FOSTERING COMMUNICATION AND COLLABORATION

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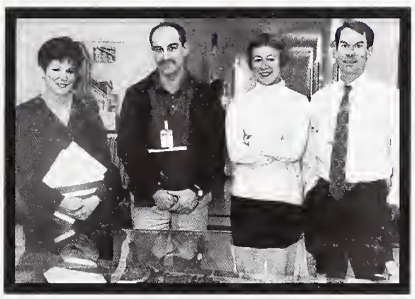
THE PRESS MEETS NIH



Bill Branson

The Knights of the Press Table: *(left to right): Anita Manning, Ken Garber, Leigh Hopper, and Mike Stobbe*

by Celia Hooper

With thanks to the largess of the nonprofit Knight Center for Specialized Journalism, four journalists had the opportunity for three weeks in March to put NIH under the microscope. To the pleasant surprise of people at both ends of the viewing, the experiment was a success.

The four journalists were selected from a competitive field of applicants vying for the opportunity to visit NIH as foundation-funded Knight Center Fellows. The writers' reasons for wanting to come to NIH, the publications they work for, and what they plan to write in the wake of their NIH experience vary. The four who came were Ken Garber of *The Ann Arbor Observer*, an upscale, monthly southeastern Michigan tabloid; Leigh Hopper of a 125-year-old Texas daily newspaper, the *Austin American-Statesman*; Anita Manning of *USA Today*, a daily national newspaper with a circulation just hitting seven digits; and Mike Stobbe, formerly of the *Florida Times-Union*, the daily newspaper of Jacksonville, Fla.

Garber came to get the inside view of cancer and other research in the NCI labs of Steve O'Brien and Ira Pastan. Garber, who has written ex-

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SPEAKING TRUTH TO MEDIA: A PRIMER FOR SCIENTISTS

by Fran Pollner

There may not be a bare lightbulb swaying at eye level, nor the requisite instruments of torture to reward inadequate answers, but biomedical researchers with findings deemed of interest to the public should expect the third degree—at least from any reporter who's been schooled in the art of interview by veteran science writer Vic Cohn, formerly of the *Washington Post* and a visiting fellow at the Harvard School of Public Health.

"We can learn to separate probable truth from probable trash," Cohn told a couple hundred journalists and scientists gathered at Cold Spring Harbor (New York) Laboratory to participate in a weekend colloquium titled "Breakthrough! How News Influences Health Perception and Behavior." The gathering was sponsored by CSHL and the NCI-designated cancer centers public affairs network. Its objective was to explore how the media cover health-related news, how researchers and reporters can misunderstand and antagonize one another, and how they can do a better job communicating so that the public is not subjected to one contradictory "breakthrough" after another.

Sounding as no-nonsense as Sergeant Joe Friday asking for "just the facts, ma'am," Cohn hammered out the questions any reporter aiming for the real story should ask any scientist purporting to have one.

"How do you know?"

"What are your numbers?"

"How did you get them?"

"How valid, reliable, reproducible are your data?"

"Are there any flaws in your work?"

"What is your degree of certainty?"

Fran Pollner

Vic Cohn

Fran Pollner

Reminiscences*: Two former directors, NCI's Vince DeVita and NINDS's Zach Hall shared a mike and tales of relations with the press and advocacy groups during their NIH stints.*

"Who disagrees with you and why?"

These questions, Cohn said, are no reflection on the legitimacy of the research or the researcher but basic tools of medical journalism that must be applied equally to all research—whether obscure or famous, controversial or acclaimed—and to alternative as well as conventional therapeutic strategies.

And how should a researcher respond to these ques-

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Conflict of Interest: Back to Basics

Michael Gottesman

Reading the list of "thou shalt nots" in a government ethics handbook, taking a computer-based ethics training course, filling out a financial disclosure form, or perusing the Web-posted ethics memo,

<http://www1.od.nih.gov/oir/SDs_Primer/chap2/collabguide.html>,

recently sent to all intramural scientists strongly inspire the question, Why? In this column I hope to answer that question.

One fundamental source of confusion for intramural scientists in understanding the laws and standards that govern our behavior is familiarity or comparison with the rules that apply to our colleagues outside of NIH. Whereas scientists at all types of institutions fall under a universal set of ethical standards, we, as government employees, are subject to an additional layer of specific laws that define and restrict activities that create conflict of interest, or the appearance of conflict of interest, for people receiving their paychecks from the government.

Conflict of Interest for All Scientists

Ethical standards for all scientists—inside or outside the government—dictate that we must avoid situations in which we are biased for or against an individual or idea to the extent that we cannot render a fair judgment about the science.

This standard means, for example, that scientists should not serve as formal reviewers for grant proposals or journal submissions by colleagues who are close friends, relatives, recent collaborators, or sworn enemies. Similarly, colleagues from the same institution may not review each other's scientific activities for grant support from an outside organization.

These professional ethical standards are not necessarily legal restrictions, unless certain financial interests may be affected; nevertheless, these standards are an essential linchpin of ethical behavior for all scientists.

Legal Conflict of Interest For Government Workers

Beyond the bias standard that applies to all researchers, the standards of conduct for government workers require, in addition, that we not use, or even appear to use, our government positions for personal gain, for the gain of a close family member, or to unfairly help one specific, favored person benefit from a government program—unless all eligible persons can benefit equally. One reason for this legal restriction is that government workers are supposed to represent the public interest in all of their dealings. They do not represent themselves or other individuals.

An immediate consequence of this law is that, as a government worker, an NIH scientist cannot collaborate on a project as part of official duty for which he or she is paid by the government and also receive any form of compensation from outside collaborators. Thus, it is possible to have a CRADA with a company as part of official duty, but not simultaneously to receive compensation for consulting with that company.

With these "whys" as background, venture into this Web site for more information about activities that may constitute legal conflict of interest:

<http://www1.od.nih.gov/oir/SDs_Primer/chap2/conflictguide.html>.

A more subtle consequence of our obligation to ensure even-handed representation of the public interest is that we cannot act as co-investigators on grants submitted by collaborators, nor can we write such grants. To do so would be using our official positions as government employees to help one particular individual or institution obtain government funds.

However, we can collaborate on grants as part of our official government research activities, provided that our contributions are not a substantial part of the grant application. When an intramural investigator would potentially be a major contributor, the work should be managed through a cooperative agreement approved by the extramural grants manager.

All intramural scientists should have received the memorandum from my office explaining in detail what is legally acceptable in this arena and what is not. The fundamental point of the memo is that every letter of collaboration with outside investigators should be copied to your Scientific Director, who may have questions for you about the extent of the collaboration.

If you have any doubt about whether an activity represents a legal conflict of interest, you should discuss it with your supervisor, who may refer you to your agency ethics advisor. Once you have received approval for such an activity, or a waiver from conflict-of-interest rules, you may proceed, provided that you conduct the activity in compliance with the law.

Remembering the basic "whys" and knowing whom to contact if you have questions should be considerably easier than memorizing long lists of forbidden acts.

Our hope is that, by understanding the principles behind conflict-of-interest rules and standards of conduct, researchers can avoid serious legal or professional problems. ■

—Michael Gottesman
Deputy Director for Intramural Research

Catalytic Reactions

On Credit Problems

In her otherwise excellent article on the need to cultivate diplomacy and negotiating skills, Dr. Schwartz made what I believe to be a serious error of omission. This is in Scenario Four, [in which] an impatient junior author submits and publishes a paper without his section chief/coauthor's consent. Dr. Schwartz gives great advice as to how diplomacy might have been used to avoid the situation. What the junior author did was not wrong because it made the section chief furious; it wasn't wrong because it violated the NIH guidelines—it is wrong because it violated one of the central tenets of scientific ethics. This needs to be stated unequivocally and with a much stronger emphasis than was done in the article.

Any person who considers publishing a paper without *all* the authors' explicit informed consent should disabuse him/herself of the notion immediately. It's not just undiplomatic—it's a very bad career move. In the hypothetical case cited, the senior author (or any other author) would be within his/her rights to demand a public retraction. As we all know, retractions look a lot worse on your CV than do manuscripts "in prep." But more important, it's a serious violation of trust. Although it may not seem so at times, the scientific community survives only because we share a common bond of trust. Individuals who violate that trust (as the junior author did in this case) aren't just being undiplomatic—they're placing themselves outside the community, and they deserve to stay outside the community.

—Michael Lichten, NCI

I agree completely. There are legal, intellectual, and ethical mandates that all authors to a scientific paper (or any other published document) concur wholly in the work that bears their names—and are aware of and agree to any changes suggested before publication. This can't be stated too often or in too many ways. Thanks for providing the opportunity to repeat the message in a more forceful manner.

—Joan P. Schwartz, NINDS

Dr. Joan Schwartz, in her Ethics Forum article in the March-April *NIH Catalyst*, describes a serious problem that sometimes confronts junior scientists at NIH: What should they do when a senior scientist appropriates their work without giving them credit? As the title of her article indicates, Dr. Schwartz has focused on the clear-cut instances [in which], as the title states, *credit is due.*

To the junior scientist seeking credit that is due, Dr. Schwartz recommends diplomacy rather than confrontation. This is eminently sensible advice, which we, too, have often given to junior scientists coming to us for help.

Dr. Schwartz's recommendations for a particular type of diplomacy are noteworthy. She urges the junior scientist to make what amounts to a plea for the credit to which he or she is entitled and to avoid, at all costs, the possibility of antagonizing or angering a superior by complaining frankly about the latter's actions. As a practical strategy for improving the junior scientist's chances of success, this, too, appears to be sound advice.

In situations like these [in which] credit has improperly been withheld, we find it deplorable (and presumably so does Dr. Schwartz) that methods other than pleading are more likely to harm than help the junior scientist. What if the plea is rejected? Junior scientists may suffer permanent damage to their careers if they anger a superior with actions that go beyond Dr. Schwartz's extremely cautious guidelines.

This article provides clear advice to junior scientists on how to behave in a difficult situation that may be crucial to their careers. We hope that in a future article Dr. Schwartz, a leading spokes[wo]man at NIH on the subject of ethical behavior, provides an equally clear statement to senior scientists on the injustice of withholding from their junior colleagues the credit that is due.

—Ned Feder and Walter W. Stewart, NIDDK

You've raised the difficult question of what to do if diplomacy doesn't work and credit is still being denied. There are several sources a scientist may tap for advice or intercession. 1) a mentor, woman scientist advisor, or other senior scientist; 2) the NIH Ombudsperson; 3) his or her scientific director; and 4) as a final resort, the DDIR. Actually, we've written guidelines that address actions to be taken in this situation. The document is available in the DDIR office and can also be accessed on the Web at ***<http://www1.od.nih.gov/oir/SDs_Primer/chap6/Resolution.html>.***

—Joan P. Schwartz, NINDS

—Michael Gottesman, DDIR

NAS Taps Two from NIH

Celia Hooper

It's Her Party: *Susan Gottesman, chief, Biochemical Genetics Section, NCI Laboratory of Molecular Biology, smiles for herself and colleague Malcolm Martin, chief, NIAID Laboratory of Molecular Microbiology, at a celebration of their election into the National Academy of Sciences.*

NHGRI Offers Genetics Residency Training

NHGRI is launching a new three-year medical genetics residency program, one of only 10 accredited genetics residency programs in the United States. In addition to the Clinical Center, NHGRI training sites include the Children's National Medical Center, Georgetown University Medical Center, and Walter Reed Medical Center.

Trainees will receive broad clinical experience in metabolic diseases, molecular genetics, and cytogenetics, with an emphasis on the role of genetics in cancer, eye diseases, obstetrics, dermatology, and pediatrics.

NHGRI

Max Muenke

The first year is dedicated to seeing patients with rare and common genetic disorders; during the second year, residents select a laboratory to affiliate with and begin designing their own basic or clinical research project. The final year is largely spent conducting research, with minimal clinical responsibilities.

At completion, trainees will qualify for board certification in one or more of four areas of expertise: 1) clinical genetics, 2) cytogenetics, 3) biochemical genetics, or 4) molecular genetics. The program is geared to MDs and MD/PhDs who have completed their residency training, as well as PhDs seeking postdoctoral genetics training.

Although most residents start their training in July, program director Max Muenke emphasizes that there is some flexibility, and some residents may be able to start at other times of the year. The Genetics Residency program has four available spots per year—and one remains to be filled in 1998. The program is administered by an executive committee including representatives from NHGRI, NICHD, NIAMS, NCI, and affiliated training sites.

Applicants should write to Maximilian Muenke, NIH, MSC 1852, Building 10, Room 10-101, 10 Center Drive, Bethesda, MD 20892-1852. E-mail: <mmuenke@nhgri.nih.gov>. ■

— Judy Folkenberg, Office of Science Education and Outreach, NHGRI

The Press Meets NIH
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tensively about biomedical research at the University of Michigan, says his biggest surprise about NIH scientists was "how small their offices are!" Otherwise, he says, "the environment seemed very similar to academic medical research at Michigan." Like all three of his fellow participants in the Knight program, Garber was impressed with how open, friendly, and accommodating NIH scientists were. "Everyone was great. They made themselves available on short notice and gave lots of their time to talk about their work." Garber says he really appreciated "how open and transparent the work being done at NIH is. That is special to NIH. Anyone who has ever done a story on a biotech company knows how hard it is to get anything more than P[ublic]R[elations] fluff out of people."

> 'I came away with enormous respect for what they do. Now, when I interview a researcher on the phone , I have a better sense of the kind of person who does this type of work . . . . at NIH, it's someone who's not in it for the money. . . '
> *—Leigh Hopper*

Garber says that in his visits in the cancer labs, he gleaned "a lot about how molecular biology and genetics are used in the lab to solve problems. . . . What I got to see is how scientists creatively use these tools to perform experiments, answer questions, and get concrete results in the lab." He is hoping to write up what he culled from the experience—but not for the *Ann Arbor Observer.* He hopes to sell a couple of features, on a freelance basis, to a national magazine.

Hopper says the most surprising thing about her experience—mostly at NIAID— "was how interested I became in infectious diseases and the immune system. I didn't realize how intriguing all this is on the molecular level." She adds that at the outset, she didn't appreciate the significance of NIH research or the caliber of its scientists. "Way down here in Texas, I just didn't have a sense of the role NIH plays throughout the world," Hopper says. "I have been telling people I got to meet 'the rock stars of science!' "

Hopper says that much of what she learned will not appear in print but was useful in deepening her understanding of the research process, including details such as what the different fractions of blood look like coming out of a centrifuge or "what acquiring a chimp for research entails." Her time in Steve Holland's lab in NIAID showed her "why a scientist may spend nearly all of his or her career looking at one virus. . . . I came away with enormous respect for what they do. Now, when I interview a researcher on the phone . . . I have a better sense of the kind of person who does this type of work," says Hopper. "In general, at NIH, it's someone who's not in it for the money, or personal glory, but simply for finding answers." Hopper plans to write stories on tuberculosis research at the Texas-Mexican border, a Biosafety Level–4 laboratory being considered for Texas, and the Tropical Diseases Center in Galveston.

Manning, like her colleagues, was surprised at how willing scientists were to speak to the journalists. She observed that more senior scientists seemed more comfortable dealing with the press. "It has to do with . . . practice and fear," Manning suggests. "Many scientists rarely, if ever, speak to a journalist, and most, I think, suspect we are out to misquote them or make them look foolish in some way. Those who have been interviewed frequently are less nervous and realize . . . that they have much to teach us." Manning concludes that for this reason, "having this three-week opportunity to talk with scientists, to get to know them a bit and let them know us, will be invaluable for all parties involved."

> 'Many scientists rarely, if ever, speak to a journalist, and most, I think, suspect we are out to . . . make them look foolish in some way. Those who have been interviewed frequently are less nervous and realize . . . they have much to teach us.'
> *—Anita Manning*

Like Hopper, Manning was impressed by NIH scientists' motivation—and motives: "how completely dedicated, not to say obsessed, they are to find the solution to the puzzles they're facing." She says she "also was very touched to realize that they don't always have the tunnel vision I suspected they had—most of the researchers I met were well aware of the ultimate goal of helping sick people." Manning has already published one story on NIH's new Biosafety Level–4 lab and plans other features on genetic counseling and families that participate in vaccine trials.

NHGRI's Rick Morgan, who was Manning's main host at NIH, took a combination of approaches in tutoring her on viruses and their modification and application in gene therapy research. The week before her visit to the lab he gave her background reading, which they discussed exhaustively. Then, he says, "I decided that the best way to 'educate' her on what we do was to stick her in the lab." Manning gowned up and assisted Morgan in an HIV-p24 ELISA in the Biosafety Level–2/3 Room. "She worked with me for nearly a full day harvesting cell-culture media, setting up the ELISA, which is a very tedious procedure, but is visually interesting, as it . . . has the blue-yellow color reaction when the ELISA is developed."

Stobbe, on returning to Florida after his NIDDK stint, landed a job as healthcare reporter for the *Tampa Tribune.* He says his experience at NIH prepared him well for the package of stories on diabetes, insurance coverage, and health research funding he'd completed for the Jacksonville paper just before he left. And he was confident that NIH experiences would equip him well for his new post. "It was an opportunity I never had before to sit down with researchers and to learn how the federal government funds, plans, and does science research. I can't tell you how important it was for a journalist who covers this stuff."

Summing up an NIH perspective of the Knight program, NHGRI's Morgan says "these types of visits are incredibly valuable for the journalist and for NIH. They demystify the scientific process and are an excellent way to help journalists understand the subjects that they are reporting on." Howard Bray, who directs the Knight Center, sees the journalism program's NIH debut as "very successful. The Knight Center expects to award the fellowships again next year." ■

Speaking Truth to Media
continued from page 1

tions? "Honest people will answer honestly," Cohn said, based on his experience that, generally, "any honest researcher will admit a degree of uncertainty." In fact, Cohn believes, it's the "certainty of uncertainty" that, if acknowledged, could preempt the fiasco of tomorrow's headline toppling today's medical breakthrough and undermining the credibility of public health messages. (But scientists can also be pilloried for "uncertainty," according to NCI's Barbara Rimer; see story, page 8.)

Fran Pollner

Robert Young

Cohn advised reporters to beware of "artful dodgers." When researchers offer conflicting findings or interpretations, a reporter ought to view with more skepticism anyone who dodges questions. Similarly, small numbers, findings that have not been replicated, and "anecdotes and miracles" should give reporters pause, he said. "Have results been repeated among different populations? Are they supported by animal or other biological evidence? Is there a hint of bias or conflict of interest?" These are all legitimate and necessary lines of inquiry, said Cohn, whose manual *News & Numbers: A Guide to Reporting* is in its sixth printing and used in journalism schools around the country.

Fran Pollner

Marcia Angell

He also posited a hierarchy among clinical research studies, with randomized, controlled clinical trials offering the best hope of valid results. Several scientists, however, including Robert Young, president of the Fox Chase Cancer Center in Philadelphia, were quick to cite transforming medical findings that had emanated from research that did not reach this "gold standard."

Young also cautioned against overappreciating highly statistically significant results: "A great p-value can sometimes signify a statistical benefit that exceeds any biological benefit."

Marcia Angell, coeditor of the *New England Journal of Medicine*, agreed that "P-values are no substitute for common sense." Statistics, she observed, can be reported in different ways that are mathematically correct but impart different meanings. For instance, a 1 percent difference in survival (93 percent vs. 94 percent) in a controlled clinical trial comparing streptokinase to tPA in the treatment of myocardial infarction could also be reported as a 14 percent reduction in mortality with tPA over streptokinase if the 6 percent and 7 percent mortality rates, respectively, are compared, she noted. Angell and Young concurred with the journalists in attendance that when scientists communicate with the press and public, they need to put statistical findings in a context that conveys their biological significance and health impact.

Otis Brawley, director of the NCI Office of Special Populations Research, cautioned reporters, however, to pay close attention to the interests of the individual relaying the findings. He pointed to an Associated Press story carried in newspapers all over the country that led to a marked temporary decline in accrual in, and increased dropouts from, a major prostate cancer prevention trial of the 5α-reductase inhibitor Proscar vs. placebo. In reporting the findings of another study comparing Proscar, Hytrin (an α-blocking antihypertension agent), and placebo in the treatment of benign prostatic hypertrophy, the reporter quoted a urologist who extolled the advantages of Hytrin over Proscar. The urologist's financial interests in Hytrin were not mentioned, nor was the fact that Hytrin's effectiveness varied with prostate size. Proscar was portrayed as no better than placebo in a condition involving the prostate gland. "That story did significant harm; the context was wrong," Brawley said.

Fran Pollner

Otis Brawley

He challenged scientists to meet their "professional responsibility—to talk to the media more," especially to correct misconceptions. A leading misconception—generated by the use of young women in mammography posters and the publicity about screening between ages 40 and 49—is that the "average breast cancer patient is 44 years old, instead of 68." Prostate cancer, too, has areas of distortion. "Early detection has become a religion, but with prostate cancer screening, we're raising hopes unjustifiably," Brawley said, citing unchanged postdiagnosis survival rates:

Seeking an Unhypey Medium

Although reporters and science writers of the popular press may overstate research findings, they are "educable," *Boston Globe* science writer Richard Saltus assured the scientists gathered at Cold Spring Harbor. "But they're under pressure to make the strongest statements possible because if their stories aren't placed on page one, they get lost," especially if they have to compete with political scandals to make the front page, Saltus said.

Another reason for hype, offered by veteran health reporter Cristine Russell of the *Washington Post*, is that "scientists have PR firms. They vie for attention. It's business now." The commercial aspects of biomedical research have contributed also to the flip side of hype: hiding information, Saltus added: "We've seen sponsors try to gag negative stories."

And, Russell added, sometimes scientists—if they're concerned that an issue is too complex, controversial, or new to bear press exposure—try to bar reporters from access to information that would actually improve understanding and accuracy. For instance, the Asilomar meeting on then-emerging recombinant DNA techniques was initially closed to the press; 12 journalists, she among them, clawed their way in. The result was superior reporting on a topic fraught with panic potential, she said. Saltus agreed that the more complicated the research, the wiser an open door policy (see also "The Press Meets NIH," page 1). ■

Fran Pollner

Cris Russell *Richard Saltus*

72.7 months in 1972 and, despite increased screening, 72.4 months in 1994.

Researchers are not the only ones who may bend the truth in the direction of self-interest, Brawley added—so may patient advocacy groups. He relayed an incident in 1997: A prostate cancer advocacy group actually attempted to stop the American Cancer Society from publishing a downward correction of its numbers of projected prostate cancer cases from 344,000 to 209,900.

War Stories

Similar manipulations plagued Zach Hall, who recently left NIH after three years as the director of NINDS and is now associate dean for research and Lange professor of physiology at UCSF. "I was least prepared for advocacy groups, Congress, and funding issues, primarily around Parkinson's disease," Hall said of his tenure at NIH. One of the incidents he found most astounding involved the request of an advocacy group that NIH forgo its intended release to the press of data showing advances against a particular disease. To mount a campaign for more money, "they needed to de-emphasize success, and they typically inflated patient numbers by a factor of two," he said of some advocacy groups. They also wanted NINDS to support only clinical trials, not basic research.

Former (1980–1988) NCI director Vincent DeVita, now director of the Yale Cancer Center in New Haven, Conn., and professor of medicine and of epidemiology and public health, faulted both "loose-lipped scientists and the desire of reporters for the front page" for overblown headlines and misleading medical news. But DeVita was one of the few people at the conference who defended the "War on Cancer" and castigated the press for dealing with it unfairly when its accomplishments appeared to fall short of its vaunted promise.

The War on Cancer served as the conference's prime example of media hype that backfired, leaving a legacy of unmet goals and public disillusionment.

"Launched with hyperbole" in 1971 with the signing of the National Cancer Act by President Richard Nixon, the War on Cancer was "meant to distract the public from the war in Vietnam," said Eric Rosenthal, conference cochair and director of public affairs at the Fox Chase Cancer Center. "Cancer was an enemy

Fran Pollner

Eric Rosenthal

the nation could defeat in the age of Vietnam," he observed, and the "war" against it could capture headlines and news magazine cover stories that proclaimed the victories of the Nixon administration in biomedicine, diverting attention from the body count in the real war. For instance, the words "New Gains in War on Cancer" filled the cover of a Vietnam era issue of *U.S. News and World Report* save for "Vietnam Showdown" boxed in a corner.

But the media eventually cloaked both wars in failure, using body count as the benchmark in the cancer war as well. This narrow approach, DeVita charged, undervalued advances that prolonged and improved quality of life. He credited the War on Cancer and the additional money it brought to cancer research with the development of hybridomas, monoclonal antibodies, biologics, radiolabeled antibodies, and antiangiogenesis approaches. And the scientific yield of the Cancer Virus Program, the first initiative of the War on Cancer, which the media also panned, included discovery of restriction enzymes, reverse transcriptase, the oncogene cascade, and cancer genetics, to name a few. Moreover, he said, even the body count has begun to decline.

It was during his tour of duty as NCI director, DeVita recalled, that he "learned how to deal" with the public and the press. "I was taught by my public affairs officer," Paul Van Nevel, NCI's associate director for cancer communications. "'Be honest,' he told me." ■

Fran Pollner

Paul Van Nevel

Culture Clashes Revisited:
At Least Two Sides To Two Tales

Lamb Stew

The story of Dolly, the sheep cloned from adult sheep cells, said *New York Times* reporter Gina Kolata, who was among those who broke the story in this country and then wrote a book about it, "shows how scientists communicate." In retelling the story and related events, Kolata also held a mirror up to the way reporters and newspapers operate.

Publications like *Science* and *Nature* typically send out "tip sheets" a week in advance of each issue's publication, alerting science reporters to the upcoming contents. Reporters can request the full paper and conduct interviews but cannot print anything until the journal's publication date. The language describing the Ian Wilmut paper in the *Nature* tip sheet was low-keyed and somewhat obscure, but to Kolata the words "derived from adult tissue" were a call to action. She called Scotland and prepared a story that would be ready to go in case anyone broke the embargo—which a small British newspaper, *The Observer*, did in a roundabout way: It did not allude to the *Nature* report but presented enough of the Dolly plot to undo the embargo. The *New York Times* got the story onto the first page of its second edition the next day; by the time the third edition rolled out, the story had taken lead position (upper right) on the first page, overtaking the political piece on Democratic tax policies that earlier had held the top spot.

Gina Kolata

Fran Pollner

Joe Palca

Kolata's journalistic judgment led her to decline to report on several subsequent would-be cloning stories after she concluded they lacked validity. One such a piece involved an outfit called Clonaid whose representatives claimed they had scientists all over the world

by Fran Pollner

Mammography Mosaic

Neither the media nor the public deals very well with uncertainty," commented Barbara Rimer, reflecting on her experiences over the last five years as a member of various review panels on screening mammography that were beset by political pressures and media distortions. "It was sometimes demoralizing for me, as a scientist, to see our complex story reduced to sound bites," she said of the coverage of the 1993 and 1997 panel reports she'd worked on.

Fran Pollner

Barbara Rimer

In the former, she was "stunned to read that we'd capitulated" to the administration's desire to save money when it had been "evidence, not politics," that had directed their conclusion at that time that screening mammography had not been proved to reduce breast cancer mortality in women ages 40 to 49.

Four years later, she served as chairman of the National Cancer Advisory Board when it revisited the issue at a coincidentally contentious time just after an NIH consensus panel had declined to recommend screening mammograms for women in their forties and the NCI director had suggested such screening could be of benefit. Members of Congress were demanding that screening be endorsed.

"We found that a 17 percent decrease in breast cancer mortality, though small, was statistically significant," she said.

The panel recommended screening for this age group, in a carefully worded statement that identified the limits and benefits of screening," recounted Rimer, who last year became the director of the new NCI Division of Cancer Control and Population Sciences. But the press painted the group as "having capitulated to Sen. Arlen Specter [R., Pa.]."

Meanwhile, she added, a review of 233 news stories on the mammography debate revealed that only 58 percent mentioned any of the limits, fewer mentioned the risk of false-positives, and less than a third mentioned the risk of false-negatives.

No Winner

Kirsten Goldberg, editor of *The Cancer Letter*, faulted all parties in what she called a "case study in communications disaster."

"It was like covering the Mayan ballgames, which were played until one side succumbed to exhaustion and death, and then the survivors were sacrificed."

NCI, she said, had not been "forthright," Congress had leveled a "blatant attack on scientists," and the press "did little (and perhaps could do no more) to stop it."

Part of the problem, she suggested, could be that the "screening-saves-lives mantra" was overplayed. ■

working quietly in their labs to clone dying people for private clients. Another story she dismissed was the announcement by Chicago-based physicist Richard Seed that, presidential proclamations notwithstanding, he planned to proceed with human cloning in the treatment of infertile couples—abroad if necessary. Determining that Seed was an "unemployed physicist in debt," Kolata decided not to pursue the story. It was broken, instead, by National Public Radio's Joe Palca, who reckoned that Seed "wouldn't need the expertise, per se, just the interest of those who do have it." Palca had done a Medline search on Seed, found one fertility-related article, and was told by Seed during a telephone interview that he'd made a deal with an embryologist and a gynecologist, had clients who were good candidates, and might go overseas to do the work. "It seemed newsworthy," Palca said.

"Once I heard about Joe's story, I had 30 minutes to decide what to write," Kolata said, explaining how some of the "news that's fit to print" gets into print. "Once there's competitive pressure, we *have* to cover it. What others are doing, what people want to hear about, that's what dictates what gets onto the pages of the *New York Times*."

In an exchange that displayed the disconnect between the scientific and news communities—or at least some of their members—panelist Carol Greider, a Johns Hopkins University molecular biologist and geneticist and a member of the National Bioethics Advisory Commission, expressed her astonishment at the publicity generated by Dolly. "We basic scientists had a different reaction from the general public. What's the big deal? We couldn't figure it out. One animal touted as a breakthrough made our jaws drop."

Kolata responded: "Dolly was proof of concept! The whole idea of cloning humans from adult cells has been part of the scientific imagination and sci-fi horrors for decades." To which Greider replied: "There really is only one sheep Dolly. I'm skeptical until it's reproducible." At which point Palca exclaimed: "It's stunning because it contravenes the fundamental tenet that a differentiated cell can't go back." "No," Greider said, "it was just the next step, not that revolutionary, not that big a leap." ■

Quotables?

Robert Cook-Degan

The first chapter of Gina Kolata's book [*Clone: The Road to Dolly and the Path Ahead*] "will drive scientists crazy," promised bioethicist Robert Cook-Deegan, director of the National Cancer Policy Board of the National Academy of Sciences. "It's a compilation of outrageous statements from scientists and bioethicists who wanted to be on the front page of the *New York Times*—and they succeeded." ■

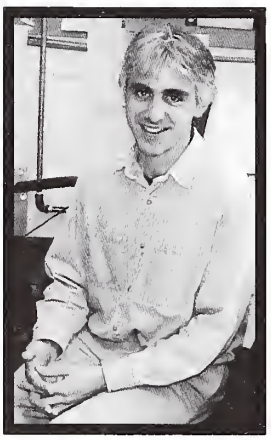
Mammalian Pheromone Reception: Of Mice and Men?

The recent report (1) that a short daily exposure of women to volatile compounds from sweat can significantly alter their menstrual cycles brought some new ripples of interest to mammalian pheromone research. This study reports opposing effects of sweat secretions gathered from groups of women at different stages of the menstrual cycle, providing some of the best evidence that pheromones—or perhaps a changing mixture of pheromones—may have significant effects on humans, as they do in other mammals. What the human pheromones are and where and how they act are unknown. It may be tempting—but premature—to try to fill in the unknowns in humans with speculations based on research in other animals.

In contrast to the very primitive understanding of human pheromones, a little more is understood about how rodents detect pheromones, thanks to significant progress over the past three years. Key steps were the cloning of two large families of putative pheromone receptors (2–5) in the labs of Richard Axel at Columbia and Linda Buck and Catherine Dulac, both at Harvard, and in our lab. In this article, we summarize some of this recent progress in research on rodent pheromone receptors, but strongly warn readers that this information may prove to have no bearing on *Homo sapiens*, for which, to date, there is no evidence that homologous receptors mediate pheromone responses. If there is one finding that we expect will carry over to humans from the rodent research, it would be that the pheromone receptor system is full of surprises.

Pheromones are used for intraspecific communication in organisms ranging from fungi to mammals. For example in yeast, specific peptides are secreted and result in a stereotyped mating response. Many insects have developed exquisitely sensitive systems that use volatile pheromones to attract and find mates. In most terrestrial vertebrates, pheromone effects have been well documented, and several unrelated molecules, including proteins, have been suggested as candidate mammalian pheromones. Many of these active molecules are contained in urine, sweat, or sexual or specialized gland secretions, and it is possible that specific mixtures rather than individual components are necessary to evoke the behavioral responses.

Pheromones are classified into two groups according to the timing or duration of their evoked responses. Releaser pheromones induce relatively fast behavioral responses, for example, sexual activity, parental care, or aggression. Primer pheromones elicit a sequence of slow physiological events that eventually influence specific aspects of reproduction. Lesion experiments in rodents suggest that the vomeronasal organ (VNO; see diagram), a chemosensory organ located at the base of the nasal septum that is distinct from the main olfactory epithelium (MOE), is responsible for several pheromone responses. These include: 1) Lee-Boot effect: the grouping of several female mice in a cage suppresses or modifies estrous; 2) Whitten effect: the induction of synchronized estrous by urinary cues of male mice in females with group-dependent estrous suppression; 3) Bruce effect: the physical presence or the urine of a male mouse of a different strain from the mouse to which a female has been recently mated prevents the implantation of embryos; and 4) Vandenbergh effect: puberty onset in female mice can be advanced by pheromones, most likely nonvolatile molecules contained in the urine of adult males.



Fran Pollner

Nick Ryba

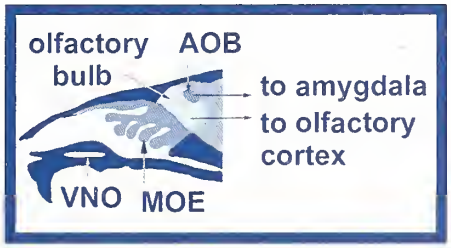
The receptor cells in both the VNO and MOE are unusual neurons that turn over rapidly throughout life. Their axons take different routes: MOE neurons project to the olfactory bulb, whereas those of the VNO converge on the structurally distinct accessory olfactory bulb (AOB). The secondary projections of the MOE and VNO are also to separate areas of the brain. The principal connections of the olfactory bulb are toward the olfactory cortex. In contrast, the AOB projects to hypothalamic areas of the brain involved in hormonal and reproductive functions. However, during embryonic development, both the VNO and the MOE are derived from the same infolding of the olfactory placode, and the organization of the two neurosensory epithelia is similar. Given the similarities, it might be expected that both would make use of similar signaling mechanisms.

Elegant work from several laboratories has provided a molecular explanation for the sense of smell. Early work from Randy Reed's group at Johns Hopkins established that olfactory reception probably involves a G-protein that controls the concentration of cAMP through a specific adenylate cyclase. A rise in cAMP in olfactory neurons directly gates a plasma-membrane ion channel and generates action potentials. Buck and Axel made use of the information that odorant receptors were linked to G-proteins to clone a vast family of about 1,000 distinct genes (6). The size of the family (perhaps 1% of all genes expressed in mammals) was completely unexpected. The first definitive evidence that any one of these mediates responses to a particular odorant was obtained this year (7). However, work principally from Axel's and Buck's laboratories demonstrating other properties of these receptors has already revealed much of the mechanism involved in the detection and encoding of the sense of smell (8). Discrimination of odors is possible because any olfactory neuron expresses only one of the repertoire of receptor proteins. Thus, there are effectively 1,000 different types of olfactory neuron, and the problem of discrimination is reduced to determining which neurons have been activated. In the epithelium, the distribution of receptors is essentially random (though in mammals, there are four distinct zones in which specific subsets of receptors are expressed). However, the axonal projections of olfactory neurons expressing specific receptor proteins converge. In fact, neurons expressing a given receptor have been shown to send axons to two specific glomeruli in each lobe of the olfactory bulb, and each glomerulus seems to receive innervation only from one type of sensory neuron. Moreover, the relative positions of the glomeruli where neurons expressing particular receptors converge are fixed. Thus, specific odorants produce a fixed pattern of activity in the olfactory bulb. How this pattern is set up and maintained as the neurons are continually replaced throughout life is quite relevant to under-

by Nicholas Ryba, PhD, NIDR, and Roberto Tirindelli, PhD, Istituto di Fisologia Umana, Universita di Parma, Italy

standing the sense of smell and broader mechanisms of neural development.

As this work on odor detection evolved, our lab began exploring pheromone detection. The first surprise in the VNO was that most of the major components of the olfactory signaling system are absent: The olfactory G-protein and adenylate cyclase are not expressed at detectable concentrations; only a nonconducting subunit of the olfactory ion channel is present; and there are no close homologues of the odorant receptors. However, even though the molecular details are quite different, there still appear to be parallels between the ways the VNO detects pheromones and the MOE responds to smell.



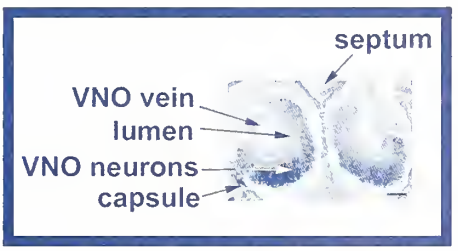
A. Schematic rodent head showing the location of the VNO and AOB relative to the MOE and olfactory bulb.

Important evidence that VNO signaling is also likely to be G-protein–mediated was the finding that two distinct G-protein α-subunits are expressed at high concentrations in nonoverlapping populations of VNO neurons (9). However, attempts to clone receptors from the VNO based on homology to other G-protein–linked receptors were unsuccessful. The first breakthrough in identifying putative pheromone receptors was provided by a new, almost assumption-free approach that Dulac introduced (2). She argued that if the receptors were expressed with a pattern similar to odorant receptors, individual VNO neurons would express high amounts of one specific receptor and that this expression pattern would constitute the major difference between any two cells. Accordingly, she made libraries from individual VNO neurons, compared their cDNAs, and cloned a family of novel receptors (2). Perhaps the most important aspect of this work was the comparative single-cell approach, which points to differentially expressed genes and molecular expression patterns at a cellular level.

The sequences of the new family of VNO receptors revealed why the homology-based search for pheromone receptors had been unsuccessful. The receptors have no significant similarity to any known proteins, and the only clue that they might be G-protein–linked remains the fact that they contain seven stretches of sequence predicted to form membrane-spanning helices. The family is quite large: There appear to be 30–100 different genes with 50–90% sequence identity with one another (2). The size of the family immediately suggests that the neurons in the VNO are likely to be able to respond to a relatively wide range of ligands. Another important observation was that these receptors, now referred to as V1Rs, are only expressed in the apical neurons of the VNO. The neurons expressing the different G-proteins also are segregated, with those expressing $G\alpha_{i2}$ located in the apex and those expressing $G\alpha_o$ located in the base of the VNO. This discovery opened the possibility that there could be a second family of receptors expressed in more basal $G\alpha_o$-containing neurons.

As it turns out, we had already identified a receptor from a second family of VNO receptors using essentially a nondirected approach (3). Dulac and Buck independently applied the single-cell comparison approach to clone other receptors from the same family (4, 5). The second family of VNO receptors, which we named V2Rs to distinguish them from the unrelated V1Rs, comprise as many as 100 genes that share homology with the parathyroid calcium-sensing receptor and the metabotropic glutamate receptors (3–5). The only similarity between V2Rs, odorant receptors, and V1Rs is structural: All three classes are predicted to have seven membrane-spanning helices. V2Rs are distinguished by their long N-terminal extracellular domains preceding the transmembrane helices. Ca^{2+} and glutamate appear to bind to this extracellular domain, and, as might be expected for receptors that bind multiple distinct ligands, they appear to be more divergent in this region than in their transmembrane domains. In contrast, V1Rs and odorant receptors exhibit most sequence divergence within the membrane-spanning helices, which are their presumptive ligand-binding regions.

Do the V1Rs and V2Rs function as pheromone receptors? Comparison of their expression patterns with those of the odorant receptors indicates that it is likely. First, just as odorant receptors are expressed in small subpopulations of MOE neurons, individual V1Rs and V2Rs are expressed in 0.5–3% of the VNO neurons. As is also the case for the odorant receptors, the subpopulations of neurons expressing any one receptor do not appear to overlap with those expressing other receptors. Moreover, the expression of V1Rs and V2Rs is restricted to sensory neurons in the VNO and they are not expressed elsewhere (2–5). These properties are consistent with both V1Rs' and V2Rs' functioning as pheromone receptors. Moving beyond such circumstantial evidence is harder, however: It took seven years to unambiguously demonstrate that one particular odorant receptor mediates a specific response (7). Therefore, even though V1Rs and V2Rs are good candidate pheromone receptors, it is likely that they will remain merely candidates for some time. As yet there are no clues to whether V1Rs and V2Rs bind distinct classes of ligand. However, given that compounds that have been reported to be vertebrate pheromones seem to be either small hydrophobic volatile molecules or proteins, it is conceivable that V1Rs bind one class of ligand and V2Rs the other. Clearly, if these families encode pheromone receptors, they must bind many active compounds, supporting the idea that mixtures of compounds elicit pheromone responses.



B. In situ hybridization of a coronal section of a neonatal rat. Probe stains mature VNO neurons; the bar is 250 mμ.

The presence of two families of unrelated receptors is, at present, the most surprising and intriguing aspect of signal transduction in the VNO. Why are three distinct families of G-protein receptors (with similar expression patterns

but not sequences) required for chemosensory perception, and how is their expression controlled? The first question will probably best be answered by analyzing the evolution of the three families. The second question is the one that we are most keen to examine.

A particular problem encountered by all three groups that cloned the V2Rs was obtaining full-length clones. Despite evidence that the quality of mRNA we isolated was very good, most of the V2Rs were 5'-truncated mRNAs, appeared to contain introns, or lacked exons.

Surprisingly, some labs found that the V2R family of receptors is expressed in the olfactory epithelium of fish, which lack a VNO. Yet, in fish there is no problem obtaining full-length uninterrupted transcripts. This result raises the possibility that many of the mammalian counterparts are expressed pseudo-genes. Like higher vertebrates, fish respond to pheromones, and it is possible that this response is mediated through V2Rs. But unlike mammals, fish are able to smell amino acids. Given the similarity of V2Rs to the metabotropic glutamate receptors, it is conceivable that V2Rs are actually amino-acid or peptide receptors in fish. One possible evolutionary scenario is that as terrestrial vertebrates lost an unneeded ability to detect amino acids, there was no selective force against the mutation of many V2R genes, leaving only a few—adapted to recognizing pheromone cues—intact. While these observations lead some scientists to think many of the mammalian V2Rs encode expressed pseudogenes, other aspects of sequences suggest they encode proteins. Even if the majority are pseudogenes, many are expressed at high concentrations in small subpopulations of VNO neurons.

One fascinating observation made by Dulac and a colleague is that one V2R displays some sexual dimorphism (4). In contrast, V1Rs and other V2Rs are expressed equally in female and male rodents. This finding suggests that the sexual dimorphism of most pheromone responses stems not from differences in signal reception but rather from differences in the way these signals are processed. Another aspect of the VNO revealed by these studies is its laminar organization: There are several distinct layers of neurons that express particular subsets of V2Rs. Moreover, the expression of some V2Rs extends even into what appears to be the $G\alpha_{i2}$ zone (3, 4) of the VNO. The $G\alpha_{i2}$ and $G\alpha_{o}$ layers of the VNO project to distinct and contiguous regions of the AOB, suggesting that the receptor layers may also be preserved in the AOB. One major difference between these layers and the zones of the MOE is that the layers of the VNO develop during the first few postnatal weeks. In contrast, the MOE zones are defined early in embryonic development, before olfactory neurons make synaptic connections (10). This difference suggests that study of neural projections of specific VNO neurons may tell a rather different story from that of the MOE neurons and therefore may do more than just help explain pheromone signaling.

Do these molecular findings in rodents bear any relevance to the report of human pheromone responses? Perhaps the greatest surprise to scientists working in the field was that humans respond to pheromones at all. Humans have long been thought to possess only a vestigial accessory olfactory system, though some experts ranging from otolaryngologists to electrophysiologists now question this. Human genomic DNA encoding both classes of VNO receptors have also been isolated, but to date, all homologues are pseudogenes. Thus, the questions of where and how human pheromones work remain entirely open, as do the identity of the pheromones, whether humans possess a VNO, and whether it functions in the responses seen in Martha McClintock's headline findings. ■

References

1. K. Stern and M.K. McClintock. "Regulation of ovulation by human pheromones." *Nature* **392**, 177-179 (1998).

2. C. Dulac and R. Axel. "A novel family of genes encoding putative pheromone receptors in mammals." *Cell* **83**, 195-206 (1995).

3. N.J.P. Ryba and R. Tirindelli. "A new multigene family of putative pheromone receptors." *Neuron* **19**, 371-379 (1997).

4. G. Herrada and C. Dulac. "A novel family of putative pheromone receptors in mammals with a topographically organized and sexually dimorphic distribution." *Cell* **90**, 763-773 (1997).

5. H. Matsunami and L.B. Buck. "A multigene family encoding a diverse array of putative pheromone receptors in mammals." *Cell* **90**, 775-784 (1997).

6. L. Buck and R. Axel. "A novel multigene family may encode odorant receptors: a molecular basis for odor recognition." *Cell* **65**, 175-187 (1991).

7. H. Zhao, L. Ivic, J.M. Otaki, M. Hashimoto, K. Mikoshiba, and S. Firestein. "Functional expression of a mammalian odorant receptor." *Science* **279**, 237-42 (1998).

8. R. Axel. "The molecular logic of smell." *Sci. Am.* **273**, 219-230 (1995).

9. M. Halpern, L.S. Shapiro, and C. Jia. "Differential localization of G proteins in the opossum vomeronasal system." *Brain Res.* **677**, 157-161 (1995).

10. S.L. Sullivan, S. Bohm, K.J. Ressler, L.F. Horowitz, and L.B. Buck "Target independent pattern specification in the olfactory epithelium." *Neuron* **15**, 779-789 (1995).

Pockets of Poetry

Surely biomedical research and poetry have more in common than the chance meeting of an umbrella and a sewing machine on a dissecting table. Testing this hypothesis on June 25th, at 3:00 p.m. in Masur Auditorium, will be Robert Pinsky, 39th Poet Laureate of the United States, who will read and comment on his poetry at the NIH Director's Cultural Lecture.

As a preliminary experiment, we issued a call to any closet NIH poets to share their creations with us. What they sent represents solid data that the poetry-science connection is more than surreality. Their poems shed light—and laughter—on our lives and world. Lest any NIHers be so cold of heart that they cannot appreciate the beauty, economy, perceptiveness, or humor of poetry, let them at least appreciate that the writing and reading of poetry is a superb exercise for toning up writing and thinking skills: It works the senses, improving perceptiveness; it sharpens the eye and ear to eloquence and clarity in expression; it stretches the imagination and improves agility for analogy. Our call for poetry also brought us a sampling of poems written by pediatric HIV patients at NCI. These will be on display at the Visitor's Center reception after Pinsky's reading.

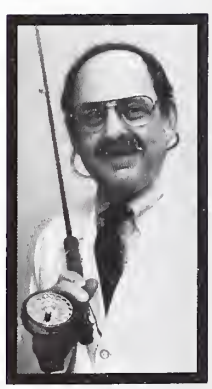
—C.H.

Poets' Corner

Nancy Weissman
DCEG/NCI

Frederick Langheim
NIMH/CBDB

Judah L Rosner
LMB/NIDDK



Marshall E. Bloom
LPVD/NIAID
Rocky Mountain

1
The evening sun, low in the sky
Hurts my eyes.
Scanning the river
Bright yellow - white water
Glittering like diamond tears
in constant motion,
Circling changing rocks in shadow,
Lizards in the darkening light.

I dip my toes. Quick, careful!
The bottom is rough with pebbles,
muck. Algae—green and foamy
Coats the river like a pox.

But the yellow light
Entrances.
Diamonds dancing
Call to me.
A young deer shoots across
the bubbling stars.

2
The trees deceive me.
They are not silent
They speak their lovers' secrets
—in whispers
Or in shouts—with flapping fingers
and jealous tongues.
They reach
They bend and sway.
Leaning forward,
They dance and touch each other
with bony limbs
Or flirt with a curve of their hips.

<Pipestem State Park
West Virginia, 1993>

—Nancy Weissman

Time Dilation in an Inertial Frame

$\Delta_x\Delta_p > = {}^{h}/_{2\pi}$ is Heisenberg's principle of uncertainty
that explains those dim stars you can only see
when you're not quite looking at them.

F = ma defines force in terms of
how much it can hurt
when things happen too fast.

$E = mc^2$ says that angels travel at the speed of light
so all their mass is converted to energy
and they become lighter than any feather.

$V_F = (m_1v_1 + m_2v_2)/(m_1 + m_2)$ shows momentum is conserved
so father hits son hits grandson and so on.

$x_F = x_I + v_It + \frac{1}{2}at^2$ tells where you are going and how fast
even if you're traveling in circles.

$\Omega = \frac{1}{2}H$ describes
the phenomenon of frame dragging
where reality is warped
by a rotating object
causing those closest to it
to be unaware
of what's going on.

$\Delta t = \gamma\Delta_t$ explains that time is relative
and the days speed up with age
that's why the elderly walk so slowly
they're holding on to the rails
of a spinning merry-go-round
working their way towards the center.

—Frederick Langbeim

Hematopoesia

Five thousand frozen hearts
in plastic bags
hold an eternity of verse
in code.
Expressed within the selfish
intron's tomes
are stanzas, iambs, and
anapests, tagged
and accented in chromosomal
choriambs -
or chamber villanelles
that follow forms
laid down in pastoral
and primordial loam
cast off by scientists
as second-hand

genetic nonsense - Caesurae
in The Code
of terza rima guanine
and adenine
spellings of amino acids
on sugar bones
producing all of nature's
prized proteins
responsible for ills
and antidote,
and skin and lungs and tongue
and arms and wings.

—Frederick Langbeim

Untitled

igogagawheniseeasequencewheniseeasequencethatwaswritten
longagobeforetherewereistoseethesequenceootagagoguoytnod

—jlrosner

When I Was a Lad (apologies to Gilbert and Sullivan)

1. When I was a lad, I served a term
As research aide in a Biotech firm,
I scrubbed the beakers and I washed the floors,
And I polished up the handle on the cold room door.
Chorus: He polished up the handle on the cold room door.
I polished up the handle 'til it looked so swell
And now I am a scientist at RML[1]
Chorus: He polished up the handle 'til it looked so swell,
And now he is a scientist at RML.

2. As research aide I made such a name
That a graduate student I soon became.
I went to classes and I stood all the jabs,
And I studied all night in the biochem labs
Chorus: He studied all night in the biochem labs.
I studied all night and I worked like hell
And now I am a scientist at RML
Chorus: He studied all night and he worked like hell
And now he is a scientist at RML.

3. As graduate student my mistakes were few,
So I landed a job at MSU[2].
They gave me a lab and I grew up the strains
And I analyzed the samples again and again
Chorus: He analyzed the samples again and again.
I analyzed the samples on an agarose gel
And now I am a scientist at RML.
Chorus: He analyzed the samples on an agarose gel
And now he is a scientist at RML.

4. As senior post-doc I was bold,
And gained a spot in the NIH fold.
I asked no questions and bent my knee
So they let me work on HIV.
Chorus: They let him work on HIV.
My HIV work went so well
That now I am a scientist at RML.
Chorus: His HIV work went so well
That now he is a scientist at RML.

5. On HIV I built my fame,
And learned to play the HIV game.
Tat and *rev* and *barf*[3] and *snore*,[3]
Gag and *pol* and a hundred more.
Chorus: *Gag* and *pol* and a hundred more.
My papers all got into *Cell*
And now I am a scientist at RML.
Chorus: His papers all got into *Cell*
And now he is a scientist at RML.

6. So, post-docs all, wherever you may be,
If you want to rise to the top of the tree.
If your soul isn't fettered to a laboratory stool,
Be careful to be guided by this Golden Rule.
Chorus: Be careful to be guided by this Golden Rule.
Stick close to your bench and always do well—
You too may be a scientist at RML!
Chorus: Stick close to your bench and always do well
And you may be a scientist at RML!

—Marshall E. Bloom

[1] RML=Rocky Mountain Laboratories of NIAID
[2] MSU=Montana State University
[3] *barf* and *snore*=lesser known regulatory genes of HIV

People

Recently Tenured

Kuni Iwasa *received his Ph.D. in physics from Nagoya (Japan) University in 1974 and continued his work in chemical physics at Dalhousie University (Nova Scotia), Indiana University (Bloomington), University of Ljubljana (Slovenia), and Rice University (Houston). He began his work in membrane biophysics after arriving at NIH in 1979 as a senior staff fellow. He worked at NIMH and NINDS before joining NIDCD in 1991, where he currently heads the Section on Biophysics in the Laboratory of Cellular Biology.*

The ear is a mechanoreceptor organ that converts sounds into electrical signals. It is not as simple as a microphone because it also splits signals into their component frequencies and attenuates larger signals. Perhaps for this reason, the ear has a number of cells with intriguing properties.

Fran Pollner

Kuni Iwasa

The outer hair cell is one such cell. It is a cylinder-shaped mechanoreceptor whose cell body shortens and elongates (as much as 5 percent of its length) very quickly, as the membrane potential goes up and down in response to pushes and pulls at its sensory hairs.

Recent studies have revealed that this cell uses electrical energy available at the plasma membrane. By contrast, most biological motility is based on chemical energy, particularly that of ATP. Direct use of electrical energy, which enables fast responses, is suited to the ear, which is sensitive to frequencies up to 20 kHz. The outer hair cell is a key factor in the fine-tuning capacity and wide dynamic range of the mammalian ear.

The mechanism that enables this cell to perform its biological role is not, however, as clearly understood as the role of the cell itself. My goal is to clarify the motility mechanism of the outer hair cell and its biological role.

The lateral membrane of the cell has charges that flip-flop across the membrane, analogous to gating charges of voltage-gated ion channels. These charges are the biophysical basis for voltage sensitivity of the cell, enabling it to use electrical energy.

Charge transfers across the hair-cell membrane are very large (equivalent to several million electrons per cell) and coincide with the cell motility.

If, indeed, such charge transfers provide energy used for length changes, one would expect the system could be run in reverse: The charges should be affected by externally applied tension. I found that is exactly the case.

This experiment also demonstrates that the membrane motor of the hair cell has at least two states that differ in their charges and membrane areas, in contrast to the opened and closed states of ion channels. Detailed knowledge of the motor was obtained by analyzing the charge transfers across the cell membrane induced by changes in voltage and tension. This analysis gives the number of motor units, the differences in charge, and the membrane area per motor unit in its two states.

Combining these data on the motor with data on the passive mechanical properties of the cell membrane, I have constructed a self-consistent biophysical model of the outer hair cell. The model can explain most existing observations on hair-cell motility and predicts forces that can be generated. We have experimentally confirmed the predicted value of 0.1 nN/mV for force production. I plan to use this model for further clarification of the motile mechanism.

To test whether the model can predict kinetic behavior as well as static properties, my group is trying to determine the relaxation time of transitions between motor states by measuring the frequency dependence of the membrane capacitance and the noise spectrum of membrane currents. This project is, in part, designed to address the question of how fast the cell can respond to voltage stimuli.

Perhaps the most intriguing question is which molecular elements contribute to the motility. One approach is to analyze whether the present model can explain the behavior of the cell treated by chemical reagents specifically targeting the cytoskeleton, the membrane, or the motor.

So far my group has shown that softening of the cytoskeleton reduces both cell stiffness and force production in a manner consistent with the model. Another approach to the molecular identity of the motor is via molecular biological methods.

My model predicts that the key element of the motor has a membrane-spanning domain and a charge transferable across the membrane. If candidates for the motor protein can be selectively expressed in a host cell, the electrophysiological techniques that we have developed can then be used to identify the role of individual elements in the motility. One important question is whether the membrane protein needs links to cytoskeletal proteins to function as a motor as the model predicts.

Roland Arvel Owens *received his Ph.D. in biology from Johns Hopkins University in Baltimore in 1985. He came to NIH as a National Research Service Award Fellow in the Laboratory of Developmental Pharmacology in NICHD. In 1988 he moved to the Laboratory of Molecular and Cellular Biology in NIDDK, where he is now a senior investigator in the Molecular Biology Section.*

Fran Pollner

Roland Arvel Owens

My group studies the *rep* gene and Rep proteins of adeno-associated virus type 2 (AAV). AAV is a nonpathogenic human parvo-virus that is being developed as a vector for human gene therapy. AAV requires coinfection with a helper virus, usually an adenovirus or herpesvirus, for efficient productive infection.

It is therefore also a good model system for the study of virus-virus interactions. In the absence of helper virus, the DNA of AAV integrates into the host genome with a strong preference for a 2-kb region of human chromosome 19 (the only example of site-specific integration in a mammalian virus system).

The *rep* gene of AAV encodes four overlapping proteins involved in AAV replication, gene regulation, and preferential integration. The Rep68 and Rep78 proteins bind specifically to the AAV inverted terminal repeat (ITR) origins of DNA replication and have ATP-dependent, strand-specific endonuclease activity at specific sites within the terminal repeats. Rep68 and Rep78 also have ATP-dependent DNA helicase and

DNA-RNA helicase activities, negatively and positively regulate AAV and heterologous gene expression, and can inhibit the production of HIV-1. Rep proteins can inhibit cell division and oncogenic transformation by adenovirus E1A plus an activated *ras* oncogene.

My group was the first to identify a specific DNA motif within the AAV ITRs that is recognized and bound by Rep78 and Rep68. It is an imperfect repeating ([GCTC]/[GAGC]) motif. We identified a similar Rep recognition sequence (RRS) within the chromosome 19 preferred integration locus and demonstrated that Rep78 or Rep68 can mediate the formation of a complex between the AAV ITRs and the chromosome 19 integration locus. This result led directly to the current model for AAV preferential integration.

We also demonstrated the involvement of an RRS in the regulation of AAV promoters by Rep proteins and have identified more than 20 RRSs within the human genome. Many of these sequences are within genes associated with cell proliferation or DNA repair, such as *c-sis*, *gadd45*, and *brca1*.

We suspect that there has been selection for the Rep proteins to regulate the expression of cellular proteins important for the AAV life cycle. Our working hypothesis is that the inhibition of cell division by Rep proteins is a consequence of this regulation.

We wish to understand better the role of the *rep* gene and gene products in the AAV life cycle and in AAV's interactions with its host cells and helper viruses. We will use this knowledge to aid in the exploitation of AAV as a gene-therapy vector.

We also wish to understand and exploit the antioncogenic and antiviral properties of the Rep proteins. Over the years, we have developed a unique set of mutant Rep proteins containing subtle mutations throughout the amino acid sequence. We plan to use these mutants, and others we are creating, to identify various functional domains and motifs required for the many activities of the Rep proteins.

Toward these ends, we will test our mutants for the ability to block cell division, interact with various cellular and viral proteins, and regulate the expression of key viral and cellular genes. We will also characterize further the endonuclease activity. This strategy will allow us to explore further the interrelationships between Rep protein functions. ■

The 'Inter'National Institutes of Health

The NIH intramural program has been the destination of foreign scientists for five decades, primarily through the NIH Visiting Program. In the 1950s, fewer than 100 foreign postdoctoral fellows and more senior researchers were attached to intramural laboratories. Today, they number more than 2,000, or one-fifth of the intramural community.

The program is one of several international programs administered by the Fogarty International Center (FIC) in collaboration with foreign governments and international organizations, some of which offer reciprocal opportunities for NIH intramural scientists.

Japan: Give and Take

In a program aimed at promoting Japanese–American scientific exchange, the Japan Society for the Promotion of Science (JSPS) supports Japanese fellows at NIH and visits (from one week to two years) by U.S. researchers to Japanese laboratories.

NCI's Susanna Rybak, who has pioneered novel therapeutics involving members of the pancreatic RNase A superfamily, was one of last year's recipients. Notice of the fellowship inspired her to contact Masakazu Ueda at the Keio University School of Medicine in Tokyo, whose related work she'd followed in the literature.

NIEHS' Sharon Bryant credited her two-month stay in Japan with yielding a "groundbreaking role in my research, expand[ing] my perspectives and [teaching] me a lot about my own culture." Her project in the lab of Yoshio Okada's group at Kobe-Gakuin University involved the structural analysis of newly synthesized ligands for the δ-opioid receptor using two-dimensional 'H-NMR spectroscopy. Bryant had met Okada at a peptide symposium, and their labs had collaborated in the study of peptides synthesized by Okada's group before the research visit.

Pan American Fellowship

NIH also takes part in two Pan American Fellowship programs, one with Mexico and one with Chile. Under a 1996 agreement signed by NIH and the National Council of Science and Technology of Mexico, 14 Mexican postdoctoral scientists have received fellowships to work in NIH intramural and extramural laboratories. In 1997–98, five fellows were placed in intramural labs for research experience in neuropharmacology, cytogenetics, immunotoxicology, cellular biology, and biochemistry. A new agreement between NIH and the government of Chile will bring as many as five Chilean investigators to intramural laboratories.

U.S-Russian Collaboration

NIH researchers also have benefited from a program developed by the U.S. Civilian Research and Development Foundation (CRDF), a private nonprofit organization authorized by Congress and established by the National Science Foundation in 1995 to facilitate scientific and technological cooperation between the United States and the countries of the former Soviet Union. Financier-philanthropist George Soros provided initial funds of $5 million as an unrestricted gift to the U.S. government. These were matched by another $5 million from the Department of Defense (DoD). In 1996, NIH contributed $1 million for an NIH/CRDF Biomedical and Behavioral Sciences competitive grants program. With additional funds from NSF, DoD, and the Ukraine government, 41 grants were announced in September 1997. CRDF has awarded an additional five grants, supported by funds provided directly from IC budgets. Recently, with DoD funding, CRDF awarded three more grants.

NICHD's Andreas Chrambach, in collaboration with Valery Chestkov of the Medical Genetics Center in Moscow, received a two-year CRDF grant to detect and isolate preapoptotic and early apoptotic cells (lymphocytes) by free-flow electrophoresis. In a mutually beneficial arrangement, the study is being conducted in the Moscow lab, where there is the manpower that Chrambach's group lacks—with NIH's electrophoretic instrumentation, which the Moscow group lacks. ■

—Irene Edwards, FIC

Deadlines

The deadline for the next round of JSPS fellowships is **July 10**. Contact Kathleen Michels in FIC's Division of International Training and Research (phone: 496-1653; fax: 402-0779; e-mail: <JSPS@nih.gov>).

Applications for the NIH-Chile Pan American Fellowship are due on **June 15**. Contact Jahna Stanton, FIC Division of International Relations (phone: 496-4784; fax: 480-3414; e-mail: <js264e@nih.gov>).

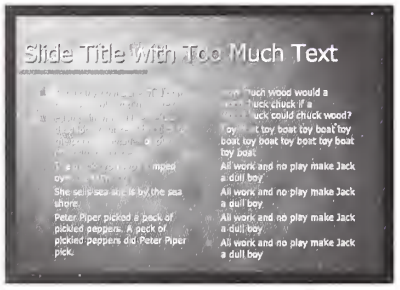
Effective Slide Presentation: How To Enlighten the Sleep-Deprived when the Lights are Dimmed

Have you ever suffered through a slide presentation that provided too much (or not enough) information, used a garish color scheme or illegible type, or had overly cute clip art instead of useful data? There may be only one thing worse: the thought that you may have been guilty of presenting such a slide show. Next to journal articles and poster sessions, a slide presentation is the most common method used by scientists to communicate their findings, so the chances are you *have* experienced poorly designed slides—one way or the other. Luckily, there are some simple rules of thumb you can use to improve the quality, readability, and usefulness of a slide presentation.

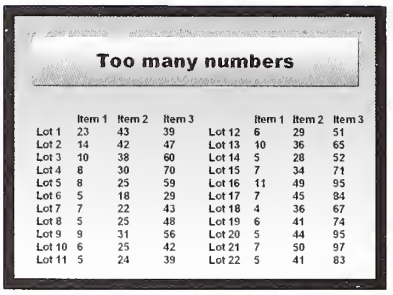
Tips on Slide Content

Most slides in a presentation can be divided into two types: text slides and data slides. A basic truism about text slides is that they should reinforce the points you are making in your talk—they shouldn't be the full text of your talk, or the audience will be trying to read the slides instead of listening to you. Limit the amount of text per slide to include only a brief summary of your key points; these will be your "bullet list" items on each slide that you'll expand upon with your talk.

In addition to limiting the amount of text on each slide, consider also limiting the number of points you present on each slide. Providing more than six to eight points on a slide will make it too cluttered and full of text and will overload the audience with topics. If you have multiple points to make on a single topic, spread them across multiple slides, possibly using "continued" in the slide title to clarify the connection. Some presentation packages also have the ability to dim points as they are made, which helps focus attention on the point at hand.

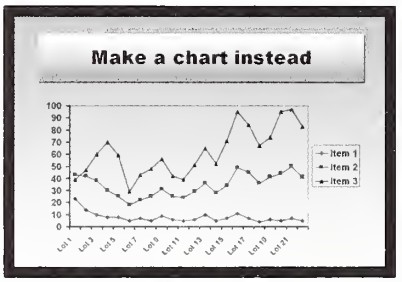


For data slides, remember that slides should be visual aids—so be visual, and use graphs wherever possible rather than multiple rows and columns of numbers. An audience will grasp a well-designed graph much more rapidly than an array of numbers. And, as above, overloading a slide with numbers means your audience will be trying to analyze data on the fly, rather than listening to what you are saying.



	Item 1	Item 2	Item 3		Item 1	Item 2	Item 3
Lot 1	23	43	39	Lot 12	6	29	51
Lot 2	14	42	47	Lot 13	10	36	65
Lot 3	10	38	60	Lot 14	5	28	52
Lot 4	8	30	70	Lot 15	7	34	71
Lot 5	8	25	59	Lot 16	11	49	95
Lot 6	5	18	29	Lot 17	7	45	84
Lot 7	7	22	43	Lot 18	4	36	67
Lot 8	5	25	48	Lot 19	6	41	74
Lot 9	9	31	56	Lot 20	5	44	95
Lot 10	6	25	42	Lot 21	7	50	97
Lot 11	5	24	39	Lot 22	5	41	83

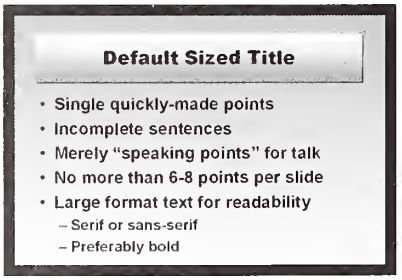
If you must provide data in numerical format on a slide, do so only with small arrays of numbers. Three rows and five columns of data are an approximate maximum to consider using on a slide. Sets of numbers larger than this are best delivered via a handout, preferably after your talk is over (to avoid distracting page-flipping and attempts at reading in a darkened room).



Tips on Slide Design

One of the trickiest points in creating a good slide is using effective colors. In selecting colors for your text and your background, your main concern should be contrast. The more your text contrasts with your background, the easier it will be to read. Because white and black are neutral colors, you can always use white text with a dark background or black text with a light background. Black text on light backgrounds has the additional advantage of being more legible when room lights can't be turned all the way down.

If you want to use colored text as well, pick colors that are complementary with the slide background. The topic of complementary colors is far too involved for this article; fortunately, most slide-creation software (such as Microsoft PowerPoint, Lotus Freelance Graphics, or Corel Presentations) includes color schemes that are complementary. As long as you stick to the default color schemes, your presentation should be within the realms of good taste.



One practical topic of color selection should be mentioned: color blindness. Approximately 10% of the male population is color blind, with red-green color blindness the most common. To make your presentation as accessible as possible, try to avoid red-green combinations, unless you also provide a difference in contrast, such as dark red text with light green background.

In addition to providing color schemes, presentation software packages also include prepackaged slide templates. These templates vary widely in look and feel, with everything from conservative to outlandish. Pick the more conservative of these templates—the others tend to include patterned backgrounds and background artwork that distract rather than inform. If you are creating your own background, or modifying an existing one, a solid color, or simple blue-to-black or green-to-black blend is often the safest, albeit overused, choice. Avoid background patterns unless they are very subtle.Your choice of typeface can also help to improve readability. Stick with bold typefaces and larger point sizes. The title of each slide should be larger than any subheadings, which in turn should be larger than the bullet points. Sans-serif typefaces such as Helvetica and Arial are usually preferred in slide presentations over serif typefaces such as Times or Garamond (the typeface used for *The NIH Catalyst*), but this is not a hard-and-fast rule. Some commercial serif typefaces, such as Adobe's Minion or Myriad, are much more readable than Helvetica. Finally, never use ALL UPPERCASE text, even in slide titles—it is very difficult to read.

Tips on Slide Output

After you've created your presentation materials, your on-campus resources for making slides from a PowerPoint file are

by Chris Vargas
Scientific Computing Resource Center
Center for Information technology

twofold. For the do-it-yourselfer, or those short on time or funds, the Center for Information Technology (CIT) is located in Building 10, Room 1C282, where a slide maker is available to Clinical Center staff; however, you should make an appointment to familiarize yourself with the equipment. For more details, visit its Web site at

<http://www.cc.nih.gov/isd/itc/>.

If you prefer to drop off your file and pick up finished slides, the Medical Arts & Photography Branch (MAPB), located in Building 10, Room B2L323, has high-end slide-making capabilities at a cost of $4 per slide. Presentations can be dropped off via the NIH network or on disk, and there is a 24-hour turnaround time on slide production. MAPB can also create entire slide presentations, as well as custom illustrations and slide templates. Call MAPB at 496-3221 for more information, including specifics on how to avoid problems with slide output and preferred programs for creating slides.

For overheads, the Scientific Computing Resource Center (SCRC), Building 12A, Room 1018, offers a Canon color laser printer and transparency material, as well as dye-sublimation printers for high-quality transparency printouts. If you are going to run overheads on your own printer, read the printer's manual carefully and only use recommended overhead material—the wrong media will give poor results, or possibly even melt in your laser printer. More information on SCRC services is available at its web site:

<http://scrc.dcrt.nih.gov/>.

Of Course, There's a Course

CIT's training program introduced a new course in April, entitled "Designing Effective Scientific Slides" and taught by Karen Ours and Larry Ostby of MAPB, which covers this information in more detail. There are plans to offer this course in future semesters; consult the CIT Training Web page at

<http://livewire.nih.gov/training/training.asp>

for dates and times. In the meantime, the foregoing tips can serve as a starting point for creating slides that wake listeners up when the lights go down. ■

Footnote: *Mention of a specific product in* The NIH Catalyst *does not constitute an endorsement, and failure to mention a product does not imply its inferiority.*

Festivities the Other Side of Summer

What: The NIH Research Festival
When: October 6–9
Poster deadline: June 5, 5:00 p.m.
Poster submission: on line or by fax. Details are available at the Festival '98 Web site: **<http://silk.nih.gov/silk/fest98/>**, accessed via the News and Events section of the NIH home page. To obtain a printed entry form or for more information, visit the Web site or call 301-496-1776.

Art Levine, NICHD scientific director and chair of this year's festival organizing committee, says he and his colleagues—NINDS scientific director Story Landis and NEI clinical director Scott Whitcup—have put together a program that's both "less diffuse" and scientifically diverse.

The festival kicks off Tuesday, October 6, with a day-long Job Fair for NIH postdoctoral fellows. The following three days of scientific meetings begin each morning with a plenary session of broad interest to the scientific community: Wednesday's is "The Origins of Life," a joint NIH-NASA program; Thursday's is "Apoptosis"; and Friday's is "Insight from the Bedside," a look at clinical science. The plenaries will be followed each day by six concurrent minisymposia. Poster sessions are slated for each afternoon.

On Thursday and Friday, the Technical Sales Association will again run its popular Research Festival Exhibit, with displays of the latest lines of lab equipment. And for the *pièce de résistance*, TSA will also host a lunch-time picnic each day, complete with musical entertainment provided by some "local talent," including The [legendary] Directors, appropriately named for the day jobs of band members Stephen Katz of NIAMS, Francis Collins of NHGRI, and NCI's Richard Klausner. ■

—Greg Roa

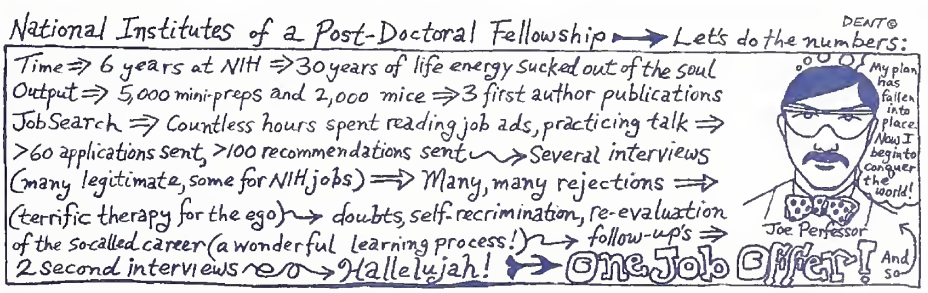
Fare Thee Well for '99

This year, 130 basic science and clinical fellows will win a Fellows Award for Research Excellence (FARE), including $1,000 toward domestic travel and other costs associated with a scientific meeting, to be used between October 1, 1998, and September 30, 1999.

Applications and abstracts may be submitted between June 15 and **July 24, by 5:00 p.m.** The application form and instructions, as well as examples of last year's winning abstracts, can be accessed at Felcom, the fellows Web site, at **<ftp://helix.nih.gov/felcom/index.html>**. Applications and abstracts may be electronically submitted to the same site or hand delivered to the Office of Education, Building 10, room 1C129. Questions should be directed by e-mail to **<fellows@box-f.nih.gov>** or to your institute's Fellows Committee Representative.

Abstracts are assigned by the author to one of 37 different study sections, with second and third choices also designated. Abstracts are judged after all identifers (names and institutes) are removed and are read by at least three reviewers. If an abstract is recognized by a reviewer as originating from a specific laboratory, or there is a perceived conflict of interest, that individual finds someone else to evaluate the abstract.

FARE is sponsored by the scientific directors, the Office of Education, and the Office of Research on Women's Health. FARE '98 was very competitive: 605 abstracts were submitted, of which 120 were selected to receive an award, for a 19.8 percent overall success rate. ■



Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: cartoon crisis, government scientist work ethics, scientist-press relations, and hitting home with slides.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 1, Room 209.

In Future Issues...

- Research Ethics: 20th-Century Lessons
- Interest Group Directory & Poll
- Magainins on Deck

1) URGENT: "Joe Postdoc" and his creator, cartoonist Alex Dent, have landed academic positions in the Midwest. *The NIH Catalyst* is desperately seeking another soul with a cartooning bent. No money, but plenty of fame and glory attend this entertaining gig. Anyone interested in a shot at the job should fax us a sample cartoon (402-4303), including name and phone number.

2) What are your reactions to the clarified rules governing the interactions of intramural scientists with extramural colleagues? Do they seem reasonable and workable? What would you add to the basic ethics points outlined in Michael Gottesman's column?

3) What do you see as basic conflicts between scientists and science journalists? What have been the greatest successes and worst disasters in press coverage of NIH-supported science?

4) What additional tips or warnings would you offer to colleagues to improve their slide presentations?

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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