FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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CHUTES AND LADDERS: NIH SCIENTISTS DISCUSS THE ART AND STRATEGY OF BIOMEDICAL PUBLISHING

by Celia Hooper

Anyone who has been in biomedical research for more than five minutes is acutely aware of this fact of life: It is not just *how much* you publish, but also *where* you publish that counts. And in the last decade or so, another measure of professional status has assumed increased importance — *how much do other scientists cite your papers?*

These facts of life were brought home to NIH last spring when the Institute for Scientific Information, which maintains a huge database for measuring citation rates, added its two cents to debates about the quality of NIH's intramural research program. In the March issue of its newsletter, *Science Watch,* ISI maintained that "Research papers by NIH scientists published over the last five years are failing to carry quite the same clout as those published during the early-to-mid-1980s." The unsigned article, entitled "Intramural Research at NIH: Cracks in the Crown Jewel," was based on ISI's analysis of citation data for 92,961 NIH papers published from 1981 to 1993. Graphs of the citation rates for papers from individual institutes sometimes showed inexplicable peaks and troughs; but the graph of citations per paper for NIH as a whole, relative to the biomedical baseline (expressed as percent above the average citation rate) was remarkably flat—migrating vaguely between 85% and 75% above average.

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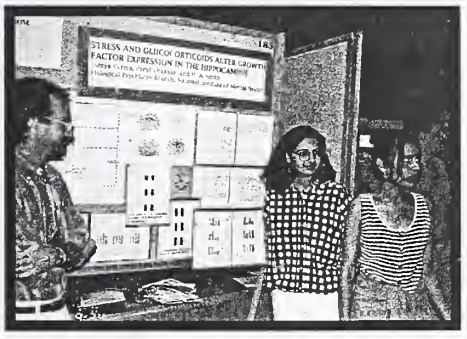
LIFE AFTER NIH: CAREER DEVELOPMENT AND MENTORSHIP TAKE ON RENEWED IMPORTANCE AT NIH

by Seema Kumar

With more than 2,500 scientists in training, NIH is easily one of the largest postdoctoral training facilities in the country. More than 50,000 scientists, including 11 Nobel Prize winners, conducted their early work here; nevertheless, say the experts, this success has come in spite of, not because of, NIH's formal career development and mentoring programs. Virtually nonexistent until a few years ago, "formal mentoring programs could be neglected in the past, when young scientists came to NIH only to gain technical competence," says Griffin Rodgers of NIDDK. In today's competitive scientific climate, where winning grants, publishing papers, and establishing contacts are as important as technical acumen, "senior scientists at NIH will have to teach young trainees not just the trade, but the tricks of the trade" if NIH hopes to attract and retain top-quality trainees, says Rodgers. This, he adds, will require new ways of thinking about and restructuring mentoring and career development programs for young scientists.



Summer students Parul Thakkar (left) and Somya Verma, with their preceptor, NIMH's Mark Smith, presented their summer's work on Poster Day 1994, held in August. The event, organized by the Office of Education, provides summer students an opportunity to communicate their work to NIH scientists and other students and is part of NIH's efforts to develop the next generation of biomedical scientists.

Several groups on campus are now trying to do just that, according to Michael Fordis, Director of the four-year-old Office of Education. "NIH is going to see a tremendous change in the quality of training experience that is unduplicated in recent years and that will provide [successful] models for the country to copy." Fordis says that career development "is a tremendously high priority [for NIH]" and that the new leadership's support in this regard "has been invaluable in setting the stage for new career development programs for the future."

Kanak Iyer, an NIMH postdoc, can't wait for the future and says that new career development programs can't come soon enough. "Postdoctoral fellows are floundering here at NIH," says Iyer. "We need guidance

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CLINICAL RESEARCH AT NIH

Michael Gottesman

If there is a unique feature of research at NIH, it is the Clinical Center. Conceived as a meeting place of bench and bedside biology, it has spawned innovative new disease therapies for more than 40 years. At a time of limited availability of funds for extramural clinical studies, the role of the Clinical Center in translational research is more important than ever for NIH Intramural Research Program (IRP) and for biomedical research in the country as a whole. Yet clinical researchers at NIH feel they are underappreciated and under siege. What does the future hold for clinical research at NIH?

In the recent External Advisors' Report on the Intramural Program, the physical infirmities of the Clinical Center were judged to be of sufficient severity to recommend strongly the reconstruction of a new hospital with associated laboratories. Although the report raised concerns about whether all Clinical Center protocols were truly innovative and suggested that the current hospital facility was almost twice as large as needed to support our essential research activities, the report did contain a ringing endorsement of the importance of the Clinical Center.

Acting on the recommendations of the External Advisory Committee, the Department of Health and Human Services has funded a concept competition as the first step toward construction of a new 250-bed hospital with laboratories, and has given tacit approval for future funding of such a facility. Although not the total replacement facility dreamed of by NIH planners, when completed around the year 2000, this new hospital attached to the Ambulatory Care Research Facility will be the most modern, forward-thinking facility of its kind in the world, and it will be an attractive venue for the conduct of translational research in the 21st century. Beginning next year, the extant Building 10 will undergo essential maintenance and repair to central plumbing, electrical, and air-handling systems. This plan assures that clinical research will have a comfortable home at NIH for the foreseeable future.

What about the funding of clinical research? Because of the rising costs of clinical care, the assessment from each institute, center, and division (ICD) for clinical research activities has been increasing. Approximately 30% of the $1.1 billion NIH IRP budget now supports clinical research: $220 million dollars comes through the management-fund tap and the rest, approximately $100 million, is an estimate of the other costs paid by the ICDs to maintain clinical branches. One of the consequences of these rising costs is that some ICDs have begun to decrease their clinical research activities. It should be possible to stop this trend by increasing the efficiency of patient-care delivery by consolidating and closing patient-care units, managing Clinical Center services more carefully, and honing our protocols to eliminate expensive research and routine clinical care that are unlikely to yield important new findings. These goals will be accomplished at the ICD level through more rigorous scientific review of protocols and centrally, through improved management. In addition, the new hospital itself will be more efficient, saving as much as 10 - 15% in operating costs. Our hope is to keep the cost of clinical research from rising much above the current 30% of our total intramural budget.

AT A TIME OF LIMITED AVAILABILITY OF FUNDS FOR EXTRAMURAL CLINICAL STUDIES,, THE ROLE OF THE CLINICAL CENTER IN TRANSLATIONAL RESEARCH IS MORE IMPORTANT THAN EVER FOR NIH.

Another concern has been the increasing administrative complexity of conducting clinical research. Public attention has been drawn to clinical research by recent media coverage of the use of radiation in medical research and of the recent deaths during NIH trials of the antiviral agent FIAU. Some researchers may feel there is an endless and needless proliferation of rules and regulations governing research on human subjects. Clearly, we do human subjects research at NIH under an explicit written assurance to the public that we will observe all relevant guidelines and regulations. Many of these regulations derive from a history of actual or perceived abuse of human subjects at other institutions, and they have evolved into explicit and verifiable ethical standards to which all bona fide clinical researchers subscribe. It is imperative that we adhere to these regulations for three reasons: 1) they represent high standards of ethical care for our patients, 2) strict adherence to the regulations protects both our patients and our researchers from the inherent risks involved in clinical research. We must remember that clinical research involves unknown risks to patients who have the courage and altruism to volunteer for these studies, and we must do everything possible to protect their interests and inform them about the research in which they are willing participants, and 3) violation of these guidelines and regulations will result in penalties to individual investigations and to NIH as a whole.

Recently, new Federal regulations have been developed that require that clinical research include women and minorities – groups that have been excluded from certain studies in the past. A set of guidelines has been drawn up to allow our Institutional Review Boards (IRBs) to evaluate the proposed subject population for specific clinical studies. The IRBs will monitor the recruitment of women and minorities into these protocols. The point of this effort is not just to adhere to legal requirements; it is good science to determine whether there are human subpopulations with distinct physiologies or pharmakokinetics.

We are seeing significant progress in making the salary scale for our senior clinical researchers more competitive with salaries offered to physicians with patient-care responsibilities at other institutions. The Veterans Administration currently hires physicians under a legislative authority known as Title 38. For several years, NIH has attempted to use this authority, and recent discussions at the Department of Health and Human Services suggest that Title 38 salary supplements for physicians directly involved in patient care may be forthcoming.

I would also like to comment on changes in our clinical research training programs that should make the Clinical Center a more attractive environment for trainees. Currently, 20 different fellowship programs have been accredited by the Accreditation Council for Graduate Medical Education or boards in their respective disci-

plines. John Gallin, the new Associate Director for Clinical Research at NIH, has been working with a committee to construct a new training program in clinical research to attract young investigators to NIH. We have just launched a loan-repayment program for the educational debts of women, minority-group members, disabled people, and other disadvantaged physicians . This program will serve several functions: 1) it will allow us to recruit physicians to clinical research who would normally be constrained to the private practice of medicine because of personal financial limitations, 2) the quality and quantity of clinical researchers will increase, and 3) more minority clinical researchers will help us recruit more minority patients to our clinical research protocols.

I believe the future of clinical research at NIH is bright. The current NIH leadership strongly supports the high-quality, innovative clinical research for which the Clinical Center has become known. With John Gallin now poised to bring many initiatives to fruition – with the building of a new hospital, the development of strong clinical research training programs, the redefinition of clinical protocols to minimize routine care and maximize innovative research, and the development of a personnel system to optimize salaries of our clinical researchers – we can look forward to substantial improvements in the environment for clinical research at NIH. John Gallin will discuss details about these improvements in future issues of *The NIH Catalyst.*

Michael Gottesman
Acting Deputy Director for
Intramural Research

FAX-BACK Feedback

Below is a sample of the FAX-BACK comments we received for each topic raised in the May issue.

On the Minority Task Force Report

"The report on the "Status of Intramural Minority Scientists" concerning underrepresentation of minorities at NIH [July issue] points out what reports have been stating over the past 25 years. A problem persists despite substantial efforts by NIH to remedy it. This is not unique to NIH. Of all the reports I have reviewed, the one by H.W. Nickens, T.P. Ready, and R.G. Petersdorf in the Aug. 18, 1994 issue of *The New England Journal of Medicine* (pages 472 - 76) is the only one that addressed the true issue and offered some working solutions, not suggestions. I think we can agree that there is a problem. The problem is that members of society have always viewed change as a threat to their existence when they feel it is being imposed on them. History has shown that we have always viewed issues like this one as emotional, and one must never forget that change in attitudes comes slowly. With this fact stated, my experience here as a minority has been a very positive one. This is not to say that there have not been some problems. My experience with the scientists here at NIH has been that they are concerned with ability to perform at the highest level, and not with race or sex issues. Because of space constraints, I cannot state all of

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Acting DDIR's Electronic Bulletin Board: Essential News Now!

Many scientists still don't know where to get the latest information emanating from Building 1 – critical news on changes in radiation safety policy, recycling, disposal of medical-pathological waste, space allocation, review of the intramural research programs, new tenure-track positions, and even what OSHA says we can and cannot store in the corridors. Turn on (your computer)! Tune in (to the Bulletin Board)! Print out (a copy for your lab)! To access the DDIR's Electronic Bulletin Board, click on Gopher's NIH Campus Info menu, then select the Bulletin Board from the Intramural Research News menu. If you do not currently have access to Gopher, contact your local area network (LAN) administrator and have him or her walk you through procedures to down-load the programs needed to tie into this useful service. The Bulletin Board is also available through Mosaic. ■

Letter to the Editor

I am writing this letter to bring to your attention a serious problem at NIH dealing with travel to meetings outside the United States. Recently, I submitted an abstract to a meeting entitled "Regulation of Eukaryotic DNA Replication" that is being sponsored by McGill University in Montreal. I thought that presenting our data at this meeting would provide a great way to exchange ideas with a highly regarded group of scientists working on DNA replication. Our abstract was accepted by the meeting committee, and a paper describing this research is currently in press in *The Journal of Biological Chemistry.* I have been informed by an administrative officer here at NIDDK, Ms. Mary Espada, that travel costs for this meeting will not be covered by NIH since the meeting will be held outside the United States. I am not sure what the purpose of this restriction is. What it certainly seems to say is that it is not worth sending young NIH scientists outside the country to discuss science. Why is there this restriction on international discussion for postdoctoral scientists? Is this not part of the mission of science? Because I cannot afford to pay for this trip form my own pocket, I am forced to withdraw our abstract from the meeting program. In my withdrawal letter, I intend to make the committee aware of the NIH policy on foreign travel for postdoctoral scientists. I am shocked that this policy has been practiced for any length of time and thought it warranted being brought to your attention.

Sincerely,
Renee M. Howell, Ph.D.

Editor' Note

Although senior scientists are more likely to receive support to attend international meetings from NIH's limited foreign travel funds, postdocs are also eligible for support. They must obtain advance approval for international travel from their supervisor and Scientific Director. Howell has since received money to attend the meeting.

AIDS Research's Intrepid New Navigator

by Seema Kumar

Earlier this year when William Paul, a noted immunologist (read hard-core scientist), accepted the politically charged job of heading the NIH Office of AIDS Research (OAR), a few eyebrows in the scientific and political communities rose a couple of inches: Some questioned whether Paul had the political pizzazz to pull this job off, and others wondered why he was putting himself under the microscope where his science belonged. Now six months later, the eyebrows are still raised, but with pleasant surprise at the way Paul has deftly weaved his way through the fiefdoms and bureaucracies surrounding AIDS politics, emerging unscathed.

"Bill Paul is one of the most thoughtful of an extremely talented group of laboratory chiefs at NIAID, and I was very happy that Dr. Varmus had the imagination to select him to head the OAR, even though he did not have a track record in AIDS research," says John Gallin, Paul's ex-boss and now Director of the Clinical Center and Associate Director for Clinical Research. "Bill seems to be applying the same careful and thoughtful approaches to leading OAR as he did at NIAID." So far, Paul seems to have won the approval and support of the various factions involved in the fight against AIDS — policymakers, Congress, activists, and intramural and extramural researchers.

But some of the truly tough scrutiny that Paul must face is yet to come. As Director of the reorganized OAR with new funding powers, Paul holds a $1.3 billion purse string and has the power to direct which areas of AIDS research will be funded and how the money will be divided among the 21 institutes. But more importantly, Paul will be making global decisions about the direction AIDS research will take, and various groups in the scientific and political circles, including the intramural scientists at NIH, are anxious to see what those decisions will be. They will include how he sets the balance between clinical and basic research in AIDS, what he deems to be AIDS and AIDS-related research, and whether his office will control the intramural AIDS budget.

Clinical vs. Basic Research on AIDS

One of the most important issues that OAR faces is selecting the proper mix of clinical and basic research on AIDS. On the one hand, says Paul, there seems to be general agreement among the various stakeholders, including activists, that real progress in combating AIDS will result from basic research on the immune response to HIV-1 and on the pathogenesis of AIDS. On the other hand, says Paul, "there is also a desperate need to move rapidly in the clinical front.... We don't have the luxury of simply saying, 'All we are going to do is basic research and as soon as we have [that] well understood, we will turn our attention to a more clinically oriented program,' because this epidemic is decimating large parts of the world."

However, given that "money is not infinite, you have got to make choices," says Paul. Although many activists, disillusioned with inadequate current therapies for AIDS, now support substantial shifting of resources from clinical to basic research, Paul says his own view is a little more conservative. "I would prefer not to see large shifting in the level of effort" and resources from clinical to basic research, says Paul, because it won't be long before new generations of vaccines and drugs, such as the protease inhibitors, are ready to be tested. Instead, says Paul, OAR plans to streamline the clinical program, which grew too rapidly under emergency room-like conditions at a time when saving lives was the only priority. "When you are responding to a medical emergency, you not only grow rapidly but also in ways that are not very efficient," says Paul. By making the AIDS clinical program give "more bang for the buck," Paul hopes to free up funds for basic research.

But even for the basic research areas, Paul will have to make tough choices among the growing number of AIDS-related research subdisciplines — an issue that has some NIH-supported scientists worried.

AIDS and AIDS-Related

Paul says that the decision to fund will be easy for "areas of research that provide fundamental insights into the nature of the disease, effective therapies, good vaccines, and other preventative approaches." Unfortunately, says Paul, there is no telling where those insights will come from; "they may come from a [non-AIDS] area." OAR will certainly fund research in related areas where a reasoned case for AIDS-relatedness can be made, but it will be harder to fund areas that show only peripheral or tangential connection to AIDS. To guard against the possibility that some currently unrelated but potentially important research may be squelched by the lack of OAR funding, "the research budget for the NIH as a whole will need to grow," says Paul.

William Paul heads the newly reorganized Office of AIDS Research.

"We believe that to support AIDS research generously and at the same time to starve the rest of biomedical research is a very unwise thing and will run the serious risk of slowing the progress in AIDS," says Paul. "The better the biomedical research program at NIH is supported, the less important it becomes for the AIDS research to start supporting things that are more and more difficult to show a direct connection to AIDS," he says.

Paul also points out that whether or not a given area of research has a valid connection to AIDS is very subjective. "Each individual [has] a different view of what is AIDS-related, and that view is going to be predicated on their vision of the key factors in the pathogenesis of AIDS." For example, says Paul, for a researcher who believes that HIV's crossing of mucosal barriers is a key step in sexual transmission of HIV, any research that sheds light on mucosal barriers would be important to AIDS. But for a researcher from an alternative school of thought, who believes that the virus does not cross the mucosal barriers at all but only enters through wounds or abrasions, mucosal barriers would constitute an area unrelated to AIDS.

Paul says that he would prefer not to have to make these choices, but since he must, he relies on OAR's coordinating committees and representative members of the various factions in the AIDS community to provide him with the knowledge base on which to make the decisions. OAR's five coordinating committees, each with 10 extramural and intramural NIH scientists, meet for one to two

months to produce a draft plan that is distributed to the institutes for comment. OAR then convenes a two-day workshop in which the coordinating committees meet with scientists from universities, research institutes, and pharmaceutical and biotech firms and with members of various community and activist organizations to review and revise the plan to reflect a consensus. OAR then reviews the plan with a smaller ad hoc group, consisting mainly of outside scientists, to look at the balance of clinical and basic research and at AIDS vs. AIDS-related research and to prepare the final version of OAR's strategic plan. The plan is submitted to the NIH Director, HHS, and Congress. "We did this last year and we will do it again this year. We really feel that the only way to have any broad support for this effort is by the reality and the perception that the scientific community as a whole has a strong input into this plan," says Paul.

OAR and the Intramural AIDS Budget

One issue that has not been fully resolved is whether OAR will control the intramural AIDS budget. The answer, says Paul, is no — at least for the moment. Paul explains that the legislation gives OAR responsibility for funds over and above those needed for the continuation of ongoing research. Money that is already committed to ongoing research, such as grants and contracts that are not up for competitive renewal, for example, must be transferred promptly to the institutes. The entire intramural program has been interpreted, at least for this year's budgeting process, as falling within the purview of already-committed money. However, says Paul, "this interpretation is an issue that needs to be discussed."

Paul argues that the legal interpretation that the intramural program falls into the commitment base is, for intramural scientists, a double-edged sword. Although it may simplify life and make resources more predictable, "It does have a potential bad point, however, and that is that because funds committed to the intramural program will never be reviewed again, it makes the OAR inherently more conservative about increasing funding to the intramural program compared to the extramural program." Paul says that in the extramural setting, if increased funding in a given area turns into a dead end, OAR has the authority to change the level of funding when the grant or contract comes to an end. But any increase of funds to the intramural program remains there, even if the project is no longer fruitful. "Clearly, then, we would be much more willing to try [a risky] experiment outside of NIH because if it doesn't work, we can redirect the money. Inside, we cannot. That is a problem," says Paul. "In the long run, being considered part of the commitment base may not be good for the intramural program."

Paul suspects that many people will disagree with him, and he wants to tread softly on this matter "because it is a very tender area and we certainly don't want to give the idea that this is a power grab." However, says Paul, "the logical consequence seems to me inescapable: it is not necessarily in the intramural program's interest to be fully isolated." Paul would like to see the institutes and OAR jointly devise a solution that gives OAR a voice in the intramural AIDS funding but is at the same time as unintrusive as possible.

No Regrets

In the meantime, Paul has no regrets about accepting the position. He says he took the job simply because he thought it was a very important one and he owed it to NIH — where he has been since 1968 — to try to help if he could. "Very few of us who work in the lab, no matter how successful we are, [get a chance] to make such a direct contribution to human health," says Paul. "Here was a challenge of a very high order to make a great impact on the health of many people. If you can make a contribution, you have a responsibility to try. So while I might not have sought the position, I had great difficulty [turning it down]." The decision, says Paul, was made easier because "the new leadership at NIH made me believe that there would be a kind of setting in which one could really carry out this work."

Paul admits that his job does encroach on the time he can spend at his lab, where he has retained his research group and remains Chief of the Laboratory of Immunology at NIAID. "I accepted the position [as head of OAR] with the agreement that I would do it for a limited period of time and return to the lab. I am still interested in doing that." Paul says that being the OAR Director does not present any conflicts of interest with doing his own research at NIAID. "I don't do AIDS research, so I don't get any AIDS money," he says.

Paul says he has already profited from his current position which has given him an appreciation for the challenges and difficulties that people in the administration face and the creativity it takes to solve the problems. "I have a better appreciation than those of us who work in labs often do of how important and difficult and challenging the roles of people who do administration are. And it is very exciting and new, and it is very important," says Paul. ■

The Office of AIDS Research

When it was first established in 1988, OAR served merely as a clearinghouse for NIH-supported AIDS research. Last year, under pressure from activist groups to centralize the NIH-supported AIDS research, Congress passed the NIH Reauthorization Act, reorganizing OAR and giving it new responsibilities and clout. The legislation specifies that OAR must prepare a strategic plan to define the areas of priorities for AIDS research in a given year, then submit a budget to Congress. Once the funds are appropriated, OAR distributes the money among the various institutes in accordance with the plan. The institutes retain all their responsibilities in making the grants and in establishing contracts or cooperative agreements to carry out the research, but OAR has the responsibility of determining the areas where research would be emphasized. In that sense, OAR will determine how much money the individual institutes will receive to fund the research they would be supporting in future years. Currently, the five areas of focus for OAR are natural history and epidemiology, etiology and pathogenesis, therapeutic research, vaccine research, and behavioral research. In addition, OAR has two smaller areas of emphasis: information dissemination, and research training and infrastructure. Using the coordinating committees and other outside and inside expertise, OAR decides priorities within each of these areas, and across them, for its annual strategic plan. ■

CLINICAL MINISABBATICAL BRINGS FRESH BLOOD TO NIH

by Seema Kumar

Every Thursday morning for the past month, Ralph Schumacher, Acting Chief of the Division of Rheumatology at the University of Pennsylvania, has been taking the 6:24 from Philadelphia's 30th Street Station to participate in an new experiment that NIAMS launched last month – a minisabbatical to foster clinical research collaboration with the extramural community. And already, says John Klippel, NIAMS's Clinical Director, the experiment is proving that intramural-extramural collaborations are not just convenient ways to share expertise and resources – they can yield impressive results.

"Our sabbatical is only in its first month, but we are confident it will be a great success," says Klippel. "Many cutting-edge advances from the extramural program [can benefit from] the unique resources we have here at NIH, and we should ... provide extramural investigators the opportunity to use these facilities and collaborate with scientists on campus."

Extramural-intramural collaborations are also high on NIH Director Harold Varmus' agenda, and his endorsement has provided renewed vigor to the idea of establishing a formal sabbatical-at-NIH program for extramural investigators. Klippel says the minisabbatical experiment started by NIAMS's Arthritis and Rheumatism Branch might serve as a prototype for NIH and provide a good model, albeit not the only one, of how formal intramural-extramural collaborations can be established.

During his sabbatical, Schumacher is studying patients in the early stages of arthritis to find out whether external factors, particularly infectious agents, trigger the disease. The idea that infectious agents can cause difficult-to-diagnose arthritis is not new: Lyme disease, caused by the spirochete *Borrelia burgdorferi*, is a well-known example. What is new, says Schumacher, are the methods he will use to investigate the idea. Schumacher is looking for evidence of infectious agents in biopsies of joint tissues and by using electron microscopy, immunoelectron microscopy, polymerase chain reaction (PCR), and in situ hybridization – techniques that have been perfected in the past few years but not yet applied systematically to the study of potential infectious agents in arthritis.

Schumacher is pretty sure that he is going to find something. In similar studies on patients with Reiter's syndrome, a type of arthritis associated with urethritis or cervicitis, conjunctivitis, and mucocutaneous lesions, he and his colleagues found evidence of *Chlamydia* and *Ureaplasma* in joint tissues. They also found these agents in joint biopsies from patients with early unexplained arthritis and, tantalizingly, in a few patients with early rheumatoid arthritis. Schumacher says a key to the success was the use of newer laboratory techniques. "We think there may be hidden infections in other diseases that these techniques might be able to pick up, where in the past, routine cultures did not," says Schumacher.

"*Chlamydia, Borrelia,* and *Ureaplasma* are probably much more common than we realize and may cause not only some of the yet-unclassified arthritis, but also recognized syndromes and even some of what we currently call rheumatoid arthritis," says Schumacher. Although these agents are the most likely culprits in arthritis in general, scientists have also speculated that other agents, such as mycobacteria, gram-positive bacteria, and even viruses may be implicated in rheumatoid arthritis. Although the big payoff in Schumacher's study would be finding one or more pathogenic organisms responsible for rheumatoid arthritis, the success he has already had finding bacteria in unclassified arthritis guarantees that his NIH work will yield clinical rewards. "Even if we don't find [a pathogenic organism] for rheumatoid arthritis, many of the other people who have unclassified synovitis or arthritis can probably be treated better if we prove what the cause of their arthritis is."

Arthritis expert Ralph Schumacher of the University of Pennsylvania and Vanessa Gluck, an IRTA fellow, examine biopsies of joint tissue from patients with early arthritis. During his one-year sabbatical at NIAMS, Schumacher will be studying at least 100 patients to find out whether infectious agents trigger arthritis.

Many of the current treatments for arthritis, which affects an estimated 1% - 2% of adults, are immunosuppressive, blocking the body's immune response, and "it may, in fact, be that in some of these cases, we need to stimulate the body's immune response, and so [this research] may make some very dramatic changes in the way we think about the disease," says Schumacher.

Although the current NIH protocol does not include treatment, if an infectious agent is proved to be the cause, Schumacher, Klippel, and their colleagues plan to develop clinical trials to evaluate the role of antibiotics. So far, such treatment has only been partially successful because the organisms have developed survival strategies, as with the Lyme disease spirochete, which makes it impossible to eradicate the organisms completely.

The search for infectious triggers is the main emphasis of Schumacher's studies, but he also plans to collaborate with Daniel Kastner at NIAMS in immunogenetic studies of early-arthritis patients to see what genes influence the type of arthritis people get. Schumacher and his collaborators plan to do immunologic studies in these patients to determine how differences in their immune systems affect the way their bodies respond to infection. "There are a lot of good immunologists, cell biologists, and molecular biologists at NIH who might like to get specimens from

patients with very early arthritis and look at whether the system that they are interested in is turned on very early in the disease and thus is important, or whether it is just a late manifestation of the disease," says Schumacher. "So we would like to get people who are studying growth factors and cell differentiation and various aspects of cell and humoral immunity [to come] out of the woodwork and see if they would be interested in looking at patients with us."

Schumacher also has many other collaborations lined up. Ronald Wilder at NIAMS, with whom Schumacher has collaborated in the past, is studying hormonal aspects of the disease; Mark Ghourley, an investigator at NIAMS, is studying the status of bone – which the synovitis eventually eats into, thus crippling patients – in early disease to determine whether changes at that stage can be used to predict the course of the disease. Social worker Louise Meister will be studying whether patients' social and economic support and resources can influence their prognosis. Finally, Lynn Gerber, a rehabilitation specialist, will be looking at whether a patient's level of physical activity can determine their prognosis.

By the end of his sabbatical next August, Schumacher hopes to have studied 100 patients and accumulated valuable research material in the form of joint tissues. "We are going to prepare cDNA libraries from all of these [tissues] and will be able to share that with other researchers. We are also talking to people in other institutes to see if they are interested in possibly applying some of their techniques," says Schumacher.

Schumacher, Klippel, and colleagues are looking not only for collaborators but also for patients who have had one or more swollen painful joints for less than one year, but preferably less – even for as little as a week. Patients who are interested in participating in this study should call Cheryl Yarboro, Study Nurse Coordinator, at 402-6409.

"It is great to work here at NIH," says Schumacher. "Everyone seems enthusiastic, and the staff is very cooperative. But the beauty of this arrangement is the combination of the expertise and facilities from Penn and NIH." ■

Some More Interest Groups

Postdoctoral Structural Biology Interest Group

The NIH Postdoctoral Structural Biology Group was formed to enable NIH postdoctoral fellows of diverse scientific backgrounds to become familiar with structural biology techniques and their applications. Participants will learn about basic principles of structural biology techniques and about new techniques, and they will have a chance to discuss problems in their work.

The group's monthly meetings will feature informal talks and time for discussions and social interactions. The first meeting will be held on Oct. 4, 3 - 5 p.m., in the Lipsett Auditorium. For more information, please contact Teresa Strzelecka, Laboratory of Chemical Physics, NIDDK, by phone at 496-2815, fax at 496-0825, or e-mail strzel@speck.niddk.nih.gov.

Signal Transduction Interest Group

Interested in participating in a signal transduction interest group? If so, attend this new group's first organizational meeting Wednesday, Oct. 5, 4:00 p.m., at Building. 37, Room. 6B25. The group seeks to bring together scientists interested in receptors, GTP binding proteins, protein kinases, effectors, and second messengers. The group hopes to foster the sharing of ideas and reagents, organize general or specific discussions, and explore possibilities for inviting outside speakers.

If you would like to be on the mailing list, call, e-mail, or fax Richard Kahn (Bldg. 37, Room 5D02; phone: 402-2063; fax: 480-2514; e-mail: rakahn@helix), John Northup (Bldg. 36, Room 2D30; phone: 496-9167; fax: 496-4103; e-mail: JKNGTP@helix), or Jim Battey (Bldg. 37, Room 5D02; phone: 496-2966; fax: 480-2514, e-mail: jbat@helix).

Cell Cycle Interest Group

The NIH Cell Cycle Interest Group has been formed to facilitate communication between scientists working at the NIH campus and nearby institutions who are interested in the cell cycle and related problems. Members can learn what others in the field are doing, make suggestions, discuss information from recent meetings, and swap technical tips. An organizational meeting for the group was held July 12, and regular meetings will be held at 12:30 p.m. on the first Tuesday of each month, starting on Oct. 4 in Building. 37, Room 6B23. The meeting format will feature short, informal talks by members of the interest group, alternating every third or fourth month with a longer talk by an invited, external speaker. It will be a pleasure to welcome George Vande Woude from NCI-Frederick as our first external speaker at the inaugural meeting. The title of his seminar is "Oncogenes, Cell Cycle and Antineoplastic Drugs." The group also hopes to organize a one-day symposium next year and an electronic bulletin board that can be accessed via Gopher. If you are interested in joining the Cell Cycle Interest Group, please send your name, telephone and fax numbers, and mailing and e-mail address to Patrick O'Connor (Bldg. 37, Room 5C19; phone: 496-3269; fax: 402-0752; e-mail: OConnorP@dc37a.nci.nih.gov) or Mary Dasso (Bldg 18, Room 101; phone: 402-1555; fax: 402-0078; e-mail: mdasso@HELIX.NIH.GOV).

The NGF Club

The Nerve Growth Factor (NGF) Club is looking for new members. To become a member, send your name, address, and phone number to Gordon Guroff (Bldg. 49, Room 5A64; phone: 496-4751). The first meeting of the 1994 - 95 year will be on Oct. 11 at 2 p.m. in Building 49, Conference Room B. The featured speaker will be George DeVries of the Medical College of Virginia. He will discuss "What's new with neu in the CNS and PNS?" ■

CHUTES AND LADDERS:
continued from page 1.

It is difficult to know whether NIH should lose sleep over citation rates that are only 75% above average. What kind of blips are statistically significant in such a massive number crunch? What might lie behind changes in citation rates for a given institute? Could a few early blockbuster papers on AIDS temporarily elevate NIH's average citation rate? How quickly would the relocation of a few highly cited authors show up in the numbers? What if NIH researchers developed a predilection for sending their papers to *PNAS* (ranked 37th for its citation-rate impact in 1992 in *Science Journal Citation Reports*) rather than *Cell* (ranked third)?

Stymied by these imponderables, *The NIH Catalyst* turned its attention to the more personal, immediate, and comprehensible issues. Where is the best place to publish these days? What journals possess the greatest cachet? What journals do intramural scientists actually read, and in which ones do they publish? What new journals are in ascendance? And what journals should be avoided?

The answer to these questions is to some extent subjective, so *The Catalyst* explored these issues accordingly. With disregard for the principles of experimental design, we faxed off a survey to members of *The Catalyst*'s editorial board and to an unscientifically selected cross-section of researchers representing all of NIH's institutes. The approximately 50 returns that we received included responses from senior- and junior-level scientists; American- and foreign-born scientists; and intramural and extramural staff. Respondents were molecular and cellular biochemists, immunologists, geneticists, neurobiologists, and clinical and behavioral researchers.

We asked respondents to list the most prestigious journals in which to publish nonclinical and clinical research papers; the journals that they would rank in the second tier of respected general-interest publica-

Table 1: Publication Data on Journals Highly Rated by Surveyed NIH Scientists

A. Basic Research Journals

NCF rank	*Journal*	*ISI rank*	*Acceptance rate*	*Average time to publication*	*Page charge*[a]	*NIH editorial board members*
1	*Science*	10	13%	8 wk[i]	None	0; 2[c]
2	*Nature*	8	≈10%	2 - 3 mo	None	no board
3	*Cell*[d]	3	NA[e]	NA	None	NA
4	*PNAS*[f]	37	Special[f]	6 wk	$70	47[f]
5	*JBC*	67	50%	7 - 10 wk[g]	$65	17
6	*EMBO J.*	28	25%	10 wk	None	0
7	*Mol. Cel. Biol.*	51	43.12%	6 - 10 wk	$55	4
8	*J. Cell. Biol.*	35	27%	3 mo	$40	2
9	*Biochem.*	111	52%	9 wk	$30	5
10	*J. Neurosci.*	65	≈33%	4 mo[b]	$40	3
11	*Genes Dev.*	22	27 - 30%	2 - 3 mo	$25	1
12	*J. Exp. Med.*	30	20 - 25%	2.5 mo	$40	8
13	*Neuron*[d]	19	NA	NA	$35	NA
14	*Brain Res.*	42	50-55%	3 or 6 mo[g]	None[i]	3
15	*Cancer Res.*	115	35%	69 d	$65	18
16	*J. Immunol.*	69	≈43%	2 mo	$40	9

B. Clinical Journals

NCF rank	*Journal*	*ISI rank*	*Acceptance rate*	*Average time to publication*	*Page charge*[a]	*NIH editorial board members*
1	*N. Engl. J. Med.*	5	10%	10 wk	None	1
2	*J. Clin. Invest.*	49	22%	3 - 4 mo	$55/125[i]	3
3	*Lancet*	16	25%	10 wk	None	0
4	*JAMA*	97	10%	2 mo	None	1
5	*Ann. Intern. Med.*	38	13%	5 mo	None	0
6	*J. Exp. Med.*	30	20 - 25%	2.5 mo	$40	8
7	*Br. Med. J.*	160	15%	10 wk	None	No board
8	*J. Infect. Dis.*	99	≈55%	4 - 4.5 mo	None	0
9	*Nature*	8	≈10%	2 - 3 mo	None	No board
10	*Science*	10	13%	8 wk[b]	None	0; 2[c]

[a] Many journals charge extra if an author wants graphics reproduced in color.

[b] Will expedite publication of papers when competing papers have been submitted for publication.

[c] No NIH scientists on editorial board; two NIH scientists on board of reviewing editors.

[d] Benjamin Lewin, editor of *Cell* and *Neuron*, informed *The NIH Catalyst* that he and his staff did not have the time to provide this information, and that there are no page charges for publishing in *Cell*.

[e] Not available.

[f] The National Academy of Sciences, which publishes *PNAS*, does things differently: all papers must be "communicated," or forwarded to *PNAS* by a member of the Academy, after the Academy member has sent the paper out for two anonymous reviews (47 NIH scientists or scientists emeritus are members of the Academy). Each Academy member may submit up to five papers per year.

[g] Short communications published in shorter period; full-length papers take longer.

[h] *The Journal of Neuroscience* aims for a delay of 4 months or less between acceptance and actual publication of manuscripts. Currently, there is a substantial backlog of manuscripts in the publication pipeline, so the actual delays exceed this target, but *The Journal* expects the backlog to be eliminated in early 1995.

[i] No page charges or lower page charges for short communications.

Table 2.
In which five journals are you most likely to publish?

Rank	*Journal*
1	*Journal of Biological Chemistry*
2	*Proceedings of the National Academy of Sciences*
3	*Science*
4	*Cancer Research*
5.5	*Journal of Immunology*
5.5	*Nature*
7	*Journal of Clinical Investigation*
8.5	*Journal of Neuroscience*
8.5	*Biochemistry*
10	*Journal of Experimental Medicine*
11	*New England Journal of Medicine*
12	*Endocrinology*
13	*Journal of Infectious Diseases*
14	*EMBO Journal*
15.5	*Journal of Cell Biology*
15.5	*Journal of Virology*

Table 3.
Prestige aside, what five journals are on the top of your reading list?

Rank	*Journal*
1	*Science*
2	*Nature*
3	*Cell*
4	*Proceedings of the National Academy of Science*
5	*Journal of Biological Chemistry*
6	*New England Journal of Medicine*

tions; the top specialty journals in their areas of expertise; the journals they are most likely to read and publish in — regardless of prestige; exciting new places to publish; and journals that are problematic — slow to get papers reviewed and published, for example.

We summarize the responses to our query about the most prestigious journals as the "NIH Cachet Factor" (NCF) in Table 1 (page 8). We also include data on these journals from ISI's 1992 *Science Journal Citation Reports* indicating their ranks in terms of citations. The ISI Ranks listed in Table 1 are the 1992 Impact Factor rankings. The tables also include information, provided by the journals, on the acceptance rate for papers and the average time it takes each journal to publish a paper once it is accepted and in final form. These numbers are approximate and the average time to publication is affected by when, within the publishing cycle, the paper is accepted. The last two columns show page charges and the number of NIH scientists on the editorial boards of each journal. These numbers also are approximate.

We spotted some interesting differences between the list of journals in which our survey respondents publish (Table 2) and the journals with the highest NCF. Not surprisingly, workhorse journals, such as *Cancer Research, Endocrinology, Journal of Biological Chemistry, Journal of Immunology, Journal of Infectious Diseases,* and *Journal of Virology,* assume greater importance in the list of likely places in which NIH scientists publish than they do in the list of NCF rankings. *Cell* and *Neuron* — both published by Benjamin Lewin's Cell Press in Cambridge, Mass. — and *Lancet,* a British journal, although ranked as highly prestigious, were infrequently listed as journals in which respondents were likely to publish. One anonymous respondent said he would advise against submitting papers to *Cell* "unless you are a member of the 'club.'" Another observed, "*Cell* appears to have: a) somewhat of a sliding scale [in acceptance decisions], adjusted by lab of report origin, and b) some editorial pressure to 'hyperextend' hypotheses, leading to a fair percent of reports with exciting general conclusions that don't hold up." *Molecular and Cell Biology* and *Genes and Development* — both comparatively new journals — appear to have risen more quickly in cachet than as likely outlets for NIH scientists' papers, and both journals were singled out in comments by several survey respondents as exciting new journals in which to publish.

When it comes to precious reading time, there appeared to be three patterns governing which journals NIH scientists peruse: some scientists read the big-name, broad-interest journals; some focus on journals in their specialty area; and some go for a mixture of the two. Because many of the specialty journals were listed by only one or two respondents, they didn't make the summary list of journals ranked as top reading by NIH scientists (Table 3).

Survey respondents had many suggestions for exciting new places to publish — including two publications by Cell Press, *Neuron* and *Immunity.* Several respondents recommended *Nature*'s new monthly, *Nature Genetics.* Several others suggested *Molecular Biology of the Cell* and *International Immunology.* In neurobiology, respondents recommended *Neuro Report, Neurobiology of Disease, Cerebral Cortex,* and *Synapse.* One respondent noted that the *Journal of Neurochemistry,* although not new, was changing and "has made the transition to a good molecular neuroscience journal. This fills an important gap for reports that are significant, but not 'full' enough for *Neuron*...." In structural biology, *Structure* and *Protein Science* received endorsements. *Mechanisms of Development* and *Develop-*

continued on page 10

CHUTES AND LADDERS:
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mental Dynamics were cited as good new development journals. *Cancer, Molecular Carcinogenesis, Bone Marrow Transplantation, Endocrine Journal, Mammalian Genome,* and *Molecular Microbiology* were also mentioned as good new speciality journals. One anonymous respondent recommended *Current Biology* as an attractive journal having the same scope as *Cell*, but that is "not as capricious as *Cell*." Respondent Graeme Wistow of NEI bemoaned the lack of interesting new general-interest journals. "We need another good general journal," he wrote.

In responding to an open-ended request for other comments, respondents offered seasoned perspectives on the art and politics of publishing, and some excellent tips for scientists submitting papers. For example, NCI's Ira Pastan, advised, "If it [a submitted paper] comes back, reformat it and send it right out to a comparable journal. Don't sit on it. Remember, not all editors are perfect." NIAID's Ron Germain wrote, "1-Do first-rate work and do it first!! 2-Get to know the editors where you want to publish. 3-Learn the journal's preferences (e.g., *Science* in the past has liked HIV-related work better than *Nature*...' Peng Loh of NICHD advised, "Try to publish in the highest-impact journals." Jim Nagal of NIA urged, "Be realistic when evaluating the quality of your work and submit accordingly." Another respondent observed, "So many times, the reviews you receive will be opposite opinions [...] you begin to realize that the process is a crap shoot."

"ALL OF THE MAJOR JOURNALS HAVE A HISTORY OF PREJUDICE WITH SOME REVIEWERS. THIS IS FREQUENTLY A PROBLEM, ESPECIALLY FOR YOUNG SCIENTISTS WITHOUT EXTENSIVE NAME RECOGNITION."

Several respondents commented on long-standing and widespread concerns about the publishing and review processes, citing, for example, the importance of having "rebuttable, accountable, documented reviews." Another respondent opined that papers should be published along with reviewers' comments. Others are concerned that women continue to be underrepresented on the editorial boards and boards of reviewing editors for many of the top journals. "One notable exception is the highly rated *Journal of Cell Biology*, with about 28% women on the board," wrote one respondent.

NINDS' Monique Dubois-Dalcq observed that sometimes some of the slower journals have excellent reputations and may ultimately be a better choice than the big-name journals. "For most of us who get reviewed and who review others, the crucial point is how fast and well the reviewers are working and how fair the process is. Even the best journals should have three reviewers whenever possible, or allow for a third review if there is some controversy." Another senior scientist also has observed that the best reviews don't always emanate from the most prestigious journals. "Some highly rated journals are not as critically reviewed as *JBC*, or even *PNAS*, which are more 'democratic' and merit-driven," he says.

Dubois-Dalcq notes that keeping the peer-review process working efficiently and effectively can be a challenge to journal management. "An editor should require concise, crisp, clear reviews with constructive criticism whenever possible — this means work! Similarly, editors should drop reviewers who do not do their job in a timely manner." Wistow notes that, ironically, hot-shot scientist-editors may not always be up to the task: "Famous editors are sometimes too busy to take care of editorial responsibilities."

We also asked survey respondents to identify any journals that they would advise against publishing in. We summarize many of these comments in *"A Young NIH Scientist's Breaking Into the Big Name Journals Blues Rap"* (see box). *Proceedings of the National Academy of Sciences*, with its unusual method for acquiring papers (see footnote to Table 1), drew the most comment. One scientific director wrote, "Although I have published in *PNAS* in the past, I feel quite negatively about this journal. The articles vary widely in quality and rigor (much worse than other top-rank journals). In general this is due to extreme variability in rigor of the review process." A young scientist warned that some members of the Academy —the only route to getting a paper into *PNAS* — "are known to take in more papers than they can review and communicate" to the journal for publication. Another researcher may have suffered exactly this experience: "Since *PNAS* has no editorial board oversight, the review process can take forever if the sponsor is slow." Several respondents advised against publishing in *PNAS* but gave no explanation for why.

Several scientists criticized *Science* for perceived discrimination against all but the most famous authors. One young clinician wrote, "All of the major journals have a history of prejudice with some reviewers. This is frequently a problem, especially for young scientists without extensive name recognition." A senior immunologist advised against publishing in *Science* because, "except for 'hot' papers, [it's] SLOW and there is no re-review if the paper is initially rejected." Another warns that "*Science* may reject papers on grounds of space [limitations] even after recommended acceptance by reviewers." This respondent observed that, in general for researchers submitting papers, "It helps to be famous."

Two other journals high in NIH Cachet Factor rankings — *Nature* and the *Journal of Biological Chemistry* — also took hits from survey respondents. *Nature* was cited by two respondents as being very slow in its reviews. One respondent attacked *Nature* — which, unlike most of the top journals, has no editorial board — for having a "very arbitrary editorial policy." Two different

respondents from NEI complained that *JBC* was also slow and had some troublesome, idiosyncratic editors.

In addition to the negative comments above, at least one respondent recommended avoiding publishing in, or reported negative experiences with, each of the following journals: *Annals of Epidemiology, Biopolymers, Brain Research, Brain Research Bulletin, Calcified Tissue International, Cancer, Cancer Research, Cellular Immunology, Cell Growth and Differentiation, Experimental Eye Research, Gene, JAMA, Journal of Experimental Medicine, Journal of Immunology, Journal of Infectious Diseases, Lancet, Life Sciences, Matrix Biology, Neuroscience Letters,* and *Pediatrics.* The two most common complaints were publication delays and arbitrary or overly picky editors requiring (or even providing!) extensive revisions. One scientist complained that the journal *Blood* charges a $50.00 fee, up front, when manuscripts are submitted, "And that doesn't entitle you to a review." NIDR's Hynda Kleinman did not single out any particular journal, but urged colleagues not to publish important results in meeting reports and proceedings. "It's very time consuming, and when people look at your c.v., they look at peer-reviewed articles, not symposia. Also, publications like that take much longer to publish and are never timely."

David Rodbard, Director of DCRT, predicted that in the not-too-distant-future, "electronic publication, especially of preprints, will assume increasing importance. I think that all NIHers should have an option to put manuscripts into Gopher or Mosaic, either as a preprint or after acceptance [by a journal]. In this manner, we could get results to our colleagues weeks to months ahead of the printed form." Noting that physicists have started just such pre-publication exchanges of results, Rodbard acknowledges that there are some problems to resolve, including copyright, standardized formatting, and funding.

But until information superhighways can handle the traffic jam of information coming out of biomedical research labs today — or until some other miracle comes to pass — NIHers and the rest of the scientific community may just have to persevere and accept the problems and indignities in the status-conscious name-game of publishing. For, as Harvey Pollard of NIDDK explained, "The reason why people are more concerned with where an article is published, rather than its intrinsic merits, is that many readers cannot evaluate the latter any more outside their own nar-

A Young NIH Scientist's Breaking Into the Big Name Journals Blues Rap

Off in Bethesda, or down in NC,
Up in Frederick, or out in MT,
Just hang around and you'll hear the sad song:
Gosh dang journal's gone 'n done me wrong.

Giving my mentor zero defiance,
In May I sent my oeuvre to *Science*
Ten days later I let out a groan,
When they mailed back the envelope, "SENDER UNKNOWN."

Next I harkened to *Nature's* call,
Heeded and loved by one and all.
In a mere three months, the chaps told me, "Hey,
This belongs in a journal beginning with 'J'."

But my very hip mentor said, "Here's what we do:
Call my friend Ben -- he'll push it through."
So I phoned up *Cell* to say, "Look what we learned!"
But all my calls went unreturned.

The saddened boss said he wouldn't think bad of me
If at least we made *Proceedings of the National Academy.*
"So-so data are all that's needed,
Given the way their garden gets weeded."

So I called up a National Academician,
A colleague and friend in that envied position.
"Could you get this reviewed and communicated?"
Her answer suggested my life is ill-fated.

"I've already used my allotment this year
Of five papers I can have published there,
But your data and ideas sound great to me,
And I bet you could get into *JBC.*"

Her advice possessed wisdom's very kernel,
So next it went to that favored journal.
When I started this tale, the month was May,
As *JBC* wrote back, the year'd slipped away.

Acceptance was contingent on a few little changes:
A few more experiments checking the ranges,
Clean up the data, rewrite conclusions,
Re-format references, make these exclusions.

By March, one very quirky reviewer-
's added demands were notably fewer.
By May, all was in total compliance
As a similar paper came out in *Science.*

--Celia Hooper

HOT METHODS CLINIC: PHAGE EPITOPE DISPLAY LIBRARIES

by Lance Liotta, M.D., Ph.D., NCI, and Mark Sobel, M.D., Ph.D., NCI

Identifying an unknown protein ligand has traditionally been a daunting task. Typically, when a researcher has wanted to identify the protein that binds to a particular receptor, antibody, enzyme, or acceptor molecule of interest, he or she has had to resort to exhausting trial-and-error testing of suspected ligands, screening of expression libraries, or serial testing of peptide analogs or protein cleavage fragments. These traditional methods are being improved by a variety of highly sophisticated techniques in which large libraries of ligands are synthesized in parallel and screened against the binding partner (1,2). The new techniques fall into two categories: chemical methods and biological libraries (1). Chemical methods employ instrumentation to synthesize and screen randomly generated peptides. Biological libraries, the subject of this Hot Methods Clinic, utilize tens of millions of bacteriophage clones, each of which has a cDNA sequence cloned into the phage genome in such a way that the phage expresses a unique polypeptide on its surface (3,4). Using a method called "biopanning," the phage with the DNA encoding the protein of interest is isolated. The selected phage is then propagated in *Escherichia coli,* and the amino acid sequence of the ligand is determined by sequencing the corresponding coding region of the viral DNA.

The technology for these biological, or phage, display libraries is rapidly accelerating and offers great promise as a research tool for the rapid cloning of protein peptides and entire, fully folded large protein ligands (2,5). Phage constructs may even include libraries of "phage antibodies" that could display an array of binding specificities large enough to recognize any possible antigen (4,6). Many NIH intramural scientists are gearing up to try phage display, but at this moment, none have the technique fully up and running. The purpose of this article will be to provide an introduction to this powerful technique. A future article will provide trouble-shooting tips when more NIH intramural scientists have experience with phage display.

Phage Display Libraries: What are they?

Biological libraries displayed by phage include peptide libraries and full protein libraries. Peptide phage display libraries are batches of filamentous bacteriophage virions each displaying one or more copies of a different short amino acid segment on its surface (3,7). For example, Scott and Smith assembled a 200 million clone hexapeptide epitope library and used two monoclonal antibodies (Mabs) to screen a 23 million clone subset and pull out a sequence that corresponded to the mobile region of the protein antigen myohemerythrin (3). Dower's group constructed a hexapeptide library of 300 million clones and screened with Mab 3-E7, which, like the opioid receptor, binds tightly to the amino terminal four residues (YGGF) of beta endorphin (3).

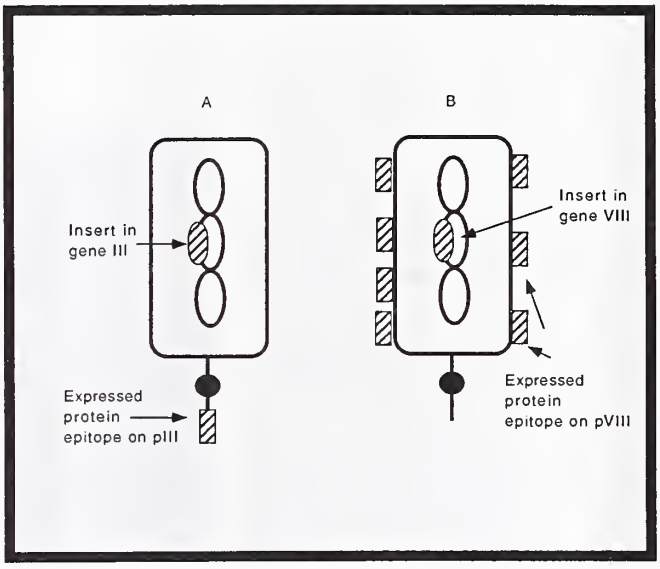


Figure 1. Filamentous bacteriophage displaying peptide epitopes fused to A, the minor viral coat protein pIII and B, the major coat protein pVIII. The DNA sequence encoding the protein of interest is inserted into the single stranded DNA genome of the phage.

Protein phage display libraries are libraries of large, multidomain proteins bearing variations in selected amino acid residues displayed on the surface of a filamentous bacteriophage. These large, folded proteins have included functional domains of antibodies (5,6), hormones (4), lectins, and enzymes (7). Maruyama et al. (7) have developed the λfoo phage vector and used it to express functionally active β-galactosidase (β–gal) and a plant lectin, BPA. β-gal and BPA are tetramers of four identical subunits and have large molecular masses, 465 kDa and 120 kDa, respectively.

How is the protein displayed?

Phage coats typically consist of two viral proteins: minor coat protein — protein pIII — and major coat protein, pVIII. pVIII forms the body of the phage. Copies of the minor coat protein are added at the trailing end of the emerging virion. Both pVIII and pIII are synthesized with short signal sequences that allow them to be transported to the inner membrane of the bacteria. The cDNA of interest is inserted into the phage genome to allow it to be synthesized as a fusion protein with the coat protein of the virus.

How is the variable protein library created?

A variable protein library can be created by generating combinations of randomly encoded amino acids (3). Hexamers (6mers) of oligonucleotides can be constructed with the degenerate sequence NN(G-or-T),NN(G-or-C), where N is any of the four nucleotides. The hexamers are randomly encorporated into the viral DNA. Culturing large batches of phages that have encorporated this degenerate code will generate phage clones bearing all 20 possible amino acids (and one possible stop codon) at encorporation sites. All possible combinations of 6mers can generate a library of more than a billion phage clones. The number of peptides encompassed by this technology exceeds by a factor of 100 to 1000 the number that can be screened by conventional expression systems.

How do you detect the desired protein that binds to your given target ?

"Biopanning" (Figure 2) is one term used to describe the method for purifying the phage clone that expresses the epitope of interest. A specific example is the isolation of a peptide antigen epitope. The researcher starts with a monoclonal antibody for which an antigen epitope is sought. The antibody is biotinylated and mixed with the phage library. Only the phage clones that express the correct antigen protein will bind to the biotinylated antibody. To separate the phage bound to the antibodies, the mixture is incubated with plates coated with streptavidin. The biotinylated antibodies stick to the streptavidin and carry the bound phage with them. In a variation of this selection technique, the plate is coated directly with the binding partner protein. When panning is conducted, only the phage expressing the desired binding ligand sticks to the plate. The unbound phage are washed away,

and the bound phage are subsequently eluted with acid. The eluted phage are amplified by growth in bacterial cells, then used in successive rounds of biopanning, infection, and propagation.

A commercial variation on the theme: Recombinant phage antibody system

One of the most exciting versions of the phage display system is the recombinant phage antibody system, described by Hoogenboom et al. (4) and recently commercialized by Pharmacia Biotech in Piscataway, N.J. Pharmacia offers this system as a kit for the cloning and expression of monovalent antibody fragments that bind to a known antigen for which a genetically known antibody is sought. The company's literature claims, "The system's integrated modular format greatly simplifies the task of isolating and cloning antibody genes and expressing and detecting their products." The starting material, prepared by the researcher, is mRNA from antibody-producing mouse hybridoma or spleen cells from mice that have been injected with the antigen for which an antibody is desired. The antibody variable heavy (V_H) and light (V_L) chain genes are separately amplified and assembled into a single chain S_CF_V fragment with a short, linker DNA. The V_H and V_L module is then cloned into an expression vector and ultimately, when tranfected into the phage, both V_H and V_L genes are expressed on the same polypeptide chain, fused with phage pIII protein. Once selected by biopanning on a plate coated with the known antigen, the phage expressing the correct antibody is then used to infect *E. coli* and produce large amounts of the antibody chains. Soluble antibodies can be produced in large quantities using the proper conditions. According to the company's literature, yields ranging from 0.2 to 10 mg/l of culture are possible. The soluble antibodies can then be labeled and used for immunoassay or immunoblots to detect the antigen.

What are the applications of phage display?

Phage display methodology is at an early stage in what can be expected to grow into a widely adopted technology. It offers great promise for identifying novel ligands that bind to a protein of interest, or for mapping the functional domains of known proteins. Clinical utility of phage display includes the development of new drugs through peptide-mimetics and the refinement of vaccine reagents. The recombinant phage antibody system could potentially be applied to analysis of antibody functional domains, sequence analysis of antibody genes, and large-scale production of antibodies for immunoassays or immunotherapy.

What are the limitations and challenges of phage display?

As can be seen from the sample protocol below, the methods have multiple steps and may be time-consuming to set up. In addition, both the short peptides selected by phage display and monovalent antibodies from phage cloning may produce antibodies and peptides of relatively low affinity (6). Short peptides may not contain the secondary and tertiary structure required for ligand recognition, and until Maruyama et al. (7) devised their protocol, large proteins with complicated 3-D structures could not be expressed. Unfortunately, phage bearing large fusion proteins may have reduced infectivity (7) and thus be difficult to produce and cultivate in quantity. Results may also be somewhat ambiguous but still potentially valuable in drug design: it is possible for a specific short peptide to mimic the binding epitope but still be different from the natural ligand (1,7).

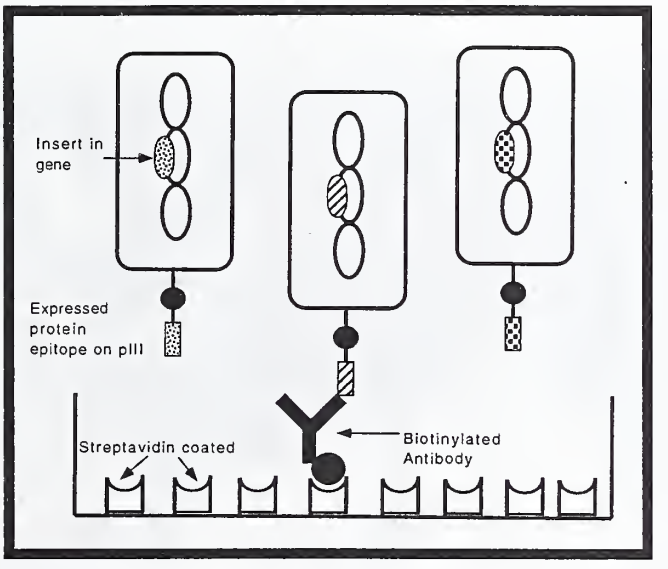


Figure 2. Biopanning, or affinity purification of phage that express the epitope of interest. Only the phage expressing the correct protein bind to the biotinylated antibody, which in turn binds to the streptavidin coated dish.

Outline of a general protocol for the recombinant phage antibody library

This protocol is derived from the Pharmacia Biotech Recombinant Phage Antibody System Kit. It assumes that you have an antigen of interest and want to produce a genetically defined recombinant antibody that will recognize the antigen. The kit provides everything but your antigen and the spleen lymphocytes or hybridoma cells.

I. Construction of the library

1. Starting material can be either mouse hybridoma cells or spleen cells from mice that have been injected with the antigen for which an antibody is sought.

2. Isolate mRNA from the mouse spleen (lymphocyte) or hybridoma cells.

3. Synthesize cDNA from the mRNA.

4. Set up two PCR reaction tubes, one for amplifying cDNAs encoding the antibody's immunoglobulin heavy chain and the other for amplifying cDNAs encoding the light chain protein. The PCR reactions are primed with variable region probes.

5. The PCR products from these two reactions are purified by gel electrophoresis.

6. Using a linker fragment that is designed to anneal to the 3' end of the heavy chain and to the 5' end of the light chain PCR products, the purified heavy and light chain DNAs are assembled into a single gene. Using the 5' primer from the heavy chain PCR reaction and the 3' primer from the light chain PCR reaction, single antibody genes are amplified in another PCR reaction.

7. The assembled antibody genes are reamplified using modified 5' and 3' primers that now include different restriction sites to permit directed cloning. The particular restriction sites selected rarely occur within mouse antibody genes, thus guaranteeing that mostly intact antibody sequences will be cloned. After purification, the antibody DNA fragments are restricted to generate cohesive ends for ligation into the cloning vector.

8. The cloning vector is a phagemid (genetically engineered bacteriophage) that has appropriate restriction sites positioned such that the recombinant antibody genes will be cloned as fusion genes with

continued on page 15.

BONE MARROW CYTOKINES IN THE PATHOPHYSIOLOGY OF OSTEOPOROSIS

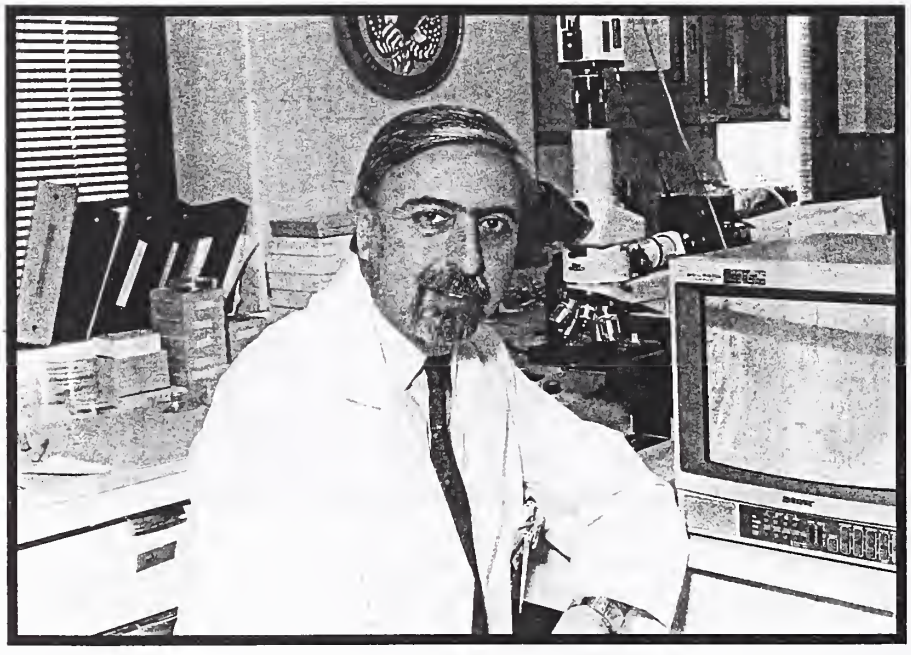
by Stavros Manolagas, M.D., Ph.D., Professor of Medicine and Director, Division of Endocrinology and Metabolism, University of Arkansas for Medical Sciences, at the Inter-Institute Interest Group Lecture Series, July 13, 1994

ABSTRACT:
Osteoclasts and osteoblasts, originating in the bone marrow from hematopoietic progenitors and mesenchymal stromal cells, respectively, are responsible for remodeling the skeleton throughout adult life. A series of in vitro and in vivo studies in animal models suggests that altered production of, and responsiveness to, cytokines in the bone marrow are key pathogenic events in diseases associated with abnormal skeletal remodeling, such as osteoporosis. Indeed, upon loss of sex steroids, the production of osteoclasts in the bone marrow is increased. This is mediated by an increase in production of interleukin-6 (IL-6) and increased sensitivity of the osteoclastic precursors to cytokines such as IL-6, due to an upregulation of the gp130 signal-transduction pathway. Consistent with this, estrogens as well as androgens inhibit the expression of the gp130 gene and inhibit IL-6 production through an indirect effect of its specific receptors on the transcriptional activity of the human IL-6 gene promoter. With advancing age, the high rate of bone remodeling and the loss of bone caused by loss of gonadal function slows, probably due to a relative decrease of the ability of the marrow to maintain the high rate of osteoclastogenesis caused by the acute loss of sex steroids. This appears to be the result of a negative effect of senescence on the ability of the marrow to produce stromal or osteoblastic cells, which provide the essential support for osteoclastogenesis; hence, inappropriate production of osteoclasts or inadequate production of osteoblasts in the bone marrow may represent fundamental cellular changes in the pathogenesis of postmenopausal and senescence-associated osteoporosis, respectively.

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 idea that the critical cellular changes leading to osteoporosis occur at the early stages of development of osteoclasts and osteoblasts in bone marrow. Specifically, we postulated that loss of sex steroids, a primary cause of the imbalance between resorption and formation of bone mass that characterizes osteoporosis, must somehow interfere with normal, orderly replenishment of cellular constituents of skeleton, rather than affecting the function of fully differentiated cells. This general concept was initially tested in in vitro studies examining the effect of sex steroids on the production of cytokines that influence osteoclast development in the bone marrow. The results of these studies demonstrated that estrogens and androgens are potent inhibitors of interleukin-6 production. We then went on to examine in vivo whether loss of sex steroids upregulates IL-6 production. Using ovariectomized mice and specific antibodies that neutralize IL-6, we were able to demonstrate that, indeed, loss of ovarian function leads to an IL-6-mediated upregulation of osteoclast production in the marrow and increased numbers of osteoclasts in bone. These findings, as well as the demonstration of the essential role of IL-6 in the bone loss associated with loss of estrogens, were confirmed later by another group using IL-6 - knockout mice. They observed that IL-6 - deficient mice were protected against loss of bone following loss of ovarian function.



Stavros Manolagas

Knowing that loss of sex steroids increases bone remodeling, we subsequently hypothesized and found that loss of ovarian function upregulates not only osteoclast but also osteoblast precursors in the bone marrow. Adding to this the fact that the action of osteoclastogenic cytokines (such as IL-6) and osteoblastogenic cytokines (such as LIF) are mediated by the gp130 signal-transduction pathway, we went on to examine the effects of sex steroids on this particular pathway in cells of the bone marrow stromal-osteoblastic lineage. We found that the gp130 signal transduction pathway is, indeed, regulated by sex steroids; hence, changes in the status of gonadal hormones could affect not only the production of cytokines, but also the responsiveness of osteogenic precursors to cytokines.

Our findings that sex steroids inhibit – whereas parathyroid hormone and vitamin D stimulate – the expression of the signal transducer gp130, raise the possibility that the high rate of remodeling following loss of gonadal function (and perhaps other states such as hyperparathyroidism) may be due to increased sensitivity of bone marrow progenitors to both osteoclastogenic and osteoblastogenic signals, resulting from upregulation of gp130.

Finally, in an attempt to explain why bone loss associated with menopause slows with advancing age, we attempted to dissect loss of gonadal function from the effects of senescence on bone cell progenitors of the marrow. These studies revealed that aging may interfere with the ability of bone marrow to maintain a normal rate of development of osteoblast precursors.

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

A: That IL-6 was redundant in terms of osteoclast development in the physiologic state, and that nonetheless, it could play such a critical role in the pathologic bone resorption caused by loss of sex steroids. Equally surprising was the observation that gp130 is regulated by systemic hormones. Assuming that gp130 is regulated by sex steroids in tissues other than bone and bone marrow cells, the significance of these observations may extend to the mechanism(s) underlying the protective effect of estrogens on the cardiovascular system and brain, as suggested by the lower incidence of Alzheimer's disease in postmenopausal women receiving estrogen replacement therapy.

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

A: Once we were convinced that estrogens do indeed regulate cytokine production in the bone marrow, I don't think that we experienced major stumbling blocks. In fact, we were surprised to see how easily the pieces of the puzzle fit together. The availability of large quantities of specific neutralizing antibodies against IL-6 was critical in our ability to demonstrate the role of this cytokine in the bone marrow changes caused by loss of estrogen.

Q: *Do you see any potential areas where this research might provide insight to clinical scientists?*

A: This work is of direct and immediate relevance to clinicians. Our observations provide insight into the cellular and biochemical basis of osteoporosis — knowledge that is essential for clinical scientists attempting to either treat or develop rational and specific therapies for the management of this widespread disease.

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

A: We have just initiated an extensive NIH-funded study to assess the relevance of animal-findings to humans. Specifically, we are investigating the effects of the loss of ovarian function in women on the behavior of the bone marrow. In addition, we are trying to determine whether production of specific cytokines by bone marrow cells – or the sensitivity of these cells to cytokines – is altered by the aging process. Finally, we are attempting to control bone remodeling by manipulating the development of bone-cell progenitors in the marrow by antagonizing the cytokines that have adverse effects on bone balance, or by enhancing the effectiveness and targeting of cytokines with beneficial effects. Theoretically, by such means, one could tilt the balance between bone resorption and bone formation in favor of the latter and thereby restore skeletal mass. The best of our current therapeutic options can only slow or stop bone deterioration. ■

HOT METHODS CLINICS
continued from page 13.

a phage coat protein that is expressed on the phage surface.
9. The restricted antibody DNA fragments are ligated into this cloning vector, which has been appropriately restricted.
10. *E. coli* cells are transformed with the recombinant phagemids, thus generating millions of copies of candidate antibodies.
11. Transformed bacteria are infected with helper phage that rescue the phagemids, facilitating their reproduction and protein expression.

II. Detection of recombinant phage
1. An ELISA is used to detect recombinant antibodies that are expressed on the phage surface.
2. The antigen for which an antibody is being sought is coated onto the wells of a microtiter plate.
3. The recombinant phage are added to the wells, allowing the antigen to interact with the antibodies that are expressed on the surface of each phage.
4. The plate is washed.
5. Horseradish peroxidase-conjugated antibody that recognizes the phage coat protein is added to detect the presence of any antigen-bound recombinant phage. A positive color reaction in a well identifies a recombinant antibody-producing phage.
6. These phage are eluted from the ELISA-positive wells and are used to reinfect bacteria to purify the phage through multiple rounds of detection until a pure clonal population is achieved.

III. Production of recombinant antibody
1. If desired, the original phagemid vector can be replaced with a modified phagemid that will produce soluble antibody molecules with an epitope tag at the

continued on page 22.

The Electronic Catalyst

The NIH Catalyst is now available electronically, as is the latest news from Building 1 on the DDIR's Bulletin Board. Current and back issues of both electronic publications can be accessed through the Campus Information Menu on Gopher or Mosaic. ■

RECENTLY TENURED

Stephen Altschul *received his Ph.D. from the Massachusetts Institute of Technology in Cambridge in 1987. He came to the National Center for Biotechnology Information (NCBI) at NLM in 1989 and is currently a mathematician in its Computational Biology Branch.*

My research interests center on developing improved computer methods to compare DNA and protein sequences. The problems that I study may be divided roughly into three domains: the definition of measures that reflect biological relatedness, the development of algorithms for locating similar sequence regions, and the statistical assessment of sequence similarities. These domains are interconnected, and I try to approach each with the other in mind. For example, the choice of a biologically sensible but overly complicated measure of relatedness or similarity may entail unacceptable algorithmic and statistical complications. Alternately, a statistical understanding can sometimes point to more sensitive measures and improved algorithms.

One focus of my work has been to develop rapid and sensitive methods for searching biological-sequence databases. Collaborating with scientists at NCBI and elsewhere, I helped develop the BLAST family of database search programs which are more sensitive than their predecessors. My contribution to this project centered on the statistical description of the similarities among database searches. Optimal segment-pair scores obey an extreme value distribution, and generalizations to multiple high-scoring segment pairs and multiple scoring systems are possible. These statistical results have suggested alternative definitions of sequence similarity and led to the construction of amino acid and nucleotide substitution matrices of greater sensitivity.

I have also been interested in the many questions that spring from the global or local alignment of multiple sequences. One such question is how to deal with the biases present in any collection of related biological sequences where none of the "data points" are independent, but all are correlated to one degree or another. I have helped develop the MSA program that constructs global multiple alignments and the MACAW and Gibbs programs, which are used for local multiple alignment. These latter two programs are particularly useful in the discovery of shared sequence patterns among proteins.

Most recently, I have been working on various problems that arise in the construction of position-dependent weight matrices or profiles for the description of protein motifs. Many different methods for building such matrices have been described, but a good theory to guide their construction has only recently begun to emerge.

David L. Armstrong *received his Ph.D. from Caltech in 1979. He has been the leader of the Membrane Biophysics group in the Laboratory of Cellular and Molecular Pharmacology (LCMP) since he came to NIEHS in 1987 as a Senior Staff Fellow.*

My postdoctoral collaborators and I use the patch-clamp technique to study the physiological properties and regulation of ion channel proteins in immortalized cells from the mammalian neuroendocrine system. On the time scale of milliseconds to hours, these membrane proteins are primary determinants of neural signalling, hormone secretion and cardiovascular contractility. By measuring the ionic current through individual channel proteins as they open and close in small, cell-free patches of membrane, we have demonstrated that both voltage-activated calcium channels and calcium-activated potassium channels are regulated reciprocally by reversible protein phosphorylation.

We have also used these channels as a sensitive molecular assay to identify two new signal transduction pathways through which inhibitory neuropeptides stimulate the serine/threonine-directed protein phosphatase, PP2A. One pathway is activated by neurotransmitters like somatostatin that stimulate archidonic acid metabolism through pertussis toxin-sensitive GTP-binding proteins. The second pathway is activated by natriuretic peptides through receptors with intrinsic guanylyl cyclase activity. Understanding these pathways may have important implications for human health disorders because PP2A has been identified as the primary target of a growing number of potent microbial toxins and xenobiotics in the environment. The recent demonstration that tyrosine-directed protein kinases regulate PP2A and that somatostatin and other neuropeptides inhibit cell proliferation, suggests that the same protein phosphatase cascade may potentially modulate both electrical excitability and cell proliferation.

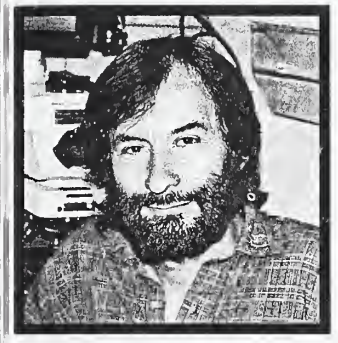
Fred Miller *received his M.D. and Ph.D. from Case Western Reserve University in Cleveland in 1979. He came to NIH from Stanford University Medical Center in Stanford, Calif., in 1983. Since 1990, he has been a Medical Officer in the Molecular Immunology Laboratory, CBER.*

Our laboratory has been studying how the interactions of environmental and genetic factors can give rise to human autoimmune disorders. We are using a multidisciplinary strategy involving epidemiologic, immunologic, genetic, and molecular biologic techniques and are focusing our efforts on idiopathic inflammatory myopathies, a group of systemic connective tissue diseases marked by chronic infiltration of muscle by activated T and B lymphocytes.

Because many diseases are actually collections of different disorders grouped together by a common feature, we have been investigating ways of dividing diseases into their minimal components to understand risk factors and pathogenesis. We have discovered that the myositis syndromes are in fact composed of many distinct disorders, some of which are characterized by unique clinical or serologic features, and tend to develop in individuals who inherit specific combinations of genes encoding immunoglobulin and human leukocyte antigen (HLA) molecules.

The acute onset of myositis and the geographic clustering and seasonal associations with the onset of disease in groups of patients who make autoantibodies directed against cytoplasmic translational components imply that environmental agents may be important in initiating myositis in some patients. In addition to conducting worldwide epidemiological studies of myositis, we are investigating the possible role of environmental exposures to certain infectious agents, drugs, dietary supplements, medical devices, and occupational and other toxins as triggers of inflammatory muscle disease in susceptible individuals. Our data suggest that the development of myositis in groups of people with some of these exposures is related to the presence of specific HLA alleles that regulate immune responses. One of our current goals is to understand the mechanisms responsible for the genetic risk factors linked to these environmentally associated autoimmune diseases.

Milan Jamrich *came to NIH in 1983 from Yale University in New Haven, Conn. He is currently a scientist at the Laboratory of Developmental Biology, Division of Cellular and Gene Therapy, CBER.*

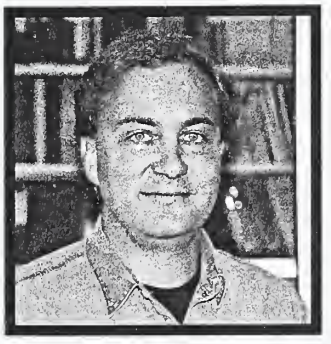


The goal of our laboratory is to understand pattern formation in *Xenopus* embryos. We are concentrating specifically on two groups of transcriptional regulators – those containing the fork head and the homeobox DNA-binding domains. We isolated the first *Xenopus fork head* gene *(XFKH1)* and showed that it is likely to be involved in axis formation. We showed that this gene belongs to a larger gene family that, like the homeobox genes, seems to be involved in aspects of pattern formation and cell differentiation.

During the past five years, we have also isolated several novel homeobox genes involved in pattern formation. We are now specifically concentrating on those involved in craniofacial development. Most recently, by using the example of two novel homeobox genes specific for anterior pituitary and retinal development, we demonstrated that ammonium chloride can induce anterior regions of the amphibian head in uncommitted ectoderm. We expect this research to provide insights into the early processes of amphibian head formation.

In addition, we have initiated similar research into pattern formation in zebra fish embryos, and we have constructed a cDNA library specific for regenerating *Xenopus* limbs that should be helpful in understanding amphibian limb regeneration.

Michael Lichten *joined the Laboratory of Biochemistry at NCI in 1987, and he is now a Microbiologist in the Microbial Genetics and Biochemistry Section there. He received his Ph.D. in biology from the Massachusetts Institute of Technology, Cambridge, in 1982.*



My laboratory studies meiotic recombination in the yeast *Saccharomyces cerevisiae*. In addition to playing an important role in the meiotic chromosome pairing and disjunction events that ensure the segregation of an intact haploid genome to gametes, recombination is an important component of the cell's efforts to maintain genome integrity in the face of DNA damage. Yeast are ideal organisms in which to study the molecular mechanism of recombination because the high recombination frequencies and temporal synchrony of meiosis in yeast facilitate the study of recombination events at the DNA level. We are also interested in uncovering factors and control mechanisms that determine where and when recombination occurs during meiosis.

Our general strategy in studying the mechanism of meiotic recombination has been to identify loci that display high frequencies of recombination. To help characterize molecular events that occur in the course of meiotic recombination, we introduce mutations that create both genetically scorable markers and restriction-site polymorphisms and we use physical techniques to probe DNA structure at these loci. We have used this approach to determine when and how meiotic recombination is initiated, when parental contributions to recombinants are first stably joined by heteroduplex DNA, when intermediates are resolved to form mature recombinant products, and what the structure of those products are. We plan to continue this approach to isolate and characterize early intermediates in recombination and as a tool to help determine the gene products and enzymatic activities responsible for their formation and resolution.

Our lab is also interested in the factors that determine the frequency and location of meiotic recombination events and the relationship between meiotic recombination and homolog pairing. In yeast, the distribution of meiotic exchange events is determined primarily by the location of meiosis-induced double-strand DNA breaks (DSBs), which initiate meiotic recombination. We have demonstrated a one-to-one correspondence between DSB sites and sites that display nuclease hypersensitivity in digests of chromatin. This indicates that chromatin structure plays an important role in determining where meiotic recombination is initiated and also shows the utility of DSB site analysis as a probe of chromatin structure in vivo. Experiments in progress point toward the existence of elements that act over large regions (about 3 - 5% of a chromosome) to modulate the level of recombination in a gene and also suggest that homologous chromosomes associate before the onset of meiotic recombination.

Teizo Yoshimura *received his M.D. in 1979 and his Ph.D. in 1983 from the Kumamoto University School of Medicine, Kumamoto, Japan. He came to NIH in 1985 as a Guest Researcher and is now a Visiting Scientist in the Immunopathology Section of the Laboratory of Immunobiology, NCI-FCRDC.*

My main focus since I began my research at Professor Hideo Hayashi's lab in Japan in 1979 has been to investigate the mechanisms of leukocyte infiltration into inflammatory reaction sites. The immigration of blood leukocytes to inflammatory reaction sites appears to be mediated by chemoattractants such as N-formyl-methionyl-leucyl-phenylalanine (FMLP); C5a, a component of serum complement; and chemotactic cytokines, also known as "chemokines," which are produced at the sites. In 1987 and 1988, my colleagues at NCI and I purified and cloned two major chemokines, neutrophil attractant protein-1 (NAP-1)/interleukin-8 and monocyte chemoattractant protein-1 (MCP-1), that, as their names indicate, attract neutrophils and monocytes, respectively.

On the basis of in vitro studies and findings by immunohistochemistry and in situ hybridization on human tissues, we speculate that NAP-1 and MCP-1 are involved in various infectious diseases and tumors with neutrophil or monocyte infiltration. This would include tumors such as malignant glioma or malignant fibrous histiocytoma, which are infiltrated by macrophages. But the role of the infiltrated macrophages, and whether they are beneficial to the host, remains controversial. My current interest is in the roles of the two factors in animal models. Although mice and rats would be a first choice for this in vivo work, NAP-1 cannot be found in these animals. Therefore, we have been pursuing other animal models while continuing to study the roles of MCP-1 in rats.

After years of steady progress toward our goal of understanding these proteins, we are excited that we have finally come to a stage where we can test the effects of a neutralizing antibody against rat MCP-1 in rat disease models. I hope that my continued research at NIH will lead us to a better understanding of the involvement of NAP-1 and MCP-1 in inflammatory diseases and tumors, possibly paving the way for new approaches to the control of leukocyte infiltration that can result in tissue destruction. ■

FUNCTIONAL INTERACTION BETWEEN P53 AND HUMAN CYTOMEGALOVIRUS PROTEINS: POSSIBLE ROLE IN RESTENOSIS FOLLOWING CORONARY ANGIOPLASTY

One of the major breakthroughs in cardiovascular therapeutics over the past two decades has been the development of catheter-based angioplasty to open constricted coronary and peripheral arteries without surgery. This is accomplished by passing a catheter with a deflated balloon at its tip into the obstructed artery and then inflating the balloon. Atherosclerotic plaque is compressed and remodeled by the expanded balloon, thereby relieving the obstruction. Although the initial success rate of balloon angioplasty in opening stenotic coronary arteries approaches 95%, recurrent narrowing, or restenosis, occurs in 25 - 50% of patients within six months.

The causes of restenosis are complex and undoubtedly multifactorial; however, one of the dominant mechanisms involves injury-induced activation of the smooth muscle cells (SMCs) located in the media of the vessel wall. Activiating the SMCs results in their proliferation and migration to the subintima, where they continue to proliferate and secrete extracellular matrix. As this neointima expands, it obstructs the vessel lumen and diminishes blood flow, thereby causing myocardial ischemia. The SMC proliferative response to angioplasty is a normal healing response to injury, and hypothetically, the development of restenosis might well be due to individual differences in the magnitude of a response that has a normal bell-curve distribution. Although this is a plausible explanation, we were intrigued by an alternative hypothesis.

WE WOULD SPECULATE THAT HUMAN CYTOMEGALOVIRUS MAY BE AN ADDITIONAL, PERHAPS POTENT, RISK FACTOR FOR THE DEVELOPMENT OF RESTENOSIS AND ATHEROSELEROSIS.

More than 20 years ago, Benditt and Benditt (1) published a seminal but still-controversial paper in which they postulated that atherosclerotic plaques might be a form of benign neoplasia. Their hypothesis was based on the studies of atherosclerotic plaques of women who were heterozygous for glucose-6-phosphate-dehydrogenase and who, therefore, expressed both of the two major isoforms of the allele. Instead of finding the expected normal mosaic pattern of expression for these two isoforms, the large majority of atherosclerotic plaques contained SMCs expressing only one isoform. This finding was compatible with the idea that each plaque contained SMCs derived from the clonal expansion of a single cell. The authors postulated that the SMCs of an atherosclerotic plaque were the progeny of a single cell that had acquired a genetic mutation conveying a selective growth advantage, thereby leading to clonal expansion to form the plaque. They further suggested that the mutational genetic event could be due to a virus.

To examine further the basic tenets of the Benditts' hypotheses about atherosclerosis, we explored the possibility that restenosis may, at least in a subset of patients, be caused by some mutational process that conveys to an SMC, or group of SMCs, a selective growth advantage, such that when the cells are activated, as by injury, they will proliferate excessively and contribute to the development of restenosis.

We focused on p53 as the candidate gene in initializing the growth response. Wild-type p53 is a tumor-suppressor gene; its gene product is a nuclear protein that, in its hyperphosphorylated state, blocks progression of cells through the cell cycle. Mutations of this gene eliminate the suppressor function and constitute the most common genetic defect associated with a large number of human cancers (2). Cell transformation and the development of malignancies associated with p53 mutation require multiple genetic defects. We wondered whether, in at least some patients undergoing angioplasty, an *isolated* defect in p53 function in a subset of vascular-wall SMCs might contribute to excessive proliferation (without transformation) and, thereby, to restenosis.

Wild-type p53 protein has a very short half-life (about 20 minutes) (3). Partly as a result of this, its steady state concentrations are so low that the protein cannot be detected in normal cells by conventional immunohistochemical methods. In contrast, many missense mutations that impair the suppressor function of p53 and are associated with malignant transformation also prolong p53's half-life, leading to elevated protein concentrations and p53 immunopositivity. We, therefore, first determined whether restenosis tissue, obtained by atherectomy, contains SMCs that are p53-immunopositive. (Atherectomy involves advancing a catheter with a cutting implement at its end into a stenotic coronary segment. The lesion is then resected, and the catheter allows retrieval of the atherosclerotic tissue. Atherectomy can be used as an alternative to balloon angioplasty and is the procedure of choice when morphological characteristics of the lesion suggest balloon angioplasty will not successfully open the stenosis.)

Analysis of the lesions of 60 patients who had restenosis showed almost 40% of the lesions were immunopositive for p53. When we made this observation, it was commonly believed that p53 immunopositivity of cells in a malignant lesion was synonymous with p53 mutation. Indeed, David Lane of the University of Dundee in Scotland and one of the world's experts in the immunohistochemistry of p53, wrote, "Overexpression of p53 is synonymous with mutation." (4). So at this point in our studies, we really thought we had come upon an extremely important linkage between mutations in the p53 gene and an atherosclerotic-related process. On a molecular level, this observation would have connected the mechanisms responsible for cancer with those involved in atherogenesis.

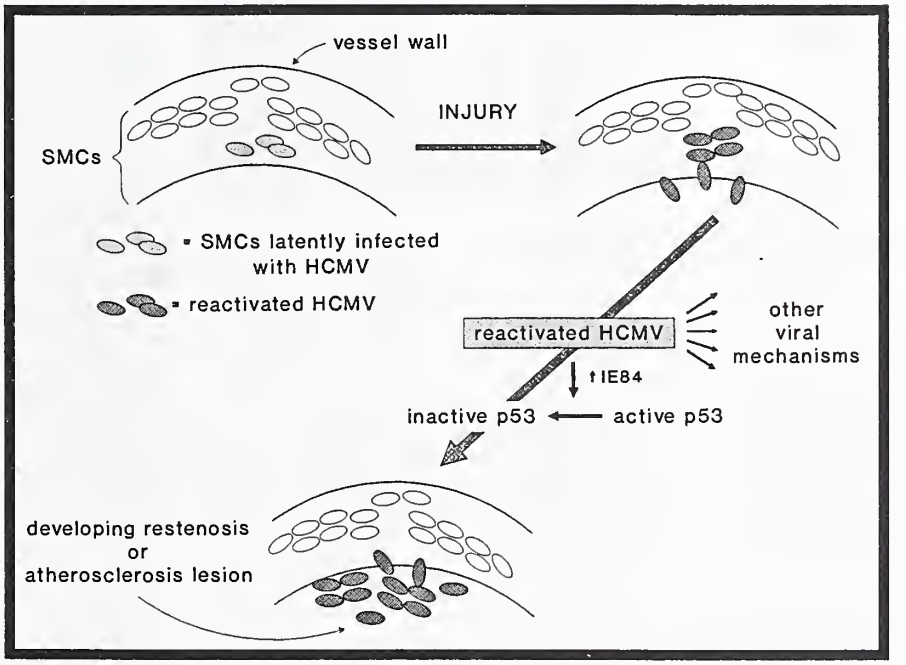
Our next task was sequencing the genomic p53 DNA present in the restenotic tissue, and the original research team, Speir and Epstein, enlisted the aid of Rama Modali, who had previously studied p53 with Curt Harris at NCI. (We also received extremely helpful advice from Harris as well as from his associate Bill Bennett.) Expecting to find a mutant p53 gene in the atherosclerotic tissue, we were dismayed when sequencing revealed only normal p53.

This left us initially at a loss to explain the p53 immunopositivity. At about this time, however, we became aware of the work of several labs, including those of Peter

Edith Speir, Toren Finkel, and Stephen E. Epstein
(Cardiology Branch, NHLBI)

Howley, then at NIH (5), and Arthur Levine at Princeton University (6), demonstrating that occasionally tumors are immunopositive for p53 despite the absence of mutations. Both Howley and Levine found that some of these p53 immunopositive-but-nonmutant tumors were triggered when wild-type p53 formed complexes with cellular (7) or viral oncoproteins (5), prolonging p53's half-life and steady state levels. These complexes, which also inactivate p53's suppressor function, are formed with oncoproteins encoded by DNA tumor viruses such as adenovirus, SV40, and Epstein-Barr virus. We wondered whether the p53 immunopositivity we found in the restenosis lesions was caused by a similar mechanism.

We then began to search for a candidate virus and settled on human cytomegalovirus (HCMV) as the most likely suspect because the literature was replete with studies suggesting that this herpesvirus plays a potential causal role in the genesis of atherosclerosis. A large percentage of individuals over age 50 have been infected with HCMV. Several studies have demonstrated HCMV sequences in the wall of atherosclerotic vessels. Marek's disease virus, a herpesvirus, produces lesions in chickens and Japanese quail very similar to those seen in human atherosclerosis (8). Evidence implicates a causal role of HCMV in the development of accelerated coronary atherosclerosis in cardiac transplant patients (9). Finally, other studies have shown cellular effects of HCMV that predispose infected cells to processes identified with atherogenesis, including potentiating DNA replication and mitotic activity (10); inducing the secretion of growth factors and the expression of cell adhesion molecules; and inducing defects in mechanisms responsible for removal of cholesterol from cells.



Hypothetical model of human cytomegalovirus in atherosclersis and restenosis. Upper left: Blood vessel wall containing smooth muscle cells (SMCs), some of which are latently infected with HCMV. Upper right: Following exposure of the vessel wall to prologed hypertension, elevated cholesterol, substances contained in cigarette smoke, or other risk factors or injury, as in angioplasty, HCMV is reactivated and expresses many of its genes — including immediate-early genes. Through multiple mechanisms, including inactivation of the tumor-supressor gene product p53, the proteins encoded by these genes augment the SMC response to injury, encouraging extensive SMC proliferation. The resulting mass of tissue compromises blood flow.

At this critical juncture of our studies, we sought the advice and collaboration of Eng-Shang Huang, who was working at the University of North Carolina at Chapel Hill and who is one of the world's experts in HCMV. Also, Toren Finkel, a cardiologist and molecular biologist, joined the lab and began to play an important collaborative role in the project.

Our expanded team then started a series of studies designed to test the hypothesis that HCMV was playing a role in restenosis. We first analyzed the tissue on which we had performed our immunohistochemistry to determine whether HCMV sequences were present. We found a highly significant concordance between p53 immunopositivity and the presence of HCMV sequences, as determined by the polymerase chain reaction (PCR): 85% of the p53 immunopositive lesions contained HCMV sequences, whereas only 27% of the p53 immunonegative lesions contained HCMV sequences. The correlation between p53 immunopositivity and HCMV suggested that HCMV was not just an innocent bystander, present only because of the high prevalence of HCMV in the adult population. To test whether HCMV plays causative role, we performed an additional series of studies.

We first cultured smooth muscle cells derived from the lesions to determine whether the HCMV sequences present in the lesions were capable of expressing viral protein products. Immunohistochemical evidence indicated that IE84, one of the two major immediate-early gene products of HCMV, could be expressed. Moreover, whenever SMCs expressed IE84, they also were immunopositive for p53.

We next demonstrated that when cultured normal human SMCs were infected with HCMV, infection caused p53 immunopositivity, with remarkable temporal concordance between the appearance of IE84 and p53; moreover, the two proteins co-localized within cells. Then, searching for a functional interaction between IE84 and p53, we co-transfected expression vectors containing the genes encoding each of these proteins and a reporter-gene construct. We wished to determine whether IE84 could inhibit the demonstrated capacity of p53 to transactivate a promoter containing p53 binding elements placed upstream

continued on page 22.

LIFE AFTER NIH:
continued from page 1.

not just on how to design a good experiment, but on how to get things done through the bureaucracies." Iyer is not alone in her feelings. In studies last year, two NIH task forces — the Taskforce on the Status of Women Scientists at NIH and the Taskforce on the Status of Minority Scientists in the Intramural Program — concluded that NIH has failed to provide career guidance to women and minority postdocs at NIH. But, says Rodgers, who headed the committee to implement the recommendations of the minority task force, the problem goes beyond women and minorities. When Rodgers and his team talked to nonminority postdocs as controls for the data they were gathering on minorities, they found that nonminority scientists echoed minority scientists' views on the inadequacy of mentoring at NIH.

Griffin Rodgers, who heads the committee to implement the recommendations of the minority task force, says, senior scientists must teach trainees not just the trade but the tricks of the trade.

Michael Fordis, director of the four-year-old Office of Education, says that career development is a tremendously high priortiy for NIH.

"Career development and mentorship are really crucial issues that are coming into the fore at NIH," says Rodgers. He speculates that there may always have been a lack of structured career development guidance at NIH but that its absence is being felt keenly now because more and more, "young scientists are finding that learning science is not enough, they need somebody to show them the ropes."

The issue, says Rodgers, is not that NIH does not have good mentors — "there are many good mentors at NIH" — but that the quality of mentorship is not uniform throughout the institution. Further, say Fordis and Rodgers, until recently, NIH did not keep track of what happened to trainees once they left the NIH, and therefore had no definitive measure of the effectiveness of mentorship and training programs. Fordis adds that unless NIH addresses these issues, it cannot maintain its standing as an excellent postdoctoral training ground. "The point is that you cannot attract quality people unless you offer them the highest-quality training experience with a host of opportunities, for long-term career development," says Fordis.

Rodgers, who is now heading a task force to examine mentorship issues at NIH, outlines a few themes for discussion: first, says Rodgers, it is important for people to understand the distinction between a supervisor and a mentor. "Supervisors oversee your work, whereas mentors are trusted counselors who take Fellows under their wings and teach them not just technical competence but also how things work, how to get things done, how to network, and who can help them grow professionally. Mentorship also means adapting your style to each trainee, says Rodgers. "'One size fits all' is not going to work with trainees," says Rodgers. "Some trainees are very independent and others require a lot more guidance," and scientists should change their mentorship styles to suit each individual. Mentors must also know how to read trainees' signals and learn to let go when it is time, says Rodgers.

Some administrators have suggested that mentorship at NIH can be improved by rewarding good mentorship and making it a part of scientists' performance evaluation. Rodgers is ambivalent about this suggestion. Some scientists are born mentors, says Rodgers, but those who are not can learn essential mentorship skills through formal training. He says NIH may want to develop a training program that teaches would-be mentors these skills. Another option, says Rodgers, is that if the trainee's preceptor is unable to be anything more than a supervisor, NIH may be able to establish other avenues that postdocs can turn to for the help that a mentor would provide.

Fordis says that the Office of Education already has several such programs in place. The OE's advisory and support services, available to postdocs on an individual basis, provides guidance on educational programs on campus and helps fellows locate employment opportunities, says Fordis, who has contacted biotechnology firms, pharmaceutical companies,

Pharmacology Fellowships Available

The Pharmacology Research Associate (PRAT) Fellowship Program is currently accepting applications for postdoctoral fellowships at NIH. Completed applications are due Oct. 1, 1994 for two-year fellowships beginning on Oct. 1, 1995. The goal of the PRAT Program is to develop future leaders in pharmacological research. The procedure involves co-application of a potential fellow with an approved preceptor in the PRAT Program. A brief research plan is required, as well as a statement of how the research will advance the field of pharmacology, along with transcripts and letters of recommendation. Applications must be U.S. citizens or permanent residents and cannot already be fellows at NIH at the time of application, but may join NIH prior to Oct. 1, 1995. For information on the eligible preceptors and for application forms, please call Sandy Cain, PRAT Program Assistant, NIGMS at 4-7808 or fax inquires to 4-7728. For further discussion of the PRAT Program, contact Alison Cole or Rochelle Long, PRAT Program Co-Directors, NIGMS, at 4-7808." ■

and other institutions for possible position openings. Fordis is also urging NIH faculty to fax vacancy announcements that they receive by mail to his office. Fordis plans to post a compiled list of vacancies on the EMPLOY conference on NIH-EDNET (see box on page 22 for instructions on accessing this network). Also in the works at OE is a handbook for all postdoctoral fellows that covers, among 70 other topics, educational resources, counseling services, daycare facilities, intellectual property issues, parking, scientific equipment rental, and policies and procedures under the different funding mechanisms at NIH. The first edition of the handbook is expected to be out by the end of this year.

Kanak Iyer, an NIMH postdoc, says new career development programs can't come soon enough.

The OE has also helped postdocs organize a Fellows Committee. This year-old group tackles several issues that are relevant to postdocs, including the quality of their life on campus, the problems they face, and their sense of community. The committee also started the Fellows Seminar Series, put together by Fellows to cover topics they are interested in. The seminar series also functions as an advertisement for the committee and their representatives. Recently, the committee has focused on career development issues and held a seminar on "Pursuing a Career in Academia," featuring talks by former NIH postdocs who now have successful academic careers. Speakers recounted their experiences getting jobs, funding, and tenure and spoke of things they would do differently. In another pilot program, called the Ambassador Program, Fellows interested in recruitment went back to their home institutions to talk about NIH training. To provide incentives to NIH teachers, the committee offers an annual teaching award in clinical research and is planning to offer a similar one for basic research.

The OE is also compiling a list of all NIH Fellows and each institute's representative to make it easier for Fellows to get to know each other and provide a means to select future representatives. Fordis says that his office has also set up a new electronic conference called P-DOC TALK on NIH-EDNET (see box on page 22 for instructions on accessing this network) in which fellows can announce activities, suggest ideas, and discuss issues. In addition to working on issues of long-term career development, the committee is working on ways to make new Fellows feel welcome, Fordis says. In addition, the OE is also developing a tracking system to record how Fellows leaving NIH are faring in the outside world.

Fordis is hopeful that these programs and others in the future will improve the quality of life and training at NIH, but he adds that for these efforts to really succeed, it will take a recommitment from everybody on campus, including the postdocs, "who also have to be proactive." He adds that the renewed commitment is already coming from various groups on campus, where the buzzwords now seems to be "career development and mentorship." ■

FAX-BACK FEEDBACK

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the specific things we must do here at NIH. But one thing is for sure: we must not just address these issues with well-written intellectual reports, but we must deal with them as we do scientific issues and mandated problems. I've witnessed several complicated problems solved in less than the six years I've been here. My concern is the young minority (Black) scientists. The most important element in preparation for a research career is the opportunity to conduct research in an environment that is structured to do so. It must be under the supervision of skilled mentors unhampered by diversions (cultural differences, low pay, etc.) in a high-quality research setting. I would highly recommend that all those concerned with this issue review the article in *The New England Journal of Medicine* mentioned above. I believe it provides an excellent historical perspective on these issues as well as excellent recommendations on solving the problems." — *Joseph L. Bryant, NIDR*

"As a minority scientist, I was told that children and relatives of NIH scientists are not encouraged to participate in the NIH Summer Internship Program since they have little chance of and low priority for acceptance. This is counterproductive, because these are the kids who will be most interested in following in the footsteps of their elders." — *M. Datiles, NEI*

"Tenured IRP scientists in 1992: Blacks and Hispanics, 1.39%; Native Americans, 0%; others, 98.61%! As 'one cannot build a pyramid from the top,' support of minority education and opportunities for research are especially required if these dismal statistics are to be improved significantly. Scientists can make a difference by investing as little as a few hours a month to tutor, mentor, and train students." — *R. Mejia, NHLBI*

Grants vs. Grant Applications

"In your very useful article in the July issue of *The NIH Catalyst*, you summarized Dr. Jerome Green's advice to those applying for a grant. You say that he recommends that they observe the rules of good writing. In the parlance of many aspirants for NIH funds, we note that they often fail to distinguish between the word *grant* (an appropriate or award) and the phrase *application for a grant.* Thus they speak of "grant writing" or "having grants rejected," etc., when, of course, they mean "writing an application for a grant" or "having their grant application rejected." However, both the headline of your lead article and much of your own text perpetuates their malapropism. I'm sure you would agree that those of us who are responsible for disseminating Dr. Green's advice should also follow it." — *Charles Kennedy, NIMH* ■

FUNCTIONAL INTERACTION
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from the CAT reporter gene. We found such an interaction; the transactivational effects of p53 were markedly inhibited by co-expression of IE84. We also found that the two proteins were capable of physical association, demonstrating that they co-immunoprecipitated in a baculovirus - insect cell system.

These findings, in addition to the fact that herpesviruses can remain in a latent state in infected host cells for decades, suggested to us a new pathophysiologic model for restenosis development: in that subgroup of patients who have been exposed to HCMV, angioplasty-induced injury to the vessel wall reactivates latent HCMV, which in turn causes p53 inhibition and other cellular changes that predispose SMCs to proliferate. If HCMV plays such a role, the mechanisms underlying its actions must be complex because the virus is large and has more than 200 open-reading frames. Our results suggest that one key mechanism is the interaction between HCMV-encoded protein(s) and p53. And because of the many similarities between restenosis and atherogenesis itself, it is also possible that similar HCMV-mediated mechanisms might contribute to the initial development of arteriosclerosis.

If additional studies confirm this working hypothesis, we would speculate that the most likely role for HCMV would be as an additional, and perhaps potent, risk factor for the development of restenosis and atherosclerosis. It might play a role analogous to that of hypercholesterolemia — not everyone with elevated cholesterol concentrations develops atherosclerosis, but the elevated concentrations predispose individuals to its development in the presence of additional risk factors.

We are currently pursuing several lines of research. Zhou Yi-Fu in our lab has just found that CMV-infected rats undergoing balloon injury of the carotid artery show greater neointimal response to the injury than do uninfected controls — a finding that supports the hypothesis that HCMV contributes to the development of restenosis in patients. We are also gathering data in a collaborative, prospective study with Martin Leon at the Washington Hospital Center to determine whether patients with previous HCMV infection have an increased incidence of restenosis following successful angioplasty. Zhou and Tom Johnson are exploring other cellular mechanisms by which HCMV might contribute to atherogenesis. Esther Guetta is studying the molecular mechanisms by which the virus is reactivated from latency, and, with Tomoko Shibutani, we are exploring the role of free radicals in viral gene expression and trying to develop clinically useful inhibitors of such expression. ■

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HOT METHODS CLINICS
continued from page 15.

carboxy terminus. A monoclonal antibody is available that recognizes this epitope tag.

2. Soluble antibody molecules are produced by the phagemids and accumulate in the periplasm of the bacteria, and then leak into the culture medium. The bacterial culture medium is collected.

3. The epitope tag antibody is used to purify the recombinant antibody molecules from the culture medium via affinity chromatography. ■

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Recombinant phage antibody system protocol and ordering information: 1994 Pharmacia Biotech Data File available by fax from Verna Frasca, Ph.D., phone 800-526-3593; fax 908-457-8100 or 800-329-3593.

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How to Access NIH EDNET

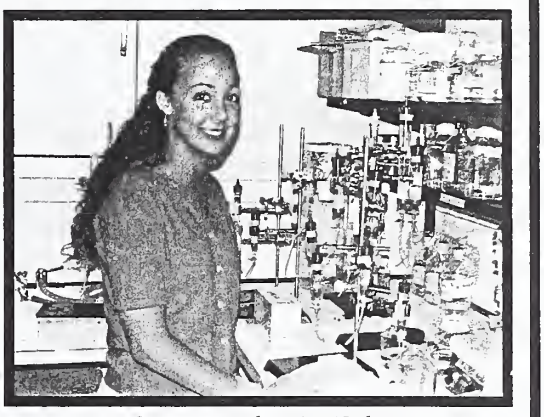
You can access the NIH EDNET Bulletin Board conferences via Internet (wylbur.cu.nih.gov) or modem (1,301-402-2221 or 1,800-358-2221) with parameters set at "7,Even,1". When connected to NIH, type in ",vt100" for terminal emulation, and "NAK" for initials. For help, call Liz Hickman at 402-1908. ■

NIH Summer Students Hope to Launch Journal For Youngest Scientists

If you think postdocs have trouble getting their articles into prestigious journals, just imagine the problems of authors who don't even have M.D.s or Ph.D.s yet....

Shervin Pishevar, an undergraduate who has spent two summers at NIH, felt the problem so acutely that he decided to do something about it with the help of Iris Kedar, another summer student. Pishevar and Kedar decided to start a scientific journal for high- school students and undergraduates.

"It's about empowering young people," Pishevar says of the quest to create the *International Journal for Young Scientists.* Now a junior at Berkeley, Pishevar says, "It is very hard for students to get the opportunity to publish. Many students — especially women — are not given the opportunity" to publish the results of experiments they have conducted as summer students or for honors projects at their schools. Pishevar says that if a mentor doesn't sign onto a paper and then coach a student through the publication maze, the process can be extremely discouraging, if not impossible, for young students. Kedar, now a junior at Stanford, says, "The idea [behind the new journal] is to provide some recognition for young scientists to encourage them to get into research."



Summer student Iris Kedar

In a letter seeking support from Harold Varmus, Pishevar and Kedar wrote, "Isaac Newton was only 23 when he developed his theorems, Charles Darwin was only 27 when he developed his ideas about evolution, and Albert Einstein was still in his twenties when he made his greatest discoveries. It is ironic that in today's age of technology, young scientists have remained such an untapped resource."

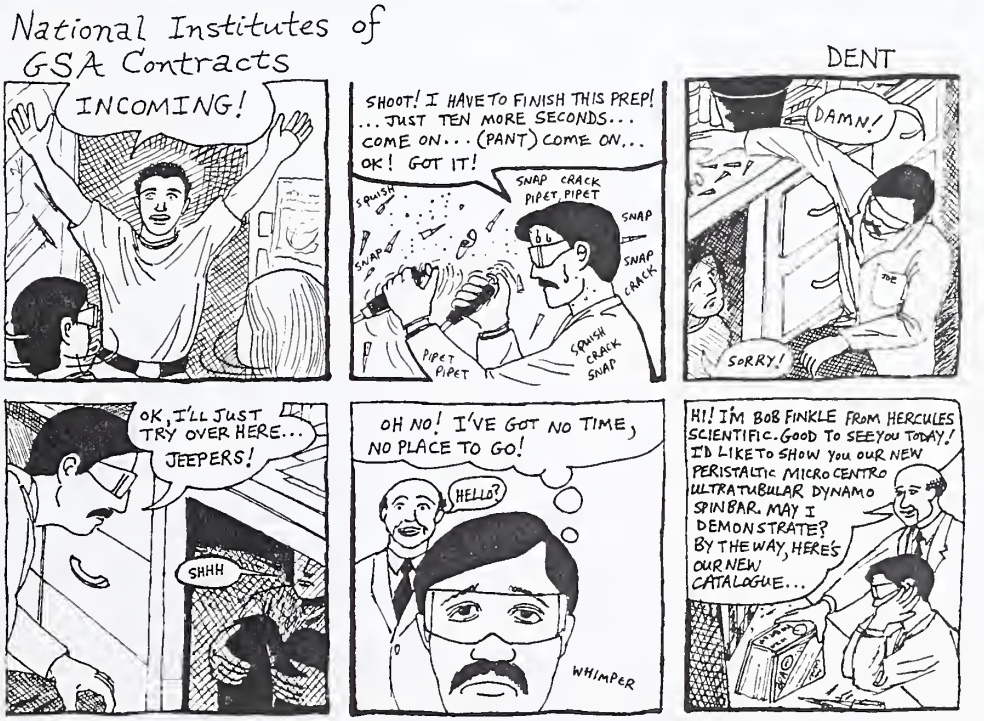
As they envision it, the journal would be refereed by full-fledged scientists, and Kedar and Pishevar extracted promises from several NIH researchers to serve as editors on the journal if and when it comes to be. Initially, they envisioned a pure-research journal, but Kedar says they are now contemplating including some news and how-to articles on topics such as "how to choose a preceptor." Kedar and Pishevar hope to base the journal and its supporting foundation, the Society for Young Scientists, at Berkeley and Stanford and to encourage the establishment of society chapters at all major universities and many high schools connected through e-mail. Pishevar would like to see monthly e-mail conferences and extensive collaborative projects and sharing of data among young scientists.

For now, Pishevar and Kedar are gathering ideas and soliciting potential backers. "Our goal is to get the first issue out by the fall of 1995," Pishevar says. "We had good experiences as summer students doing research here [at NIH]," says Kedar. "Doing your own research gives you a personal experience that makes your education your own. It is wonderful, and we want more people to get involved and to get some recognition." —*C.H.* ■

AWIS Announces '94-'95 Seminars

The Association for Women in Science (AWIS) has announced the first topics in its seminar series for 1994 - 95. AWIS seminars are held in the chapel of the Cloisters (Bldg. 60). Light refreshments and networking are on the agenda at 4:30 p.m., with seminars from 5:15 to 6:30 p.m. The first discussion, "Balancing Career and Family," led by Karen Gale of Georgetown University Medical School, was scheduled for Tuesday, Sept. 27.

The next meeting, on Tuesday, Oct. 25, features Kristina Testor, a financial consultant with Smith Barney Shearson, speaking on "Investing in Your Future." NIH's Donna Dean, Chief of the Biological and Physiological Sciences Review, Division of Research Grants, will discuss "Grantsmanship" on Thursday, Dec. 1. On Feb. 7, 1995, NIH's Florence Haseltine, Director of the NICHD Center for Population Research, will discuss "Leadership in Science: Changing the Status Quo." ■



FAX-BACK

In this issue we are asking for your feedback in four areas: improving mentorship and career development at NIH; opinions on ethical conflicts facing NIH scientsts, tips and suggestions for our Hot Methods Clinic; and clinical research at NIH. **Fax your responses to 402-4303** or mail it to us at Building 1, Room 334.

In Future Issues. . .

- Boosting Recycling and Waste Reduction
- The Office of Research on Women's Health.
- The Science Ethics Forum
- OTT Reorganizes

1) Attention Postdocs: Is it true that posdocs feel that they are floundering at NIH? How could we improve the mentorship at NIH?

2) *The NIH Catalyst* is considering starting a new column called "Science Ethics Forum" for the discussion of critial issues in the conduct of research. What do you perceive as the most problematic ethical areas for NIH scientists? What issues would you like to see discussed?

3) Do you have any tips or comments about the Phage Display and Epitope Libraries featured in this issue's Hot Methods Clinic? Do you have any tips for our next Hot Methods Clinic feature on fluorescent in situ hybridization (FISH)?. What techniques would you like to see covered in future issues? What problems have you had with hot methods described in previous issues?

4) What suggestions do you have for revitalizing the Clinical Center and maintaining the quality of clinical research at NIH? How can NIH expedite the translation of basic science into innovative clinical research? What suggestions do you have for making the Clinical Center a more attractive environment for trainees?

5) Can you provide additional insights or experiences with scientific journals that could help other researchers in the art of publishing?

The NIH Catalyst is published bimonthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 334, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; e-mail Seema_Kumar or Celia_Hooper %NIHOD1E.BITNET@CU.NIH.GOV.

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