aimed at examining the possible deposition of complement in retinas damaged by various mechanisms.

So far, she has tested eyes damaged by light and inflammation induced by transgenic expression of IL-7. The deposition was found to be particularly intense in the IL-7 transgenic eyes.

Deposition of activated components of complement (including C3) is commonly seen in inflammation sites and is an integral part of the inflammation process because these deposited molecules further enhance the pathological process, mainly by recruitment of inflammatory cells.

Clinical implications of Montalvo's research are expected to become more apparent when she tests eyes of mice that serve as "animal models" for AMD. We hope, therefore, that her study will shed new light on the process of complement deposition and its pathogenic role in AMD.

It is of interest that a recent study, by the group of Michael Gorin at the University of Pittsburgh (in press, Am. J. Hum. Gen.*), discovered that AMD is also strongly related to variants at three genes, all on chromosome 10q26.*

One of these genes, PLEKHA1*, encodes the protein TAPP1, an activator of lymphocytes. These new data thus re-emphasize the suspected role of the immune response in the pathogenesis of AMD.*

Research by Montalvo and her coworkers will be expanded to investigate the involvement of TAPP1 and related molecules in experimental models of retinal degeneration.

—Igal Gery and Chi-Chao Chan
Laboratory of Immunology, NEI

Body Mass Index: Different Things to Different People

Brenda Davis, Bethune-Cookman College, Daytona Beach, Fla.
Body Mass Index is a Superior Marker of Obesity in Women than Men
Preceptor: Anne Sumner, Clinical Endocrinology Branch, NIDDK

Obesity is a contributing factor in a host of serious diseases, including heart disease and diabetes, and its prevalence is high and increasing.

Approximately 30 percent of Americans are classified as obese because they have a body mass index (BMI) greater than 30. BMI is calculated by dividing a person's weight in kilograms by the square of his or her height in meters.

Currently, the same BMI standards are used to diagnose obesity in both men and women.

Davis' research suggests, however, that women tolerate high BMI significantly better than men, suggesting that BMI, at least in its present formulation, may not be an adequate tool for predicting obesity-related disease.

Karen Ross

Brenda Davis

Davis and her colleagues measured BMI and glucose intolerance, a marker of impending diabetes, in 141 African Americans—66 men and 75 women.

The BMI at which 50 percent of the subjects were glucose intolerant was 30 kg/m^2 for the men and 40 kg/m^2 for the women.

These results were especially surprising because, at any given BMI, men generally have a lower percentage of body fat than women, the team noted.

The group is now looking into the reasons why women seem to be less susceptible to the ill effects of obesity.

Davis, who will be a junior at Bethune-Cookman College in Daytona Beach, Florida, in the fall, commented that the study was particularly interesting to her because there are people in her family who have diabetes. "Now I have more insight into something that could affect me," she said.

—Karen Ross

The Mitochondrial Connection in Insulin Resistance

Benjamin Mantell, Brown University, Providence, R.I.
Restoring Mitochondrial Integrity in the Insulin-Resistant State
Preceptors: Michael Sack, Ines Pagel, Cardiovascular Branch, NHLBI

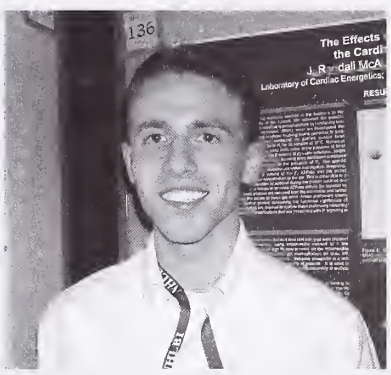
Several lines of evidence suggest that mitochondrial dysfunction may be an important part of the pathology of type 2 diabetes.

First, total aerobic capacity, which measures how efficiently mitochondria use oxygen, is typically poor in people with diabetes.

Second, genes involved in the formation and function of mitochondria are downregulated at an early stage in the development of diabetes.

Third, a family of drugs used to treat diabetes—glitazones—may work by stimulating mitochondrial function.

Using mouse skeletal muscle cells as a model system, Mantell further explored the link between mitochondria and diabetes.



Karen Ross

Benjamin Mantell

Feeding the muscle cells high levels of glucose causes them to become insulin resistant, one of the hallmarks of type 2 diabetes.

Insulin-resistant cells fail to appropriately adjust their metabolism in response to insulin.

Mantell found that the insulin-resistant cells had smaller-than-normal mitochondria, decreased oxygen consumption, and decreased expression of genes encoding mitochondrial proteins.

Treating the cells with one of the glitazones partially restored insulin sensitivity and corrected the mitochondrial defects.

Glitazones increase the activity of PPAR-γ, a transcription factor that is important for the expression of mitochondrial genes. Therefore, Mantell next wants to deplete PPAR-γ in cells.

He predicts that these cells will become insulin resistant and that glitazones will no longer be an effective treatment.

Mantell observed that because normal heart muscle cells are chockfull of mitochondria, defects in mitochondria could contribute to the poor prognosis for diabetic patients with heart disease.

—Karen Ross

People

Recently Tenured

Peter Bandettini *received his B.S. in physics from Marquette University in Milwaukee in 1989 and his Ph.D. from the Medical College of Wisconsin in Milwaukee in 1994. There, he contributed to the early development of functional MRI (fMRI). After postdoctoral training at the Massachusetts General Hospital, Boston, from 1994 to 1996 and then serving as an assistant professor of biophysics at the Medical College of Wisconsin, he joined NIMH in 1999 as an investigator in the Laboratory of Brain and Cognition and as the director of the NIH fMRI core facility. Chief of the Section on Functional Imaging Methods, he is also president of the Organization for Human Brain Mapping.*

fMRI is a technique that rapidly captures time series images of changes in blood flow, oxygenation, and volume induced by local brain activation. Applications of fMRI are growing rapidly. These range from basic neuroscience to assessment and comparison of clinical populations and presurgical mapping.

Peter Bandettini

Although the technique is widely used and is acknowledged to have high potential impact across neuroscience and medicine, it also has major, but solvable, shortcomings. These include:

- The ambiguous and variable relationship between neuronal activity and measured hemodynamic-based signal changes
- Inability to cleanly map transient activity on the order of milliseconds
- Lack of a means to map slow "state" changes
- Difficulty distinguishing inhibition from excitation
- Inability to draw inferences about individual activation maps as they relate to averaged population brain activation maps

My research, including technology, methodology, interpretation, and research at the interface of applications and development, is aimed at addressing these and other issues in fMRI.

My research group, the Section on Functional Imaging Methods, is a team of physicists, psychologists, engineers, neuroscientists, and computer scientists committed to developing fMRI to its full potential through interrelated advancements in fMRI.

My research has four primary themes. The first is to understand more fully the relationship between measured MRI signal changes and underlying neuronal activity. My main approach to this is the use of multimodal (MEG and EEG) brain activation assessment comparisons, as well as pulse sequence manipulations that allow differential sensitivity to vascular components.

The second theme is to develop methods for increasing spatial and temporal resolution of fMRI through hardware and methodological development. We are collaboratively developing high-sensitivity coils and high-resolution imaging techniques as well as calibration methods that enable us to characterize more fully the hemodynamic response through which fMRI "sees" brain processes.

The third theme is to develop methods for cleanly extracting more subtle spatial and temporal information from the fMRI time series. It has become increasingly evident that the fMRI time series contain significantly more information about brain connectivity and resting-state activity than was previously thought.

What is required—and what my group is working on—are pulse sequence and processing methods to distinguish more robustly the artifacts of physiologic fluctuations from real brain activation fluctuations over space and time.

The fourth theme is to explore new types of functional contrast with fMRI. I am currently working on MRI methods for direct detection and mapping of neuronal activity, bypassing hemodynamic contrast altogether. We have obtained evidence—from in vitro cell cultures and through modeling of neuronal currents in the context of MRI—that NMR signal changes associated with microscopic magnetic field changes from coherent neuronal activity are detectable.

Orna Cohen-Fix *received her Ph.D. in 1994 from the Weizmann Institute in Rehovot, Israel, and did postdoctoral work at the Carnegie Institution in Baltimore. She joined NIH in 1998 as a tenure-track investigator in the Laboratory of Molecular and Cellular Biology, NIDDK, and is currently a senior investigator in that lab.*

Ever since I was a kid I wanted to be a scientist. On weekends my father, who is a microbiologist, would take me to his lab and let me transfer water with a pipet from one test tube to another. We called it an experiment, and I thought science was amazing.

These days my experiments are somewhat more sophisticated, but the fascination remains the same. My lab studies cell-cycle regulation and nuclear architecture in budding yeast.

You'd be hard-pressed to find a yeast researcher who is not infatuated by this model system. With it, one can use a myriad of experimental approaches (for example, genetics, biochemistry, genomics, proteomics, cytology) to examine the biological question at hand. The yeast life cycle is very rapid, it can be manipulated easily, and most processes are evolutionarily conserved, making yeast highly suitable for cell-cycle studies. Sometimes I feel that as yeast researchers, we are limited only by our collective imagination.

I did my graduate thesis on the mechanism of ultraviolet mutagenesis in *Escherichia coli*, at the Weizmann Institute of Science under the guidance of Zvi Livneh. It was largely a biochemistry project, but during that time I took the "Advanced Bacterial Genetics" course at Cold Spring Harbor Laboratories (CSHL) in Cold Spring Harbor, N.Y. As a graduate student, I didn't practice much of what I'd learned in the course, but I was still struck by the remarkable power of a genetic approach. Thus, turning to yeast for my postdoctoral training was a logical choice.

In 1994, I started my postdoc in Doug Koshland's lab at the Carnegie Institution in Baltimore. As part of my research project, I characterized a mitotic inhibitor that plays a key role in ensuring accurate mitotic progression. This inhibitor, called Pds1 in yeast, or securin in higher eukaryotes, binds to a protease called separase, whose activity is necessary for the separation of duplicated chromosomes at the onset of anaphase.

As a postdoc I found that anaphase initiation is brought about by the degradation of Pds1, and that Pds1 is part of a regulatory mechanism—the DNA damage checkpoint pathway—that inhibits mitotic progression in the presence of DNA damage. These studies set the stage for the current research in my lab.

In the Laboratory of Molecular and

Cellular Biology, NIDDK, we used Pds1 as a launching pad to explore various processes related to mitosis. Pds1 is at the epicenter of the metaphase-to-anaphase transition.

This transition is irreversible, and cells pay dearly for any mistakes that occur during this process.

Orna Cohen-Fix

Thus, multiple regulatory pathways converge on the metaphase-to-anaphase transition, and on Pds1 in particular, to ensure that chromosome segregation takes place in an accurate fashion.

With Pds1 as a starting point, we began studying some of these regulatory pathways. We elucidated the molecular mechanism by which Pds1 is targeted for degradation at the onset of anaphase. We learned how the nuclear import of separase is regulated by Pds1. We discovered new aspects of the DNA damage checkpoint pathway. We uncovered a novel mechanism that affects nuclear positioning during mitosis.

Through various genetic screens, we identified novel proteins that affect mitotic regulation, and these have now become research subjects in their own right.

More recently we began studying the underlying proteins and structures that affect yeast nuclear architecture. The yeast nucleus is different from its metazoan counterpart in two important ways: (1) There are no nuclear lamins in yeast, and (2) the yeast nuclear envelope does not break down during mitosis.

Nonetheless, intranuclear organization affects fundamental processes, such as DNA replication and transcription, in both yeast and higher eukaryotes. We reasoned that this genetically amenable model organism would yield important insights into nuclear organization in human cells.

This project is at an early stage, but we have already identified domains in the nuclear envelope that differ in their susceptibility to expansion in the presence of elevated phospholipid levels.

An important part of being a scientist is the involvement in activities that affect the scientific community at large. Shortly after I joined the NIH I began teaching the CSHL Yeast Genetics course, a three-week-long intense course that is taught, coincidently, in the same lab as the Bacterial Genetics course I took as a student.

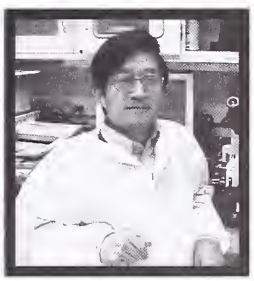
The decision to teach the course was a difficult one, because as a starting tenure-track investigator I feared that being away from the lab for an extended period of time would harm the progress of my own projects, as well as that of my postdocs.

As it turns out, teaching the course was one of the best things I did as a starting scientist, because I had the opportunity to interact closely with dozens of scientists who either participated in the course as students or were invited to the course to give informal seminars.

It was also a humbling experience: Not only did my NIH lab not fall apart in my absence, but also my postdocs discovered that they were fully capable of making important decisions on their own.

By being in constant contact with the outside world, one increases the chances of stumbling across an interesting piece of information. If there's one thing I learned from teaching the yeast genetics course and other such activities, it is that one never knows what will stimulate the next exciting idea. And the way I see it, having exciting ideas is what being a scientist is all about.

Bin Gao *received his M.D. and Ph.D. from the Wanna Medical College, Wuhu, and the Norman Bethune University of Medical Science, Changchun, China, in 1986 and 1991, respectively. After postdoctoral training at NIH and the Medical College of Virginia (MCV) in Richmond, he became an assistant professor at MCV in 1996. In 2000, he joined the Laboratory of Physiologic Studies at NIAAA. He is now a senior investigator and chief of the Section on Liver Biology.*



Bin Gao

The primary interests of my laboratory are the molecular pathogenesis of liver diseases and their immunology. In particular, the lab is focused on the study of signal transducers of activators of transcription (STATs) and their roles in liver injury and repair.

Using animal models in examining liver injury, we demonstrated that (1) STAT1, primarily activated by interferons (IFNs), plays a critical role in liver injury and inflammation in T cell–mediated hepatitis and endotoxin-induced liver injury, and that (2) STAT1 is also involved in TLR3 ligand/IFN-γ–mediated suppression of liver regeneration.

In the presence of cellular damage, the liver initiates processes to repair itself. Our lab found that, in contrast to STAT1, STAT3 activated by IL-6 and IL-22 in the liver is an active factor in liver repair. Among our findings were that:

- IL-6–deficient mice were more susceptible to ethanol-induced liver injury. They were also more susceptible to concanavalin A–induced T cell hepatitis, which was prevented by IL-6 treatment.
- In vivo IL-6 administration ameliorated alcoholic and nonalcoholic fatty liver and ethanol-induced liver injury.
- In vitro IL-6 treatment prevented mortality associated with alcoholic and nonalcoholic fatty liver transplants.

Collectively, these findings suggest that IL-6 possesses therapeutic potential for treating alcoholic liver disease and fatty liver transplantation. In fact, we think in vitro application of IL-6 could significantly transform the success rate of liver transplantation.

Investigations into the cellular and molecular mechanisms underlying the hepatoprotective effect of IL-6 in the liver have identified multiple mechanisms.

Our findings show that IL-6 activation of STAT3 can induce anti-apoptotic genes, improve hepatic microcirculation, inhibit NKT cells, inhibit oxidative stress, and ameliorate the accumulation of fatty deposits—powers that combine to prevent further cellular damage and repair existing injuries.

Other studies conducted in our lab show that the T cell–derived cytokine IL-22 is also a survival factor for hepatocytes and plays a protective role in T cell–mediated hepatitis via activation of STAT3.

While investigating the effects of alcohol consumption on STAT1 and STAT3 activation, we found that acute and chronic ethanol consumption attenuates both STAT1 and STAT3 activation, which could be an important mechanism contributing to the pathogenesis of alcoholic liver disease.

So far, our findings suggest that STAT1 and STAT3 play opposite roles in liver

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injury and repair. Interestingly, STAT1 and STAT3 also negatively regulate one another through the induction of SOCS (suppressors of cytokine signaling) proteins in the liver.

Because both STAT1 and STAT3 are activated in chronic liver diseases, modulation of the mutual antagonism between STAT1 and STAT3 could offer a novel approach in the treatment of T cell–mediated liver damage in human liver disease.

Related findings from our studies include a determination that ethanol and hepatitis viral proteins synergistically (or additively) produce hepatocyte damage and stimulate inflammatory signals, and that alcohol drinking accelerates concanavalin A–induced T cell hepatitis via dysregulation of NF-κB and STAT3 signaling pathways.

More recently, we also demonstrated that natural killer cells ameliorate liver fibrosis through elimination of activated stellate cells in NKG2D/RAE1- and TRAIL-dependent manners, and IFN-γ/STAT1 plays an important role in the activation of natural killer cells.

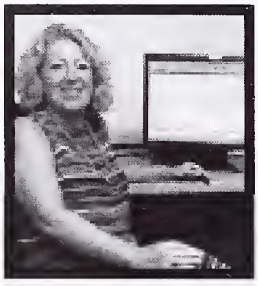
Marilyn Huestis *received her Ph.D. in toxicology in 1992 from the University of Maryland at Baltimore (UMAB) School of Medicine and joined NIDA in 1995 in the Clinical Pharmacology and Therapeutic Research Branch—with more than 20 years of experience in analytical and forensic toxicology. In 1998, she was converted to tenure-track and selected as acting chief of the Chemistry and Drug Metabolism Section. Currently, she is chief of this section and conducts her research at the NIDA facility in Baltimore. She also directs clinical research of toxicology doctoral students from UMAB School of Medicine.*

My clinical research program uses chemical and toxicological tools to address drug abuse and addiction. My work focuses on mechanisms of drug action and pathological consequences of human drug exposure.

One area of focus is illicit drug use by pregnant women and the resulting toxicity to their children. Fetuses exposed in utero to excessive amounts of alcohol may suffer from fetal alcohol syndrome. In a similar manner, we believe that fetuses exposed in utero to excessive licit and illicit drugs may experience fetal drug syndromes.

Some consequences are apparent at birth, but subtle cognitive and behavioral abnormalities may not become evident for years.

To date, we do not know the prevalence of illicit drug use during gestation, the most accurate method to identify affected children, or the effects of drugs on developing fetuses. Our studies on the toxicity of prenatal opiate, methamphetamine, and nicotine exposure are helping to provide answers to these important public health problems.



Doug Hansen

Marilyn Huestis

One of the first challenges is accurate differentiation of drug-exposed vs. nonexposed children. I am a co-investigator on the first large-scale study of the developmental consequences of prenatal methamphetamine exposure.

We determined infants to be methamphetamine exposed if the mother self-reported use or if infant meconium, the child's first fecal material, contained methamphetamine.

Surprisingly, more mothers reported use than were identified by meconium analysis, suggesting a need for additional biomarkers of in utero methamphetamine exposure. We detected 68 percent of neonates whose mothers reported third trimester use, while detection rates were ≤10 percent for self-reported use earlier in gestation.

Methamphetamine concentration was significantly correlated with frequency of third-trimester self-reported use. Prior to these data, scientists believed that in utero drug exposure in the last six months of pregnancy might be detected. We are using tandem mass spectrometry to search for unique biomarkers in meconium potentially produced by the fetal liver and kidney.

Research on cannabinoids and the endogenous cannabinoid system is a rapidly developing field of neuroscience due to cannabinoids' role in mediating important biological processes and the therapeutic potential of cannabinoid agonists and antagonists. Cannabis also is the most commonly abused illicit drug. My research focuses on the neurobiology and pharmacokinetics of cannabinoids.

Rimonabant, the first specific antagonist at CB1 cannabinoid receptors, is a key pharmacological tool for investigating the mechanisms of action of cannabinoids. I led the first investigative team to utilize rimonabant in phase I studies in human cannabis users.

We demonstrated that physiological and psychological effects of smoked cannabis were blocked by pretreatment with oral rimonabant, documenting for the first time in humans that cannabis' effects were mediated through the CB1 cannabinoid receptor.

We also showed that rimonabant's blockade of cannabis' effects was not due to a pharmacokinetic interaction between rimonabant and Δ^9-tetrahydrocannabinol, the primary psychoactive component of cannabis.

We extended these findings in a second clinical study comparing cannabinoid receptor blockade from single and multiple oral doses of rimonabant. We reasoned that the long half-life of rimonabant could lead to drug accumulation and antagonism at lower multiple doses.

Tachycardia associated with active cannabis was significantly lower for the 40-mg 15-day group and the single 90-mg-dose rimonabant groups. Peak subjective effects also were reduced.

Rimonabant holds great potential to treat disorders of the endogenous cannabinoid system and perhaps to treat cannabis and other illicit drug dependence.

Phase III trials of rimonabant have now documented its usefulness in the treatment of obesity and tobacco dependence. If it is approved for two such common indications, it could be prescribed to a large segment of the population, including cannabis users. For this reason, we plan to study the phenomenon of antagonist-elicited withdrawal. These studies of withdrawal may also shed light on retention vs. relapse of cannabis users in drug treatment programs.

Karel Pacak *completed his medical training at Charles University, Prague, the Czech Republic, in 1984. He completed a residency program in internal medicine at the same institution and also earned a Ph.D. in 1993 and a D.Sc. in 1999. In 1990, he joined NINDS as a postdoctoral fellow in the Clinical Neu-*

roscience Branch, working with Irwin Kopin and David Goldstein. In 1995, he left NIH to start the residency program in internal medicine at the Washington Hospital Center, Washington, D.C., and in 1997 returned to NIH as a clinical associate in the Inter-Institute Endocrinology Training Program. In 2000, he joined the Pediatric and Reproductive Endocrinology Branch, NICHD, as a tenure-track investigator and chief of the Unit on Clinical Neuroendocrinology, working with George Chrousos. He is currently also an adjunct professor in the Department of Medicine at Georgetown University in Washington.

After joining NINDS in 1990, I focused on the role of catecholamines in the regulation of the hypothalamic-pituitary-adrenocortical axis under stress.

Fran Pollner

Karel Pacak

Together with my mentors, Drs. Kopin and Goldstein, as well as Richard Kvetnansky (NINDS), and Miklos Palkovits (NIMH), we established a method to sample and measure catecholamines from individual brain nuclei. We also described new feedback mechanisms between catecholamines and glucocorticoids, and mapped novel stressor-specific brain pathways.

In 1999, I introduced a patient-oriented Pheochromocytoma Research Program as a new initiative at NICHD. The program emphasizes bedside to bench projects and multidisciplinary and multiinstitutional collaborations, with three main objectives:

- To develop and test novel methods and criteria to diagnose and localize pheochromocytoma in a cost-effective manner
- To develop improved treatments for malignant pheochromocytoma
- To identify molecular and genetic mechanisms of pheochromocytoma tumorigenesis and clinical manifestations of disease

Following from earlier collaborative work with Harry Keiser (NHLBI) and Graeme Eisenhofer (NINDS), we initiated large, prospective, multicenter cohort studies to introduce a novel biochemical test—the measurement of plasma-free metanephrines—in the biochemical diagnosis of pheochromocytoma.

Later, we introduced a novel clonidine-suppression test, coupled with the measurement of plasma-free normetanephrine, for diagnosis of this tumor and established new reference ranges for plasma-free metanephrines in adult patients and children. Recommendations of my group and collaborators about the use of plasma-free metanephrines were endorsed by a panel of experts convened for an NIH Consensus Development Conference.

With other colleagues (Goldstein, Jorge Carrasquillo, Clara Chen, CC Nuclear Medicine Department), we introduced a new nuclear imaging method, [^{18}F]-6-fluoro-dopamine positron emission tomography scanning, for diagnostic localization of pheochromocytoma. This approach proved to be a superior imaging method—especially for metastatic tumors—compared with conventional nuclear imaging approaches such as ^{131}I-MIBG.

This is an important advance because correct detection of disease extent often determines the most appropriate therapeutic plan and future evaluation. This new imaging method has substantially changed the imaging algorithm and clinical approach, and many patients have now profited from the correct localization of their tumors.

In the area of treatment, together with Goldstein and James Reynolds (CC Nuclear Medicine Department), we have initiated a new clinical protocol: using pretreatments with certain agents to increase the efficacy of ^{131}I-MIBG therapy in metastatic pheochromocytoma.

We also introduced radiofrequency ablation as a novel treatment of metastases. Frederieke Brouwers from my lab, in collaboration with Tito Fojo (NCI), introduced the use of depsipeptide and trichostatin A (histone deacetylase inhibitors) to increase expression of norepinephrine transporter system in pheochromocytoma cells.

This important development could open the door to a new clinical trial to test whether these compounds may increase entry of ^{131}I-MIBG into pheochromocytoma cells.

Recently, Shoichiro Ohta from my lab, in collaboration with John Morris, Jeff Green, and Mones Abu-Asab (NCI), established a new mouse model of metastatic pheochromocytoma. Ohta and Wai-Yee Chan (NICHD) also uncovered how metastasis-suppression genes might be involved in tumorigenesis of metastatic pheochromocytoma.

In concurrent collaborations with investigators from the Urologic Oncology Branch of NCI (Marston Linehan and McClellan Walther) and Zheng Ping Zhuang, Irina Lubensky, and Alexander Vortmeyer (NINDS), we described mechanisms linking underlying mutations in multiple endocrine neoplasia type 2A (MEN 2A) and von Hippel–Lindau (VHL) syndrome to different pathways of tumorigenesis, biochemical phenotypes, and clinical presentations of pheochromocytomas in the two syndromes.

We also described the distinct histopathologic phenotypes of MEN 2A and VHL pheochromocytomas.

This work was extended to collaborations with Abdel Elkahloun (NHGRI) and Peter Munson (CIT), focusing on new approaches to classify various types of pheochromocytomas by gene expression profiling. The work aims to provide much-needed approaches for distinguishing tumors with benign or malignant characteristics and behavior and to identify new molecular and genetic markers for diagnosis and targets for treatment.

We also established the International Working Group on Endocrine Hypertension under the auspices of the European Society of Hypertension and set up a new international consortium to foster collaborative research on the tumor (the Pheochromocytoma Research Support Organization). We are now organizing the 1st International Symposium on Pheochromocytoma, to be held in Bethesda, October 20–23, 2005.

Xin Wei Wang *received his Ph.D. from New York University in 1991. He did postdoctoral studies on cancer genetics and molecular carcinogenesis with Michael Newman at the Roche Institute of Molecular Biology in Nutley, N.J., and with Curtis Harris at NCI. In 1998, he became a tenure-track investigator in the Laboratory of Human Carcinogenesis, NCI, where he is currently a senior investigator and head of the Liver Carcinogenesis Section. He is also an adjunct associate professor at the University of Maryland School of Medicine, Baltimore.*

Since the beginning of my undergradu-

People

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Fran Pollner

Xin Wei Wang

ate studies at Shanghai First Medical College, I have been fascinated with the complexity of multicellular organisms, especially their development of fine controls for maintaining homeostasis. The study of cancer is an ideal approach to dissect the underlying mechanisms of homeostasis and its breakdown.

The current paradigm suggests that a tumor evolves through a multistage process, with selection and clonal expansion of an initiating cell undergoing a series of changes.

In the last six years, my laboratory has been investigating the genetic and biochemical pathways involved in human liver carcinogenesis—an excellent model to explore the multistage process of human neoplasms of unknown underlying etiology.

The overall goals of our research are to learn how cancer cells initiate and metastasize and to identify biomarkers that are helpful for early diagnosis and molecular targets for therapeutic intervention.

A key step in our research is identifying molecular fingerprints to elucidate the molecular mechanisms of human cancer and to provide molecular diagnostic tools to guide individualized care for patients with cancer.

Toward this end, we use state-of-the-art gene expression profiling technologies to identify molecular signatures at initiation and progression of hepatocellular carcinoma, particularly those attributable to hepatitis B and C viruses.

For example, by comparing liver samples from chronic liver disease patients with varying degrees of risk for developing hepatocellular carcinoma, we have identified unique fingerprints that may be useful in diagnosing patients with early onset of liver cancer.

Comparing hepatocellular carcinoma with or without accompanying metastasis led us to identify a molecular signature that can be used to predict which liver cancer patients have the potential to develop metastases or recurrence.

In addition, we are examining the role of the liver microenvironment in metastasis and recurrence by focusing particularly on the functions of immune cells and the inflammatory process in liver cancer progression. We identified several potential therapeutic targets that may be useful in eliminating liver cancer cells or metastatic progression.

Because viruses have been invaluable tools for discovering key pathways for human carcinogenesis, a second research emphasis in my laboratory is exploring the interaction between cellular targets and viral hepatitis–encoded proteins. Our initial study focused on molecular aspects of HBx, a viral oncoprotein encoded by hepatitis B virus.

We discovered that HBx contains a functional nuclear export signal motif using the Ran/Crm1 complex, a component essential in nucleocytoplasmic transport of many cellular proteins. Interestingly, this viral protein not only uses but also disrupts Ran/Crm1-dependent activities, presumably to prevent host antiviral response.

The finding implicates the Ran/Crm1 complex in the molecular pathogenesis of HBV.

Our approach also allowed us to uncover a novel role of the Ran/Crm1 complex in regulating cellular proteins that control centrosome duplication and mitotic spindle assembly. Recently, we revealed nucleophosmin as a novel substrate for Ran/Crm1 that negatively regulates unnecessary centrosome duplication.

These results led us to generate a new hypothesis: that the Ran/Crm1 complex serves as the centrosome duplication checkpoint by providing a "loading dock" mechanism to control cellular homeostasis.

Disruption of this complex may result in genomic instability, which may be an early step in viral-mediated hepatocarcinogenesis. Currently, we are exploring other potential partners associated with this complex that may regulate spindle assembly.

Exploration of the roles of these genes and molecular interactions in liver cancer initiation and metastasis has been extremely rewarding, because the findings may be useful in patient management and also challenge current theories of tumor evolution.

Gene expression profiling and exploration of viral-host molecular interactions have expanded our knowledge of the global changes that occur in liver cancer and provide numerous insights into the molecular mechanisms of this disease. ■

On the NIMH MAP: Manji Named Director

Husseini Manji, chief of the Laboratory of Molecular Pathophysiology in the Mood and Anxiety Program (MAP), NIMH, has been appointed MAP director. Manji is a psychiatrist by training, with a special emphasis in psychopharmacology and cellular and molecular biology.

The major focus of his ongoing research is the investigation of disease- and treatment-induced changes in gene and protein expression profiles that regulate neuroplasticity and cellular resilience in mood disorders.

His laboratories' scientific goals are to build on recent insights into the signaling pathways mediating the effects of mood stabilizers to better understand the pathophysiology of severe mood disorders and to develop improved therapeutics.

Husseini Manji

The recipient of numerous distinguished research awards in his field, Manji has also been honored at NIMH with awards for excellence in clinical care and research, and Mentor of the Year and Supervisor of the Year awards.

He developed and directs the NIH Foundation for Advanced Education in the Sciences graduate course in the neurobiology of mental illness. He has published extensively on the molecular and cellular underpinnings of severe mood disorders and their treatments, authored many textbook chapters, and edited a book on the mechanisms of action of treatments for bipolar disorder. He is a councilor for the Collegium Internationale Neuropsychopharmacologicum and a fellow of the American College of Neuropsychopharmacology (ACNP); he chairs the ACNP's Task Force on New Medication Development, and is a member of ACNP's Credentialing Committee.

Manji serves on the advisory boards of several scientific and research organizations, is editor of two academic journals, and is a visiting professor in the Departments of Psychiatry at Columbia University in New York and Duke University in Durham, N.C. ■

Principles and Practice Of Clinical Research

Registration for the 2005–2006 "Introduction to the Principles and Practice of Clinical Research" is underway; the deadline for registering is **October 5**. The course runs from October 17, 2005, through February 21, 2006; classes will be held Monday and Tuesday evenings from 5:00 p.m. to approximately 6:30 p.m in the Lipsett Amphitheater, Building 10.

There is no charge for the course, but students must buy the required textbook. A certificate will be awarded upon successful completion of the course, including a final exam. More than 700 students registered for the 2004–2005 program, which was also broadcast to several domestic and international locations.

For additional information or to register, visit the website at

<http://www.cc.nih.gov/researchers/training/ippcr.shtml>

or call the NIH Clinical Center, Office of Clinical Research Training and Medical Education, at 301-496-9425. An e-mail confirmation will be sent to those accepted into the program.

For reasonable accommodations, call 301-496-9425 between 8:30 a.m. and 5:00 p.m. at least seven business days prior to the event.

Course Objectives

- To become familiar with the basic epidemiologic methods involved in clinical research
- To be able to discuss clinical research ethics and legal issues and the regulations involved in human subjects research, including the role of IRBs
- To become familiar with the principles and issues involved in monitoring patient-oriented research
- To understand the infrastructure required for clinical research and the steps involved in developing and funding research studies

The course is designed for physicians and others training for a career in clinical research.

Interested persons are strongly encouraged to take a course in biostatistics such as STAT 200 or STAT 500, currently offered by the NIH/Foundation for Advanced Education in the Sciences, which is accredited by the Accreditation Council for Continuing Medical Education to provide CME for physicians. ■

NCCAM Seeks Mentors for New Fellowship Program

Intramural scientists interested in mentoring an NCCAM Director's Fellow are invited to add their name to a list of potential mentors.

The mentor-fellow match will be determined by the fellow's research interest and the mentor's willingness to host the fellow, who will be selected in early 2006 from among NIH and non-NIH applicants. The two-year fellowship, fully funded by a Prince of Wales Foundation grant, is expected to begin in summer 2006.

Under the mentor's guidance, the fellow will serve as a "bridge" between the mentor's intramural lab, where the work will be performed, and NCCAM. The mentor will supervise the fellow in conducting clinical, translational, and/or laboratory research as he or she would any other fellow. It is suggested but not required that this research—whether at the bench or the bedside—be related to complementary and alternative medicine (CAM).

The intramural lab that hosts the fellow will need to provide space and the mentor's time but will incur no cost in supporting this collaborative opportunity.

The fellowship offers full salary, benefits, professional travel, and two years of research support. The selected fellow must have an MD, DO, PhD, DC, ND, or equivalent degree and be committed to a career in CAM research.

Those interested in joining a list of available mentors or in recommending a qualified candidate for this fellowship are encouraged to contact Ruth Kirschstein, senior advisor to the NIH director, at

<kirschr@od.nih.gov>

Fellowship details are available at

<http://nccam.nih.gov/about/jobs/dir_fellowship.htm>.

Demystifying Medicine

Demystifying Medicine—a course to bridge the gap between PhDs trained in basic science and the medical problems to which their skills and insights could be applied—will be offered again in 2006.

Starting January 10 and ending May 2, the course will be held each Tuesday from 4:00 to 6:00 p.m. in the ground-floor auditorium of Building 50 (rooms 1227 and 1233). All presentations will be videocast and archived.

The course is geared toward graduate and medical students, clinical and PhD fellows, and staff. Those seeking academic credit can register with FAES:

<http://www.faes.org>.

Others may register at the Listserv:

<http://list.nih.gov/archives/demystifyingmed.html>.

The course schedule will appear in the November-December issue of *The NIH Catalyst*. ■

Hot Off the CyberPress

To be notified when the latest issue of *The NIH Catalyst* comes online, send an e-mail message to this address:

<listserv@list.nih.gov>

that says: Subscribe catalyst-l Your Name—or send an e-mail request to **<catalyst@nih.gov>**. ■

Spirituality and Health

The eighth in the NCCAM Distinguished Lectures series—"Is Spirituality Good for Your Health? Historical Reflections on an Emerging Research Enterprise"—is set for **October 28, 2005,** from 11:00 a.m. to noon in Masur Auditorium, Building 10.

The lecture, delivered by Harvard's Anne Harrington, will be videocast at

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

For more information or for reasonable accommodations (sign language interpretation will be provided), call 301-594-5595 or the Federal Relay at 1-800-877-8339. .More information about the series can be found at

<http://nccam.nih.gov/news/

FAES Late Registration

The deadline for late registration for the FAES 2005–2006 session is **October 7**. The late fee is $10.

The FAES Course Catalog is available at at the FAES Scientific Bookstore in the Clinical Center, Bldg. 10, B1 level, and the FAES office, One Cloister Court, Bldg. 60, Suite 230—and online at

<http://www.faes.org>.

For more information, call 301-496-7976. FAES welcomes suggestions for classroom space. ■

Town Hall Meeting on Taking Care of Business

A Town Hall Meeting to acquaint scientific and administrative staff with the NIH Business System (NBS) will be held Monday, **October 31, 2005**, from 8:00 a.m. to 12:00 noon in the Natcher Auditorium.

The event begins with a plenary-session discussion of scientific and administrative management perspectives, followed by a series of concurrent sessions of system demonstrations in three functional areas: acquisition/supply (iProcurement, Prism & Oracle Systems), property (Sunflower System), and finance (Oracle System).

Information about registration will be provided via e-mail closer to the date of the event. Sign language interpreters will be provided. Individuals with disabilities who need reasonable accommodation to participate in this conference should contact Leslie Linden in the NBS Project Office at 301-451-0004 or via e-mail:

<lindenl@mail.nih.gov>.

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...

- Informationists At the NIH Library
- Research Festival 2005
- Ever in Training: GPP, HHMI, OIR

Kids' Catalyst

Eureka! Part 2: A Penny for Your Thoughts

Last issue we learned about Archimedes' problem-solving powers—how he discovered that Greek King Heiro was cheated and how water displacement led him there. He was dealing with a gold crown that might have contained less gold than it was supposed to contain.

We here in the United States today can use pennies—which are not quite what they used to be—to tackle the same kind of problem. (For our international readers, you may be surprised to find that your coinage has undergone similar changes, and you can apply the same experiment to the coins of your realm!)

In 1982, the U.S. Mint made a big change in our coin of lowest value: The main ingredient of our pennies changed from copper to zinc (zinc pennies cost less to make). But the two kinds of pennies look the same—the zinc-based penny has a copper-plated coating—and if you drop ten zinc pennies into a full glass of water, they will displace the same amount of water as would 10 copper pennies (same volume).

So how can you tell the difference? Weight.

If you have a scale that can measure tenths of a gram, great, but you may want to try making your own home scale. There are many ways to do this, but here's a start:

Tie a piece of string around the middle of a ruler and hold up the string so the ruler hangs in the air. Adjust the string until it balances perfectly (be patient—this is much harder than it sounds). For greater stability than your arm may be able to muster and for a better receptacle for the objects you are weighing, straighten out the hook of a wire hanger, and attach a string to where the metal twists; tie the end of the string around a doorknob. Attach a paper cup to each end of the hanger, and there's your scale!

Perhaps the hardest part of your experiment will be finding pennies minted before 1982 (here's where an old penny jar comes in handy, but there are still plenty of these pennies in circulation).

Once you've got your two sets of pennies, place the 10 copper pennies and the 10 zinc pennies into their opposing cups—and voila! The heavier side will bow down. Same volume, different weight. (You will see that the coin that costs more to make is also the heavier coin.)

See how Archimedes figured it out? The fake crown weighed the same as the gold, but displaced a different amount of water. The pennies displace the same amount of water, but don't weigh the same. Caveat emptor!

—Jennifer White

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 2, Room 2E26, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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FIRST-CLASS MAIL
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DHHS/NIH
Permit No. G-802

Official Business
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Printed on 50% recycled content paper and can be recycled as office white paper.