FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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> the Sum of the Parts

COPELAND AND JENKINS AND THE DEVELOPMENT OF MOUSE CANCER GENETICS

by Peter J. Kozel

Nancy Jenkins

Neal Copeland

It's hard to say what the NIH scientific directors were honoring when they picked husband-and-wife cancer genetics investigators Neal Copeland and Nancy Jenkins to present this year's Mider Lecture.

Was it their legacy—almost 700 papers and the reference mouse genome map? Was it their astonishing record of training successful scientists? Was it their innovative "recombineering" technique that's revolutionizing the manipulation of DNA?

Or was it their almost unparalleled, highly productive collaboration, now in its third decade?

The NIH Catalyst spoke with Copeland and Jenkins—chief and senior investigator, respectively, of the NCI-Frederick Mouse Cancer Genetics Program—shortly before they taught a short course on mouse genetics at the Jackson Laboratory in Bar Harbor, Maine, this past summer.

Jenkins and Copeland met in 1977 as postdoctoral fellows in Geoffrey Cooper's retrovirus laboratory at the Dana Farber Cancer Institute in Boston. At the time, retroviruses were at the "very forefront of molecular biology," according to Jenkins. "Mo-

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CC Celebrates 50th at Research Festival

GIANTS STANDING ON THE SHOULDERS OF GIANTS

by Fran Pollner

Vince DeVita put it this way: "It's nice to come home."

And in one way or another, each of the speakers who took the stage to commemorate the CC's 50th anniversary expressed an affection for the daily working environment at NIH and its research hospital that conjured up the image of home:

■ The collaborative and feisty spirit among colleagues reminiscent of the best kind of sibling camaraderie—and squabbling

Bill Branson

CC Director John Gallin salutes former and current NIH scientists and a half-century of transforming research

Bill Branson

Back in the Day: *Former NCI director Vince DeVita displays the senior faculty of the NCI Medicine Branch, circa 1975· (left to right) George Canellos (now at Harvard), Bruce Chabner (Massachusetts General Hospital), Phil Schein (University of Pennsylvania), DeVita ("with more hair and polyester"), and Bob Young (Fox-Chase Cancer Center). DeVita's talk not only tracked the rise of chemotherapy and the decline in cancer mortality, it was a paean to dozens of his NCI colleagues and the Friday afternoon Society of Jabbering Idiots*

■ The perseverance, warmth, and mutual regard that characterized the relationships between the physician-researchers and the patients undergoing experimental treatments, sometimes extending through decades of follow-up

■ The culture of NIH, like that in a nurturing family, that supported the pursuit of new ideas and personal intellectual expansion

They all saw the past—studded with the gems of biomedical research that contributed enormously to science and human health—as prologue to the future.

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Highways and Byways: 50 Years of Research at the Clinical Center

Michael Gottesman

This year we celebrate the 50th anniversary of the opening of the NIH Clinical Center. On October 14, 2003, a symposium was held in Masur Auditorium to recognize the scope and depth of research accomplishments that represent some of the history of the Clinical Center.

Those who attended—whether newcomers to NIH or longtimers who were here when the doors to the Clinical Center first opened—could not help but be impressed by the enormous impact the Clinical Center has had on the practice of medicine, from developing the current paradigm for the chemotherapy of cancer, to changing the way in which ischemic heart disease is treated, to creating new approaches to the treatment of multiple sclerosis.

This kind of occasion also inspires reflection on the constellation of causes of past success to assist us in imagining how best to ensure continued success in the future.

In listening to the presentations and reviewing other contributions made at the Clinical Center, I was struck by the fact that some of the major paradigm-shifting research was accomplished in the face of great resistance and with enormous investment of time, staff, and resources.

In keeping with the current road map metaphor, Clinical Center research built the major highways, bridges, and tunnels that have transformed the face of medicine.

Vince DeVita's recounting of the need for protracted persuasion of influential skeptics in the development of multiagent chemotherapy of cancer—and the involvement of so many physicians and patients over so many years—illustrates the kind of major effort to which I am referring.

Similarly huge efforts informed NIH contributions to cardiac surgery (the first implantation of an artificial mitral valve), to the treatment of manic-depressive illness (demonstration of the dramatic effect of lithium), and to identification and control of HIV infection.

So, too, will current and future undertakings related to major public-health problems require a large commitment of resources and energy. The payoff, however, is certainly larger. We are now in the process of planning a major initiative to better understand the physiological causes and consequences of obesity, an effort that will require a substantial trans-NIH commitment.

But the success of clinical research at NIH is as much written in the shortcuts and scenic byways as in its major highways. When we study rare diseases, we never know at the outset where research will take us, but the results are invariably useful and frequently have profound effects on human health. To paraphrase the novelist E.L. Doctorow: Research "is like driving a car at night. You can only see as far as the headlights, but you make the whole trip that way."

> To paraphrase the novelist E.L. Doctorow: Research 'is like driving a car at night. You can only see as far as the headlights, but you make the whole trip that way.'

The history of the Clinical Center has many examples of circuitous trips without maps that have arrived at unexpected and far-reaching destinations. For example, studies of the rare human embryonic cancer choriocarcinoma, by Roy Hertz and Min Chiu Li, led to a need to follow success of treatment by measuring human chorionic gonadotropin. Judy Vaitukaitus developed the first radioimmunoassay for this hormone—and this assay became the basis for the home pregnancy test, which, needless to say, has had profound social consequences.

Tom Waldmann, in searching for a way to diagnose and treat a rare form of T-cell leukemia, developed an anti-TAC antibody to the α-chain of the interleukin-2 receptor. This antibody blocks T-cell activation and has found important use in the treatment of several autoimmune disorders at the Clinical Center, including multiple sclerosis and autoimmune uveitis.

Finally, our courageous patient volunteers and the observations made by astute clinicians have led to new pathways to discovery. The combined observations of Isaac Asimov and Dr. Seuss summarize the NIH research terrain. Asimov put it this way: "The most exciting phrase to hear in science, the one that heralds new discoveries, is not Eureka!, but Hmm, that's funny." And from Dr. Seuss, we append a key road map legend: "From there to here, and here to there, funny things are everywhere." We need to continue to be accessible to patients with a large variety of disorders, and observe them carefully as we care for them, to learn more about human health and disease.

We are awaiting the imminent recommendations of a Blue Ribbon Panel on Clinical Research at the NIH, co-chaired by Ed Benz, president of the Dana-Farber Cancer Center in Boston, and Joe Goldstein, professor at the University of Texas Southwestern Medical Center, Dallas, on how best to ensure that the new Clinical Research Center has as much impact as the Clinical Center has had in the past.

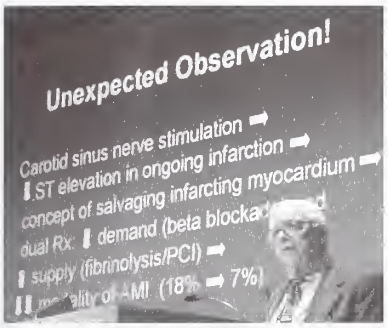
I am confident that NIH will be asked to continue to take on important public health issues—but not eschew the rare diseases that have led to so many important insights about human pathophysiology.

If you are interested in watching and listening to the many outstanding presentations given at the Clinical Center 50th anniversary symposium, they are archived at <**http://www.cc.nih.gov/50th/**>, as are the special 50th-anniversary series of Clinical Center Grand Rounds.

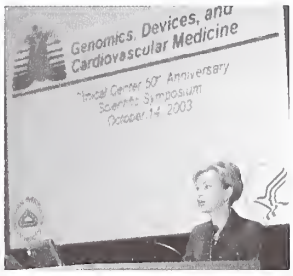
—Michael Gottesman
Deputy Director for Intramural Research

CC Celebrates 50th at Research Festival: Giants Standing on the Shoulders of Giants

photos by Bill Branson
text by Fran Pollner

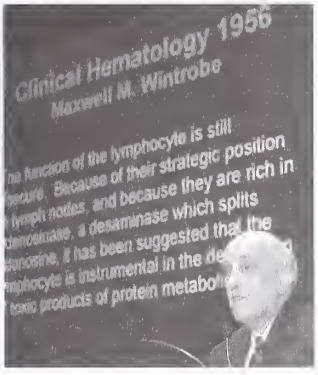


***Eugene Braunwald**, Hersey distinguished professor of medicine, Harvard Medical School (NIH: 1955–1968; hangout: CC, 7th floor, cardiovascular physiology lab): Thanks to the disobedience of a patient on self-activated carotid sinus nerve stimulation, it was learned that ST segment elevation decreases in the midst of an ongoing infarct—and the concept of myocardial salvage was born. With β-blockade and fibrinolysis, acute MI mortality dropped from 18 to 7 percent*

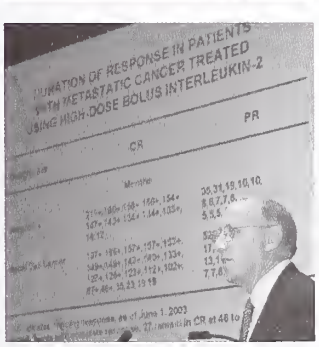


***Elizabeth Nabel**, scientific director for clinical research, NHLBI (at NIH since 1999): Genomics and stem cells are involved in much of cardiovascular disease research at the CC today. Researchers are correlating gene polymorphisms with drug sensitivity and with the propensity for restenosis, and injecting endothelial progenitor cells into ischemic scar tissue to repair vascular damage*

***Vincent DeVita,** professor of medicine, epidemiology, and public health, Yale University (at NIH 1963–1988, as NCI director from 1980): Lead author of the 1970* Annals of Internal Medicine *report establishing that some advanced cancers could be cured by combination chemotherapy, a strategy that launched the era of cancer survival, with rates going from 0 to 80 percent today for some cancers*

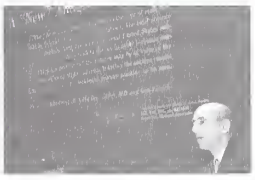


***Thomas Waldmann,** chief, Metabolism Branch, NCI (at NIH since 1956, when, according to the textbook in the background, "the function of the lymphocyte [was] still obscure"): Developer of anti-TAC, the first antibody to a cytokine receptor (IL-2Rα)—used clinically in the management of cancer, transplant rejection, and autoimmune disease and in studies underway at six NIH institutes. The IL-2/IL-15 interface now commands much of his attention. The T cell, Waldmann says, "is the sun of the immunological system"*

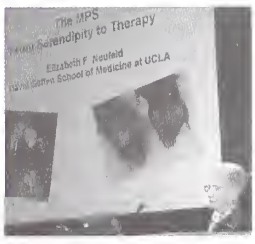


***Steven Rosenberg,** chief, Surgery Branch, NCI (at NIH at this post since 1974): A 30-year odyssey to develop cancer immunotherapy has established that this approach can achieve cures; tumor-infiltrating lymphocytes and tumor-specific antigens are central to a strategy whose latest development involves nonmyeloablative conditioning followed by adoptive transfer of antitumor lymphocytes targeting specific tumor antigens*

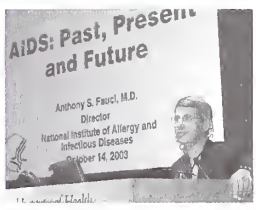
***Francis Collins**, director, NHGRI (at NIH since 1993): What's next after you've mapped the human genome?—a human haplotype map to chart the variants that contribute to common diseases—an international project involving six countries and support from 18 NIH institutes*



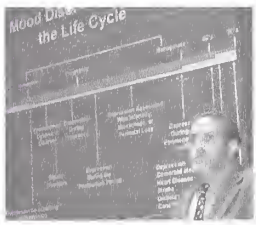
***Harvey Alter**, chief, CC Infectious Diseases Section (at NIH since 1969), Co-discoverer of the Australia antigen, eradicator of posttransfusion hepatitis, and poet: "When I came to NIH as a lowly fellow, I saw that patients were turning yellow . . ."*



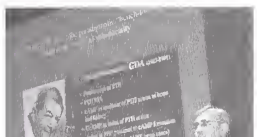
***Elizabeth Neufeld,** professor and chairman, biological chemistry, UCLA David Geffen School of Medicine (at NIH 1963–1984)) devoted to the study of lysosomal enzyme deficiencies, recalled the "inadvertent mix in the Petri dish of Hurler and Hunter cells, which together produced a normal pattern—proving that two wrongs can make a right"*



***Tony Fanci**, NIAID director (at NIH since 1968): Seeing AIDS patients for the first time on the CC's 11th floor, "I didn't fully appreciate this was a new disease, but I was anxious because I couldn't understand it. . . . I turned over my (host immune defense) lab to the study of HIV"*

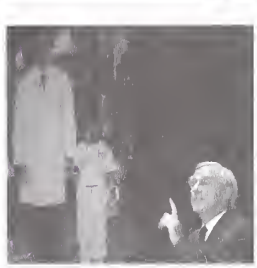


***Dennis Charney**, chief, Mood and Anxiety Disorders Research Program, NIMH (at NIH since 2000): Collaborative proof-of-concept trials are underway that aim at new targets to fight depression, an underappreciated, crippling disorder that can potentiate conditions like heart disease, diabetes, and osteoporosis*



***Allen Spiegel**, NIDDK director (at NIH since 1973), world-renowned for his research in G-protein dynamics and hormone disorders, paid homage to his NIH mentor G.D. Aurbach, who purified parathyroid hormone and launched the study of signal transduction disorders*

***Henry McFarland**, director, Clinical Neurosciences Program, NINDS (at NIH since 1976): "[Early on], multiple sclerosis is inflammatory; later it's degenerative. . . . There are both upregulated and downregulated genes. . . . The key is to conduct small trials of innovative therapies"*



***French Anderson**, director, Gene Therapy Laboratories, USC Keck School of Medicine (at NIH 1965–1992), shown with the first gene therapy patient—age 4 in 1990—whose adenosine deaminase levels are still normal. He asks: "Why is it that she has been able to develop a T-cell response to new antigens? Did some stem cells get in there? Can T cells de-differentiate and be reeducated?"*

Host Response to Infectious Diseases: Scientists Use New Tools, Tricks to Block Infection

text and photos by Peter J. Kozel

New animal models for SARS, the role of T cells in SIV infection, and new vaccine targets were some of the intramural research highlights at the "Host Response to Infectious Diseases" minisymposium on October 15.

SARS Model

Kanta Subbarao

Kanta Subbarao kicked off the session with a description of work by NIAID's Laboratory of Infectious Diseases, which is evaluating animal models for severe acute respiratory syndrome (SARS).

Subbarao delivered the virus into the noses of mice and observed that the virus replicated efficiently, although the animals didn't become ill and displayed only mild histopathology. SARS virus was detected in lungs, and virus-specific hyperimmune sera from infected mice could be used to block infection in other animals. These results are similar to those for influenza and respiratory syncytial viruses in mice.

Subbarao also described her work with primates, including rhesus and African green monkeys and cynomolgus macaques. The virus replicated in the respiratory tract of all three monkey species without causing illness. All species developed neutralizing antibodies, but African green monkeys were protected from a second infection with SARS and proved to be the best model. Subbarao said both the primate and the mouse models would be useful in screening future SARS vaccines and antivirals.

Reducing Cytokine Scarring

Thomas Wynn

Up to 600 million people in 74 countries suffer from chronic schistosomiasis infections. The schistosome parasites cause spleen and liver enlargement and the formation of fibrous scars. Thomas Wynn, a senior investigator in NIAID's Immunopathogenesis Section in the Laboratory of Parasitic diseases, says cytokines are responsible for the scarring.

Wynn's group looked at T-cell responses to different cytokines and determined that by blocking IL-13, fibrosis was reduced. Mouse knockouts and IL-13 receptor agonists confirmed this observation.

Using additional knockout models, Wynn and his colleagues also demonstrated that when the decoy receptor for IL-13 was knocked out, fibrosis increased, arguing that there are both stimulatory and inhibitory receptors for this cytokine. Animals treated with a soluble form of the IL-13 receptor reversed the phenotype in the knockout mice, confirming that the IL-13Rα2 is acting as a "decoy receptor system," inhibiting fibrosis. Wynn's work is applicable to other chronic inflammatory diseases, including asthma and kidney conditions, that exhibit a "terminal stage of inflammation" comparable to the scarring in schistosomiasis.

Cytokine Keys and Intracellular Bugs

Karen Elkins

Intracellular pathogens pose special problems for treatment. Karen Elkins from CBER/FDA's Laboratory of Mycobacteria demonstrated that B-cell knockout mice respond differently to infections of tuberculosis and Francisella, offering new insight into the basic biology of the diseases.

During aerosol tuberculosis infection, lung histopathology showed less-severe damage in B-cell knockout mice, and there was less dissemination of bacteria out of lungs to spleens and livers compared with wild-type controls. But lung tissues were more damaged, and dissemination restored, when B cells were added back to the mice. In contrast, secondary immunity to Francisella was impaired, not improved, in the absence of B cells.

Elkins was able to tease out a "common thread" in how infected macrophages control these kinds of bacteria. Macrophages and dendritic cells secrete IL-12 when infected; this cytokine helps activate production of interferon gamma (IFN-γ), which increases nitric oxide production in macrophages. IFN-γ is a necessary but not sufficient component of adaptive protective immunity; in fact, macrophages from mice lacking the interferon receptor eliminated up to 95 percent of bacteria.

Elkins' elucidation of the varied roles immune cells play in infection by intracellular pathogens could have important long-term consequences for the treatment of these diseases.

For example, IFN-γ is often suggested as both an additional treatment for intracellular pathogens (in combination with antibiotics), and as a marker or "correlate" of protection for vaccine studies. But these data, Elkins observed, suggest that IFN-γ, while important, is far from the only T-cell function needed for protection against these bacteria. In fact, it may actually be a rather minor player; another cytokine, TNF-α, may be key. Further research is necessary to better define those other players, improving treatment options and aiding vaccine development.

New Vaccines Could Foil the Flu—And Other Viruses

Against a background of colorful autumn leaves that coincided with the return of flu season, Suzanne Epstein, chief of FDA-CBER's Laboratory of Immunology and Developmental Biology, described new mechanisms to protect against the flu.

Epstein ascribed "lots of excess deaths" to this highly transmissible virus. Current vaccines provide a measure of protection, but would not stop pandemics such as those in 1918, 1957, and 1968. She cited the basic biology of influenza as the reason. The high mutation rate of this negative-strand RNA virus ensures that the outer coat proteins, to which many vaccines are directed, are constantly changing. Also, entire segments of the viral genome can be swapped between strains (genetic reassortment), bringing in new coat proteins.

Suzanne Epstein

In contrast, Epstein said, the proteins inside the viral particle are fairly conserved, making them excellent vaccine targets. The broad cross-protection they can induce, so-called "heterosubtypic immunity," can be achieved in animals by immunization with live virus and also with DNA vaccines. These new vaccines can deliver a conserved antigen, conferring immunity to many different viral strains and even across subtype differences, which occur in pandemics.

DNA vaccines have another advantage:

Through a Glass Darkly: Strategies To Probe Complex Genetics

by Peter J. Kozel

The tools of molecular genetics have given scientists powerful insights into cellular processes and the diseases that result when pathways break down.

But currently, that vision is limited.

Although hundreds of genes have been associated with diseases, many of these diseases are rarely seen. Meanwhile, major public health problems, such as diabetes, neurological diseases, and lung cancer, resist molecular deconstruction. "Bringing Genetics to the Public" sought to update investigators on the status of complex genetic disease research and strategies to peer through the fog to find causative genes.

Kathleen Merikangas, chief of the Section on Developmental Genetic Epidemiology at NIMH, summarized why complex diseases are so recalcitrant.

Most known disease genes confer a high risk of disease, but such diseases are relatively rare in the population. On the other hand, common diseases are often associated with combinations of multiple disease alleles—at least 10 are associated with type 1 diabetes, for example. Thus, Merikangas said, the risk attributable to a single gene may be so small that it may be missed. In addition, many complex diseases lack narrow, precise clinical definitions, further clouding the interpretation of whole-genome scans.

Merikangas proposed a new model for complex disease research—analytical genetic epidemiology. Combining traditional family studies with biologically validated phenotypes and disease pathogenesis, this model espouses that investigators share kindreds, pool positive—and negative—results, and collaborate with investigators trained in different fields to interpret data.

Kenneth Buetow, chief of NCI's Laboratory of Population Genetics, fleshed out this approach. He urged the audience to "embrace the complexity" of disease and illustrated how bioinformatics can clarify disparate observations. By putting experimental results in the context of pathways and ontogeny, Buetow is creating a "User's Guide to the Human Genome" that will allow researchers to look across gene families and understand disease from a systems perspective.

Buetow's Cancer Genome Anatomy Project links genes and genetic information with mapping and expression data, ontogenies, and biochemical and signaling pathways to help scientists "begin to construct models at different levels."

Noting that useful models for many diseases and processes existed well before genes—or even DNA—had been described, Buetow said he believes that bioinformatics will allow scientists to "connect the dots" to develop a deeper understanding of complex disease.

NIA's John Hardy, chief of the Laboratory of Neurogenetics, addressed the genetic complexities of neurodegenerative diseases. He laid out his path to the study of complex disease: Starting with familial diseases and positional cloning to identify early disease features and rare causes of disease, respectively, scientists can develop an understanding of disease pathogenesis in cellular models.

Testing that pathway in animal models would identify additional candidate genes. Population genetics would associate risk factors with mutant alleles to those genes. This integrated approach would also identify new opportunities for therapy. Hardy concluded by illustrating how this "bench and bedside and back" model was applied in Alzheimer's disease to generate new treatment strategies.

Approaching patients and the public, especially about diseases with behavioral risk factors, introduces another layer of complexity. Colleen McBride, chief of NHGRI's Social and Behavioral Research Branch, showed how genetics can be combined with public-health initiatives to reach large numbers of at-risk individuals. But motivating specific behaviors can entail even more mystifying forces than the most complex cellular pathways (see "Recently Tenured," page 16).

Despite the murkiness, it seemed that NIH investigators left the workshop with a sense of challenge, not despair—reminiscent of Michael Gottesman's paraphrase of Doctorow (see page 2) about night driving and being able to see only so far as the headlights—all the way to the destination. ■

Peter Kozel

Embracing the Complexities: *(left to right) Colleen McBride, Kenneth Buetow, Kathleen Merikangas, and John Hardy*

they do not have to be kept cool, allowing millions of people to be immunized in places lacking adequate refrigeration. Epstein concluded by noting that influenza is not the only virus for which vaccines inducing broad cross-protection might be useful. The knowledge gained in the influenza system can suggest strategies for partial protection to other families of highly variable viruses, such as Hantaviruses and HIV.

Tracking Memory Cell Loss In SIV-infected Macaques

Joseph Mattapallil, a research fellow in the flow cytometry core laboratory of the VRC, and his colleagues are using a rhesus macaque model in an attempt to gain insight into the extensive early loss of CD4 T cells in HIV infection.

Joseph Mattapallil

Initial findings in rhesus monkeys infected with SIV showed that loss of memory CD4 T cells from the peripheral blood was preceded by a severe loss of B cells within a week of infection; this loss could not be accounted for by the expression of CCR5 (a SIV coreceptor) or the mucosal homing receptor CD103.

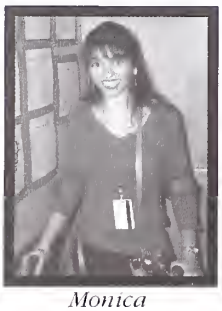
To determine how these memory CD4 T cells were lost, the investigators initiated a second study, which revealed that there was an extensive loss of CD4 memory T cells in the mesenteric lymph nodes within two weeks of infection. The loss was deemed due to direct infection, since more than 90 percent of these cells carried a single copy of SIV.

Whether this mechanism reflects the kind of depletion of memory CD4 T cells that occurs in human infection remains to be determined, Mattapallil said. ■

A Random Sample of Festival Fare

text and photos by Peter J. Kozel

Sun, Genes, And Melanoma



Monica Ter-Minassian

The sun-drenched Italian climate is good for growing both olives and skin cancer. Melanomas have been linked to mutations in two genes involved in cell cycle regulation, *CDKN2A* (protein p16) and *CDK4*.

These genes, however, are not mutated in the population of Northeastern Italian melanoma patients studied by NCI's Monica Ter-Minassian.

Ter-Minassian and her NCI colleagues in the Genetic Epidemiology Branch, DCEG, have now begun whole-genome scans of pedigrees to find linked loci, and eventually genes, in hopes of harvesting the genetic source of melanomas in this region.

Retinoblastoma Mutants

Ruth Kleinerman

Retinoblastoma is caused by mutations in the RB-1 tumor suppressor gene.

In the familial form of the disease, which is characterized by disease in both eyes, children inherit one germline mutation from a parent and acquire a second somatic mutation. Both mutations are acquired somatically in the sporadic form of the disease, which affects only one eye. Sporadic and hereditary RB have been effectively treated by high-dose radiation, a treatment that can induce additional cancers.

Ruth Kleinerman and colleagues at NCI's Division of Cancer Epidemiology and Genetics wanted to determine whether patients with familial forms of RB were more susceptible to additional cancers than those with the sporadic version. A retrospective study of 1601 patients—some diagnosed as early as 1914—revealed that inherited mutations in RB-1 do confer increased sensitivity to radiation-induced cancers, especially in the head and neck.

Kleinerman also observed an elevated risk of other cancers, unrelated to radiation exposure, in children inheriting a mutation in RB-1.

Presenting Cancer E-mice And More...

Fei Xu

A favorite model for studying disease, mutant mice have now been created and examined by the hundreds of thousands. NCI's Mouse Models of Human Cancer Consortium created a new website to help scientists navigate the sea of mouse models for cancers. In his poster, NCI's Fei Xu, of NCI's Center for Bioinformatics, pointed out some of the site features (see <**http://emice.nci.nih.gov**>).

Scientists can search through a cancer model database containing information on all cancer mice by gene, lab, diagnosis, and tumor location. Links interconnect genes with publications, therapeutic strategies, images, and microarray data. Sister sites provide clinical trial information, point mutation databases (human and mouse), SAGE profiles for cancerous and normal tissues, and clickable pathway diagrams. Many of these data are interlinked, allowing scientists to identify new research targets, plan experiments—and predict results.

Autofluoresence —Turning Lemons Into Lemonade

Maria Campos

Fixing tissue samples in formaldehyde or glutaraldehyde has long been the best way to preserve cellular structure. Unfortunately, prolonged exposure to these fixatives causes samples to fluoresce, and this complicates analysis using newer imaging techniques such as confocal microscopy. But Maria Campos and her colleagues at NEI have turned this disadvantage into a strength.

Campos uses differential interference contrast (DIC) to identify blood vessels of interest in preserved eye tissue from people with diabetes and experimental rat models. She then switches to confocal microscopy, using specific wavelengths to exploit the auto-fluorescence characteristics of aldehydes.

Campos' technique opens up repositories of eye and other tissues—collected for decades—to study via contemporary imaging techniques.

Tracking MS With MRI

Stasia Anderson

Being able to track immune cells in vivo would improve understanding of autoimmune disease. Early-stage multiple sclerosis (MS) is thought to involve a reaction to myelin.

Stasia Anderson, an NINDS staff scientist working in the CC's Experimental Neuroimaging Section, is developing a method to visualize anti-mylelin T cells via MRI. She used ferumoxides-poly-L-lysine iron nano-particles to label T-cell endosomes (iron cannot be applied to the cell membrane because it might interfere with antigen binding).

Anderson and her colleagues demonstrated that labeled T cells are functionally identical to their unlabeled counterparts. Using the experimental allergic encephalomyelitis mouse model of MS, she visualized labeled T cells in spinal columns of live mice at a resolution of 78–80 μM; higher resolutions can be achieved on sacrificed animals.

Due to the limitations of in vivo MRI, individual cells could not be visualized. However, Anderson did observe the temporospatial migration of groups of T cells that initiate myelin damage in the spinal cord in the live mice—suggesting that this technique may allow monitoring of disease course, as well as therapy used to change the immune response.

Glucosamine and Chondrocytes

Many people take glucosamine as a nutritional supplement to ward off, or at least lessen, the effects of arthritis. Amy Miyoshi, working in Rocky Tuan's NIAMS laboratory, wanted to examine glucosamine's effect on human cells.

Collagen and proteoglycan deposition, measures of chrondrocyte differentiation, declined when glucosamine

was added to mesenchymal stem cells. Mesenchymal progenitor cells have the potential to differentiate into chondrocytes.

Amy Miyoshi

Miyoshi and her colleagues added glucosamine to high-density mesenchymal stem cell cultures undergoing chondrogenesis and saw an inhibition of collagen and proteoglycan expression. In contrast, collagen and proteoglycan levels rose in primary chondrocytes, which were prepared from normal and osteoarthritic cartilage taken from human knee replacement surgeries.

The next step will be to test mesenchymal stem cells and chondrocytes growing on a synthetic matrix in order to mimic an in vivo environment. It may be, she speculated, that glucosamine works to maintain a correct balance between mesenchymal stem cells and existing condrocytes.

Sniper Attacks And Stress

Beatrice Del Riccio

Completing everyday errands, such as buying gasoline, in the greater Washington, D.C., area last fall was complicated by random sniper attacks. But did the shootings increase depression and anxiety?

Summer intern Beatrice Del Riccio, a senior at Georgetown Day High School in Washington, and her colleagues at NIMH tried to answer that question in a study involving women with depression who were already participants in the POWER (premenopausal, osteoporosis, women, alendronate, depression) study and a control group of women.

Depression and anxiety levels, as well as biological measures of stress, including plasma cortisol and ACTH, were assessed before and during the sniper attacks. In neither group did the biological and psychological parameters of stress change during the sniper attacks, Del Riccio reported. ■

ProtoType: According to Protocol

According to Bob Nussenblatt, it's a "very smart" package.

"It knows the format to use for the various institutional review boards.

"It asks you what kind of study you're doing, and if you click on to 'interventional,' it will ask a series of questions to determine if you need an IND [investigational new drug].

"In most cases, you will—and when that occurs, there will be another module with a form to fill out for the IND submission [to the FDA]. And much of that form will be prepopulated with the information you already put into the clinical protocol.

"It has links to important regulations. And you won't have to worry that you're doing something with rules that expired three years ago, or that you're missing some form that is now necessary.

"Everything we could think of is under one roof."

Fran Pollner

Robert Nussenblatt

That roof is ProtoType, a web-based software program that standardizes the framework for writing a clinical protocol but does not box the PI in to rigid descriptions of the nature of the research. Among the menu items is IC selection, so that if there are any institute-specific protocol requirements, the appropriate format will be offered. ProtoType will be available to the intramural community by year's end—at:

<https://prototype.cc.nih.gov>.

The builders of ProtoType are Nussenblatt, chief of the Laboratory of Immunology, NEI, and director of the CC Office of Protocol Services, and a "small group" of NIH clinical investigators and administrators who "all saw the need for more standardization but with continued flexibility"—as well as the desirability of being able to capture electronically the evolving protocol in all its iterations as it goes through the various levels of of review and revision. The program also automatically alerts the PI to any information gaps and guides the user on how to include the missing piece before proceeding.

The idea, Nussenblatt says, is to provide the PI with a more rapid and better way to do things, minimizing the chances of overlooking some crucial bit of information that will delay protocol approval and also enabling better tracking of patient status once the trial gets going, a safety feature.

A reporting system for adverse events is built into ProtoType, enabling the investigator to keep accurate records of these findings and also ensure that the wording is right. "The goal," Nussenblatt says, "is that required adverse event reports go directly to the relevant agencies, such as the FDA if an IND is involved, and in the right time frame, which varies depending on the severity" of the adverse event.

Using ProtoType is not now viewed as a prerequisite for conducting clinical trials at the CC. "It's not mandatory, but we're hoping that investigators will see it as counterproductive not to use ProtoType. There are just so many positives, it's hard to guess why someone would choose not to," Nussenblatt observes.

The prototype for ProtoType had been germinating for about two years, beginning with discussions between Nussenblatt and CC director John Gallin and gradually including other clinical investigators at NIH whose experiences in writing clinical protocols and conducting clinical trials at the CC informed their opinions on how the protocol-writing process could be improved. "The product is definitely a reflection of what clinicians wanted," Nussenblatt says, "and as it turned out, it also harmonizes very well with the international committee on harmonization of all aspects of clinical protocols and clinical trials."

For ProtoType's journey from vision to reality, Nussenblatt hastens to credit Kim Jarema, chief of the Office of Protocol Services; Steve Rosenfeld, chief of clinical research informatics; Elaine Ayres, ProtoType project officer, and, especially, Gallin.

In his closing remarks at the day-long symposium celebrating 50 years of CC clinical research, Gallin referred to ProtoType as the answer to investigators who have come to his office saying that they "would like to do clinical research, but it's just too hard." ProtoType, he noted, will hook into the new Clinical Research Information System, the informatics arm of the new Clinical Research Center (see Guest Editorial, *The NIH Catalyst*, November-December 2002, page 2).

The future of clinical research at the CC, Gallin observed, "is now."

—Fran Pollner

For more information about ProtoType, including training, contact Robert Nussenblatt at ***<rnq@helix.nih.gov>*** *or 6-4449, Kim Jarema at* ***<kjarema@mail.cc.nih.gov>*** *or 5-2401, or Phil Lightfoot, ProtoType administrator, at* ***<plightfoot@mail.cc.nih.gov>*** *or 6-0744.*

Mouse Cancer Genetics

continued from page 1

lecular biology was just flourishing," Copeland continues. "They lifted the cloning ban shortly after we arrived in Boston and Boston became a hotbed of molecular research. I think we probably did the first Southern blot at Harvard Medical School, with David Livingston's help," he recalls.

By 1980, Jenkins and Copeland had decided to marry and began to look for institutions that would hire them both. One offer, from the Jackson Laboratory, was an intriguing, albeit curious, choice.

"We didn't know mouse biology at all," Copeland recounts. The pair quickly realized that "JAX" and its mouse mutants were a gold mine—"models for human cancer and a lot of developmental disorders in people. We could apply molecular biology to mouse genetics and the combination of the two would hopefully be better than each of the parts," Copeland says.

"It was a very unique time at JAX," Jenkins continues. "There were no other molecular biologists. We were the first [at JAX], and they were very excited about learning molecular biology, and they reciprocated by teaching us formal genetics."

"A lot of the projects we worked on for the last 20 years, and what we work on today, got their start when we were at The Jackson Lab," Copeland reminisces. "It was a magical time to be there. It set the tone for our whole career."

After three years of learning, teaching, and groundbreaking publications, Jenkins and Copeland were getting restless. As much as they loved the research environment, "we were just going stir crazy," says Copeland. Jenkins found Bar Harbor "a little too isolated" by 1983, and the pair moved to the University of Cincinnati, the only place to which they applied.

It wasn't long before they started to be recruited by, and interested in, other programs. Jenkins remembers, "We weren't looking for jobs, but the draw of having a really large animal colony that we could devote to our numerous interests—we think the whole genome is interesting—was just too strong to let go."

George Vande Woude offered the couple the chance to pursue their interests as he was setting up the NCI-Frederick Applied BioSciences Laboratories–Basic Research Program in 1985. They saw it as a unique opportunity to conduct mouse genetic research on an unprecedented scale. "We really wanted to fuse molecular biology and developmental biology on a large scale in mice . . . . this was the only place we could really do it," says Copeland.

The Royal Beginnings Of Mouse Genetics

"The first geneticists were the Japanese emperors," Jenkins notes. "They collected the unusually colored mice and the neurological mutants, the waltzers. When trade finally opened between Europe and Japan, the mice were given as pets or presents to Europeans.

When Mendel's laws were rediscovered at the beginning of the 20th century, all they had for reagents were these funny colored mice and ones that had neurological phenotypes."

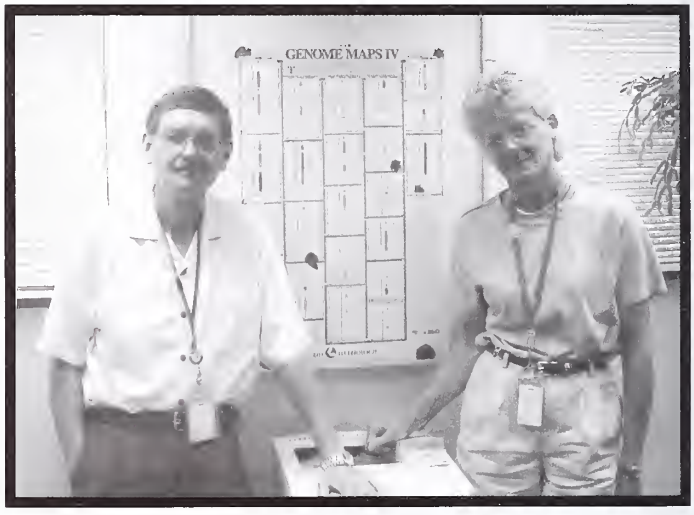
Copeland says the mouse fanciers bred coat color mutants such as "*dilute*," "*brown*," and "*non-agouti*." These mutations were incorporated into early inbred strains, such as "DBA," which had all three traits.

"Dilute" has a special significance for the lab, Copeland says. "The first paper we ever published together at JAX was a 1981 article in *Nature* that showed that *dilute* was caused by the integration of a retrovirus into the mouse genome that happened hundreds of years ago. That was the first insertional mutation ever described in mammals." This mutation could be traced back to a mouse fancier in the 1700s, and from there to the Japanese emperors. "We've been studying that mutation ever since."

Dilute was just the beginning. In the ensuing years, Jenkins says, "there's almost no area of biology that we haven't touched on." The overall theme has remained constant, however. Copeland says, "We specifically tried to work on mutations that were models of human disease."

The translational emphasis has permeated Jenkins' and Copeland's work in both development and cancer biology and the intergrading and interacting zones of these fields. Copeland notes that the coat color mutations, for example, led to a deeper understanding of deafness disorders, such as Waardenburg syndrome type 2A.

Jenkins says the goal of their work "has always been to manipulate genes and understand their biology, their physiology, [and] their interaction pathways in mouse and [to] try to translate that back into human."



Peter Kozel

Neal Copeland and Nancy Jenkins backlit by their famous map of the mouse genome

She sees the mouse as an excellent model for human diseases—about 80 percent of human genes have mouse orthologs.

The human-murine genetic similarity has led to some amazing genetic feats. Shyam Sharan, an investigator in the Mouse Cancer Genetics Program, has "rescued the embryonic lethality of the loss of a mouse *BRCA* gene with a human ortholog." Copeland notes that this is even more astonishing because "the regulatory sequences are not conserved at all" between the two species.

Copeland says his more than 20 years of experience has forged his impression that, as a model of human disease, the mouse is "much better than we expected." Noting that it's not perfect, Jenkins says, "the mouse has three very strong advantages: it's a mammal; you can manipulate its germline . . . and you have very good genetics." As if tossing down a latex glove, Copeland adds, "I

challenge you to find a better one."

One way that Jenkins and Copeland linked their mouse mutants to human disease was by mapping and cloning the genes responsible for the spontaneous mutations in JAX mice. The pair learned about interspecific backcrossing needed for this linkage at a conference shortly after arriving in Frederick.

Realizing its potential, Copeland recalls, "when we came back, we announced to the postdocs, 'we've decided to make a map of the mouse genome. Would you like to participate?'"

The project quickly took on a life of its own. Copeland and Jenkins spoke about their map at meetings, and it quickly attracted the appreciation and contributions of other scientists. Copeland recalls, "People would say, this is really cool! And so we had more and more people contacting us, and pretty soon we were overwhelmed."

Although other groups also made maps of the mouse genome, it was the Jenkins-Copeland map that was the standard in the field for several years. They note that there are several reasons for this success. Their map was gene-based, and human gene-hunters could use their mouse map to predict locations—and proximity to disease genes—on human chromosomes. As new genes were mapped, the resolution of the map improved.

Another key advantage of the pair's map was that it focused on the markers and repeated questionable results until they "disappeared." Finally, all the mapping experiments were carried out in-house—making for "extremely high quality," according to Copeland.

The map eventually became an international resource that Jenkins, Copeland, and their collaborators used to localize and clone entire families of new and important genes.

Technology for the Future: Recombineering

With the mouse genome nearly complete, Jenkins and Copeland have moved beyond mapping. "Technology has always been a real interest," says Jenkins. In 2001, they described a groundbreaking new method for precisely manipulating cloned DNA by homologous recombination, alleviating the need for restriction enzymes and DNA ligases.

Dubbed "recombineering," this technology sprang from the brainstorm of an excited postdoc returning from a meeting. Developed in collaboration with Donald Court's bacterial genetics lab across the hall, recombineering "has widespread implications for mouse functional genomics," according to Copeland. "Everybody's using it," he adds. "As far as I can tell, it's not limited to any species, prokaryotic or eukaryotic."

Recombineering takes advantage of enzymes from bacteriophage λ to precisely manipulate DNA cloned in plasmids, BACs, or PACs, or even the *Escherichia coli* chromosome.

For example, Copeland explains that they use recombineering to "make conditional targeting vectors in less than two weeks," a process that takes months using conventional cloning techniques.

Epitope tags can also be introduced "to the nucleotide, anyplace you want in cloned DNA, and it does not depend on the location of convenient restriction enzyme sites," Jenkins adds. "It's almost like PCR was in its infancy," Copeland continues. "There are so many uses. The more we give it out, the more people think about what you can do with it."

The method is extremely popular—"most every system that has a BAC library at some stage of development has requested this," Jenkins notes.

In addition to the conditional targeting vectors they are making for their own mouse research, Copeland and Jenkins are setting up a recombineering core to make targeting vectors for NCI's Mouse Models of Human Cancer Consortium.

Even before developing the revolutionary recombineering technique, the Copeland-Jenkins lab had generated such powerful new tools, data, and strategies that in 1999 it was given an expanded mission and renamed the Mouse Cancer Genetics Program.

The team could now offer to other early-career investigators the lure that had brought them to Frederick. In addition to tenure-track investigators Sharan, in breast cancer, and Lino Tessarollo, a neurogeneticist, Jenkins and Copeland have successfully recruited another two "spectacular" tenure-track investigators: Karlyne Reilly, who works on brain cancer modifier genes, and angiogenesis researcher Brad St. Croix. "They were our top two candidates," remembers Copeland. They are now about to begin a search for the program's next recruits.

While Copeland and Jenkins recognize it would be impossible to support their research program at a university, they still "really like training and teaching." Speaking like a proud parent, Jenkins credits much of the success of their lab to their "incredibly talented postdocs." She says they try to encourage creativity and then send the postdocs on their way only when "their creativity is fully in bloom."

The postdocs usually don't leave empty-handed, but take with them the research projects and mutant mice they've developed. "We've trained, frankly, some of the best people in mouse genetics," Copeland says. "They've been successful because they have projects that are great for grants, and they didn't have to compete with us."

Copeland and Jenkins also avoid competing with one another. Although administratively separate, their labs function as a single entity, as they have since they began work at JAX, where they shared an office, research projects, and publications. "It was never clear to us what you gain by splitting everything up," Jenkins says.

"A lot of fairly well known scientists have looked at our careers and have said that we're better working together than we would be on our own," Copeland says.

After more than 20 years and nearly 700 co-authored papers, the couple often finishes each other's sentences, but can't precisely explain how the symbiosis of their careers evolved.

"It just happened that way," Jenkins reflects. "Each one of us has strengths and weaknesses that the other one complements. People who know us say that the sum is better than the parts." ■

Copeland & Jenkins To Deliver Mider Lecture

Neal Copeland and Nancy Jenkins are this year's Mider Lecture honorees, a recognition of their significant contributions to the biomedical research eminence of NIH.

They will deliver their lecture—"Retroviral insertional mutagenesis provides a road map for navigating the cancer genome"—on Wednesday, **January 14, 2004, at 3:00 p.m.,** in Masur Auditorium, Building 10. ■

Selected NIH Intramural Research Accomplishments 2002–2003

Organized According to Government Performance and Results Act Goals

Goal A: Add to the body of knowledge about normal and abnormal biological functions and behavior

Identification of disease genes

- Identification of *Vang12* as a gene important for the correct organization of stereocilia within the sensory cells of the inner ear, the appropriate movement of which is the first step in the detection of sound (NIDCD, NCI)
- Identification of the gene responsible for the ability to taste phenylthiocar bamide contributes to understanding phenotypic variations in bitter taste sensitivities, with implications for clinical interventions related to diet and behaviors such as smoking (NIDCD)
- Identification of a novel mutation of *PCDH15* that accounts for a large proportion of cases of type 1 Usher syndrome among Ashkenazi Jews (NIDCD)
- Identification of genetic defects in two drug-metabolizing enzymes, CYP2C9 and CYP2C19, offering the prospect of genetic testing to customize drug prescriptions; among drugs metabolized by these enzymes are anticoagulant, anticonvulsant, antidiabetic, antihypertensive, antiinflammatory, antiulcer, and antianxiety agents (NIEHS)
- Discovery of a gene involved in congenital hydrocephalus in mice—*Rfx4*—which establishes a model system to study genetic and environmental causes of hydrocephalus in humans and lays the groundwork for developing screening assays for defects in the *Rfx4* human gene (also cloned) (NIEHS)
- Identification of the gene *HRPT2*, whose inactivation predisposes to hyperparathyroidism–jaw tumor (HPT-JT) syndrome (NHGRI, NIDDK)
- Identification of *SUFU* as a susceptibility gene for medulloblastoma (NCI)
- Discovery of mutations in a novel kidney cancer gene (*BHD*) that lead to kidney tumors, lung wall defects, and benign tumors of the hair follicle in patients with Birt-Hogg-Dubé syndrome (NCI)
- Identification of the genetic basis for Hutchinson-Gilford progeria syndrome, which may shed light on the general phenomenon of human aging (NHGRI)
- Identification of the genetic basis for Charcot-Marie-Tooth disease type 2D and distal spinal muscular atrophy type V, a finding that could have implications for other inherited neuropathies and motor neuron diseases as well (NHGRI, NINDS)
- Identification of de novo *CIAS1* mutations in about 50 percent of clinically recognized neonatal-onset multisystem inflammatory disease, a pyrin-associated autoinflammatory disease, with implications for IL-1 receptor blockade treatment (NIAMS, NIAID)
- Identification of *H2AX*, a core histone component, as a tumor-suppressor gene in mice that works in concert with *p53;* the absence of even one allele increases tumor formation in the absence of p53 (NCI)
- Identification of the human chromosomal regions that contain allelic variants that predispose to addiction vulnerability (NIDA)
- Mutation in a gene that encodes the largest subunit of the axonal transport protein dynactin found to cause motor neuron disease characterized by muscle weakness and vocal fold paralysis (NINDS, NIDCD)
- Identification of a novel ubiquitin ligase as a new Fanconi anemia gene—the first of the Fanconia anemia genes found to encode a product, PHF9, with catalytic activity that might serve as a target for new therapeutic modalities (NIA)
- Correlation of an amino-acid–altering polymorphism in the *BDNF* (brain-derived neurotrophic factor) gene with ability to remember past experiences, measures of hippocampal neuronal activity, and hippocampal activation patterns (as seen on functional MRI), findings that advance the study of Alzheimer's disease, depression, and normal aging (NIMH, NIAAA, NCI, NICHD)
- First demonstration in humans of a genetic basis (*COMT* gene variations) for individual differences in the brain's response to amphetamine, suggesting that COMT genotype be taken into consideration in managing such disorders as depression, schizophrenia, Parkinson's disease, attention deficit disorder, and traumatic brain injury (NIMH)

Important new animal models

- Claudin 14 knockout mice, a model for autosomal recessive deafness DFNB29, tracks the rapid degeneration of cochlear hair cells during the second and third weeks of life, when hearing function in mice is being established (NIDCD, VRP)
- Mouse models of mutations in the A-type lamins—structural proteins in the nucleus associated with congenital forms of muscular dystrophy, cardiomyopathy, peripheral motor neuropathy, lipodystrophy, and premature aging—cast light on how nuclear organization relates to cell function in developmental and disease processes (NCI)
- A pyrin-truncation mouse model of familial Mediterranean fever exhibits heightened sensitivity to endotoxin, suggesting that in affected humans, transient bacteremias might provoke systemic inflammatory response and pointing to potential treatments involving recombinant IL-1 receptor antagonist and pharmacologically manipulated pyrin (NIAMS, NHGRI)
- A chemokine receptor mutant that resulted in impaired adhesive function is found to be associated with reduced risk of atherosclerotic cardiovascular disease in humans; a mouse model demonstrated the mutation's effect on the development of atherosclerosis (NIAID, NHLBI, NICHD)
- A new mouse model for S-Ag–induced uveitis supports an etiological role for retinal antigens and facilitates development of antigen-specific therapies tailored to particular HLA haplotypes; the model presents a vehicle to engineer the development of autoimmunity (NEI)
- Discovery that the regulation of epidermal factors controlling the skin's permeability barrier depends on a kruppel-like transcription factor leads to the development of a mouse model for studying how to accelerate the process of barrier acquisition in premature infants (NHGRI)

Basic discoveries in cell, molecular, and structural biology with implications for the treatment of human disease

- Study of the interaction of *cadherin 23*, and accelerating alleles in mice, sheds more light on predisposition to age-related hearing loss and noise-induced hearing loss in humans and informs the exploration of stem cell treatment strategies (NIDCD)
- The actin cytoskeletal core that supports the stereocilia within the inner ear sensory cells is not rigid, as previously thought, but undergoes dynamic renewal in about the same time it takes to recover from temporary noise-induced hearing loss (NIDCD)
- Single-cell mutational analysis of the c-*kit* gene demonstrates that systemic mastocytosis is a clonal disorder of a pluripotential hematopoietic progenitor cell; the study establishes the precision of the single-cell PCR technique and also suggests that the development of mastocytosis may require two lesions of the c-*kit* gene (NIAID, NIAMS)
- The finding that cell-free hemoglobin limits nitric oxide availability in sickle cell disease suggests the potential benefit of therapies that accelerate cell-free ferrous hemoglobin oxidation (NIDDK, CC, NHLBI)
- Individuals with risk factors for coronary artery disease have reduced numbers of circulating endothelial progenitor cells, which may contribute to impaired angiogenesis and ventricular remodeling in myocardial ischemia (NHLBI)
- Reduction of nitrite to nitric oxide by deoxyhemoglobin in the circulation leads to vasodilation of blood vessels (NHLBI)
- A novel cytokine-receptor–binding aminopeptidase (ARTS-1) may regulate inflammation by promoting release of three families of soluble cytokine receptors: type I tumor necrosis factor, type II interleukin-1, and interleukin-6 receptor-α (NHLBI)
- The chromatin-binding protein HMGb3 is required to prevent differentiation of he-

matopoietic stem cells and must be downregulated to enable differentiation of myeloid and B cells; HMGb3 deficiency causes a functional loss in stem cell activity (NHGRI)

■ Elucidation of the aggregation of α-1-proteinase inhibitor (PI) deficiency and associated liver disease may improve the manufacture of α-1-PI augmentation products (CBER, NIDDK)

■ A new type of prion, based on autoactivation in trans rather than amyloid formation, is discovered (NIDDK)

■ Continuing studies of the pathogenesis of HIV infection suggest that integrin avb3 (the vibronectin receptor) plays a role in HIV infection of peripheral blood monocyte-derived macrophages and may be a CD4 cofactor in promoting viral entry into cells (CBER, NIDCR)

■ Recognition that the synuclein gene locus is triplicated in Parkinson's disease, with a concomitant increase in the production of synuclein mRNA and protein, advances understanding of Parkinson's mechanisms and informs treatment strategies (NIA, NINDS, NHGRI)

■ A single treatment of recombinant humanized erythropoietin after coronary artery ligation in rats dramatically reduces the extent of myocardial infarction (MI) and left ventricular functional decline that occurs in untreated animals, a finding that supports the initiation of clinical studies in MI patients (NIA)

■ Animal studies show that nitric oxide signaling and brain-derived neurotrophic factor (BDNF) together regulate neurogenesis in the mammalian brain and that dietary restriction increases neurogenesis, apparently by stimulating production of BDNF; drug and dietary strategies to prevent or treat human neurodegenerative disorders might be entertained (NIA)

■ Dietary restriction (intermittent fasting) in *huntingtin* mutant mice, an animal model for Huntington's disease, increases levels of BDNF and the protein chaperone heat-shock protein-70, slows the progression of neuropathological, motor, and metabolic abnormalities, and extends lifespan, suggesting that dietary intervention may suppress the disease process in humans who carry the mutant *huntingtin* gene (NIA)

■ In a study for the first time linking two signaling pathways—β-1 adrenergic receptor (AR) and the Ca^{2+}/calmodulin kinase II—sustained β1AR stimulation precipitates cardiac myocyte apoptosis, suggesting signaling-selective receptor stimulation in the management of cardiovascular disease—for example, selective β1AR blockade with concurrent β2AR activation as a potential approach to chronic heart failure (NIA)

■ HuR, an RNA-binding protein whose depletion via AMP-activated protein kinase activity is associated with cell senescence, is found to play a major role in enhancing p53 translation in response to ultraviolet irradiation, suggesting that it has a broad role in cellular response to toxic agents (NIA)

■ Ovarian cancer cells engineer resistance to cisplatin by remodeling the extracellular matrix through upregulation of *COL6A3*, increasing tumor cell collagen VI expression; strategies to inhibit ECM-tumor interactions may enhance chemotherapy (NIA, NHGRI)

■ The role of receptor channels in mediating calcium signaling leading to the secretion of pituitary hormones essential for normal breast development, lactation, and reproductive function is elucidated (NICHD)

■ Demonstration of a physical association between anaphylatoxins and the constant region of immunoglobulin (F9ab)2 fragment suggests a strategy for interference with the inflammatory process (NINDS, NICHD, NIAID, NHLBI, CBER)

■ Discovery of a mechanism for the development of AIDS-related lipodystrophy and insulin resistance in successfully treated AIDS patients—two small proteins encoded by HIV that are produced by the patient's cells and usurp the normal proteins that regulate hormone actions and gene transcription—suggests a therapeutic role for antagonists to these two viral proteins (NICHD, NCI)

■ Glial cell-line–derived neurotrophic factor and neurturin are demonstrated to be new neuromodulators that regulate the development of the neuromuscular synapse through both pre- and postsynaptic mechanisms (NICHD, NCI)

■ Elucidation of the immune-suppressing mechanisms of human herpesvirus 6, a HIV co-pathogen, provides the first evidence in a physiologically relevant model (human lymphoid tissue) that HHV-6 can severely affect the physiology of secondary lymphoid organs through direct infection of T lymphocytes and modulation of key membrane receptors and chemokines (NICHD)

■ Structural and functional studies of glutamate receptors, including high-resolution X-ray structures of glutamate receptor agonists, provide detailed insight into the molecular basis of ligand-receptor subtype specificity that may aid in the design of selective agonists to manage stroke damage and other CNS disorders associated with dysfunctional glutamate receptor activity (NICHD)

■ Development of a new method for culturing *Plasmodium falciparum* at high erythrocyte concentrations demonstrates that *P. falciparum* can replicate at packed densities and offers a new approach to studying the pathogenesis of cerebral malaria (NICHD)

■ The mechanism by which anthrax lethal toxin suppresses normal protective anti-inflammatory response—by repressing certain nuclear hormone receptors—can aid in the development of new treatments and prevention of the toxic effects of anthrax (NIMH, NIAID, NIDDK)

■ Elucidation of the mechanism by which IL-2 adjunctive therapy expands peripheral CD4+ T cells in HIV-infected patients is elucidated (CC, NIAID)

■ The DNA polymerase, DnaE2, is found to contribute to the survival and emergence of drug resistance in *Mycobacterium tuberculosis,* suggesting a potential new target for therapeutic intervention (NIAID)

■ Intravenous immunoglobulins are found to neutralize the pro-inflammatory effects of complement fragments C3a and C5a—potent anaphylatoxins—in a mouse model of asthma and a pig model of cardiopulmonary distress, suggesting a possible expansion of the clinical applications of therapeutic doses of immunoglobulins (NINDS, NICHD, NIAID, NHLBI, CBER)

■ Animal studies of scrapie transmission into a resistant species produces subclinical infection with underlying persistence, replication, and adaptation of infectivity, suggesting that subclinical infection of humans exposed to bovine spongiform encephalophy (mad cow disease) could lead to dangerous transmission in the future (NIAID)

■ Discovery of elevated levels of IL-6 in patients with mastocytosis has implications for therapy (NIAID)

■ Studies in yeast and human cell extracts demonstrate that cadmium acts as an environmental mutagen and carcinogen by inhibiting the DNA mismatch repair system, rather than by direct DNA damage (NIEHS)

■ Elucidation of the molecular mechanism by which chelation therapy effects methylmercury excretion after mercury-induced renal damage suggests that variations in organic anion transporters may explain individual susceptibility to methylmercury toxicity (NIEHS)

■ Mesoamerican Mestizos and North American Caucasians with idiopathic inflammatory myopathy display differing patterns of clinical manifestations, autoantibodies, and immunoglobulins, suggesting that expression of this condition is modulated by different genes and environmental exposures around the world (NIEHS)

■ Postpartum uterine tissue remodeling appears to be the mechanism by which parity confers protection from uterine fibroids (NIEHS)

■ A polymorphism in the *COMT* (catechol-*O*-methyltransferase) gene affects opioid μ-receptor mediated responses to pain and was found to be associated with anxiety disorder among Caucasian and Plains American

Selected NIH Intramural Research Accomplishments 2002–2003

continued

Indian women (NIAAA)

- Demonstration of impaired synaptic plasticity in the brain and well-defined functional consequences of prolonged marijuana use (NIDA)
- Description of the ascending pathway from the primate brainstem to the cortex sets the stage for tracking other ascending pathways, and the impaired feedback is thought to contribute to such conditions as acquired nystagmus, spasmodic torticollis, Parkinson's disease, and schizophrenia (NEI)
- Identification of a cellular phenotype characteristic of Lowe syndrome provides a model system to test possible interventions in the disease process (NHGRI)
- The results of a 10-year imaging study show that although children and adolescents with attention deficit hyperactivity disorder have smaller brain volumes than healthy controls (whether previously medicated or not), their brain development throughout childhood and adolescence is similar to controls, evidence that stimulant drugs do not disturb brain development (NIMH, NINDS)
- Elucidation of the process by which inhibitory synaptic neuronal endings absorb glutamate, which leads to the production of GABA and may prevent seizures resulting from excess glutamate, advances understanding and control of epilepsy (NINDS)
- Neurocognitive effects of chronic marijuana, cocaine, and alcohol use are found to persist after 28 days of abstinence, with severity related to dose; multiple drug use produces additive negative effects (NIDA)
- The finding that T cells reactive to myelin basic protein contribute to disease activity in multiple sclerosis points to a more specific target in future therapeutic trials (NINDS)
- Discovery of second-site, function-restoring mutations in Wiskott-Aldrich syndrome suggests that such genetic reversions may take place more frequently than generally believed and that identification and characterization of the mechanisms underlying back mutations can aid in the development of new therapeutic strategies for genetic disorders (NHGRI, NCI)
- The potential for blood-cell–associated prion proteins to transmit transmissible spongiform encephalopathies through blood transfusion is elucidated (NHLBI, CBER)
- Embryonic epithelial branching in the morphogenesis of salivary glands depends on regulation by the extracellular matrix protein fibronectin, just as do lung and kidney development (NIDCR)

Goal B: Develop new or improved instruments and technologies for use in research and medicine

- Use of more relevant computed tomography measures to determine visceral adipose tissue (VAT) volume, which refutes findings in other studies that sex differences documented in other racial groups do not apply to African Americans (NIDDK, NICHD, CC)
- Design and manufacture of a unique acupuncture needle with a microdialysis probe that enables the recovery of biological agents from the tissue surrounding the needle tip (DBEPS, CC)
- Development of fine-bore immunoaffinity capillary electrophoresis enabling multiple analyte analysis on collected samples (DBEPS, NINDS, NICHD)
- Development of a 3-D anatomically correct computational model of the human spinal cord to model drug delivery and tissue distribution, with the aim of studying this system to treat chronic pain (DBEPS, NIDCR, NINDS)
- Development of a variant of green fluorescent protein that allows selective marking of proteins through photoactivation (PA-GFP), a labeling method preferable to photobleaching for studying temporal and spatial dynamics of proteins and addressing fundamental questions in cell and developmental biology (NICHD)
- Measurement of the kinetics of folding of a single protein molecule (NIDDK)
- Delineation of a molecular structural model of amyloid fibrils formed by the 40-residue β-amyloid peptide associated with Alzheimer's disease (NIDDK)
- High-resolution microscopy, high-throughput imaging, and computer simulations to study the positioning of entire chromosomes and gene loci within the nucleus and their rearrangements during differentiation and tumorigenesis, which enhances understanding of how spatial organization affects genome expression and could lead to new diagnostic and analytic cytogenetic tests based on interphase genome organization (NCI)
- Human lymphoid tissue studies to elucidate the dynamics of HIV-1 variants, which show that the later-stage CXCR4-utilizing variant upregulates CC-chemokines that suppress the replication of early-stage CCR5, ushering in accelerated progression to AIDS; development of a real-time PCR-based assay to evaluate the replication of HIV variants and the R5-to-X4 switch (NICHD)

Advances in imaging

- A novel real-time MRI system for guiding intramyocardial injections of therapeutic agents affords better visualization of the target tissue than traditional X-ray fluoroscopy and the ability to monitor drug effects immediately (NHLBI)
- An MRI system that allows physicians the ability to visualize 3-D volumes inside a patient in real-time, rather than individual slices, is particularly useful for tracking interventional devices; a method to obtain maps of the blood flow in the cardiac chambers enables evaluation of pressure differences in different locations in the heart and great vessels and assessment of the severity of certain types of cardiovascular disease (NHLBI)
- Combining electron tomography with energy-filtered electron microscopy yields high-resolution images of 3-D distributions of specific chemical elements in cells; this technique will be useful for elucidating the organization of DNA in the nucleus because the intrinsic image contrast mechanism clearly distinguishes between protein and nucleic acid (DBEPS)
- The use of semiconductor-based nanocrystals as a nontoxic angiographic contrast agent is explored (DBEPS, NICHD, NCI)
- The first radiolabeled nonpeptide ligand for the corticotropin releasing hormone type 1 receptor that can be used for PET scanning is designed and synthesized (NIDDK)
- Stem cells labeled with magnetic particles are amenable to magnetic resonance imaging, which has been used to track mesenchymal stem cells injected directly into the left ventricle (NHLBI, NINDS)

Advances in bioinformatics

- Launching of the Cohort Consortium—an interdisciplinary public-private, intramural-extramural collaboration—to facilitate subset data analysis and the examination of gene-gene and gene-environment interactions in cancer, diabetes, and cardiovascular, neurological, and other complex diseases (NCI)

Advances in biotechnology

- The finding that over a lifetime the mitochondrial DNA of single bone-marrow progenitor cells accumulates multiple mutations has implications for the aging process, forensic identifications, and anthropological conclusions based on mitochondrial DNA sequence (NHLBI)
- The finding of sequence-based bias in the integration of murine leukemia virus and human immunodeficiency virus–1 into the human genome has ramifications for gene therapy (NHGRI)
- Generation and analysis of a phylogenetically diverse set of genomic sequences from 12 vertebrate species is accomplished, as well as the demonstration of how comparative sequence analysis can be used to identify small genomic regions that are highly conserved across multiple species (NHGRI)
- A new, highly specific molecular tracking technique—T-cell clonotype tracking—allows ex vivo determination of clonal frequency without prior in vitro expansion that can aid in the study of pathogenesis of neurological immune disorders and in designing therapeutic interventions in such condi-

tions as multiple sclerosis, HTLV-1–associated myelopathy/tropical spastic paraparesis, and chronic Lyme neuroborreliosis (NINDS)

■ Description for the first time of the global differences between expression profiles of the two stem cell lineages—embryonic and trophoblastic—derived from the early embryo, and identification of genes expressed specifically in TS and ES cells, sets the stage for further study of the differences between the lineage-committed and pluripotent stem cells and their genes (NIA)

■ Buccal epithelial cells collected from women who had received male-to-female bone marrow transplant show the Y phenotype in the overwhelming majority of cells—with no evidence of fusion—supporting the idea that adult stem cells retain plasticity and have a role in regenerative medicine (NIDCR, NHGRI. NHLBI, NIMH, NINDS)

■ Engineering of an anthrax toxin activated by urokinase plasminogen activator transforms this toxin into a potent suppressor of a broad array of malignant tumors, eradicating established tumors without damaging normal cells (NIDCR)

Goal C:
Develop new or improved approaches for preventing or delaying the onset or progression of disease and disability

■ Neither estrogen nor prolactin exposure is found to be related to the risk of developing systemic lupus erythematosus, but breastfeeding is associated with reduced risk in a population-based, case-control study (NIEHS)

■ Continuing post-trial follow-up of the Finnish ATBC (α-tocopherol, β-carotene cancer prevention) trial reveals no new findings that would alter the recommendation that smokers should not take supplemental β-carotene (NCI)

■ Continuing very long-term follow-up of sibling patients with gyrate atrophy show that the earlier in life an arginine-restricted diet is begun, the greater the protection against retinal lesions that ultimately lead to blindness (NEI)

■ Epidemiologic studies indicate that DDT use for malaria control in sub-Saharan Africa is accompanied by an increase in infant mortality from DDT toxicity equal to a decrease in infant mortality attributable to malaria prevention, suggesting that other means to control malaria be used (NIEHS)

■ Analysis of data from the Breast Cancer Detection Demonstration Trial shows that the risk of ovarian cancer is increased in women who use estrogen-only replacement therapy and increases with duration, especially beyond 10 years (NCI)

■ The risk of breast cancer after successful treatment for Hodgkin's disease increases with radiation dosage to the breast and is ameliorated by the degree of damage to ovarian function from radiation or alkylating agents; the risk of lung cancer is associated with both radiation exposure and alkylating agents; these risks persist for decades, supporting the need for long-term follow-up of these patients (NCI)

■ Data generated from the ALTS Cervical Cancer Screening Study demonstrate that human papilloma virus testing helps distinguish women with equivocal cytological findings who have potentially precancerous lesions from those whose abnormalities are not life threatening (NCI)

■ Circulating free testosterone levels correlates with specific measures of cognitive performance among men 50–90 years old in the Baltimore Longitudinal Study of Aging, a finding that could lead to study of the safety and efficacy of testosterone supplementation to prevent or attenuate cognitive loss in healthy aging men (NIA, NCCAM)

■ Differences in characteristics of African American and non-African American teenagers suggest the need for ethnoculturally sensitive treatment strategies for smoking cessation in adolescents—and the need to be mindful that the number of cigarettes smoked daily may reflect nicotine clearance rate rather than degree of dependence and addiction (NIDA)

■ Skipping meals (without calorie reduction or weight loss) was found to have beneficial effects on resistance to diabetes, cardiovascular risk factors and response to stress, and nerve cell integrity in mice; a controlled trial to test the effect of reducing meal frequency in humans is in development (NIA)

■ Synthetic p53 inhibitors improves behavioral outcome in a mouse model of Parkinson's disease and may have clinical implications (NIA)

Vaccine development

■ A recombinant hepatitis E vaccine is highly immunogenic and efficacious in preventing hepatitis and even infection in rhesus macaques after I.V. challenge with three different genotypes of hepatitis E virus, strongly suggesting it will prove highly efficacious in preventing hepatitis E in an ongoing field trial in Nepal (NIAID)

■ A phase I multiclade HIV-1 DNA plasmid vaccine trial is underway (VRC)

■ A phase I/II clinical trial of modified vaccinia virus Ankara is being tested against Dryvax challenge in vaccinia-naïve individuals (VRC)

■ A phase I study of a lipooligosaccharide-based conjugate vaccine against nontypeable *Haemophilus influenzae*, the cause of about one-third of cases of purulent pediatric otitis media and a common cause of adult pulmonary infection, proved safe and immunogenic in adults and is now being planned for evaluation in a phase II trial in children (NIDCD)

■ A single injection of a conjugate vaccine containing *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides is safe and immunogenic and provides some protection for approximately 40 weeks against *S. aureus* bacteremia in patients with end-stage renal disease, an immunocompromised population at especially high risk for *S. aureus* bacteremia; testing of booster doses is suggested (NICHD)

■ Isolation and characterization of two glycolipid surface antigens of *Borrelia burgdorferi* advances the study of immunity to this pathogen and the quest for an effective vaccine against Lyme disease (NICHD)

■ Persistence of antibodies and efficacy against typhoid fever is documented for up to four years follow-up in children 2 to 5 years old vaccinated with conjugate *Salmonella typhi* vaccine (Vi capsular polysaccharide bound to a recombinant mutant Pseudomonas exotoxin) (NICHD, NIDDK)

■ Development and testing of conjugate shigella and cholera vaccines and purification of *Campylobacter jejuni* and *Mycobacterium tuberculosis* polysaccharides continues (NICHD, NIDDK)

■ An improved anthrax vaccine that induced capsular antibodies in mice expands the immunity conferred by available anthrax vaccines and could prove to provide more protection against the greater number of spores that might be released in a deliberate anthrax attack (NICHD, NIDDK, NIAID)

■ Studies showing that *Brucella abortus* interacts with two different toll-like receptors to trigger the release of both TNF and IL-12 inform the use of bacteria in designing adjuvants and/or carriers for vaccines and immunotherapy (CBER, NIAID, NCI)

Goal D:
Develop new or improved methods for diagnosing disease and disability

■ A computer-aided detection algorithm identifies large polyps missed by CT in patients at risk for colorectal cancer (CC)

■ Establishment of the best predictors of fibrosis progression in chronic hepatitis enables the safe deferral of treatment for patients with normal aminotransferase levels and mild liver histology (NIDDK, NCI, CC)

■ The uncovering of three immunogenetic markers provides additional evidence for linkage disequilibrium in familial Hodgkin's disease (NCI)

■ High-throughput microarray genetic testing and novel imaging techniques with image-analysis software improves early identification of neovascularization in patients with age-related macular degeneration (NEI, CIT)

Selected NIH Intramural Research Accomplishments 2002–2003

continued

- MRI proves more accurate than cardiac risk factors, ECG, and troponin assays in detecting acute coronary syndrome in patients arriving at the emergency room with chest pain (NHLBI)
- Only one-third of children with Smith-Magenis syndrome are found to have a normal lipid profile, suggesting that hypercholesterolemia can be an early marker of the syndrome in children younger than 4 or 5, the age when the disease is usually diagnosed (NHGRI)
- New hepatitis B surface antigen assays proves superior to currently licensed tests for detecting hepatitis B virus in blood donations; two of the newer tests were subsequently licensed; work continues on developing nucleic acid tests to assay for HBV DNA (CBER, NHLBI)
- Sequential evaluation of changes in visual memory test scores are predictive of Alzheimer's disease up to 15 years later in a study involving more than 1,400 people enrolled in the Baltimore Longitudinal Study of Aging, providing a tool for early identification of increased risk and lengthening the window of opportunity for preventive measures (NIA)
- Cerebrospinal fluid levels of β-amyloid and *tau* proteins appear to be early biomarkers of Alzheimer's disease that offer a tool more reliable than current methods to prospectively track changes in people at risk for the disease; long-term studies to evaluate this potential are now underway (NIMH)

Gene expression patterns

- Gene expression profiling proves to be the most precise prognostic index yet described for mantle cell lymphoma and suggests that therapeutic modulation of the cell cycle has the potential to significantly prolong life (NCI)
- The Clinical Proteomics Program pioneers the use of serum proteomic patterns to detect early-stage ovarian cancer, achieving 100 percent sensitivity in identifying all stages of ovarian cancer—including stage 1—and 95 percent specificity; serum proteomic patterns also correctly predict 95 percent of prostate cancers and 78 percent of benign prostatic conditions; specificity for men with marginally elevated PSA levels is 71 percent, suggesting that this assay become an adjunct to PSA in deciding whether to biopsy men with marginally elevated PSA levels (NCI, CBER)
- The Clinical Proteomics Program has produced more than 20 publications in the past year elaborating on signal pathway analysis of metastasis models and human cancers and proteomic pattern diagnostics, with particular reference to prostate, ovarian, and colon cancers (CBER, NCI)
- Gene expression profiling demonstrates for the first time that the transcription defect in Werner's syndrome (WS) is specific to certain genes and that transcription alterations in WS are strikingly similar to those in normal aging, identifying which genes are important in the aging process and supporting the use of WS as an aging model (NIA)
- Gene expression patterns in the postmortem cortex of cocaine abusers reveals cocaine-regulated transcripts associated with an array of signaling mechanisms, neuronal plasticity, and oligodendrocyte function, including alteration in the extracellular signal–regulated kinase (MEK/ERK) pathway (NIDA)
- Ex vivo gene expression profiles differ among multiple sclerosis patients according to responsiveness to interferon-β, a finding that can elucidate the mechanism of action of IFN-β in relation to different disease patterns and lead to optimized therapy; profiling after short-term treatment may enable prediction of long-term treatment response (NINDS, NCI, CC)

Goal E:
Develop new or improved approaches for treating disease and disability

- Cyclophosphamide and glucocorticoids for induction and methotrexate for maintaining remission prove an effective and well-tolerated regimen in patients with active Wegener's granulomatosis (NIAID)
- Itraconazole proves effective in preventing fungal infection in patients with chronic granulomatous disease; recurrent infections in patients with CGD are most likely reinfections , not relapses (NIAID, CC, NCI)
- Pretreatment of fatty donor livers with IL-6 in vitro dramatically improves the take of such livers in liver transplantation, a finding with major clinical implications because one-third of all donor livers are fatty and at high risk of transplantation failure (NIAAA)
- Endocannabinoids acting on cannabinoid receptor 1 (CB1) in the brain have a major role in regulating alcohol preference in mice and also in the age-dependent decline in alcohol preference, findings that support the planned use of CB1 antagonists in the treatment of alcoholism (NIAAA)
- Recombinant leptin-replacement therapy improves glycemic control and decreases triglyceride levels in patients with lipodystrophy and severe insulin resistance (NIDDK, CC)
- Maintenance therapy with ribavirin alone in patients with chronic hepatitis C maintains biochemical improvements obtained with combination interferon-ribavirin but with lower incidence of necroinflammatory changes in the liver (NIDDK, NCI)
- Safety is established for nonmyeloablative allotransplantation in HIV patients with hematologic malignancies (NIDDK, NIAID, NHGRI, CC, NHLBI, NCI)
- Melanoma patients offered nonmyeloablative conditioning followed by adoptive transfer of antitumor lymphocytes specific for the MART-1 melanocyte differentiation antigen experience both the destruction of metastatic tumors and an autoimmune attack on normal tissues that express the MART-1 antigen; these results support the efficacy of this new approach in melanoma treatment and suggest that normally expressed "self-antigens" can be useful as targets for human tumor immunotherapy in other settings if the autoimmune consequences of such treatment are acceptable, as may be the case in prostate, breast, ovary, or thyroid cancer (NCI, NEI)
- A Phase I trial involving patients with a variety of solid tumors at advanced stages and prior treatment histories establishes a safe dose for further clinical trials of an epothilone B analog—a member of a novel class of nontaxane microtubule-stabilizing agents that has shown promise in vitro (NCI)
- Bevacizumab (anti-VEGF antibody) prolongs time to progression in patients with metastatic renal cancer in a randomized controlled trial (NCI)
- In the most favorable outcome yet documented for this incurable disease, treatment of aplastic anemia with immunosuppression results in remission and a favorable long-term response (NHLBI)
- Autologous lymphocyte-depleted peripheral blood stem cells mitigates the myelosuppressive effects of high-dose cyclophosphamide in the treatment of refractory chronic autoimmune thrombocytopenia (NHLBI, CC)
- Different "trajectories of dying" and degrees of dependency during what turned out to be the last year of life are observed in elderly individuals who died of cancer, of organ failure, suddenly, or in a frail state, underscoring the need to create more-tailored programs of care for elderly patients (NIA)
- A short course of humanized anti-CD40 ligand antibody improves serologic activity and decreased hematuria in a pilot study involving patients with proliferative lupus glomerulonephritis, but the potential for increased risk of thrombotic events needs study (NIAMS, NIDDK)
- A new clinical program for the study of allograft tolerance introduces four novel immunomodulation regimens, including Campath-1H, a humanized CD52-specific monoclonal antibody (alemtuzumab) (NIDDK, NCI)

■ High daily doses of sublingual buprenorphine significantly reduces both cocaine and opiate use in outpatients dependent on both substances—the first direct demonstration of this agent's efficacy in treating dual dependence (NIDA)

■ Immunological tolerization to E-selectin, an adhesion molecule on endothelial cells, provides protection against development of ischemic and hemorrhagic strokes in animal studies; plans for human trials using this approach are underway under a CRADA with industry (NINDS)

■ Dopamine D3 receptor antagonists show promise as anti-addiction and anti-relapse agents (NIDA)

■ Methadone treatment induces attenuation of cerebrovascular deficits associated with prolonged cocaine and heroine abuse (NIDA)

■ Enzyme replacement therapy improves peripheral nervous system function, corrects abnormal cerebral perfusion, and improves quality of life in a controlled clinical trial involving patients with Fabry disease (NINDS, NHLBI)

■ Long-term follow-up of patients in the Early Treatment Diabetic Retinopathy Study shows that 15 to 20 years after laser photocoagulation therapy and despite progression of other diabetic complications, retinopathy remains largely stabilized, with 80 percent still having good vision and no patient becoming blind. (NEI)

■ Elucidation of the role of ocular surface inflammation in Sjögren's syndrome helps secure the approval of cyclosporine-A eye drops in the treatment of dry eye (NEI)

■ In vitro studies demonstrated that accelerated programmed cell death of the retinal pigment epithelial cells, a major cause of blindness in age-related macular degeneration, is not related to the caspase-dependent system of proteins but to an apoptosis-inducing factor, the effects of which can be prevented by treatment of RPE cells with hepatocyte growth factor/scatter factor—the first observation of a potential therapy of this form of AMD (NEI)

■ Antibody therapy (humanized monoclonal antibody directed against the α-chain of the interleukin-2 receptor—daclizumab) continues to be safe and effective in the treatment of uveitis in a cohort of patients with the longest history of use of this agent in the world (up to four years); clinical trials are being planned to test expanded uses in uveitis and in other autoimmune diseases (NEI, NCI)

■ Daclizumab is not only well tolerated in multiple sclerosis patients unresponsive to standard therapy but also dramatically inhibits its inflammatory activity in a phase II clinical trial that establishes the drug as a promising candidate for immunomodulatory treatment of MS (NINDS, NCI)

■ Primate studies showing that adenovirus-induced thrombocytopenia is the result of a reversible increase in platelet clearance rather than bone marrow suppression may inform the design of safer gene-therapy delivery methods (CBER, OAR)

■ Small clinical studies in which exendin-4, an amino acid found in the saliva of the Gila monster and an agonist of glucagon-like peptide-1 (GLP-1) receptor in humans, is well tolerated and a potent, long-acting insulin-releasing agent in patients with type 2 diabetes, setting the stage for larger phase III clinical trials (NIA)

■ GLP-1 agonists are shown to be neurotrophic and neuroprotective in cell cultures subjected to toxic insults emulating stroke and Alzheimer's disease and to be effective in well-established animal models of neurodegenerative conditions; novel GLP-1 analogs are synthesized and patented and are being assessed for use as experimental drugs in humans with a wide array of neurodegenerative diseases (NIA)

■ A potential therapeutic agent for spinal muscular atrophy is identified (NINDS)

■ Deacetylase inhibitors reduce the toxicity associated with the mutant polyglutamine that underlies many hereditary neurodegenerative disorders and are being considered for clinical trials in Huntington's disease, spinal muscular atrophy, and other diseases associated with polyglutamate expansion and aberrant histone acetylation (NINDS)

■ Identification of a drug that drastically reduces the toxic homogentisic acid produced by alkaptonuria patients suggests moving toward long-term safety and efficacy studies (NHGRI, NICHD, CC)

■ Generated under a CRADA with industry, a new class of immunosuppressive drugs that inhibit JAK3 proves effective against allograft rejection in nonhuman primates and is of likely use in the treatment of autoimmune and inflammatory disorders as well; human trials are anticipated (NIAMS) ■

Coming Soon: Next Class of PRATS

The NIGMS Pharmacology Research Associate (PRAT) program is now accepting applications for positions to begin in October 2004. This 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. Applications must be received by **January 5, 2004**. For more information or application materials, contact the PRAT program assistant at 301-594-3583 or <prat@nigms.nih.gov> or visit the PRAT website:

<http://www.nigms.nih.gov/about_nigms/prat.html>.

ClinPRAT

The Clinical Pharmacology Research Associate (ClinPRAT) Program is intended for physicians who want specialized clinical and laboratory training in the pharmacological sciences. For more information, contact Art Atkinson at 301-435-8791 or by e-mail <aatkinson@mail.cc.nih.gov>, or visit the ClinPRAT website at

<http://www.cc.nih.gov/OD/clinprat/>

Demystifying Medicine: Take Three

Tuesday **January 6** marks the beginning of the third year of one of the most popular postgraduate courses offered at NIH: "Demystifying Medicine." The course is designed to help bridge the gap between basic science and medicine and is open to all students, fellows, and staff, although it is primarily designed for Ph.D. scientists and students. It will meet every Tuesday from 4:00–5:30 p.m. in the ground-floor auditorium of Building 50.

Individuals seeking academic credit may register with FAES. Those not seeking academic credit should register through the course e-mail list. To subscribe, for more information on registration, and to see the class schedule, go to:

<http://www1.od.nih.gov/oir/DemystifyingMed/index.html>.

People

Recently Tenured

Crystal Mackall *received her M.D. from Northeastern Ohio Universities of Medicine, Rootstown, Ohio, in 1984 and completed a combined internal medicine/pediatrics residency in Akron, Ohio, in 1988. In 1989, she joined NCI in the Pediatric Oncology Branch as a clinical associate. She was a postdoc in the Transplantation Biology Section of the Experimental Immunology Branch, NCI, from 1990 to 1996 and is currently a senior investigator in the Pediatric Oncology Branch, NCI.*

Fran Pollner

Crystal Mackall

Dramatic advances in the basic understanding of cellular immunity over the past several decades have opened up the real possibility that clinically relevant immune-based therapies for many human cancers will soon emerge. Translating these basic insights into clinical gains requires a fundamental understanding of both sides of the host-tumor interface. The major long-term goal of my lab is the development of immune-based therapies for pediatric cancers. My research focuses heavily on the study of the immune system in cancer patients, especially those who have undergone standard cancer therapies.

After completing clinical training in the Pediatric Oncology Branch, I undertook postdoctoral work in transplantation biology in Ron Gress' lab. There, I focused on basic questions related to the regeneration of T-cell populations after T-cell depletion due to therapy and/or disease. Using mouse models, I identified markers to distinguish T cells regenerated via thymic-dependent vs. thymic-independent pathways and identified differences in levels of immune competence depending upon which pathway was utilized.

Translating these findings to the clinic, we then undertook studies of T-cell regeneration in children and young adults treated with intensive chemotherapy for cancer. I identified reduced thymic function as the primary cause of slow immune recovery in these patients. Diminished thymic function as a primary cause of slow immune recovery was subsequently confirmed in other states of T-cell deficiency, including those attributable to HIV infection and bone marrow transplantation.

I then began to focus on identifying factors that regulate T-cell regeneration that could potentially be used to enhance immune reconstitution. We identified IL-7 as a potent therapeutic capable of enhancing T-cell regeneration in mouse models.

More recently, my laboratory demonstrated that endogenous IL-7 levels rise in response to CD4 depletion in a variety of clinical settings. These observations, as well as the demonstration by other groups that IL-7 is required for thymic-independent homeostatic expansion, led to the paradigm that IL-7 is a "master regulator of T-cell homeostasis." On this basis, we have worked to develop early clinical trials of recombinant human IL-7. The first such trial recently opened in the Clinical Center.

In addition to T-cell regeneration, the immunobiology of pediatric cancer is another area my lab pursues. We have focused primarily on Ewing's sarcoma, an aggressive, poorly differentiated bone and soft tissue tumor that afflicts children and young adults. We have identified Ewing's sarcoma as highly responsive to both Fas-based and TRAIL-based apoptosis. Recently, we published the first evidence that endogenous immune responses exist in patients with Ewing's sarcoma. Work is underway to find the best way to immunize patients against Ewing's sarcoma and/or adoptively transfer T cells reactive to it.

My long-term goal is to use the discoveries we have made in immune reconstitution to develop immune-based therapies for patients with minimal residual disease. This is particularly pertinent to pediatric tumors, where intensive multimodality therapy is the rule in treatment regimens. As a means toward this end, we are currently conducting clinical trials of tumor vaccines, allogeneic bone marrow transplants, and adoptive transfer of autologous lymphocytes, after chemotherapy for pediatric sarcomas.

Ultimately through this work, I hope to develop clinical trials that integrate immune restoration with state-of-the-art adoptive therapy and/or tumor vaccines to direct the regenerating immune system to react against tumor antigens. I believe that through this approach, immune therapy will be effectively integrated into the oncologic armamentarium and yield the greatest benefit.

Colleen McBride *received her Ph.D. from the University of Minnesota, Minneapolis, in 1990 and did her postdoctoral training at Group Health Cooperative of Puget Sound in Seattle. She came to NIH in October of this year as a tenured senior investigator to lead NHGRI's newly formed Social and Behavioral Research Branch.*

Fran Pollner

Colleen McBride

Before coming to NHGRI, I spent 15 years developing innovative public-health interventions to promote behavior change to reduce health risks. In a series of randomized controlled trials, I developed and evaluated a broad range of behavior change interventions including:

- smoking prevention and cessation
- treatment decision-making
- dietary change
- physical activity
- sexually transmitted disease prevention

The common aim of these trials was to design and evaluate low-cost, self-directed behavior change interventions for large and geographically dispersed populations at risk for chronic diseases and cancer. In particular, my research maximized the potency of brief interventions by taking advantage of "teachable moments"—health-related events that naturally increase motivation for making lifestyle changes.

My early research in smoking and pregnancy suggested that feedback of test results could yield teachable moments. For example, learning they are pregnant prompts up to half of women to stop smoking spontaneously. Unfortunately, without formal behavioral interventions, most women return to smoking after giving birth.

I also tested annual Pap screening and receiving test results showing low-grade cervical abnormalities as a possible teachable moment for quitting smoking. Generally, women were unaware of the link between cigarette smoking and cervical cancer and did not understand the

mechanisms through which their risk might be increased.

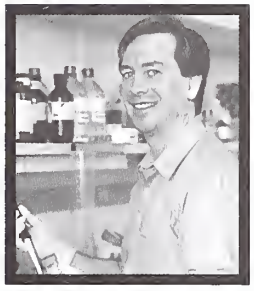
My colleagues and I developed and evaluated a quit-smoking intervention for women receiving Pap smear results. Unfortunately, this intervention resulted in no greater smoking quit rates among women with an abnormal Pap test than among women with normal results. These results piqued my interest in exploring how to communicate "normal" and "abnormal" results or to explain biological mechanisms in ways that could be understood by lay audiences and would motivate behavior change.

This led to the idea of using feedback from genetic susceptibility testing as a motivator for behavior change. With funding from NCI, my colleagues and I evaluated feedback on genetic susceptibility to lung cancer to motivate smoking cessation among African Americans. For this campaign, we developed a car-wash metaphor and graphical images to communicate what the genetic marker glutathione S transferase enzyme could and could not tell a smoker.

The study showed that smokers could understand genetic results they got in the mail—with follow-up counseling on the telephone—just as well as results and counseling received in person. But we also found that learning that one was genetically susceptible to lung cancer was not associated with higher rates of smoking cessation. The data indicated only about half of the smokers fully understood the meaning of the test result. Results also showed that smokers may have been biased in remembering the result: Those with results indicating the greatest health risk, who got the most threatening message, were most likely to recall their results incorrectly.

Looking ahead, in my next five years at the NHGRI Social and Behavioral Research Branch, my goal is to work with colleagues to build a leading-edge, collaborative research program using diverse scientific perspectives and genomic discoveries to develop public-health interventions with the promise of real-world dissemination. I also want to continue to explore psychological processes that might help explain misunderstanding of biomarker feedback. Another goal is to develop tools to assess key elements of teachable moments so that we might capitalize on these events to increase the efficacy of health promotion efforts.

Peter Aplan *received his M.D. degree from Pennsylvania State University at University Park in 1983. He was a pediatric intern, resident, and chief resident at the Children's Hospital of Buffalo, New York, from 1983 to 1987. He was a pediatric hematology-oncology fellow and then a biotechnology fellow at NIH from 1987-1992. He moved to Roswell Park Cancer Institute in Buffalo, where he was an assistant professor and then associate professor of pediatrics and microbiology before joining the Genetics Branch at NCI in 1999. He is now a senior investigator and head of the Leukemia Biology section in that branch.*



Peter Aplan

My laboratory studies non-random chromosomal translocations associated with hematologic malignancy. Translocations have proven to be a rich source of insights into cancer biology as well as many fundamental biologic processes. For instance, the anti-apoptotic *bcl2* gene was initially identified due to its involvement in a recurrent chromosomal translocation.

Our studies begin with a clinical observation, namely, a chromosomal abnormality associated with hematologic malignancy. Our general approach is to clone the translocation and identify the gene(s) involved, determine a mechanism by which the translocation might have occurred, and develop animal models of leukemia using the genes identified. Our ultimate goal is to identify causes of these oncogenic translocations (so that they might be avoided), and to identify pathways activated by these translocations, so that these pathways might be targeted for therapeutic intervention.

As a postdoctoral fellow, I identified and characterized several chromosomal rearrangements involving the *SCL* gene, which is activated by chromosomal rearrangements in approximately 30 percent of patients with T-cell acute lymphoblastic leukemia. Our laboratory has developed a mouse model for this type of leukemia using SCL transgenic mice. Almost 100 percent of the mice develop a fatal leukemia that resembles the human disease in clinical presentation, pattern of spread, invasion, morphology, and immunophenotype. To mimic the human disease more closely, we have used Cre-lox technology to generate inducible rearrangement and expression of the SCL transgene.

More recently, we have begun experiments aimed at modeling leukemia in zebrafish. Zebrafish offer several advantages to the cancer biologist: Adult fish are approximately one inch long, and many fish can be housed in a small space. They have large, easily manipulated eggs. These can be microinjected to generate transgenic fish. Because the fish are transparent for the first weeks of life, we can track development using fluorescent proteins.

Over the past several years, my lab has cloned and characterized several chromosomal translocations that are seen in patients with acute myelogenous leukemia and produce NUP98 fusion genes. NUP98 is normally a component of the nuclear pore complex, which mediates transport of RNA out of, and protein into, the nucleus. We have developed lines of transgenic mice that overexpress an NUP98-HOXD13 fusion gene. These mice develop pancytopenia and a myelodysplastic syndrome that progresses to acute myeloid leukemia.

The experiments I described above focused on demonstrating that genes activated by chromosomal translocations lead to leukemia. This is just the beginning for us. If the chromosomal translocation does cause leukemia, it becomes important to determine what caused the chromosomal translocation. Therefore, in addition to studies aimed at characterizing the downstream effects of leukemic chromosomal translocations, we are also quite interested in learning the mechanisms by which chromosomal translocations (and other gross chromosomal rearrangements) occur.

We showed that we can reproducibly cleave genomic DNA at or near sites of known translocation breakpoints within the MLL (mixed lineage leukemia) gene using known genotoxic agents. Improper repair of these breaks could result in chromosomal translocation. We are now developing a system in which we can use the rare-cutting restriction enzyme I-SceI to induce a single double-strand break in cells and determine whether improper repair of this break leads to chromosomal translocation. ■

Catalytic Reactions

On Review of Intramural Research

Joram Piatigorsky's recent commentary (*The NIH Catalyst*, March-April 2003) raised concerns about acquiescence to the Board of Scientific Counselors (BSCs) for determination of the direction of the NIH Intramural Research Program (IRP). In conversations with friends and colleagues, it is clear that many agree with Dr. Piatigorsky that the changing role of the BSC may "threaten the most important features of the IRP."

His commentary also raises an additional dilemma—the disenfranchisement of intramural investigators from the review process. The BSC was established in 1956 to assist the scientific directors in evaluating the quality of the intramural research programs for which they are responsible.

The IRP now has more than 1,250 intramural investigators, many of whom are internationally recognized experts, yet these scientists are systematically excluded from the scientific review process that determines the fate of their research projects. Is it not time that the collective expertise of senior investigators in the IRP be utilized in evaluating the scientific direction of the IRP?

In his response to Dr. Piatigorsky, Dr. Gottesman, DDIR, points out several details of the BSC review process. He notes that three institutes utilize site-visit teams, led by at least two BCS members, but consisting principally of extramural "expert" investigators. These "subject matter experts" from the extramural research program conduct the initial review of intramural investigators, which is then sent to the full BSC for further review and recommendations. The criteria for scientific review of intramural investigators are significance, approach, innovation, environment, support, investigator training, productivity and mentoring; see guidelines for intramural scientific reviews

<http://www1.od.nih.gov/oir/sourcebook/sci-review/bsc-toc.htm>.

However, the criteria for review of extramural grant proposals are quite similar, and extramural experts reviewing intramural investigators may fail to appreciate the distinct circumstances associated with the IRP.

Although instructions to extramural reviewers and BSC members state that IRP review is primarily retrospective, extramural experts often seek additional details of the type requested in the review of R01 proposals at study sections. In both extramural review of grant proposals and BSC review of intramural research, the past research accomplishments of the investigator under review are usually used as a measure of ability to carry out the proposed studies and not as a basis for a final recommendation.

The blurring of the subtle difference between a retrospective review based on quality of total work and a prospective review has resulted in BSC reviews becoming as prospective as they are retrospective and "substitutes for NIH R01 grant applications."

Perhaps the most difficult problem with BSC review of the IRP is interinstitute inconsistency. As pointed out in Dr. Gottesman's reply to Dr. Piatigorsky's comments, only three institutes conduct site visits led by at least two BSC members. Other institutes have other approaches. Quality assessment mechanisms are therefore inconsistent, and expectations may also be.

How can an equitable review for all members of the IRP be ensured and reflect the unique aspects of the IRP research environment? Members of the IRP research community ought to be included in the BSC process. Intramural investigators have outstanding scientific credentials and are committed to providing rigorous, objective reviews. They would bring a sensitivity to issues specific to intramural research that would complement the perspective of extramural reviewers. Moreover, the use of IRP scientists from different institutes would help standardize the review process across the NIH intramural program.

I know of an instance in which an intramural investigator participated in the review team for another institute and was well received by both the site-visit team members and the institute under review.

Intramural scientists currently have no input into the design of the review mechanism or in the decisions of the BSC regarding the direction or quality of the IRP. If the NIH administration truly values the unique aspects of the IRP and believes that intramural scientists are not and should not appear to be extramural scientists, then our opinions regarding the funding and future direction of the IRP should be heard.

—William Stetler-Stevenson, NCI

Response

Dr. Stetler-Stevenson has clearly described some of the similarities and differences in intramural and extramural review of science and argues that we underutilize intramural expertise on our review groups.

There is, in fact, no prohibition against the inclusion of such scientists as ad hoc reviewers, and several institutes use intramural scientists from other institutes as part of their review groups. In addition, I routinely assign intramural scientists to attend reviews of all tenure-track investigators (approximately one-quarter of all of our principal investigators), and they provide reports that help determine the response of the NIH to the BSC reviews.

Critical career decisions, such as appointment of tenure-track investigators, promotions to tenure, and other intramural promotions, are all made using internal committees of intramural scientific experts. I believe that we make good use of the enormous scientific talent in the intramural program, but also strive to avoid the conflict of interest that may result from using reviewers who are close to the people being reviewed.

There is both real and perceived value of outside review as one way to exercise good stewardship of taxpayer funds.

—Michael Gottesman, DDIR

On Tenure and Tuition: A Proposal

Recently tenured researchers at NIH have been encouraged to consider themselves faculty, and that reminds me of one of the most important privileges of faculty members at most public and private universities that we haven't been awarded as NIH faculty.

That privilege is the opportunity for dependents to attend affiliated universities on a tuition-free basis—a privilege also available to employees at other national labs such as Los Alamos, where they may enroll dependents tuition-free at any of the University of California campuses.

As most of the current tenured NIH faculty will attest, this is a very significant financial reward for a family, and it encourages loyalty to, and involvement in, the academic institution the faculty member belongs to. It would be a significant advantage in recruiting and retaining the best and brightest young investigators at NIH and add real substance to the use of the term faculty for tenured investigators. I urge NIH to develop formal agreements with a select number of public and private universities so that dependents of tenured NIH investigators could choose to enroll at these universities tuition-free. I should

also mention that this privilege is extended to all permanent employees at some universities.

There are several mechanisms used by different universities to support this privilege that could also be used by NIH—so the cost of its implementation need not be an issue.

—Jordan Grafman, NINDS

—Though a tuition benefit for employees sounds desirable, NIH is a government agency with no legal authority to provide such a benefit—nor could it solicit such a "gift" from a university. Unsolicited tuition waivers would be considered a gift and subject to analysis under standards of conduct rules. The situation at Los Alamos is not comparable because the laboratory is run by the University of California.—Ed.

Relay Revelry

This year's NIH Relay demonstrated that NIH scientists are just as competitive outside the lab as they are in it. More than 70 teams competed in a five-leg, 2.5-mile relay race around Building 1. The prize: a place for the team on the coveted Allen Lewis NIH Memorial Trophy.

Inscribed this year on the trophy, which is located in the fitness center in Building 31, will be "Parasites on the Run," the team that also bested competitors (and host defenses?) to win last year. In 14 minutes, 20 seconds—believed to be a course record—"Parasites" prevailed over "Rapid Relaxation" by a mere 9 seconds. "A Man and the P-Funk Allstars" came in third, 26 seconds later.

Among other creatively named teams, the "Fighting Geneticists" boot camp training paid off, with a respectable 16:29 time. The "Differentiating Keratinocytes" showed some muscle with their skin, coming in 23rd, followed by the "Pox Jox."

"The OD/OA Creeping Bureaucracy," slowed by red tape and carbon paper, finished in the more leisurely time of 19:15.

—Peter Kozel

In a run for most politically incorrect, "3 Slow Guys and 2 Fast Chicks" runner leads "3 Damn Yanks and 2 Darn Canucks" racer

"Parasites on the Run" and "Wurtz Possible Runners" competitively review their positions

"Howard Huge (Hughes) Heads" take a hot-aired approach to warm-up

Clinical Research Training Programs

NIH-Duke

The NIH-Duke Training Program in Clinical Research, implemented in 1998, is designed primarily for physicians and dentists who desire formal training in the quantitative and methodological principles of clinical research. The program is offered via videoconference at the Clinical Center and includes formal courses in research design, research management, and statistical analysis.

Academic credit earned in this program may be applied toward a Master of Health Sciences in Clinical Research degree from Duke University School of Medicine, Durham, N.C.

Applications for 2004–2005 are available in the NIH Clinical Center, Office of Clinical Research Training and Medical Education, Building 10, Room B1L403. The deadline for applying is **March 1, 2004**. Applicants who have been accepted into the program will be notified by July 1, 2004.

For additional information on course work and tuition costs, visit **<http://tpcr.mc.duke.edu/>** or e-mail **<tpcr@mc.duke.edu>**

University of Pittsburgh

The University of Pittsburgh Training in Clinical Research Program, designed for Ph.D.s and allied health professionals (such as pharmacists and nurses), consists of an integrated core curriculum taught over three semesters starting with an intensive eight-week summer session. The program has been modified so that NIH trainees are required to spend only the first five days of the summer session in residence at the university. Physicians and dentists also may enroll in this program.

Participants have the option of receiving a Certificate in Clinical Research (15 credits) or a Master of Science in Clinical Research (30 credits) from the University of Pittsburgh School of Medicine.

Enrollment is limited. Prospective participants should consult with their IC regarding the official training nomination procedure. The deadline for applying is **March 1, 2004**. Successful applicants will be notified by May 29, 2004. Applications for the 2004–2005 session are available in the Clinical Center, Office of Clinical Research Training and Medical Education, Building 10, Room B1L403.

For more information, including tuition costs, visit **<http://www.cc.nih.gov/ccc/cc_pitt/index.html>** or e-mail **<tcrp@pitt.edu>**.

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 2W23.**

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

In Future Issues...

- Leto's Plowshares
- To the Beat Of the Tabors
- What's New At NBIB?

Digit Designs: An Experiment with Fingerprints

We're all born with them, we know they're used to catch criminals, but how much do we really know about fingerprints? With this experiment, you will learn more about fingerprints, including their differences and frequency, and amaze your classmates, all while doing a science project!

Fingerprinting your entire class isn't time-consuming or messy at all. All that you need are:

- A roll of large, clear packing tape
- Baby powder
- Dark construction paper, cut into 3 x 5 sections, enough for two cards per person

Left four fingerprints of an anonymous NIHer

Ask your classmates to rub their hands in a little bit of baby powder. (Your teacher will thank you—the science room will smell great!) Then carefully remove a 6" section of the clear tape from the roll, making sure not to put any smudges anywhere. Put the tape sticky-side up on a flat surface, and have your classmates roll each powdered finger on the tape. You will see beautiful fingerprints!

Then put the fingerprinted tape on the dark card. The fingerprints show up even better! Have your classmates repeat the process with the other hand, and write their names on each of the cards. All of the prints will be different (even if you have twins in the class?), but will fall into three major categories (check out the pictures): loop, whorl, and arch. Whorls look like a tornado, arches look like a hill, and loops look like a mountain.

Now, to the analysis. Write the name of each classmate down the left side of a piece of paper. Across the top write loop, whorl, and arch. Now count the number of loops each person has and write it down in the appropriate box. Is one pattern more frequent than another? Now, within each person's set of fingerprints, are almost all of them one pattern, but one is different? If you figure it out, please write!

For more information on fingerprint analysis and forensic science, visit <**http://www.dermatoglyphics.com/**>. (What does that word mean?) Or, for a really fun site dealing with all things criminal, visit a kids' page that is definitely not just for kids: <**http://www.fbi.gov/kids/6th12th/6th12th.htm**>.

Now go print!

—Jennifer White

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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