

The NIH CATALYST

A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

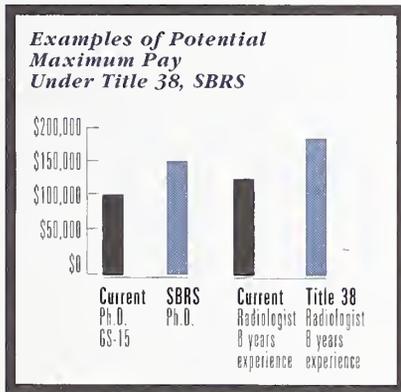
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TITLE 38, SBRS RAISE SALARY CAPS

By Celia Hooper

It's been a long time coming, but NIH is finally getting two key authorities to raise salary ceilings to help attract and retain top clinicians and other biomedical researchers. The newly approved authorities — which have been wending their way through the executive branch for months, or years, depending on how you count — are the Senior Biomedical Research Service (SBRS) and Title 38.

SBRS will be a new appointment category for outstanding scientists who do biomedical research or who evaluate clinical research. To be eligible for SBRS, scientists must be at or above the GS-15 level. SBRS personnel may earn a maximum salary equal to Executive Level I (or Cabinet Secretary's pay, currently



\$148,400), but the bulk of appointments will initially start closer to the lower end of the scale, now \$67,941.

Title 38 will allow key medical staff (at the GS-13 level and above) who provide patient care in certain subspecialty areas to earn as much as \$200,000 per year — given they qualify for the maximum salary add-ons in all categories and provided the Deputy Assistant Secretary of Health approves pay above the Executive Level I level.

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WHERE THE RUBBER MEETS THE ROAD: INSIGHTS FROM OEO'S NEW LEADER

by Rebecca Kolberg

If the new Director of the Office of Equal Opportunity (OEO) has her way, every intramural research laboratory will have a copy of NIH's new Affirmative Action Plan sitting next to the ubiquitous stacks of methods manuals, lab notebooks, and journal reprints.

"Information is knowledge. The old process really kept affirmative action in the Equal Employment Opportunity [EEO] offices, and if you wanted information, you practically had to pry it out. We want this document to be a living one that is broadly distributed," says Naomi Churchill, who became Director of OEO last September. Churchill says she also wants to make the new plan more user-friendly and thus has tried to strip away much of the legal jargon used in earlier affirmative action plans in favor of "bare-bones" language understandable to all NIH employees. "The traditional affirmative action planning process has been, frankly, pretty complicated. It was driven by lawyers at the Equal Employment Opportunity Commission [EEOC]," says Churchill, who in the 1980s worked as a staff attorney for EEOC.

After the final version of the plan comes out this spring, Churchill urges rank-and-file researchers to contact her if they find provisions that are unwork-



Naomi Churchill

For more on the Affirmative Action Plan, and a summary of the Scientific Directors' discussion of the plan, see pages 18-19.

—Lorna Heasley

able or difficult to implement. "I need to know whether or not the policies we frame are going to play in the lab," she says. "At the point where the rubber meets the road, does it make sense?"

Placing details of the Affirmative Action Plan in the hands of more scientists may help dispel what Churchill finds to be the most offensive misperception about affirmative action initiatives: that nonwhites and women are hired or promoted for jobs that they are not qualified to hold. In the past, NIH affirmative action plans based their

hiring and promotion goals on data *continued on page 16.*

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GAZING INTO THE CRYSTAL BALL: NIH'S CLINICAL RESEARCH FUTURE, PART II



John Gallin

In the previous issue of *The NIH Catalyst*, we focused on our plans for strengthening clinical research. Much of our thinking about future changes and improvements in our clinical program has centered on adapting the physical environment and streamlining operations to fit the size, abilities, and interests of our clinical research staff. But a second key consideration in the future of the Clinical Center is our charge to train clinical investigators.

Virtually since its inception in 1953, the Clinical Center has embraced a mandate that extends beyond its mission as a research hospital: to define what physicians and scientists need to know to conduct safe, effective clinical research and to make that information available to the scientific community.

With those goals in mind, NIH Director Harold Varmus has encouraged the development of a major new training initiative at the Clinical Center, and work on a core curriculum is under way. The curriculum will comprise four modules, each containing both didactic lectures and practical experience, such as interacting with mock Institutional Review Boards (IRBs) and data safety-monitoring panels. The training initiative will proceed in the following manner:

- The first module will address clinical research methods and focus on epidemiology. It will include lectures on study design and development, measurements, and issues in alternative medicine.
- The second module will address ethical and regulatory issues, including legal concerns, the role of IRBs, sex and race diversity in study populations, and scientific conduct.
- The third module will cover patient-oriented research and will review quality assurance, how to monitor clinical trials, relations with the Food and Drug Administration, information and data management, and information dissemination.
- The final module will focus on preparing and funding a clinical research study, including writing a research proposal, and technology-transfer issues.

We plan to offer the first class in April, and the course will be offered to the new group of Clinical Associates this fall. More than 100 Clinical Associates come here each year.

We must also make sure that our researchers are located in an ideal environment for training these Clinical Associates, and for conducting patient-oriented research. Clearly, the new hospital and reallocation of the Clinical Center's physical plant will have payoffs for our teaching efforts commensurate with their contribution to improving research. It is also imperative that the institutes work toward parity in the support of clinical researchers.

Some institutes have structured a superb network of computers, research nurses, and support staff to facilitate that training. Others have developed a less efficient framework. A goal of mine is to reduce this variance among institutes.

One step in that direction is to develop guidelines for training clinical researchers and for performing clinical research at the Clinical Center. The guidelines will provide criteria against which our educational tools — including teaching, mentoring, assessment practices, and the research infrastructure of the various intramural programs — can be judged. The guidelines will tell us what our training and clinical research programs should look like to produce high-quality clinical research and to train researchers

capable of conducting that research.

These guidelines must be developed with broad NIH consensus and need to be flexible so that the different institutes can tailor intramural programs to individual needs. Eventually, such guidelines may evolve into a national yardstick for training in clinical research. I believe that such guidelines are needed and that they must be sharply honed and responsive to changing needs and requirements.

In sum, this is an exciting time for clinical research and the training of clinical investigators as NIH scientists continue their roles as the nation's premier scientists. We are committed to maintaining and expanding the Clinical Center as NIH's most valuable and most efficient scientific resource.

John I. Gallin, M.D.

Director

*Warren Grant Magnuson Clinical Center
Associate Director for Clinical Research*

THE CLINICAL CENTER
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CLINICAL RESEARCH.

RE-INVENTING THE MEDICAL BOARD

by Clifford Lane, Clinical Director, NIAID

The changing face of the Clinical Center (CC) is also bringing changes to its Medical Board, giving the body a more prominent, dynamic role in the decision-making process for clinical research at NIH. Traditionally, the mission of the Medical Board, which represents and acts for the Medical Staff, has been to advise the Director of the CC and help develop policies governing standards of medical care. Until recently, the expertise of the advisory panel in other areas has gone largely untapped. However, the new challenges and opportunities for intramural research have prompted the Board to take a hard look at both its makeup and its mission.

The Medical Board is currently composed of the Clinical Directors of the Institutes and Centers that have intramural clinical research programs, the CC's Deputy Directors, the CC's Associ-

continued on page 23.

FAX-BACK FEEDBACK

On the purpose of SBRS

"Please have an article on the Senior Biomedical Research Service (SBRS) in a future issue [see article on page 1]. It was my understanding that the original purpose of the SBRS was specific — to make the NIH intramural research position pay scales and other aspects of employment more like those at universities. It seems now only to be for recruiting — why bother? Why even tell us about it? It's not for us." — J.M. Ward, NCI

The Senior Biomedical Research Service was always intended as a personnel mechanism for recruiting and retaining scientists of exceptional merit and for rewarding scientists within the intramural program with an improved career track and with higher salaries. The current formulation of SBRS emphasizes the recruitment activity but certainly does not limit SBRS appointments to outside recruits. Many of our colleagues will be placed in SBRS "tracks." We thought you would want to know about this. ■

— Michael Gottesman,
Deputy Director for Intramural Research

LETTER TO THE EDITOR

In the course of preparing a genetics core curriculum for the Genetics Interest Group, we became aware of a lack of integrated educational opportunities in several basic areas of genetics. We set to work devising an appropriate curriculum at NIH, and in the process, realized that, despite the fact that NIH has many scientists who would be well-qualified to teach these courses, it may be very difficult to induce them to do so because of the way teaching is viewed at NIH.

Specifically, tenure-track researchers and postdoctoral fellows, often the most enthusiastic teachers, are strongly discouraged from seeking or accepting teaching responsibilities. This is because they are evaluated almost solely on productivity, that is, publications. Tenure decisions depend entirely on research performance, and teaching commitments are not taken into account. Those at NIH who teach must do so under the auspices of an "outside activity," regardless of whether there is reimbursement for the time and effort spent. Teaching is not considered part of their professional responsibilities.

For a core curriculum in genetics to be successful, NIH must recognize that teaching is a valid scientific and career endeavor. Individuals who choose to participate in teaching, and thereby benefit the entire NIH genetics community, should not be penalized when the time comes to evaluate their scientific accomplishments. If the proposed curriculum is to become a reality, those who teach it should have some evidence that the NIH administration supports this view. This could come in the form of removing teaching at NIH from its classification as an "outside activity." It may also be desirable to establish some way to recognize outstanding teachers for their contribution to the NIH community.

Members of the Education Subcommittee Genetics Interest Group:

Sherri J. Bale, Ph.D., NIAMS
Miles B. Brennan, Ph.D., NIMH
Michael J. Lichten, Ph.D., NCI
Dilys M. Parry, Ph.D., NCI
Sharon Suchy, Ph.D., NCHGR
Nancy Trun, Ph.D., NCI

I heartily support your recommendation regarding course work in genetics at NIH.

The recognition of teaching as a valid function of NIH personnel is also important to me. NIH now has legal training authorities, so our staff must be teachers as well as researchers. I certainly consider teaching contributions positively when tenure decisions are being made.

With respect to teaching being an "outside activity," this should only be the case when compensation is sought from an outside source, such as FAES. According to my legal counsel, teaching intramural colleagues and students on campus and other scientists, students, and teachers off campus should be part of one's official duty if it is done without compensation, without an official appointment from the school, without unduly interfering with other NIH responsibilities and clearly within the scope of NIH's usual training and administrative authorities. The decision about whether a teaching situation meets those requirements is usually made by a supervisor and, ultimately, by a director of an institute, center, or division. I have tried to encourage such activities by example, through the Office of Education, and by persuasion. If you know of instances in which teaching activities have been unreasonably restricted, I would be willing to try to exercise my persuasive powers. ■

Michael Gottesman,
Deputy Director for Intramural Research

REAL-WORLD ETHICAL DILEMMAS: A QUESTION OF CORRECTION

In the cool, abstract atmosphere of ethics training classes, it can seem easy to discern proper conduct, especially when it comes to what other people should do. But in the real world — right now, right here, among our colleagues, even in our own labs — the issues become blurred. For example, the decision to “call” someone on their science — to say that you cannot repeat the experiments — always comes at a price and rarely earns one plaudits or pay raises. The price may be lost time, the resentment of colleagues, or even castigation as a troublemaker. If the error in the literature is inconsequential for human health or advancement of the field, a paper correcting the mistake may not get published — even though we may all agree that such a correction should be made in the best of all possible worlds. This was the situation facing a young scientist as a postdoc at an academic institution before she came to NIH. What follows is her account. I urge you to put yourself in her place — and in the place of her adviser — and consider what you would have done.

While working as a postdoctoral fellow, I started a research project that built upon results of experiments done by a former postdoc in the laboratory. Although I followed the methods exactly as described by the postdoc, my results were at odds with his previously published data. There was little question about the techniques involved because they were quite simple and widely used in the lab. What’s more, I repeated the experiment a second time and again found my results at variance with the previous work. When I reported my results to my supervisor, I was met with apparent indifference. I was encouraged to move on to another project, which I did.

The upshot was that I wasted about six months on the project. Although I was running concurrent experiments, this

particular project accounted for most of my time. I wasn’t the only person in the lab who failed to replicate results collected by the particular postdoc. I didn’t think that the trainee had intentionally misled anyone. I saw this not as misconduct but as “borderline science” — work that is not intentionally deceptive, but that through failure to follow rigorous scientific methodology results in misrepresentation of the facts. My impression was that the postdoc whose work I could not replicate believed in the results but had poor analytical skills and simply failed to recognize the weakness of the findings.



Joan P. Schwartz

Lorna Heantley

My supervisor was clearly not interested in co-authoring a report of my data, which would have been the norm for data collected in this lab. Perhaps I could have corrected

the scientific record by publishing on my own, although I seriously doubted that reviewers would have accepted my contradictory results. The published paper had virtually no implications for human health and the work occupied a specialized niche that was dominated by the lab in which I worked. Thus, it was extremely unlikely that anyone outside that particular lab would have tried to replicate the published data.

Had I been confronted with a situation in which the breach of ethics was both clear and consequential, I would have attempted to pursue the matter further. However, I didn’t view it in that light. Although the apparently honest mistake wasn’t fully rectified in the literature, it was self-correcting in the sense that, eventually, that line of research was discontinued.

This young postdoc was clearly dependent on her adviser for success in publishing, getting recommendations, and ultimately, launching her scientific career. All this might have been jeopardized had she insisted that her supervisor acknowledge that his earlier postdoc was a poor scientist and, by implication, poorly trained.

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

One particularly distressing consequence of this episode was that it left the postdoc somewhat cynical.

At NIH, I would expect that our supervising scientists would have taken a course different from the *laissez-faire* approach of the postdoc’s supervisor. Acknowledging that work cannot be repeated — even, or especially, when it is work from our own lab — should not be a big deal. After all, it’s central to the self-correcting nature of the scientific process and is in no way tantamount to an allegation of misconduct. Failing to correct errors may compound the problem many times over if others end up wasting time and resources, and if it fosters undue cynicism among our next generation of researchers.

But I suspect that similar incidents occur all the time. Few scientists would go out of their way, investing precious time, money, and personnel, to correct a suspected error in a colleague’s work if the research appeared to be largely unimportant. This choice is part of stewardship. But if the line of research has a chance of leading somewhere (and who can really know this in advance?), and if some investment has been made that provides tentative data indicating an error in the literature, we enter a gray area. How important should the research be? How much effort should we invest? What if our correcting paper is rejected? Clearly, the obligation to correct our own mistakes and those of our students is compelling. But what about the errors of a fellow postdoc or a more senior staffer in our lab?

We want to make this forum a place for frank discussion among NIH scientists, and we welcome all comments on these questions and on what you see as the best course of action in the incident described above. In a future issue, we will publish your responses. Please send your comments to *The NIH Catalyst* (fax: 402-4303) or to me (e-mail: joan_schwartz%nihod1e@cu.nih.gov). ■

INTRAMURAL BLISS? REFLECTIONS ON MIXING SCIENCE WITH MARRIAGE

*Couples are wholes and not wholes,
What agrees disagrees,
The concordant is discordant
From all things one
And from one all things.*

Heracitus, *On the Universe*, fragment 59.

With the largest concentration of biomedical scientists in the world, it's only logical that NIH would also be home to the largest number of biomedical researchers who happen to be married to each other. However, with all the attention focused on individual scientific achievement and career advancement, the strength that researchers themselves, as well as NIH as a whole, derive from these personal, and occasionally professional, alliances goes largely unrecognized.

Although NIH keeps no official tally of the number of intramural research couples, almost any intramural scientist can tick off the names of a half-dozen or more colleagues who are married to other intramural researchers. Furthermore, almost since its inception, NIH has been considered one of the more hospitable environments for dual-scientist couples, although many postdoc couples now frantically searching for tenure-track positions on the same coast — let alone the same institution — may find that difficult to believe.

"Nepotism rules were so terrible at universities when we were starting out that we were afraid that we could not work at the same place," says Thressa Stadtman, Chief of NHLBI's Intermediary Metabolism and Bioenergetics Section, who, along with her husband, Earl, Chief of NHLBI's Laboratory of Biochemistry until 1995, came to NIH in 1951.

The Stadtmans, both of whom are members of the National Academy of Sciences, have been married 51 years and tied the knot while they were still in graduate school at the University of California at Berkeley. During the couple's job hunts in the early 1950s, some universities that were courting Earl offered Thressa, who is a Ph.D. biochemist, positions with salaries scarcely better than those paid to graduate students. One benevolent institution suggested a job in the home economics department! Even when the Stadtmans were further along in their scientific careers, the dean of Tufts University

School of Medicine in Boston only half-jokingly suggested that the pair get a divorce if both wanted positions with his institution.

Although the hiring outlook for research couples may have brightened somewhat over the decades, Thressa Stadtman acknowledges that it remains a serious problem, although these days, the difficulties seem to be more evenly distributed between the sexes. She cites the case of one of her postdocs, who was not in nearly as much demand as his wife, whose research is in a more trendy field.

Typical of many scientific couples of their generation, the Stadtmans elected not to have children. "There was no way I

by Rebecca Kolberg

ther of us cared what the other said," Thressa Stadtman recalls.

In contrast, and much to their surprise, marriage has led to several fruitful scientific collaborations for another pair of intramural researchers: Karen Berman, a clinical investigator at NIMH, and Michael Iadarola, a basic scientist at NIDR. Berman and Iadarola had both been at NIH for several years before another intramural research couple introduced them, a meeting that eventually led to their marriage nine years ago.

In addition to their separate research projects, Berman and Iadarola are working together on a brain-imaging study of patients with chronic pain. Iadarola, a Ph.D. research pharmacologist in NIDR's Neurobiology and Anesthesiology Branch, says he never would have become principal investigator on a clinical trial without the encouragement and technical advice of Berman, an M.D. who is Chief of the Positron Emission Tomography (PET) Unit at NIMH's Clinical Brain Disorders Branch.

"It's actually been a lot of fun for me. I'm used to doing a lot of esoteric molecular biology," Iadarola says. "I'd probably not have taken concrete steps to implement it (the human imaging project) without Karen."

Berman, who is board certified in nuclear medicine, convinced Iadarola of the feasibility of using

PET for his studies of chronic-pain patients. She also helped him navigate the unfamiliar paperwork pertaining to radiation safety and human subjects. The imaging project is actually the couple's third, and largest, collaboration. In their first joint effort, the couple worked on an enkephalin peptide in the cerebrospinal fluid of schizophrenic patients treated with antipsychotics. The second was on the development of a SPECT ligand for the opiate receptor. So far, this union has given rise to three jointly authored papers, two patents, and another paper submitted.

As for the pros and cons of working at NIH, Berman says one drawback is that research couples usually make less money than if one or both partners were in academia or industry. "But I think we have more flexibility in lifestyle being here," Berman adds, noting that in the past few years, since the couple's two boys were born, she and her husband have made it a point to head home together in time for dinner.



Thressa and Earl Stadtman

could have children and do science and not do damage to one or the other," says Thressa Stadtman. "We have our scientific 'children,'" she says, referring to the hundreds of scientists that the couple has mentored.

Although Earl Stadtman says he doesn't think research couples at NIH fare worse than those in academia, his wife says she thinks her career might have advanced faster if she had not chosen to remain in the same intramural research laboratory as her husband. "But for every advantage, there is a price. As soon as you learn to take that view, you don't complain," she says.

Like most intramural research couples interviewed, the Stadtmans characterize their scientific relationship as one of cooperation, rather than competition. Cooperation crossed the line into collaboration only once — when they co-authored a review article on bacterial metabolism. "By the end, we were so tired of arguing, nei-

Lorna Hearley

Another benefit of being located at the same institution and working in similar fields is that it's easier for each partner to understand the pressures and demands on the other. "I think it's easier for us to understand the time you do have to put in, as well as suggest ways to compromise and anticipate time problems," Berman says.

Ronald and Gale Germain, Chief of the Lymphocyte Biology Section at NIAID and a research psychologist at NIMH, respectively, say that they think NIH research couples actually have a better quality of life than many other types of two-career couples, such as two lawyers or top executives, "whose time is much less their own." However, the Germaines, who have been married just under 10 years, add that intramural couples pay a higher price than research couples in academia with respect to the more limited scope of permitted outside activities, and to the constraints on new job opportunities because of the lack of portable grants, retirement plans or suitable local academic institutions in many fields.

However, in some instances the price paid by intramural research couples can be even higher. An intramural researcher, who asked not to be named, says that after he married a fellow in his lab about five years ago, she was forced to leave NIH due to strict nepotism rules that stipulate one spouse cannot directly supervise the other. Before their marriage, the couple had collaborated on several projects for four years, with the woman being responsible for performing some of the more innovative techniques. His wife's departure "slowed my work considerably," the researcher says. Although the female researcher has since found a job at a local university, it's not nearly as desirable a position as the one she was forced to leave at NIH, her husband says.

"I'd say it's only a good idea to get married [to another intramural researcher] if you have different skills and interests. Otherwise, it's a bummer," the researcher says. "NIH neither condones nor encourages husband-wife collaborations."

Perhaps the most commonly heard complaint in the NIH community about intramural research couples is that one partner appears blind to the other's scientific shortcomings. However, many intramural research couples say they feel they are actually harsher in their assessments of their spouse's

work than they are of other colleagues'.

"Our work areas are largely nonoverlapping, so we do not compete. For this reason, we are less specifically critical of each other's research per se, but at the same time, we are more emotionally invested in and critical of the process involved in conducting the work and getting it published, i.e., how one runs a lab or deals with working for someone else," the Germaines wrote in response to



Michael Iadarola and Karen Berman

questions posed by *The NIH Catalyst*.

As for Bruce Bunnell, a Senior Staff Fellow in gene-therapy research at NCHGR, and Paula Gregory, a Ph.D. cell biologist who is Chief of NCHGR's Genetics Education Office, Bunnell says, "We both tend to be extremely critical when we write papers. We both do it to help the other become a better scientist." That sentiment is echoed by Ann M. Gins-

berg and Marc Reitman, Senior Staff Fellows at NIDDK. Ginsberg, who studies proteins involved in mammalian fertilization, and Reitman, who studies regulation of the chicken globin gene cluster, state, "We are equally or more critical of each other's research since we care more about its outcome."

However, some researchers concede they may look more kindly upon their spouses' work — especially if it is in an unfamiliar

field — than on the work of researchers in their own specialties. "Because I am not competent in the field in which he works, I'm not critical of his work. I always assume, however, that the work he does is great," says Brenda Kirkby, a doctoral student in neuropsychology at NIMH who has been married for three years to Duncan Kirkby, a postdoc electrophysiologist with NINDS.

If the couples interviewed for this article are any indication, the inappropriate exchange of scientific information or the granting of special privileges does not seem to be a problem for intramural couples. "I've never encountered criticism or hostility that lab secrets would be revealed at home, possibly because colleagues work with the assumption that secrets will be exchanged!" Brenda Kirkby says. Typically, surveyed couples in which one partner is higher up the NIH career ladder than the other said they take particular pains to emphasize their separate professional identities and avoid *continued on page 22.*

WEDDED WORDS OF WISDOM

Despite their general satisfaction with their careers and their marriages, intramural research couples say there's no single formula for happiness to pass along to newlywed scientists or to those who are contemplating tying the knot. Here's a sampling of their advice and comments — some specific and some general, some serious and some light — to the next generation of research couples:

"Enjoy yourselves!" — ANN GINSBERG AND MARC REITMAN, NIDDK.

"If you want to have children, do it early rather than later. It never gets easier, and it's too much fun to pass up." — ROBERT NUSSBAUM, NCHGR.

"Be flexible. Keep talking." — JENNIFER PUCK, NCHGR.

"See that there are many ways of getting to a satisfying career. Changes aren't always bad." — JUDITH RAPOPORT, NIMH.

"Maintain separate mailing addresses! This might help them to score carpool stickers." — DUNCAN KIRKBY, NINDS

"Be open and honest with each other. And both of you should expect to sacrifice for the good of the other once in a while." — BRUCE BUNNELL, NCHGR.

"We have no advice, only 'good luck' in an increasingly tough environment." — RONALD AND GALE GERMAIN, NIAID AND NIMH.

"Take the plunge! Being married to another scientist can help iron out the bumpy parts that you are bound to encounter in marriage." — MICHAEL IADAROLA, NIDR.

"Mutual respect is essential." — EARL STADTMAN, NHLBI. ■

HOW TO KEEP UP WITH CURRENT LITERATURE (AND AVOID HAVING OSHA CONDEMN YOUR DESK BECAUSE OF DANGEROUSLY HIGH PILES OF UNFILED REPRINTS)

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

An increasingly difficult aspect of doing science is keeping up with the literature: How do we locate the papers we need to know about, set aside time to read them, and store the reprints in an organized way so we can easily find them when we need them? Indeed, how can we even find space for storing reprints? Furthermore, how can we reduce the time needed to type and proof bibliographies for papers, curricula vitae, annual reports, and other important documents?

I would like to suggest an integrated approach to these problems that uses computer software that is readily available at NIH. Although much of this software is already being used by a number of laboratories, only a few intramural scientists appear to be applying these computer resources extensively in an integrated fashion, and many remain unaware of the various software packages and what the software can do to

enhance their professional lives.

Literature Searches

Probably the most widely used computer program for searching scientific literature is Grateful Med — one of the great software bargains of all time. Grateful Med, available for both PCs and Macs, is distributed free to NIH personnel, or, for about \$30, you can purchase the software along with a tutorial, user manual, and unlimited free upgrades to the latest version. The current versions of Grateful Med are 6.6 for DOS and 2.1 for Macintosh. Using a simple search parameter screen, Grateful Med runs Medline via network or modem to retrieve references. A highly user-friendly program for searching Medline literature dating back to 1966, Grateful Med also provides access to other databases such as AIDSLINE, CANCERLIT, CHEMLINE, TOXLIT, and PDQ. Abstracts of papers from 1975 to the present and authors' addresses from 1988 to the present are also available. There is no charge to NIH Library-card holders for Medline searches via Grateful Med. In addition, photocopies of the complete text of

papers retrieved through such searches can be ordered at no charge from the NIH Library via the Loansome Doc module within Grateful Med. Each Loansome Doc user has a daily order limit of 10 papers, which are delivered via NIH mail. Grateful Med account numbers and passwords are available to all NIH Library-card holders. You can request a registration form for Grateful Med by



James E. Strickland

contacting the library (phone: 496-1156; fax: 402-0254). The NIH Library also offers, at frequent intervals, free one-hour, walk-in instructional sessions how to use Grateful Med and Loansome Doc, as well as on other aspects of searching Medline and other databases.

After installing Grateful Med, you will be able to do literature searches, read abstracts, and order photocopies without leaving your desk. You should remember, however, that Medline is about two months behind publication date — hardly the thing for keeping up with the current literature!

Current Literature

Many of us leaf through the journals to which we subscribe, reading the abstracts of papers that catch our eye and then ordering reprints or making photocopies of the papers of greatest interest. Many researchers are running out of space to store their reprints. And even those who have enough space often cannot find enough time to file the reprints, or have difficulty remembering where they filed their reprints when they need them.

An efficient method of keeping up with current literature is provided by

two computer programs, Reference Update or Current Contents. These programs, which can be purchased for individual computers or local-area networks (LANs), or accessed via the NIH Gopher, allow scientists to set up a search strategy — based on names of journals, researchers, and topics — to conduct weekly searches of the current literature. Using the same thought process he or she normally employs for browsing journals, each member of a lab can create a customized strategy that can be saved and rerun each week. The retrieved references, which include abstracts, have the term highlighted that led to their selection. This computerized search takes less time than thumbing through printed journals, is much more comprehensive, and can partially replace files of paper reprints, because references can be marked for transfer into a bibliographic-management program. In my opinion, the most cost- and time-effective method of keeping abreast of the current literature is to use the recently available LAN version of Reference Update, which allows the transfer of weekly updates via the Internet. Other options are to receive weekly updates by modem or mail. A single administrator can do this for all members of the LAN to minimize duplicated effort and save hard-disk space on local computers.

As a basic scientist, namely a research chemist in NCI's Laboratory of Cellular Carcinogenesis and Tumor Promotion, I prefer Reference Update to Current Contents for several reasons, including the better readability of Reference Update on screen. The NIH Library, however, has a site-license for Current Contents, which operates through the same network interface that the library uses for other databases. Current Contents offers several editions, including a Clinical Edition that might be better for clinically oriented researchers than the general biomedical edition. Current Contents also offers a CD-ROM version.

For NIH researchers on a limited budget, both Reference Update and Current Contents are available free via the NIH Gopher. However, using these programs

via Gopher carries significant limitations: you cannot save search strategies or see the retrieval with the helpful browsing formatting (colors and highlighting) that comes with the individual or LAN versions of the program. Because search strategies cannot be saved, you must retype large amounts of text, using Boolean logic, each time a search is to be run. It is also difficult to transfer retrieval results into a bibliographic database — an important feature in integrating a program for current literature awareness with a bibliographic-management program. I think the money NIH spends for Reference Update and Current Contents on Gopher could be better spent buying licenses for NIH LANs.

The NIH Library also provides free access to Current Contents in a form that's superior to Current Contents on Gopher. However, that form of Current Contents is only available by going to the library in Building 10, and the features are still limited compared with those of Reference Update. A Windows version is due in March, and a Mac version will follow soon thereafter, a move that should improve the usability of Current Contents at the library.

Bibliographic Management

The third interacting member of the reference-software triumvirate is Reference Manager, also produced by Research Information Systems. There are a number of similar bibliographic management packages, including Bookends, End-Note, Pro-Cite, Papyrus, REF-11, and Sci-Mate. Most are able to convert and import reference databases from other packages. Through my years of experience, I've concluded that Reference Manager is a good choice for me because of its ease of use, convenient interaction and similar "look and feel" with Reference Update. It is available for both PCs and Macs, although at the moment, only a Windows version is

available for LANs and other networks. The licensing agreement is very generous: any number of computers can use the software to access the same database. For more information about Reference Manager and other bibliographic-management software, or to schedule a personal tutorial, contact the NIH Library (phone: 496-1156).

Reference Manager is a great time saver. Once you enter a reference, you never need to retype or proof it again! Even if you never type your own references, the time wasted in proofing the same references over and over again is a major loss. In general, no typing is required to enter references and abstracts into a Reference Manager database if they are transferred directly from Grateful Med and Reference Update searches. In addition to inserting citations and composing bibliographies for manuscripts, Reference Manager can help create and update all laboratory c.v.'s, annual bibliographies, and reference lists. By using the program to create your own computerized reference database of abstracts, you can replace a large portion of your reprints. This not only



Lorna Hearley

saves you storage space, but, more importantly, it allows you to find abstracts by searching on any element (author, year, journal, or key word). The small percentage of references for which you still need the entire manuscript can be acquired as needed through Loansome Doc or saved as reprints, still occupying much less storage space.

Getting Started

The best way to get started building a bibliographic database is with the bibliographies of all the senior staff. These references can be downloaded from Medline via Grateful Med with no typing or proofreading. Key words can be added to link each reference to an individual investigator so that subsets of references can be extracted if necessary.

Have a single individual manage references to minimize chances of bibliographic database corruption. Keep archival floppy disks as back up.

Using your bibliographic database is easy. While writing a paper, for example, you can jump from a manuscript in your word processor to Reference Manager to insert a reference citation wherever needed. Find and mark the reference in Reference Manager, pop back to your manuscript, and Reference Manager will copy its reference ID number in the location you designate. When all the reference ID numbers have been inserted into the manuscript, run the manuscript file through Reference Manager to create the bibliography. After you indicate the name of the journal, Reference Manager creates this bibliography in the style of the specified journal and generates a new manuscript file with the reference numbers in the appropriate style, with the newly created bibliography's numbers substituted for the Reference Manager ID numbers. Redoing the references after a revision or change of journal takes about five minutes.

In summary, making integrated use of this triumvirate of computer resources for dealing with scientific literature should help keep you up to date, free up your filing space, and free your hands for pushing back the frontiers of science!

Grateful Med — Free software for NIH personnel. If you are networked, contact your Technical LAN Coordinator for a network-ready copy of the software (DOS users) or for help in getting a copy off PUBnet (Mac users) by sequentially accessing the Mac Software Science, and Grateful Med folders. You can also call DCRT's NIHnet Customer Support (phone: 402-3140; e-mail: nibnet@list.nih.gov). If you are using a modem, you can obtain a copy from the NIH Library (phone: 496-1156). Grateful Med can also be ordered (for approximately \$30) from the National Technical Information Service (5285 Port Royal Road, Springfield, VA 22161; phone: 703 487-4064).

Current Contents — Pricing for *Current Contents* is more complex due to a choice of several editions and options, such as CD-ROM. A single, stand-alone subscription to the 1200⁺-journal *Life Sciences* edition with abstracts is \$1,085 on disk and \$2,495 on CD-ROM. A network version, with abstracts, is \$10,850 for three simultaneous users. NIH users may access *Current Contents* for free via NIH Gopher or at the NIH Library in Building 10. A free demo is available from the Institute for Scientific Information (3501 Market St., Philadelphia, PA 19104; phone: 800 336-4474; the NIH sales representative is Francis Staples at ext. 1336).

Reference Update — The cost of the single-user, Deluxe Abstract version of *Reference Update* is \$1,595. Prices per user are less for more than nine users. A Deluxe Abstract LAN edition, which will accommodate 10 simultaneous users with either Macs or PCs, is \$10,590. NIH users can access *Reference Update* for free via NIH Gopher.

Reference Manager — The cost of a stand-alone version, which is available for DOS, Windows, and Macintosh computers, is \$349 plus \$199 for the Capture module to download from such sources as Medline. Network versions are available only for DOS and Windows at the moment. For new users, the price for either the DOS or Windows network version, with Capture, for five-database licenses is \$995. Each additional database license is \$199. Additional five-database licenses are \$695. An additional complete network package for a second operating system on the same computer (DOS or Windows) is \$299.

Free demos of both *Reference Update* and *Reference Manager* are available from Research Information Systems (2355 Camino Vida Roble, Carlsbad, CA 92009-1572; phone: 800 722-1227; the NIH sales representative is Christie Glasby at ext. 222; e-mail: ris60012ris.risinc.com). ■

AN ALTERNATIVE VIEW

by Dale Graham, Ph.D., DCRT
(e-mail: degraham@helix.nih.gov)

Dr. Strickland has hit the nail on the head: NIH researchers should be making more effective use of bibliographic-management programs and computerized reference-update services. I have a somewhat different perspective on the paths to getting there, but it doesn't alter his excellent advice.

Current Literature

I prefer updating my references via NIH-net and Gopher because the service is free and requires no maintenance on my part. There are some inconveniences to using Gopher, especially in having to restate searches every time and getting references one at a time. On the other hand, for a quick and easy search of the literature, it's usually quite adequate. Gopher also allows you to search references as far back as eight weeks. This is not the case for reference services provided via software installed on individual or local-area network (LAN) servers, which only allow you to search a single week's data at a time. Furthermore, in contrast to Strickland's experience, I've found that references obtained from NIH Gopher are incorporated into database files just as easily as those from Grateful Med.

Researchers who routinely browse the literature using the same complex search schemes can make use of Auto-Gopher, which will mail you the results of automatic, complex searches on a regular schedule that you determine — weekly or monthly, for example. In addition, this service retrieves your references in a single file that can be taken up by any bibliographic-management program that can read Medline format. In addition to the automatic search service, Auto-Gopher also provides special, one-time searches for researchers who want to get a particular set of references in a single file and not have to retrieve them one by one as they do in a Gopher search. The only drawback to Auto-Gopher is that it only runs via the Helix computer. That means it's not available if you use method other than the Helix computer to access Gopher files, such as a browser program.

A disadvantage to buying *Reference Update* or *Current Contents* software for

an individual computer — besides the cost to the lab — is that it takes up disk space and also requires maintenance (someone has to copy the updated data as they arrive). As for access via a LAN, the major shortcoming of *Reference Update* is cost. In fact, just three LAN licenses, each accommodating 10 users, would exceed the cost of supplying all of NIH with *Reference Update* over Gopher. Furthermore, just as for individual computers, installing reference-services updates on a LAN server takes up hard-drive space and requires maintenance. Not every group has LAN coordinators to do this.

Nonetheless, using reference service software such as *Reference Update* or *Current Contents* on your individual computer or via your LAN or Internet is more sophisticated than anything you could hope to do on any Gopher. So, if you have requirements that can only be met by this software, it may be worth the expense. (Note: I think that *Current Contents*, although available on disk, is not available by Internet.)

Current Contents' major disadvantage is that it displays references with the authors' names, titles, and journal names all in upper-case letters. This results in the references being taken up in all-upper-case letters by bibliographic-management programs such as *Reference Manager* or *Bookends Pro* — a style not accepted by most journals, which usually prefer an upper-case/lower-case format. To change the style while in *Current Contents*, you have to edit the individual references and change the entries back to lower case. To save typing, you can open the original reference file(s) with a word processor that will "de-capitalise" everything past the first character. Then, you re-save the file as text and take it up with your bibliographic-management program. You will probably still have to do some editing, but it will be much less than if you made all the changes from within your bibliographic-management program. Also, mistakes in re-entering data will be avoided. Only the End Note bibliographic-management program strips the caps after the first letter, and even that program sometimes makes

continued on page 21

NATURE'S ROTARY MOTOR: THE BACTERIAL FLAGELLUM

By David J. DeRosier, Ph.D., Department of Biology, Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, Mass. DeRosier presented this at the Wednesday Afternoon Lectures Series, on Dec. 21, 1994.

ABSTRACT

The bacterial flagellum, the organelle of propulsion in *Salmonella typhimurium*, is astoundingly like a man-made machine except that it is assembled from proteins — about 15 different kinds. At the cell membrane, the rotary motor of the flagellum spins at about 15,000 rpm. It is more than 1,000 times smaller than the smallest man-made motor, and 10 times smaller than a photon of visible light. About 1,000 protons, passing down a proton motive gradient across the cell membrane, provide the energy for one revolution of the flagellum. A periplasmic drive shaft, held by a bushing in the outer membrane, transmits torque from the motor to the hook — a helical assembly of a single protein that acts as a universal joint, permitting the motor to drive the propeller off-axis. Two junctional proteins couple the hook to the cell's filament, or "propeller." Made of up to 20,000 copies of a single protein, called flagellin, the filament has a left-handed corkscrew shape. A cap sits at the tip of the filament.

Assembly of large protein complexes is always amazing, but the filament assembly is especially so because most of the process takes place outside the cell. Flagellin subunits, made inside the cell, flow through a channel in the hook and filament and assemble at the distal end of the elongating filament just at the cap.

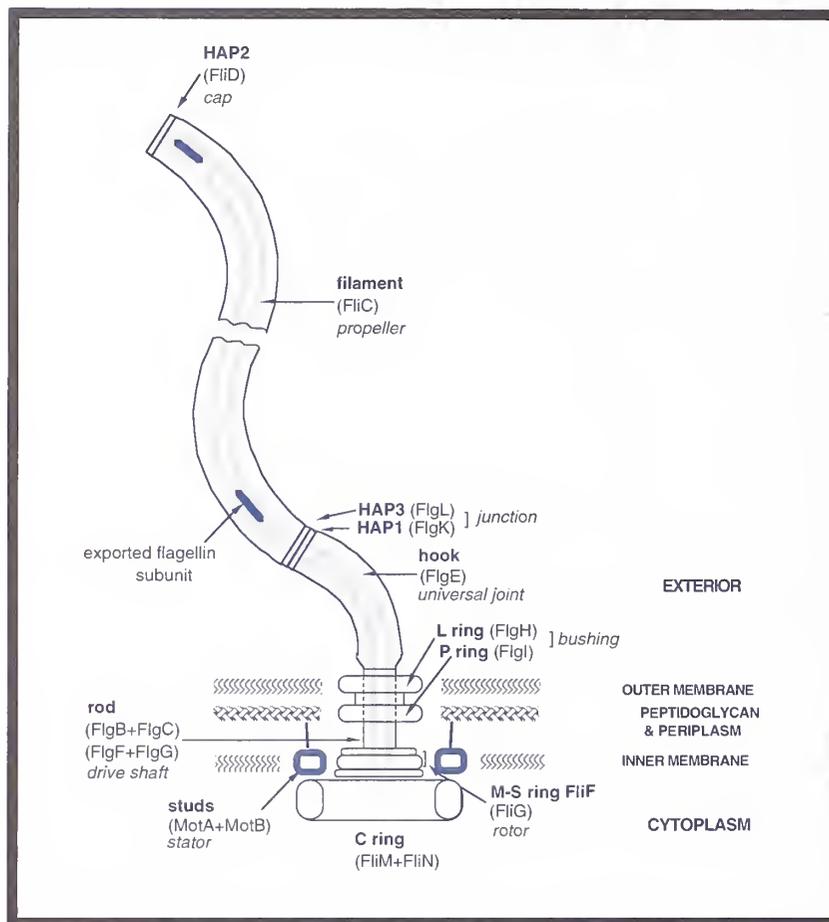


Figure 1. Locations of flagellar parts (e.g., rod), their component proteins (e.g., FlgB, FlgC, FlgF & FlgG), and their functions (e.g., drive shaft).

Using low-dose electron cryomicroscopy, we obtained images of filaments, hooks, and motors that we had isolated from cells. The micrographs are relatively noisy, but by averaging many images, we produce clean, three-dimensional maps that reveal the subunit and domain organization of the component proteins. We now believe the motor consists of three rings of subunits: the stator, which conducts protons; the rotor, or M-S-ring; and the C-ring, which could be part of either rotor or stator. Our maps suggest the hook and filament both possess a 30-Å-diameter protein export channel, suggesting that the proteins forming the filament must pass through the channel in an unfolded state.

QUESTIONS

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

A: About 15 years ago, I began work on the bacterial flagellum in collaboration with Lucy Shapiro at Stanford University in Palo Alto, Calif., who was working on the developmental aspects of flagellar biosynthesis. Shapiro believes that we must recognize structural organization as a key element in our understanding of the developmental program of an organism. I have focused on visualizing the isolated flagellar components in order to understand how they fit together and act coordinately to produce function.

We began with the hook and motor and then undertook studies of the filament. Recently, we shifted from simply obtaining three-dimensional images to assigning protein sequences to structural features. We have pushed the resolution of the filament to about 10 Å, which permits us to visualize alpha helices. For the motor, we have been trying to locate the components that are known, from other genetic studies, to generate torque. We also want to visualize the export apparatus that directs flagellin subunits into the flagellar channel.

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

A: We were all amazed and delighted by the intricacy of the flagellar structures, especially the motor. The pro-

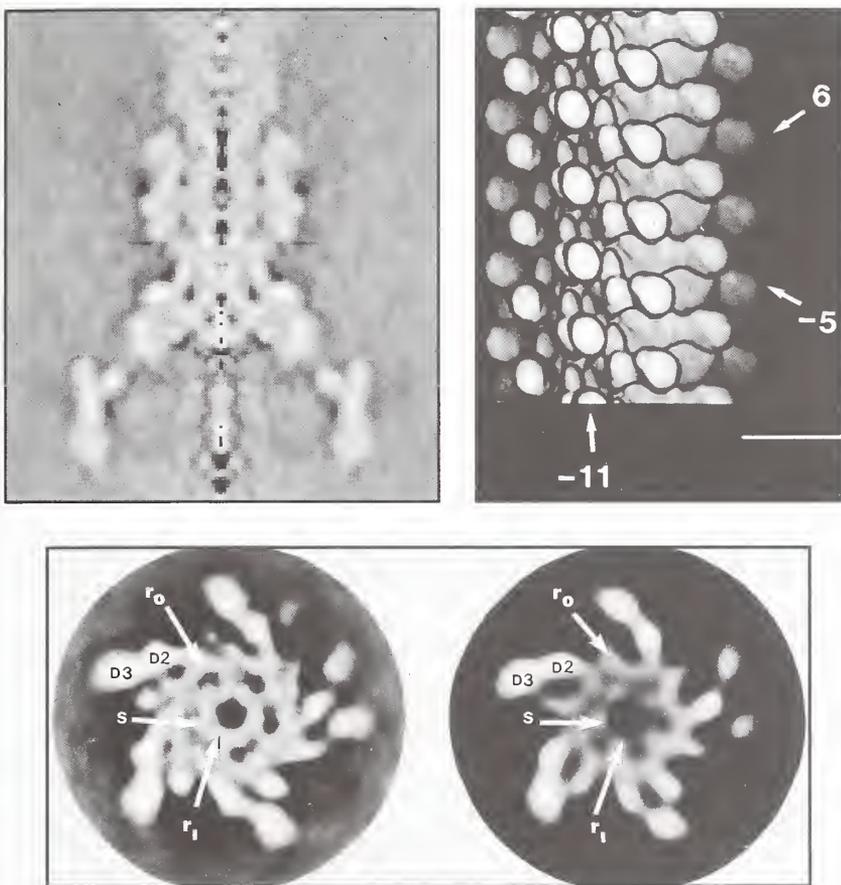


Figure 2. Images of flagellar parts obtained by electron cryomicroscopy and image analysis. **A)** A section through the three-dimensional map of the flagellar motor. The y -shaped feature on the lower left and right sides correspond to the C-ring, which is about 450 Å in diameter. **B)** Surface view of the flagellar filament (propeller). The numbered arrows point to the main helical ridges. This mutant propeller lacks a corkscrew shape, which is essential for function but makes structural studies difficult. **C)** A transverse section through the filament with the domains marked. D3 corresponds to the outer knobs seen in image B. D2 denotes the stubby features behind the knobs. Ri and Ro mark the inner and outer cylindrical domains, which we believe are made of alpha helices. The lumen of the inner cylinder, which we think is the subunit-export channel, is 30 Å in diameter.

teins are not compact blobs, but instead fold into exquisite shapes. The L-ring protein, for example, looks like an upside-down letter J. The filament also has an unusual concentric tubular structure built from alpha helices. The inner cylinder is the export channel. I wonder whether the character of the protein side chains that face into the lumen is essential to the flow of exported subunits.

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

A: It was a challenge to find gentle methods for separating the flagellum from cell debris while retaining the torque-generating proteins. The availability of antibodies was essential to demonstrating that we had been suc-

cessful in this. The relationships of the export proteins to the flagellar structure remain mysterious. A battery of antibodies would simplify detection of these proteins in our preparations. If the proteins are present, then immunomicroscopy would help localize them to flagellar features.

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

A: Virulence in bacteria such as *Shigella flexneri* — a cause of bacterial dysentery — requires an export apparatus that appears homologous to that of the flagellum. Structural studies of the flagellum and its export apparatus might suggest ways to attack the mechanism by which bacteria export pathogenic proteins.

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

A: We are trying to extend our structural studies of the filament and hook to yet higher resolution, where we might be able to trace the peptide chain. We also want to obtain images of the complete motor and export apparatus and to assign each feature to a particular polypeptide sequence. We would especially like to see what structural changes cause the motor to reverse its direction of rotation causing the bacterium to change directions as it swims.

I am indebted to my collaborating colleagues at Brandeis, Noreen Francis, David Morgan, Gina Sosinsky, and Dennis Thomas; those at Teikyo University in Utsonomiya, Japan, Shin-ichi Aizawa and Kenji Oosawa; and others at Yale University in New Haven, Conn., Robert Macnab and members of his laboratory. This work was supported by NIGMS. ■

FLUORESCENCE IN SITU HYBRIDIZATION AND COMPARATIVE GENOMIC ANALYSIS

Fluorescence in situ hybridization (FISH) has become an increasingly important means of identifying the chromosomal location of human genes. FISH probes are known pieces of DNA bound to chemicals that fluoresce when excited with a certain wavelength of light. FISH probes may be gene- or locus-specific — such as cosmids or yeast artificial chromosomes (YACs) — or may be probes that “paint” an entire chromosome (1,2). FISH is now being used in routine prenatal screening for numerical chromosomal aberrations and diagnostic testing for chromosomal disorders in specific diseases such as acute lymphoblastic lymphoma. FISH is also widely used to visualize the chromosomal locations of newly discovered genes. In this Hot Methods Clinic, we discuss the use of FISH to localize genes, and then describe a new application of FISH — called comparative genomic analysis — that allows researchers to scan the entire genome for localized or gross changes in DNA copy number.

The Method And How It Works Putting cDNAs On the Map

Although FISH is very useful for localizing genes within a chromosomal band that is 10 to 20 megabases in width, it is most effective when large insert clones are available to pinpoint the chromosomal location. At this time, the optimal strategy for mapping a newly isolated cDNA is to combine FISH with other genomic resources including sequence database searches and YAC mapping. Thus, when an investigator wishes to map a new human cDNA to its chromosomal location, genome experts such as NCHGR's Mihael Polymeropoulos advocate first searching the sequence databases (to confirm that the gene or a homolog hasn't already been mapped), then generating oligo probes that can be hybridized to a series of known YAC markers that have been developed to span the entire genome. Positive signals within this YAC pool will usually identify a YAC contig, or collection of overlapping clones, that contains the new marker, thus placing the cDNA on a given chromosome. If the investigator wants to pinpoint the sequence's location more precisely, it is possible to isolate a YAC and tag the YAC with a fluorescent marker. The labeled YAC can then be used to perform FISH within the now-known chromosome.

As the genetic and physical map (and ultimately the sequence) for the human genome become more complete, it is increasingly likely that mapping by computer search will become routine, and band-region information will become available for all markers. However, at the current time, the strategy of combining FISH with YAC mapping is an efficient means for finding the chromosomal location of new genes.

Comparative Genomic Hybridization

A powerful new research application of FISH, called comparative genomic hybridization (CGH), now permits

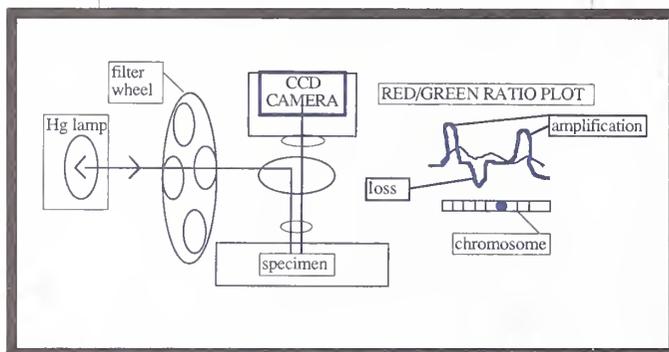
by Lance A. Liotta, M.D., Ph.D.,
NCI; Thomas Ried, M.D., NCHGR;
and Jeffrey Trent, Ph.D., NCHGR

ored DNA are mixed and hybridized on a metaphase spread of normal cells. The red-labeled and green-labeled sets of DNA compete for binding to the normal chromosomes, permitting visualization through fluorescent microscopy and computerized imaging. Each chromosome appears to be painted with fluorescent bands of color, and the specific colors indicate differences in the ratio of normal to tumor DNA. In chromosomal domains that are not altered in the tumor, the red and green sets of DNA will compete equally, resulting in a uniform hybridization pattern of red and green. However, in areas of amplification, or increased gene copies in the tumor, relative to the normal DNA, there will be a higher intensity of green. Areas in which the tumor has lost DNA will be highlighted in red. Using appropriate computerized-image analysis, the red-to-green ratio can be plotted along the length of each chromosome, generating a survey of gross genomic changes across all the chromosomes.

Improvements in image capture and analysis have contributed substantially to the development of CGH. Conventional FISH is very difficult to photograph

because the images consist of pinpoint signals on a bright counterstain against a black background. Photomicrography of these images requires long exposure times, and the automatic exposure settings are often inaccurate because most of the image is black.

New image-capture techniques for FISH begin with the use of a cooled, digital charge-coupled-device (CCD) camera to acquire three grayscale images (5). Each image is captured by use of a different excitation filter, in series with a triple-band-pass beam splitter. The filters are mounted on a wheel so that they can be switched rapidly. The three separate images, captured with different exposure times, are then electronically merged to form a single color image. The entire process can be automated to produce a 24-bit color image. Operators running commercial imaging systems can adjust the spatial resolution and identify individual chromosomes, and software used with these systems will generate a fluorescence red-to-green ratio along the central axis of each chromosome. After corrections are made for uneven illumination and chromosome overlap or bends, all 23 chromosomes can be plotted and displayed on the same screen.



researchers to scan an entire test genome, and in the process, highlight DNA-sequence copy-number abnormalities on normal, reference metaphase chromosomes (3,4). Recent technical improvements in imaging and fluorochrome application are responsible for the new FISH refinement, which has proven especially useful in solid-tumor analysis.

A single-step CGH comparison of a normal genome with an abnormal genome can highlight the copy-number differences for either individual whole chromosomes or regions of specific chromosomes.

In the analysis of tumors, for example, CGH can be used to locate chromosomal regions of amplification or deletion in paired samples of a patient's DNA, allowing a reconstruction of the course of gene-loss or -duplication events that have occurred in the tumor. In this instance, the investigator begins CGH with two sets of genomic DNA: one extracted from a patient's normal tissue and the second extracted from the tumor. Each set of DNA is labeled with a fluorochrome of a different color. Typically, the normal genome is labeled with a red fluorochrome, and the tumor DNA is labeled with green. Two hundred nanograms of different sets of col-

Protocol

The protocol below is taken from Trent, Thompson and Meyskens (6) and describes the preparation of metaphase chromosomes from human lymphocytes for FISH and three-color FISH. The protocol could also be used to study cells from other species or other human tissues, such as aneuploid tumor cells. A protocol for Comparative Genomic Hybridization can be found in (3,4), but it involves equipment that is not readily available. For further information on CGH, contact Thomas Ried. Mention of a specific product does not constitute an endorsement.

Fluorescence In Situ Hybridization

1. *Sterile preparation and microdissection of metaphase chromosomes.* Using sterile technique, human lymphocyte cultures stimulated with phytohemagglutinin (PHA) are treated with colcemid and harvested (6). The cells are then fixed in 3:1 methanol:acetic acid for up to two hours. Next, the metaphase cells are spread on clean coverslips (22 x 60 mm) and stored at 37°C for two to three days. Standard G-banding with trypsin-Giemsa (GTG) (7) is performed prior to chromosomal microdissection (2).

2. *Amplification of dissected DNA.* Initially, cells are subjected to eight cycles of polymerase chain reaction (PCR) (denaturation at 94°C for 1 min., annealing at 30°C for 2 min., and extension at 37°C for 2 min.), with approximately 0.3 units of T7 DNA polymerase (Sequenase Version 2.0, USB) being added at each cycle [Sequenase (13 units/μL) was diluted 1:8 in enzyme-dilution buffer (USB), and 0.2 μL was added to 5 μL reaction mixture] (8,9). Following this pre-amplification step, a conventional PCR reaction, catalyzed by *Taq* DNA polymerase, is performed in the same tube. PCR reaction mix (50 μL) is then added [10 mM Tris-HCl, pH 8.4, 2 mM MgCl₂; 50 mM KCl; 0.1 mg/mL gelatin; 200 μM each dNTP; and 2 units *Taq* DNA polymerase (Perkin-Elmer/Cetus)]. The reaction mixture is heated to 95°C for 3 min., followed by 35 cycles at 94°C for 1 min., 1 min. at 56°C, and 2 min. at 72°C, with a 5-min. final extension at 72°C.

3. *Fluorescence in situ hybridization.* Two microliters of amplified, microdissected DNA is labeled with biotin-16-dUTP (BMB) in a secondary PCR reaction. This reaction is identical to the PCR reaction described above, except for the addition of

20 μM biotin-16-dUTP. The reaction is continued for 12 to 16 cycles of 1 min. at 94°C, 1 min. at 56°C, and 2 min. at 72°C, with a 5-min. final extension at 72°C. The PCR products are then purified through a Centricon 30 (Amicon) filter and used for FISH. Hybridization of the FISH probes follows standard procedures (10,11). Briefly, for each hybridization, about 100 ng of probe is used in 10 μg hybridization mixture [containing 55% formamide, 2X standard saline citrate (SSC), and 1 μg of a DNA fraction that is enriched for repetitive sequences, human Cot 1 DNA (Bethesda Research Laboratories)], which is denatured at 75°C for 5 min. The slide with metaphase spreads is denatured in 70%



Comparative genomic hybridization (CGH) of DNA extracted from a small-cell lung cancer specimen. Only the fluorescence that is specific for tumor DNA is shown. Note the inhomogeneous staining of many chromosomal subregions, which reflects copy-number changes in the tumor genome.

formamide, 2X SSC at 70°C for 2 min., and hybridized with probes at 37°C in a moist chamber overnight. The slide is then washed three times in 50% formamide in 2X SSC at 45°C for 3 min. each. The hybridization signal of the probe is detected by two layers of FITC-conjugated avidin (Vector) and amplified with one layer of anti-avidin antibody (Vector). The slide is next counterstained with 0.5 μg/mL propidium iodide in an anti-fade solution and examined with a microscope equipped for epifluorescence.

4. *Three-color FISH.* Whole-chromosome paints (WCPs) for three-color FISH are labeled in a secondary PCR reaction identical to the one described above by directly incorporating fluorescently tagged nucleotides. Hybridization of the FISH

probes is identical to that described above except that all three WCPs are used simultaneously (100 ng each) in a 10-μL hybridization mixture (containing 55% formamide, 2X SSC, and 1 μg human Cot 1 DNA). Probes are detected by two layers of FITC-conjugated avidin and amplified with one layer of anti-avidin antibody amplified between the two avidin treatments. Slides are counterstained with 0.5 μg/mL of the fluorescent DNA-specific dye 4,6-diamidino-2-phenylindole (DAPI) in an antifade solution. ■

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RECENTLY TENURED

David Bodine joined the *Clinical Hematology Branch (CHB), NHLBI, in 1984 as a postdoc. He remained with the CHB until 1993, when he joined NCHGR as the Chief of the Hematopoiesis Section. Bodine did his graduate work at Jackson Laboratory in Bar Harbor, Maine, and received his Ph.D. from the University of Maine in 1984.*



Lorna Hearley

Recent research in my laboratory has focused on pluripotent hematopoietic stem cells (PHSCs). PHSCs are the ultimate progenitors of all circulating blood cells and have the ability to self-renew numerous times without losing the ability to differentiate into cells as diverse as red blood cells and T lymphocytes. PHSCs are found in the bone marrow, and due to the great proliferative capacity of their descendants, they are exceedingly rare, less than one per 100,000 bone marrow cells. We have recently concentrated our efforts on describing gene expression in PHSCs and devising methods to introduce genes into PHSCs via retrovirus-mediated gene transfer.

To study gene expression in PHSCs, these rare cells must be greatly enriched. Our work, using mice as a model system, has shown that murine PHSCs express high levels of c-kit, the receptor for the hematopoietic growth factor, on their surface. By combining this observation with techniques to subtract cells expressing markers of mature blood cells, we were able to use

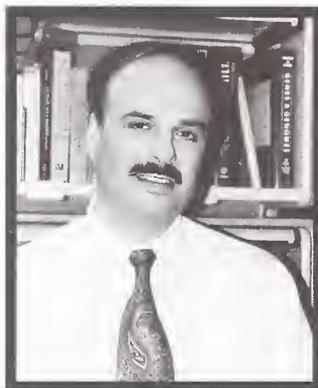
fluorescence-activated cell sorting to isolate a population of cells highly enriched in PHSCs. It only takes 100 of these cells to fully reconstitute the hematopoietic system of a mouse, at least a 1,000-fold enrichment over the concentration of PHSCs in the original bone marrow cell population. Examination of messenger RNA purified from those highly enriched PHSCs revealed that c-kit, stem cell factor (SCF), and the receptors for the hematopoietic growth factors interleukin-3 (IL-3) and interleukin-6 (IL-6) were all expressed at high levels. Other work showed that when bone marrow cells were cultured for six days in SCF, IL-3, and IL-6, the number of PHSCs in the cultures increased two to threefold.

Efficient retrovirus-mediated gene transfer requires that the target cell divide, thus allowing the virus to become integrated into the host-cell DNA. Our finding that PHSC numbers could be increased by culture in SCF, IL-3, and IL-6 suggested that treatment with these growth factors might significantly increase the frequency of retrovirus-mediated gene transfer into these cells. Our results showed that the frequency of gene transfer into mouse PHSCs cultured without growth factor or in just a single growth factor was approximately 5%. The frequency of gene-transfer into mouse PHSCs cultured in all three factors was as high as 75%. These observations were successfully extended into a rhesus monkey model, and the success of our monkey gene transfer experiments helped serve as preclinical justification for human gene-therapy experiments in which retroviruses containing the adenosine deaminase (*ADA*) gene were introduced into the bone marrow of patients with severe combined immunodeficiency syndrome. These human trials were performed in Europe and the United States in 1993.

In the future, we hope to isolate novel genes that control

PHSC division and differentiation from c-DNA libraries generated from mRNA from highly enriched populations of PHSCs. In addition, we are continuing our efforts to further define the factors required for the growth and differentiation of PHSCs both in vitro and in vivo.

Mark Boguski received his *M.D. and Ph.D. from Washington University in St. Louis in 1986, and in 1988, he joined the Mathematical Research Branch, NIDDK, as a medical staff fellow. He became one of the first staff members of the newly formed National Center for Biotechnology Information (NCBI) in 1989, where he remains as a researcher in the Computational Biology Branch.*



Lorna Hearley

My earlier work at NIH focused on sequence motifs and conserved domains in proteins involved in signal transduction, particularly those that interact with and regulate GTPases. Although I continue to study the interrelationships of sequence, structure, and function in proteins, I have also been working on information analysis and retrieval problems in genome research. Three years ago, NCBI's Carolyn Tolstoshev and I founded the database of expressed sequence tags (dbEST) which is a division of GenBank for cDNA sequence and mapping data. Now, dbEST contains more than 100,000 sequences, has been queried by

researchers more than 100,000 times, and is currently used nearly 7,000 times per month by intramural and extramural scientists.

We are now collaborating with researchers who are working on genetic and physical mapping to build a "transcript map" of the human genome. Only a small fraction of human DNA, probably less than 5%, consists of transcribed coding sequences. Our goal is to locate all of these transcribed coding sequences, starting with a comprehensive set of cDNAs, called expressed sequence tags, and map them back with high resolution onto the chromosomes. Such a map will help us to understand gene regulation, to pinpoint gene-rich regions for concerted genomic-sequencing efforts, and to greatly accelerate positional cloning of genes responsible for genetically complex diseases such as diabetes.

I am also collaborating with Phil Hieter's group at the Johns Hopkins University of School of Medicine in Baltimore on a project to identify and map all homologous genes in the yeast and human genomes. In so many instances, such as the recent studies of cystic fibrosis, neurofibromatosis and familial colon cancer, yeast biochemistry has shed tremendous light on human pathophysiology. However, these connections are usually made late in the research process, and much effort and expense could be saved if the relationships are identified earlier. Now, however, we're working toward making both the complete sequence of the *Saccharomyces cerevisiae* genome and a comprehensive sampling of human coding sequences available within the next 18 months. This creates an unprecedented opportunity to construct a molecular cross-reference between yeast and humans and to populate the human-genome map with yeast-gene functions and phenotypes. This will facilitate the

identification of candidate genes for human diseases and the development of assay systems for studying the functions of human gene products.

Seong-Jin Kim received his Ph.D. from the Tsukuba University in Japan in 1987. He came to NIH in 1987 and is currently a visiting scientist at the Laboratory of Chemoprevention, Division of Cancer Etiology, NCI.



Lorna Hearnley

Our laboratory has been studying the transcriptional and posttranscriptional regulation of the set of three homologous isoforms of transforming growth factor- β (TGF- β), TGF- β s 1, 2, and 3. My research program has focused on the regulation of the TGF- β gene by etiologic agents that are involved in disease: tumor-suppressor genes (retinoblastoma gene and Wilms' tumor gene), oncogenes (*jun*, *fos*, *src*, *abl*, and *ras*), and viruses (human T-lymphocyte virus type 1, human cytomegalovirus, and hepatitis B virus). Taken together, these studies of gene regulation have delineated the molecular basis for the observation that the type 1 isoform of TGF- β is upregulated by cells in response to injury and pathological processes such as fibrogenesis and carcinogenesis. In contrast, the type 2 and 3 isoforms of TGF- β are regulated principally by developmental cues and hormones.

We have also demonstrated that the protein encoded by the

retinoblastoma susceptibility (*Rb*) gene can regulate expression of the TGF- β 1 and - β 2 genes through the Sp1 and activating transcription factor-2 (ATF-2) binding sites in the TGF- β 1 and TGF- β 1 promoters, respectively. In the latter case, ATF-2 can form a complex with the Rb protein with the help of an additional, and as-yet-unidentified, bridging protein. We are currently trying to clone the gene that encodes the bridging protein.

I have also been interested in posttranscriptional regulation of TGF- β isoforms. It has been suggested that TGF- β expression is regulated at the posttranscriptional level by members of the steroid-retinoid superfamily of nuclear receptors in an isoform-specific manner. Retinoic acid stabilizes TGF- β 2 mRNA, while the serum cholesterol-lowering drug lovastatin specifically downregulates the TGF- β 2 mRNA through a posttranscriptional mechanism. We are attempting to identify the factors controlling the stability TGF- β 2 mRNA.

Most recently, we have begun to explore mechanisms that regulate the expression of the TGF- β receptors in human gastric cancer cell lines that are resistant to the growth-inhibitory effect of TGF- β . We have found alterations in the gene that encodes the type II receptor for TGF- β . One of our current goals is to characterize the mechanisms of transcriptional regulation of the TGF- β type II receptor gene because several TGF- β -resistant cell lines that displayed no alterations of the TGF- β type II receptor gene expressed no detectable TGF- β type II receptor mRNA.

Lois Travis received her M.D. from the University of Florida College of Medicine in Gainesville, Fla., in 1980. She received her Sc.D. in Epidemiology from the Harvard School of Public Health in Boston in 1994 and joined the Radiation

Epidemiology Branch of the Epidemiology and Biostatistics Program, NCI, in 1989.



Lorna Hearnley

One of my major areas of interest is the study of multiple primary cancers, particularly the evaluation of cancer risk following exposure to ionizing radiation and/or chemotherapeutic drugs. As long-term-survival rates improve for many types of cancer patients, it becomes critical to identify the late consequences of therapy. One of the most serious side effects of cancer treatment is the induction of new malignancies. Characterization of therapy-related risks is crucial to enabling the clinician to make an informed decision regarding treatment, balancing efficacy against acute and chronic sequelae. In addition, quantification of the late effects of cytotoxic drugs and radiation therapy provides a unique opportunity for interdisciplinary studies of carcinogenesis because humans are deliberately treated with measured amounts of potentially cancer-inducing agents.

When I arrived at NCI, little work had been carried out in the area of secondary cancers following therapy for non-Hodgkin's lymphoma (NHL). Since then, in collaboration with investigators worldwide, our group has provided quantitative estimates of the risk of secondary malignancies among several populations of NHL patients. In one of my first projects, we identified a significant excess of solid tumors after

NHL, noting that the pattern of risk increased with time, consistent with the late effects of treatment. In a subsequent study, we showed that the increased risk of secondary malignancies persisted for up to two decades after the initial NHL diagnosis. We also quantified the association between the risk of secondary leukemia and the dose of various cytotoxic drugs, such as prednisone, chlorambucil, and cyclophosphamide. We found a dose-response relationship between the cumulative amount of cyclophosphamide and bladder cancer, and we described the combined effect of cyclophosphamide and radiotherapy in the induction of bladder cancer. Now, with the Laboratory of Human Carcinogenesis at NCI, we are collaborating on molecular studies examining the mutational spectrum of the p53 tumor-suppressor gene in cyclophosphamide-related bladder cancer.

Our group also coordinated an autopsy evaluation of a woman who had been injected with radioactive Thorotrast (thorium-232) decades previously during angiography. Thorotrast, once used as a radiologic contrast agent, is not excreted from the body to any appreciable extent and has induced high rates of liver angiosarcoma and leukemia. I organized an international workshop that assembled the clinical and pathologic findings with dosimetric, radiochemical, autoradiographic, and molecular evaluations for this unique case. Our efforts enabled correlation of concentrations of radioactive-decay products in various organs with epidemiologic, histo-pathologic, and molecular observations.

We are now characterizing the risk of cancer after long-term exposure to radioactive Thorotrast among several large populations. This study may provide a special opportunity to evaluate the potential effects

continued on page 22.

OEO LEADER*continued from page 1.*

showing the representation of women and minorities in the Civilian Labor Force's extremely general occupational categories, which lumped together workers with such disparate job titles as nuclear physicist and school teacher. The new strategy allows each institution, center, or division (ICD) to base its goals for hiring women and minorities on their representation in the pool of workers who are actually available to perform each type of job. A key part of determining the available labor force for a given scientific opening involves selecting the most appropriate occupational databases, such as those from the National Science Foundation and the National Research Council that track the race and ethnicity of people receiving doctorates in a variety of scientific fields. Examples of how the choice of a database can influence the degree of "underrepresentation" seen at NIH for various minority groups are shown on page 17.

"We think this plan will help make some decisions a lot easier," Churchill says. "In a downsizing environment, everybody wonders how do you balance diversity . . . When should diversity be the element that tips the scale one way or the other? And we really think a lot of those questions will be answered if scientists, managers, supervisors, and scientific directors do their homework and use the Affirmative Action Plan in an appropriate manner."

Recruiting is one area in which researchers may be most likely to notice the impact of the new Affirmative Action Plan, Churchill says. The OEO Director says that in the past, NIH has sometimes approached minority hiring in a "less than methodical" manner, simply assuming that the addition of a woman or nonwhite would add diversity without assessing the level of diversity that already exists.

"With this plan, in some cases, there will be no need for affirmative action — at least not for some groups. So it's

going to force a manager to think a little more. For example, if you have an adequate representation of white women, or of Asian scientists, or of black women in administrative (positions), how do you reach the Hispanic population?" she says. "We can't really go with a cookie-cutter strategy — that one approach works for all."

Churchill says she thinks that, for blacks and women, the biggest issue confronting NIH may not be how to bring more of those groups into the scientific work force, but how to move them up the career ladder. In addition, she says, NIH has a problem retaining



Lorna Heintley

some women scientists. Because the amount of effort currently devoted to such issues varies widely among the ICDs, OEO is working with the Office of Human Resources Management to explore the possibility of developing centralized services for career development, mentoring, retention, and recruitment at NIH. In particular, Churchill says the lack of across-the-board exchange of information is a major handicap in the recruitment of researchers. Currently, there is no formal mechanism for ICDs to exchange information on job candidates, nor is there any way to provide candidates with an NIH-wide list of jobs that match their scientific qualifications.

However, the most critical factor holding NIH back in terms of the diversity of its scientific work force, according to Churchill, is the serious shortage of certain racial and ethnic groups in the educational pipeline. For example, based on national data from the 1990 Census, blacks account for only 3.6

percent of physicians and Hispanics represent only 3.2 percent of biological and life scientists. Churchill acknowledges that NIH, like the rest of government, is at an economic disadvantage compared with the private sector when it comes to attracting outstanding minority scientists. But she adds, "I believe there is no place on the planet that can make you feel as good about biomedical research as NIH. It would seem to me that the majority of the people on the medical side of the house are not here because they are planning to make a lot of money. They are here because they absolutely love it. Those are the things we have to play to when we are recruiting."

Churchill, who previously directed equal employment opportunity efforts at the U.S. Department of Agriculture and the Federal Deposit Insurance Corporation, says she has found NIH to be no better or worse than other federal agencies when it comes to equal employment opportunity issues. However, she does think that NIH collectively has tended to be rather hard on itself about its shortcomings in the diversity area.

"I would hope that everybody in the lab and in the offices would be able to relax a little bit. It's my feeling that NIH has been functioning in a heightened sense of awareness and sensitivity to race and gender issues for the past two years or so," Churchill says. "This plan is not a 'gotcha activity.' I don't envision that anyone is going to be immediately fired because the goals that are set are not reached. So the labs, as well as every other corner of the NIH community, should be able to become a lot more contemplative about how we are going to reach and maintain diversity." The OEO Director adds that she plans to visit the intramural campuses in Research Triangle Park, N.C., and Baltimore later this year to answer questions and to see whether there are any aspects of the new Affirmative Action Plan that need to be tailored to their regional needs.

Although OEO is probably best

Baseline Data Comparison: General Biological Scientists

NIH Current Work Force (as of 9/30/94)
Biologist* (401)

	Men	Women	Blacks	Hispanics	Asians	Native American	Nonminority Women
Number	281	425	80	9	64	0	323
Percentage	39.8	60.2	11.3	1.3	9.1	0.0	45.8

*All grades, both Ph.D.s & non-Ph.D.s



National Research Council: Affirmative Action Table 1993
Biological Sciences

1990 Census Data Detailed Occupation by Sex & Race
Biological & Life Scientists (National)

	Men	Women	Blacks	Hispanics	Asians	Native American	Nonminority Women
Number	1,969	1,437	63	93	190	7	1,271
Percentage	57.8	42.2	1.8	2.7	5.6	0.2	37.3

	Men	Women	Blacks	Hispanics	Asians	Native American	Nonminority Women
Number	36,199	25,923	2,434	1,975	4,554	233	21,599
Percentage	58.3	41.7	3.9	3.2	7.3	0.4	34.8



Underrepresentation Index (URI)*
General Biological Scientist (401)

Underrepresentation Index (URI)*
General Biological Scientist (401)

	Men	Women	Blacks	Hispanics	Asians	Native American	Nonminority Women
Labor Force Percent	57.8	42.2	1.8	2.7	5.6	0.2	37.3
URI	100.0	100.0	100.0	48.1	100.0	0.0	100.0

	Men	Women	Blacks	Hispanics	Asians	Native American	Nonminority Women
Labor Force Percent	58.3	41.7	3.9	3.2	7.3	0.4	34.8
Percentage	100.0	100.0	100.0	40.6	100.0	0.0	100.0

*Formula: NIH Work Force Percent divided by NRC Labor Force Percent multiplied by 100 = URI

*Formula: NIH Work Force Percent divided by 1990 Census Percent multiplied by 100 = URI

The two sets of tables above — one comparing National Research Council occupational data to the NIH workforce and the other comparing 1990 Census occupational data to the NIH workforce — illustrate how the choice of baseline data can shift the underrepresentation index (URI) for general biological scientists at NIH. Note the difference between the two data sets in the URI for Hispanics. However, it must be emphasized that neither of these “pools” adequately represents the “populations” from which NIH recruits its scientists. For example, for black and Hispanic scientists, NIH often needs to look at M.D.s who might be interested in research. These data could also be misleading because they represent only working scientists as opposed to recruitable researchers.

known among NIH employees for handling approximately 200 complaints of racial discrimination, sexual harassment, and other bias issues each year, Churchill wants scientists to know that her office does far more than mediate and adjudicate specific cases. OEO actually spends about two-thirds of its time on its general advisory and monitoring responsibilities. The OEO Director's five-year strategy for NIH, entitled “A Framework for Change,” includes developing an initiative called “Manag-

ing Diversity” next year to address conflicts that do not fall into traditional race or gender categories, such as complaints from nonsmokers that smokers spend too much time away from their work areas or misunderstandings among people who speak with different accents. The plan also calls for establishment of an alternate dispute-resolution mechanism for handling discrimination and sexual harassment complaints and for tying affirmative action, diversity, and dispute resolution

to “total quality management” and other means of reducing conflicts between workers and their supervisors.

Churchill says her personal framework for viewing equal opportunity issues is flexible. “My only philosophy is one of inclusion — and that includes white males,” she says. Over the years, “questions of discrimination have moved from being very overt to being very covert. I think, as an equal opportunity professional, I have to be prepared to change.” ■

FREEZE FRAME: A SNAPSHOT OF NIH'S EVOLVING AFFIRMATIVE ACTION EFFORTS

For more than a year, the message has been clear: NIH needs to revamp its Equal Employment Opportunity efforts. In 1994, the Task Force on Minority Employment made its recommendations and the private consulting firm, Alexander & Associates, presented its conclusions to NIH Director Harold Varmus. Public interest groups, including Blacks in Government and the NAACP, have urged swifter action, as have members of Congress. Now, guided by Naomi Churchill, the new Director of the Office of Equal Opportunity, NIH is responding by drafting a new affirmative action plan. As The NIH Catalyst prepared to examine the new plan, it became clear that it is a work in progress. Thus, we present a view of the plan's evolution — snapshots from the journey rather than a final diorama. We begin with the preface to the latest draft, followed by a summary of the Scientific Directors' recent discussion of the plan. The next steps will be finalizing the plan sometime this spring, seeking approval from the NIH Director, and drafting and implementing institute-specific plans mandated by the NIH-wide plan.

Affirmative Action Plan Preface

As a federal agency, NIH has been tasked with reengineering inefficient processes, streamlining its supervisory and overall work force, and furthering its equal opportunity goals. At the same time, NIH has been cited by the Equal Employment Opportunity Commission (EEOC) and charged with moving aggressively to improve representation of minorities and women at all levels. These mandates have been viewed by many as contradictory because NIH is committed to accomplishing both streamlining and improved-diversity goals.

NIH is responding with a new streamlined affirmative action planning process that is designed to focus the energies of all managers and supervisors toward ensuring that all individuals have an equal opportunity to work at NIH and to advance to their full potential once they become NIH employees. This effort is a significant departure from prior affirmative employment planning at NIH. The new process places more responsibility on the people that hire and promote, and especially on the Directors of institutes, centers, or divisions (ICDs). It includes, for the first time,

establishment of ICD hiring and promotion goals, timetables, and direct accountability for accomplishment of goals.

The plan also establishes a realistic and more accurate baseline of the availability of minorities and women for scientific occupations, as well as for administrative, technical, clerical, blue collar, and temporary positions. The plan is inclusive of all individuals associated with NIH whether they are employed in permanent, temporary, trainee, contractor, or volunteer positions.

The leadership of NIH is committed to making a diverse work force a reality at all levels of NIH and to managing diversity in a way that ensures the capabilities and potential of all employees are realized.

Adapted from Minutes of Jan. 4, 1995, Meeting of NIH Scientific Directors

Michael Gottesman, Deputy Director for Intramural Research, welcomed Naomi Churchill and Sharrell Butler from the NIH Office of Equal Opportunity (OEO) to discuss the draft Affirmative Action Plan. The plan was subsequently characterized by Churchill as a workable one to replace the "dinosaurs" of the past. She added that the new plan provides both control at the ICD level as well as flexibility; it is driven by results rather than process and places heavy responsibility on each ICD to reach the goals it sets.

Churchill highlighted several differences between the old and the new plans. For calculating affirmative action goals, the old plan used the minority representation calculations based on Civilian Labor Force Data, which consisted of large numbers not applicable to biomedical research, while the new plan uses availability data consisting of smaller and more specific numbers based on the 1990 census. She added that OEO is also looking at National Research Council and National Science Foundation data to determine reasonable numbers. Another change dealt with the number of elements monitored to gauge the success of affirmative action efforts, from eight in the old plan, to only four in the new plan with special focus on hiring and promotions.

Finally, Churchill told the Scientific Directors that the OEO only sets broad parameters within the new plan, while the ICDs develop their own affirmative action goals. Guidance will be available soon as to which items of the Federal Equal Opportunity Recruitment Program (FEORP) are no longer in effect ...

Many Scientific Directors applauded the direction of the new plan and commented on its strengths. They also expressed certain general and specific concerns about the draft plan. One such general concern focused on the rather severe punitive tone of the document, in terms of its holding ICD Directors accountable for its implementation. Churchill felt the step-by-step instructions can be redrafted to include a softer, more reasonable philosophical approach.

Edward Korn, Scientific Director of NHLBI, expressed concern about the size of the [recruiting] pools for both small ICDs and small groups of research specialists, for example, nuclear magnetic resonance (NMR) spectroscopists. Churchill responded by saying that the ICDs will help determine these pools and that there is room for redefinition. She also commented that once an ICD identifies underutilization of minorities, it is that ICD's responsibility to figure out the best way to solve the problem.

Arthur Levine, Scientific Director of NICHHD, asked specifically what must be accomplished by September 1996. In response, Churchill emphasized that

an ICD's best efforts count and that their responsibility is to do the best possible job for the ICD, within a downsizing environment.

Henning Birkedal-Hansen, Scientific Director of NIDR, asked that areas be described where the affirmative action goals have been met NIH-wide. Churchill emphasized that each ICD is accountable and stands on its own. She also mentioned that not only are full-time permanent employees covered under the new plan, but also part-time employees as well as postdoctoral fellows and even contractors and special volunteers. It was pointed out

THE PLAN WAS
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that intramural research training awards (IRTAs) are referred to in the document as employees, and this will be corrected. It was suggested that, in some instances, where ICDs are small and recruitments very specialized and made infrequently, the achievements of NIH as a whole may satisfy the goals of affirmative action. Churchill emphasized that primary responsibility for affirmative action resides with the ICDs, but that the OEO will be involved with institutional monitoring, recruitment assistance and assistance with goal setting where necessary.

Concern was expressed about the lack of data on employee separations from NIH and the difficulty of retaining excellent minority postdoctoral fellows because NIH cannot compete with outside salaries. Churchill responded that she and Stephen Benowitz, Director of Human Resources, are working on separation issues, and they will collect data on why people leave NIH. She urged the Scientific Directors to share with OEO information on how they would deal with this problem.

The plan was critical of the practice of considering recruiting pools that are perhaps too constricted, and it urged ICDs to consider both physicians and research scientists when "seeking a senior research scientist." Gottesman concurred with several Scientific Directors that this concept should refer to recruitment of entry-level postdoctoral scientists, since physicians often lack research experience. The point did underscore the need to develop a broad pool of interested people for entry-level postdoctoral jobs by means of the summer programs, among other approaches. -

Bruce Chabner, Scientific Director of NCI, noted that while the ICDs are held responsible for recruiting, this represents an NIH-wide problem as well. Churchill responded that the draft plan is not intended to be a recruitment document, and Benowitz agreed. He added, however, that we need to refocus on this issue, and there may be some techniques that should be addressed by the Office of Intramural Research, Office of Education, etc. Churchill concurred that NIH needs good scouting efforts and NIH-wide recruitment. Gottesman said he has endorsed one position for recruitment within the Office of Education.

When asked about a possible increased salary band for minority scientists, Churchill was not in favor, nor did she favor a separate tenure track for minority scientists.

George Uhl, Scientific Director of NIDA, asked if a professional search firm might assist in an NIH-wide recruitment effort, and Benowitz responded affirmatively. Edward Lakatta, acting Scientific Director of NIA, informed the Scientific Directors that the results of a feasibility study on the use of such a firm conducted by NIA will be presented at a future meeting of the ICD Directors. Gottesman suggested that the Scientific Directors share information about qualified people identified, but not selected, as a result of a search.

Korn asked if the draft plan applies to foreign nationals at NIH too. Churchill responded that affirmative action plans traditionally exclude foreign nationals; the application of affirmative action to foreign nationals cannot legally be required. Nev-

ertheless, Gottesman argued that Visiting Fellows and other foreign nationals bring diversity into the intramural programs and that the Scientific Directors might wish to reconsider at some future time whether principles of affirmative action should be applied to foreign nationals.

Other suggestions included the use of central resources (such as the Director's transfer authority) to recruit minority scientists, or the possible creation of a reserve through the Resource Allocation Group (RAG) that could be used by ICDs that do not have flexibility to hire. It was also felt that the use of Title 38 would be very helpful in meeting affirmative action goals.

In conclusion, Churchill reported that she will address the philosophical tone of the draft Affirmative Action Plan, as well as begin to address other global issues such as separations, recruitment, and tracking. Gottesman thanked Churchill for both her time and dedicated efforts in developing the new draft Affirmative Action Plan. ■

OFFICE OF EQUAL OPPORTUNITY AT A GLANCE

Complaints Management and Adjudication Branch

Chief: Linda Morris

Phone: 496-1551

Location: Building 31, Room 2B47

Resources: This branch counsels employees who believe they may be the targets of discrimination or sexual harassment and handles actual complaints. Any NIH employee can file a complaint directly with OEO without going through his or her institute, center, or division (ICD). However, OEO urges employees to first try to settle such matters with their supervisors. If that doesn't work, an employee should proceed to the equal employment opportunity (EEO) officer in his or her own ICD. If the matter still isn't resolved, the employee should, as a last resort, contact OEO. A helpful EEO fact sheet is available upon request. The branch can also provide information to NIH supervisors who have been accused of discrimination or harassment.

Affirmative Employment and Programs Branch

Chief: Joan Brogan

Phone: 402-3663

Location: Building 31, Room 2B40

Resources: This branch provides a wide range of advisory and evaluation services. General feedback and concerns about the affirmative action plan, as well as other OEO policies and procedures, should be directed here. Employees can obtain literature on issues and programs of particular interest to various gender, race, and ethnic groups. ■

SBRS

continued from page 1.

Deciphering Title 38

Calling Title 38 "the most important personnel structure for physicians [at NIH] in the last 20 years," Associate Director for Clinical Research John Gallin says the measure "should go a long way toward improving morale and helping us recruit physicians involved in patient care at the Clinical Center." Another consequence may be that Clinical Center services that have been contracted out to private firms that could pay doctors more than NIH may return to being provided by staff physicians, says Gallin, who, along with Director of Human Resources Steve Benowitz, began pursuing Title 38 authority for NIH last spring.

Director of the Office of Equal Opportunity Naomi Churchill also believes that Title 38 may bolster efforts to attract top female and minority physicians, saying the authorization "is perceived as really opening some doors to make it easier for salaries to be negotiated."

An important feature of the Physician Specialty Pay (PSP) provided by Title 38 is that once a doctor has 15 years of Public Health Service (PHS) experience, his or her total pay, including all the PSP salary add-ons, are counted in determining the "high three" — the three highest-pay years on which retirement benefits are based. Gallin says the good news is that with PSP, the total package counts toward retirement, unlike bonuses that can raise pay for Commissioned Corps officers. But he adds, "The bad news is that you have to be in the Civil Service for 15 years to get it [the higher retirement pay]." A decision on whether prior Commissioned Corps service can be counted toward the 15-year PHS service requirement is pending at the Office of Personnel Management.

Restrictive definitions of who is covered under Title 38 and who is eligible for various categories of PSP suggest that fewer than 250 doctors will be transferring to the new pay program or joining NIH under the new plan. Individual calculations on whether it will be more lucrative than current pay systems may require both higher math and an insider's knowledge of government benefits. Physicians with specific questions about PSP are advised to contact the personnel officers at their institutes, centers or divisions. However, in general, physicians who have more years of experience and who are in the most scarce specialty areas are most likely to realize salary increases under Title 38.

Gallin points out that neither Title 38 authority nor SBRS bring with them any increase in the number of staff that NIH may have at GS-14-and-above pay levels. A cap on

the number of these higher-paid positions at NIH has sharply restricted promotions and hiring at the upper echelons of scientists over the past year. "Initially, Title 38 will be used to recruit and retain our needed clinical staff," says Gallin. "Conversion of Commissioned Corps staff to Civil Service positions will be allowed but will be restricted by the availability of positions at the GS-14 level and above." The exact procedures for proposing and approving doctors for PSP are still being worked out.

The Scoop on SBRS

SBRS received final sign-off from the Office of Management and Budget (OMB) as *The NIH Catalyst* went to press. Ultimately, NIH hopes to get 383 of the 500 SBRS slots that have been granted to the Department of Health and

Human Services (HHS). By agreement with PHS and OMB, these will be used primarily for recruitment and retention of Civil Service scientists, with the majority of appointments at the lower end of the pay scale.

Until recently, NIH's pursuit of SBRS seemed like a Sisyphean saga. Shortly after the Civil Service Reform Act of 1978 spawned the Senior Executive Service (SES), the NIH Board of Scientific Directors appointed a Committee on Pay and Personnel Systems in Intramural Research. In 1984, that committee concluded that SES was not ideally suited for NIH and what was needed was a system more akin to personnel systems found in academia — a scheme with a tenure system; promotions based on scientific productivity; portable, vested retirement; and salaries based on the pay in comparable academic institutions. The panel's

TITLE 38 AT A GLANCE

Eligible: Civil-service physicians, GS-15 level and below, who are proposed by their institute, center, or division directors. They must regularly see patients and provide direct patient care or services related to such care, such as radiology or pathology.

Ineligible: Physicians who primarily perform basic research or develop drugs and devices. Physicians for whom the Assistant Secretary for Health has determined there is no significant recruitment or retention problem. Physicians employed through the Commissioned Corps, SES (or other senior-level systems), or Title 42 (Staff Fellows, Special Experts). Physicians receiving Physicians Comparability Allowances (PCA). Re-employed annuitants, dentists, veterinarians, interns, residents, and part-timers working fewer than 20 hours per pay period.

Calculating Physician-Specialty Pay (PSP): On top of normal GS-13, GS-14, or GS-15 clinical physician pay, PSP adds the following amounts:

- Full-time workers: \$9,000 (80-hour tour of duty per pay period; 24-hour, 7-day-work-week obligation).
- Experience pay: \$4,000 (for two to three years of service) to \$18,000 (14 or more years of service).
- Nationwide Scarce Medical Specialty pay: zero to \$40,000 (anesthesiology, open-heart cardiac surgery, ob-gyn, neurosurgery, ophthalmology, orthopedic surgery, plastic surgery, radiology, thoracic surgery and vascular surgery), zero to \$30,000 (other cardiology, general surgery, nuclear medicine, otolaryngology, and urology), zero to \$20,000 (gastroenterology, psychiatry, and pathology), and zero to \$15,000 (physical medicine-rehabilitation, primary care, internal medicine, oncology, and pediatrics).
- Exceptional qualifications within a specialty, as approved by the Assistant Secretary for Health on a case-by-case basis: up to \$15,000.
- Board Certification Pay: \$2,000 for the first certification, \$500 for each additional subspecialty or secondary certification
- Executive responsibility pay: \$4,000 to \$15,000 for a "Service Chief" and \$14,500 to \$25,000 for a "Chief of Staff." Pay is in lieu of scarce medical specialty pay and will be prorated for the proportion of time spent performing executive vs. clinical duties.
- Geographic location pay: up to \$17,000 in locations with extraordinary difficulty in recruiting and retaining a specific category of physicians. ■

proposal made it no further than HHS despite multiple attempts to jostle it forward. Modest success came in 1990, when the late Rep. Silvio O. Conte (R-Mass.) managed to get SBRS tacked on to an urgent appropriations bill. "If it had not been for Conte's interest in NIH, we might never have gotten this authority," recalls Benowitz. "Persistence pays off." The official name for the SBRS is now the Silvio O. Conte Senior Biomedical Research Service.

The struggle since 1990 has been to translate the congressional authorization into a functional program. "Originally, we wanted a lot more flexibility than this [approved version of SBRS] gives us," says Benowitz. "We wanted to be able to let Commissioned Officers enter the SBRS and transfer their time. This does give us a better system for performance appraisal, based on the Board of Scientific Counselor's reviews every three to four years — evaluation tied entirely to the science a lab produces." Benowitz notes that "people have gotten pretty cynical" about SBRS. "It wasn't that it took 10 years to get the authority — although that contributed to it — but because it has been four years since the law passed, and we're still not using it," he says.

In addition to higher salaries, SBRS offers the benefit of "portable" retirement benefits similar to those in academia, but only if a scientist is recruited to SBRS from outside the government. Benowitz says this feature "should appeal to academics who may not want to stay in the government for 20 years." Some senior scientists now in the Commissioned Corps or other employment systems may profit by retiring and starting a second career in SBRS, but Benowitz notes the financial pros and cons will vary for each individual. Members of the SBRS are not eligible for Physicians' Comparability Allowance, performance awards, or other bonuses or awards for recruitment, relocation, or retention. Unlike Title 38, SBRS does not require that members spend 15 years before counting their new salaries toward the "high three" pay years used to fix retirement benefits. PHS recently approved an SBRS credentialing/policy committee, which is expected to begin work quickly, now that OMB's final approval has been received.

Although they were a long time coming, Benowitz notes that Title 38 and SBRS authorities are particularly welcome at this point — just as a more-than-year-long hiring freeze is being lifted. "Institutes have not been able to go out and recruit senior scientists for awhile. We have a number of Scientific Directors' positions open, plus a number of Lab Chiefs'," Benowitz says. "The need was there, and now the opportunity is there to use the new authorities." ■

ALTERNATIVE VIEW continued from page 9.

mistakes on unusual words.

The biggest shortcoming of Reference Update, no matter how you gain access, is that far fewer journals are referenced by this database than by Current Contents. However, depending on your field of interest, this may not be significant, and there may also be journals in Reference Update that are not represented in the Current Contents database. Try an experiment: do the same search for the same week on both Reference Update or Current Contents. How many references did you get, comparing them to each other? If Reference Update seems to be doing a good job, then stick with it because its reference format is far superior.

Recently, the company that owns Current Contents, The Institute for Scientific Information in Philadelphia, bought Research Information Systems of Carlsbad, Calif., which produces Reference Manager and Reference Update. So, there's hope that the best features of both reference-update programs may soon be combined into one product.

Bibliographic Management

There are advantages and disadvantages to every bibliographic-management program, and Reference Manager is no exception. Although very powerful, Reference Manager is expensive, slow, and more difficult to use than some other programs. You are also limited to a single "registered" database per copy of the program, which could either be an advantage if you want all lab-related references in a single location or a problem if your research group requires multiple reference databases. For example, in my work with the BioInformatics and Molecular Analysis Section of DCRT's Distributed Systems Branch, I like to create a database for each paper I am writing by taking references stored in previous databases. No other program that I am aware of besides Reference Manager limits you to a single database, and some, such as EndNote Plus and Bookends Pro, make it easy to combine and change databases. A problem related to Reference Manager's single-database limitation is that people tend to create very large databases, which causes the program to bog down.

For a booklet, published in 1993, comparing features of three Macintosh bibliographic-management programs, Reference Manager, EndNote Plus, and Bookends Pro, contact DCRT's Technical Information Office (fax: 402-0637; e-mail: sdl@cu.nih.gov). ■

Charge Cards: Coming Soon to a Lab Near You?

The NIH procurement process is finally gearing up to enter the age of plastic — a move that could make it much easier and faster for intramural researchers to get the reagents and equipment they need. The Office of Acquisitions Management and the Office of Financial Management are working on plans for a pilot procurement project that would allow scientists to use charge cards to purchase up to \$10,000 in merchandise per month, with an annual limit of \$20,000 (unless the researcher is certified as a procurement officer). As planned, there would be a price cap of \$2,500 per item.

The initial experiment, scheduled to begin this spring, is expected to be limited to 15 cardholders at NCHGR and 15 at NCI, Associate Director for Administration Leamon Lee says. The charge cards, to be issued by Rocky Mountain BankCard System, would be similar to the familiar American Express cards, requiring balances to be paid in full at the end of each billing period. At the end of each month, researchers would receive a statement to review and would be responsible for confirming that they'd received all the merchandise for which they'd been billed.

Before placing an order via charge card, researchers are expected to check to see whether the item is available at the NIH warehouse or stores, or through Blanket Purchase Agreement vendors. If the item is not available from those sources, researchers can go ahead and place an order with the vendor of their own choosing, Lee says.

Ultimately, the Intramural Research Program hopes to completely computerize the system and extend it to all NIH labs, a process that Lee hopes to see accomplished by the end of this fiscal year. Similar charge-card systems are already in place at other federal agencies, including the Food and Drug Administration and the Social Security Administration. ■



INTRAMURAL COUPLES*continued from page 6.*

even the appearance of impropriety.

Jennifer Puck, Chief of the Immunological Genetics Section at NCHGR, and her husband Robert Nussbaum, Chief of the Laboratory of Genetic Disease Research at NCHGR, had quite a few years to work out ways to keep their signals clear with one another and with their colleagues before they came to NIH 11/2 years ago. The couple married when both were medical school students. After residencies at Washington University at St. Louis, both went into academic research — first, at Baylor College of Medicine in Houston and then at the University of Pennsylvania School of Medicine in Philadelphia.

Puck attributes her happiness and success in the intramural program — as well as in marriage — to simple straightforwardness developed over the years. “I have had to make it clear to people that I do not necessarily receive information given to my husband, nor do I want to be counted on to pass things on to him. We’re both busy, independent people and not each other’s secretaries.”

Nussbaum adds that at other institutions in the past, “There have been times when I have felt that people assumed that when I support my wife over an administrative issue, as opposed to a scientific one, that I am doing it out of loyalty rather than because I agree with her.” In reality, presentation of a united front is the result of the couple’s hard work thrashing out the issues in private before joining the public discussion. “If I don’t agree, I talk it over with her in private before having any public discussion and tell her that I don’t agree,” he says.

Couples, such as Puck and Nussbaum and Bunnell and Gregory, who are relatively new arrivals at NIH after spending years in academia, are perhaps more finely tuned to the unique advantages and disadvantages of NIH than those who’ve been here most of their careers.

“I found academic life to be more stressful,” says Nussbaum, who along with his wife spent 15 years in academic research before coming to NIH. Bunnell agrees, saying that if he had an equivalent position in academia, he’d have to devote many of his evenings and weekends to writing grants, rather than spending time with his family. “Here we can do science. We don’t have to spend our time begging for money,” says Bunnell, who met Gregory while teaching her how to clone genes at the University of Alabama at Birmingham. The couple then pulled up stakes

and moved to the University of Michigan at Ann Arbor before coming to NCHGR last year.

Gregory notes that there are also far more administrative opportunities for Ph.D.s at NIH than at most universities, giving a bench researcher who is trying to relocate with his or her spouse the chance to make a career shift rather than simply not have a job. On the downside, she points out that intramural salaries are generally below those in academia and, unlike many universities, NIH doesn’t offer the option of a nine-month work year — an option that many dual-scientist couples with young children find convenient.

So, adding up all the pluses and minuses, would most intramural researcher couples do it all over again? For most of the couples interviewed, the answer is a resounding yes.

One senior intramural research couple, Judith Rapoport, Chief of the Child Psychiatry Branch of NIMH, and Stanley Rapoport, Chief of the Laboratory of Neurosciences at NIA, report their scientific careers turned out far better than they expected when they got married 33 years ago. “We met in medical school ... and thought of research at the time, but we were not sure it would work out,” Judith Rapoport says. When she looks back, Rapoport says it’s clear that having a scientist for a spouse has enriched her marriage, although it was not always obvious at the time. But even when both partners have notched impressive scientific achievements, it’s not always a bed of roses for intramural research couples because problems facing the NIH scientific community hit such marriages doubly hard. “Sometimes I wish we did not share so much of the current concerns over changes at the NIH,” Rapoport says.

Acting Director of NIDR Dushanka Kleinman, who has been married for 20 years to Joel Kleinman, Chief of the Section on Neuropathology at NIMH, says that the pairing of two scientific minds “has enriched our marriage and helped our careers. We have a receptive and understanding ear at home. We do not need to translate issues related to the ‘process’ of research and feel we get a relatively unbiased assessment at the home front.”

With all the clouds on the employment horizon, some of today’s young scientists might be more than a bit hesitant about getting hitched to another biomedical researcher. But, noting that their research careers evolved into areas they could not have foreseen at the time they got married, the Kleinmans offer these words of encouragement to those standing on the brink of an intramural marriage: “Go for it!” ■

RECENTLY TENURED*continued from page 15.*

of low-level radon exposure. In our investigation, excesses of lung cancer has been noted among patients exposed to Thorotrast. Since thorium-232 decays into radon, which is continuously exhaled over the course of the patient’s life, it is possible that this exposure caused the excess lung cancer. Detailed dosimetric studies are under way to quantify the dose of radon to pulmonary tissues and to relate dose to lung cancer risk. This study has public-health relevance because indoor radon is considered the single most important source of radiation exposure and risks of low-level exposure are poorly understood.

I am also interested in understanding the patterns and determinants of cancer risk following bone marrow transplantation, an increasingly common procedure used in the treatment of cancer, and in examining the possible interactions among immunosuppression, total-body radiotherapy, chemotherapy, viral cofactors, and graft-vs.-host disease. Our recent studies of more than 20,000 recipients of bone marrow transplants identified high rates of secondary lymphoma, and solid tumors are just now emerging as an important late consequence. With the Laboratory of Pathology at NCI, we are investigating the histologic and immunophenotypic characteristics of posttransplant lymphoproliferative disorders, Epstein-Barr virus status, and host-vs.-donor origin.

Whenever possible, my research in cancer epidemiology seeks to integrate new laboratory approaches in efforts to clarify mechanisms of carcinogenesis. Ultimately, one goal is to develop methods that might predict which cancer patients are at substantial risk for developing new malignancies and would thus benefit from targeted screening and preventive measures. Toward this end, we welcome further collaboration with clinical and laboratory colleagues at NIH. ■

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. ■

MEDICAL BOARD

continued from page 3.

ate Director for Nursing, a representative of the CC Department Heads, and a representative of the Junior Staff. The Board met Jan. 12-13 in Annapolis, Md., to review the issues that currently confront investigators interested in clinical research at NIH. The Board drew up the following list of goals that it plans to pursue over the next year:

- Achieve an improved Clinical Center. This includes providing input to the CC Director on the type of new hospital that will be needed, helping develop guidelines to ensure the quality of the services delivered within the CC, improving the budgetary process, and establishing clear linkages between bench- and patient-oriented research.
- Identify and reduce obstacles to clinical research. As was pointed out at the organizational meeting of the Clinical Research Interest Group on Jan. 11, an increasing number of forms and committees need to be cleared before a clinical trial is initiated. Although the protection of human subjects remains foremost in our concerns, it is also important to facilitate the rapid implementation of clinical research projects.
- Promote education, training, and career development for individuals who have an interest in clinical investigation. This includes establishing incentives for retention, such as the recently approved Title 38 pay scales, as well as developing educational programs for clinical associates and senior staff.
- Improve the efficiency of CC operations, including an evaluation of the current satellite clinical programs, the CC consultative services, and shared support services such as DCRT, BEIP, DES, and Ober United Travel Management, NIH's contract travel agency.
- Develop guidelines to ensure that appropriate standards are met by those who conduct and support clinical research programs.
- Redefine the roles of the Clinical Directors and the Medical Board. It is not clear whether the Board, as currently configured, is best suited to carry out its mission and whether the mission as originally stated is appropriate in the current environment.
- Improve the public relations image of NIH, in particular, the research conducted in the CC. These efforts should be linked with efforts to improve the

recruitment of patients and fellows.

- Develop a state-of-the-art medical information system that can keep accurate and complete medical records and meet the evolving needs of investigators to store, retrieve, and analyze data.

The work in these areas will involve members of the Medical Board, members of the CC, and members of the Institutes. Volunteers interested in helping with this work are encouraged to contact their Clinical Directors. The recently established Clinical Research Interest Group should serve as a key forum for ensuring that the thoughts and concerns of all NIH investigators with an interest in clinical research are addressed. For more information on the Clinical Research Interest Group, contact Jack Klippel (phone: 496-3374; e-mail: klippelj@arb.niams.nih.gov). ■

Subscription Service

To get the Deputy Director for Intramural Research's electronic bulletin board delivered directly to your e-mail box, send an e-mail message that reads "Subscribe DDIRBB-L Your Name (First Last)" to listserv@list.nih.gov. ■

Honoraria Update

The Supreme Court, in a narrow ruling, has struck down the so-called honoraria ban that prevented federal employees from accepting money for writing or speaking engagements outside of work. The new ruling pertains only to employees at the GS-16 level and below and permits them to accept honoraria only for outside activities that are unrelated to their work. Conflict-of-interest rules still prevent employees from accepting outside money from organizations whom they regulate or work with as part of their jobs. Michelle Russell-Einhorn, Assistant Special Counsel for Ethics for NIH, notes that the honoraria ban remains in place for researchers in the Senior Executive Service. Russell-Einhorn adds that although the new policy forbids NIH scientists from receiving honoraria for discussing their current research, they can receive honoraria for articles or speaking engagements pertaining to their "general expertise." ■

*National Institutes of
The Science Game*

Have you ever wanted to be a SCIENTIST? Have you ever wanted to see how successful you might be in SCIENCE? Have you ever wanted to win the NOBEL PRIZE? JUST PLAY THE SCIENCE GAME! Any number of people can play. The rules are easy. FIRST PERSON TO GET:
10 PTS — gets a "PhD"
40 PTS — gets a "faculty-job"
100 PTS — gets "tenure"
500 PTS — gets THE NOBEL PRIZE!!

DENT

THE TURN

"DO AN EXPERIMENT"

roll two 6-sided dice
add the numbers on the dice
consult the experiment success chart:

THE EXPERIMENT SUCCESS CHART

1-11: experiment fails *
12: experiment succeeds
collect 1 point if experiment succeeds

BEGIN NEXT TURN

*if fail 10 times in a row, automatically lose the game

OPTIONS

A PLAN YOUR EXPERIMENT:
SKIP A TURN TO PLAN;
CAN SKIP UP TO 6 TURNS
BEFORE DOING AN EXPERIMENT;
EACH PLANNING-TURN
ADDS 1 TO DICE ROLL

DISAPPOINTMENT FACTOR:
IF PLANNED AN EXPERIMENT
AND IT FAILED, SUBTRACT POINTS
EQUAL TO NUMBER OF
PLANNING TURNS!

B HIGH RISK EXPERIMENT

GET MORE POINTS BY DOING A "HIGH RISK" EXPERIMENT: ROLL EXTRA "EXPERIMENT DICE" AND NEED TO GET A 6 ON EACH EXTRA DIE FOR EXPERIMENT TO WORK — EACH EXTRA DIE GIVES SIX EXTRA POINTS.
E.G. If roll 2 extra dice, need to get 2 sixes for experiment to succeed.
If experiment is successful, get 14 pts.
APPLY DISAPPOINTMENT FACTOR if fails, equal to number of extra dice. GOOD LUCK!!

FAX-BACK

In this issue, we are asking for your feedback in four areas: equal employment opportunity initiatives, scientific computing, tips and suggestions for our Hot Methods Clinic, and frequently cited scientists. **Fax your responses or comments on other intramural research concerns to 402-4303** or mail them to us at Building 1, Room 334.

In Future Issues...

- OTT's New Directions
- Protein Expression Lab, On the Move in More Ways Than One
- Fogarty's Latest Crop Of International Scholars
- Electronic Journals: Is Paper Becoming A Thing of the Past?

1) Do you have any specific suggestions for implementation of the Affirmative Action Plan at your particular institute, center, or division? What strategies do you suggest for recruitment?

2) What is your response to the "Scientific Cybernauts" articles? What other topics would you like to see addressed about applications of computer technology in biomedical science?

3) Do you have any suggestions or comments about the FISH techniques featured in this issue's Hot Methods Clinic? What updates can you provide on previous Hot Methods? What techniques would you like to see covered in future issues?

4) In a future issue, we would like to conduct interviews with several of NIH's most-cited intramural research scientists about their seminal papers and the ensuing scientific reaction. Who should be interviewed? What questions would you like us to ask?

The NIH Catalyst is published bi-monthly 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: Rebecca_Kolberg or Celia_Hooper %NIHOD1E.BITNET@CU.NIH.GOV.

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