Fostering Communication and Collaboration

The NIH Catalyst

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Tasty Carbonation

. . . Protein Receptor Discovered

By Bob Kuska, NIDCR

In 1767, chemist Joseph Priestley came up with an idea to help English mariners stay healthy on long ocean voyages. He infused water with carbon dioxide to create an effervescent liquid that mimicked the finest mineral waters consumed at European health spas.

Priestley's manmade tonic, which he urged his benefactors to test aboard His Majesty's ships, never prevented a scurvy outbreak. But, as the decades passed, his carbonated water became popular in cities and towns for its enjoyable taste and later as the main ingredient of sodas, sparkling wines, and all variety of carbonated drinks.

Missing from this nearly 250-year-old story is a scientific explanation of how people taste the carbonation bubbling in their glass.

Late last year, NIDCR researchers and Howard Hughes Medical Institute investigators at the University of California, San Diego (UCSD), discovered the answer in mice, whose sense of taste closely resembles that of humans.

They reported in *Science* that the taste of

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The Road to Greener NIH Labs:

Greening Your Workspace is Challenging but Possible

By Christopher Wanjek

You recycle your newspapers; you tote a reusable bag to the supermarket; you've insulated your house; you've installed low-flow showerheads.

But what about your lab, that enclave where you may very well spend half of your day?

Considering the energy-gobbling machines, potentially toxic solvents and reagents, and thirsty water needs typical in most labs, your greatest contribution to environmental sustainability might be greening your own research space.

Maggie Bartlett, NHGRI

With hundred of labs at NIH, the impact of their going green is significant.

The NIH Environmental Management System (NEMS) team lays claim to several environmental success stories at NIH in recent years, such as a nearly mercury-free NIH Bethesda campus. Now the group's focus has turned to you—yes, you, a mere individual who can help make or break NIH's goal of being the nation's model research facility for environmental sustainability—and they aren't afraid to use peer pressure to win you over.

NIH has a unique responsibility to reduce any negative impact on the environment given that our mission is to alleviate human suffering, some of which is caused by diseases resulting from environmental assaults.

"How many labs have you been to in which equipment is running?" asks Kenny Floyd, director of the Division of Environmental Protection (DEP) in the NIH Office of Research Facilities (ORF). It's a rhetorical question for Floyd, who has never visited a lab that wasn't running a machine.

Yet often that machine doesn't need to be on, Floyd said, particularly overnight. One of ORF's pilot studies found that some labs could save $3,000 to $6,000 a year by better managing only two or three pieces of equipment, such as water baths or hot plates. Less energy use, of course, translates to fewer greenhouse-gas emissions. With hundreds of labs on the NIH

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Guest Editorial From the Scientific Director of NIAMS

A New Era of Biology

John O'Shea

Perhaps you remember Ian Wilmut's 1997 lecture in Masur, describing the cloning of Dolly the Sheep. If you were among the hordes of scientists who crammed the auditorium, you experienced a truly extraordinary event. Though astonishing, the lecture was also a bit puzzling (at least for me). What were the general implications of reprogramming by nuclear transfer? Could this be translated to other situations (that is, without making a new sheep)?

Fast forward a decade. When Kazutoshi Takahashi's and Shinya Yamanaka's paper appeared in *Cell* in 2006 (*Cell* **126**:663–676, 2006), it was clear we had entered a new era of biology. Four transcription factors completely reset the clock in vitro; piece of cake—nothing to it! Now with each week that goes by, new discoveries continue to come at a fast and furious pace, changing the way we think about cell biology. Just this month we learned that transdifferentiation to neurons can be induced with three transcription factors! What will be the next amazing discovery?

These advances have immense basic science implications for lineage commitment and terminal differentiation, and the approaches present amazing opportunities to ask fundamental questions about cell development. If this is how life works, a very different view of biology is required from what we were taught. But even more important, think of the clinical implications. If somatic cells from any donor can be reprogrammed or transdifferentiated, how soon will it be before we are able to replace diseased cells and tissues? The use of autologous induced pluripotent stem (iPS) cells or transdifferentiated cells could overcome the barrier of transplant rejection and the need for immunosuppressive therapy. Coupled with advances in gene therapy, these approaches could revolutionize the practice of medicine. In this context, what should the NIH intramural program be doing?

Challenge

Last year when Francis Collins started as NIH director, he met with the scientific directors, challenging them to consider bold new trans-NIH projects that would have a potential clinical impact. One topic he suggested was the creation of an iPS center. The scientific directors discussed this possibility at their annual retreat, and then Dr. Collins sponsored a workshop featuring the world's leaders in iPS research, including Dr. Yamanaka. Afterwards, NIH Deputy Director for Intramural Research Michael Gottesman convened a task force of IRP scientists and clinicians to brainstorm. The ideas that emerged from these sessions were incorporated into a proposal that was submitted for consideration of Common Fund support.

It was proposed that an NIH iPS Cell Center (NiPC) be established within the IRP as a center of excellence in iPS cell technology and translational applications. The NIH IRP has numerous strengths that make it an ideal vehicle for enabling iPS technology to move to the clinic. These include the Clinical Center with its many carefully studied patient cohorts as well as its expertise in gene therapy and bone-marrow stem-cell transplantation; the NIH Bone Marrow Stromal Cell Transplantation Center and NIH Stem Cell Unit; a Good Manufacturing Practices facility for cell therapies; and the NIH Chemical Genomics Center. Coupled with the IRP's immense basic science capability, expertise in genomics, epigenetics, transcriptional regulation, chromosome biology, and computational biology, the IRP and NIH Clinical Center offer an ideal environment to commit to long-term, high-risk, large-impact projects such as the NiPC.

Goals

The NiPC's goals will be to serve as a nidus for promoting stem-cell research in the IRP and to facilitate translation of iPS basic science and technology to patients who can benefit from this endeavor. As cells are generated and differentiated, the center will make them available to intramural and extramural investigators. NiPC will also collaborate with the NIH Clinical Genomics Center to identify small molecules that influence reprogramming and ameliorate abnormal disease phenotypes.

The ultimate goal will be to develop clinical-grade iPS cells for cell-based therapy and other clinical applications. Suggested pilot projects, which are directed toward eventual clinical applications, include generating hepatocytes for liver failure; hematopoietic stem cells for the eventual treatment of malignancy, bone marrow failure, and immunodeficiency; epithelial cells for possible replacement of corneal epithelium and retinal pigment epithelium; and bone for repair of severe cranial defects.

Our proposal was accepted and the next step is to quickly recruit a world-class director to lead this exciting new initiative. The NiPC will provide seed money to jump-start pilot projects that will enable the ultimate clinical use of iPS technology. This year the center will be looking to support iPS-related projects to help catalyze interest and expertise on campus. Projects that have potential clinical applicability will be of particular interest. Extramural partnerships will be encouraged to facilitate addressing the most challenging and exciting problems.

As we harness the power of iPS technology through the NiPC, we are optimistic that this may very well revolutionize the practice of medicine in our lifetimes; we are indeed fortunate to have the opportunity to participate in this exciting venture. ■

—John O'Shea, NIAMS

John O'Shea spearheaded the NiPC initiative and has been asked by NiPC co-sponsors NINDS Director Storey Landis and NIAMS Director Stephen Katz to coordinate the initial efforts to implement it.

Commentary

Translational Medicine—Doing It Backwards

A recent candidate for a postdoctoral fellowship position came to the laboratory for an interview and spoke of the wish to leave in vitro work and enter into meaningful in vivo work. He spoke of an in vitro observation with mouse cells and said that it could be readily applied to treating human disease. Indeed, his present mentor had told him that was the rationale for doing the studies. When the candidate was asked if he knew whether the mechanisms he outlined in the mouse existed in humans, he said that he was unaware of such information and upon reflection wasn't sure in any event how his approach could be used with patients. This is a scenario that is repeated again and again in the halls of great institutions dedicated to medical research.

Any self-respecting investigator (and those they mentor) knows that one of the most important key words today is "translational." In reality this clarion call for medical research, often termed "Bench to Bedside," is far more often ignored than followed. The paucity of real translational work can make one argue that we are not meeting our collective responsibility as stewards of advancing health. We see this failure in all areas of biomedical research, but as a community we do not wish to acknowledge it, perhaps in part because the system, as it is, supports interesting science, which could always lead to something major.

Even the peer review of journal articles is one subtle way this concept is perpetuated. The incentive structure built around impact and citations favors elaboration of popular work, that is, more and more detailed experiments on model systems. Papers have been rejected by prestigious journals because reviewers decry the fact that the results have been shown in human systems but not in animal models.

Because of this great dependence on in vitro and animal models, which often have little relevance to human disease, we believe there has been a marked diminution recently in the introduction of fundamental new agents and diagnostic tools into clinical medicine, despite the immense expenditures for biomedical research. Indeed, it can be readily argued that we understand the normal and abnormal states of mice better than we do those of humans. As Lawrence Steinman wrote recently, "Animal models actually sometimes give results that are the opposite of what is ultimately seen in human disease." (*Nat Immunol* **11**:41-44, 2010)

Basic differences between rodent and human exist—as was emphasized at a recent NIH symposium on macrophage activation in health and disease—often yielding disappointing clinical studies. For example, randomized cancer vaccine trials more often than not demonstrate poor efficacy and in some cases worse outcomes. The conclusion was that "vaccines do not work," in spite of their ability to elicit measured cellular and immune responses. But in reality we still know little about the requirements in human pathophysiology that allow antigen-specific T or B cells to exert their effector function.

What is needed is a different template to return the focus of our attention to the normal and diseased human state. As Mark Davis (Howard Hughes investigator at Stanford University in Stanford, Calif.) recently noted, although animal models are successful tools for understanding basic immunology, they have not been successful as models of human disease. He rightly advocates a new strategy directed to human immunology. (*Immunity* **29**:835-838, 2008)

The paucity of real translational work suggests we are not meeting our responsibility of advancing health.

This can only mean abandoning the misnamed "Bench to Bedside" approach. What is needed is an approach that begins at the bedside and then goes to the "clinical bench" (associated studies done with patients), then to the animal or cellular models, and, most importantly, then back to the bedside. Clinical realities should play a primary role in framing scientific questions.

A significant impediment to progress in biomedical research is the lack of appreciation in the current system for descriptive, evidence-searching studies (sometimes called "omics") upon which to begin a rethinking of much biomedical research. Rather, our system is locked into testing poorly conceived hypotheses, often starting from the models, thus bypassing one of the basic elements of the scientific revolution: the Baconian principle of relevant observation and experimentation, in this case, clinical studies.

It is incongruous to rely on cell or animal models if we don't know what the human pathways are. At a time when genomic and other molecular approaches allow us to ask sophisticated questions about normal and pathological processes in human beings our increasing reliance on systems regarded as "models" for human disease makes little sense. Clearly, research on model systems can bring fundamental new biological insights (for example, Mendel's peas, Morgan's flies) and animals may be necessary and invaluable for certain work (toxicology, pharmacokinetics) in the advancement of clinical research, when systems in humans and animals are proven to be very similar.

Many naysayers will quickly come to the defense of the present system, pointing to some important advances of the last two decades. That our current system has produced results is undoubted. The issue is, rather, how efficient is our approach in meeting the NIH's goal (and for us, the intramural program's responsibilities) of making important medical discoveries that improve health and save lives with its current resource base.

Clinical physicians and non-physicians who are trained to understand human disease processes need to take a far more proactive role in determining the paths of discovery. Today's training of physician-scientists and clinical investigators still remains weak in spite of efforts by the NIH and others to fortify training programs. The recently inaugurated Clinical and Translational Research Centers are the most tangible indication of how the NIH as a whole is trying to address these problems.

The increased role of "clinicians," whatever their degrees, in many ways would be a return to the concept outlined by D.E. Stokes, in which the most relevant science in each discipline is performed in the (Pasteur's) quadrant of scientific approaches most applicable to the clinic, as largely was the case in years past. Indeed, NIH Director Francis Collins has enunciated the need to have a stronger focus on clinical research as an important way to justify the NIH budget.

If we wish to remain true to our self-pronounced goals, we must begin to think about new approaches to performing translational research, so it is not yet another way to perpetuate a system that is no longer optimal. ■

—Robert B. Nussenblatt, NEI
—Francesco M. Marincola, CC
—Alan N. Schechter, NIDDK

This article is adapted from an editorial that first appeared in the Journal of Translational Medicine (J Transl. Med. *8:12, 2010).*

The Training Page

From the Fellows Committee: Toward a National Culture of Postdoctoral Training Excellence

By Kristofor Langlais, NICHD; FelCom Liaison to the NPA

To ensure that the United States retains its competitive edge in scientific research and innovation, future generations of scientists must receive the most comprehensive training possible. The National Postdoctoral Association (NPA), founded in 2003, advocates for policies that enhance the quality of the postdoctoral experience and addresses widely acknowledged shortcomings in training programs, such as insufficient stipends and benefits, lack of recognition for postdoc contributions to research, and limited opportunities for professional development.

NPA works with federal agencies and universities to improve training programs, mentoring, and resources for the almost 50,000 postdoctoral scholars at institutions across the country. To date, more than 160 institutions have adopted portions of the NPA's recommended practices, including establishing a curriculum for postdoctoral training, appropriate compensation and benefits, and a timeframe for postdoctoral transition to independence. The NPA also facilitates networking through annual and regional meetings and online forums.

NIH's Intramural Research Program (IRP) has been especially responsive to the call for training excellence. With the help of IRP leadership, FelCom, and OITE, the training program at NIH is positioning itself to become the gold standard that will undoubtedly influence programs at research institutions around the country. Several NIH institutes and centers, as well as FelCom, are institutional members of NPA, and some NIH leaders and postdocs are active as individual members. "Since NIH is the steward of medical and behavioral research for the nation, it makes sense for the NPA to collaborate with NIH," said extramural project director Jennifer Reineke Pohlhaus, a recent vice chair of NPA's board of directors.

The NPA is recruiting volunteers to serve on its committees: Advocacy, Outreach, Meetings, and Resource Development. Being a member of NPA's Outreach Committee allows NCI postdoc Raed Samara "to work on issues that directly affect the entire postdoc population, strengthen my communication and leadership skills . . . and network nationally."

"The skills, opportunities, and networks that I formed helped me to gain practical experience that led to an actual job," said Lori Conlan, OITE's director of postdoctoral services and current NPA board member. Conlan has been involved with NPA since 2003, when she was a postdoc.

Any NIH fellow can sign up for a free membership at http://www.nationalpostdoc.org. For more information contact Kristofor Langlais (langlaik@mail.nih.gov). NIH is hosting NPA's 2011 Annual Meeting on the Bethesda campus. To serve on the local planning committee, contact Lori Conlan (conlanlo@mail.nih.gov). ■

On Effective Communication: It's All About the Message

By Ken Michaels, Staff Writer, NCI-Frederick

Mass media expert Marshall McLuhan, in his 1964 masterpiece *Understanding Media*, famously declared, "The medium is the message." He went on to explain that the assimilation of any new communication medium, in itself, has an impact on those whom it affects; that is to say, the presence of radio, television, the Internet, Twitter—the very existence of these various communication media—changes our lives. I do not dispute his premise. But in the context of preparing to give an oral presentation, I must contend that the *message* is the message.

More than once I've heard said something like, "I'm doing a PowerPoint next week on [topic]." And then there's, "[Name] just showed me how to make a word in a PowerPoint spin around. Cool! I'm going to use that in my next talk!"

The focus is in the wrong place. Now please don't misunderstand: I don't mean to say that we shouldn't be concerned about the presentation itself. We should. A good presenter takes care to prepare effective visual aids, when needed, to illustrate key points and concepts. But crafting the visuals should be "Phase Two" of preparation. "Phase One" should be crafting the message.

First, line up the first four W's: *Who* is the audience? *Why* are you talking to them? *When*, and *Where*? *What* do you plan to say to them? I think too often we get the steps out of sequence, sometimes even going straight to PowerPoint to make slides before really thinking about the message.

Think of giving a presentation as similar to telling a story. You wouldn't start talking before knowing what the point of the story was, would you? Start by asking what is it that—when the presentation is over—you want the audience to know, to know how to do, to understand, or to feel? The desired outcome informs the message itself.

So, first we get clear on what story we're going to tell, and then comes "Phase Two": deciding how we're going to tell it. If my memory serves me correctly, we communicated before PowerPoint, and even before 35-mm slides and overhead transparencies. It's my feeling that unless your story simply can't be told without PowerPoint, you ought to consider other options.

Perhaps a live demonstration of a technique or procedure will tell the story better. Or maybe motion media is really needed, or audio, or a combination of audio and video. Or perhaps a printed handout or workbook will do the trick. Or possibly you might simply stand up and talk and use no visuals at all. In any case, the medium you decide to use should be the one that gets the message across most effectively.

The preoccupation with "what I can make PowerPoint do" can, and sometimes does, get in the way of crafting a powerful and memorable presentation. Your real objective, after all, should not be to impress your audience with your mastery of flashy technology. It's not about "doing a PowerPoint" and it's not about exhibiting a parade of showy visuals. An effective presentation is all about the message. ■

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Letters

Authors Deserve Equal Credit

In your "Hottest Paper" article in the January-February 2010 issue of *The NIH Catalyst* ("NHLBI Behind 3rd-Hottest Paper of 2009," page 11), you mentioned "... lead author Artem Barski," which may be a little bit misleading given that the first seven authors contributed equally to the work (but are listed alphabetically). I think it is probably unfair to the other authors, who deserved mentioning.

—Concerned researcher in another institute

*Indeed, the footnote on the journal article (*Cell *129:823–837, 2007) indicates that the first seven authors "contributed equally to this work and are listed alphabetically." Our apologies to Artem Barski, Suresh Cuddapah, Kairong Cui, Tae-Young Roh, Dustin Schones, Gang Wei, Zhibin Wang, Iouri Chepelev, and Keji Zhao.*

Think Globally

Michael Gottesman's commentary in the January-February 2010 issue of *The NIH Catalyst*, "Think Globally, Act Intramurally," was very informative as it portrayed clearly the various aspects of the global-health initiative of the intramural program. I even went to the website and examined the very comprehensive Intramural Research Sourcebook. For even a veteran of the NIH intramural program, I found it to be very informative and comprehensive. (See http://www1.od.nih.gov/oir/sourcebook/oir/IRP_transition.pdf.)

I was prompted, however, to write this note because I was surprised when I read the statement in the *Catalyst* commentary (and later also similarly in the Sourcebook) that "The three infectious diseases that produce the most morbidity and mortality in the world—prematurely ending the lives of millions of children and adults and severely affecting the welfare and productivity of millions more—are tuberculosis, malaria, and HIV," because it differed from WHO data (World Health Organization, *The Global Burden of Disease: 2004 Update*. Geneva: WHO Press, 2008), which indicated that among infectious diseases, lower respiratory infections and diarrheal diseases are ranked as number one and two, respectively, whereas HIV/AIDS, tuberculosis, and malaria are ranked as number three, four, and six, respectively.

It is of interest that Dr. Hans Rosling—at his informative and entertaining talk at NIH on February 22, 2010, on "The New Health Gap: Science for Emerging Economies versus the Bottom Billion"—related that at the Global Health Initiative Meeting, Blair, Bush, and Bono did not want to present a complicated list of diseases so they dropped pneumonia and diarrhea and focused on AIDS, tuberculosis, and malaria as the three diseases to emphasize. Dr. Rosling also commented that this action was not evidence-based and not ethical. He also noted that the term "ATM diseases" had caught on in certain low-income settings as diseases for which there would be money available because the "ATM diseases" were supported internationally, and he made reference (pun) regarding an ATM machine and money availability. (See http://www.fic.nih.gov/news/events/rosling.htm.)

I hope that this information is helpful.

—Albert Z. Kapikian, M.D., NIAID
Chief, Epidemiology Section
Laboratory of Infectious Diseases

Chemistry Will Keep Us Together

Like Dan Appella who confessed to teaching his children the language of chemistry (*NIH Catalyst*, January-February 2010, back page), I too am pushing a chemical agenda on my child. They say love is the bond that ties, but I'd add benzene to that—or any covalent bond, for that matter. Nothing brings me closer to my four-year old than teaching her about hexagonal rings.

On one level I'm embarrassed. But, then again, kids love to play with shapes, so why not add a little excitement to those mundane circles and squares. There's the aforementioned hexagon; a cross, and by that I mean sulfuric acid; an airplane, known in my mind as boron trichloride; and various kinds of pyramids, such as carbon tetraiodide and phosphorus trichloride.

There is the occasional awkward moment. "Look, it's a Buckyball-man," my daughter exclaimed last month at school as her little friends put the finishing touches on a snowman. My wife worries that our child will be teased relentlessly with her drawings of a house with benzene windows, pyrrole lampshades, and a polycyclic aromatic hydrocarbon fence. But maybe she'll rise above all that ridicule, like helium; shine in school, like ionized xenon; and then emulate her old man and grow up to be a chemist, with all the wealth and respect that brings.

Hmmm, maybe that's something else to worry about, too.

—Name Withheld

NIH ABBREVIATIONS

CC: NIH Clinical Center

CIT: Center for Information Technology
FAES: Foundation for Advanced Education in the Sciences

FelCom: Fellows Committee

IRP: Intramural Research Program

HHS: U.S. Department of Health and Human Services

NCCAM: National Center for Complementary and Alternative Medicine

NCI: National Cancer Institute

NCMHD: National Center on Minority Health and Health Disparities

NEI: National Eye Institute

NHGRI: National Human Genome Research Institute

NHLBI: National Heart, Lung, and Blood Institute

NIA: National Institute on Aging

NIAAA: National Institute on Alcohol Abuse and Alcoholism

NIAID: National Institute of Allergy and Infectious Diseases

NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases

NIBIB: National Institute of Biomedical Imaging and Bioengineering

NICHD: National Institute of Child Health and Human Development

NIDA: National Institute on Drug Abuse

NIDCD: National Institute on Deafness and Other Communication Disorders

NIDCR: National Institute of Dental and Craniofacial Research

NIDDK: National Institute of Diabetes and Digestive and Kidney Diseases

NIEHS: National Institute of Environmental Health Sciences

NIGMS: National Institute of General Medical Sciences

NIMH: National Institute of Mental Health

NINDS: National Institute of Neurological Disorders and Stroke

NINR: National Institute of Nursing Research

NLM: National Library of Medicine

OD: Office of the Director

OITE: Office of Intramural Training and Education

OIR: Office of Intramural Research

Deciphering the Genetic Code:

In the Late Marshall Nirenberg's Own Words

Marshall Nirenberg's death on January 15, 2010, ended a long and very distinguished scientific career that resulted in the elucidation of the near-universal genetic code. This discovery, along with that of the structure of DNA, can be considered the two pivotal mid-20th century research accomplishments that opened the life sciences to explanation at the molecular level. Nirenberg became NIH's first Nobel Laureate, when he and two others received the 1968 Nobel Prize in Physiology or Medicine "for their interpretation of the genetic code and its function in protein synthesis."

*Numerous obituaries on Nirenberg have already been published, including two by former co-workers Philip Leder (*Science *19:972, 2010) and C.T. Caskey (*Nature *464:44, 2010) and one in the February 5, 2010, issue of the* NIH Record *(http://nihrecord.od.nih.gov/newsletters/2010/02_05_2010/story3.htm). On November 12, 2009, a daylong symposium was held to honor Nirenberg when the American Chemical Society designated NIH as a National Historic Chemical Landmark to commemorate his achievement of cracking the genetic code. A videocast is available at http://videocast.nih.gov/launch.asp?15434.*

Following is one of the few historical accounts of the central years of the deciphering of the genetic code at NIH (roughly from 1961 to 1966), written by Nirenberg himself. In this article, excerpted from one that appeared in Trends in Biochemical Sciences *(*TIBS*) in 2004, he describes the roles of his many colleagues and research fellows as well as the collaborative spirit at NIH at the time. These aspects, as well as the scientific details of the crucial and elegant experiments, may be of general interest and relevance even almost half century later.*

We thank TIBS *for facilitating our use of these excerpts and encourage readers to consult the original article for further information (*Trends Biochem Sci *29:46–54, 2004).*

—Alan N. Schechter, NIDDK

I would like to tell you how the genetic code was deciphered from a personal point of view. I came to the National Institutes of Health (NIH) in 1957 as a postdoctoral fellow with Dewitt Stetten, Jr., a wise, highly articulate scientist and administrator, immediately after obtaining a Ph.D. in biochemistry from the University of Michigan in Ann Arbor. The next year, I started work with William Jakoby and, by enrichment culture, I isolated a Pseudomonad that grew on gamma-butyrolactone and purified three enzymes involved in the catabolism of gamma-hydroxybutyric acid.

There were weekly seminars in Stetten's laboratory in which Gordon Tomkins, participated. Gordon's seminars were superb, especially his description of the step-by-step developments in the problem that he intended to discuss.

In 1958, toward the end of my postdoctoral fellowship, Gordon became the head of the Section of Metabolic Enzymes and offered me a position as an independent investigator. He was brilliant, highly articulate and very funny. He was a charismatic individual who created a stimulating atmosphere and encouraged exploration. The other independent investigators in the laboratory were Elizabeth Maxwell and Victor Ginsberg, who were carbohydrate biochemists, and Todd Miles, a nucleic-acid biochemist. It was a wonderful opportunity and I decided that if I was going to work this hard I might as well have the fun of exploring an important problem.

The most exciting work in molecular biology in 1959 were the genetic experiments of [1965 Nobel Prize winners] Jacques Monod and François Jacob on the regulation of the gene that encodes beta-galactosidase in *Escherichia coli*. The mechanism of protein synthesis was one of the most exciting areas in biochemistry. Some of the best biochemists in the world were working on cell-free protein synthesis, and I had no experience with either gene regulation or protein synthesis, having previously worked on sugar transport, glycogen metabolism and enzyme purification. After thinking about this for a considerable time, I decided to switch fields. My immediate objective was to investigate the existence of mRNA by determining whether cell-free protein synthesis in *E. coli* extracts was stimulated by an RNA fraction or by DNA. In the longer term, my objective was to achieve the cell-free synthesis of penicillinase, a small inducible enzyme that lacks cysteine, so that I could explore mechanisms of gene regulation. I thought that in the absence of cysteine the synthesis of penicillinase might proceed, whereas synthesis of most other proteins might be reduced.

In England, M.R. Pollock had shown that penicillinase is inducible in *Bacillus cereus* and had isolated mutants that differed in the regulation of the penicillinase gene. In 1959, tRNA was recently discovered but mRNA was unknown. At that time, the only clues that RNA might function as a template for protein synthesis were a report by A.D. Hershey et al., showing that a fraction of RNA is synthesized and degraded rapidly in *E. coli* infected with T2 bacteriophage, and a paper by E. Volkin and L. Astrachan, which showed that infection of *E. coli* by T2 bacteriophage resulted in the rapid turnover of a fraction of RNA that had the base composition of bacteriophage rather than the DNA of E. coli. If mRNA did exist, I thought that it might be contained in ribosomes because amino acids were known to be incorporated into protein on these organelles. I estimated that it would take two years to set up a cell-free system to determine whether RNA or DNA stimulated protein synthesis. It did.

I knew this was a risky problem to work on because starting out as an independent investigator you are supposed to hit the deck running and prove that you are effective and productive. One evening I saw Bruce Ames working in his laboratory. I thought he was one of the best young scientists at the NIH so I described my research plan and asked for his evaluation. He looked at me and said, "It is suicidal." Although we both agreed that it was a dangerous project to work on, I thought suicidal was extreme. On the one hand I wanted to explore an important problem, on the other I was afraid of failure. But my wish to explore was much greater than my fear of failure.

As soon as I moved to Gordon's laboratory I started to make cell-free extracts that incorporated amino acids into protein, and to prepare DNA and RNA from ribosomes of penicillinase inducible and constitutive strains of *B. cereus*. I devised a sensitive assay for penicillinase and starting with conditions that had been devised by M.R. Lamborg and P.C. Zamecnik and

his colleagues. I tried to obtain the de novo synthesis of penicillinase following addition of either RNA or DNA fractions from either *B. cereus* or *E. coli*. Systematically, I explored the optimum conditions for cell-free synthesis and showed that RNA prepared from ribosomes of *B. cereus* that expressed penicillinase constitutively stimulated penicillinase synthesis by 10–15%, but RNA from either uninduced ribosomes or DNA had no effect. However, the stimulation of penicillinase synthesis was small. I needed a more sensitive assay.

Usually around noon, Gordon would come into my laboratory with a sandwich and we would go into the hall and talk about my work, his work, and various exciting results that had been published. I always stopped to talk to him, even though the extract that I was preparing was slowly dying in an ice bucket, because these were wonderful conversations. Gordon encouraged me and created an exciting atmosphere for young investigators.

After about a year and a half, Heinrich Matthaei came to my laboratory as a postdoctoral fellow. Heinrich was a plant physiologist from Germany who was a postdoctoral fellow at Cornell and wanted to work on protein synthesis. He was under the impression that, because the NIH is such a big institution, many people would be working on protein synthesis. He stopped in Roy Vagelos's laboratory and Roy sent him to me because I was the only person at the NIH who was studying cell-free protein synthesis. We needed a more sensitive assay, so I suggested that Heinrich use the cell-free amino-acid-incorporating system that I had optimized to measure the incorporation of radioactive amino acids into protein. Heinrich insisted on preparing 20 14C-labeled amino acids by growing algae in the presence of 14C-bicarbonate, hydrolyzing the protein and purifying each of the 14C-labeled amino acids, because this is what he had done previously.

Using this more sensitive assay it was immediately apparent that RNA from ribosomes, but not DNA, stimulated incorporation of radioactive amino acids into protein. I jumped for joy because this was the first definitive demonstration in vitro that mRNA existed and was required for protein synthesis. We fractionated RNA from ribosomes and found, as expected, that only a small portion stimulated amino acid incorporation into protein.

I then obtained yeast rRNA and tobacco mosaic virus (TMV) RNA and we found that both were as active as mRNA. However, RNA from TMV was 30–50 times more active than ribosomal RNA at stimulating amino acid incorporation into protein. I called Heinz Fraenkel-Conrat in Berkeley, a world expert on TMV who had a mutant with an amino acid replacement in the viral coat protein, to tell him our results. He invited me to come to his laboratory to synthesize radioactive protein directed by RNA from wild-type and mutant TMV, with the intention that he and a colleague would purify and characterize the products to determine whether the radioactive protein synthesized was TMV coat protein. I felt like Marco Polo exploring a new area.

Before going to Frankel-Conrat's laboratory I obtained some poly(U) and instructed Heinrich to make 20 different solutions, each with 19 cold amino acids and one radioactive amino acid, to detect poly(U)-dependent incorporation of a single radioactive amino acid into protein. After I had been in Fraenkel-Conrat's laboratory for a month, Heinrich called me excitedly to tell me that poly(U) was extraordinarily active in stimulating the incorporation of only phenylalanine into protein. I immediately returned to Bethesda. We also showed that single-stranded poly(U) functions as mRNA, but double-stranded or triple-stranded poly(U)–poly(A) helices do not. This was the first RNA antisense experiment. We also showed that poly(C) directs the incorporation only of proline into protein.

I thought the poly(U) result wouldn't be believed unless we characterized the radioactive polyphenylalanine product of the reaction very carefully. Hydrolysis of the 14C-labeled polyphenylalanine by HCl recovered stoichiometric amounts of 14C-labeled phenylalanine. I also thought we should show that the solubility of the 14C-polyphenylalanine was the same as that of authentic polyphenylalanine, but because I knew nothing about this I went to Chris Anfinsen's laboratory, which was directly under mine, to ask for names of investigators who might have characterized polyphenylalanine. Michael Sela was the only person in the laboratory at the time; I knew that he worked with synthetic polypeptides so I asked if he knew anything about the solubility of polyphenylalanine. He said, "I do not know much, but I can tell you two things: one, polyphenylalanine is insoluble in most solvents; and second, it does dissolve in 15% hydrobromic acid dissolved in concentrated acetic acid." I looked at him in delight as well as astonishment because I had never heard of such

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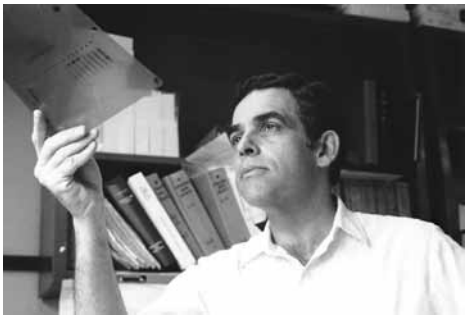


OPPOSITE: Marshall Nirenberg became NIH's first Nobel Laureate in 1968 for his work on interpreting the genetic code.

TOP: Heinrich Matthaei (left) worked with Nirenberg (right) to crack the genetic code.

MIDDLE: The charismatic Gordon Tomkins (left) offered Nirenberg a position in his laboratory. Maxine Frank Singer (right) was one of many NIH scientists who helped Nirenberg with his coding research.

BOTTOM: Philip Leder was a postdoctoral fellow in Nirenberg's laboratory who went on to become an important researcher in the field of oncogenes.

(Photos courtesy of NIH Office of History)

Intramural Research News:

NINR: Pain

The study of pain and pain relief has been nothing short of tortuous.

"Most drugs to treat pain are derivatives of either aspirin or narcotics," said pain researcher Raymond Dionne, scientific director of the National Institute of Nursing Research (NINR). "We've developed some improved versions of these drugs but nothing revolutionary."

But as Dionne and other researchers probe and prod to get a better understanding of pain's molecular underpinnings, they may indeed develop revolutionary treatments for pain one day.

NINR and NIDCR scientists, for example, are employing genomic analysis techniques to gain new insights into the mysteries of pain. In a 2009 cover article in the journal *Pain*, lead author NINR researcher Xiao-Min Wang, Dionne, and others reported on chemical pathways associated with inflammatory pain (*Pain* **142**:275–283, 2009).

The group used an oral surgery model—people who were undergoing surgery to remove impacted molars—to explore the changes in gene expression that lead to inflammation and pain. Applying microarray and qRT-PCR technologies to analyze oral mucosal biopsies, the researchers compared changes in the gene expression of a cascade of cytokines to patient-reported pain levels.

"With these unbiased methods we can begin to look at chemicals we didn't even think were involved," Dionne said.

The experiment showed that prostaglandin interleukin 6 (IL-6) and chemokines IL-8, CCL2, CXCL1, and CXCL2 were significantly upregulated three hours after oral surgery at the onset of acute inflammatory pain. In addition, there was a correlation between pain intensity and higher levels of IL-6, IL-8, and CCL2. Interestingly, none of these signals were diminished when the patients were treated with ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) related to aspirin.

That ketorolac has no apparent impact on these messengers could be related to the limited pain-alleviating effects of NSAIDs. Although the researchers acknowledge that further studies are needed, Wang suggests that IL-6, IL-8, and CCL2 could provide useful new targets for drug treatments.

"We can use these new technologies to find new targets for pain treatment," said Dionne.

—Eric Schaffer

NIEHS: DNA Sequences Associated with Lung Function

A collaborative research effort led by NIEHS scientists has identified genetic factors that increase the risk of impaired lung function. The study provides insight into the biological mechanisms that contribute to pulmonary function and possibly to the pathogenesis of chronic lung diseases—such as asthma and chronic obstructive pulmonary disease (COPD).

NIEHS scientists—including senior investigator Stephanie London and postdoctoral fellow Dana Hancock, who was first author of the paper—and colleagues analyzed data generated from several studies that involved more than 20,000 participants. The authors identified genetic variations in eight previously unrecognized DNA regions that correlated with altered lung function. These DNA sequences contain genes with biological activities that may play a role in pulmonary function.

The investigators determined that individuals carrying the identified genetic variations have lower pulmonary function and are at greater risk for developing COPD. Moreover, predictions involving these genetic alterations were consistent with those for known risk factors associated with decreased lung function, such as smoking and increasing age.

Although further study is required, the investigators hope their findings will one day lead to new interventions to manage pulmonary diseases. [*Nat Genet* **42**(1):45–52, 2010]

—Laura Hall, NIEHS
—Omari J. Bandele, NIEHS

NIEHS scientists Stephanie London (left) and Dana Hancock (right) led a collaborative study that provided insight into the biological mechanisms that contribute to pulmonary function and possibly to the pathogenesis of chronic lung diseases—such as asthma and chronic obstructive pulmonary disease. Hancock recently received an NIH Fellows Award for Research Excellence. (Photo courtesy of Steve McCaw)

Research Briefs

NCBI: Inflammatory Bowel Disease

An international team including NCBI researchers has discovered that mutations in either of two related genes cause a severe and rare form of inflammatory bowel disease (IBD) in young children. The study is the first to show that a single mutation is sufficient to cause IBD. Other research groups focusing primarily on adult-onset IBD have identified dozens of genes and variants that affect the risk for IBD, but none that singly can cause the disease.

The mutated genes identified in the study encode the cell receptor proteins IL-10 receptor 1 (IL10R1) and IL-10 receptor 2 (IL10R2), which together trigger signals by binding the cytokine interleukin-10 (IL-10). IL-10 plays a crucial role in keeping the body's inflammatory responses in check. When either IL-10 receptor 1 or IL-10 receptor 2 is mutated, the signals from IL-10 cannot be received, and the resulting inflammation causes tissue damage, especially in the gastrointestinal system. NCBI researchers led the computational analysis to pinpoint the genes. [*New Engl J Med* **361**:2033–2045, 2009]

NIAID: Barrier in Mosquito Midgut Protects Invading Pathogens

NIAID scientists studying the *Anopheles gambiae* mosquito—the main vector of malaria—have found that when the mosquito takes a blood meal, that act triggers two enzymes—immunomodulatory peroxidase (IMPer) and dual oxidase (Duox)—to form a network of crisscrossing proteins around the ingested blood. The formation of this protein barrier, the researchers found, is part of the normal digestive process that allows so-called "healthy" or commensal gut bacteria to grow without activating mosquito immune responses. But the barrier also prevents the mosquito's immune defense system from clearing any disease-causing agents that may have slipped into the blood meal, such as the Plasmodium malaria parasite, which in turn can be passed on to humans.

Disrupting the protein barrier, however, can trigger mosquito immune defenses to intervene and protect the insect from infection. The researchers believe it might be possible to prevent the formation of the protein barrier by immunizing people with IMPer or the proteins that crisscross. This vaccine would generate antibodies that, after a mosquito feeds on a human, could

disrupt the barrier, reduce parasite survival in the mosquito, and prevent malaria transmission. The role of IMPer-Duox in forming a protective barrier was unexpected—and previously unrecognized. [*Science*. DOI 10.1126/science.1184008, 2010]

NCI, NIAID, NHGRI: New Targets for Treating Non-Hodgkin Lymphoma

NCI, NIAID, and NHGRI researchers have discovered genetic mutations that may contribute to the development of an aggressive form of non-Hodgkin lymphoma—diffuse large B-cell lymphoma (DLBCL). The findings provide insight into a mechanism that cancer cells may use to survive, and they highlight potential new treatment targets.

Of the several different subtypes of DLBCL, the activated B cell–like (ABC) subtype is the least responsive to currently available therapies. The researchers identified critical points in the B-cell receptors (BCR) signaling pathway that affect the survival of lymphoma cells. Interfering with several components of the pathway caused lymphoma cells to die. The team tested dasatinib, a drug that is approved for the treatment of chronic myelogenous leukemia, in ABC-subtype DLBCL cells. They found that the drug turned off BCR signaling by inhibiting the activity of one of the pathway's components, thereby killing the cells. The results suggest new therapeutic opportunities for the ABC-subtype of lymphoma. [*Nature* **463**:88–92, 2010]

NIDCD, NHGRI: Stuttering Genes

Stuttering may be the result of a glitch in the day-to-day process by which cellular components in key regions of the brain are broken down and recycled, according to a study led by researchers at NIDCD and NHGRI. They identified three genes as a source of stuttering in volunteers in Pakistan, the United States, and England. Mutations in two of the genes have already been implicated in other rare metabolic disorders also involved in cell recycling, and mutations in a third, closely related, gene have now been shown to be associated for the first time with a disorder in humans.

These investigators refined the relevant location on chromosome 12, sequenced the genes surrounding a new marker, and identified mutations in a gene known as *GNPTAB* in the affected family members. The *GNPTAB* gene, carried by all higher animals, helps encode an enzyme that assists in breaking down and recycling cellular components inside lysosomes. The group analyzed the genes of 123 Pakistani individuals who stuttered—46 from the original families and 77 who were unrelated—as well as 96 unrelated Pakistanis who didn't stutter and who served as control subjects.

Individuals from the United States and England also took part in the study, 270 who stuttered and 276 who didn't. The researchers found some individuals who stuttered possessed the same mutation as that found in the large Pakistani family. Roughly 9 percent of people who stuttered possess mutations in one of the three genes. A long-term goal is to use these findings to determine how this metabolic defect affects structures within the brain that are essential for fluent speech. [*New Engl J Med* **362**:677–685, 2010]

NHGRI, NIA: Rare Disease Gene Tied to Parkinson's

NHGRI and NIA investigators led an international team that found that carriers of a rare genetic condition called Gaucher disease are five times as likely as the general public to develop Parkinson's disease. In previous studies, several genes had been linked to Parkinson's disease. However, the researchers say their work conclusively shows that mutations in the gene responsible for Gaucher disease are among the most significant risk factors found to date for Parkinson's disease.

The team examined the frequency of alterations in the gene *GBA* in 5,691 patients with Parkinson's disease, including 780 Ashkenazi Jews, a population in which a particular type of Gaucher disease is more prevalent. Those data were matched against data for 4,898 control subjects, which included 387 Ashkenazi Jews. At least one of the two common *GBA* alterations was found in 3.2 percent of Parkinson's patients and 0.6 percent of control subjects. Among the Ashkenazi subjects, 15.3 percent of those with Parkinson's disease carried a *GBA* alteration compared with 3.4 percent of Ashkenazi control subjects.

In addition, Parkinson's patients with *GBA* alterations developed symptoms an average of four years earlier than other Parkinson's patients. Overall, the researchers found that the association between *GBA* and Parkinson's disease is not confined to any single ethnicity or to specific *GBA* mutations, though they did find that some gene alterations are seen more frequently in certain populations. [*New Engl J Med* **361**:1651–1661, 2009]

NEI: Nearsightedness on the Rise

The prevalence of nearsightedness (myopia) is substantially higher now than it was about 30 years ago, according to a study published by NEI researchers. Using data from the ongoing National Health and Nutrition Examination Survey (NHANES), the researchers found that myopia was almost 67 percent higher among people aged 12 to 54 years in the 1999–2004 survey than in the 1971–1972 one (42 percent versus 25 percent, respectively). NHANES is conducted by the National Center for Health Statistics, Centers for Disease Control and Prevention.

Although the cause of myopia is not known, scientists believe it is likely due to a combination of genetic and environmental factors. Several recent studies have documented an increased prevalence of myopia in younger generations, suggesting that environmental risk factors for myopia may have become more common. Identifying modifiable risk factors for myopia could lead to the development of cost-effective interventional strategies. [*Arch Ophthalmol* **127**:1640–1647, 2009] ■

Colleagues

Recently Tenured

Peter Choyke, NCI

As chief of NCI's Molecular Imaging Program, Peter Choyke is leading the effort to develop imaging technologies to detect and treat cancer. Choyke's enthusiasm for medical imaging grew out of his early love for physics. In fact, he earned a B.S. in physics from Pennsylvania State University (University Park, Pa.) and decided to apply his knowledge to medicine. After earning an M.D. from Jefferson Medical College (Philadelphia), he went on to train in medical imaging: he did a residency in diagnostic radiology at Yale–New Haven Hospital (New Haven, Conn.) and a fellowship focusing on magnetic resonance imaging, computed tomography, and ultrasound at the Hospital of the University of Pennsylvania (Philadelphia).

In 1988 he came to NIH as a staff radiologist in the CC's Diagnostic Radiology Department, became chief of Clinical MRI in 1992, and in 2004 started the Molecular Imaging Program in NCI. He has also held an appointment as a professor of radiology at the Uniformed Services University of the Health Sciences (Bethesda, Md.) since 1992.

Choyke enjoys the stimulating environment at NIH. "Every day something happens, either an interaction with a scientist or a new idea, that makes me excited to be doing the kind of work I am doing," he said. "We are lucky to work here."

There have been great strides in both molecular biology and imaging in the past decade. These advances come together in the new field of molecular imaging. Our goal is to accelerate therapies for cancer by using molecular imaging biomarkers: We do optical, nuclear, and magnetic resonance imaging with custom-designed molecular probes.

Each technique has unique advantages for selective use. For example, optical imaging is best used for improving endoscopy. Nuclear techniques are highly sensitive and can image throughout the body, while MRI provides the highest anatomic resolution. We combine these technologies with targeted contrast agents, which consist of a targeting ligand, an imaging beacon (optical, radioactive, or paramagnetic), and a carrier or linker molecule. We test these novel agents when we do preclinical imaging and use them to develop better cameras for imaging animals and patients. We also test them when we do clinical imaging of patients with cancer.

Clinical imaging takes place in the newly renovated Molecular Imaging Clinic located in the basement of Building 10. Here, we investigate the role of novel imaging agents in patients who are undergoing therapy. We hope that by using these new imaging agents we can better select patients for personalized therapies and monitor their progress noninvasively. We trust that our work is accelerating the search for a cancer cure. ■

Paul S. Albert, NICHD

"NIH provides a unique opportunity for statistical scientists to work on important scientific problems," said mathematical statistician Paul Albert, who is senior investigator and chief of the Biostatistics and Bioinformatics Branch at NICHD. "The synergy between collaborative and statistical science at NIH leads to important methodological advances" that help researchers in the design and analysis of their studies. In recognition of his work the American Statistical Association (ASA) elected him as a fellow in 2005. ASA Fellows are nominated by their peers as having made outstanding contributions in some aspect of statistical work. Albert, who hails from Staten Island, N.Y., earned an A.B. degree in mathematics and psychobiology from Oberlin College (Oberlin, Ohio) and a Ph.D. in biostatistics from Johns Hopkins University (Baltimore).

Paul S. Albert, NICHD

He began his career at NIH in 1988 as a staff fellow in the Biometry and Field Studies Branch at NINDS. Later he became a mathematical statistician, working first in NHLBI's Office of Biostatistics Research and later in NCI's Biometric Research Branch. He joined NICHD in 2009.

My research has primarily been in the areas of disease modeling, longitudinal data analysis, biomarker data analysis, and the development of statistical methods in diagnostic medicine. I focus on developing new statistical methodologies to address important scientific problems.

In disease modeling, I have developed statistical models for monitoring such diseases as relapsing-remitting multiple sclerosis (MS) by measuring monthly serial magnetic resonance imaging results. These models were instrumental in the design of many of the phase II MS clinical trials conducted at NINDS. I also developed probabilistic models called hidden Markov models to describe nonrandom seizure patterns in patients with intractable epilepsy.

In longitudinal data analysis (analysis of data collected over a period of time), I have developed new approaches for evaluating repeated ordinal data, some of which have been misclassified, and robust procedures for analyzing discrete and continuous longitudinal data, including data with missing values. I have also developed new approaches for simultaneously modeling longitudinal and time-to-event data in an efficient manner.

My biomarker data research has included developing new longitudinal models to analyze circadian rhythm and menstrual cycle biomarker data. This methodology allows investigators to examine the effect of individual factors such as demographic variables or environmental exposure on complex circadian or menstrual cycle patterns.

Much of my research in diagnostic testing has involved developing new methods for estimating diagnostic accuracy in situations in which a gold standard measurement is either impossible to obtain or is very expensive to obtain on all subjects. These methods are important for assessing the ability of new biomarkers and diagnostic tests to predict disease.

Proper statistical design and analysis is essential in biomedical research. NIH provides an ideal environment for a research statistician to make important contributions to many areas of medical and epidemiologic research and to develop new innovative statistical techniques to extract the most information from existing and future research studies. ■

Scientific Interest Groups

NIH Inter-Institute Interest Groups are assemblies of scientists with common research interests.

These groups are divided into seven broad, process-oriented parent groups, or faculties, and more than 100 smaller, more focused groups centered on particular research models, subjects, or techniques. The latter groups are initiated and run by scientists in the Intramural and Extramural Research Programs at NIH.

The interest groups sponsor symposia, poster sessions, and lectures; offer mentoring and career guidance for junior scientists; help researchers share the latest techniques and information; act as informal advisors to the Deputy Director for Intramural Research (DDIR); provide advice for the annual NIH Research Festival; and serve as hosts for the Wednesday Afternoon Lecture Series.

Many of these groups are cosponsored by neighboring academic and government institutions and welcome interested non-NIH scientists. Information about group activities or new groups is published in *The NIH Catalyst* and on the DDIR's Bulletin Board. (The latter is available only to NIH staff.) Some central coordination for the groups is provided by the Office of Intramural Research (OIR).

For a complete list of Scientific Interest Groups go to http://www.nih.gov/sigs/sigs.html. In addition, the August issue of *The NIH Catalyst* (http://www.nih.gov/catalyst) published an annual directory of interest groups.

To create a SIG, contact the OIR Communications Director Christopher Wanjek (wanjek@od.nih.gov). ■

The SIG Beat:
News from and about the NIH Scientific Interest Groups

New SIG: Antibody Interest Group

The NIH Antibody Interest Group (ABIG) aims to promote information exchange and interaction among NIH scientists who work on various aspects of antibody engineering and therapy. The success of antibody therapy requires a deep understanding of biological systems in relation to molecular and cell biology, immunology, biochemistry, and microbiology as well as to diseases such as cancer, autoimmunity, and infectious diseases. Interest in antibody therapy crosses traditional biomedical disciplinary boundaries. ABIG provides an open forum for multidisciplinary discussion among colleagues who otherwise may have limited contact.

The principal ABIG activities are monthly meetings on current topics as well as an annual symposium on the NIH campus. The monthly ABIG meetings are open to everyone interested. These meetings are devoted to research seminars on numerous aspects of antibody engineering and therapy that will be presented by both NIH scientists and outside speakers.

An advisory committee composed of NIH scientists from basic and clinical disciplines is responsible for running the ABIG. The committee's principal job is to select speakers for the monthly meetings. The committee consists of Mitchell Ho, chairman (homi@mail.nih.gov); Dimiter Dimitrov (dimitrov@ncifcrf.gov); Christoph Rader (raderc@mail.nih.gov); and Raffit Hassan (hassanr@mail.nih.gov). Website: http://sigs.nih.gov/antibody. ■

Calling All Recently Tenured

If you are an NIH intramural scientist or clinician and have been tenured within the past year or so, we'd like to feature you in an upcoming issue of *The NIH Catalyst.*

All you have to do is respond to our invitation. We'll ask you to provide your CV and a photo, answer a few questions, and then write a brief description of your work.

To find out more, contact Laura Carter, managing editor of the *Catalyst,* at carterls@od.nih.gov or 301-402-1449. Or just say "Yes" when you get that e-mail invitation. ■

Green NIH Labs

continued from page 1

Trevor Blake is helping NHGRI labs go green.

Bethesda campus—let alone in the entire Intramural Research Program, from Baltimore and Research Triangle Park all the way to Montana—the impact is significant. That's just for starters.

Green, or Less Than Rosy?

The broad objectives for environmentally sustainable NIH labs include reducing paper use (going paperless or printing duplex), reducing energy needs (turning off lights and computers), reducing use of potentially toxic chemicals, and purchasing "greener" products up front.

Admittedly, change isn't easy. Many scientists here do consider themselves green—very green, in fact, and knowledgeable about how to best manage their energy and chemical use—and thus are troubled by mandates to eliminate certain chemicals from the lab or otherwise change research practices.

These are reasonable concerns, Floyd said, because at first glance the mandates and other requirements may seem cumbersome and a hindrance to the NIH mission "to extend healthy life and reduce the burdens of illness and disability." Many scientists spend years perfecting experiments in specific ways—with specific reagents and specific tools—and naturally are hesitant to switch methods midstream or to burden themselves with the complicated paperwork needed to justify the use of, say, a mercury-containing instrument.

Although the DEP has little control over how to implement mandates, many of which are executive orders, what the group does hope to better exploit is peer networking by creating a resource of best practices. The logic is that if researchers see their own peers switching to alternative reagents and the like, documenting successes and pitfalls, they would be more comfortable with making the transition as well.

Sharing Green Ideas

In this vein, the DEP has established "green teams" in 25 of the 27 NIH institutes and centers. Team leaders meet monthly. The fruits of their labor are beginning to ripen, said DEP environmental protection specialist Terry Leland, who's leading the NEMS Implementation Team and the Sustainable Laboratory Practices Working Group.

For example, Trevor Blake, who works with lab managers and a go-green committee within NHGRI, has helped several labs switch from ethidium bromide, a nucleic acid stain, to the slightly more benign SYBR Green. She also helped introduce a technique using Phase Lock Gel tubes to provide a barrier between phenol and chloroform during extractions to isolate DNA, RNA, or proteins. This technique reduces fumes and also makes extractions easier.

Such ideas are slowly populating the NEMS website at http://www.nems.nih.gov. Further facilitating the sharing of ideas, Dawn A. Walker, the lab manager for NCI's Laboratory of Molecular Biology and moderator for the Lab Managers Interest Group, created a listserv, greenserve-l@list.nih.gov, now with over 300 subscribers.

Phase Lock Gel tubes

Left: Tube, before use. Right: After DNA extraction, the phase-separating material (middle) is between the DNA (top) and the phenol/chloroform layer.

"We are not looking for a 'perfect' set of green ideas; rather, we are putting out all the possibilities for the researchers to consider," said Leland. "There are many types of labs at NIH implementing thousands of types of protocols, so what may be feasible for one may be completely out of the question for others."

The Green Challenge

If you are leaning toward greening, Leland said a good first step is to take the "Go Greener Lab Challenge" at http://www.nems.nih.gov/challenge/lab. This is an evaluation to baseline how green your lab is.

You may find that some suggestions are too difficult to implement. But something is better than nothing, said Floyd. Consider energy use: Shakers, water baths, lights, and computers collectively use much energy.

Sometimes things must stay on for practical reasons; other times it's just a matter of old habits to not turn off machines. For example, your lab might need to keep a continually used water bath on all day because it takes time for the water to reheat. And your lab might be active around the clock. "It is sometimes hard to know when the workday ends," Walker said.

Yet does the light in the cold room need to stay on, asks Walker, who often finds herself switching off lights (not to mention pulling recyclable objects out of the trash and placing them in recycling bins). Do computers need to be on overnight? Are they configured to take advantage of the Energy Star settings they have? Although some labs report conflicting instructions from their IT folks to keep the computer on overnight for updates, monitors can be turned off and usually the IT staff notifies the community about planned updates.

Powering down isn't necessarily efficient if powering up soon after consumes more energy. Confronted with so much equipment and so many unknowns, Paul Randazzo, chief of the Membrane Trafficking section in NCI's Laboratory of Cellular and Molecular Biology, turned to Greg Leifer of the ORF Division of Property Management to help him assess the energy consumption patterns of his and a neighboring lab, together employing more than 15 workers. Leifer is now working with the DEP to set up monitoring equipment.

Aside from what may be no-brainers—turning off lights, installing energy-saving software on the computers—Randazzo said he is open to new technologies that would dramatically cut energy use. For example, are DNA samples best stored in a freezer or refrigerator, or is it possible to keep these at room temperature in special containers, as some companies do?

Reducing the use of potentially toxic chemicals follows a similar pattern of obvious switches, better management, and thinking outside of the box. Maybe you can't part with certain chemicals, at least not now. You can, however, take better stock in what you and your neighbors have. Jeremy Smith, the lab manager at NIH's Chemical Genomics Center, has introduced an electronic laboratory notebook that has enabled better inventory control and greatly reduced the disposal of unused bottles of solvents.

You might be able to buy them in recyclable containers, too. Blake worked with DEP's Don Wilson to create a list of solvents and reagents that come in recyclable packaging. NEMS has its own growing list of "green" purchasing recommendations, and the group also suggests using MIT's "Green Chemical Alternatives Purchasing Wizard" at http://web.mit.edu/environment/academic/purchasing.html.

Without sacrificing research quality, and in some cases improving quality, these scientists and lab managers have made steps, however incremental, toward reducing greenhouse-gas emissions, NIH's hefty $4 million monthly energy bill, and the consumption and disposal of potentially harmful chemicals. ■

LEED-ing the Way

With hundreds of labs and thousands of researchers, the NIH Bethesda campus inevitably has a substantial effect on the environment. This includes an annual energy use of 6.6 trillion BTUs, approximately equal to that from 53,000 houses; approximately 1.2 billion gallons of potable water; and the generation of approximately 40,000 pounds of solid waste daily.

Yet where there is significant negative impact there can be significant positive impact. Indeed, signs of sustainability are all around the NIH Bethesda campus.

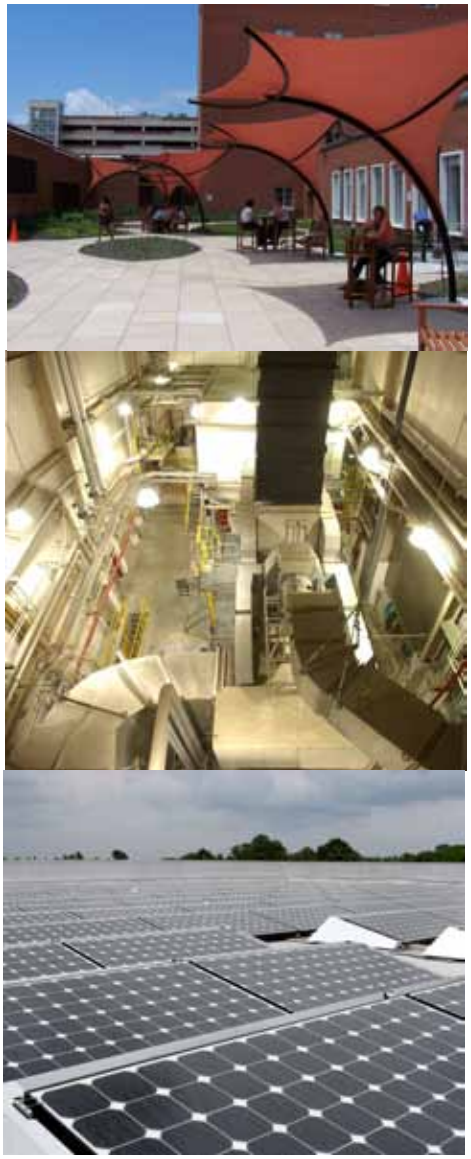
• The NIH Library is hoping to be LEED certified (Leadership in Energy and Environmental Design), meeting a suite of standards for environmentally sustainable design, construction, and operation. The library's features include carpeting made of recycled content, nearly paperless operations, and a green terrace with plants and solar panels.

• The Commercial Vehicle Inspection Facility and the Children's Inn have solar panels, and you can track the energy generation for the latter at http://www.sunviewer.net/portals/CINIH/index.shtml.

• The natural-gas power plant on the Bethesda campus produces over a third of the campus's energy, significant particularly because natural gas is cleaner than the coal-generated power that fuels most of this region. About three percent of NIH Bethesda's power comes from renewable energy, mostly wind.

• Many labs and offices have made duplex printing (automatic printing on both sides) the default to save paper, and the push is on to increase duplex printing across NIH and to hold "paperless" days.

• Floyd's team has placed a multitude of recycling bins in labs; bins have already been a fixture in offices. Many labs previously were not recycling for lack of bins. NIH-wide recycling continues to increase yearly and stood at 46.5 percent of all waste in 2009, although much of this included heavy building material. NIH as a whole has reduced its energy use per square foot by 21.7 percent since 2003.



TOP: The NIH Library's green features include a green terrace with plants and solar panels. (Photo by Bradley Otterson)

MIDDLE: The natural-gas power plant on the Bethesda campus produces over a third of the campus's energy. (Photo by Ernie Branson)

BOTTOM: NIEHS's green initiatives include composting bins and solar panels. (Photo by Steve McCaw, NIEHS)

• External facilities have separate environmental management systems; the National Institute of Environmental Health Sciences in Research Triangle Park, N.C., has compost bins and solar panels, for example.

NEMS goals include making NIH Bethesda carbon neutral by 2020 and energy independent by 2050; achieving "zero waste" (that is, 90 percent solid waste diverted from landfill and incineration) by 2020; and requiring all construction and renovation to be LEED Platinum certified or better by 2020.

These and other highlights, as well as setbacks and other goals, are listed in NEMS's first annual report, which will be published in early spring and placed on the NEMS website. *—CW*

Bumps on Road to Green

All is not rosy when thinking green. Many NIH researchers have expressed their annoyance with NEMS mandatory training, which they view as a time sink with little added benefit. The Office of the Director is coordinating a committee to review all NIH mandatory training—considered, well, mandatory yet perhaps something that can be streamlined.

Other beefs include:

• True success is a result of technological change, not mandates; reduction in use of radioactive material happened because of better technologies, not because researchers decided it was time to use fewer radioactive materials. Similarly, the reduction in photographic chemicals was the result of digital photography and scanners, primarily a boon to research and secondarily a boon to the environment.

• Eliminating mercury, to name one chemical, has been a burden to researchers who need to use mercury but who now must fill out more paperwork.

• The purchase of Energy Star equipment, duplex printers, or "greener" chemicals often doesn't jibe with stagnant or reduced lab budgets.

• NEMS adds a level of bureaucracy and thus cost to the NIH budget, and researchers question NEMS's effectiveness in promoting change and in providing the funding needed for labs to spend money to save money (for example, buying a duplex printer to save paper costs or Energy Star equipment to save on "someone else's" energy bill).

• Many NEMS recommendations have been too general to be of use for specific labs, and green teams across NIH vary greatly in the enthusiasm and focus needed to initiate change.

Only dialogue can smooth the path to a greener NIH, Floyd said. He encourages feedback via green@mail.nih.gov. *—CW*

Resources

Green listserv: https://list.nih.gov/archives/greenserve-l.html

Go Green general e-mail: green@mail.nih.gov

Go Green lab assessment: http://www.nems.nih.gov/challenge/lab/

MIT's Green purchasing wizard: http://web.mit.edu/environment/academic/purchasing.html

Marshall Nirenberg

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a solvent. Fifteen years later I learned that Michael Sela was the only person in the world who knew that polyphenylalanine dissolved in this esoteric solution because it is used to characterize C termini of proteins and he had mistakenly added it to polyphenylalanine, which, to his surprise, dissolved.

I was scheduled to give a talk in 1961 at the International Congress of Biochemistry in Moscow. Just before leaving for Russia, I married Perola Zaltzman, a biochemist from Rio de Janeiro who worked with Sidney Udenfriend at the NIH, and we planned to meet for a leisurely, two-week vacation after the meeting. I gave my talk in Moscow to 35 people. However, Francis Crick invited me to talk again in a large symposium that he was chairing on nucleic acids. This time there was an extraordinarily enthusiastic audience. After I returned to Bethesda, Fritz Lipmann generously gave me a partially purified transfer enzyme and we showed that phenylalanine-tRNA is an intermediate in the synthesis of polyphenylalanine directed by poly(U).

Several NIH investigators played major roles in deciphering the genetic code. Bob Martin synthesized and characterized many randomly ordered polynucleotides and helped decipher the base compositions of RNA codons. Leon Heppel was one of the few nucleic acid biochemists in the world at that time. He gave me compounds and advice when I needed it and suggested the use of pancreatic RNase A to catalyze trinucleotide and higher homologue synthesis, a method that he had discovered earlier. Maxine Singer came to the NIH as a postdoctoral fellow working with Leon Heppel. She was an expert on polynucleotide phosphorylase and helped devise conditions for the synthesis of trinucleotides catalyzed by polynucleotide phosphorylase.

Phil Leder came to my laboratory as a postdoctoral fellow and played a major role in deciphering the genetic code. He was the first to decipher the nucleotide sequence of a codon. Dick Marshall and postdoctoral fellow Tom Caskey compared the genetic code of *Escherichia coli* with that of *Xenopus* and hamsters and showed that the code is universal. Later, Tom Caskey and his colleagues worked on the mechanism of termination of protein synthesis.

Deciphering the genetic code was the first project I worked on as an independent investigator. It was an exciting, fun-filled project to explore and solve. Although many excellent problems related to the code and protein synthesis remained after the code was deciphered, I decided to switch to the more challenging field of neurobiology. ■

Carbonation

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carbonation is initiated by an enzyme tethered like a small flag to the surface of sour-sensing cells in taste buds. The enzyme, called carbonic anhydrase 4, or CA-IV, interacts with the carbon dioxide in the soda, activating the sour cells in the taste bud and prompting it to send a sensory message to the brain, where carbonation is perceived as a familiar sensation. (*Science* **326**:443–445, 2009)

"Of course, this [explanation] raises the question of why carbonation doesn't just taste sour," said NIDCR scientist Nicholas Ryba, a senior author on the study. "We know that carbon dioxide also stimulates the mouth's somatosensory system. Therefore, what we perceive as carbonation must reflect the combination of this somatosensory information with that from taste."

A somatosensory system transmits sensory information within the body from protein receptors to nerve fibers and onward to the brain, where a sensation is perceived. Common sensory information includes taste, touch, pain, and temperature.

The taste of carbonation is quite deceptive. "When people drink soft drinks, they think that they are detecting the bubbles bursting on their tongue," Ryba explained. "But if you drink a carbonated drink in a pressure chamber, which prevents the bubbles from bursting, it turns out the sensation is actually the same. What people taste when they detect the fizz and tingle on their tongue is a combination of the activation of the taste receptor and the somatosensory cells. That's what gives carbonation its characteristic sensation."

Scientists believe that our sense of taste generates a limited palate of distinct qualities: the familiar sweet, sour, salty, bitter, and savory tastes. Much of the flavor of food (the "tickling of taste buds") comes from a combination of this taste information with input from other senses such as touch and smell.

Over the past decade, there has been tremendous progress in identifying the basis for detection of the five major taste qualities. The laboratories of Ryba and UCSD scientist Charles Zuker had previously teamed up to identify the receptor proteins and cells responsible for sweet, bitter, and savory tastes and the receptor cells that detect sour.

Recent work from several groups has suggested taste buds might detect other qualities such as fat and metallic tastes. It also indicated that the gas carbon dioxide induces strong responses in the taste nerves.

The body senses carbon dioxide on many levels—in the somatosensory system (including touch and pain), through smell, and in the brain and blood to control respiration. But it was unclear how carbon dioxide is detected by taste sensors.

So the researchers decided to explore the taste of carbonation. They discovered that the enzyme CA-IV is selectively expressed on the surface of sour taste-receptor cells.

CA-IV is one of a family of enzymes that catalyze the conversion of carbon dioxide to carbonic acid, which rapidly ionizes to release a proton (acid ion) and a bicarbonate ion (weak base). By so doing, carbonic anhydrases provide cells and tissues with a buffer that helps prevent excessive changes in pH levels.

The scientists found that if they eliminated CA-IV from the sour-sensing cells or inhibited the enzyme's activity, they severely reduced a mouse's sense of taste for carbon dioxide. (To determine how the mice "tasted" CO_2, the scientists measured electrophysiological responses from one of the major nerves enervating taste receptors in the tongue.)

Thus, CA-IV activity provides the primary signal detected by the taste system. Because CA-IV is expressed on the surface of sour cells, the researchers concluded that the enzyme is ideally poised to generate an acid stimulus for detection by these cells when presented with carbon dioxide.

Why do mammals taste carbonation? The scientists are still not sure whether carbon dioxide detection itself serves an important role or is just a consequence of the presence of CA-IV on the surface of the sour cells, where it may be located to help maintain the pH balance in taste buds.

As Ryba says, "That question remains very much open and is a good one to pursue in the future." ■

AAHRPP Update

In the December 2009 issue of *The NIH Catalyst*, I wrote that the NIH Office of Human Subjects Research (OHSR) was ramping up for the Association for the Accreditation of Human Research Protection Programs (AAHRPP) accreditation process. To achieve accreditation, we are aiming to create an integrated human research protection program that is effective yet user-friendly and efficient and that puts the minimum burden on investigators and IRBs. AAHRPP can take us there. So here's where we currently are, as relayed to me by Leody Bojanowski, the accreditation team leader in OHSR.

Since January 2010 the HRPP Policies & Procedures Committee (P&P Committee) has been holding weekly two-hour meetings to review and update existing HRPP policies and to develop new ones to enhance human subjects protections at the NIH. The P&P Committee members are highly engaged; the meetings are dynamic and interactive; and the work is 70 percent finished, Bojanowski said. These policies will next go through a vetting process. With the self-evaluation and preparation of materials nearly completed, we are on schedule to submit the AAHRPP application within the next few months. This would lead to an AAHRPP site visit this fall. Since a major emphasis of the AAHRPP site visit is participation by all of our clinical investigators and human subjects protection support staff, we anticipate a major educational effort prior to this site visit. ■

—Michael Gottesman, DDIR

One Site: All the Intramural Programs

The NIH Web site once again has a page providing links to all the intramural programs. This page, http://www.nih.gov/science/labs.html, was long outdated and hard to find. Now it is a more visible link from http://www.nih.gov/science, one step from http://www.nih.gov. This is a no-frills, straight-list kind of page, but it offers one-stop shopping and might be worth a bookmark. ■

ANNOUNCEMENTS

"Of Tissue Specificity, Plasticity and Breast Cancer: Are There Any Linear Principles in Real Life?"
Monday, April 5, 2010, 3:00–4:00 p.m.
Lipsett Amphitheater (Building 10)

Speaker: Mina J. Bissell (Lawrence Berkeley National Laboratory). For more information, call 301-228-4027 or e-mail kochersbergerks@mail.nih.gov.

"Influenza and the Immune System"
April 9, 2010
Masur Auditorium, Building 10

This one-day meeting will cover such topics as pathogenesis and disease; host factors required for virus replication, immune responses, and evasion; and vaccines. Confirmed speakers include Nobel Prize recipient Peter Doherty (University of Melbourne), Brian Murphy (NIAID), Megan Shaw (Mount Sinai), and Philip Dormitzer (Novartis). Sponsored by the NIH Center for Human Immunology, Autoimmunity, and Inflammation. A full agenda will be posted at http://web.ncifcrf.gov/events/CHI/default.asp. Attendance is free but registration is required; see http://web.ncifcrf.gov/events/CHI/register.asp.

Director's Seminar Series
Fridays, 12:00–1:00 p.m.
Wilson Hall (Building 1)
Contact Information: 301-496-1921

April 16: Raffit Hassan (NCI), "Targeted Immunotherapy for Treatment of Malignant Mesothelioma"
May 21: Richard Siegel (NIAMS), "TNF Family Cytokines: From Molecule to Malady and Back Again"
June 18: Yasmine Belkaid (NIAID), "Control of Treg Induction and Function by Microbes"

Wednesday Afternoon Lectures
Wednesdays, 3:00–4:00 p.m.
Masur Auditorium (Building 10)

April 7: Judy Cho (Yale), "Genetics after Genome-wide Association Studies: Inflammatory Bowel Disease"

April 14: Catherine Costello (Boston University), "Proteins as Chameleons: The Good, the Bad and the Ugly"

April 21: Ronald Breaker (Yale), "Ancient RNA Relics and Modern Drug Discovery"

April 28: Sandra Schmid (Scripps Research Institute), "Protecting your Borders: Regulated Entry into the Cell"

For more information and for a listing of lecturers through June, go to: http://wals.od.nih.gov/2009-2010/home.html

Intramural Funding Opportunity: Dietary Supplements
Deadlines: May 5 and June 30

The Office of Dietary Supplements (ODS) entertains proposals for extramural grants, intramural training projects, and conference co-funding quarterly. Primary consideration for support is given to applications that deal with dietary supplement ingredients or groups of supplements for which current research is lacking or lagging or there is a likelihood of stimulating further research. Also, there may be dietary supplements where the data appear conflicting or there is a need to clarify research gaps and opportunities as well as assess the balance between benefits and risks. Additionally, the office will seek to co-fund activities that target special population groups for whom additional investigations on supplements is needed. Topics focusing on the use of supplements in reducing the risk of chronic disease are of keen interest to the ODS.

Contact Rebecca Costello at costellb@od.nih.gov with questions or for a copy of the ODS referral guidelines for submission of conferences, extramural grants, and intramural projects. A complete listing of ODS co-funded grants with abstracts is available on the ODS website at http://ods.od.nih.gov or, more directly, http://ods.od.nih.gov/Funding/Grants__Contracts.aspx.

National Day of Prayer
May 6, 2010, 11:30 a.m.–1:00 p.m.
In Front of Building 1

All are welcome!

SAVE THE DATE
Monday, May 17, 2010
Natcher Auditorium (Building 45)

Memorial Service to commemorate the life and accomplishments of Ruth Kirschstein.

Spring Research Festival
May 12 and 13, 2010
Parking Lot 10-H, next to Building 10

This two-day festival includes poster presentations by postbacs and medical students who are spending the year at NIH. Vendor and equipment show, too. For information on the poster presentations visit http://www.training.nih.gov and for the list of exhibitors see http://www.gtpmgt.com.

For more events information visit:
http://calendar.nih.gov
http://www.nih.gov/ddir/DDIR.html

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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: 301-402-4303; or mail: *The NIH Catalyst*, Building 1, Room 333.

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

In Future Issues...

- Stem Cells
- Prions
- Undiagnosed Diseases

Laboratory Confessions:

Personality Is Personal

By Name Withheld

I lied about myself. I'm not who I've reported myself to be, at least not on a personality test my supervisor made me take.

I took the test in preparation for our laboratory retreat. Every year, more than a million people worldwide use the DiSC behavioral model—a test to measure Dominance, Influence, Steadiness, and Conscientiousness—to improve performance and deal more effectively with conflict and value differences. So says page one of the DiSC survey. But I already know my personality well: I'm the type who hates personality tests.

I remember taking a similar test when I was in grade school. According to that test, I was destined to be a lumberjack. But I never knew whether I was to be one of those happy, suspender-wearing, yodeling lumberjacks with a felling ax over my shoulder, or a somber, no-nonsense type with loud power tools and stubble instead of a plush beard.

Regardless, I never understood how I managed to answer those 28 personality questions in such a way as to score so high in the lumberjack category. I hate mud. Two roads diverged in a wood, and I—I took the one back to a big city with lots of bars. I've been wary of such tests ever since.

So here I was at NIH faced with another test attempting to define me. It was set up so that one couldn't race through by clicking "A" over and over, as is usually my plan. Trapped, I decided to fudge the answers instead. The test had 28 sets of words, and I was asked to choose the words in each set that described me the most and the least. This quickly became a game. I chose answers to portray myself as meek and self-confident, an egocentric team player, a self-assured fidgety diplomatic loner, a conservative risk-taker who weighs pros and cons and shoots from the hip, a sociable snob who values the opinions of others in my own obstinate way. I cruised through the test, providing conflicting information for each question.

The results were tallied, and it turns out that I am "creative." Actually, that's not too far off. My supervisor should be happy, too, seeing how the NIH hopes to foster creativity.

Editor's note: Have a late-night laboratory confession? We might print it if it is indecent enough.

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 333, NIH, Bethesda, MD 20892. Ph: 301-402-1449; fax: 301-402-4303; e-mail: catalyst@nih.gov

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Publisher
Michael Gottesman
Deputy Director
for Intramural Research, OD

Editors
John I. Gallin
Director, NIH Clinical Center

Henry Metzger
Scientist Emeritus

Managing Editor
Laura Stephenson Carter

Writer-Editor
Christopher Wanjek
Director of Communications, OIR

Copy Editor
Shauna Roberts

Contributors
Omari J. Bandele, Laura Hall, Bob Kuska, Kristofor Langlais, Francesco M. Marincola, Ken Michaels, Robert B. Nussenblatt, John O'Shea, Eric Schaffer, Alan N. Schechter