FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 6, ISSUE 6 ■ NOVEMBER–DECEMBER 1998

ORS: ANOTHER DIMENSION

Office of Research Services

by Fran Pollner

The NIH Office of Research Services (ORS) may actually become what everyone knows is impossible: all things to all people at NIH, especially the "bench scientists," says Leonard Taylor, acting director of a year-old division within the ORS that was assembled with the needs of intramural researchers in mind.

The fiscal year just departed saw the transfer of four programs out of the predominantly extramural National Center for Research Resources and into ORS to make them more responsive to the intramural community. The four—Medical Arts and Photography, the NIH Library, Veterinary Resources (see story, page 8), and Biomedical Engineering and Instrumentation—formed the ORS Division of Intramural Research Services (DIRS).

A more recent reconfiguration has divided the last mentioned of these programs into two distinct entities: the Scientific Equipment and Instrumentation Branch, centering on laboratory and electronic equipment services, and the Bioengineering and Physical Science (BEPS) Program, a new division-level organization unique among ORS components in that its mission is actually collaborative research.

"The lines are blurring now between biology, bioengineering, and the physical sciences. Interdisciplinary approaches are becoming essential," observes Cherie Fisk, acting director of BEPS. BEPS—and its 20 engineering, mathematics, and physical sciences experts with a passion for invention—offers that support (see page 10).

With the addition of the 300 people on the DIRS and BEPS rosters, ORS now numbers more than 1,300, says ORS Director Steve Ficca, "and we stand behind the researchers in so many ways that even the scientific di-

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RESEARCH AT THE BIOLOGY-PHYSICS INTERFACE: FROM OUTER SPACE TO INNER EAR

by Doug Loftus

The Past Is Prologue

I remember a Sunday dinner at my grandmother's house when I was young, some time well before July 1969, at which the adults were discussing the seemingly impossible task of putting men [sic] on the moon. Also at the table was the elderly gentleman we knew as "Jimmy," a jeweler, barber, and repairer of watches, from Naples, Italy. Still not comfortable with English, he typically remained quiet during these dinners, keeping his attention focused on his plate and the jug of wine on the floor at his side. That Sunday, the topic of conversation apparently piqued his interest and after a few minutes, Jimmy, in a Chianti-fueled outburst of aerospace theory, earnestly weighed in on how to accomplish the lunar mission. It would take a "big, big cannone" (cannon), he explained, stretching very far into space, aimed squarely at the moon. The astronaut, fired from the cannon's barrel, would go "Boom! Straight to the moon!" It's unlikely that NASA engineers ever grappled with the logistics of Jimmy's approach; when Apollo 11 astronauts did reach the moon a few years later, it was by alternative, though perhaps no less fantastic, means.

Fran Pollner

Extraterrestrial Meets Intramural: *NASA Director Daniel Goldin and NIH Director Harold Varmus share a pleasant view at NIH Research Festival.*

Listening to NASA director Daniel Goldin's plenary address that kicked off the 1998 NIH Research Festival on October 7, I couldn't help but recall those pre-moonshot, pre-shuttle wonder years. In broad techno-evangelical terms, Goldin outlined his agency's vision for the future of space exploration, spelling out some of the developments in materials science, computing, and medicine that must necessarily precede any attempts to move beyond near-Earth missions. Central to all of these emerging and anticipated technologies, according to Goldin, is marrying NASA's traditional strengths in physics and engineering to that which is near and dear to us at NIH: biology. "My biggest concern," he said, citing the rapid pace of progress in biotechnology in the last 20 years or so, "is that NASA has been locked out of the biological revolution. . . . We have to integrate what we are doing in the physical sciences with the biological sciences."

Goldin used the term "biomimetics" to describe materials and processes born of a biology-physics merger. For ex-

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The Quality of Scientific Life at the NIH

Michael Gottesman

My time over the past several months has been consumed by matters related to physical space on the NIH campus—assignment of space in the new Clinical Research Center, construction of new laboratory spaces, and, yes, even parking spaces. In this column, however, I would like to address a different but equally pressing kind of space issue—finding the space in a busy schedule to foster scientific creativity and a broader perspective on biomedical research.

Given the pace of modern biomedical research, it is all too easy to become obsessed with individual experiments and to lose sight of the larger context in which we do our work. But our value as scientists also depends on having the space to explore new ideas, to devise different approaches to familiar problems, and to step back from what we are doing in the laboratory to take stock of its significance and relevance to our long-term goals.

Space of this kind comes in different size packages. The hour a week devoted to attending the Wednesday Afternoon Lecture (WAL) series provides a guaranteed respite from the intense focus of the laboratory.

With the help of our more than 70 special interest groups and the scientific leadership at NIH, Dr. Varmus and I have assembled a series of lectures intended to provide a broad overview of exciting developments in research that no one ought to miss.

Attendance at all of these lectures will provide a broad perspective that cannot help but improve the quality of research in our labs. If you cannot get to an individual lecture, simultaneous broadcast is available either via our closed circuit TV system at seven viewing sites (Gateway Bldg., NIA: Bldg. 31, Rm. 2C, NIA; GRC, Baltimore, NIA; Hamilton, Montana, Rocky Mountain Labs, NIAID; Twinbrook II, NIAID; the Solar Building, NIAID; and Frederick, NCI) or at your individual computer via the M-bone system; see

<http://www1.od.nih.gov/wals/MBONE.html>

for instructions.

If all else fails, videotapes of all WALs are available in the NIH library. The scores of other lectures and journal clubs within our laboratories provide additional opportunities to broaden one's scientific perspective, but they require that we commit space to them in our schedules.

Flexible schedules for scientists afford yet another means to veer away from the laboratory for those few hours a week to delve into the reading and writing and thinking that is essential for quality science to flourish. I encourage supervisors to be flexible in assigning and scheduling tasks so that scientists working at all levels of the enterprise can enjoy a few hours of protected time for these critical activities. In my own lab, I am pleased and supportive when a fellow wants to spend a morning or afternoon away from the bench reading the literature or writing up some work. This may extend on occasion to taking care of a nagging personal problem that may distract from laboratory work. I hope that other scientists at NIH see the importance of providing this personal space to improve the quality of life here.

> "Given the pace of modern biomedical research, it is all too easy to become obsessed with individual experiments . . . . But our value as scientists also depends on having the space to explore new ideas, to devise different approaches to familiar problems, and to step back from what we are doing in the laboratory in order to take stock of its significance and relevance to our long-term goals."

The longest blocks of time for reflection and enrichment of scientific life come from more formal sabbaticals. Sabbaticals can range from a few weeks spent in a different lab at NIH to many months or a year in another laboratory in the United States or abroad.

Nearly everyone who experiences such a departure from the established routine rejoices in a renewal of excitement for science and an opportunity to reconsider scientific directions and make appropriate changes in focus and methodology. For our senior scientists, there are various mechanisms that can make sabbaticals possible, and I urge you to explore these options with your scientific directors.

Whatever the physical space constraints at NIH, they need not impinge on the reach of our minds. Each of us can find some space in our schedules for activities that improve the quality of scientific life at NIH.

As always, I welcome your ideas about this and other issues concerning quality of scientific life at NIH.

—Michael Gottesman
Deputy Director for Intramural Research

Catalytic Reactions

Birdseye View

Honeymoon Suite

On the Rocky Mountain Labs

I was delighted to see you feature the Rocky Mountain Laboratories in the Sept.ember-October *Catalyst*. But let me take this opportunity to correct some mistaken history that found its way into the article.

First, the captions for the two historical photos on p. 6 are wrong. The group in the left photo were entomologists and wildlife surveyers (including a young Clarence Birdseye, later of frozen food fame) funded by the State of Montana, the U.S. Bureau of Entomology, and the U.S. Biological Survey. They called their research station, established in 1910, "Camp Venustus" (see below). They were at odds with the physicians of the U.S. Public Health Service over which professional group should control spotted fever work. For five years, the groups divided the Bitterroot Valley in half and even called the same tick by two names, *Dermacentor venustus* (entomologists) and *Dermacentor andersoni* (physicians). (Does this remind you of the HTLV-III/LAV controversy?)

The photo on the right is not vaccine development, ca. 1925 in the old Schoolhouse lab. Instead, it is a picture of Dr. Ralph R. Parker and his bride, Adah Nicolet Parker, studying ticks on their honeymoon in Powderville, Montana, in 1916. Spotted fever had just been reported from Eastern Montana, and Parker—a young entomologist then employed by the Montana State Board of Entomology—had been sent there to to set up a field station to study it.

A couple of other corrections: (1) There were other Rocky Mountain spotted fever researchers before Ricketts, and their differences of opinion about the cause of the disease reflected their incorrect assumptions about how diseases were spread by insects—a fascinating episode in the intellectual history of science. (2) The RML (today's Building 1 at RML) was built in 1927 by the State of Montana to support vaccine production (the vaccine had been introduced in 1925 and proved effective in keeping people alive if they'd been infected, not in preventing infection). By 1930, the state was feeling put-upon as demand for the vaccine increased throughout the Western states. In 1931, as the Montana congressional delegation was trying hard to get the U.S. Public Health Service to take over the laboratory, spotted fever was found by other NIH researchers on the East Coast—the first definitive case identified in Virginia. That provided the additional justification needed for a federal takeover of the laboratory, and the bill rapidly went through Congress.

You might be interested to know that during World War II, another PHS investigator, Mason Hargett, set up a vaccine production unit for a new type of yellow fever vaccine at RML. It was made without the human serum used by the Rockefeller Foundation vaccine laboratories—the same human serum that had caused an outbreak of hepatitis B (then called serum jaundice) among U.S. troops in 1943. Dr. Hargett's new type of vaccine literally saved many soldiers who might not have been vaccinated once the Rockefeller's vaccine was pulled because of the contamination. But that is another story.

—Vicky Harden

Editor's Note: Victoria Harden, NIH historian and director of the DeWitt Stetten, Jr., Museum of Medical Research at NIH, is the author of Rocky Mountain Spotted Fever: History of a Twentieth-Century Disease *(Baltimore: Johns Hopkins University Press, 1990). The book won the 1991 Henry Adams Prize, awarded by the Society for History in the Federal Government. For info about these awards, see*

<http://www.shfg.org/tawards.html>.

Congratulations on your *Catalyst* RML article and the great photographs. I hereby volunteer for any future venture you sponsor there!

—Paul Torrence, FAES

On Slide Preparation

I would add that it is wise to prepare one slide in html, and make it available to appropriate services and/or requests and via a personal web page. Before doing so, I suggest looking at some web pages to get ideas of style, color, etc. I think that aesthetics do matter.

—Ray Mejia, NHLBI and NIDDK

Those Who Can, Teach!

Did you know that NIH has a graduate school on campus (it's part of the Foundation for Advanced Education in the Sciences, FAES) and that NIH fellows are encouraged to ***teach courses at FAES!***

Here's the perfect opportunity to share your knowledge with the NIH community. FAES offers a broad range of courses that you can teach—from basic and clinical sciences to languages and photography. For a complete list of FAES courses of study, visit

<http://faes.org/academic.htm>.

The FELCOM Subcommittee on Teaching can assist anyone interested in teaching, whether you'd like to teach an entire course yourself or be a guest lecturer. *We want to hear from you!*

We're compiling a list of possible instructors to organize ideas for teaching opportunities for Fall 1999 and Spring 2000 semesters at FAES. We will be making suggestions to groups of fellows with similar interests and supplying possible guest lecturers.

To add your name to the list, simply e-mail **<kerrk@nih.gov>** with your areas of interest. ■

NIH Meets Y2K

It's Approaching 2000: Do You Know Where your Equipment Is?

In the realm of science, data are everything. Results must be accurate, valid, and reproducible. That's why researchers around campus are taking steps to avert the Year 2000 problem, popularly known as the Y2K problem.

Caused by the failure of some computer systems and software to handle the date conversion from 1999 to 2000, the glitch could disrupt not only computers but also up to 20 percent of biomedical equipment, according to a recent survey.

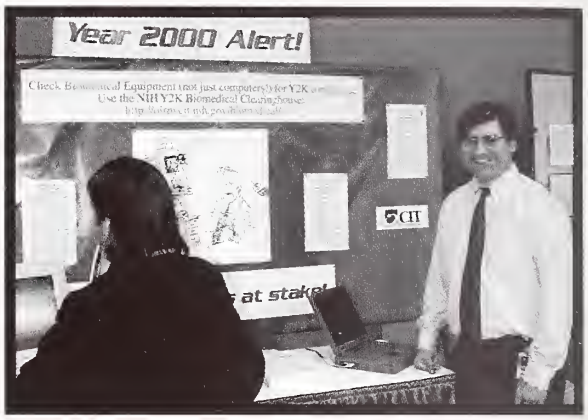
Any system that has date or time functions or operates with embedded chips or microprocessors has a potential problem. Experts do not know the full extent of Y2K's impact, but no one can afford to gamble with the quality of research data.

Responsibility for ensuring equipment accuracy has always rested with scientists—and still does—but because the Y2K phenomenon has added another dimension to what can go wrong with equipment it has also summoned forth a network of resources to help scientists address the problem. First, NIH is urging researchers to check all their biomedical equipment with date and time sensitivity between now and December 31, 1998, identify equipment and software concerns, ascertain compliance status, and initiate appropriate action. (See "Bug-Bitten" for a list of likely candidates for the Y2K-vulnerable ranks.)

Fortunately, a number of resources are aiding scientists in identifying and managing Y2K problems in their laboratories. One major source of help is the Y2K Biomedical Clearinghouse, developed by the NIH Center for Information Technology (CIT) at <**http://oirm.cit.nih.gov/biomedical/**>. The web-based Clearinghouse hosts a database compiling Y2K compliance information from NIH, the Food and Drug Administration, and the Veterans Health Administration. Using the interactive search engine, a researcher can check the status of equipment and submit an electronic request form to find out about items not listed on the site. NIH contractors will do the research leg work and promptly post that information. The staff also researches biomedical software applications. Updates are published weekly.

"Although scientists will always have the responsibility for accurate data, the clearinghouse offers them a useful information-gathering tool to help protect their work from potential Y2K problems," says CIT's Jaren Doherty, who chairs the NIH Y2K Work Group of IC representatives.

"Many researchers don't realize the Y2K threat to lab and clinical instruments with noncompliant embedded chips," says CIT's Cheryl Seaman. While "some machines will simply produce a wrong date-stamp," she says, others could malfunction in a more consequential way. For example, "certain vital-sign monitors work fine until they archive data; the Y2K defect causes current data to be written over historical records." In research laboratories, date functions can also be extremely important for patent documentation, she adds.



Fran Pollner

Greg Roa staffs the Y2K "Alert" table at the NIH Research Festival

Bug-Bitten

Anesthesia monitors
CT scans
Densitometers
Chemotherapy and radiation equipment
Echocardiography systems
Fetal monitors
Heart defibrillators
Gamma counters
HPLCs
Imaging equipment
Infusion pumps in intravenous drips
Intensive care monitors
MRI machines
Patient information and monitoring systems
PCR equipment
Pharmaceutical control and dispensing systems (such as infusion pumps)
Radiology systems
Renal (including dialysis) equipment
Spectrometers
Spectrophotometers
Ultrasound systems
Uninterruptible power supplies (UPS)
Water treatment

Risk Factors

- Equipment operated by a PC—the PC itself, operating systems, and software must be compliant.
- Lack of maintenance and service agreements that cover costs of upgrades or repairs.
- Customized or "home-grown" software—individual owners must verify compliance.
- Old equipment—manufacturers may not be testing equipment over eight years old for Y2K problems.
- Equipment with multiple technology interfaces.
- Cannibalized equipment (systems with multiple parts from different manufacturers).
- Users who take a wait-and-see attitude.

Lab and Branch Chiefs Certify Y2K Compliance

NIH's plan to address Y2K compliance of biomedical equipment requires that scientists assess and correct (upgrade, replace, repair, or retire) their own equipment as part of a certification process conducted at the laboratory or branch level within each IC. Researchers must inventory and record the Y2K compliance status of all equipment that could affect patient or animal safety. This inventory must be maintained on site by lab and branch chiefs and made avail-

by Gregory Roa, CIT

able for auditors to review. For all other types of equipment, lab and branch chiefs are required to certify that their researchers understand which equipment could be affected and that they have obtained compliance information, made necessary remediation, and developed contingency plans.

The NIH Y2K Biomedical Clearinghouse provides a useful set of questions (see "Checklist") surveyors can ask in identifying suspect systems. Also available for downloading is a helpful EXCEL spreadsheet to facilitate collecting data and keeping track of remediation follow-up.

Checklist

Does your system . . .

- interface with a personal computer, scanner, or other computer peripherals?
- contain an embedded chip?
- exchange data with other components?
- implement a timed control sequence or operate on a timed basis (for example, within five-minute cycles)?
- shut down unless a maintenance cycle is adhered to?
- report or handle timed events and alarms?
- calculate totals over time?
- calculate averages, rates, or trends?
- rely on external timed data?
- rely on external geographical data?
- use or produce time-stamped data?
- maintain historical state-of-system data?
- have an internal operation dependent on a clock (all timing devices)?

20,000 Desktop Machines Audited

The biggest Y2K headache involves personal computers (PCs). In some PCs the BIOS or real-time clock (RTC), programmed to interpret dates in two digits, may misread "00" as 1900. Left uncorrected, the date flaw could cause software running on a machine to archive records improperly, perform spreadsheet miscalculations, or otherwise corrupt data. "Don't assume your system is compliant just because it's new—even some recently purchased Pentium computers contain noncompliant BIOS chips," Doherty advises. Macintosh and UNIX systems are for the most part compliant, although Macs sometimes have DOS cards that are not Y2K-ready. "Another concern is commercial off-the-shelf software (COTS) and custom applications for all platforms, including Macs and UNIX. It's important to certify that your versions are Y2K compliant," he says.

IC technicians are currently auditing 20,000 desktop computers with ClickNet, a diagnostic tool for both hardware and software. Machines that pass the initial hardware test receive a Y2K-compliant sticker. Researchers should make sure auditors do not overlook any systems connected to biomedical equipment. ClickNet also compares executable programs to a database of known compliant software. A report can then be generated to list unrecognized programs that require further scrutiny. ClickNet does not examine documents or other data files, nor can it assess custom-built (user developed or non-COTS) applications unavailable in its library. Individual developers of custom software must verify Y2K compliance themselves.

Those using NIH computers at home can ask their IC for "walk-around" diskettes to check their systems. For hardware that fails the test, a BIOS upgrade can be attempted with another set of tools. Software applications can usually be fixed with patches, sometimes available for free or for purchase directly from a vendor's Internet site.

The Clock is Ticking. . .

"We face a rapidly approaching, nonnegotiable deadline," warns NIH Chief Information Officer Alan Graeff, who urges scientists to upgrade, repair, replace, or surplus noncompliant systems now to avoid costly, extended back-order delays. If they deal with Y2K in the next few months, however, scientists can really celebrate next New Year's Eve knowing their research is safe. ■

411 on Y2K

For more information, see NIH's Y2K homepage, **<http://irm.cit.nih.gov/y2000/>**. It lists IC representatives on the Year 2000 Work Group and the Medical and Laboratory Work Group and provides links to both the biomedical equipment clearinghouse and a parallel IT (information technology) clearinghouse. For general information, registration for Y2K classes, or assistance with ClickNet, call the **CIT Help Desk at 301- 594-3278.**

Or surf these sites for other news:

<www.y2k.gov/>

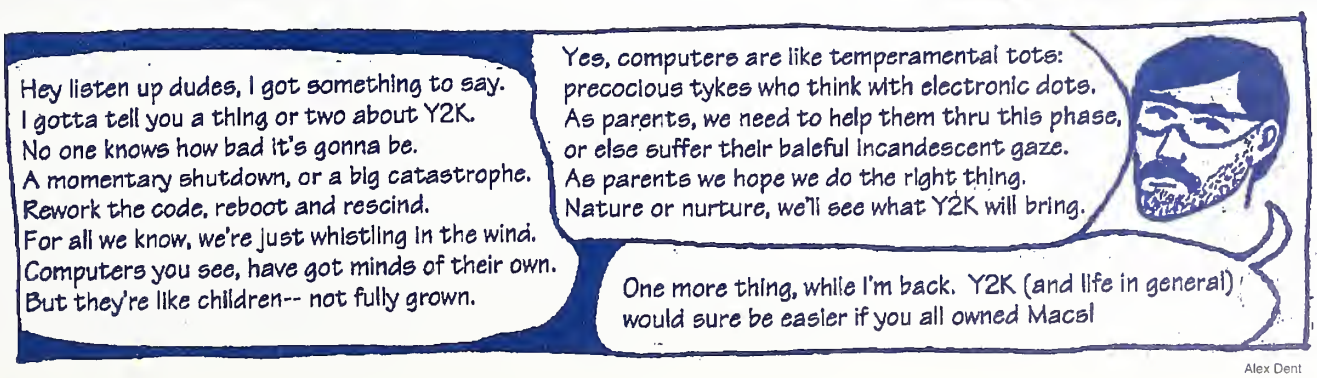
<www.itpolicy.gsa.gov/mks/yr2000/y2khome.htm>

<www.y2knews.com>

<www.year2000.com>

<www.fda.gov/cdrh/yr2000/y2kintro.html#definition>

<www.yahoo.com/computers_and_internet/year_2000_problem>



Alex Dent

NIH's Web of Science: Today Porpoise, Tomorrow the WHALES

by Susan Chacko, PhD, Computing Facilities Branch, CIT

How can any scientist possibly keep up with the scientific literature in her own mini-specialty, let alone the broader perspective of the field and hot new topics in other areas? Well, if she's at NIH, it's pretty much a piece of cake.

First, like scientists anywhere, an NIH scientist needs only her favorite web browser to access Medline, a research staple for many years—in its earlier incarnation as Grateful Med and now as PubMed. Produced by the National Center for Biotechnology Information (NCBI) at the National Library of Medicine, Medline indexes abstracts and citations from about 3,900 biomedical journals in the United States and 70 foreign countries and is updated weekly. Searching PubMed is straightforward, and search terms can include author names, journal titles, MESH (Medical Subject Headings—a dictionary of biomedical terms) words, and phrases. In addition, PubMed offers an entry point to the nucleotide and protein databases in NCBI's Entrez. PubMed is free and open to the world.

Beyond PubMed, however, NIH-based scientists are lucky enough to also have access to the Web of Science, a proprietary literature database offered by the NIH Library and the NIH Center for Information Technology. Ever used the Science Citation Index to track a research topic, starting from a seminal paper in the field? Or do you occasionally look to see how often your own papers have been cited? Well, the Web of Science is an on-line version of the Science Citation Index Expanded. It includes 5,300 major journals, almost twice as much as the print or CD-ROM version.

The Web of Science is licensed to the Bethesda NIH campus, and some (but not all) other NIH locations. It can be accessed only from NIH computers. (This includes dial-in access through Parachute.) If you have questions about whether you are eligible to access it, call the NIH Library.

Once you reach the Web of Science web page, it's best to do a "Full Search." You can search by subject term, author name, journal title, or author affiliation. In addition, the Web of Science can search for articles that cite a particular paper or author. Unlike Medline, there are no indexing terms; the system searches only for words in the title, citation, author names and affiliations, abstract, and the key words supplied by the authors.

These are wonderfully useful services, but short of spending an hour a week running your searches, how can you keep track of new articles? That's where Porpoise comes in. Porpoise (Publish or Perish with POISE), developed by Peter FitzGerald at CIT, will automatically search each week's updates to the Web of Science for your own favorite search terms, and will send you a weekly e-mail message with the results in one of several available formats.

To use Porpoise, you will need a valid NIH e-mail alias, the 4- or 5-letter code that uniquely identifies you in the NIH Directory Service. There is an e-mail address associated with your NIH e-mail alias, and your Porpoise search results will be mailed to that address. Go to the Porpoise web page, choose "Create a New Search Profile," enter a profile, and look at your results. You can modify your profile endlessly (with "Edit Search Profile") until it is tailored precisely to give you citations from a particular, well-defined field of interest. Then sit back and read your weekly e-mail update in comfort! (A useful tip: If your favorite journal tends to wander around the lab before it reaches your desk weeks later, enter its name as "Source" in Porpoise. The table of contents of that journal will be e-mailed to you in the weekly updates.)

What if your weekly update informs you of a fascinating paper in the field, but you don't have the time to walk over to the library to photocopy it? The NIH Library has purchased the complete text of over 300 major scientific journals, including *Science* and *Cell*. You can read the paper on-line, or download the paper of interest and print it. Don't have the time or patience for this? Go to the Porpoise web page and choose "Process a Search Profile NOW." Search for the article, select it, go to "Marked List," and select "Order from NIH Library." A copy of the article will be sent to you by campus mail in two to three days. You can also order documents through the Web of Science and through PubMed's Loansome Doc feature.

It's even possible to save the citations from a search into a reference-managing program like Reference Manager or EndNote Plus. For Web of Science or Porpoise output, you'll need to download the ISI/RIS Web Capture Utility and an appropriate filter. See the Porpoise Help page for details.

And soon to come: WHALES (Web Homology ALErt Service), a sequence-alerting service from the Helix Systems at CIT. If you want to know when new sequences relating to fibroblast growth factors are deposited in Genbank, or when new sequences with high homology to your favorite membrane protein sequence appear in the Swissprot database, WHALES is for you.

For a text search, it's much like Porpoise: You can set up a profile with a text search for some word or phrase, and choose to search Genbank, Genpept, Swissprot, or the Protein Data Bank. Once a week, WHALES will search through the new sequences in your chosen database(s) and e-mail you with the result. For homology searches, you put your own sequence into the profile, and WHALES will run a weekly Blast, gapped Blast, or Fasta search (at your choice) against the new sequences and send you e-mail with the alignment result. Watch the WHALES web page for announcements. ■

Fishing Lines

All the services offered have on-line help—look for a Help button or link on their web page. The NIH Library has handouts on searching PubMed and the Web of Science and on requesting documents electronically. The library also holds seminars and tutorials on using these tools efficiently. You need a library barcode sticker on your NIH ID to order documents electronically.

Medline:
<http://ww.ncbi.nlm.nih.gov/PubMed/>
Web of Science & Porpoise:
<http://publishorperish.nih. gov>
WHALES:
<http://molbio.info.nih.gov/whales/>
NIH Directory Service:
<http://directory.nih.gov>
NIH Library:
<http://nihlibrary.nih.gov>
(helpline 496-1080)
Parachute:
<http://radiant.net.nih.gov/PARACHUTE/Parachute.html>
ISI/RIS Web Capture Utility:
<http://www.risinc.com/webcap/isicap.html>

Office of Research Services

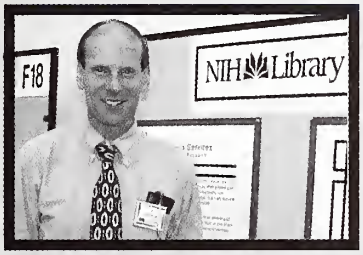
ORS
continued from page 1

rectors have been heard to say, 'Gee, I didn't know you did that!'"

Anyone who meandered through the posters at the NIH Research Festival, however, couldn't help but be exposed to the ORS influence, displayed on dozens of boards depicting such activities as hazardous waste disposal, postexposure prophylaxis against retrovirus infection, maintaining the Shared Resources Database, and overseeing the construction on campus of the new Vaccine Research Center.

There are more initiatives in store for ORS, Ficca adds. The process for recruitment of permanent directors for both DIRS and BEPS has begun, and by the by fiscal year 2001, the way ORS is funded will have changed. ORS now gets most of its operating money from the central management fund, with the remainder coming from fees for service. But the millennium will bring an 85-percent fee arrangement. "The scientific directors," he notes, "will know exactly what their money is buying." ■

Service with a Smile at the NIH Research Festival



Sunshine on a Rainy Day: *Ed Sunderland sings the praises of the NIH Library document delivery services (including the Web of Science and Porpoise programs; see story, page 6) providing desktop access to full-text on-line journals for the entire intramural research program–"even Rocky Mountain Labs can log on" to the home page (<**http://nihlibrary.nih.gov**>) "with a few clicks, at no additional cost." This year, Sunderland says, the library's on-line stacks have increased from "a handful to about 300" titles, including* Cell, Immunity, Neuron, PNAS, *the* Journal of Biological Chemistry, *the* Journal of Experimental Medicine, Brain Research, Lancet, Neuroscience, *and* Gene*—"the most heavily used in the library, the ones that are practically destroyed from use before it's time for them to be bound."*

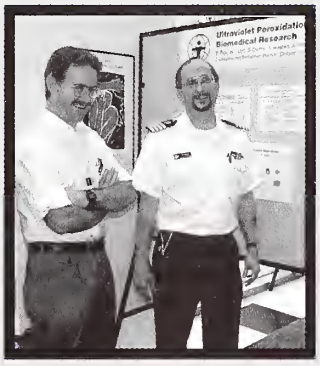
Two days of free seminars on the library's electronic resources are scheduled for December and will be held in the NIH Library Training Room. Registration is not required.

December 3

9:30 am–10:30 am: Web of Science
11:00–12:00 noon: Internet Grateful Med
1:00 p.m.–2:00 pm: Reference Manager Windows

December 17

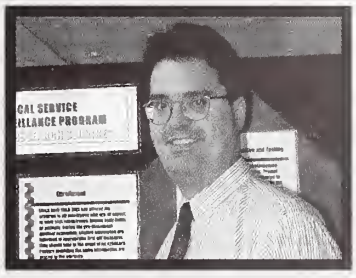
9:30–10:30 am: PubMed
11:00am–12:00 noon: Web of Science
1:00 pm–2:00 pm: EndNote plus Windows



photos by Fran Pollner

Green Giants: *Capt. Ed Rau (right), Environmental Protection Branch, ORS Division of Safety (with Jack Keboe, a Safety Kleen, Inc., chemist), elaborates on NIH's "one-of-a-kind" ultraviolet peroxidation system, used to treat on-site almost all of NIH's aqueous mixed wastes (hazardous chemical wastes that contain low levels of radioactive materials). "We pioneered this method," says Rau, "It's environmentally friendly, totally enclosed, and leaves no residues."*

Desperately Seeking Centrifuge: *Ron Edwards (left), director of computer systems, ORS Division of Intramural Research Services, demonstrates the wonders of the Shared Resources Database, a free, on-line swap meet that enables the transfer of still useful (and, in some cases, never been used) items from one lab or office to another. Created in June 1997 by ORS, CIT, and NIAID, the database has been accessed by 9,935 individuals; 1,800 surplus pieces have been listed—mostly lab equipment, like centrifuges, incubators, and DNA sequencers, says Edwards, but also items like computers, printers, and cabinets. In addition to an "available resources" section, which currently lists and exactly describes about 80 items, there's also a "requested resources" list for those in search of specific elusive (or otherwise expensive) materials. The database can be accessed at <**http://dirs.info.nih.gov/resource.htm**>.*



Reaction Time: *Jim Schmitt, medical director of the Occupational Medical Service, ORS Division of Safety, runs a service that's available "24 hours a day, every day"—the Retrovirus Exposure Surveillance Program, which has enrolled about 5,000 people since it opened in 1988. NIH, Schmitt says, is one of a very few research institutions in the country that offer both routine testing for employees who may be inadvertently exposed to a retrovirus at work and postexposure evaluation and treatment (available also to anyone exposed while at NIH). About one-quarter of enrollees work with a primate retrovirus in a lab or animal care setting; the rest work with human body fluids or patients. Nearly 34,000 enzyme immunoassays have been done, most for HIV-1. Of the 334 injuries reported over the past 11 years, 119 were considered serious enough to result in infection; 79 percent of those offered postexposure prophylaxis accepted treatment. The time taken to report to OMS and initiate prophylaxis has decreased over the years, to less than an hour in the past two years. As yet unknown, however, is how well used the program is. "Awareness at NIH is high," Schmitt says, "but we have no idea how much injury goes unreported."*

Veterinary Resources Discloses Its Frozen Assets

Office of Research Services

Until last year, when the Veterinary Resources Program (VRP) was moved into the Office of Research Services (see "ORS," page 1), only animal models maintained by the NIH Animal Genetic Resource (NIHAGR, see below) were cryopreserved and banked. Since then, however, intramural investigators from NCI, NIMH, NHLBI, NIDDK, NIDR, CBER, and NIA have availed themselves of the service.

Fran Pollner

William Rall

According to William Rall, a cryobiology physiologist in the VRP, "The primary motivation to bank-down animal models is the NIH policy that new animal models be made available to other investigators. The NIH director very much supports this," he said, answering questions during the NIH Research Festival related to his poster on "The Effect of Genotype on the Efficiency of Mouse and Rat Embryo Cryopreservation and Banking." Several years ago, he noted, Harold Varmus asserted a need for rules for preserving and sharing animal models, and Michael Gottesman, deputy director for intramural research, followed up with a letter so directing the intramural community.

"We have the responsibility," Rall said, "for banking the embryos and distributing them"—a service, he added, that not everyone on campus is aware of. "Investigators reach a point where there's no more room in the animal room, and then they realize they must bank the models they're not using." The place to turn to, of course, is the VRP.

Investigators are "charged by the actual effort," Rall said; donor females are superovulated with the aim of generating large numbers of embryos. "Sometimes only a fraction produce embryos," however, because "the science is imperfect. We can estimate, based on genetic background and experience, whether it will be a problem."

At the moment, 500 frozen embryos are stored in straws, up to 20 per straw, in a liquid nitrogen refrigerator (at -196° C) in a building on campus and at a similar facility in Gaithersburg, Maryland. Most are eight-cell mouse embryos; some are rats; and fewer are rabbits. Since 1980, when the Embryo Cryopreservation Program was established, more than 250,000 embryos from 300 mouse, rat, and rabbit genotypes have been cryopreserved and banked.

Cryopreservation is one component of the NIHAGR, which has created "hundreds of animal models for investigators, mostly inbred strains and congenics (inbred strains carrying spontaneous mutations), and have begun incorporating transgenic and knock-out models into the program," Rall said, noting that embryo collection and cryopreservation of the poorly reproducing immunocompromised NIHAGR models is quite challenging.

The NIHAGR serves commercial breeders all over the world, he added: "It's, in effect, an international resource. This means that our investigators can buy from commercial breeders and know that the genetics meets high standards—NIHAGR standards—and that these companies will vary only on service and quality control. The end result is reduced animal costs for NIH," Rall said. Sixty percent of the world's research animals, he added, can trace their ancestors to the NIHAGR colonies.

For more information about VRP cryopreservation services, contact William Rall at 496-0468. ■

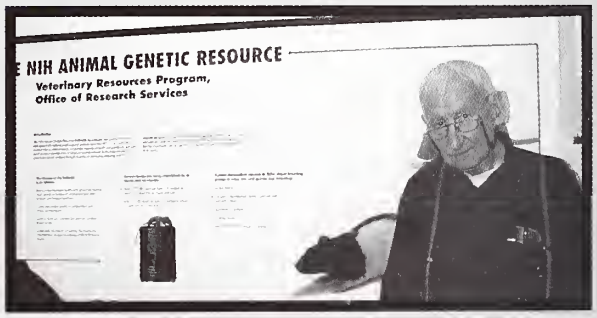
—Fran Pollner

VRP Services

- Care and husbandry
- Clinical care
- Diagnostics
- Embryo cryopreservation
- Environmental enrichment
- Facility management
- Genetic monitoring
- Genetic repository
- Health surveillance
- Intensive care
- Nutrition
- Pharmacy
- Procurement
- Quarantine/conditioning
- Radiology
- Rederivation
- Surgery
- Transgenic technology
- Transportation

In the Beginning . . . .

"This is where it all begins," said Carl Hansen, drawing an analogy between the NIH Animal Genetic Resource (NIHAGR) and the first chapter of Genesis and noting that his resource colonies provide the breeding stock for 60 percent of all the laboratory animals produced in the United States—and, indeed, the world. He recalled making imaginary site visits to all his stocks about 10 years ago: It was an around-the-world trip that would take several months to complete. He estimated that he sends out 2,000 to 3,000 animals a year to biomedical researchers and commercial breeders..



Fran Pollner

Carl Hansen

The FVB/N mouse—the standard background strain for transgenic mice—was "developed here," Hansen said, running through a quick inventory of his wares: "immunodeficient models; models for obesity, diabetes, high blood pressure, arthritis, cancer; models used in behavioral research—mice, rats, some guinea pigs."

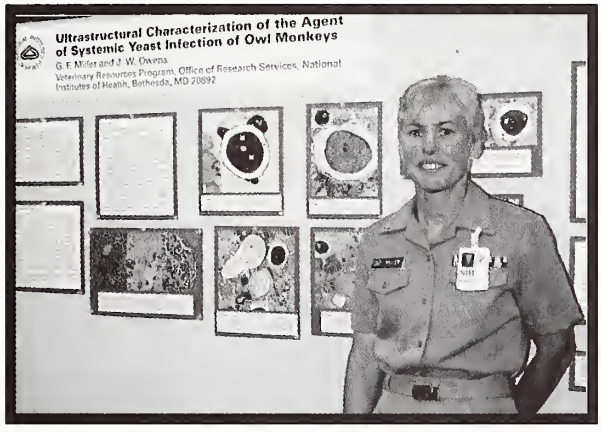
An NIHAGR fact sheet boasts a "series of mouse models (that) yields a complete experimental system for T and B lymphocyte as well as natural killer (NK) cell studies" and the "largest collection of genetically defined rats in the world," including a "unique stock of genetically heterogeneous rats developed from a cross of eight inbred strains specifically as a resource for selective breeding studies for behavioral and metabolic traits." ■

—Fran Pollner

Office of Research Services

The Owl Monkey Mystery Agent: Dimorphic and Culture-Resistant

For about seven years now, Georgina Miller has been helping NIH investigators figure out what's wrong with their research animals. "It's very important to know if a sick animal has a research-related complication or not; it's important to find out why a research animal died. This is pretty obvious. Researchers certainly don't want to endanger the health of their colonies," says Miller, one of five veterinary pathologists in the Diagnostic Services Section of the Veterinary Resources Program.



Fran Pollner

Georgina Miller

For the past three years, Miller has also been pursuing a "mystery," an agent that has infected owl monkeys used by NIAID in malaria research. She spoke of her quest during an interview at the NIH Research Festival, where she presented a poster on "Ultrastructural Characterization of the Etiologic Agent of Systemic Yeast Infection of Owl Monkeys."

The owl monkeys—"the only ones that can be infected with human malaria"—are caught wild in the tropical forests of Peru, and it's there, Miller said, that the yeast infection was most likely acquired before they were shipped here. Three years ago, Miller received a splenic biopsy from a sick but still living owl monkey whose clinical symptoms included weight loss, debilitation, and anemia.

"The spleen was filled with wall-to-wall yeast cells," she said, but, unlike most other fungal organisms, these could not be cultured (she sent samples to the NIH's Clinical Center Mycology Lab as well as to the Centers for Disease Control and Prevention; neither was able to grow the fungus on artificial media). The yeast cells infect almost every organ in the body without provoking an immunologic reaction. Another peculiarity is that the agent is dimorphic, with two forms discernible on electron microscopy—with and without a nucleus. "To my knowledge, no other fungus works like that," Miller said. Since finding that first case in 1995, she has found the infection in two other monkeys at necropsy and has identified through bone marrow aspirates two more cases in clinically healthy monkeys.

Infected animals will live for many years with their infection. The yeast, Miller said, is "engulfed by macrophages and just sits there, causing no further inflammation. The yeast cells continue to multiply and become so numerous thatn they displace blood-producing cells in the bone marrow," generating the clinical symptoms that bring the infection to the attention of researchers and the veterinarians caring for the animals.

The agent resembles a variety of *Histoplasma capsulatum* found only in Africa (var. *duboisii*), but the differences are clear on electron microscopy, Miller said. Even more, however, the mystery yeast resembles a disease-causing agent called *Loboa loboi*, which is found only in humans living in tropical regions in Central and South America and dolphins in the waters of the southern Atlantic. The disease, lobomycosis, causes a disfiguring dermatitis in humans and is confined to the skin and draining lymph nodes.

Though larger than the owl-monkey yeast, *Loboa loboi* cannot be cultured, is dimorphic, and has a similar cell wall. "Loboa is not well researched; it's probably never been sequenced. If we could sequence *Loboa loboi*, and determine that it and the owl-monkey agent are closely related, infected owl monkeys might be used to find therapies for humans," Miller remarked, noting that there is currently no treatment now for the human disease.

Earlier this year, Miller and her colleagues published the first report in the literature on the Peruvian owl-monkey yeast and its antemortem diagnosis through bone marrow aspirates—"Systemic yeast infection in owl monkeys (*Aotus vociferans*): ante-mortem screening and diagnosis by examination of bone marrow aspirates," *Lab. Anim. Sci.*, **48:**391–394, 1998. Another manuscript, similar to the poster presentation at the NIH Research Festival, has been accepted for publication by *The Journal of Medical Mycology*. Miller is now investigating the reliability of a urine antigen assay as a less invasive diagnostic tool.

Although animals may appear clinically healthy, they can harbor infections that add undesirable variables and may compromise the validity of a study's findings. The owl monkey yeast infection cases, Miller said, "clearly illustrates the benefit of routine pathologic evaluation of even healthy-appearing animals used in biomedical research."

Miller can be reached by e-mail at **<millerg@vrp.ncrr.nih.gov>**. She and the VRP pathology service can be called at 496-4465. ■

—Fran Pollner

CIIG Is Here!

The Clinical Immunology Interest Group (CIIG) is now official. It meets monthly in the Bunim Room, Building 10, and boasts both intramural and outside speakers on the theme of patient-related basic immunological findings.
Contact: Oral Alpan
Phone: 301-402-3447
Fax: 301-496-4682
e-mail: **<OAlpan@nih.gov>**

Meeting: Make the Most Of Your Mouse

NCI and NIEHS are sponsoring a symposium on "Pathology of Genetically-Engineered Mice: So You've Got A New Genetically-Engineered Mouse, What Do You Do Next?" to be held at NIH in the Natcher Conference Center, February 24-25, 1999.

Complete information on the symposium and on-line registration is at the web site:
<http://www.ncifcrf.gov/vetpath/symposium.html>.

BEPS: The NIH Bioengineering and Physical Science Component Of the 'Biology–Physics–Engineering Interface'

Office of Research Services

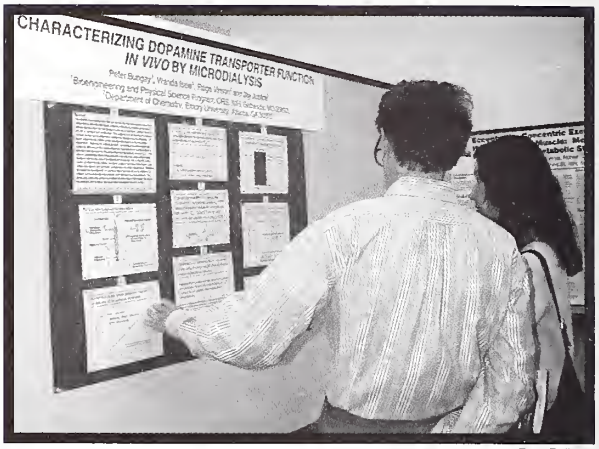
Chemical engineer Peter Bungay describes the Bioengineering and Physical Science (BEPS) Program as "not quite like anything else" in the far-ranging and omnipresent NIH Office of Research Services (ORS).

BEPS exists to bring research dreams into the material world, to develop the technology necessary to carry out envisioned investigations. It's the intellectual partner of all the research institutes. "We're collaborative researchers," Bungay says of himself and his BEPS colleagues. "We are 20 engineers, physical scientists, biophysicists, mathematicians."

For Bungay, the excitement of his work lies in the technology itself, in inventing and developing something new that has applications, rather than the applications, per se. When he and his colleagues meet the demands of a scientific challenge, it's not just NIH collaborators who benefit, but the biomedical research community at large, he observes.

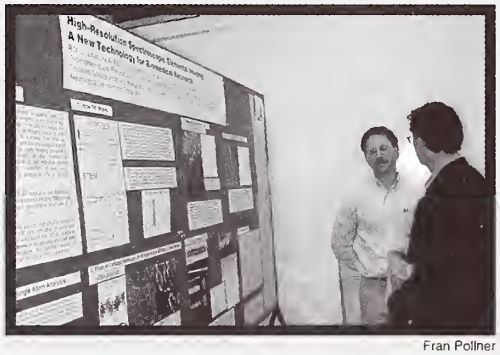
Bungay works in the Drug Delivery and Kinetics Resource, one of the five "resources" that make up the BEPS program; the others are Image Processing and Information Analysis, Instrumentation Research and Development, Molecular Interactions, and Supramolecular Structure and Function. BEPS welcomes inquiries from intramural scientists on potential collaborative projects. For more info, see

<http://www.nih.gov/od/ors/beps/>.



Fran Pollner

BEPS chemical engineer Peter Bungay explains his Research Festival poster, "Characterizing Dopamine Transporter Function in Vivo by Microdialysis," developed in conjunction with investigators at the Emory University (Atlanta) Chemistry Department, this illustrates a technique broadly applicable to quantitative measurements in vivo.



Fran Pollner

Physical Scientist Richard Leapman (left), chief of the BEPS Supramolecular Structure and Function Resource, discusses "High-Resolution Spectroscopic Elemental Imaging: a New Technology for Biomedical Research," developed in collaboration with NIAID and NINDS investigators.

Fran Pollner

Emilios Dimitriadis, senior staff fellow in the BEPS Molecular Interactions Resource, elaborates on "Interactions Among DNA Repair Enzymes in the Analytical Ultracentrifuge," a joint project with NIEHS investigators.

DNA Workshop

The Center for Scientific Review (CSR) is hosting a workshop **February 2–3, 1999**, on "Chromatin, Transcription, and DNA Replication." Additional sponsors include NIA, NCI, and NIGMS.

The conference will be held at the Natcher Conference Center, NIH, Bethesda, Maryland. There is no fee, and registration is not required.

Anyone interested in attending is asked to e-mail a response to **<rny@drgpo.drg.nih.gov>**, so that the organizers can keep track of attendees.

Feel free to forward this to colleagues at NIH and beyond.

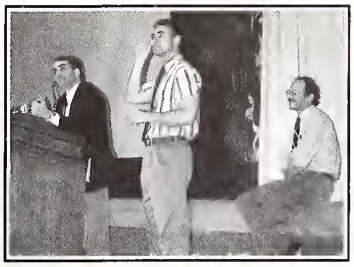
Organizers are Ramesh K. Nayak, CSR; Catherine Lewis, NIGMS; Huber Warner, NIA; Cheryl Marks, NCI. ■

A Day at the Mall

The IntraMall will come alive at the Natcher Conference Center December 11. Vendor booths and a shopping room for on-line IntraMall ordering are the order of the day, sponsored by NIH to showcase the IntraMall program and the US Bank/VISA purchase card program. Vendors are being encouraged to discount orders placed through the IntraMall that day and for the week following the event. For more info and to register, click on

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

Poetry for All Seasons



Fran Pollner

Laureates: *Robert Pinsky (left), signer Derwood O'Quinn, and Harold Varmus, NIH, June 1998*

There was poetry in the campus air—and on the Catalyst *pages—in the verdant spring of '98. In anticipation of the arrival of U.S. poet laureate Robert Pinsky to deliver the season's final Wednesday Afternoon Lecture in late June, the* Catalyst *put out a call to all the NIH poets hidden in labs and behind desks. We asked that they submit their poetry for publication in the issue that would coincide with the Pinsky reading (the May–June 1998 issue). Some poetic souls did, and the result was a page of whimsy and interdisciplinary splendor. Several, perhaps shyer, individuals sent poems in after the issue had closed. We put these away for a rainy, or snowy, day. Here's one set. (The last will likely appear next issue, accompanying an interview with the poet, who is leaving his day job as director of the Office of Alternative Medicine.)* ■

—F.P.

Alexander Wilson
NHGRI

teoP the alchemist

alchemist—
mixing,
like ancient elixirs,
distilled emotions
(intensely boiling).

stirring imagination
with quicksilvered grace
and
incantation:

"fox fire phrases in darkness,
bring unfound light to life."

bottled essence of emotion,
touchstone testing

(lead or gold?)

toil,
tempest of creation—

seek,
the philosophers' stone.

—a.f. wilson
© 1975

Perspective

the training wheels came off today
and she got on her bike and just rode away

all legs and elbows
blond hair and red bows
streaming out like signal flags
waving in the wind

she promised to try when she turned seven
promised to fly
alone and unsteadied

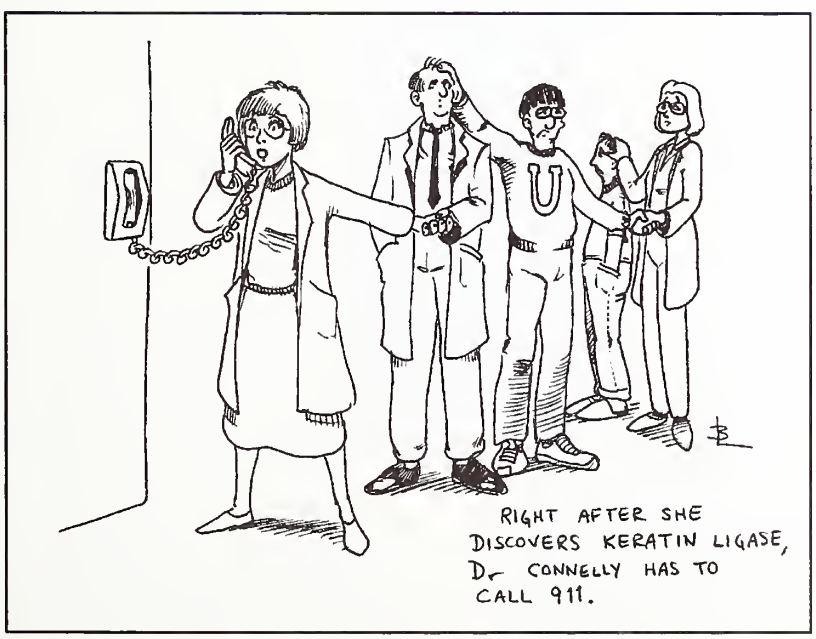
and she grew taller in the distance

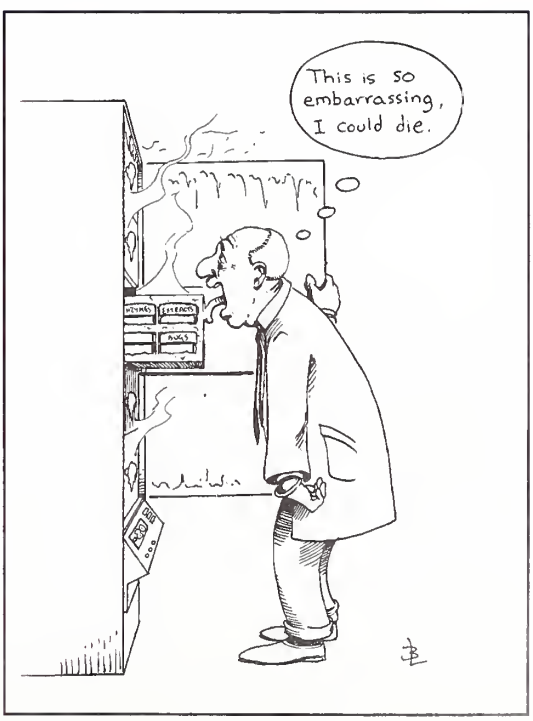
a day so much like all the others
a promise kept for fathers and mothers

some memories
like the girl on the bike
grow brighter
as they get farther away

—a.f wilson
©1994

Levity





From Outer Space to Inner Ear
continued from page 1

ample, obtaining high-resolution images of planets perhaps dozens of light years away will require, as Jimmy might have put it, a "big, big" telescope, positioned in distant space. The NASA director envisions a lens that would span several football fields, made not of glass but of a biomembrane that weighs only about 100 grams per square meter. Such technology "hasn't been invented yet," he noted, "which is one of the reasons I'm here—to get the collaboration going with you folks."

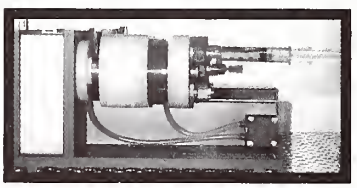
Also on Goldin's wish list is the development of suits that incorporate biomimetic "skins" capable of sensing and adapting to different atmospheres that would permit humans to work in space more comfortably and safely. Robots, too, figure in future efforts, but would need an intelligence and adaptive capabilities that far surpass those of the boulder-bumping Rover that patrolled Mars last summer. Goldin advocates revolutionary developments in computing, invoking the need for nondeterministic algorithms and low-power requirements to carry out high-performance operations intelligently and efficiently. He believes we need to learn more about the best hardware-software combination on the market—the human brain—which, he remarked, "operates a million times faster than a teraflop [10^{12} floating point operations/second] computer, but takes only a few watts of power," compared to the megawatt needs of today's best supercomputers.

Not the least of the challenges facing space missions is coping with the physiological stress to humans. Prolonged stays in zero gravity are known to induce bone loss, muscle atrophy, immunosuppression, and perhaps a host of other metabolic disturbances. NASA needs to know how to keep people in good physical and mental condition and how to administer general health care as well as surgical and trauma care, according to Goldin—another reason for closer ties to the biological-biomedical community.

The NASA-NIH Partnership

Goldin's wish for close connections to NIH and its resources has been fulfilled in part by the establishment, four years ago, of the NASA-NIH Center for Three-Dimensional Tissue Culture, directed by NICHD's Joshua Zimmerberg (1). However, the Center's purpose is not necessarily to further NASA's mission, but rather to promote a technique of three-dimensional tissue culture using a specially designed bioreactor, developed by NASA, within the biomedical research community. According to the Center's deputy director, Leonid Margolis, the facility is "open to all groups at NIH. Anybody can come and do their pilot experiments if they think the use of three-dimensional tissue or cell culture would be useful. If the pilot experiments turn out to be promising researchers can enter a competitive stage II process, which includes application for the NASA-NIH intramural grant to continue the study" (2).

The NASA-designed bioreactor consists of a rotating, horizontally mounted cylindrical growth chamber completely filled with culture medium (also known as a rotating wall vessel, or RWV). Gases are efficiently exchanged through special membranes incorporated into the design of the growth chamber. Together, these features make for a very cell- and tissue-friendly environment that is virtually free of turbulence and shear forces and conducive to the culture of tissue explants and co-culture of mixed cell types. (A review article profiling the bioreactor appeared recently in *Nature Medicine* **4**: 901–907, 1998).



A widely publicized additional feature of the bioreactor is that cells growing in the RWV experience "microgravity"—or something that resembles it, according to Wendy Fitzgerald and Jean-Charles Grivel, two members of the Margolis group. As Fitzgerald puts it, there's "a randomization of the gravitational vector" within the RWV, which leads to a microgravity-like condition. Grivel says the force in a chamber rotating at 15 rpm is estimated to be about 0.01g. Margolis explains further, "The whole thing rotates as a solid body. The cells do not move relative to the medium or to each other. If you stop [the rotation], then they will fall to the bottom of the vessel."

Doug Loftus

Wendy Fitzgerald

Doug Loftus

Jean-Charles Grivel (Left) and Leonid Margolis

Microgravity and Immune Response

Although microgravity effects are not the focus of the group's research, Fitzgerald and Grivel were inadvertently led to explore the bioreactor's influence on immune response in vitro in the course of experiments assessing HIV infectivity and tropism within tonsil tissue blocks. Previous work by the lab showed that tonsil explants, growing either on a collagen support in a normal tissue culture dish or in the RWV, support productive infection by several HIV strains showing different tropism. When tonsils are grown on collagen in dishes, T-tropic viruses also suppress antibody recall.

Says Grivel, 'The virus does replicate nicely in in the bioreactor, so we wanted to look at immune responses in this system—but we never got any." That is, uninfected tonsil blocks grown in the RWV did not make antibodies upon challenge with recall antigens, though such responses are readily made by their counterparts grown under normal gravity conditions. He and Fitzgerald did further experiments to see whether the microgravity conditions of the RWV were responsible for this observation. Their results, presented in a poster at the Research Festival, suggest that, indeed, microgravity transiently impairs the ability of lymphoid tissues to become activated upon exposure to antigens or mitogens. Not too surprisingly, these results are consistent with the observations made for shuttle astro-

nauts, who, Grivel notes, become immunosuppressed under the near-zero gravity conditions experienced during their missions, but attain normal function after returning to Earth.

Although it is not a full-time pursuit, Grivel says they hope to understand the basis for microgravity-induced immunosuppression. He adds that NASA biologists have made similar observations of lymphocytes grown in the bioreactor, and that there has been discussion with NASA of including their tonsil culture experiment on a future Shuttle mission.

Wendy Fitzgerald is no stranger to microgravity experiments. She hails from Houston, where her employer, Wyle Laboratories, a NASA-contracted firm, developed the RWV bioreactor in collaboration with NASA and provided staffing to help establish the Tissue Culture Center at NIH. She was sent here to offer her bioreactor know-how to the NIH community. Several years ago, while still in Houston, Fitzgerald engaged in what could be termed "extreme field biology," conducting microgravity experiments on cell morphology in parabolic flight. Strapped with bungee cords into NASA's KC-135 Zero Gravity Training turbojet aircraft, simply yet graphically nicknamed the "Vomit Comet" (3), she did videomicrography of cells as the pilot guided the plane through some 40 successive sharply arcing ascents and descents. At the top portion of each arc, weightlessness is achieved for a period of 20–25 seconds. She flew several of these missions. When asked what she learned, she jokingly replied, "Make sure your bungee cords are secure." On one flight, she recalled, she wound up on the plane's ceiling after a cord dislodged. As for the cells, they did indeed respond to the flight by changing from a spherical morphology in microgravity to ellipsoid in hypergravity. ■

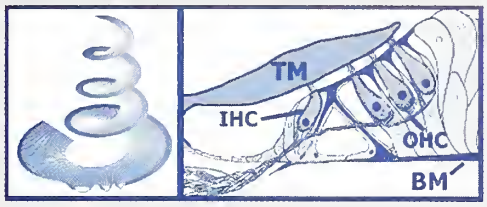
1. The NIH-NASA joint enterprise was highlighted in the September-October 1995 issue of *The NIH Catalyst*; the article resides at **<http://www.nih.gov/campus/irnews/catalyst/back/95.09/nasa.html>**.

2. Contact person: Dr. Leonid Margolis. Bldg 10, Rm. 9D58, tel: 4-2476, fax: 00857, e-mail: **<margolis@helix.nih.gov>**.

3. To learn more about why they don't serve peanuts on the KC-135 turbojet, click on **<http://zeta.lerc.nasa.gov/kjenks/kc-135.htm>**.

For general information on astrobiology, visit NASA's recently revamped Astrobiology web site at **<http://astrobiology.arc.nasa.gov/home.html>**.

The Speed of Sound



Left: The cochlear partition, showing the path taken by the basilar membrane through the interior of the cochlea. A wave is shown traveling through a portion of the basilar membrane, at bottom. Right: The arrangement of the basilar membrane (BM), outer hair cells (OHC), inner hair cells (IHC) and tectorial membrane (TM).

Among biosensors, the ear rates highly as an exquisitely sensitive and sophisticated device, arguably on a par with the eye. The human ear is capable of responding to frequencies from about 20 Hz to 20 kHz with fine pitch discrimination and is sensitive to the slightest whisper. Much regarding how the ear itself actually works, however, remains unknown. NIDCD researchers Richard Chadwick and Daphne Manoussaki are trying to better understand the workings of the cochlea (inner ear). Although their research is not directly related to a NASA project, it's a good example of the marriage of the physical and biological sciences NASA director Daniel Goldin advocates (see story, page 1) and represents a step toward understanding how sophisticated sensing systems function. Chadwick, acting chief of the auditory mechanics section in the Laboratory of Cellular Biology, explains that his section's research aims to "understand the mechanical and electrical properties of hearing." Manoussaki, whose background is in applied mathematics, joined the section last year as a fellow and has focused on producing a computational model of the mechanical properties of the cochlea—a daunting task.

Doug Loftus

Daphne Manoussaki and Richard Chadwick

The cochlea is a coiled, fluid-filled structure that receives its input from a tiny bone called the stapes, or "stirrup." Vibrations of the eardrum are transmitted through the ossicles in the middle ear—through the "hammer" and "anvil" to the stirrup, which strikes the membranous "oval window" of the cochlea, sending waves through its fluid interior. Winding through the cochlear interior is the "organ of Corti," consisting of the basilar membrane, atop which sit the outer and inner hair cells, bounded at their apical surfaces by the tectorial membrane. Vibrations of the basilar membrane cause the hair cells to deform against the tectorial membrane, stimulating the neurons that innervate the hair cells.

"There are many basic, interesting things about normal hearing that are puzzling, things we just don't understand," says Chadwick. For example, "The transduction process should be too slow—it should take time to charge up the cell membranes—somehow, there's something there that bypasses that." Another curious phenomenon he points to is that of "otoacoustic emissions"—sounds produced by the ear itself in response to an acoustic stimulus. He notes that such events are not rare, though typically not noticed, and that detection of these sounds is used clinically to assess normal auditory function in infants.

A more obvious feature of the cochlea is its geometry, something that initially caught the eye of Manoussaki. "When I came here, I didn't know much about the cochlea, and the first thing that intrigued me was the shape," she says. She explains that prevailing ideas concerning the cochlea's coiled shape pointed to more efficient use of space, or to a presumed benefit related to the innervation pattern it produced. However, no one had adequately dealt with the effect of coiling on wave propagation within the cochlea; most attempts made by others to model the inner ear simply treated it as a long rectangular tube. But Manoussaki "just couldn't believe" the coiled shape would not contribute critical properties to the cochlea. After all, she observed, water flowing through a coiled hose will force it to uncoil, a result that would not be produced in a straight hose.

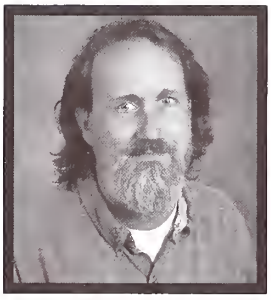
To test her idea, Manoussaki produced a coiled model of the cochlea, the complex geometry of which, Chadwick suggests, may account for others' preference to treat the system in simpler terms. Their findings, presented in a poster at the Research Festival, suggest that coiling amplifies traveling waves in the cochlea. Manoussaki is working to achieve a more detailed, realistic physical model of the cochlea to better discern what happens as sound waves move through its interior. Chadwick observes that even cochlear implant technology, which bypasses cochlear mechanics to stimulate auditory nerve branches, would benefit from a finer understanding of normal hearing. ■

——Doug Loftus

For more information on hearing, see the NIDCD web site: **<http://www.nih.gov/nidcd/hearing.htm>**; info on ear anatomy and hearing is also at **<http://www.earaces. com/>**.

Recently Tenured

Douglas Bell *gave up a promising career as a middle school science teacher and soccer coach to attend graduate school at the University of North Carolina–Chapel Hill and carry out research in environmental and molecular mutagenesis. After receiving a Ph.D. in environmental biology in 1988, he became a National Research Council fellow in the Genetic Toxicology Division at the Environmental Protection Agency. In 1990, he joined the Laboratory of Biochemical Risk Analysis at NIEHS, where he is currently head of the Genetic Risk Group.*



Steve McCaw

Douglas Bell

Environmental risk assessment requires estimation of the differences among humans in their response to toxic chemical exposures. We hypothesize that human genetic variabilities in their biochemical capacities to detoxify chemicals and repair DNA damage are important early susceptibility factors in environmentally induced disease. Thus, individuals with high-risk genotypes will accumulate more genetic damage (such as DNA adducts and somatic mutations) and therefore have a greater risk of developing cancer.

My research has focused on variation in the Phase II metabolism enzymes, particularly the polymorphic forms of *N*-acetyltransferase (*NAT1* and *NAT2*) and glutathione-*S*-transferase (*GSTM1*, *GSTT1*, *GSTP1*). During the course of our studies, we characterized new variant alleles in these genes and developed genotyping methods for human population studies. We are studying the proposition that the effects of exposure may be detectable in some genetically defined subpopulations, for example, NAT slow acetylators. Our findings from epidemiological studies support this, suggesting that the *NAT* genes, particularly *NAT1*, have an important role in modulating risk for bladder, oral, and colorectal cancer.

In addition, findings on *GSTM1* null genotype suggest that this common trait conveys an 80 percent increased risk for bladder cancer, and that the genetic risk depends on cigarette smoking exposure. Similarly, variation in the *GSTT1* gene appears to be important in mediating damage from exposures to ethylene oxide and dichloromethane. There are many candidate genes that may influence risk for environmentally induced disease; however, of the approximately 100,000 human genes, only a few dozen—those with easily determined phenotypes—have been explored for polymorphism. We are actively engaged in projects to discover new polymorphisms in genes involved in responses to environmental exposures.

With the encouragement of a mentor at NIEHS, George Lucier, I have established a number of productive collaborative projects, including work with outstanding epidemiology groups from NIEHS, NCI, University of North Carolina, Columbia University (New York), and the Johns Hopkins University (Baltimore). It is our hope that studies incorporating markers of genetic susceptibility and/or exposure will continue to help us understand the distribution of risk in human populations. To the extent that we can quantify risk differences among groups, we can reduce the uncertainty in risk assessment and enhance our ability to reduce the societal costs of environmental hazards. In addition, identifying subpopulations or individuals who might be at particularly high risk from exposures due to inherited or acquired factors should be useful in disease-prevention strategies.

Barry Kaplan *received his Ph.D. from Cornell University Medical College (New York) in 1974 and did his postdoctoral training at the E.P. Andrus Gerontology Center of the University of Southern California (Los Angeles). He was a professor of psychiatry and the director of the Molecular Neurobiology and Genetics Program at the University of Pittsburgh Medical Center before joining NIMH in 1997. He is currently the associate director for fellowship training and a senior investigator in the NIMH Laboratory of Molecular Biology.*

Fran Pollner

Barry Kaplan

Axons and nerve terminals are unique subcellular structures of the neuron that play a critical role in the development and maintenance of neural connectivity. One of the central tenets in neuroscience is that the protein constituents of these distal neuronal compartments are synthesized in the nerve cell body and are subsequently transported to their ultimate sites of function. Hence, the structure and function of these highly specialized distal domains of the neuron are totally dependent on slow anterograde axoplasmic transport.

In contrast to this viewpoint, work in my laboratory focuses on the hypothesis that de novo protein synthesis occurs within microcompartments in the neuron to include the axon and presynaptic nerve terminal. Our studies use the squid giant axon, which serves as a model invertebrate motor neuron system.

Using this model, my colleagues and I have shown that the axon contains a heterogeneous population of approximately 100–200 different mRNAs. These mRNAs are full-length gene transcripts capable of synthesizing protein in a cell-free translation system. We have cloned and characterized several axonal mRNAs that encode B-actin, B-tubulin, spectrin, kinesin, MAP I, neurofilament protein, and enolase.

In addition, we have identified several mRNAs that code for novel proteins. The axonal localization of these mRNA species was definitively demonstrated by in situ hybridization histochemistry, and the presence of these sequences in the polysome fraction was established by reverse transcription–PCR methodology. Using biochemical labeling experiments and electron spectroscopic phosphate imaging, we were also able to show that the giant axon contained biologically active polyribosomes.

Concurrent with this work, we have demonstrated that protein synthesis occurs in the large presynaptic terminals of squid retinal photoreceptor neurons. This finding was obtained using cell-free translation analysis, high-resolution autoradiography, and electron spectroscopic imaging. Our most recent results suggest that the level of protein synthesis in these presynaptic terminals is affected by calcium ions and, hence, could be regulated by the activity of the terminal itself.

Based upon the information gleaned

from this invertebrate model system, we have postulated that key elements of the cytomatrix, molecular motors of the axon transport systems, and proteins involved in energy metabolism are locally synthesized in the distal structural and functional domains of the neuron. In the mature neuron, a local system of protein synthesis could contribute significantly to the maintenance and remodeling of axonal architecture, as well as the dynamic properties of the nerve terminal.

This system might prove especially important in large asymmetric motor and sensory neurons, where the axon and terminal fields are far removed from the cell body.

Currently, my colleagues and I are using differential mRNA display methodology to identify novel constituents of the axonal mRNA population, and we are beginning to explore the mechanisms involved in the intracellular trafficking of axonal mRNAs. These latter studies will involve mRNA-protein binding assays, as well as deletion mutation analysis and microinjection of fluorescently labeled mRNAs into isolated squid giant axon preparations. We hope that these investigations will augment our understanding of the molecular mechanisms that play a key role in neuronal development, regeneration, and plasticity. ■

FARE Returns: 130 Winners

The results of FARE 1999 are now available. The NIH Fellows Committee received a total of 666 abstracts (an increase of 10% over last year), from which they selected 130 winners. Each of these winners receives a $1,000 travel award to attend a meeting during the 1999 fiscal year.

The committee would like to thank all fellows who participated in this year's competition and acknowledge the Scientific Directors, the Office of Research on Women's Health, and the Office of Education for their continuing support of FARE.

The results can be viewed on the Fellows Committee website at **<ftp://helix.nih.gov/felcom/index.html>**.

Day Care Board Spaces

The NIH Day Care Board is seeking volunteers from the intramural research community to serve for a three-year term. The board meets about two hours each month and works to ensure that NIH daycare programs and access to facilities are fairly administered and to identify and rectify employee concerns.

Board members ponder prospects during NIH site visit.

Membership is open to federal employees who work on the NIH Bethesda campus or at off-site facilities. Anyone interested may self-nominate by sending a letter cosigned by their supervisor to the Director, DSFM, EPS/Suite 200; include name, NIH mailing address, IC, branch, section, job title, and brief biographical sketch. Nomination letters should describe why you'd like to serve and note any daycare-related concerns or interests. Members are selected to be representative of the diverse NIH population. Voting members may not have a financial interest in NIH-sponsored daycare, except that they may have a dependent enrolled in an NIH daycare program. For more information, contact Carol Wigglesworth at 2-5913 or Chris Steyer at 6-0436. ■

PRAT Fellowships

The deadline for NIGMS' Pharmacology Research Associate (PRAT) Program is **January 5, 1999**.

The PRAT Program supports two years of training for postdoctoral candidates in the pharmacological sciences and related research areas. These may include but are not limited to molecular pharmacology, signal transduction mechanisms, drug metabolism, immunopharmacology, chemistry and drug design, structural biology, endocrinology, and neuroscience. PRAT Fellows receive competitive salaries as well as supply and travel funds to support research in their preceptors' laboratories.

Candidates apply in conjunction with an identified preceptor, who may be any tenured or tenure-track scientist at the NIH or FDA. Applicants may have been at the NIH for up to 12 months before the application receipt date and must be either U.S. citizens or permanent residents.

To receive more information or application materials, contact the PRAT program assistant at 301-594-3583; e-mail: **<PRAT@nigms.nih.gov>**.

Fellowships in Japan

Through arrangements made with the Fogarty International Center (FIC), the Japan Society for the Promotion of Science (JSPS) is offering fellowships for American researchers in the biomedical and behavioral sciences to pursue collaborative research in Japanese universities, laboratories, and other institutions.

The JSPS Short-Term Fellowship provides for research visits of 7 to 60 days; the JSPS Short-Term Postdoctoral Fellowship provides for research visits of 3 to 11 months. Applicants must be U.S. citizens or permanent residents, and research plans must be arranged in advance with the Japanese host. Application deadline is **January 15, 1999**.

Full announcements, application instructions, and additional information may be found on the FIC web site at: **<http://www.nih.gov/fic/opportunities/ff.html#japan>**. Information is also available from Kathleen Michels: fax 301-402-0779 or e-mail: **<jsps@nih.gov>**. Inquiries may be sent by mail to: FIC, Division of Training and Research, Building 31, Room B2C39, 31 Center Drive MSC-2220, Bethesda, MD 20892. ■

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: creating space for unfettered thought, research services, the NIH Research Festival, and intriguing research the *Catalyst* should cover.

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...

- Wayne Jonas On Alternatives
- Gene Therapy For Pain
- Firing Up Clinical Research

1) How would you recommend NIH scientists make intellectual space in their lives? What fuels your greatest moments of insight and creativity?

2) What has been your experience with ORS services such as those offered by the Bioengineering and Physical Science and Veterinary Resource programs? What types of services and collaborations would be most helpful to you in your research?

3) What did you like best about this year's Research Festival? What recommendations would you make for next year?

4) We're still interested in hearing from you about research going on in labs on campus that you find particularly intriguing and think the *Catalyst* should feature.

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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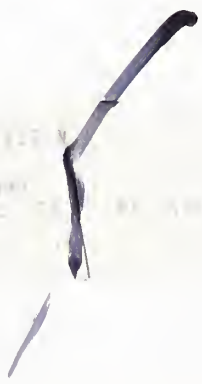

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