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Menopausal Hormone Rx DISPARATE VOICES REFLECT ON WHI DATA, ICs LOOK TO FUTURE

by Fran Pollner

"The reaction to a new scientific finding is proportional to the strength of the dogma it overturns."

—Elias Zerhouni, concluding the scientific workshop on menopausal hormone therapy, October 24, 2002



Ernie Branson

NIH Deputy Director Ruth Kirschstein (left) welcomes former NIH director Bernadine Healy, who launched the Women's Health Initiative in 1991; behind them is NIH Director Elias Zerhouni

When the Women's Health Initiative (WHI) halted the estrogen-progestin arm of its hormone study last July, a bit of medical dogma bit the dust. That dogma held that hormone therapy protects postmenopausal women against heart disease; the part overturned related to the hormone combination most prescribed in this country for postmenopausal women with an intact uterus.

The ensuing strong reactions found a forum for expression at a scientific workshop here October 23–24 to review those WHI results and their implications for clinical practice and future research.

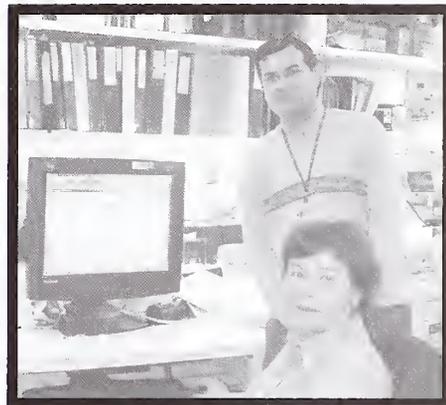
NIH took some heat for the way it had handled the halting of the study

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A RESEARCH FESTIVAL SAMPLER: NIH SCIENTISTS ARE ALL OVER THE MAP

DATA MINING YIELDS MYSTERIOUS CONSERVED GENE FAMILY

by Celia Hooper



Celia Hooper

NEI's Cynthia Jaworski and Shahabuddin Alam

NEI's Cynthia Jaworski says she loves "to play in front of the computer." It was this playing that led her and Shahabuddin Alam and Nataliya Gordiyenko in Ignacio Rodriguez's NEI lab to discover the 12 genes encoding human oxysterol-binding proteins (OSBPs) and then, more deliberately, to find mouse orthologs for these genes.

The group began mining mouse data when its lab work showed some unusual transcripts in the human versions of the proteins, which are expressed in retina, brain, liver, kidney, heart, spleen, lung, and the organ of Corti in the ear, for example. Jaworski found very similar orthologs for each of the human OSBPs in the mouse.

Greatest similarity between mouse and human lay in pleckstrin homology domains, which were completely identical for several of the OSBPs. Jaworski says the genes are found beyond mammals—in yeast (7 genes), worms (5 genes), fruit flies (4 genes), and plants (12 genes in Arabidopsis), for example.

Knocking out the genes in yeast points

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PHARMACOKINETIC DATA INVITE NEW LOOK AT VITAMIN C AS CANCER RX

by Fran Pollner



Fran Pollner

NIDDK's Mark Levine (left) and Sebastian Padayatty

Nutritional bioavailability studies undertaken by NIDDK investigators to update the RDA for vitamin C have cast new light on old studies that dismissed vitamin C as an anti-cancer agent. The findings are considered intriguing enough by NCI's Office of Cancer Complementary and Alternative Medicine (CAM) to be used as a starting point for a phase I trial to re-evaluate vitamin C's possible role in cancer treatment.

"We chanced upon this," said Sebastian Padayatty, of the Molecular

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FROM MIS TO CRIS: STATE-OF-THE-ART INFORMATION SYSTEM TO SERVE AS THE 'NERVE CENTER' OF THE NEW CLINICAL RESEARCH CENTER



John Gallin

The roots of information technology at the Clinical Center run deep. We've operated an electronic medical information system—the MIS—for a quarter century. Designed to support day-to-day patient care, the MIS sends orders where they need to go, can be used to check results, and allows clinicians to perform some care documentation. As the needs of the intramural clinical research community have grown, the MIS has adapted, through continual customization, as best it could.

It's appropriate that as the new Clinical Research Center's walls go up we are simultaneously building the next generation of information systems to support the work that will be carried out there. I consider the Clinical Research Information System—CRIS—a project as important as the new hospital. It will serve as the CRC's nerve center, providing a strong, flexible information backbone for the conduct of clinical research.

A continuous record of patient care, adverse event detection, and enhanced communications with referring physicians are a few of the hallmarks of the new clinical information system. CRIS will incorporate capabilities to enhance patient care, including delivery of clinical alerts in real time and online access to reference and resource materials.

At least 24 distinct information systems ultimately will plug into two broad CRIS hubs, the Clinical Data Repository and the Clinical Data Warehouse, both supporting aspects of clinical care, clinical research, and operations management.

The Repository will serve as the electronic medical record, housing information related to patient care and hospital operations—lab results, pharmacy orders, information from referring physicians, and multidisciplinary care documentation, for example. Clinical systems such as radiology, nutrition, pharmacy, and protocol services will feed the Repository.

The Warehouse will be the central resource for historical patient data. Its ancillary systems will provide information needed to support safety and organizational efficiency programs. The Warehouse will be available for data retrieval and analysis while protecting patient privacy and confidentiality. It will offer us remarkable new opportunities for capturing, exploring, analyzing, and using information generated by clinical research.

Innovations in information technology are being introduced at an astonishing rate. Our challenge is to be prepared to use the data at our disposal in ways that speed the contributions of clinical research while safeguarding even more closely the well-being of our patient volunteers.

New capabilities offered by CRIS will mean more users. Projections are that nearly 6,500 CC and clinical research staff will use CRIS, 50 percent more than currently use MIS. Training in how to use the new systems will be an ongoing priority, as will smart project management. Systems integration—

making sure that all these new and enhanced systems work together as envisioned—is critical. That team is already in place to ensure project integrity across all stages of development, testing, implementation, and management.

A vendor will soon be selected to provide the core patient-care system. Dedicated teams from throughout NIH invested months of work to detail requirements for the core's capabilities. Resulting proposals have been closely evaluated. The final decision is critical because the core literally is the foundation for all that we expect from this project.

We have high expectations for CRIS and correspondingly high expectations of those who will use it. We are planning a series of well-publicized, hands-on demonstrations. Members of the clinical research community can try out what's being proposed during these test-drives. We want and need your opinions about how the system will handle everything from ordering medications and accommodating charting to clinical alert displays and protocol pathways.

Better treatments and therapies for patients are the clinical researcher's ultimate goals. The highest level of training in the conduct of clinical research is an important foundation for achieving this goal. Just as critical is the availability of a dependable framework of support.

In 2000, the Medical Executive Committee detailed overarching principles and processes for NIH's intramural clinical research community. Topping the list of focus areas are standards in clinical informatics, data management, and protocol tracking. The Clinical Research Information System will be a key element in meeting these standards.

—John Gallin

Clinical Center Director

For more about CRIS, visit <<http://cris.cc.nih.gov>>.

CRIS Steering Committee

Cliff Lane, NIAID clinical director (chair)

John Gallin, Clinical Center director, NIH associate director for clinical research, and CRIS program official

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Robert Nussenblatt, chief, NEI Laboratory of Immunology; chief, CC Protocol Services; and chair, Medical Executive Committee Information Technology Subcommittee

Jo Anne Zujewski, head, NCI Breast Cancer Clinical Research Branch

CROSSING PATHS ON THE ROAD TO PHARMACOLOGY: PRAT FELLOWS MIX, MINGLE, AND MOVE ON

Pharmacology is a very special area, and the PRAT [Pharmacology Research Associate] program is a very special program," Peter Blumberg told a gathering of individuals whose presence at a PRAT awards ceremony in July signaled their likely agreement with his enthusiasm for the field.

Chief of the Molecular Mechanisms of Tumor Promotion Section, NCI, and chairman of the PRAT advisory committee, Blumberg keyed the first formal occasion to recognize those fellows completing the NIGMS-sponsored PRAT program—this year there were seven. The ceremony included a reception, a poster session, a plenary session, and presentations of the research of four

current PRATs. The newest class, comprising six fellows working at five different NIH institutes, came on board October 7.

Established in 1965, the PRAT program offers training, career advice, and networking opportunities to postdoctoral researchers interested in the field of pharmacology. It is a two-year program with the possibility for a third year and, like the field of pharmacology, is cross-disciplinary. Research presented at the summer event ranged from the discovery of new genetic targets for breast cancer drugs to the molecular mechanisms of chemotaxis.

The fellows, who interact regularly through PRAT-sponsored events, con-

sider bumping shoulders with those in other fields to be one of the most valuable aspects of the program. There is a monthly seminar series at which second-year fellows present their work and guest speakers elaborate on career options—not only research in various environments but also in such lines as patent law, science education, and grants administration.

Most PRATs gravitate to research careers in academia—and most arrive at that destination. Of the 340 PRAT program graduates, more than 90 percent have continued in research careers, with more than 60 percent of these in academia.

—Alisa Zapp Macbalek



(Left) Peter Blumberg (center), chair, PRAT advisory committee, girded by Richard Okita and Pamela Marino (PRAT program co-directors)

(Right) Juanita Sharpe, a third-year PRAT fellow, speaks on "Cardiolipin modulation by the Bcl-2 family members in apoptosis regulation"



(Left) Erik Snapp, newly graduated PRAT fellow, presents poster on "Remodeling of the endoplasmic reticulum in living cells"

(Right) Kristi Egland, a second-year PRAT fellow, speaks on "Discovery of new breast cancer genes encoding membrane and secreted proteins for use as immunotherapy targets"



photos by Ernie Branson

Coming Soon: Next Class of PRATs

The deadline for applications to the NIGMS Pharmacology Research Associate (PRAT) program is **January 3, 2003**, for positions starting in October 2003. The PRAT program supports two years of training in NIH or FDA laboratories for postdoctoral candidates in the pharmacological sciences and related research areas. These may include, but are not limited to, molecular pharmacology, signal-transduction mechanisms, drug metabolism, immunopharmacology, chemistry and drug design, structural biology, endocrinology, bioinformatics, and neuroscience. PRAT fellows receive competitive salaries as well as supply and travel funds to support research in their preceptors' laboratories. Candidates apply in conjunction with an identified preceptor, who may be any tenured or tenure-track scientist at NIH or FDA. For more information or application materials, contact the PRAT program assistant at 301-594-3583 or

<prat@nigms.nih.gov>.

ClinPRAT

A sister program called Clinical Pharmacology PRAT, and nicknamed ClinPRAT, was launched four years ago and is open to individuals with M.D. degrees. It is designed to create a cadre of scientists in the clinical development, evaluation, and therapeutic use of small molecule- and biotechnology-based pharmacotherapy. For more information on this program, contact Art Atkinson at 301-435-8791 or <aatkinson@mail.cc.nih.gov> or visit the ClinPRAT website at <<http://www.cc.nih.gov/OD/clinprat/>>.

RESEARCH FESTIVAL—DATA MINING

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to a high degree of interchangeability or redundancy in their function, Jaworski says. "You have to knock out the whole family to see a lethal effect in yeast."

These features of the OSBPs suggest that they must be important in the life of the cell. And just what is this critical function? It's not yet clear, Jaworski says. With a little arm-twisting, she mentions that some folks think OSBPs might have a role in vesicular trafficking.

From here, the lab could move on to designing knockout mouse-model experiments to see whether any knockout results in retinal damage. Jaworski is quite certain of one thing: With the growth of gene and protein databases for a cornucopia of organisms, data-mining work like hers will be very much a part of the future of genetic research—quickly pointing to commonalities in the regulation of genes and directing searches for function. "I think that the current wave of data-mining will continue until the human genome is not only completely sequenced, but also completely annotated and understood," Jaworski predicts. ■

TOWARDS TOLEROGENIC TRANSPLANTS

For a few years, scientists have had an enticing idea for how to induce the body to accept a transplant of non-self tissue from a donor: Give a tolerogenic transplant of bone marrow to reprogram a recipient's immune system to accept an organ transplant as "self." This induced



Adip Akpinar

natural tolerance would permit a heart, kidney, or pancreatic islet cell recipient, for example, to live indefinitely with a transplant, without having to take immunosuppressive drugs.

Evidence—in mice—has hinted that the scheme might work. At the Research Festival, Edip Akpinar, working in David Harlan's NIDDK lab with Nancy Craighead, Jenny Park, and Douglas Hale, revealed some key tricks they have discovered that could bring tolerogenic transplants a few steps closer to practice.

Working with mice, the scientists identified and collected a strongly tolerogenic population of cells—bone marrow cells that are positive (bright) for c-Kit, the receptor for stem cell factor. Although the c-Kit-positive cells constitute only 4–5 percent of the cells in marrow, the great news was that these cells grew "like

crazy" in culture, Akpinar says, increasing better than 250-fold and producing immune tolerance equal to that from whole bone marrow. The NIDDK group tested tolerance with the most immunogenic transplants possible: skin grafts between mice that were complete genetic mismatches. In addition to permitting smaller, simpler tolerogenic transplants, using a subpopulation of bone marrow is also less likely to have unwanted side effects, such as graft vs. host and host vs. graft reactions, Akpinar observes.

Members of the NIDDK group are currently conducting trials on immune tolerance induction in monkeys using bone marrow, with trials in kidney transplant patients expected to begin early next year. They plan to extend to primates what they learned from mice about fractionation of the marrow for c-Kit-positive cells. Until those experiments yield results, Akpinar reminds cautiously that, "It is easier to achieve tolerance in small rodents than in primates."

—C.H.

INTRA-NUCLEAR SPACE:
THE FINAL FRONTIER?

Jeff Roix (left) and Luis Parada

Two posters facing one another at the Research Festival raised the provocative suggestion that it is not just the proteins your genes encode that are important, but also the physical location of your genes and chromosomes within the nucleus.

Poster CB-8, presented by Jeff Roix, from Tom Misteli's NCI lab, studied nuclear positioning of loci disrupted in Burkitt's lymphoma. Poster CB-9, presented by Luis Parada, also in Misteli's lab, used chromosome painting to detect consistent patterns in the relative position of chromosome pieces in other cancerous and normal cell lines. Parada's work is published in the Oct. 1 issue of *Current Biology* (12:1692–1697, 2002).

Roix and Parada, who also collaborated with CIT's Philip McQueen and Peter

Munson, along with Misteli, say measuring the relative location of genes and chromosomes is technically very challenging. Nevertheless, they were able to detect consistent patterns, and they say these probably reflect positions of entire chromosomes, not just the specific loci they examined.

What are the causes and consequences of this subnuclear spatial patterning of the genome? It's not yet clear, the pair say. Some evidence, published in *Nature* (418:975–979, 2002) points to interphase sequence clustering of myogenesis genes in *Caenorhabditis elegans*. But it's not known if interphase location of chromatin determines the arrangement of chromosomes—or vice versa.

As for consequences, Roix and Parada say proximity of loci may contribute to increased frequency of translocation between them. This can result in cancer and other deleterious gene changes. But understanding the gene regulatory advantages of proximity—during interphase, presumably—awaits further research. This final frontier, they say, could benefit from better methods for analyzing intranuclear space.

—C.H.

KILLING CANCER
THROUGH COPPER CHELATION

Cancer researchers think a key vulnerability of tumors lies in the way they aggressively commandeer angiogenesis. Induction of new vessels feeds tumor growth, and if scientists could inhibit angiogenesis, they could cut off the nutrient pipeline to expanding tumors.

NCI tenure-track investigator Kevin Camphausen knew that copper was somehow important to angiogenesis, and he speculated that if he could mop up copper with a chelator before endothelial cells got it, perhaps he could block angiogenesis.

Camphausen asked his colleague Martin Brechbiel to make some copper chelators. Brechbiel sent him 40 chelators in a brown box. Working also with Mary Sproull, Steve Tantama, Tamalee Scott, and Cynthia Menard, Camphausen tested



Chane Jackson

Kevin Camphausen

the compounds for their ability to inhibit angiogenesis (the growth of human umbilical vein endothelial cells).

The winner was #20, a member of the tachpyridine family of compounds. Members of the tachpyr family were effective in blocking the growth of endothelial cells in vitro, but did not harm other types of cells the team tested.

As small molecules, the tachpyrs have excellent potential as drugs. If they pan out as angiogenesis inhibitors, they would have two additional advantages over other anti-angiogenic proteins such as angiostatin and endostatin: Tachpyrs are much easier and cheaper to make, and their uptake could make cells sensitive to radiation. This trait enables tachpyr to deliver a doubly deadly blow to tumors.

Camphausen does not yet know which molecules in angiogenesis are so voracious for copper, but plans to find out. The group will also be working with collaborators to refine the tachpyrs and move them to in vivo animal trials.

—C.H.

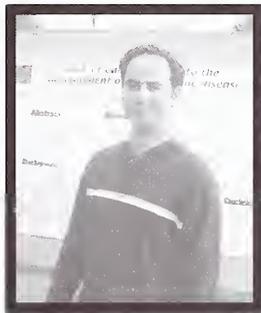
A NEW LUPUS MODEL

One serious challenge for the study of autoimmune disease in general, and lupus in particular, has been a lack of good animal models.

At the Research Festival, Jesus Salvador, of the NCI Gene Response Section, Basic Research Laboratory, offered a promising new autoimmune disease mouse model: the Gadd45 γ knockout.

The NCI group—including lab chief Albert Fornace, Christine Hollander, Heraa Haj-Elsafi, Chui Cheng, Anh Thu Nguyen, Svetlana Speransky (Germline Mutation Core Facility), and Jonathan Ashwell (Laboratory of Immune Cell Biology)—has now deduced that genes in the Gadd45 family appear to be autoimmunity suppressor genes. The team has published a report, with NIDDK collaborators Jeffrey Kopp and Laura Barisoni, on its knockout of the Gadd45 α gene (*Immunity* 16:499–508, 2002), is soon to publish on the Gadd45 γ knockout, and eventually hopes to knock out the entire family of Gadd45 genes.

Salvador says the Gadd45 γ knockout



Fran Pollner

Jesus Salvador

is not a perfect mimic of lupus, but does exhibit leukopenia, lymphopenia, and proteinuria, as found in the disease. Also present are high titers of antibodies to double-stranded and single-stranded DNA and to histones. These antibodies and proteinuria are present in the MRL mouse—the best mouse model scientists had developed before—but the MRL mouse does not have the leukopenia and lymphopenia found in the NCI mouse and in most people with systemic lupus erythematosus.

Salvador says that T cells derived from Gadd45 knockout mice have a hyperproliferative response and lower threshold of activation than wild-type cells. The group proposes that the hyperproliferation of T cells is sufficient to provoke the loss of tolerance that leads to the development of this autoimmune disease. Thus, the Gadd45 knockouts may prove to be good models for several autoimmune diseases.

—C.H.

USING PROTEOMICS TO DIAGNOSE INTERSTITIAL CYSTITIS

Interstitial cystitis (IC) is a chronic inflammation of the epithelium that lines the bladder. The resulting pelvic pain, frequency of urination, and psychological consequences afflict between 450,000 and 700,000 people, mostly women, in the United States. As common and painful as IC is, to date its diagnosis has been by exclusion of infections and other disorders, resulting in an inefficient, protracted, and expensive ordeal for patients.

DaRue Prieto of NCI's SAIC contract at Frederick worked with scientists from NCI, SAIC, the University of Maryland, and FDA-CBER—including Thomas Conrads, Susan Keay, Vincent Fusaro, Emanuel Petricoin, Lance Liotta, Haleem Issaq, and Timothy Veenstra—on a promising new way to identify the disease more directly. The group's poster at the Research Festival demonstrated that SELDI-TOF/QqTOF could be used to recognize patterns of proteins in the urine of people with IC and distinguish these from samples taken from people who did not have the condition.

After "training" an artificial intelligence-based computer algorithm (developed by Ben Hitt at Correlologic Systems, Inc.) to distinguish the protein patterns in 50 urine samples from IC patients and 30 normal controls, the team tested the system on a 37-sample testing set that included 16 control subjects and 21 IC samples. The proteomics recognition was

perfect, with 100 percent specificity and sensitivity.

Prieto presented the poster just one day after NCI scientists, working with colleagues from the FDA, academia, and Correlologic Systems, Inc., published studies in the *Journal of the National Cancer Institute* (94:1576–1578, 2002) showing that a similar proteomics/informatics analysis could be used on blood samples to identify men with prostate cancer more efficiently and accurately than is possible with prostate-specific antigen.

—C.H.



Marti Welch

DaRue Prieto

MARS, VENUS, AND MARRIAGES

In a poster sure to stimulate household debates, second-year NIMH summer student Aaron Bobb looked at how sex roles—the masculinity or femininity of husbands and wives—affected marital adjustment, or sense of satisfaction with their marriage.

Working in the laboratory of NIMH's Carolyn Zahn-Waxler, Bobb analyzed data on the parents of children enrolled in an unrelated NIH study. The Cornell senior used the Bem Sex Role Inventory to gauge the husbands' and wives' sex roles and the Dyadic Adjustment Scale to rate their self-assessed marital satisfaction.

On the Bem scale, "masculine" people rate themselves high for traits such as forcefulness, athleticism, analytical ability, dominance, and independence; "feminine" people rate themselves high for being compassionate, affectionate, loyal, sensitive to the needs of others, and loving children. Those with high values for both "masculine" and "feminine" traits are classified as "androgynous," and those scoring low on both sets are classified as "undifferentiated."

The only relationship Bobb detected between sex role combinations and marital satisfaction was that "femininity" in both husband and wife correlated with greater personal satisfaction in the marriage. "Masculinity" had neither positive or negative correlations, and no optimal combination of men's and women's roles emerged. The marriage of a feminine woman and a masculine man appeared no more satisfying than the reverse, for example.

Bobb acknowledges that the study begs for follow-up. He plans to return to NIH after graduation and before going on to graduate study in psychology.

—C.H.



Aaron Bobb

RESEARCH FESTIVAL—NEW LOOK AT VITAMIN C

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and Clinical Nutrition Section, Digestive Diseases Branch, NIDDK.

"We were studying vitamin C pharmacokinetics—from a nutritional point of view, looking for the correct daily intake—and saw a huge difference in bioavailability following oral and i.v. administration. We were also aware of the controversy over vitamin C in cancer treatment in the 1980s, when no one had i.v. pharmacokinetic information. That whole issue immediately—and naturally—came to mind."

Elaborating on their poster at the Research Festival, Padayatty and co-investigator Mark Levine, chief of the Clinical Nutrition Section, recounted the vitamin C–cancer history: In the 1970s, Ewan Cameron and Allan Campbell reported that high-dose (10 g) vitamin C yielded clinical benefit and prolonged survival in terminal cancer patients, a finding later repeated in large retrospective studies conducted by those two investigators in collaboration with Linus Pauling.

There was considerable debate over

the validity of these findings—since the studies were not randomized or controlled—and when Charles Moertel and his colleagues at the Mayo Clinic tested the same vitamin C dose in two NCI-supported randomized, controlled clinical trials and found no vitamin C effect, most of the scientific community dropped vitamin C from consideration as a cancer therapy.

There was one hitch, however, that was not appreciated until the NIDDK investigators undertook their nutrition studies some 15 years later: Vitamin C was delivered intravenously in the studies that reported benefit, and it was delivered orally in the Moertel studies.

In pharmacokinetics simulation studies and in studies with healthy volunteers, presented at the Research Festival, the NIDDK team (Levine and Padayatty and colleagues Yao-Hui Wang and Arie Katz and He Sun at the FDA) established that vitamin C plasma concentrations after i.v. administration are at least tenfold those generated by oral administration. Differences in urinary

concentrations were similarly dramatic.

The i.v. route produced millimolar concentrations that are known to be toxic to a variety of cancer cell lines, Levine noted. He added that recent anecdotal case reports from some private CAM clinicians—with pathology confirmed by an NCI pathologist—suggest that megadose i.v. vitamin C may help some patients with advanced genitourinary cancers.

"We're always skeptical of case reports—and in vitro apoptosis could reflect cell culture artifact," Levine said, "but it all points to the need for further scientific study."

Jeffrey White, director of the NCI Office of Cancer CAM, agrees. "The pharmacokinetic data, along with other recent findings, justify a careful investigation of the therapeutic potential of intravenous vitamin C," he said.

White, Levine, and others from the NIDDK lab and NCI, White added, "have had preliminary discussions and are in the early concept phase of developing a clinical protocol for a phase 1 trial." ■

HEPATITIS E VACCINE PROVES SAFE AND EFFECTIVE IN MACAQUES; RESULTS PENDING IN HUMANS

NIH investigators have engineered a recombinant vaccine that protects macaques against hepatitis E and is now in clinical trials to test its mettle in humans.

"Hepatitis E virus [HEV] is the single most important cause of clinical hepatitis in adults in central and southeast Asia

and the Indian subcontinent—and Afghanistan, where our troops are," noted Robert Purcell, as he fielded questions at the Research Festival.

The recombinant subunit construct—the HEV capsid protein in a baculovirus vector—proved safe and highly immunogenic in non-human primates, fully protecting against the disease and partially protecting against infection. The inves-

tigators established the optimal dose and schedule. Hepatitis A vaccine was used as the placebo control.

The expression of recombinant protein "turned out to be easy," said Purcell, chief of the Laboratory of Infectious Diseases and the Hepatitis Viruses Section, NIAID. He compared the HEV capsid protein construct to that

of the hepatitis B envelope protein, the immunogenic ingredient of the "first recombinant vaccine ever licensed."

Should the HEV vaccine prove equally successful in humans, it will leave only hepatitis C without coverage, observed Purcell, who co-developed the hepatitis A vaccine and is also working on adding hepatitis C to the list of preventable hepatitis viruses.

Discovered in 1980, visualized in 1983,

and sequenced in 1991, HEV is a scourge in those areas of the world vulnerable to waterborne epidemics, where the population would be exposed to the massive viral doses that lead to disease. The disease is uncommon in the United States and Europe, but up to 20 percent of those populations have HEV antibody, probably through low-dose exposure. HEV infects swine and rats and can be transmitted from them to non-human primates and "maybe to humans as well," Purcell said. Its overall 1 percent mortality rises to 20 percent in pregnant women.

A clinical trial involving several thousand members of the military in Nepal is in progress. The code will be broken, said Purcell, once 25 bona fide HEV cases are documented.

Purcell's NIAID colleagues in this study were Hahn Nguyen, Ronald Engle, Doris Wong, and Suzanne Emerson.

—FP.



Fran Pollner

Robert Purcell

MENOPAUSAL HORMONE THERAPY

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and the way it had notified the public and the medical community of the unexpected findings—criticisms NIH Director Elias Zerhouni said NIH had taken to heart. Women's health advocates also decried the fact that promotional claims for the regimen under study had overstepped scientific evidence, unduly influencing the choices of women and their doctors.

The predominant concerns voiced during the workshop, however, were that the results not be extrapolated to all hormone formulations and doses and that research proceed on the risks and benefits of these and other treatments for individual women seeking relief from acute menopausal symptoms—as well as for prevention of the chronic conditions the WHI is designed to study: heart disease, osteoporosis, and breast and colorectal cancer. Many emphasized the need for fundamental research on hormonal signaling systems.

Background

Last July, NHLBI, in agreement with the Data Safety and Monitoring Board (DSMB) of the WHI halted the combination estrogen-progestin arm of the WHI hormone study three years before its scheduled conclusion. Not only did the postmenopausal hormone regimen not confer cardiovascular benefit—an expected beneficial outcome that the study was designed to quantify—but women on active drug actually had a higher rate of heart attack and stroke than those on placebo. They also experienced more thromboembolic events and breast cancer. Lower rates of osteoporotic fractures and colorectal cancer did not overcome the unfavorable risk:benefit ratio.

The cardiovascular risks emerged early in the study, persisted, and were sustained in all age groups (of the 16,600 women enrolled in the trial, 30 percent were 50–59, 45 percent were 60–69, and 25 percent were 70–79).

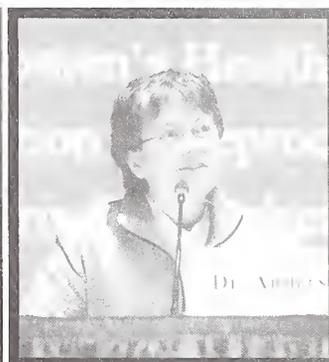
The findings were especially jarring because they flew in the face of observational studies and the climate of acceptance that had informed the prescribing habits of many clinicians with menopausal and postmenopausal patients. When the study was halted and results made public, millions of women and their physicians were left in a quandary.



Vivian Pinn, director, Office of Research on Women's Health (ORWH) emphasized the need for evidence-based practice: "The bottom line is that we now have more information for women to make informed decisions." Pinn co-chairs the WHI with NHLBI Director Claude Lenfant. The WHI is sponsored by NHLBI in cooperation with NIA, NIAMS, and NCI. For background information on the WHI, see <<http://www.nhlbi.nih.gov/wbi/factsbt.htm>>.



WHI principal investigators Marcia Stefanick (left) and Marian Limacher, professor of medicine and director of preventive cardiology, University of Florida, Gainesville, presented data that "removes combination hormonal therapy from coronary heart disease prevention strategy" for both primary and secondary disease and across the WHI age spectrum of 50–79. Major medical organizations and the U.S. Preventive Services Task Force issued statements in agreement.



photos by Ernie Branson

WHI biostatistician Garnet Anderson, Fred Hutchinson Cancer Research Center, Seattle, fielded charges of WHI "selective detection bias" in the breast cancer findings, noting that regardless of whether some women knew what they were taking, the mammography rates in both the active-drug and placebo groups were "exactly the same and the outcomes were completely blinded. It was as rigorous as a clinical trial could be for women with a uterus."



Ernie Branson

Outlining their extensive ongoing and projected basic and clinical research agendas on the effects of hormones and other agents on menopausal symptoms and postmenopausal aftereffects were NIH directors (left to right) Duane Alexander, NICHD; Steve Straus, NCCAM; Stephen Katz, NIAMS; Andrew von Eschenbach, NCI; Richard Hodes, NIA; Jacques Rossouw, acting director, WHI, NHLBI; and Claude Lenfant, NHLBI

The investigators themselves had been "shocked" on two even earlier occasions when the DSMB told them to inform study participants, first, that a small increase in heart attack, stroke, and blood clots in the legs and lungs had been identified in the combined-hormone cohort and, later, that the risk had not disappeared with time, recounted WHI steering committee chair, Marcia Stefanick, of the Stanford University Center for Research in Disease Prevention.

Torrents of Data To Come

A tremendous amount of data is yet to come from the WHI—from the halted study as well as from the continuing trials involving unopposed estrogen in hysterectomized women, dietary modifica-

tions, calcium and vitamin D, and overlapping regimens, which are scheduled to continue for several more years.

A priority of WHI investigators is to start publishing additional findings from the estrogen-progestin trial within six months. They plan to examine correlations of genetic, biochemical, and coagulation biomarkers with outcomes to identify subgroups at greater risk. They will also study whether regimen-related harms dissipate over time after discontinuation. Additional publications will address cognitive function—also the subject of a WHI ancillary study—and quality of life, as well as underlying differences among the women in the estrogen-only and combination cohorts. ■

GENERATING PHYSICIAN-INVESTIGATORS: GRADUATE MEDICAL EDUCATION AT NIH

by Fran Pollner



Valerie McCaffrey

GME Colleagues: Frederick Ognibene and Brenda Hanning

There are 7,838 accredited graduate medical education programs (GME) in the United States and 95,990 active residents and fellows in these residencies and subspecialty fellowships. NIH is home to 16 of those programs and about 160 of those residents and fellows. (Another five programs are jointly sponsored by NIH and other institutions; see list below).

NIH may be a small part of a very big GME picture, but it is a vital and growing part that is distinct in its focus on training physician-investigators. It is also subject to the same stringent and changing criteria for accreditation as the rest, although some aspects of training in clinical research cannot be captured so handily in standards meant to measure the quality of training for clinical practice.

GME at NIH is "unique," says Brenda Hanning, acting director of the NIH Office of Education, in that there are many more fellowship than residency slots (see chart), a reflection of the patient caseload at NIH. "We are ideally suited for subspecialty training because we don't treat the bread-and-butter population," observes Hanning, who for the past three-and-a-half years has co-chaired a revitalized NIH GME Committee with

Frederick Ognibene, director of the NIH critical-care medicine fellowship program at the Clinical Center.

The core requirements related to curriculum and patient contact are similar to other programs around the country, Ognibene notes, "but we have a more fertile, richer research environment in addition to the clinical exposure." Applicants to NIH programs are "self-selected," presumably having been attracted to the emphasis on the research component of the training during recruitment, he says, noting that most NIH fellowships are two to three years with an additional block of time to train to become an independent investigator.

Outreach and Selection

Although the existence of GME at NIH is less well-known around the country than Hanning would like—"We still

bump into physicians at meetings who are surprised that NIH has a hospital"—applicant numbers are "healthy." Ognibene's program, for instance, draws about 150 applicants for the four available slots each year. "We typically narrow it down to 15 interviews; we look at the academic record in its entirety and clinical and research faculty recommendations—and then the interview is very important. What are the person's long-term goals? We take our role of training the next generation of physician-scientists very seriously," says Ognibene. (See the profile of one critical care fellow, "Where the Action Is," page 10.)

As testimony to the growing GME emphasis at NIH—and the growing programs, both in numbers of slots and potential new subject areas—a principal wish of Hanning's was granted last spring with the approval of a new position for a GME executive director.

James Thompson—whose experiences as head of the American Psychiatric Association's education programs, residency review committee member, and GME provider at a university preceded his NIH appointment—arrived here in August.

One of his main charges is to oversee expanded and targeted outreach to that pool of physicians who would be most drawn toward residency and subspecialty training at NIH.

His other main charge is to oversee the development of evaluation measures that document the degree of success NIH programs have in meeting



Fran Pollner

Taking the Helm:
James Thompson,
new GME executive
director

NIH Accredited Training Programs

Residencies

Anatomic Pathology *
Dermatology (3rd year only)
Psychiatry (4th year only)

Subspecialty Fellowships

Internal Medicine:

Critical Care
Endocrinology and Metabolism
Hematology
Infectious Diseases
Medical Oncology
Rheumatology
Allergy/Immunology
Blood Banking and Transfusion Medicine
Clinical and Laboratory Immunology
Cytopathology
Hematopathology
Medical Genetics
Pediatric Endocrinology

Program Directors

Lance Liotta, NCI
Mark Udey, NCI
Donald Rosenstein, NIMH

Frederick Ognibene, CC
Monica Skarulis, NIDDK
Cynthia Dunbar, NHLBI
John Bennett, NIAID
Barry Gause, NCI
Gregory Dennis, NIAMS
Dean Metcalfe, NIAID
Cathy Conry-Cantilena, CC
Thomas Fleisher, CC
Andrea Abati, NCI
Elaine Jaffe, NCI
Maximilian Muenke, NHGRI
Constantine Stratakis, NICHD

NIH-affiliated Programs

Cardiovascular Diseases (Johns Hopkins)
Gastroenterology (Georgetown)
Neurophysiology (National Capital Consortium)
Pediatric Hematology-Oncology (Johns Hopkins)
Radiation Oncology (National Capital Consortium)

* Anatomic pathology is the only one of the 16 ACGME-accredited fellowship programs at NIH that is a full-fledged residency program conferring board eligibility in one of the recognized medical specialties. Two other programs—in dermatology and psychiatry—extend residency credits earned elsewhere. The other 13 are subspecialty fellowships open to those who have already completed their core residencies.

ONE PHONE CALL LAUNCHED A CAREER

By his third year in medical school (at Rutgers in Piscataway, N.J.), Aaron Auerbach knew he wanted to go into a diagnostic field—perhaps pathology, perhaps radiology, but the pull to pathology proved stronger. For personal reasons, he also wanted to spend as much of his fourth year in the Washington, D.C., area as possible.

"I also had an interest in research—and what better place could there be than NIH?" Auerbach says, recalling the impetus for his after-hours phone call to the NCI Laboratory of Pathology one evening to leave a message requesting information on the possibility of a rotation during his senior year of medical school. Instead of the answering machine, however, lab chief Lance Liotta, who "happened to be working late that night," picked up the phone. "He asked me what my research interests were, what I wanted to do in the future—and then he said, 'absolutely'—and the next day it was all set up, and I spent the month of October of my senior year in medical school doing clinical research in Lance Liotta's department. I was the only medical student. I didn't know anything, and then I was swept into the science, and I knew that this was where I wanted to do my residency."

During his month's stint, he did surgical pathology and research on genetic syndromes, specifically the Birt-Hogg-Dube (BHD) syndrome—work that he

continued as a resident and prepared for presentation at this year's Research Festival and the upcoming U.S. and Canadian Anatomic Pathology Society meeting. He and his colleagues reported on previously undescribed colonic lesions in BHD patients.

Auerbach suspended all other residency-selection activities and applied for the NIH anatomic pathology residency program, which does not participate in the national residency matching program. He learned in November that he had been accepted. The following June (of the year 2000), he graduated from Rutgers with his M.D. degree and a concurrent M.P.H. in health-care administration from the graduate school and returned to the Laboratory of Pathology.

Now chief resident, Auerbach cannot praise the program highly enough. "My experience has been excellent; the protocols are interesting, the research possibilities endless. My mentor (Maria Merino) has been great, and I love what I do. The residents here are not viewed as labor for others but are treated as intellectual equals whose input is appreciated and used. I came in a medical student, and I'm leaving a pathologist."

Headed for the Armed Forces Institute of Pathology, Auerbach plans to specialize in GI and liver pathology and to conduct re-



Fran Pollner

Aaron Auerbach

search on medications to reverse hepatitis-associated fibrosis. (According to the website, 143 residents graduated from the program between 1955 and 2001, with approximately 41 percent moving on to nongovernment academic pathology, 40 percent to government positions in academic pathology, 18 percent to community pathology practice, and under 1 percent to industry.)

"NIH is different from anywhere else," Auerbach says. "Not needing to earn X amount of dollars for my laboratory through grants has allowed me the freedom to shape electives and research projects—to create my career—around those things that I want to do while at the same time meeting American Board of Pathology requirements." There is, of course, the pressure to publish—a not-unwelcome pressure that has helped fuel his submission for publication of studies on ovarian cancer metastatic to the mediastinum, Cytokeratin 7 and 20 staining of hepatocellular carcinomas, and solitary fibrous tumor involving the pituitary fossa.

—Fran Pollner

ACGME (Accreditation Council for Graduate Medical Education) criteria for GME accreditation.

Measuring Competencies—and Competent Measures

ACGME conducts institutional GME reviews at least every five years; in addition, each individual GME program within an institution undergoes periodic reviews. Hanning was elated when NIH's last review in May recently earned a "favorable action," with the next review planned for five years hence. "That's as good as it gets," she says of ACGME's list of possible ratings.

As individual NIH programs come up for accreditation review from now on, however, each will have to present evidence that it is meeting six new ACGME "competency" requirements that took effect in July. The six areas are:

- Medical knowledge
- Patient care (clinical and patient

management skills)

- Professionalism
- Interpersonal skills and communication
- Practice-based learning
- Systems-based practice

Hanning and Ognibene estimate that programs will have about four years leeway to fashion and implement assessment measures that satisfy the ACGME mandate.

"Are these six competencies being taught? How can they be assessed? We are relying on the individual programs to develop their own tools for some of these—each program has its own core skills in medical knowledge and patient care, for instance," says Ognibene. "Other competencies, like communication and professionalism, transcend all programs."

For these, the GME Committee (including Thompson, Hanning, Ognibene, all the other program directors, two fellows representatives, and others) is working collectively to devise central

measures.

"We're adapting a 360-degree feedback tool to see how one's self-perception compares with others' perceptions of the quality of each resident's and fellow's interactions—at the bedside with patients and with other members of the health-care team," Hanning says. "Self-evaluations will be held to the mirror of evaluations by the program director, the teaching faculty, fellow residents, and other members of the team."

Competency in "practice-based learning"—which encompasses practicing evidence-based medicine grounded in an understanding of how to use the medical literature and how to interpret studies and meta-analyses—is a challenge to assess, Ognibene says.

And "systems-based practice," adds Hanning, "is an interesting one. In the outside market, systems-based would refer to such things as how hospital reimbursement works, third-party payers, insurance, finances. We don't have that at NIH, but we've created a tool to ful-

WHERE THE ACTION IS FOR ONE GME FELLOW: CRITICAL CARE

During the last year of her internal medicine residency at the University of Texas Health Science Center, San Antonio, Denise Gonzales spent one day at NIH. She was one of a highly select group tapped by the National Hispanic Medical Association (NHMA) to compete for a slot in one of NIH's 16 accredited fellowship programs, and she was here for interviews.

Gonzales had not known that these programs existed; it was the chairman of medicine in San Antonio, a former NIH fellow himself and her attending physician during her second year of residency, who had nominated her for an NHMA-sponsored NIH program. Looking through the information on each of the NIH fellowships, she had homed in on critical care medicine. "There was no question. That was the one I wanted," she recounts.

Critical care, Gonzales says, appealed to both of the two strong forces that had propelled her in two directions during her medical school training: surgery because she loved its "pace and demands" and internal medicine because she loved its "intellectual challenges." Her experience in the ICU during her San Antonio residency suggested that it was in the ICU environment that an internist could feel her adrenaline pumping.

And it was that one long day spent at NIH—in February 2000—that convinced her that the Critical Care Department in the NIH Clinical Center was where the action should be for her.

That day started at 7:30 a.m., observing rounds. "I saw a fellow presenting patients to four or five other fellows and



Denise Gonzales
Fran Pollner

about 15 attendings—and those attendings had recognizable faces and names—like Tony Fauci—and they were firing off all these questions. And I asked myself, 'Can I do this? Can I answer these questions every morning about why I did what to the patients of these world-famous experts?'"

After rounds, the day was spent interviewing with "every single member of the Critical Care Department." Not only the excitement of being at NIH—"where great studies are designed and performed and reviewed"—but the unparalleled freedom to pursue her own interests

pushed away any other possible fellowship choice. "Whatever I wanted, I was told, they could find the funds, the space, the time, the supervision. The physical, financial, and intellectual resources were all here—across the board."

With four other fellows, Gonzales started her four-year NIH fellowship in July 2001—two years as an "intensivist" or "criticalist" in training, providing care for critically ill patients, and two years conducting research in critical care.

She spent her first fellowship year caring for patients on protocols at NIH who required critical care, interspersed with rotations through the surgical, medical, coronary, and pediatric ICUs at the Washington Hospital Center, the National Naval Medical Center, and Children's National Medical Center—altogether five months at NIH and seven months elsewhere.

"I've been very pleased with my training. In my rotations through one of the hospitals, I saw that other fellows from other programs aren't getting such broad exposure—most other programs don't place their fellows in formal surgical ICUs." As for her critical care

experience at NIH, she finds it hard to describe. "Challenging" is not an adequate term. These are patients who have failed conventional therapy and a certain level of experimental therapy. They are here for highly experimental therapy, and if they have reached the ICU . . ."

Now in her second fellowship year, Gonzales is at the Johns Hopkins Medical Institutions fulfilling the requirements of the pulmonary care component of her dual subspecialty training. The last two years of the fellowship will be spent doing research in the Critical Care Department here—most likely in the area of DNA arrays to identify markers for sepsis. "Anthony Suffredini, a senior investigator here, is doing array analysis in sepsis models, searching for ways to identify the ARDS [acute respiratory distress syndrome] patients who may survive septic shock, who may respond to immunomodulatory drugs or activated protein C."

Beyond that, Gonzalez envisions independent research in the area of noninvasive monitoring of critically ill patients—something that would marry her intensivist training with her interests and skills in biomedical engineering (just one month before entering medical school in 1994, she had completed a three-year Master of Science in Biomedical Engineering program at Boston University, where she had designed a chip resembling the cochlear implant but utilizing a different computer platform).

"If I were ever to use my engineering training, it really should be in an ICU setting," she says, pointing to the desirability of being able to assess hemodynamic status without transport or central lines, without the risk of infection, bleeding, and lung collapse.

In the long-term, Gonzales sees herself in academic medicine, blending clinical care responsibilities with teaching and clinical research. "I could not imagine myself in private practice anywhere. I enjoy working in a research environment."

—Fran Pollner

fill this requirement that we're very excited about. It's systems-based practice in the context of NIH clinical trials. It hasn't been tested yet, but it would include things like attending John Gallin's IPPCR (Introduction to the Principles and Practice of Clinical Research) course, participating in developing an IRB protocol, enrolling in a jointly sponsored NIH masters degree program in clinical research. We've developed a template from which to choose a number of options to achieve mastery in systems-based practice NIH style. We think it's a great model."

Asked whether the new evaluation requirements might be a distraction from actual training, Thompson observed that "we have to make sure that it does not interfere with the training itself." It's not the "extremely high quality of training that would change," he said, "just the documenting of it."

"This concern with verifying competency has burgeoned throughout the house of medicine over the last 10 or so years," he added. "We would like NIH to be a model for the country in documenting quality. And I suspect many of our scientists—no strangers to documen-

tation—would welcome that challenge."

According to Aaron Auerbach, one of the two trainee representatives on the GME Committee and an anatomic pathology resident in Lance Liotta's lab, his program director is one of those people who "says we have to figure out how to do this right."

"It's a work in progress, but I don't think the changes are going to be tough for us to make—mentoring and review have always been part of the process," observes Auerbach, now in his third year of residency (see "One Phone Call Launched a Career," page 9). ■

CLINICAL BIOETHICS: ANOTHER FACET

Dan Brock was an economics major who became an investment banker and then decided to try his hand at something he thought would be more "worthwhile."

So he returned to school, got a doctorate in philosophy, and emerged with an interest in a field whose name had yet to be coined: bioethics.

Since that time, more than 30 years ago, he has contributed to some of the major doctrines shaping the ethical practice of modern medicine, including the landmark *Deciding to Forgo Life-Sustaining Treatment*. This work was performed in his capacity as staff philosopher on the President's Commission for the Study of Ethical Problems in Medicine in the early 1980s.

On June 30, Brock began a five-year appointment as an NIH senior scientist in the Department of Clinical Bioethics, where his new unit on ethics and public health will center the department's explorations into health policy and priorities.

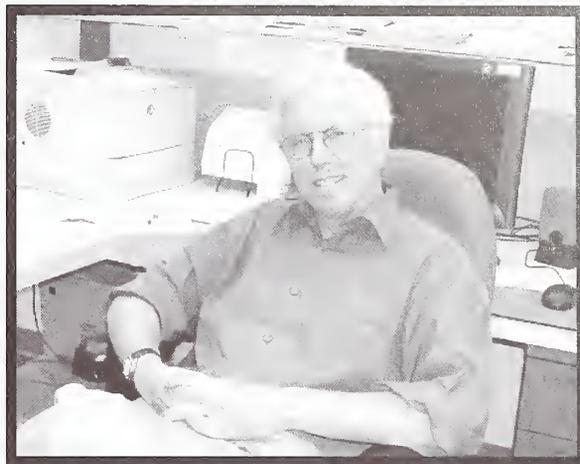
Brock intends to continue his already extensive research on the prioritization of health-care resources and the implications of advances in genetics knowledge and technology. Much of his work has involved developing alternatives to the "ethically inadequate" cost-effectiveness standard for resource allocation. "Cost effectiveness is a useful piece of information," he says, "but it ignores equity and justice"—not to mention common sense, such as when capping teeth was ranked above appendectomy in

Oregon's attempt to prioritize Medicaid expenditures using a cost-effectiveness standard.

As the recipient of an ELSI (Ethical, Legal, and Social Issues) grant from NHGRI, he and three other philosopher-co-authors produced the book *From Chance to Choice: Genetics and Justice* (Cambridge University Press, 2000). "New capacities to shape our children can raise new issues of social justice," Brock observes, noting that his writings on responding to moral obligations to prevent genetically transmitted disease have been viewed as sending a "threatening and offensive message" by some groups representing disabled people. "It's an emotionally charged issue."

On the horizon, Brock adds, is the related issue of effecting genetic modifications not to prevent disease but to enhance normal human abilities, much as is already happening in the psychopharmacology arena. He cites the use of prescription medications to boost everyday function, such as antidepressants to counteract shyness. Gene manipulation for similar ends "should be a public worry before we actually need to confront it," he says.

Brock comes to NIH from Brown University, in Providence, R.I., where he had a joint appointment in the Philosophy Department and the medical school. He



Fran Pollner

New Face in Town: Dan Brock has joined the CC Department of Clinical Bioethics

was Charles C. Tillinghast, Jr. University Professor, professor of philosophy and biomedical ethics, and director of the Center for Biomedical Ethics.

Brock has been philosopher-in-residence at Rhode Island Hospital, a member of the Ethics Working Group of the Clinton Task Force on National Health Reform (along with Ezekiel Emanuel, now director of the NIH Clinical Bioethics Department), and a consultant to the World Health Organization on genetic testing and reproductive control.

He was a senior visiting scholar at NIH from September 2001 to May 2002—and he turned down an offer of first chair in bioethics at England's Oxford University before accepting his NIH appointment.

—Fran Pollner

ON THE PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

Registration for the 2003 "Introduction to the Principles and Practice of Clinical Research" begins **November 15**. The course will run **February 18, 2003–May 21, 2003**.

Classes will be held on the NIH campus on Tuesday and Wednesday evenings from 6:00 p.m. to approximately 7:30 p.m. There will be optional breakout sessions Monday evenings to explore specific topics in greater detail.

Registration deadline is **February 1, 2003**. There is no charge for the course, but the purchase of a textbook is required. A certificate will be awarded upon successful completion of the course, including a final exam.

For additional information or to register, visit the course website at

<http://www.cc.nih.gov/introclinres/>.

SEEMS LIKE YESTERDAY . . .

Thirty years ago, Wendy Baldwin came to NIH for a two-year appointment with NICHD. She didn't expect to stay, she says, but one thing led to another as she took on expanding roles within NICHD.

In 1993, Baldwin became the NIH deputy director for extramural research, a post she will be leaving at year's end to become vice president for research at her doctoral alma mater, the University of Kentucky in Lexington. ■



Fran Pollner

Wendy Baldwin

RECENTLY TENURED

Sergey Bezrukov received his Ph.D. in physics and mathematics from Moscow State University in 1981 and did postdoctoral work at the St. Petersburg Institute of Nuclear Physics, Russian Academy of Sciences. In 1990 he joined the Laboratory of Biochemistry and Metabolism of NIDDK as a special volunteer and in 1992 as a Visiting Scientist. He is now a senior investigator in the Laboratory of Physical and Structural Biology, NICHD.

A physicist by education, I believe that interactions between physics and biology are mutually rewarding because observations on biological materials and in biology in general lead to discoveries of new physical principles.

Our Section on Molecular Transport approaches ion channels from two unique directions: (i) ion channels as molecular Coulter counters to probe metabolite and macromolecule transport; and (ii) ion channels as stochastic resonators to transduce weak sensory signals.

Molecular Coulter Counting. Bacterial porins, mitochondrial channels, gap junctions, some toxins, the nuclear pore complex, and protein-conducting channels of the endoplasmic reticulum are "mesoscopic" channels designed to transfer solutes larger than water and small ions. In order to observe the dynamics of this large-solute transport, we invented molecular Coulter counting.

The underlying idea for molecular Coulter counting is very similar to the resistive pulse principle used since 1953 in Coulter counters. The basic difference is that the pulses in current come from nanometer-sized molecules such as ATP or sugars rather than micrometer cells, as in the standard Coulter counter. Using mesoscopic channels, we are watching the passage of molecules with gyration radii as small as 5–15 Å. The dynamics and selectivity of transport demonstrate that many of these large channels, rather than being merely general-diffusion pores, are highly specialized to conduct metabolites across membranes.

We were recently able to use this approach to observe the details of a single drug molecule's translocation through a target membrane. It is well known that membrane permeability barriers are among the main contributors to bacterial antibiotic resistance. Using the bacterial porin OmpF reconstituted into planar lipid bilayer membranes, we saw how addition of the beta-lactam antibiotic ampicillin cre-

ated transient interruptions in small-ion current through the channel. The kinetics of these transients gave us reaction parameters needed to link antibiotic penetration to the molecular features of the bacterial channel and the drug. We found that the charge distribution of an efficient antibiotic complements the charge distribution at the narrowest part of the pore. Consequently, we have recognized molecular interactions that can reduce the

membrane permeability barrier and increase antibiotic efficacy.

Stochastic Resonance.

This term refers to the counterintuitive phenomenon in which random fluctuations added to weak signals actually bring out otherwise undetectable features by improving a transducer's performance. Studying the influence of ambient noise on signal transfer through the ion channels of alamethicin, we found that external voltage fluctuations could play a constructive role via stochastic resonance.

With increasing intensities of white noise, the signal-to-noise ratio actually peaks at a particular added-noise level. Thus, we had demonstrated that this surprising phenomenon actually operates at the molecular level, not just in the instruments of physicists.

Our next major contribution was to show the generality of stochastic resonance. By reducing this phenomenon to its mathematical essence, we demonstrated that noise-facilitated signal transduction is a far more general statistical property of nonlinear systems than was previously believed. In this way we liberated the concept and highlighted its ubiquitous possibilities.

Keeping in mind the enormous structural and dynamic complexity of neural organization, our next logical step is to investigate whether and how noise-facilitated signal transduction reaches the molecular scale of intra- and intercell communication. We have begun to examine the electrosensitive organs of elasmobranchs. We hope that the study of these organs will elucidate the functioning of the central nervous system as profoundly as the study of the squid giant axon has served to reveal the process of action-potential conduction.



Fran Pollner

Sergey Bezrukov



Fran Pollner

Sergey Leikin

Sergey Leikin received his Ph.D. from the Moscow State University in 1987. He did his postdoctoral work at the Frumkin Institute of Electrochemistry in Moscow, Russia, and at DCRT (CIT), NIH. He joined NICHD in 1997 and is now a senior investigator and chief of the Section on Physical Biochemistry, NICHD.

My interest lies in understanding the physics of biomolecular recognition and assembly reactions and in development of treatments for diseases related to these reactions.

I focus on collagen fiber formation and function, particularly in brittle bone disease, or osteogenesis imperfecta (OI). Although many factors in bone disease—such as collagen mutations—are known, the exact molecular mechanisms of bone pathology are poorly understood. Treatments are scarce and rarely effective.

In my early work at NIH, my colleagues and I were the first to report direct measurement of collagen-collagen forces in fibers. We described the physical nature of these forces and demonstrated that the helical domain of collagen is responsible for the recognition that governs fibrillogenesis, whereas nonhelical terminal peptides play only a catalytic role in fiber formation.

Probably the most surprising discovery stemming from this work was that collagen fibrillogenesis is initiated by melting (micro-unfolding) of the most thermally labile regions of the protein triple helix. We further showed that triple-helical collagen monomers are unstable at body temperature. For instance, human lung collagen fully denatures within 2–3 days at 37 °C rather than being stable up to 41–42 °C as previously thought.

It now appears that procollagen is forcibly folded by specialized chaperonins (for instance, Hsp47) inside cells.

Once it loses chaperonins and is secreted, it becomes unstable and begins to unfold. Initial melting triggers assembly of fibers, which in turn protects molecules from further unfolding. Proteins and processes susceptible to OI mutations include:

- Chaperonin-assisted procollagen folding
- Extracellular enzymatic processing
- Micro-unfolding and complete unfolding
- Fibrillogenesis
- Collagen-collagen interactions in fibers
- Collagen interactions with matrix proteoglycans

We continue investing a substantial fraction of our efforts in studies of complex interrelationships between these processes.

As we gain more basic knowledge, we gradually increase our involvement in studies of specific bone disorders in collaboration with NICHD clinical researchers.

Careful thinking about interactions between collagen helices required a rigorous theory. We found a solution to this rather difficult problem and demonstrated that helical symmetry of molecular structure not only creates characteristic X-ray diffraction patterns, but also determines features of molecular interactions. This theory explained the measured forces not only between collagen helices, but also between DNA helices.

The theory also gave a rationale for DNA overwinding from 10.5 bp/turn in solution to 10 bp/turn in aggregates, and for hexagonal/cholesteric transition in hydrated DNA aggregates. It clarified electrostatic interactions responsible for changes in packing of DNA aggregates, and it suggested that DNA duplexes may recognize sequence homology at a distance via electrostatic interactions modulated by sequence-dependent variation in the twist between adjacent base pairs.

We often rely on analogy with DNA and other biological helices and on theory coupled with experiments as tools for understanding underlying common physical principles. We hope that such knowledge will be used someday to design new treatments for disorders associated with pathology of molecular recognition.

In the meantime, we are trying to bring this research directly to the bedside in diagnosing and monitoring patients. We assisted NICHD clinical researchers in determining the origin of unusually severe hyperextensibility and joint laxity in several OI patients at NIH. Although we do not have a treatment, we at least now know what is wrong and what should be fixed. As I recently learned at a meeting, even such basic understanding of the origins of their disease provides hope and tremendous psychological help for OI patients.

Cecilia Lo received her Ph.D. from Rockefeller University in New York City in 1979 and did postdoctoral work at Harvard Medical School in 1979–1980. In 1980, she was appointed to the faculty of the University of Pennsylvania, Philadelphia, where she rose through the ranks to full professor in the Biology Department in the School of Arts and Sciences before joining NHLBI in 2001 as chief of the new Laboratory of Developmental Biology.

A long-standing research interest in my laboratory is the role of gap junctions in mammalian development. Gap junctions

are cell junctions containing membrane channels encoded by the connexin multigene family. They allow direct cell-to-cell movement of ions, metabolites, and cell-signaling molecules.

The gap junction gene *connexin43* plays an essential role in heart development. Our studies indicate *connexin43* modulates two extracardiac cell populations—the cardiac neural crest and proepicardially derived cells. These two cell populations play a critical role in development of the heart outflow tract and patterning of the coronary arteries.

Using transgenic and knockout mouse models, we determined that connexin43 regulates the deployment of these two cell populations to the heart. This involves modulation of cell motility by a novel signaling function of connexin43, one of which is separable from the channel-forming capacity of the connexin43 protein. Studies are currently underway using time-lapse videomicroscopy and laser capture microscopy to elucidate the cellular and molecular mechanisms regulating neural crest and proepicardial cell migration. We are also pursuing other genomic and proteomic approaches to further define cell signaling by connexin43.

Another line of investigation in my laboratory entails a discovery-based approach using chemical mutagenesis to identify genes and genetic pathways essential for mammalian cardiovascular development. For these studies, *N*-ethyl *N*-nitrosourea (ENU)-mutagenized mice are analyzed using dual genotype- and phenotype-based screens.

The genotype-based screen focuses on the identification of new mutations in the connexin multigene family and is carried out using a novel custom DNA resequencing microarray. The resequencing array provides DNA sequence information for all 20 mouse connexin genes and thus is an efficient method for identifying mutants with novel connexin mutations. These mouse mutants will be used to elucidate the cell-signaling function of connexins and their potential role in cardiovascular development and function.

For the phenotype-based screen, we use noninvasive in utero fetal Doppler echocardiography to identify mutants with structural and functional cardiovascular anomalies. This screen has identified mice with various forms of arrhythmias, outflow tract anomalies, congestive heart failure, and other cardiovascular defects. Efforts are underway to map and identify



Fran Pollner
Cecilia Lo

the genetic alterations underlying these cardiovascular phenotypes.

In summary, my lab's research program focuses on genetic, cell, and molecular biology of mammalian cardiovascular development. We are integrating whole animal imaging, microscopy, and genomic and proteomic approaches to elucidate the role of connexins and other genes and genetic pathways essential for normal mammalian cardiovascular development. We plan to extend these studies to human patient populations and determine whether connexin mutations and mutations in other genes identified in our mutagenesis screen play a role in human congenital heart disease

Michael Quon received his Ph.D. in biomedical engineering (1987) and M.D. (1988) from Northwestern University in Evanston, Ill., and Chicago, respectively. After completing an internship and residency in internal medicine at the University of Chicago, he entered the Interinstitute Endocrine Training Program at NIH in 1990 and did additional postdoctoral work in the Diabetes Branch, NIDDK. He then joined the Hypertension-Endocrine Branch, NHLBI, as a tenure-track Investigator in 1995 and was recently appointed chief of the Diabetes Unit, Laboratory of Clinical Investigation, NCCAM.

I have a long-standing interest in understanding the molecular mechanisms of insulin action and insulin resistance as they relate to the pathophysiology of diabetes, obesity, and cardiovascular diseases. My graduate school studies focused on developing detailed mathematical models of insulin signaling pathways regulating metabolic actions of insulin.

When I arrived at NIH as an Endocrine fellow in 1990, I complemented my mathematical biology background by acquiring experimental expertise in the molecular and cellular biology of insulin signal transduction in the laboratory of Simeon Taylor, Diabetes Branch, NIDDK.

In collaboration with Sam Cushman's lab, I developed a novel electroporation method to transfect rat adipose cells in primary culture that enabled us to overexpress and inhibit various insulin signaling molecules in a bona fide insulin target cell. Using this technique, we identified the insulin receptor tyrosine kinase, members of the insulin receptor substrate (IRS) family, and phosphatidylinositol 3-kinase (PI 3-kinase) as essential signaling components. These molecules regulate

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insulin-stimulated translocation of the insulin-responsive glucose transporter GLUT4 from an intracellular compartment to the cell surface. We ruled out a role for Ras in this process.

After I established my own independent laboratory in the Hypertension-Endocrine Branch, NHLBI, in 1995, we continued studies along these lines. This led us to identify the protein tyrosine phosphatases PTP1B and PTP- α as negative regulators of metabolic actions of insulin that act by dephosphorylating the insulin receptor and IRS proteins. Downstream from PI 3-kinase, we demonstrated that PDK-1, Akt, and PKC- ζ also participate in the regulation of insulin-stimulated translocation of GLUT4. Moreover, we uncovered additional complexities in metabolic insulin signaling pathways by showing that IRS-1 is a novel substrate for PKC- ζ (an example of a negative feedback pathway) and by identifying PTP1B as a novel substrate for Akt (an example of a positive feedback pathway).

In NHLBI, we also initiated a new project to investigate vascular actions of insulin. Using a nitric-oxide selective electrode, we were the first to demonstrate directly that insulin can stimulate the production of the potent vasodilator nitric oxide (NO) from human vascular endothelial cells in primary culture. More recently, we developed a fluorescent dye-based method for directly visualizing NO production in single living cells. Using these novel techniques, we elucidated a complete biochemical pathway in endothelial cells involving the insulin receptor phosphorylating IRS-1. In this pathway, the insulin receptor phosphorylates IRS-1, leading to binding and activation of PI 3-kinase, subsequent activation of PDK-1, phosphorylation and activation of Akt, which then directly phosphorylates and activates endothelial nitric oxide synthase (eNOS). Moreover, we have shown that this phosphorylation-dependent mechanism for activation of eNOS is completely independent and separable from the classical calcium-dependent activation of eNOS used by most G-protein coupled receptors.

The striking parallels we discovered between signaling pathways related to metabolic actions of insulin and signaling pathways regulating vasoactive actions of insulin support our hypothesis that regulation of metabolic homeostasis and hemodynamic homeostasis are coupled. Thus, factors causing metabolic insulin resistance may also predispose to impaired vasodilator actions of insulin and provide a molecular explanation for the frequent association observed between diabetes



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and hypertension.

Our lab also conducts patient-oriented clinical investigation of metabolic and vascular physiology in diabetes, obesity, and hypertension. The gold-standard method for measuring insulin sensitivity in humans is the hyperinsulinemic euglycemic glucose clamp. We use this method in conjunction with forearm

blood flow studies to investigate the relationship between vascular and metabolic actions of insulin in vivo.

These labor-intensive procedures are not easily applied in large studies. Therefore, we recently devised and validated a novel index of insulin sensitivity based on a mathematical transformation of fasting glucose and insulin levels. This index, which we named the Quantitative Insulin-sensitivity Check Index (QUICKI), is much simpler to use than the glucose clamp and is useful for large epidemiological studies as well as for following changes in insulin sensitivity in individual patients after therapeutic interventions. QUICKI has now been used successfully by others in more than 40 published clinical studies.

Future studies in NCCAM will aim to identify and elucidate the molecular basis of promising therapies for diabetes, obesity, and hypertension within the realm of complementary and alternative medicine.

Karen Usdin received her Ph.D. in microbiology from the University of Cape Town (UCT), South Africa, in 1986 and did postdoctoral work at UCT and in the Laboratory of Biochemical Pharmacology, NIDDK. She is now a senior investigator in the Laboratory of Molecular and Cellular Biology, NIDDK.

I am interested in the repeat expansion diseases—genetic disorders caused by an increase in the size of a specific tandem repeat sequence. Expansion beyond a threshold size has pathological consequences that depend on the location of the repeat in the affected gene. When the repeat is in the coding sequence, the connection between expansion and disease symptoms is relatively straightforward: Expansion results in the production of an aberrant protein that is toxic. It is less straightforward when the repeat is outside the open reading frame.

I am interested in both the mechanism and the consequences of expansion in this latter group of disorders, which includes progressive myoclonus epilepsy type 1 (EPM1), fragile X mental retardation syn-

drome (FXS), and Friedreich's ataxia (FRDA).

EPM1, which is characterized by tonic-clonic seizures and progressive stimulus-sensitive myoclonus, results from expansion of a C₄G₄GCG•CGCG₄CG repeat tract in the promoter of the cystatin B gene.

FXS, the most common heritable cause of mental retardation, is caused by expansion of a CGG•CCG-repeat in the 5' UTR of the *FMR1* gene. Carriers of FXS "premutation" alleles—intermediate-sized alleles at risk of expansion to the full mutation on maternal transfer—have a much higher incidence of premature ovarian failure and cerebellar dysfunction than individuals with the "full mutation." Expansion has two apparently paradoxical effects on transcription in FXS: At "premutation" lengths, it leads to an increase in *FMR1* transcription. In the "full mutation," it leads to hypermethylation of the promoter and a dramatic decrease in transcription. Expansion also results in a transcript that is translated less efficiently.

FRDA, a neurodegenerative disease associated with cardiomyopathy and diabetes, is caused by GAA•TTC-repeat expansion in the first intron of the frataxin gene.

My group initially set out to investigate the biochemical properties of the disease-causing repeats. We showed that in vitro DNA containing such repeats forms unusual secondary structures such as tetraplexes or triplexes, and that the ability to form such structures is a common property of hypervariable sequences in general. In addition, we showed that in vitro transcripts containing the FXS repeats form stable RNA hairpins containing a mixture of C•G and G•G base pairs.

These structures may have biological consequences. For example, we have

shown that triplex formation occurs during transcription of the FRDA repeats. This traps RNA polymerase on the template, leading to a deficit of full-length transcript, which mirrors that seen in FRDA patients.

We also showed that structures formed by the FXS repeat block DNA synthesis. These blocks may force pre-

mature condensation of chromatin at mitosis, resulting in the fragile site seen at the *FMR1* locus in FXS patients. These blocks may also cause expansion by promoting strand slippage or by recombinogenic repair of the stalled replication fork.

We showed a correlation between secondary structure formation and instability of the repeat tract in bacteria. In collaboration with Robert Nussbaum (NHGRI), we generated transgenic mice carrying part



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of an FXS allele with a 100 percent probability of expansion in humans. These mice partially recapitulate what occurs in FXS pedigrees, producing large deletions but no expansions. This suggests that expansion and deletion occur by different mechanisms and that specific cis- and/or trans-acting factors may be necessary for expansion.

However, crossing these mice with mice deficient in a number of important DNA repair and replication pathways also did not produce any large expansions. We are now generating mice containing a targeted insertion of a long repeat tract in the murine *Fmr1* gene in hopes of creating a better model of expansion. These mice would be the murine equivalent of FXS "premutation" carriers and thus may also be useful for understanding disease pathology in these individuals.

RNA hairpins, such as those formed by the FXS repeat, may be responsible for the symptoms seen in both "premutation" and "full mutation" carriers. For example, certain double-stranded RNAs activate enzymes like the protein kinase PKR that can lead to apoptosis. The FXS-RNA hairpins are thus a potential source of RNA toxicity that could lead to the ovarian and cerebellar dysfunction seen in FXS "premutation" carriers. Our preliminary data showing the ability of CGG-RNA to activate PKR in mammalian cells support this hypothesis.

In addition, double-stranded RNA may be a trigger for epigenetic modifications of chromatin that lead to gene silencing. Thus the FXS RNA hairpins may also cause the transcription deficit in "full mutation" carriers. We now have the cell lines that will allow us to test this hypothesis. Finally, the RNA hairpins may also block scanning of the 5' untranslated region by the 40S ribosomal subunit, thus causing the translation deficit seen in alleles with large repeat tracts.

Since the coding sequence is intact in most FXS patients, it is possible that reversing or counteracting the epigenetic events that cause promoter silencing may have therapeutic value. My group has identified the transcription factors necessary for *FMR1* gene expression and shown that the binding of one of them, NRF-1, is abolished by cytosine methylation. This suggests that DNA demethylation will be necessary to fully reactivate the gene. We are currently exploring different strategies for restoring *FMR1* gene function.

Thomas Wynn received his Ph.D. in Medical Microbiology and Immunology from the University of Wisconsin-Madison in 1991. He worked as an IRTA fellow in the Immunobiology Section of the NIAID

Laboratory of Parasitic Diseases and as an NIH senior staff fellow before being appointed to NIAID's tenure-track program. He is now a senior investigator in the Laboratory of Parasitic Diseases, NIAID, where he heads the Immunopathogenesis Section.

My research is focused on understanding the molecular and immunological mechanisms of pathogenesis in schistosomiasis and other parasitic diseases. Schistosomiasis is an important human disease, with about 200 million adults and children in 74 countries infected with the waterborne parasite. Approximately 20 million people annually develop serious complications because of chronic infection. More than 600 million people are at risk of infection, and recent estimates suggest that about 280,000 people die each year in sub-Saharan Africa alone. Schistosomiasis ranks second, just behind malaria, as a cause of morbidity and mortality from a parasitic disease. There is also emerging evidence that infection with helminthes, such as schistosomiasis, is a major aggravating factor in both AIDS and tuberculosis in the developing world. Thus, the disease imposes a high socioeconomic burden on many of the affected developing countries.

Although there are drugs for the treatment of schistosomiasis, people living in endemic areas are at a constant risk of reinfection. Indeed, a substantial portion of the population is reinfected within one to two years after treatment. Therefore, control of morbidity and mortality via drug therapy requires continuous surveillance of the population and intermittent chemotherapy. Control of schistosomiasis using conventional means is, therefore, life-long and expensive.

A relatively inexpensive alternative would be a vaccine that either prevents or reduces infection or significantly reduces the occurrence of severe disease. My work is focused on better understanding the pathogenesis of schistosomiasis, so that a more defined and rational approach to vaccination might be developed.

In murine schistosomiasis, the pathology resulting from infection with *Schistosoma mansoni* is predominantly caused by the host reaction to parasite eggs that are laid in the portal venous system and subsequently trapped in the liver and intestine. Egg-induced liver fibrosis can lead to portal hypertension, which causes much of the morbidity and mortality associated with the disease.

A major emphasis of my research program has been to dissect the contributions of type-1 (IFN- γ) and type-2-associated



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cytokines (IL-4, IL-10, and IL-13) to the pathogenesis of schistosomiasis. The mechanisms controlling granulomatous inflammation and development of hepatic fibrosis have been the primary focus. Such studies are needed because it is the host response to the eggs, rather than the parasite itself, that is the major driving force in the devel-

opment of hepatosplenic disease. An important finding in our studies was the discovery that the Th2-type cytokine IL-13 is the critical profibrogenic mediator in murine schistosomiasis.

Although there is a great deal of mechanistic information regarding the process of tissue remodeling and fibrosis, there are still large gaps in our understanding of the role of inflammatory cells and cytokines in the initiation and maintenance of the fibrotic process. In experiments conducted with a soluble IL-13 antagonist, we showed that IL-13 plays an indispensable role in the fibrotic process. In contrast, IFN- γ , IL-12, and IL-10 all appear to antagonize the profibrotic effects of IL-13. Indeed, mice that exhibit strong IL-13 and weak IFN- γ /IL-10 responses consistently display the most severe pathology from *S. mansoni* infection.

We have also identified macrophages and fibroblasts as major targets of IL-13 activity. Macrophages activated with IL-13 express high arginase-1 activity, which is critical for proline production, the basic building block of collagen. IL-13 receptors are also expressed on fibroblasts, and we showed that IL-13 could directly activate collagen deposition by these cells.

Looking ahead, a major objective of my research will be to determine whether IL-13 antagonism can be developed as a strategy to treat chronic fibrotic disease and to characterize the molecular pathway of IL-13-mediated fibrogenesis. Little information exists regarding the regulation of fibrogenesis by type-2 cytokines; therefore, a major effort of our research program in the coming years will be to further characterize this novel aspect of the Th1/Th2 paradigm.

We hope that better understanding these basic mechanisms and disease processes in general will ultimately translate into an effective disease intervention strategy for schistosomiasis. Beyond that, fibrosis is also a major complication in asthma, chronic graft rejection, and several autoimmune diseases. We therefore hope that the information we glean for schistosomiasis may also provide new directions for the treatment of fibrotic disease in general. ■

CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: the NIH Research Festival, the new Clinical Research Information System, GME at NIH, and how NIH should go about breaking bad news.

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

In Future Issues...

- Elias Zerhouni:
Settling In
- The Greening
Of NHGRI
- The 2nd Campus

1) What research made the strongest impression on you at this year's Research Festival? Do you have any suggestions on how to improve attendance at next year's Research Festival symposia and workshops?

2) What are your aspirations with regard to the new Clinical Research Information System, described in the commentary from the Clinical Center director (see page 2)?

3) Should NIH expand the number of ACGME-accredited programs (see pages 8-10)? In what areas?

4) How should NIH break the news—to the public and the scientific community— when a clinical trial must be or has been halted because the study regimen has been found wanting?

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

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