FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

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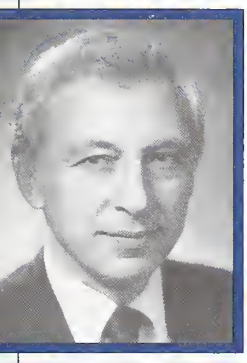
THE ONCE AND FUTURE GALLO

by Rebecca Kolberg

Most researchers enter and leave NIH without creating many ripples beyond their own small, scientific circles. Robert Gallo's arrival as yet another eager young physician attracted little attention at the Clinical Center in 1965. But his departure 30 years later is certainly making waves in Bethesda and beyond. This fall, Gallo, the longtime chief of NCI's Laboratory of Tumor Cell Biology, plans to take the helm of his very own institute: the Institute of Human Virology at the University of Maryland in Baltimore. Accompanying the pioneer in human retrovirology will be William Blattner, chief of NCI's Viral Epidemiology Branch; Joseph Bryant, chief of NIDR's Animal Care Unit; and Robert Redfield, an infectious disease expert at the Walter Reed Army Institute of Research in Washington, D.C. An as-yet unspecified number of other scientists will be joining them from NIH and elsewhere. Although Gallo is certainly looking ahead to his new challenges, in a reflective interview with *The NIH Catalyst,* he talked about the evolution of NIH over the past three decades, as well as his own evolution, or some might say trial by fire, as a scientist.



Robert Gallo

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INTRAMURAL COLLABORATION: FROM THE LECTURE HALL TO THE TENNIS COURT

by The NIH Catalyst Editorial Advisory Board

NIH scientists are no exception to the recent trend toward increased collaboration in biomedical research. Yet, intramural researchers may not be taking full advantage of the wealth of collaborative opportunities in their own back yard. Frequently mentioned obstacles to interlab or interinstitute collaborations include lack of information about other researchers' interests and expertise, reluctance to approach other NIH researchers, and a dearth of informal outlets for scientists from a wide range of disciplines to mingle and exchange ideas.

Lorna Heartley

Ira Pastan, left, and David Davies, whose competition on the tennis court led to collaboration in the lab.

The NIH Catalyst recently turned to its Editorial Advisory Board to get a reading on the current collaborative atmosphere within NIH, as well as suggestions on how it could be improved. The board members who responded said they had collaborated other NIH researchers outside their own immediate labs, and that with their collaborations were roughly divided between inter- and intrainstitute projects.

"I have been at NIH for 20 years and have always collaborated as much as possible with intramural scientists. The benefits are enormous because the people are local and generally more supportive than university people—possibly because of the availability of resources," says Hynda Kleinman of NIDR.

David Lim, who came to NIDCD 3 1/2 years ago from Ohio State University in Columbus and will be leaving Sept. 1 to become executive vice president for research of the House Ear Institute, which is affiliated with the University of Southern California in Los Angeles, says intramural, indeed interagency, collaboration is vital to his lab's efforts to develop a conjugate vaccine against nontypeable *Haemophilus influenzae*, a major pathogen causing otitis media. The vaccine project involves researchers from NIDCD, NICHD, and FDA's Center for Biologics Evaluation and Research. "Without this collaboration and pulling the resources together, this project could not have been possible for a small institute like ours," says Lim, who currently has four collaborative projects within NIDCD, five within NIH, and five outside NIH.

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National Institutes of Health: The Shape of Things to Come, Part II

Michael Gottesman

In the March–April issue, I outlined likely *physical* changes at NIH over the next 10 years. Now, I want to give you some idea of how the *administrative* changes necessitated by "downsizing and streamlining" will affect our day-to-day scientific activities.

My assumptions are the same as before: the intramural budget will remain relatively stable, but, given a 4% inflation rate for biomedical research costs, some estimates predict a loss of 5–20% in "real" funds over the next five years. More draconian reductions are possible if the NIH budget as a whole is actually cut. We are currently under a presidential mandate to shrink the size of our work force by reducing full-time equivalent (FTE) positions by making major cuts in administrative positions such as personnel and procurement. Noting that most of our FTE cuts from 1992 to 1995 have come from the intramural program because of rapid staff turnover in slots such as staff fellows, visiting scientists, and experts, the NIH leadership intends to limit FTE reductions in intramural scientific staff to 5% between now and 1999, assuming that no further FTE cuts are mandated.

Several principles are being used to guide downsizing decisions. First, the HHS Secretary has indicated that reductions in force (RIFs) will be avoided in meeting downsizing goals. However, judicious cuts in resources available to lower-priority programs will be made, as determined by the Boards of Scientific Counselors' reviews, scientific opportunities, and health-research demands. Across-the-board cuts, such as could be achieved through simple attrition, are a poor management tool and, although superficially equitable, are intrinsically unfair and do not reward merit. Second, before we cut scientific programs, we must make our administration as efficient as possible. This entails reducing redundancy and eliminating unnecessary rules, as well as promoting automation wherever possible. But simply converting cumbersome administrative processes to computerized versions of the same red tape makes little sense; streamlining demands that the processes themselves be changed before automation occurs. Finally, we can use the opportunity afforded by the reinvention mandate to restructure lines of authority to improve the scientific work environment.

These outside pressures and internal demands have prompted NIH to establish three major reinvention groups: a reinvention "laboratory" that is restructuring the extramural grants process; a reinvention working group that is trying to eliminate administrative obstacles to intramural research; and a reengineering oversight group that is seeking to streamline a broad spectrum of administrative processes including procurement, finance, proeperty, travel, and personnel. I head the intramural working group with MaryAnn Guerra, executive officer at NHLBI, and I lead the reeingineering oversight group with Michael Goldrich, deputy director and executive officer at NIAID, and William Risso, deputy director at DCRT. In addition, the reengineering group has support from Lockheed Martin Corp. of Bethesda, a contractor with experience in both government and industry "downsizing."

The intramural working group, which has members from the scientific and administrative communities, has requested that HHS designate the intramural research program a "reinvention laboratory." If granted, such designation would give NIH more freedom to remove administrative impediments to science. The group has also issued its initial report covering a gamut of concerns ranging from serious problems to "pet peeves" of scientists and administrators. If fully realized, the group's plan would slash the number of steps involved in many administrative processes, reduce the need for many administrative personnel in "control" positions at both NIH and HHS headquarters, and lift obstacles to efficient hiring, travel, purchasing, and bill paying. Unfortunately, many of the proposed changes hinge on the passage of legislation. For example, the Clinton administration's bill to overhaul the civil-service system is probably necessary to shift NIH into a "pay band" system, which allows broad salary scales for different job descriptions rather than the current complex system of multiple grades, each requiring extensive documentation. However, it may still be possible to achieve some of these goals as a "demonstration" project.

Another special focus of the intramural working group is improving procurement processes. With the leadership of Leamon Lee, director of the Office of Administration, and Francine Little, director of the Office of Financial Management, we have begun a pilot of a charge-card system (see May–June issue, page 21). The group also plans to advocate and monitor the development of a seamless electronic ordering system that would enable researchers to shop for scientific supplies, place orders, keep purchasing records, and approve payment via desk-top computers. Other administrative changes are being spearheaded by the NIH reengineering group with advice from Lockheed Martin. Subgroups have been established in areas of special interest such as purchasing, accounts payable, and time-keeping, and major recommendations are in the offing (see May–June issue, page 1).

Although many of the anticipated changes will save money and time, if successful, most will be largely invisible to scientists. However, other changes will have a profound effect on how scientists conduct business at NIH.

In some cases, reinvention efforts will lead to major shifts in authority. The goal is to delegate authority to the lowest possible level—that is, give more power to the scientist in the trenches. Personnel decisions should be made by lab or branch chiefs or other senior scientific personnel who do the hiring. Procurement should be done primarily by the scientists who need the items. There are two significant drawbacks to these changes. First, with increased authority comes increased responsibility. Scientists using the new systems must be familiar with appropriate personnel and procurement regulations. Second, a number of administrative positions will become obsolete under the new systems, and this number may be well above the projected loss of FTEs through attrition.

How will we solve these problems? One obvious answer is to redeploy centralized "control" personnel now within the institutes and the Office of the Director to the labs, where they can perform administrative and support duties. This would enhance the intramural program's emphasis on health science and scientists. On the other hand, just as administrators would need to learn more about scientific needs, scientists would also have to learn more about management. Some will resist these changes, arguing that the strength of the intramural program lies in researchers' freedom to concentrate on the creative aspects of science with minds uncluttered by mundane matters. But, with appropriate lab support based on the redeployment and retraining of administrative personnel, I believe we can have the best of both worlds. Let me know what you think.

Michael Gottesman
Deputy Director for Intramural Research

Catalytic Reactions

Below are comments we received for topics raised in the March–April and May–June issues.

On "The Shape of Things to Come, Part I"

You mention downsizing and possibly increased laboratory space as the number of scientists decreases. Among the scientists I come in contact with, there is a pervading feeling that although scientific positions are being eliminated, the number of people in administrative positions is not decreasing. Certainly streamlining government and cutting down on red tape should reduce the need for administrative support, as should the decreasing number of scientists that require such support. Are there any hard data that illustrate the trends to date?

—Rachel R. Caspi, NEI

The issue you raise about downsizing staff and streamlining is the subject of "The Shape of Things to Come: Part II" [see page 2]. A short answer to your question is that each of the ICDs has been asked to present streamlining plans for administration that result in downsizing and more efficient use of personnel. These are mandated by the change in the supervisor-to-employee ratio and by the progressive loss in FTEs projected through 1999.

It is true that the first round of FTE cuts came close to 80% from the intramural program (only about two-thirds of our FTEs are intramural) because that was where FTEs were used on a temporary basis (staff fellows, experts, visiting scientists, etc.) and where there was the most turnover. A survey of different institutes shows that intramural administrative positions occupy 5–10% of total FTEs, so this is not a very rich source of FTEs, even if all were eliminated.

Projections for the next few years are for up to a 50% reduction in control positions (many administrative positions fall into this category), with only a 5% reduction in intramural scientific FTEs, so the effect on administration should be obvious soon. All of this needs to be done very carefully because you may soon find that there is no one around to make it possible to do science.

—Michael Gottesman, Deputy Director for Intramural Research

On bureaucratic obstacles at NIH

The administrative obstacle that aggravates me the most is the three-month lead time required to bring a [Intramural Research Training Award] fellow on board. It is unclear to me why any domestic personnel action should take more than two months in this age of computers. Suggestions: 1) if the personnel system is not adequately automated, it should be made so, and 2) personnel should be centralized into one office for all of NIH. This way, we could have more people processing the paperwork and fewer people supervising the people processing the paperwork.

—Anonymous

I do computer network services. That's a very fast-changing field, and procurement hassles keep us from getting things when they are needed. Procurement needs to be reinvented. So far, they are just tweaking it. Put some trust in the people doing the work. Rules upon rules to prevent a small amount of fraud are costing the government billions because of paperwork and delays.

—Roger Fajman, DCRT

On "Bridges to Baltimore"

To quote, "Gazing out a window at the blue of the Chesapeake Bay framed by the steely glint of shipping cranes and the arch of a distant bridge, NIDA's intramural research center in Baltimore … ." I am sorry, I cannot envision how large a window that is, or who or how one can stare out of a building in Baltimore and see the Chesapeake Bay. Possibly you mean the Patapsco River?

—Norm From Baltimore

It's good to see that NIH researchers know their geography as well as their biology. Yes, a bit of poetic license was taken in that reference to the water seen from NIDA's windows. A more precise description would be the Baltimore Harbor or a tributary of the Chesapeake Bay, namely, the Patapsco River. ■

Hot Methods Clinic

After a brief vacation, Hot Methods Clinic will return in the next issue. Be sure to keep on sending us updates on previous Hot Methods, as well as suggestions of techniques to cover in future issues. ■

Quick Access

If you'd like to access *The NIH Catalyst* on the World Wide Web without going through the NIH Home Page, here's the Uniform Resource Locator (URL) for our on-line edition: http://www.nih.gov:80/news/irnews/catalyst/ ■

Susan Shoaf

Correction

In a photo accompanying "Gender Bias in the Schools" on page 16 of the March–April issue, Susan Shoaf of NIAAA was incorrectly identified as Jacqueline Crawley of NIMH. We apologize for the error. ■

Authorship and Ownership: What Are the Ground Rules?

by Joan P. Schwartz, Ph.D., NINDS

Publication of scientific work is one of the most critical components of being a scientist—it brings recognition for scientific advancement and publicly demonstrates that research funds have been well used. Perhaps because of its importance, publication often leads to disagreements about authorship, and most scientists—at some point in their careers—will be touched by an authorship dispute. What are the ground rules for decisions about authorship? Can they be improved so that disputes can be avoided?

The NIH Intramural Research Program recognizes that authorship issues are an important concern for the ethical and optimal conduct of science. An entire section of the *Guidelines for the Conduct of Research in the Intramural Research Program at NIH* is devoted to authorship. These guidelines state that "for each individual the privilege of authorship should be based on a significant contribution to the conceptualization, design, execution, and/or interpretation of the research study, as well as a willingness to assume responsibility for the study." The guidelines go on to specify that "individuals who do not meet these criteria but who have assisted the research by their encouragement and advice or by providing space, financial support, reagents, occasional analyses or patient material should be acknowledged in the text but not be authors."

Joan P. Schwartz

Most scientists would accept this definition of who should be an author and who should merely be acknowledged but might differ on what constitutes a *significant* contribution. This difference of interpretation is at the crux of many authorship disputes. Consider, for example, the varying views that might emerge in large labs and branches where a postdoctoral fellow, who may have minimal contact with the lab or branch chief, might believe that the chief's contribution is insufficient to warrant co-authorship. Our senior investigators, who function as mentors and who train fellows in good scientific thought and method, may have minimal "hands-on" input into a specific set of experiments, but their conceptualization of the field may well have established the scientific framework necessary for the work. A key question here is about the origin and development of the ideas and experimental design that contribute to the success of a scientific study—would the work have been done without the supervisor's input?

DETERMINING THE ORDER OF AUTHORSHIP ON A PAPER SHOULD BE DONE AS EARLY AS POSSIBLE TO AVOID MISUNDERSTANDINGS.

Another issue with comparable potential for generating disputes is that of "ownership"—of ideas, of a scientific problem, or of a set of reagents—and here the distinction between legal requirements and ethical rights is important. Many fellows do not realize that at NIH—which is, after all, an agency of the federal government—all research carried out in the intramural program is the property of NIH. Thus, laboratory books remain at NIH when a fellow leaves, and reagents may not be taken unless the lab or branch chief has given prior approval. When a scientist departs for a job in industry, reagents may only be taken after a Material Transfer Agreement has been negotiated. These are clear legal requirements.

Beyond these requirements, ethical rights that go to the heart of scientific collaboration also come into play in ownership disputes. For example, all collaborators on a project have an ethical right to examine the original data when a manuscript is being prepared for publication. And all the people involved in the project, including the lab and branch chiefs, have the ethical right to present the data in public forums, provided proper acknowledgment is given to all co-workers. Finally, fellows, visiting scientists, and other investigators who are transiently affiliated with an NIH lab do not have an eternal right or claim to ideas and experiments. Once they leave our labs, the issue of how much longer their contributions must be acknowledged on subsequent communications emerging from their former labs becomes a matter of negotiation.

The timing of agreements about authorship and ownership can significantly reduce the likelihood of disputes. For example, determining the order of authorship on a paper should be done as early as possible to avoid misunderstandings. Agreements made before a paper is written, or before a scientist leaves NIH, are less likely to lead to complications than those attempted after the fact.

These are the general guidelines, but as with all empirical formulas, it is their specific application, interpretation, and embodiment in common practice and standards that really matters. Are the guidelines realistic? Are they useful? Do they bear any resemblance to the way we actually do things at NIH? And finally, is there a better way to approach ownership and authorship issues? As always, this column welcomes instructive examples, questions, and other feedback from the NIH community. ■

MINI-MED SCHOOL: MAXI BENEFITS

by Ruth Levy Guyer, Ph.D.,
Office of Science Education, OD

When asked what he liked about NIH's second annual Mini-Med School, one participant remarked, "the willingness of NIH to lift its tent flap and let 'civilians' observe. ... It added to my own databank and will help me be a partner with my physicians in my health care. What did I dislike? You are kidding, right?"

For nine consecutive Thursday nights this spring, 250 "civilians"—ranging from a 13-year-old who hopes to become a physician to a 77-year-old retired chemist—gathered in the Clinical Center to spend two hours learning about various aspects of biomedicine, from anatomy to zoonoses. By the end of the free course, the students knew not only a lot about the history of medicine, bioethics, new discoveries, and therapies, but also boasted vocabularies enhanced by several hundred powerful scientific and technical terms. At the moment, more than 1,300 names are on the waiting list for next spring's Mini-Med School, which can only accommodate 250 people, enrolled on a first-come, first-served basis.

Bruce Fuchs of the Office of Science Education, who developed and runs the Mini-Med School, says he became aware of the tremendous public need—and demand—to know more about biomedical science years ago through his speaking engagements as a faculty member of the Medical College of Virginia in Richmond. One of this year's Mini-Med School students concurs, saying, "The general public is, for the most part, woefully ignorant of the most basic principles of medicine."

Another benefit of the program, according to Fuchs, is that it lets people find out what motivates NIH researchers. For example, after the final lecture by NCHGR Director Francis Collins, one participant expressed the wish "that many more people could hear of his work, so that perhaps the unconscious fear of Brave New World situations could start to be dispelled." Others reported that the "mini-med" experience affected their views on NIH funding, saying, "You have really piqued my interest in biomedical research as well as support for this kind of research," and, "It's very important to educate the general public about developments/research in medicine. It will build support for continuing funding."

Collins considers public outreach to be both a scientific responsibility and a personal passion. "No longer can we afford to hide away in the ivory tower," he says, noting that he "always learns something about public perceptions" through such talks. The NCHGR director adds that public lectures "fulfill that 'teaching instinct' that most scientists have buried down there somewhere. ... If they don't get the chance, they are missing out on a very significant part of being a scientist."

NCHGR Director Francis Collins, left, discusses genetics-related issues with Mini-Med School students.

When giving his genetics lecture, Collins says the hardest part to convey to nonscientists is the mechanism of gene linkage. "ELSI—the ethics, legal, and social issues—is the part they love," he says, "and it is the easiest part to explain and to get people excited about." Another speaker, Evan DeRenzo of the Clinical Center's Bioethics Program, says she thinks the public enjoys learning about bioethics because the issues it embraces are "everyone's newspaper reading, everyone's 6 o'clock news." Observing that people who don't have medical professionals in their family are often at a disadvantage in dealing with health issues, DeRenzo looks to the Mini-Med School and similar lectures to help equip people with the tools they need to get more out of their medical care.

NIAID Director Anthony Fauci, who spoke about AIDS, says that what he finds most difficult to explain to a lay audience is the complexity of HIV disease. "Of particular importance is the concept that although the body can partially control the replication of the virus, the virus continues to replicate in an infected individual for many years until it finally overcomes the immune system," Fauci says. "In contrast, virtually every other virus that infects humans is cleared within a matter of days to weeks by an appropriate immune response."

When asked how the Mini-Med School program could be improved, most students just wanted more—more lectures, field trips, and video and audiotapes of the sessions. A teacher in the audience asked whether NIH Director Harold Varmus' lecture on the multi-hit induction of skin cancer could be taken on the road. "If children, especially teens, can actually hear about the studies and see the results, they would be much more likely to use sun block than they are now or to stay out of the sun," she said.

Mini-Med School participants were also fascinated by the talk and video presentation by NIMH's David Pickar illustrating the behavior of schizophrenia patients before and after clozapine treatment. Said one student, "The video helped me see what schizophrenia does to people and how with proper drug treatment patients can find some relief. Thank you for the valuable research you are doing to help these people get out of the hell they are living in."

Scientists who are interested in getting involved in the Mini-Med School should contact Fuchs (phone: 402-2470; fax: 402-3034). ■

ELECTRONIC SCIENTIFIC JOURNALS: ARE WE THERE YET?

by James E. Strickland, Ph.D., NCI (stricklj@dc37a.nci.nih.gov)

One of our postdocs recently had a close call when a cabinet full of journals ripped out of the wall and collapsed onto his desk. Although a buildup of journals usually isn't life-threatening, a considerable chunk of NIH's precious funding and lab space is consumed by multiple subscriptions to the same print journals. Wouldn't it be great to have full access to all journals in a searchable form, replete with figures, right on your desktop or notebook computer?

Before delving into the details of electronic publication, let's consider a few broader issues. First, there are economic questions. Journals must have sufficient income to pay for publication. If journals are available free on-line, what will be the motivation to pay for subscriptions? And what about copyrights if a full copy of a paper can be had simply by pulling it up on a computer screen and pressing "print"? Publishers will probably have to develop a pay-per-view or pay-per-print mechanism. NCI's Office of Cancer Communications already has subscribers to its electronic publications, who are recognized by passwords and by computer domain.

Then there is the matter of human behavior. People like to thumb through paper copies of journals and newspapers. Most scientists won't carry around notebook computers just so they can browse the literature over coffee. Aesthetics are another a hurdle. Even though figures and photographs may be viewed at higher resolution on a computer screen than in a print journal, few of today's computer printers produce figures and photographs at a resolution that researchers find attractive or informative.

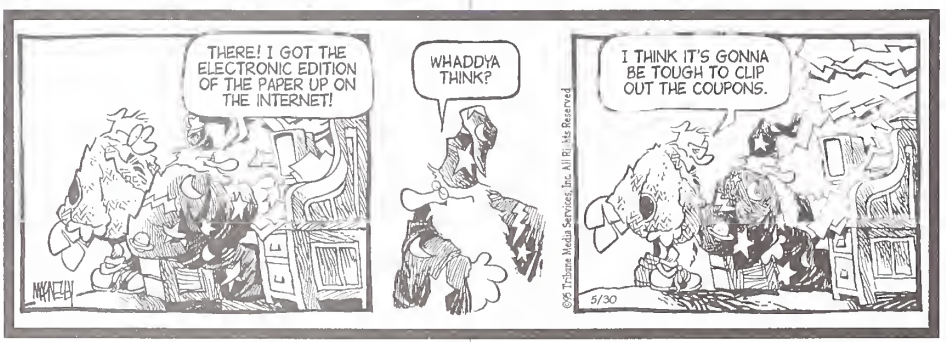
Despite these obstacles, many organizations are plunging ahead with their development of electronic journals. Currently, such journals come in two forms: compact disk read-only memory (CD-ROM) and on-line. With CD-ROM journals, you pay for a subscription and receive the issues on a compact disk delivered by mail. To view the contents, you need a computer with a CD-ROM drive and the browser software that the publisher provides. The best CD-ROM journals have everything available in the printed version, plus links to related information. With on-line journals, contents are contained in files located on a computer server, most likely at a remote site. You need a way, such as a modem or computer-network hookup, to access these files and a browser to view them. Many journals, including the old standby, *Journal of Biological Chemistry*, are now starting to appear on the World Wide Web—an international network of computers commonly called the Web—and are being viewed via Web-browser programs such as Mosaic and Netscape. A lot of these "journals" are simply text or merely a come-on, such as a cover picture or Table of Contents, to encourage you to look at a print version or pay to order a reprint. In addition to CD-ROM and on-line journals, there are hybrids of the two technologies, such as a journal on CD-ROM at an NIH Library computer that can be accessed from remote computers by using appropriate browser software.

CD-ROM Versions

The first electronic journal to pass the NIH Library's evaluation process [see box, page 21] was the *New England Journal of Medicine* on CD-ROM. This searchable journal, which is updated twice yearly and has issues dating back to July 1991, contains full text, charts, tables, graphs, and color images. It is available on library computers or on your desktop computer through your local area network (LAN). This journal and other CD-ROM titles are accessible from any PC running the LanManager or Windows for Workgroups client software and the TCP protocol stack. Macintosh computers running the Soft Windows emulation software can access NIH Library CD-ROM titles over Appletalk. Novell and IPX support will be available later this year. To arrange access through your computer, ask your LAN manager to contact Ben Hope, the NIH Library's network administrator (phone: 496-4230; e-mail: tallguy@nih.gov).

The *Journal of Biological Chemistry*, published by the American Society for Biochemistry and Molecular Biology in Bethesda, Md., can also be purchased on CD-ROM, though it is not yet available in the NIH Library. Browsing the 1994 issues illustrates how rapid the progress has been. In January, the CD-ROM journal was rather unsatisfactory, particularly when it came to accessing images, but by December, the journal was much improved. However, the amount of time required to learn how to navigate the CD-ROM's browser interface was daunting. Indeed, the lack of standardization among browser programs—which forces researchers to learn several programs just to read a few journals—was a major problem highlighted in a review of on-line journals published in Sept. 19, 1994, issue of *The Scientist*. One small ray of hope is that the American Association for Microbiology in Washington, D.C., uses the same browser software for all 11 biomedical journals it publishes on CD-ROM—*Clinical and Diagnostic Laboratory Immunology*, *Molecular and Cellular Biology*, *Journal of Bacteriology*, *Journal of Virology*, *Infection and Immunity*, *Applied and Environmental Microbiology*, *Journal of Clinical Microbiology*, *Antimicrobial Agents and Chemotherapy*, *Microbial Reviews*, *Clinical Microbiology Reviews*, and *International Journal of Systematic Bacteriology*. In evaluating a trial subscription to *Journal of Virology*, the NIH Library determined that the DOS interface was less than satisfactory, but a Windows version is being tested now.

Other scientific journals on CD-ROM include *Protein Science*, published by the Protein Society in Bethesda; *Biophysical Journal*, by the Biophysical Society in Bethesda; and the *Journal of Vacuum Science and Technology*, by



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the American Institute of Physics in College Park, Md. Gordon and Breach in Langhorne, Penn., has also announced several CD-ROM titles, including *Autoimmunity, Cancer Biochemistry Biophysics, Cancer Research, Therapy and Control, Connective Tissue Research, Developmental Immunology, Journal of DNA Sequencing and Mapping, Free Radical Research, Growth Factors, Immunodeficiency, International Journal of Neuroscience, International Reviews of Immunology, Journal of Neurogenetics, Lasers in the Life Sciences, Leukemia and Lymphoma,* and *Receptors and Channels.*

On-Line Progress

As for on-line journals, the American Chemical Society in Washington, D.C., has 23 journals available on the society's Scientific and Technical Network (STN), including *Analytical Chemistry, Biochemistry, Bioconjugate Chemistry, Biotechnology Progress, Chemical Research in Toxicology, Journal of the American Chemical Society, Journal of Medicinal Chemistry, Journal of Pharmaceutical Sciences,* and *Macromolecules.* A complete list is available via Internet at "gopher acsinfo.acs.org" or on the World Wide Web or through the uniform resource locator (URL) at this address: "http://www.acs.org". Two of these journals, *Biochemistry* and *Journal of the American Chemical Society,* are also available on CD-ROM, and the NIH Library is evaluating *Biochemistry.*

Through its Electronic Journals online program, the Online Computer Library Center (OCLC) offers *Immunology Today Online, Current Opinions in Biology, Current Opinions in Medicine,* and *Applied Physics Letters Online, The Online Journal of Current Clinical Trials, The Online Journal of Knowledge Synthesis in Nursing, and Electronic Letters Online.* All use the Guidon telecommunications and browsing software. *Current Opinions in Medicine* wraps 24 print journals into one electronic publication. Similarly, *Current Opinions in Biology* encompasses six biological print journals, and the NIH Library is considering a subscription to that journal.

In contrast to most journals, which publish a print version that is duplicated on-line or on CD-ROM, some OCLC journals have no print equivalent. After peer review, the editors send "marked-up" articles for on-line publication within 24 hours, greatly reducing the time lag compared with print publications. One totally electronic publication, *The Online Journal of Current Clinical Trials,* was launched in 1992 under the editorial control of the American Association for the Advancement of Science (AAAS). However, last fall, AAAS decided to sell the editorial control of the journal to Chapman & Hall publishers, and its future is not clear. The NIH Library subscribes to both the *Online Journal of Current Clinical Trials* and the *Online Journal of Knowledge Synthesis for Nursing.*

Many on-line browsers feature "hyperlinks" that allow users to move smoothly from a journal article to related references, figures, or databases by simply clicking on highlighted or underlined text. For example, *Current Clinical Trials* has references linked to MEDLINE citations, including abstracts. Hyperlinks also provide the ability to click on a "Letters to the Publisher" icon to comment on an article or request more information. A dubious, new feature made possible through hyperlinks

continued on page 21.

The Pathfinder

Here are some suggested "paths" for exploring the current state of on-line journals on the World Wide Web, commonly called the Web. Take care that addresses, also referred to as Uniform Resource Locators (URLs), are typed precisely as indicated, including proper case, into the "File," "Open URL" area of Mosaic or "File," "Open Location" of Netscape. If you do not have a Web browser, see your Local Area Network (LAN) administrator.

NIH Pointers to Online Journals
http://www.nih.gov/science/journals/
Path: One of the easiest routes is through the NIH Home Page on the World Wide Web. Just click on Scientific Resources, and then on Pointers to Online Journals under Library and Literature Resources. So far, there are hyperlinks to *Science, Journal of Biological Chemistry, Protein Science, Morbidity and Mortality Weekly Report,* and *Emerging Infectious Diseases.*

Weizmann Institute Posters
http://bioinfo.weizmann.ac.il:8888/26anon/posters/
Path: Choose one of the poster titles, then click on "Show all panels as one long page" to see all the graphs, photographs, and images just as you would expect to see on a poster. There is some beautiful immunohistochemistry and electron microscopy, as well as full-color graphs. You can also leave comments for the authors and read comments other people have left. This could be a prototype of a journal refereed by on-line readers, providing dialog between authors and readers (e.g., "I couldn't reproduce the experiment in fig. 1" and "Did you take care to keep pH and temperature well within the limits we indicated?").

National Library of Medicine
http://www.nlm.nih.gov
Path: Hypertext/multimedia exhibits to The Art of Medicine at the 21st Century. Although this is an exhibition rather than a journal, it shows how images are handled in hypertext journals. Click on small images to enlarge, edit, and print them.

Bioscience Resources at the WWW Virtual Library
http://golgi.harvard.edu/biopages.html
Path: Biosciences, Biology Internet Resources, BioSci & other Electronic Publications, Science Magazine. You will get this week's *Science* Table of Contents, Editorial, and This Week In *Science.*

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Path: Oak Ridge National Laboratory Review, Issues from 1992 to the present, Vol. 27, Nos. 1 & 2, "Mice and Men: Making the Most of Our Similarities." Yahoo is one of the greatest resources for locating material on the Internet. This article contains embedded graphics, photographs, photomicrographs, and hyperlinks to other information outside the article, as well as a video clip. Image resolution depends on your monitor resolution, and whether you can see the video depends on your Web-viewer setup.

—J.E.S.

O-GlcNAcylation and Phosphorylation Reciprocity On Nuclear and Cytoskeletal Proteins

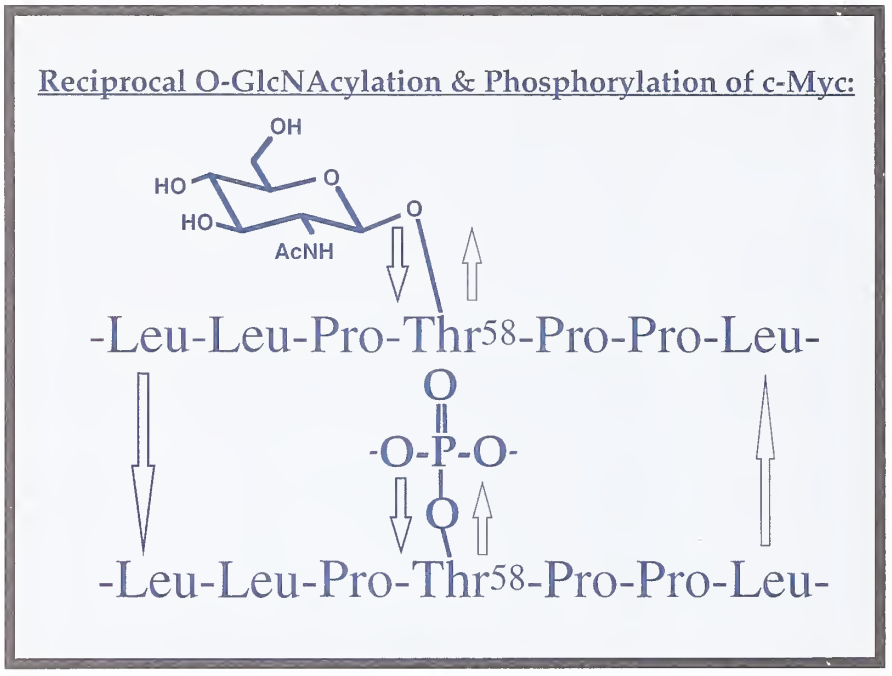
Abstract

About 11 years ago, we discovered that a very large number of nuclear and cytoplasmic proteins are modified by single *N*-acetylglucosamine (*O*-GlcNAc) residues that are *O*-glycosidically linked to serine and threonine moieties. Studies in several systems have shown that *O*-GlcNAc residues are both as abundant and as highly dynamic as phosphate groups. *O*-GlcNAcylation is also often reciprocal to phosphorylation and occurs at protein sites identical to those used by kinases that regulate cell growth (see figure). *O*-GlcNAc appears to be present in all eukaryotes, and has been postulated to play a key regulatory role in numerous cellular processes. Since these initial discoveries, our laboratory has been taking an eclectic approach to elucidate the functions of this ubiquitous form of intracellular protein glycosylation.

One part of this work examines transcription, in which *O*-GlcNAc appears to play a key role. RNA polymerase II (Pol II) and its transcriptional regulatory proteins are extensively modified by *O*-GlcNAc. Our data, together with those in the literature, suggest that the glycosylated, but not the phosphorylated, form of Pol II assembles in the initiation complex. Studies from several other labs further suggest that elongation of transcripts cannot take place until the *C*-terminal domain (CTD) of Pol II is extensively phosphorylated, which, according to our findings, would require its prior deglycosylation. Three recent results from our lab support a model of *O*-GlcNAc as a key player in transcription: 1) using synthetic *O*-GlcNAc-bearing CTD-derived glycopeptides as the substrate, we showed that *O*-GlcNAcase is present in transcriptionally active nuclear extracts, and its activity increases markedly with the addition of nucleotide triphosphates which also activate transcription; 2) using a highly specific adenovirus-2-major-late-promoter to drive transcription, we demonstrated that a highly specific inhibitor of *N*-acetylglucosaminidases also blocks Pol II-dependent transcription; and 3) we demonstrated that synthetic *O*-GlcNAc-bearing CTD glycopeptides but not the unmodified CTD peptides block transcription.

Another group of our studies examines nuclear proteins relevant to tumor growth. Using several methods, we showed that the oncoprotein c-myc, a helix-loop-helix, leucine-zipper phosphoprotein that heterodimerizes with Max and participates in the regulation of transcription in normal and neoplastic cells, bears *O*-GlcNAc residues in its *N*-terminal domain, a region involved in both transcription activation and malignant transformation. The major site of *O*-GlcNAcylation is Thr-58 (see figure), which is also the major phosphorylation site used by glycogen-synthetase-kinase-3 and is the major mutational "hotspot" in human lymphomas. Estrogen receptors, which are ligand-inducible transcription factors, are also modified by *O*-GlcNAc. An important site of glycosylation is in the PEST region (a sequence targeting the protein for degradation) of the carboxy-terminal F domain of the receptor. Data from our lab suggest that the nonglycosylated form of the receptor preferentially binds DNA. The human cytomegalovirus-tegument basic phosphoprotein, which appears to play a role in viral assembly, is glycosylated at Ser-921 and Ser-952. Importantly, we find that this protein, whether made by native virus or overexpressed in baculoviral-infected insect cells, is glycosylated at the same sites, validating the use of such overexpressed proteins in initial studies to localize *O*-GlcNAc sites on rare regulatory proteins. Recently, we have also shown that bovine brain casein kinase II alpha subunits contain *O*-GlcNAc. Studies are under way to evaluate the effects of glycosylation on kinase activity and subcellular trafficking of this regulatory protein.

The section of our work that focuses on cytoskeletal proteins centers on a protein called tau, which regulates microtubule assembly in normal brain cells and which we found to be extensively modified by *O*-GlcNAc. In the brains of patients with Alzheimer's disease, this protein becomes abnormally phosphorylated and as a result, polymerizes with itself to form the paired-helical filaments (PHF-tau) that make up the intracellular tangles that, along with extracellular plaques, typify the disease. Self-polymerized PHF-tau does not bind microtubules and does not function properly in their assembly. A major site of *O*-GlcNAc addition in normal tau is also a major abnormal phosphorylation site, accounting for 70% of the PHF-tau formation. These findings suggest the possibility that the defect in



by Gerald W. Hart, Ph.D., Teh-Ying Chou, Ph.D., Man-Shiow Jiang, Ph.D., Kenneth D. Greis, Ph.D., Robert N. Cole, Ph.D., Frank I. Comer, Chris S. Arnold, Tatsuji Matsuoka, Ph.D., Doris M. Snow, Bradley K. Hayes, Ph.D., Lisa K. Kreppel, and Betty J. Earles, Department of Biochemistry and Molecular Genetics, University of Alabama at Birmingham. Hart presented this at the Glycobiology Interest Group's annual "Glycoday" on May 30, 1995, in Annapolis, Md.

tau in Alzheimer's patients may not result from a defect in phosphorylation mechanisms, as is currently thought, but rather might result from a defect in *O*-GlcNAc regulation, with abnormal phosphorylation being a default process.

In other neuronal studies, we find that many neuron-specific proteins important to neurotransmitter release are both phosphorylated and contain *O*-GlcNAc. Using synaptosomal preparations, we are studying the role of *O*-GlcNAc in synaptic transmission and find that purified synaptosomes contain both the *O*-GlcNAc transferase and *O*-GlcNAcase. Synapsin I is a protein concentrated at nerve terminals that modulates neurotransmitter release by mediating the association of synaptic vesicles with the cytoskeleton in a phosphorylation-dependent manner, and we have mapped the *O*-GlcNAc residues on synapsin I to regions important for binding to synaptic vesicles or the cytoskeleton.

In another segment of our lab's work, we have constructed genes encoding a cytoplasmic form or a nuclear-targeted form of galactosyltransferase (GT, an enzyme that "caps" GlcNAc residues with galactose). When these genes are transiently transfected into Chinese hamster ovary (CHO) cells, the truncated GTs that they encode can only be detected within the first 12 hours, most likely because the cells die after that. In contrast, CHO cells transfected with the normal gene—encoding the full-length enzyme active in the Golgi lumen—survive for long periods. Available data suggest that cytoplasmic or nucleoplasmic expression of GT is a lethal event, perhaps due to *O*-GlcNAc-capping or to the binding of GT to *O*-GlcNAc proteins.

BEFORE *O*-GLCNAC WAS DISCOVERED, DOGMA HELD THAT CYTOPLASMIC AND NUCLEAR PROTEINS WERE NOT GLYCOSYLATED.

QUESTIONS

Q: *What was your starting point in this research, and how have your questions evolved?*

A: In 1983, Carmen-Rosa Torres, a graduate student in our laboratory, was using highly purified glycosyltransferases to probe the complex glycosylation of proteins in murine immune system cells. When she probed lymphocytes with bovine milk galactosyltransferase and UDP-[3H]galactose to measure GlcNAc-terminating glycans, she found, surprisingly, that nearly all of the label attached to *N*-acetylglucosamine monosaccharides that are *O*-glycosidically attached to Ser(Thr) residues—a linkage not previously known to exist. We have gradually progressed away from complex glycans on cell-surface receptors, and currently, virtually our entire laboratory is studying the function of *O*-GlcNAcylation.

Q: *Which findings have been most surprising to you or to other scientists?*

A: Virtually all *O*-GlcNAcylation occurs on nuclear and cytoplasmic proteins. Before *O*-GlcNAc was discovered, dogma held that cytoplasmic and nuclear proteins were not glycosylated. The most surprising finding is the very large number of important nuclear and cytoskeletal proteins that are *O*-GlcNAcylated.

Q: *What were the greatest stumbling blocks, and what new observations, techniques, reagents, or insights helped you get past them?*

A: The greatest stumbling blocks were the development of sensitive techniques for the detection and quantification of *O*-GlcNAc on low-abundance regulatory proteins. A further complication is that virtually all eukaryotic cells contain an abundance of hexosaminidases that rapidly remove *O*-GlcNAc whenever cells are damaged. The development of potent *O*-GlcNAcase inhibitors, improved site-mapping techniques by HPLC, gas-phase sequencing, mass spectrometry, and capillary electrophoresis have significantly improved our ability to study *O*-GlcNAcylation of regulatory proteins.

Q: *How can clinical scientists capitalize on this research?*

A: It is our belief that *O*-GlcNAcylation may turn out to be as fundamental and as important to cellular regulation as protein phosphorylation. The *O*-GlcNAcylation of oncogenes and tumor suppressors opens up unexpected avenues for cancer therapy. Inhibitors of *O*-GlcNAcases could potentially be valuable in the treatment of Alzheimer's disease. The hyper *O*-GlcNAcylation of transcription factors could play a role in abnormal regulation of insulin expression in certain types of diabetes. As we continue to gather more fundamental data, the reality and application of these speculations will become evident.

Q: *How are you following up on this work, and what questions would you ultimately like to answer?*

A: Everyone in our laboratory is focused on determining the functions of *O*-GlcNAcylation. Some questions we are most concerned with are, Is *O*-GlcNAc a regulatory modification, analogous to phosphorylation? Does it have a reciprocal function with respect to phosphorylation on most proteins? How is *O*-GlcNAcylation or de-*O*-GlcNAcylation regulated? What specific role(s) do the *O*-GlcNAcylation of RNA polymerase II and its transcription factors play in the regulation of cell-type-specific gene transcription? ■

Novel *N*-Linked Glycans in CHO Mutants Point to Role in Development

Abstract

To identify biological functions of mammalian carbohydrates, members of my lab have isolated a panel of Chinese Hamster Ovary (CHO) mutants with altered glycosylation of proteins and lipids and, consequently, a novel array of carbohydrates at the cell surface. Many mutant cell lines are phenotypically recessive, represent loss-of-function mutations, and display immature, or biosynthetic intermediate, carbohydrate structures on glycoconjugates. Other mutants are phenotypically dominant and represent gain-of-function glycosylation mutants. This means that the gain-of-function mutants express more complicated carbohydrates than do wild-type cells. The first examples of this that we discovered in CHO cells were the mutants LEC11 and LEC12 (see figure). Both of these cell lines express the Le^X trisaccharide determinant on cell-surface glycoconjugates, but only LEC11 cells express the sialylated version, known as SLe^X (see figure). The latter structure, unlike the Le^X trisaccharide, is an excellent ligand for the selectin group of cell-adhesion molecules, when it is presented on an appropriate cell-surface glycoprotein or glycolipid. The presence of the Le^X and SLe^X structures on the surface of LEC11 or of Le^X on LEC12 CHO cells is due to the *de novo* expression of two distinct α(1,3)fucosyltransferases that are developmentally regulated in mammals. We are now attempting to define the mutation-like event that activates transcription of these usually quiescent genes, allowing CHO cells to express the developmentally regulated carbohydrates. Additional mutants that express the Le^X determinant have been isolated, and each possesses an α(1,3)fucosyltransferase with distinctive properties, suggesting they are the products of different genes. Another gain-of-function mutant that we identified about 10 years ago is LEC10, which expresses the bisecting GlcNAc (see figure). The existence of carbohydrates with Le^X, Sle^X, or the bisGn residue was known before the CHO mutants were isolated. However, the most recent gain-of-function mutants to be characterized possess proposed structures that have never previously been described from any source. The novel modifications were discovered on pure carbohydrates unique to the LEC18 and LEC14 CHO dominant mutants (see figure), and both represent novel core structures of *N*-linked glycans, presumably reflecting the activation of quiescent genes encoding new GlcNAc-transferases. Our preliminary results are consistent with this. The properties of LEC14 and LEC18 CHO cells reveal a potentially large reservoir of developmentally regulated glycosylation genes that are awaiting discovery through gain-of-function CHO mutants.

Questions

Q: *What was your starting point in this research, and how have your questions evolved?*

A: The starting point for this work was the discovery in the early 1970s that toxic plant lectins are useful as selective agents for isolating cells with mutations in enzymes that glycosylate cell-surface macromolecules. The first CHO mutant to be characterized biochemically lacked a transferase (GlcNAc-TI), which is required for the synthesis of complex and hybrid *N*-glycans. Surprisingly, the absence of GlcNAc-TI and the major truncation of cell-surface carbohydrates that resulted did not have any effect on cell growth or viability in culture. Our lab and another group have now shown, however, that mice lacking GlcNAc-TI are severely affected and die at midgestation. This evidence supports the long-standing suspicion that specific cell-surface carbohydrates, though not important for basic somatic-cell functioning in culture, are absolutely required for mammalian development. Exploring the developmental role of these molecules led us to pursue gain-of-function glycosylation mutants. Our discovery that CHO cells express the developmentally regulated carbohydrates Le^X and SLe^X, as revealed by the LEC11 and LEC12 mutants, was tremendously exciting, and the nature of these mutants made us realize that biologically functional new molecules could be discovered by identifying the biochemical basis of these dominant mutations.

By characterizing gain-of-function glycosylation mutants, we could discover completely new molecules that would be very hard—even impossible—to discover by any other approach.

Q: *Which findings have been most surprising to you or to other scientists?*

A: The most surprising and exciting realization was that by characterizing gain-of-function glycosylation mutants, we could discover completely new molecules that would be very hard—even impossible—to discover by any other approach. The proposed new carbohydrate structures synthesized by LEC14 and LEC18 cells have not been found in secreted or membrane glycoproteins from any source to date. In vivo, *N*-glycans with such modifications may be synthesized only in one cell type during a brief stage development and may thus be virtually impossible to detect via current technologies. Also, the enzymes that synthesize these glycans may be very difficult to assay in a complex background.

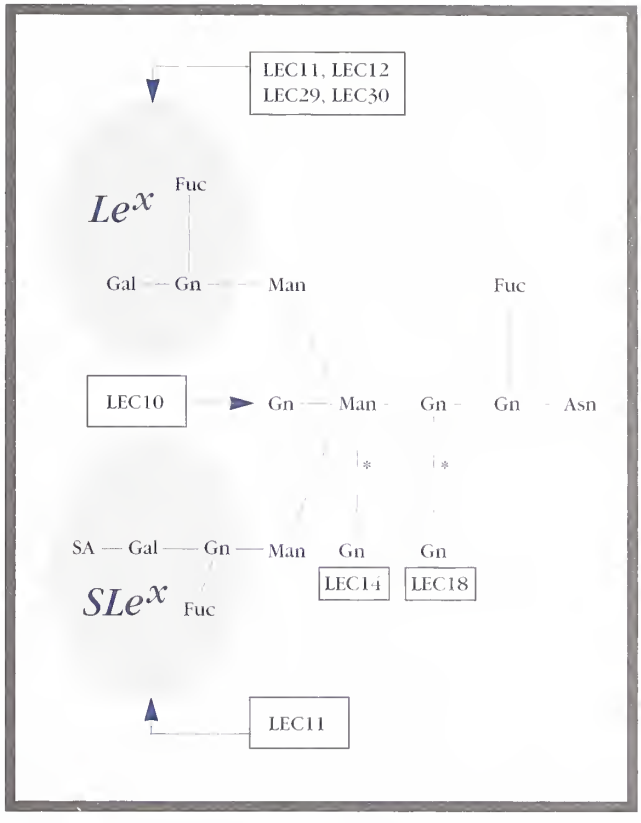
The second surprising finding was the enormous effect that the addition of one sugar residue has on the lectin-binding properties of cell-surface carbohydrates. In the case of LEC10 cells, the presence of the bisecting GlcNAc residue causes cells to become 20 times more resistant to the toxin ricin and about 10 times more hypersensitive to another toxic lectin, the erythroagglutinin called E-PHA. Both of these lectins bind to galactose (Gal) residues, and the Gal residues they bind to are still present in LEC10 cells. In LEC10 cells, however, the bisecting GlcNAc changes the conformation of the carbohydrate to make the Gal residues markedly less accessible to ricin and more accessible to E-PHA. This paradigm holds true for the single-sugar changes found in the other dominant CHO glycosylation mutants: LEC11, LEC12, LEC29, and LEC30, which have varying and characteristic degrees of increased resistance to wheat germ agglutinin (WGA) and increased sensitivity to ricin, and LEC14 and LEC18, which are resistant to the pea lectin (PSA) and *Lens culinaris* agglutinin (LCA). Thus, the regulated expression of a single glycosyltransferase gene can dramatically alter lectin-recognition specificities at the cell surface.

Q: *What were the greatest stumbling blocks, and what new observations, techniques, reagents, or insights helped you get past them?*

A: The most difficult aspect of carbohydrate work is proving that

by Pamela Stanley, Ph.D., Department of Cell Biology, Albert Einstein College of Medicine in New York. Stanley presented this report at the Glycobiology Interest Group's annual "Glycoday" on May 30, 1995, in Annapolis, Md.

you have a precise structure. We were fortunate that ^{1}H-NMR spectroscopy of complex carbohydrates was developed in the mid 1970s. For assigned structures present in the NMR database, it was then possible to determine a structure for an unknown from the spectrum of approximately 200 µg of chemically pure oligosaccharide or glycopeptide. In that manner, we were able to deduce the new carbohydrate structures characteristic of LEC10, LEC11, and LEC12 cells. The major difficulty was working out how to obtain enough of the relevant carbohydrate in extremely pure form. Although the SLe^X determinant was not in the NMR literature, we were able to assign new resonances by obtaining spectra of the carbohydrates before and after removal of the terminal sialic acid. Unfortunately, this approach yielded no structures comparable to the glycopeptides unique to LEC14 and LEC18 in the Sugabase database which lists known structures of carbohydrates. Our lifesaver in this case was the use of electro-spray mass spectrometry (ES/MS) and mass spectrometry, mass spectrometry (MS/MS) of the major molecular ions to generate fragment ions that could only have arisen from the specific structures we propose. The key here was the realization that if the sample was carefully prepared and the experiment performed under certain controlled conditions, the resulting ES/MS spectra were interpretable and reproducible. Composition and linkage analyses by GC/MS were also critical for arriving at our postulated structures.



Glycosylation Changes in N-linked Carbohydrates of Chinese Hamster Ovary Mutants. *Previously characterized gain-of-function glycosylation mutants (LEC11, LEC12, LEC29, and LEC30) add a fucose residue to generate the trisaccharide determinants (Le^X) and , in the case of LEC11, a sialylated trisaccharide determinant (SLe^X) on structures similar to the biantennary N-linked carbohydrate shown above. LEC10 adds an N-acetylglucosamine (Gn) residue to generate the bisecting GlcNAc. These additions reflect the activation of quiescent glycosyltransferase genes. The newly characterized mutants, LEC14 and LEC18, each have a novel N-linked core region with the proposed additions of a Gn residue at the sites indicated(*). A combination of compositional analysis, linkage analysis, ^{1}H-NMR spectroscopy, and mass spectrometry support these proposed structures. The conclusions summarized in the figure stem from published work from the Stanley lab for the α(1,3)fucosyltransferase mutants by C. Campbell, D. Howard and B. Potvin and for LEC10 by C. Campbell. The proposals for LEC14 and LEC18 stem from unpublished recent experiments of T. Shantha Raju.*

Q: *How can clinical scientists capitalize on this research?*

A: Right now, no biological roles for the proposed new carbohydrates of LEC14 or LEC18 are known, and, therefore, further work will be required before clinically relevant uses become apparent. However, the carbohydrates characterized by LEC10 (bisGn), LEC11 (Le^X and SLe^X), and LEC12 (Le^X) CHO cells are all expressed at high levels in some tumors. It is known that the presence of even a single sugar residue, such as bisGn, has a profound effect on the conformation of the structure to which it is added. Thus, we think that the changed properties of a cancer cell that expresses these structures may have functional consequences on tumor progression or, more likely, on metastasis. It has been shown by others that certain mouse tumor cells do not metastasize if they do not add the β1,6GlcNAc branch to complex *N*-glycans.

Many of the cell-surface carbohydrates we study are also antigenic and thus can be used to aid in cancer diagnosis, although this can be complicated by the blood-group genotype of an individual. To date, no carbohydrate antigen that is completely diagnostic has been described, but expression of SLe^X is characteristic of certain cancers.

Q: *How are you following up on this work, and what questions would you ultimately like to answer?*

A: We would now like to know the role that the unique cell-surface carbohydrates we have discovered play in development. In those cases characterized to date, the novel carbohydrates expressed by gain-of-function CHO mutants are the product of developmentally regulated transferases. We are following up on this knowledge by using CHO cells to expression-clone these and related transferase genes as well as others that regulate the expression of glycosyltransferase genes. Once we clone these genes, we will characterize their expression pattern in the mouse and construct mutants with a null mutation in the transferase gene. This approach would appear to be the fastest way to uncover biological functions of these carbohydrates. Because the mutations generated will only change particular structures by eliminating one sugar residue, they should not be embryonically lethal and may yield interesting phenotypes. Even if the null mutation does not produce an altered phenotype, however, the mice may be useful in cancer studies because their cells cannot add the sugars that normally generate tumor antigens. Such animals could be tested for response to carcinogens, and their metastatic patterns could be compared with those of other strains of mice. These are complex, multifaceted questions, and we seek collaborators with established carcinogenic or metastatic protocols that could yield insights into cancer biology using our mouse glycosyltransferase mutants. ■

Interinstitute Interest Group Directory

Apoptosis Interest Group (AIG)
Meeting time: Once a month on Monday, 4:00 p.m.
Meeting place: Building 30, Conference Room 117
Contact: Dennis Mangan, NIDR
Phone: 594-2421
E-mail: mangand@de45.nidr.nih.gov

Bioinstrumentation Interest Group
Meeting time: First Tuesday, 2:00 p.m.
Meeting place: Building 13, Room 3W54
Contact: Steve Leighton, NCRR
Phone: 435-1948
E-mail: leighton@helix.nih.gov

Cell and Molecular Neuroscience Interest Group
Umbrella group: Neurobiology
Meeting time and place: Varies
Contact: Ron McKay, NINDS
Phone: 496-6574
E-mail: mckay@codon.nih.gov

Cell Biology Interest Group
Meeting time: Varies, meetings restricted to NIH scientists
Meeting place: Building 18T, Room 101
Contact: Juan Bonifacino, NICHD
Phone: 496-6368
E-mail: juan@helix.nih.gov
ListServ: subscribe to CELBIO-L

Cell Cycle Interest Group
Umbrella group: Cell Biology
Meeting time: First Tuesday, 12:30 p.m.
Meeting place: Building 37, Room 6B23
Contact: Patrick O'Connor, NCI/DCT
Phone: 496-3269
E-mail: oconnorp@dc37a.nci.nih.gov

Chaos
Meeting time: Once a month on Thursday, 1:00 p.m.
Meeting place: Building 10, Rose Room
Contact: Julio Licinio, NIMH
Phone: 496-6885
E-mail: licinio@codon.nih.gov
Listserv: subscribe to BCMPLXTY

Clinical Research
Meeting time and place: Varies
Contact: Jack Klippel, NIAMS
Phone: 496-3374
E-mail: klippelj@arb.niams.nih.gov

Developmental Biology Interest Group
Umbrella group: Cell Biology
Meeting time and place: Varies
(see NIH Calendar of Events)
Contact 1: Igor Dawid, NICHD
Phone: 496-4448
E-mail: idawid@nih.gov
Contact 2: Joram Piatigorsky, NEI
Phone: 496-9467
E-mail: joram@helix.nih.gov

DNA Repair Group
Meeting time: Third Tuesday, 12:30 p.m.
Meeting place: Building 37, Room 6B25
Contact: Kenneth Kraemer, NCI/LMC
Phone: 496-9033
E-mail: khk@helix.nih.gov

Drosophila Interest Group
Umbrella group: Developmental Biology
Meeting time: Third Tuesday, 1:15–2:30 p.m.
Meeting place: Building 6B, Room 4B429
Contact: Susan Haynes, NICHD
Phone: 496-7879
E-mail: sh4i@nih.gov

Drug Discovery
Meeting time: Once a month on Thursday, 3:00–4:30 p.m.
Meeting place: Building 37, Room 6B25
Contact: John Weinstein, NCI/DCT
Phone: 496-9571
E-mail: weinstein@dtpax2.ncifcrf.gov

Epidemiology Interest Group
Meeting time: Third Wednesday, 3:30–5:00 p.m.
Meeting place: Building 31C, 6th floor conference rooms; or EPN conference rooms
Contact 1: Martina Vogel, OD
Phone: 496-6614
E-mail: MartinaV@nih.gov
Contact 2: Dick Havlik, NIA
Phone: 496-1178
E-mail: HavlikR@gw.nia.nih.gov

Fluorescence Interest Group
Meeting time: Fridays, 4:00 p.m.
Meeting place: Building 10, Room 5D21
Contact: Jay Knutson, NHLBI
Phone: 496-2557
E-mail: jaysan@helix.nih.gov

Gene Therapy Interest Group
Meeting time: Second and fourth Tuesdays, 12:00–1:00 p.m.
Meeting place: Lipsett Auditorium
Contact: R. Michael Blaese, NCHGR
Phone: 496-5396
E-mail: mblaese@nchgr.nih.gov

Genetics Interest Group
Meeting time: Last Tuesday, 4:00–5:30 p.m.
Meeting place: Building 49, Conference Room A and B
Contact: Robert Nussbaum, NCHGR
Phone: 402-2146
E-mail: rlnuss@nchgr.nih.gov
Listserver: subscribe to MAJORDOMO@NCHGR.NIH.GOV
post to GIG@NCHGR.NIH.GOV

Glia Club
Meeting time: Bimonthly on second Wednesday, 4:00–5:30 p.m.
Meeting place: Building 36, Room 1B
Contact 1: Vittorio Gallo, NICHD
Phone: 402-4776
E-mail: vgallo@helix.nih.gov
Contact 2: Joan Schwartz, NINDS
Phone: 496-4049
E-mail: jps@helix.nih.gov

Glycobiology Interest Group
Meeting time: Once a month on Thursday, 3:00–5:00 p.m.
Meeting place: Building 30, Room 117
Contact: Diana Blithe, NICHD
Phone: 496-6437
E-mail: blithed@cc1.nichd.nih.gov
Listserver: subscribe to GLYCO-L@LIST.NIH.GOV

Hard Tissue Disorders Interest Group
Umbrella group: Clinical Research
Meeting time: First Wednesday, 12:00 p.m.
Meeting place: Varies
Contact: Pamela Robey, NIDR
Phone: 496-4563
E-mail: probey@yoda.nidr.nih.gov

Image Processing
Meeting time and place: Varies
Contact: Bonnie Douglas, DCRT
Phone: 496-2847
E-mail: douglasb@magic.dcrt.nih.gov

Immunology
Meeting time: Wednesdays, 4:15 p.m.
(see NIH Calendar of Events)
Meeting place: Building 10, Lipsett Auditorium
Contact: Ron Schwartz, NIAID
Phone: 496-1257
E-mail: ronald_schwartz@nih.gov
Listserver: subscribe to IMMUNI-L@LIST.NIH.GOV

Integrative Neuroscience Interest Group
Umbrella group: Neurobiology
Meeting time: Alternate Thursdays, 4:00 p.m.
Meeting Place: Building 49, Conference Room
Contact: Robert Wurtz, NEI
Phone: 496-9375
E-mail: bob@lsr.nei.nih.gov
Listserv: subscribe to JLS@LSR.NEI.NIH.GOV

Lambda Lunch (Bacterial and Phage Genetics)
Meeting time: Thursdays, 11:00 a.m.–12:30 p.m.
Meeting place: Building 36, Room 1B13
Contact: Susan Gottesman, NCI/DCBDC
Phone: 496-3524
E-mail: susang@helix.nih.gov
Anonymous FTP site: FTP.CU.NIH.GOV directory "LAMBDA_LUNCH"

Mass Spectrometry
Umbrella group: Structural Biology
Meeting time: First and third Thursdays, 10:30 a.m.
Meeting place: Building 10, Room 7C101
Contact: Lewis Pannell, NIDDK
Phone: 402-2196
E-mail: lkp@sx102a.niddk.nih.gov

Matrix Metalloproteinase Interest Group
Meeting time: Scheduled Wednesdays, 11:00 a.m.
Meeting place: Building 45
Contact: W. Stetler-Stevenson, NCI/DCBDC
Phone: 496-2687
E-mail: stetler1@helix.nih.gov

Molecular Biology/Biochemistry Interest Group
Meeting time and place: Varies
Contact: Gary Felsenfeld, NIDDK
Phone: 496-4173
E-mail: gxf@helix.nih.gov

Motility Interest Group
Meeting time: First Monday (except July and August)
Meeting place: Building 10, Bunim Room
Contact: Leepo Yu, NIAMS
Phone: 496-5415
E-mail: lcyu@helix.nih.gov

Mouse Club
Umbrella group: Developmental Biology
Meeting time: Once a month on Tuesday, 4:00–5:30 p.m.
Meeting place: Building 31, Room 2A-52
Contact: Heiner Westphal, NICHD
Phone: 402-0545
E-mail: hw@helix.nih.gov

Nerve Growth Factor (NGF) Club
Meeting time: First Tuesday (see NIH Calendar of Events)
Meeting place: Building 49
Contact: Gordon Guroff, NICHD
Phone: 496-4751
E-mail: gordong@helix.nih.gov

Nerve-Muscle Interest Group
Meeting time: Every other Wednesday, 8:30–9:30 a.m.
Meeting place: Building 36, Room 1B07
Contact: Matt Daniels, NHLBI
Phone: 496-2898
E-mail: mdaniels@codon.nih.gov

Neurobiology
Meeting time: Not available
Meeting place: Building 49, Conference Room
Contact: Ron McKay, NINDS
Phone: 496-6574
E-mail: mckay@codon.nih.gov
Listserv: JLS@LSR.NEI.NIH.GOV

Neuroendocrine Immunology Research Interface Study Group
Meeting time: Once a month on Thursday, 4:00 p.m.
Meeting place: Building 49, Conference Room A
Contact: Esther Sternberg, NIMH
Phone: 402-2773
E-mail: ems@codon.nih.gov

Nucleic Acid Biochemistry Interest Group
Umbrella group: Molecular Biology
Meeting time: Third Friday
Meeting place: Building 5, Room 127
Contact: Janet Yancey-Wrona, NIDDK
Phone: 496-2038
E-mail: janety@blg10.niddk.nih.gov

Pigment Cell Research Interest Group
Meeting time: Third Monday, 3:00–4:30 p.m.
Meeting place: Building 37, Room 6B23
Contact: Vincent Hearing, NCI/DCBDC
Phone: 496-1564
E-mail: hearingv@dc37a.nci.nih.gov

Postdoctoral Structural Biology Interest Group
Meeting time: Once a month on Tuesdays, 3:00–5:00 p.m.
Meeting place: Building 31, no room given
Contact: Teresa Strzelecka, NIDDK
Phone: 496-2815
E-mail: strzel@speck.niddk.nih.gov

Protein Folding
Meeting time: Thursdays, 4:00 p.m.
Meeting place: Building 12A, Room 3026
Contact: B.K. Lee, NCI/DCBDC
Phone: 496-6580
E-mail: bkl@helix.nih.gov

Protein Trafficking Interest Group
Umbrella group: Cell Biology
Meeting time: Second Tuesday, 3:30–5:00 p.m.
Meeting place: Building 10, Room 9S-235 (Bunim Room)
Contact: Harris Bernstein, NIDDK
Phone: 402-4770
E-mail: harris_bernstein@nih.gov

RNA Club
Umbrella group: Molecular Biology
Meeting time: First Tuesday, 4:00–6:00 p.m.
Meeting place: Building 41, Room C509
Contact 1: Carl Baker, NCI/DCE
Phone: 496-2078
E-mail: ccb@helix.nih.gov
Contact 2: Susan Haynes, NICHD
Phone: 496-7879
E-mail: sh4i@nih.gov

Signal Transduction Interest Group
Meeting time: Not available
Meeting place: Not available
Contact 1: Richard Kahn, NCI/DCT
Phone: 402-2063
E-mail: rakahn@helix.nih.gov
Contact 2: John Northup, NIMH
Phone: 496-9167
E-mail: JKNGTP@helix
Contact 3: Jim Battey, NCI/DCT
Phone:496-2966
E-mail: jbat@helix

Structural Biology Interest Group
Meeting time: Announced to members by e-mail and regular mail
Meeting place: Not available
Contact: C. Hyde, NIAMS
Phone: 402-4574
E-mail: cch@disars.niams.nih.gov

Transcription Factors
Meeting time: First Thursday (except July-Sept.), 10:30 a.m.
Meeting place: Building 8, Room 122
Contact: Stoney Simons, NIDDK
Phone: 496-6796
E-mail: steroids@helix.nih.gov
Listserv: subscribe to TFACTORS

Washington Area Yeast Club
Umbrella group: Molecular Biology
Meeting time: Second Wednesday, 5:15–7:15 p.m.
Meeting place: Building 6B, Room 4A-05
Contact 1: Reed Wickner, NIDDK
Phone: 496-3452
E-mail: wickner@helix.nih.gov
Contact 2: Alan Hinnebusch, NICHD
Phone: 496-4480
E-mail: ah8j@nih.gov

Xenopus/Zebrafish Interest Group
Umbrella group: Developmental Biology
Meeting time: Last Friday (except summer), 4:00 p.m.
Meeting place: Building 6B, Room 429
Contact: Tom Sargent, NICHD
Phone: 496-0369
E-mail: tsargent@nih.gov

X-ray Crystallography
Umbrella group: Structural Biology
Meeting time: Announced to members by e-mail
Meeting place: Building 5, Room 231
Contact: James Hurley, NIDDK
Phone: 402-4703
E-mail: hurley@tove.niddk.nih.gov

This directory was compiled by Katie O'Brien, and will eventually be made available on Gopher and the World Wide Web. To make additions or changes, contact The NIH Catalyst *(fax: 402-4303; e-mail: catalyst@od1em1.od.nih.gov)* ■

Recently Tenured

Elise Kohn *came to NCI in 1986 as a fellow in the Medicine Branch's Clinical Oncology Program and has been in the Laboratory of Pathology since 1987. She received her M.D. in 1983 from the University of Michigan in Ann Arbor, where she did her internship and residency in internal medicine.*

Bill Branson

My laboratory is exploring the effects of intracellular calcium homeostasis on cancer growth and dissemination. This interest directs our current working hypotheses that the modulation of calcium and calcium-driven signaling events alters cellular activity and gene expression. This work may point to new directions for cancer therapy.

Our current line of research began when we observed that changes in cellular signaling, including blocking an increase in intracellular calcium, could abrogate the usual migration of tumor cells in response to growth factors and cytokines. Through a screening program consisting of motility assays and calcium-influx experiments, we identified a carboxyamido-triazole compound, which we call CAI, that inhibits calcium influx and calcium-influx–dependent signaling events. CAI has proven to be a useful tool in our investigation of the modulation of calcium concentrations and calcium-linked mechanisms both in vitro and in vivo.

Our studies have demonstrated that calcium homeostasis plays an important role in the process of angiogenesis, which is a form of physiologic invasion of new blood vessels into tissue that occurs during wound healing, pregnancy, and tumor growth. CAI disrupts the normal function of the cytoskeleton of endothelial cells, reduces expression of proteolytic enzymes, and decreases neovascular potential in vitro—all of which are key steps in angiogenesis, suggesting that CAI may be a useful agent in the treatment of cancer. We have also observed a marked anti-angiogenic effect of CAI in vivo, in chicken chorioallantoic membrane (CAM) assays. We are now investigating the immediate signaling effects of altered calcium balance in the endothelial cells as part of the hypothesis that calcium homeostasis is important in physiologic, as well as malignant, invasion.

We are also studying the regulation of gene expression as a function of calcium modulation, or signaling balance. We developed a human melanoma cell subline that is resistant to constant exposure to CAI and observed a phenotypic difference between resistant cells and nonresistant cells. Unexpectedly, the resistant cells displayed reduced tumorigenic potential as measured by reduced density-independent growth and reduced tumorigenesis in xenografts of human tumors in nude mice. This led to a molecular investigation comparing resistant and nonresistant cells that led to the discovery of several genes that are currently being cloned.

Early studies found that CAI treatment reversibly inhibited the proliferation and invasive capacity of more than 25 types of tumor cells. The oral administration of CAI to human xenograft-bearing mice resulted in a reduction in total tumor burden and metastatic dissemination without marked toxicity to normal tissues. Our in vitro and animal observations have led to phase I clinical trials of CAI in solid-tumor patients with advanced and refractory cancer. Since the trial was initiated in 1992, more than 60 patients have received CAI. So far, CAI has been well tolerated and has resulted in disease stabilization, as characterized by a reduction in both the size and number of tumors and by improved symptoms. Both the CAI study and a trial of CAI in combination with Taxol are ongoing and open to patient entry.

Louis Staudt *received his M.D. and Ph.D. degrees from the University of Pennsylvania School of Medicine in Philadelphia in 1982. In 1984, he joined David Baltimore's laboratory at the Whitehead Institute in Cambridge, Mass., as a postdoc. Since 1988, Staudt has been a senior staff fellow in the Metabolism Branch, NCI.*

Lorna Hearley

The major effort of my laboratory is currently focused on understanding the molecular pathogenesis of human leukemias and lymphomas caused by nuclear oncogenes. This effort often coincides with the lab's secondary interest—the molecular regulation of B-lymphocyte development. Our early work defined a novel lymphoid-restricted transcription factor, Oct-2, which was a founding member of the POU domain class of homeobox transcription factors. Now we are studying two lymphoid malignancies: diffuse large-cell lymphoma caused by the *BCL-6* oncogene and t(4;11) acute lymphoblastic leukemia caused by a fusion oncoprotein involving the *MLL* and *AF-4* genes.

Diffuse large-cell lymphoma, which is a malignancy of mature B lymphocytes, accounts for 40% of all cases of non-Hodgkin's lymphoma. In 40% of diffuse large cell lymphomas, the *BCL-6* gene is rearranged by translocations that leave the *BCL-6* coding region intact but that substitute its promoter region with regulatory regions from other genes. The *BCL-6* gene encodes a zinc-finger transcription factor that shares a 121-residue amino-terminal homology domain, the POZ domain, with a subset of other zinc-finger proteins.

In studies involving normal lymphocytes, we have shown that *BCL-6* mRNA is highly expressed in mature B cells but not in terminally differentiated, antibody-producing plasma cells, and that activation of lymphocytes downregulates *BCL-6* mRNA. The BCL-6 protein is phosphorylated and is expressed highly in the germinal center, the site where memory B cells and plasma cells are generated. These findings have led to our working hypothesis that *BCL-6* expression must be downregulated for terminal B cell differentiation to occur and that such regulation is absent in diffuse large cell lymphoma. BCL-6 presumably transforms B lymphocytes by regulating the transcription of key target genes. We have identified high-affinity binding sites through which BCL-6 functions as a potent transcriptional repressor, and we have shown that its POZ domain is necessary and sufficient for repression. Currently, we are trying to identify the mechanism underlying this transcriptional repression and the natural targets of BCL-6 repression.

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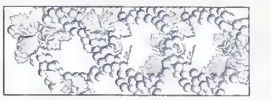
Research Grapevine



For this new Catalyst *feature, we have asked NIH scientists to give us the latest news from recent meetings. We welcome your comments and contributions.*

American Academy of Neurology

The American Academy of Neurology met May 6–13 in Seattle. Every year, several of the abstracts submitted before the meeting are selected as "Works in Progress for Expedited Presentation." There were three this year. Howard Weiner and colleagues from the Brigham and Women's Hospital in Boston reported on correlations of magnetic resonance imaging (MRI) with immune and clinical measures in multiple sclerosis (MS) patients followed closely over one year. They found that measures from the MRI scans such as lesion volume and number of lesions correlated well with clinical scores. There were also correlations with some immune measures, the best being with increased numbers of interleukin-2 receptor-bearing T cells. Other presentations supported the growing consensus that MRI is an excellent way to monitor MS patients.

Meanwhile, Stella Papa and colleagues from NINDS showed that an *N*-methyl-D-aspartate (NMDA) receptor antagonist could suppress levodopa-induced dyskinesias in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Investigators of the basic pharmacology of Parkinson's disease have become interested in the possible role of glutamatergic innervation of the basal ganglia. In this study, a competitive NMDA antagonist was given to Parkinsonian monkeys that had dyskinesias produced by overtreatment with levodopa. The NMDA antagonist relieved the dyskinesias with minimal negative influence on motor function. This suggests that it may be possible to treat clinical dyskinesias while maintaining levodopa's beneficial effects on Parkinsonian symptoms. The third abstract was from NCI's Bertrand Liang, who reported on gene amplification in human gliomas. He identified a novel cDNA with a high degree of amplification in gliomas of diverse grades—indicating that this gene may be important in the pathogenesis of gliomas.

As for clinical trials, there were many reports of drug therapies for various neurological diseases, but nonpharmacological methods were also abundant. Enthusiasm continued for surgical approaches to the treatment of Parkinson's disease, particularly pallidotomy, which was reviewed in a special session featuring Mahlon DeLong of Emory University in Atlanta, Anthony Lang of the University of Toronto, and Enrico Fazzini of New York University School of Medicine. Deep-brain stimulation of the ventral intermediate (VIM) nucleus of the thalamus was reported to be useful for severe tremors. In addition, Alvaro Pascual-Leone, formerly of NINDS and now of the University of Valencia in Spain, presented data indicating that repetitive stimulation of the motor cortex with noninvasive transcranial magnetic stimulation (TMS) may have value in treating the slowness of patients with Parkinson's disease. In other work involving TMS, Pascual-Leone's team and another group led by Mark George of NIMH both showed that repetitive TMS of the left frontal lobe had some effect in improving symptoms in patients with depression.

— Mark Hallett, NINDS

American Thoracic Society

The American Thoracic Society/American Lung Association International Conference, was held May 20–24 in Seattle. On the clinical side, there was considerable interest in barotrauma from mechanical ventilation. The recurring theme was that alveolar overdistension may cause or worsen diffuse lung injury, impair gas exchange, and increase the work of breathing. The take-home message was that total ventilation can be minimized by keeping both respiratory rate and tidal volume low and by keeping inspiratory flow rates high, even at the expense of high peak inspiratory pressure. Meeting organizers added a mini-symposium on another hot clinical area—volume-reduction surgery for treatment of chronic obstructive pulmonary disease (COPD). The procedure, dubbed the "pulmonary CABG [coronary artery bypass graft] of the '90s," improves ventilation through ablation of severely emphysematous areas of the lung. Unresolved issues include patient-selection criteria and optimal surgical technique.

The genetics of pulmonary disease, particularly asthma, also received increased attention. High immunoglobulin E (IgE) levels correlate with bronchial hyperresponsiveness and allergic asthma. Several genes on chromosome 5q, including some that encode interleukins, may be involved in the regulation of IgE and the development or progression of airway inflammation and, intriguingly, with bronchial hyperresponsiveness. Other studies indicate that airway reactivity and the susceptibility to different types of asthma may be correlated with the ß2-adrenergic receptor isoform. ß2-adrenergic-receptors containing glycine-16 were found more frequently in patients with nocturnal asthma than in those with nonnocturnal asthma; airway reactivity was less in patients with the glutamate-27 isoform. As might be predicted from the clinical findings, lab studies found that the glycine-16 isoform was associated with increased agonist-mediated receptor downregulation and the glutamate-27 isoform with less. Asthma may also be an important component in hereditary lung diseases. In studies of a1-antitrypsin deficiency, an inherited disease associated with an increased risk of emphysema and/or cirrhosis, the NHLBI-sponsored registry reported that among patients with a1-antitrypsin deficiency and emphysema, those with reactive airway disease showed a more rapid decline in lung function.

— Norton Elson, Shan C. Chu, Mark L. Brantly, N. Gerard McElvaney, N. Tony Eissa, and Joel Moss, NHLBI

American Academy of Allergy, Asthma, and Immunology

Asthma was also a major focus of the 1995 International Meeting of the American Academy of Allergy, Asthma and Immunology, held in New York City Feb. 24–28. Several epidemiological studies examined the recent rise in asthma deaths, particularly in urban areas. Evalyn Grant of Rush-Presbyterian-St. Luke's Medical Center presented evidence that asthma is underdiagnosed in the inner city of Chicago. Similarly, Ned Rupp of the Medical College of Georgia in Augusta documented the underdiagnosis of allergy in Latino inner city Philadelphia.

Progress was also reported in identifying genes that may be responsible for the atopic state. Pamela Amelung of the University of Maryland School of Medicine in Baltimore reported that a major gene regulating IgE maps to 5q. For several years, it has been known that there is an IgE-specific and IgE-dependent factor in serum and secretions that induces histamine release from basophils sensitized with IgE from certain donors. Susan McDonald of Johns Hopkins Medical Institutions in Baltimore reported the cloning of this molecule, referred to as histamine-releasing factor (HRF). Studies are now under way to characterize HRF's biologic activity and its mechanisms of action. Apoptosis of inflammatory cells including eosinophils may provide one way of controlling inflammation. Tetsuya Adachi of Kihara Hospital in Tokyo reported that corticosteroids and macrolides induce apoptosis in eosinophils stimulated with interleukin-5.

Taken as a whole, the developments discussed at the AAAAI meeting demonstrate how rapidly basic biology advances are being applied to the understanding of the pathogenesis of inflammatory diseases and to the treatment of allergic disorders.

— Dean Metcalfe, NIAID

Robert Gallo
continued from page 1.

Q: How have you changed as a researcher since you started at NIH in 1965?

Gallo: Back then, I think I saw NIH, myself, and other people with more idealism. ... Maybe that's just the normal process of maturation, or maybe that is a change in biomedical research. ... When I came, there was no biotechnology industry. ... Now, I think biotechnology and the commercial side is a good thing because it catalyzes getting new therapies to the clinic. But on the other hand, like chemistry and physics before us, the age of innocence is lost for biomedical science. ... Another factor is that there were many more young medical doctors interested in basic research and coming to NIH with their eyes wide open—and their mouths wide open with awe. I don't see that as much now.

I think the way I've changed is that my first five years were really a time of desire for intensive training in the tools of laboratory research. ... In the next decade or so, I applied what I learned in those early years to basic types of research. As for where I stand now ... my change is actually a full circle. Coming from an early clinical background, I now want to go back to seeing clinical applications of what I do in the lab—much more so than I've been able to do these past five or six years at NIH. ...

I was also much more in a hurry [as a young scientist]. Certainly, I had more spirit of competitiveness in those early years—more insecurity in a way, more desire to know everything. And then came the realization that you can't always know and do everything. I guess that's part of maturation.

Q: And how has the NIH intramural research program changed?

Gallo: There's certainly a higher percentage of people from abroad and significantly fewer young people from the United States. ... In the mid-'60s, early '70s, it was almost essential for an M.D. going into academic medicine to spend some time at NIH. That is no longer true. This also might be paralleled by a slight lessening of the number of the young M.D.s interested in academic medicine.

A second change is that there is perhaps a little less focus or priority on some of the clinical programs. ... Although there was obviously great basic research when I came to NIH, I think the visibility and focus was more on the health aspects of research. Is it better to emphasize the science, or is it better to emphasize the health? ... I submit we clearly need both sides. ... Ever since I've been here, there's always been a mixture of the two, but I think there's a tendency away from the "h" part of NIH, maybe more toward the National Institutes of Basic Biomedical Science. ... Personally, I want to be where I can have a more direct clinical outlet for our laboratory research.

> I COULD NOT HAVE DONE OUTSIDE WHAT I DID HERE, I'M SURE OF THAT.

Q: What advice do you have for young scientists just starting out at NIH today?

Gallo: I still think this is the best biomedical research institution in the world—the greatest combination of people with diverse talents, backgrounds, and technological expertise. ... I could not have done outside what I did here, I'm sure of that. ... Careerwise, I personally owe everything to NIH. So one of the things I would say to the younger people is that there is still plenty of opportunity at NIH. Although it helped build its own competition, it still is the place where you can have the most diversity of experience—have the greatest contact with the greatest number and variety of clinical and laboratory scientists of any place in the world. Take advantage of that. There is no place that gives you as many visiting scientists, as many people from abroad, as many people stopping through. Make as many contacts as you can.

Another thing to remember is that if you intend to be an experimental scientist ... begin to apply technology as soon as possible because you learn as you are applying. That's the way one really learns—plunge into the experiment, make some mistakes, and learn as you go along. ... And don't be afraid to seek contacts outside of your own laboratory even if your laboratory chief is a little possessive. ...

Also, at 35, I tended to report what I saw objectively. At 45, when we had a string of successes after some difficult years, those successes led to perhaps some overconfidence. ... So, for example, I hypothesized in '82 that AIDS would be caused by a retrovirus that targeted T cells. ... I certainly, absolutely assumed and predicted it would be a variant of HTLV [human T cell leukemia virus]. ... The reality of it, of course, was that Mother Nature plays interesting games. It would be a retrovirus, it would be a retrovirus that targets T cells, but it would not be a variant or recombinant of HTLV. It was a whole new family of retroviruses—my god! It took me too long to acknowledge that the data was going in that direction. ... That's a lesson. It's very hard to retain the freshness of the beginner with [the] knowledge and confidence of the more mature scientist. So, to translate this into concrete advice: have your hypotheses, but don't try too hard to put Mother Nature in her place.

Q: Why did you decide at this point in your career to enter the academic research setting?

Gallo: There are a number of reasons, but the most important one by far was the desire to bring the 30 years of lab research more into the clinic, which I can definitely do better outside [NIH] than inside, coupled with the fact of the timing—my 30th year ... when I'm eligible for retirement.

The reason I can do more clinical research outside [NIH] is because ... I'll be in administrative control over such decisions and I will have my own clinical program. At NIH, I chose to be head of a lab or branch that is nonclinical, but in the past five years, I sort of wished ... that I had a clinical outlet and could more prioritize what I wanted to move from the lab to the clinic. Instead, my

position at NIH is dependent upon the interests of members of the large pharmaceutical industry with whom I might have CRADAs ... or on higher [NIH] administrators' perception of the value of this or that ... .

Since the early '80s, I have had a vague dream that if I left NIH, I would like an Institute of Human Virology. ... I want to leave a legacy. ... NIH laboratories tend to be reshuffled and very often, there will be nothing left a year or two after you're gone. I'd like to see something specific left behind when I retire, if I ever totally retire.

Q: Why did you opt for academia rather than private industry?

Gallo: Because I can do everything I want in an academic setting and it's a less traumatic change, less of a psychological change. ... No, it doesn't pay the same amount of money. But I'll be fine, and that's what I want to do. I want the interaction with the academic circles. I want to be able to infiltrate, if you will, the pathology department, the medicine department, the cancer center at the University of Maryland. I want to be able to have closer collaborations with people at [Johns] Hopkins. I want to maintain close collaborations with people at NIH. I think if you are an officer in a company, these things are more difficult.

A 1966 photo of the NIH Clinical Associates finds an eager, young physician named Robert Gallo standing in the back row.

Q: Whom are you taking along from NIH? What criteria will you use for assembling your team at the University of Maryland, and what will its primary research goals be?

Gallo: I'll take the best people I can take from anywhere to build the best possible little piece of NIH that I can build. ... It also depends on what I can afford and who will follow. I can't give you specific numbers, but I can tell you that when the information came out that I was leaving, a very large number of people at NIH did write to me, including some lab chiefs. My goal would not be to make this new institute 100% ex-NIH people. I'm looking for some kind of balance in the science that is there. Some clinical, some epidemiology, some very good basic researchers. Everybody is not going to be a virtuoso ... because we are going to be practically oriented to solve a problem. ... And [the Institute of Human Virology is] not going to get big fast; it's going to grow in steps. ... If this institute is as successful as we strive for, in three to five years, it will be around 300 people. ... Our primary scientific goals will be [to study] chronic viral diseases clinically and in the laboratory and to develop better therapies for them and to have some role in preventive vaccine development, as well. The focus will be on AIDS, but ... there will be studies of some herpes viruses—some of which are relevant to AIDS, some of which aren't; the leukemia viruses, HTLV-1 and -2; and in time, we are hoping, some hepatitis viruses and some papilloma viruses.

Q: What do you consider to be your biggest achievement at NIH?

Gallo: The thing I'm proudest of is that we were the most referenced lab in all of science for the decade of the 1980s. ... As for specific sets of experiments, when outsiders introduce me, they often say I opened the interleukin field with interleukin-2 and [the] culturing of T cells. But that was not a planned experiment or an objective. Consequently, I would say it was breaking through to demonstrate that human retroviruses existed and ... that they could cause disease. ... In a practical sense, we've had things that have gone into the clinic, including interleukin 2 and the blood test for HTLV-1, which is now required [for blood donors] ... .

But obviously, the best feeling I have is to know that [the] development of the HIV antibody blood test was not only key to contributing to our knowledge and evidence and conclusion that HIV is the cause of AIDS, but that it saved a lot of lives. I'm proud that it moved fast, and I'm proud of the government role in that.

Q: What "hot" research leads are you currently pursuing, and will you be able to follow up on them in Baltimore?

Gallo: We will certainly be maintaining a heavy emphasis on Kaposi's sarcoma and HIV-associated Kaposi's sarcoma. We will be beginning an effort in HIV-associated B-cell lymphoma and continue exploring the mechanisms by which HTLV-1 causes leukemia and neurological disease. We will continue using antisense constructs to target HIV and also continue and expand gene-therapy work on HIV. We will continue and possibly expand vaccine efforts against HIV. We will continue, but not expand, work with the herpes viruses we discovered in the mid-'80s. ... We are getting increasing evidence [that] the human herpes virus 6 may play a catalytic role in HIV progression as well as being involved in harming bone marrow biology. We will look at biologic factors that regulate HIV replication and continue, but probably reduce, studies of cellular factors that HIV needs for replication. With FDA approval, we hope to initiate new clinical trials in some of these areas soon. ...

Q: Based on your experience with the HIV "discovery" controversy, how do you regard the handling of scientific-integrity issues by the government?

Gallo: I don't know where it's heading now, but obviously, it's massively improving because it's been reassessed. Before, it was nothing short of a farce. ... Nobody would realize or believe, so I don't really want to get into, the madness that was going on in that period of time. ... It was so bizarre, one could make a wonderful Broadway comedy out of it—or a tragedy.

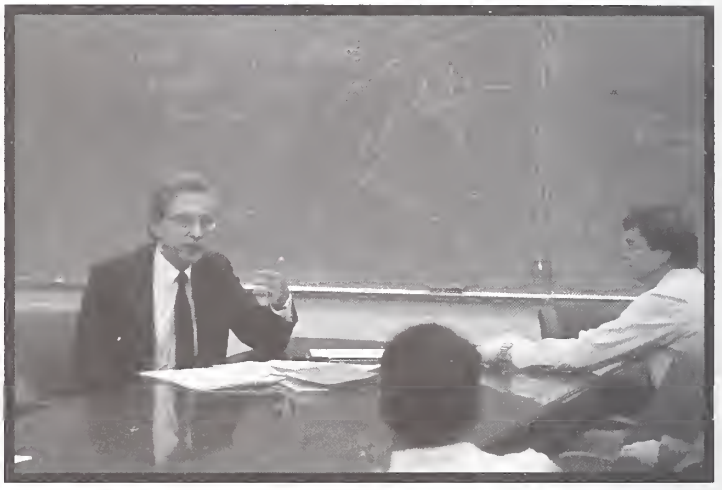
Q: Do you consider yourself fortunate that your scientific career has survived such an ordeal?

Gallo: Most people say I am fortunate. But what did I do? ... Yeah, in one sense, I feel lucky, but on reflection, obviously, this was not the case. I lost six years, and my lab was blocked for six years, and we were harassed day and night for six years. I don't know what gods I should be thanking for that. And I don't feel lucky that much of the scientific community didn't engage itself adequately. ... How could you not feel that way when nothing was done wrong? ... It's a horror. You can't fight it. You can't control it. You certainly can't do anything about a writer [John Crewdson of the *Chicago Tribune*] who follows you day and night for seven years. You feel like Jodie Foster with [John] Hinckley. ... I think that a little more vigor was needed [within the NIH community] in evaluating what was going on and maybe a few people who truly understand what was happening and would be willing to stand up for me and my colleagues. ...

Q: What do you think NIH leaders and researchers can do to improve investigations of alleged scientific misconduct?

Gallo: It would help if the leaders as well as the scientists were more vocal about abuses by the "investigators." Organize something more nationwide where scientists could come together who are fair-minded and who understand the field they are talking about. Avoid self-righteous know-it-alls. Never allow people from totally foreign fields to evaluate what they do not understand. ... Speak out when there is abuse of congressional power. Congress should be nowhere near this kind of stuff. ... And when [you] see Congress trying to control NIH through a planted person, react as strongly as possible and be willing to give up your job so this never happens again. It's not likely to happen any time soon again, but how did it ever happen in the United States in the first place?

NIH should have a strong director, which it has now, and the NIH director can have a committee to try to judge accusations rapidly. Someday somebody will cheat—that's inevitable. Minor data manipulation will sporadically occur, and sometimes will never be discovered. This hardly affects the flow of science and is not worth millions of dollars in effort and the blatant denigration and slander of innocent people. This has been the case. It is like putting the FBI, CIA, and KGB in charge of finding out who might have taken some candy from a grocery store and, in the end, finding out that no one did. ■



Robert Gallo, left, at lab meeting.

NIH Fellows Symposium

Seven scientists at the cutting edge of molecular biology—from DNA mismatch repair to cytokine signal transduction—will share their insights with the NIH community this fall, thanks to the efforts of the NIH Fellows Committee. The First NIH Postdoctoral and Clinical Fellows Symposium will be held at Natcher Auditorium from 8:00 a.m. to 5:15 p.m. on Oct. 12. The speakers are Ari Helenius of Yale University in New Haven, Conn., "The endoplasmic reticulum as a protein-folding compartment"; Kevin Campbell of the University of Iowa College of Medicine in Des Moines, "Molecular basis of muscular dystrophy: disruption of the cytoskeleton-extracellular matrix linkage"; Tom Maniatis of Harvard University in Cambridge, Mass., "Regulating the activities of the Rel family of transcriptional activator proteins"; John O'Shea of NIAMS, "Cytokine signal transduction: JAKs, STATs, and clinical implications"; Melanie Spriggs of Immunex Corp. of Seattle, "Viral genes that modulate host immune function"; Joseph Nevins of Duke University in Durham, N.C., "Alteration of cell-growth control by DNA tumor virus oncoproteins"; and Paul Modrich, also of Duke, "Mismatch repair and genetic stability in human cells." For more information on the symposium, which is being supported with funds from the institutes, centers, and divisions, contact Courtney Jones at the Office of Education (phone: 496-3887). ■

Intramural Collaboration
continued from page 1.

NINDS's Michael Rogawski says most of his collaborations have been with labs in other institutes, drawing on their expertise in medicinal chemistry, analytical chemistry, mathematical modeling, behavioral pharmacology, and neurochemistry.

"No one lab can do everything and, in times of constricting budgets, sharing of resources is a necessity," Rogawski says. "In the heyday of NIH, when resources were virtually limitless, the argument could be made that duplication of effort was an effective, if inefficient, path toward research excellence. We can't afford this anymore."

Elise Kohn, who was recently tenured in NCI's Laboratory of Pathology, agrees, noting that many of the interinstitute collaborations in which she has been involved were initiated because an outside colleague possessed a technique, a model, or expertise she did not have or would take a long time to acquire. "In most cases, it has expanded my horizons and knowledge and, in some cases, I think, also that of my collaborator."


Lorna Heartley

Hynda Kleinman

The scientific achievements of NIDDK's David Davies over the past 40 years stand as an impressive testament to the benefits of cultivating intramural collaborations. "Very few of my collaborations have been outside of NIH. It's been such a rich resource," says Davies, whose relatively rare expertise as an protein crystallographer at NIH has become increasingly in demand as intramural molecular biologists scramble to learn more about the proteins encoded by the genes they have isolated. When he was a young scientist, Davies says, he usually had to be the one to make the first move to seek out collaborators. Now, as a senior researcher with a well-established reputation, he finds that most collaborations arise from other people approaching him for help in characterizing their proteins of interest.

Davies' list of successful intramural collaborations includes several projects involving other NIDDK researchers: the discovery of the guanine, or G, tetraplex that is characteristic of telomeric DNA, with Marie Lipsett and Martin Gellert; the determination of the structure of human immunodeficiency virus (HIV) integrase, with Robert Craigie and Kiyoshi Mizuuchi; and work on the high-resolution structure of the bifunctional enzyme complex tryptophan synthase, with Edith Miles. However, over the decades, Davies has also ventured beyond his home institute to explore the structures of antibody Fab fragments with Michael Potter of NCI, antibody-antigen complexes with Sandra Smith-Gill of NCI, the ribonuclease H domain of the HIV reverse transcriptase with Paul Wingfield and Stephen Stahl of the Protein Expression Lab, and domain III of the *Pseudomonas aeruginosa* exotoxin with Ira Pastan of NCI.


Lorna Heartley

David Lim

As the Davies-Pastan work illustrates, personal interactions can sometimes serve as a springboard for professional associations rather than vice versa. For years before they launched their collaborative investigation, which shed light on the *Pseudomonas* toxin's mechanism of action by locating the nicotinamide adenine dinucleotide (NAD) binding site, Davies and Pastan had been engaged in quite a different sort of collaboration: playing early bird tennis at the Linden Hill Club. Their informal banter while waiting for courts led to more serious discussions and, eventually, Pastan's suggestion that they launch a collaborative research project. "An enormous amount of NIH business was conducted at those courts between 7 a.m. and 8 a.m.," says Davies, lamenting the club's closure in the late 1980s to make way for a condominium complex.

The nuts and bolts of setting up interinstitute collaborations may be simpler than many scientists think. One editorial board member, who asked not to be named, remarks that, lately, collaborations within the researcher's own institute "seem to have required upfront negotiations (requested by the other parties) more than my outside collaborations do, but that is probably just personalities."

As for the downside of in-house collaborations, the editorial advisers said the kinds of problems they encounter in working with NIH colleagues are not substantively different from those posed by outside collaborations, where authorship, commitment, and speed-of-work issues, for example, also come up. So, what barriers are standing in the way of NIH maximizing its collaborative potential?

"Knowing how to find people with the needed knowledge, or resources, or assays," says NINDS's Joan Schwartz, who is collaborating within her institute on a transgenic mouse line and is currently working with researchers at NEI on ongoing research related to the effects of a novel neurotrophic factor, called PEDF, that affects three different types of neural cells.

Kleinman agrees. "The biggest obstacle to collaboration is the problem of not knowing who is doing what. We use the annual bibliography when we want a cell type or antibody … to see first, if anyone on campus has the desired reagent or information. The problem is that there are not enough copies of the bibliography, and it is somewhat outdated by the time it reaches our labs."

Some of the lack of awareness about collaborative opportunities may lie in the very nature of NIH. "There is less contact among the 'faculty' at NIH than at universities, medical schools, and private research institutes. Faculty members in these environments interact on departmental and university-wide committees, in the organization and teaching of courses, and in the development of initiatives to seek funding," Rogawski says. "We often feel fortunate as NIH scientists in not being burdened with these distractions. The downside is that we don't get to know our colleagues."

Attitude can be another roadblock. "It often appears that despite the fabulous opportunities within NIH as a whole, and individual institutes separately, many investigators see themselves in competition with their colleagues here, not as potential collaborators," an editorial board

member wrote in an anonymous comment. "During visits to the outside, I see core facilities and collaborations of necessity due to personnel or funding restrictions, and sometimes more of an atmosphere of teamwork. Some of that may be necessary due to funding restrictions and the extremely tight grant situation. Some may be caused by the educational atmosphere, with graduate and undergraduate students requiring mentors and role models. We have a remarkably open environment, yet I am occasionally disappointed by what I see."

Lorna Heartley

Michael Rogawski

Young researchers, Davies says, must also learn to accept the risks of collaboration—that even within NIH, some joint research projects will not pan out the way the researcher had originally hoped. "Even though throughout my career I have had many successful collaborations, not all my collaborations have been successful," he says.

Lim notes that shifts in the focus of the NIH intramural program may also erect barriers to collaboration. "As more pressure is put on the intramural scientists to 'publish or perish,' collaboration may be viewed as a sidetrack and as unfocused. If this environment continues in the intramural program, some important aspects of the tradition of collaboration among NIH scientists may suffer."

Although one scientist observes that "it's hard to change people," *The NIH Catalyst* editorial advisers remain optimistic, offering the following suggestions on how to create an intramural atmosphere that is more conducive to collaboration—and on how NIH researchers can better exploit the opportunities that already exist.

Computer Resources—Researchers should be encouraged to take advantage of existing electronic databases on NIH scientists and their research projects, such as the Computer Retrieval of Information on Scientific Projects (CRISP) system [see box]. It may also be helpful to set up a "research matchmaker" electronic bulletin board for intramural scientists in search of collaborators who have particular interests, skills, or reagents.

Lectures and Seminars—Scientists should regard the time before and after lectures and seminars as opportunities for exchanging ideas with colleagues, as well as for discussing the speaker's presentation. Editorial board members are divided about whether the larger, more generalized seminars, such as the NIH Director's Lectures and Wednesday Afternoon Lectures, or the smaller branch/lab seminars are the best places to establish such contacts. Special events, such as the NIH Research Festival, also promote collaborative exchanges. "At research day—usually at the poster sessions—we have made a lot of connections for collaborations," Kleinman says.

Interinstitute Interest Groups—These relatively informal groups, which meet occasionally to discuss topics related to a specific interest, such as the cell cycle or hard-tissue disorders, would seem by their very design to encourage interinstitute collaborations. However, Kleinman says she personally has not found the interest groups useful, observing that some of them may be too big to allow for detailed exchanges. Davies cautions that "one needs to avoid becoming embedded in one's group," and Rogwaski adds that although the Research Festival and interest groups are steps in the right direction, he thinks they are not enough.

Social Interactions—Pausing to munch a cookie after a lecture, checking out a different cafeteria, or joining an NIH-affiliated recreational group are activities that seem to have little to do with the business of science. But, as Davies notes, some of the most innovative collaborations arise when two researchers from disparate fields meet in a social setting and discover that, much to their surprise, their scientific ideas or techniques actually complement each other. "If you don't make such efforts, it's not very easy to meet people from other institutes," says Davies, who, in addition to his many scientific activities, is a member of the NIH Sailing Club.

Administrative Leadership—The NIH administration should institute "faculty" meetings where researchers could become more familiar with the interests and concerns of their colleagues, according to Rogawski. In addition, Rogawski suggests that senior research administrators use their "broad view" to identify potential interplays between disparate research areas and then bring together scientists in those areas to promote cross-fertilization of ideas. NIH scientists with good collaborative skills, especially when it comes to working with their intramural colleagues, should be recognized. Board members say efforts to encourage collaboration are crucial to NIH's intramural productivity. As Lim says, "We should maintain this wonderful tradition that makes this place a hotbed of cutting-edge science and a training ground for young researchers." ■

CRISP and More

Many intramural scientists just think of the Public Health Services' Computer Retrieval of Information on Scientific Projects (CRISP) system as the place where they are obliged to file annual descriptions of their research. In fact, scientists should be able to get as much out of CRISP as they put in and can readily use the biomedical database as a tool for identifying promising scientific contacts and collaborators inside and outside of NIH.

To access CRISP through your desktop computer, use Gopher or a World Wide Web browser, such as Mosaic or Netscape, to go to the NIH home page. Then, enter the Grants section, click on CRISP, and follow the instructions to do a search by name, institution, or research topic. The database, which is updated weekly, includes NIH-, CDC-, SAMSA-, and FDA-funded grants, contracts, and cooperative agreements, as well as intramural projects at these institutions.

In addition to CRISP, the Grants section contains links to other computer databases that may help facilitate scientific collaboration. The "Searching for Biologists" area, a pilot project coordinated by Welchlab at Johns Hopkins University in Baltimore, has listings of e-mail addresses for researchers in a wide variety of biomedical disciplines, including yeast and crystallography. The database also allows you to search for biologists by name, location, and research interests and can connect you to the phone books of research institutions around the world. ■

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is advertising. Whenever a brand name or product is cited in a scientific paper, a click to an advertising message is possible. Despite assurances that "it will be completely low-key and be completely unobtrusive," one has doubts.

An important step forward in on-line scientific publishing occurred in May when the *Journal of Biological Chemistry* became available on the Web. With an URL of "http://www-jbc .stanford.edu/jbc/", the searchable, on-line version of *JBC* will be free for at least the next six months. After the trial period, an electronic subscription and/or a pay-per-view plan will probably be put into effect. Nevertheless, the appearance of this important journal in a form that anyone with a Web browser can access is a significant breakthrough that will likely stimulate similar online moves by other journals, especially those that are already publishing CD-ROM versions.

The *Journal of the National Cancer Institute*, published by NCI, has an excellent prototype on the Web. To see it, go to "http://wwwicic. nci.nih.gov" and look under NCI On-Line Publications, August 17, 1994. Another government entity, the Centers for Disease Control, has launched a new, completely electronic journal, *Emerging Infectious Diseases*, on the Web. Both the new journal and the CDC stalwart, *Morbidity and Mortality Weekly Reports (MMWR)*, are available at "http://www.cdc.gov/publications. htm". To view *MMWR*, you need Adobe Acrobat software, which can be obtained free from this Web site. Acrobat is a "portable document" software that allows documents created in a variety of programs to be shared via a "reader" without accessing the program used to create the document. The NIH Library is also using the Acrobat portable-document format for its newsletter on the Web, which can be accessed through the library's home page at "http://libwww.ncrr.nih.gov/home.exe?www". Acrobat can also be downloaded from the library's Web site from within your browser.

So, with all this movement along the information superhighway, how close are we to entering the promised land of paperless scientific information? I believe

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A Work in Progress, The Digital Library

by Suzanne Grefsheim, NIH Library

As part of its challenge to provide intramural scientists with cutting-edge information whenever and wherever needed, the NIH Library is exploring the rapidly expanding universe of electronic journals, reference books, and other digital resources.

After electronic journals are identified—no mean feat in today's fast-paced world of cybercommunications—they are evaluated by the Library's Electronic Resources Committee using selection criteria that include what topics are covered, how current the information in the journals is, whether tables and figures are included, and how the network-licensing terms mesh with NIH's user demands and cost constraints. If a journal meets initial selection criteria, the committee reviews the journal's software interface to determine whether it supports features such as title and index browsing, sophisticated searches, printing, and file saving. Another important consideration is whether the electronic journal provides clear instructions and/or on-line help so that the journal can be used without a printed manual.

So far, only four of 10 electronic journals evaluated by the review committee have met these basic requirements. The committee has proceeded to the next step with those four: user testing. Such testing may include trial installation in the library's reading room, trials with selected users outside the library, and surveys of people who use print equivalents. One electronic journal currently undergoing user testing is *Immunology Today Online*, which is available in the reading room through a free trial subscription through 1995.

Until this year, an electronic title that had run the testing gantlet successfully would have been ensured a place in NIH's electronic resources collection. That is no longer certain. As is the case with print subscriptions, the library now must cancel or cut back on some other electronic resource if it wants to add an electronic journal. How this works can be illustrated by a recent example.

This year, several library users suggested that the library obtain a site license for the Colorado Alliance of Research Libraries (CARL) UnCover Reveal—a table of contents service that allows a researcher to create a personal profile of the journals he or she wants to track. As each issue of the selected journals is published, the table of contents is automatically sent to the researcher's e-mail box. For almost a year, the service had been available free over the Internet. However, in March, CARL imposed a $20 annual fee for individual subscribers. The several hundred NIH staff who used the service via the Internet wanted it to continue, arguing that significant time, paperwork, and money would be saved if the library bought a single site license rather than requiring each person to subscribe individually. Although library staff agreed, there were no discretionary funds available to pay for the site license. In addition, the library already had a table of contents service—ISI's Current Contents—on its network server and DCRT offers a version of Current Contents and another table of contents service, Reference Update, on the NIH Gopher server.

The Electronic Resources Committee compared features—including cost per use—of all three electronic contents services available to NIH staff and also asked a user who is familiar with CARL UnCover Reveal to see whether resources available through the Gopher server could satisfy his needs. On the basis of these analyses, the library decided to drop its subscription to Current Contents when it comes up for renewal in October and immediately obtain a site license for Carl UnCover Reveal. Cancellation of the Current Contents subscriptions, which consumed a large portion of the library's electronic resources budget, should enable the library to buy other electronic products next year.

On the journey toward its ultimate goal of a scientist-friendly digital library, NIH will encounter many forks in the road. Through advisory groups, user testing, surveys, and other means, the NIH Library is seeking researchers' guidance on which directions to head. To voice questions about the selection and evaluation process for either print or electronic resources, or to discuss other issues related to the library's provision of electronic information, contact NIH Library Chief Suzanne Grefsheim (phone: 496-2447; e-mail: grefshes@nih.gov) or a member of the Library Advisory Committee. Lists of Library Advisory Committee members and electronic journal selection criteria are available upon request. ■

Defusing Terrorism: Bomb Precautions for Scientists

Since the late 1970s, academics and corporate leaders have been the prime targets of an elusive serial bomber whom the FBI has dubbed the "Unabomber." Recently, in a development with potentially serious implications for the NIH scientific community, the Unabomber—whose explosive packages have killed three people and injured 23—has begun to direct his terrorist actions at researchers in the fields of computer science and genetics.

Two years ago, Charles Epstein, a geneticist at the University of California at San Francisco, and David Gelernter, a computer scientist at Yale University in New Haven, Conn., were seriously injured when they opened bombs mailed by the Unabomber. This year, on April 20, the same day the bomber sent a package bomb that killed a California timber industry lobbyist, threatening letters were mailed to two Nobel laureates—Phillip Sharp, a biology professor at the Massachusetts Institute of Technology in Cambridge, Mass., and Richard Roberts, research director at New England Biolabs in Beverly, Mass. Sharp and Roberts shared the 1993 Nobel Prize in medicine for their discovey that genes can be spread over several, separated DNA segments. In a letter sent to *The New York Times* at the same time, the Unabomber wrote, "We would not want anyone to think that we have any desire to hurt professors who study archaeology, history, literature, or harmless stuff like that. The people we are out to get are the scientists and engineers, especially in critical fields like computers and genetics. ..."

The Unabomber's threats, coupled with the tragic April 19 bombing of the Oklahoma City federal building, prompted NIH's Division of Security Operations to sponsor two seminars on June 6 to discuss the proper handling of suspected letter or package bombs and bomb threats. Both seminars were conducted by Maryland's Deputy Fire Marshal Warren Gott, who is an expert bomb technician. Gott says that NIH scientists need to take more precautions than many other types of workers, not only because many scientists here are involved in the type of research targeted by the Unabomber, but because of the wide variety of packages and letters they receive from colleagues and suppliers every day. Researchers and lab staff should be alert to these possible signs that a letter or package may contain a bomb, says Gott: uneven or lopsided appearance, excessive or uneven weight, protruding wires, no return address, excessive tape, greasy black marks, odd smells, and unusual stiffness.

Suspicious packages or letters should not be opened, Gott warns. Instead, isolate the package or letter and evacuate everyone from that area. Then, notify the police immediately. At the Bethesda campus, this is done by dialing 115 or 9-911. According to the NIH police, it is not uncommon for scientists to report suspected package and letter bombs. Fortunately, to date, no bombs have been found on the NIH campus. ■

—Lorna Heartley

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that electronic journals are not likely to be widely read until a large number are published in this manner and standard browsing software is adopted. The World Wide Web currently appears to have the edge as the most likely publication route because of its standardization and the availability of several excellent browsers. ■

Additional Reading

R. Dykhuis. "The promise of electronic publishing: OCLC's program." *Computers in Libraries* **14**, 20–22 (1994).

F. Hoke. "New journals on CD-ROM help scientists to build personal libraries." *The Scientist*, Sept. 19, 1994, pp. 17–18.

R. Pool. "Turning an info-glut into a library." *Science* **266**, 20–22 (1994).

RECENTLY TENURED

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Our second major project is aimed at understanding the molecular pathogenesis of t(4;11) pro-B-cell acute lymphoblastic leukemia in which the *AF-4* gene is fused to the *MLL* gene. This translocation is found in 60% of acute lymphoblastic leukemia cases in children under 12 months old. The *MLL* gene, which is a homologue of the *Drosophila melanogaster* regulatory protein, trithorax, is translocated to several different chromosomal loci in a variety of acute leukemias. Each translocation generates an in-frame fusion protein between the amino terminus of MLL and the carboxy terminus of the fusion partner. Our interest in this leukemia stems from our cloning of a lymphoid-restricted homologue of the *AF-4* gene, termed *LAF-4*. Neither *LAF-4* nor *AF-4* show significant homology to previously cloned transcription factors. We have shown that LAF-4 is a nuclear protein and have found that both LAF-4 and AF-4 have potent transcriptional activation domains. Thus, LAF-4 and AF-4 are the founding members of a new family of nuclear transactivator proteins. Intriguingly, the AF-4 activation domain is retained in the MLL-AF-4 fusion oncoprotein, suggesting that this domain may contribute to the oncoprotein's transforming properties. ■

People With Disabilities Are Not Forgotten

by Carlton Coleman, OEO, OD

After the publication of an article in *The NIH Catalyst* about NIH's new Affirmative Action Plan ["Insights from OEO's New Leader," January–February 1995 issue], several employees raised concerns that the latest affirmative action planning process does not include information about people with disabilities. The Office of Employment Opportunity (OEO) pilot project was specifically designed to establish a new approach to address affirmative action for minorities and women based on the actual availability of these groups in various occupations in the civilian labor force. This approach relies on baseline availability data—data that neither the Equal Employment Opportunity Commission nor the U.S. Census Bureau collects on people with disabilities. Such data are essential to make the comparisons necessary for goal setting.

For example, there are no reports or records of baseline data on the number of individuals with disabilities who are working biological scientists. Although OEO could "guesstimate" a number, it would be without a rational basis. Without baseline data from a legitimate source, such as the Census Bureau, OEO cannot develop or support specific hiring goals for improving the underutilization of biological scientists with disabilities. For this reason, people with disabilities were not included in the pilot project. However, NIH does already have a separate Affirmative Action Plan for Individuals With Disabilities. Topics addressed in that Affirmative Action Plan include recruitment, reasonable accommodations, facility accessibility, and training and awareness programs.

Lorna Heartley

Craig Bash, left, a neuroradiologist in OD's Laboratory of Diagnostic Radiology Research, discusses magnetic resonance images of multiple-sclerosis patients with Tim Laughrey, a student at the Uniformed Services University of the Health Sciences who is working at NIH over the summer.

Achieving a diverse work force that is reflective of all groups, including people with disabilities, is a paramount goal of NIH and a major component of our "Framework for Change," which is OEO Director Naomi Churchill's five-year strategy for NIH. For more information on the Affirmative Action Plan for Individuals With Disabilities, call Carlton Coleman, manager of OEO's Disability Employment Program, at 496-2906. ■

Research Festival Reminder

Need a break from the daily grind? Round up the rest of the lab and head for the 1995 NIH Research Festival, Sept. 18–22, at the Natcher Building. This year's event will feature two major symposia, four poster sessions, and 28 workshops. Of particular note is the Sept. 19 symposium, "Regulation of Cellular Functions by Protein Phosphorylation and Dephosphorylation," which will include talks by two invited speakers, Tony Pawson of the University of Toronto and Philip Cohen of the University of Dundee in Scotland. If that's not enough action, there will also be a scientific equipment show sponsored by the Technical Sales Association in Parking Lot 10-D between the Clinical Center and Building 37. ■

Catalytic Reactions

In this issue, we are asking for your reactions in four areas: collaboration, authorship, the Central Tenure Committee, and ethnic diversity. **Send your responses on these topics or comments on other intramural research concerns to us via e-mail: catalyst@od1em1.od.nih.gov; fax: 402-4303; or mail: Building 1, Room 334.**

In Future Issues. . .

- Postdoc Pressures Fact or Fiction?
- Inside the Central Tenure Committee
- Changes at NCI
- Flow Cytometry: More Than A Sorted Affair

1) What has been your experience with intramural collaborations? What suggestions do you have for enhancing the collaborative atmosphere within NIH?

2) Do you think the intramural program's guidelines for authorship and ownership are realistic? In what ways could the handling of such issues be improved?

3) Has the 1-year-old Central Tenure Committee improved the way tenure is granted at NIH? Why or why not?

4) We are planning a group of articles on ethnic diversity at NIH. What issues should be addressed in such articles? What suggestions do you have for helping foreign scientists adapt to U.S. scientific culture and for helping U.S. scientists gain a better understanding of their foreign colleagues?

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