FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

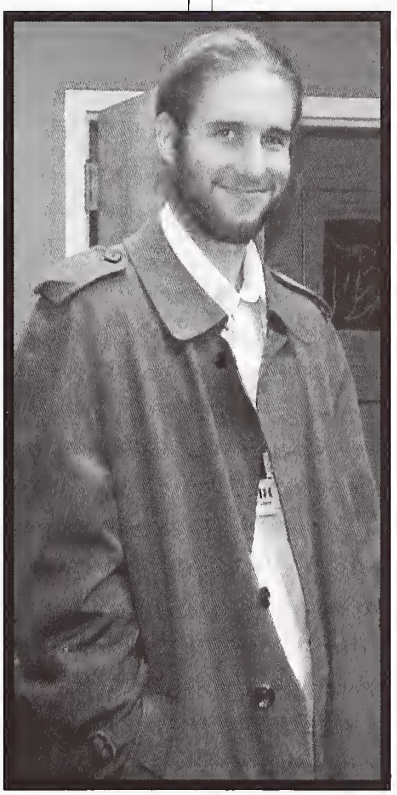
A PUBLICATION FOR NIH INTRAMURAL SCIENTISTS

NATIONAL INSTITUTES OF HEALTH ■ OFFICE OF THE DIRECTOR ■ VOLUME 6, ISSUE 1 ■ JANUARY–FEBRUARY 1998

POSTBAC TO THE FUTURE: A SNAPSHOT OF NIH'S RECENT COLLEGE GRADS

by Lee Mack

"Behold the infant! Like a shipwrecked sailor, cast ashore by the fury of the billows, the poor child lies naked on the ground, bereft of all means for existence, after Nature has dragged him in pain from his mother's womb. With plaintive wailing he filleth the place of his birth, and he is right for many evils await him in life." Lucretius, De Rerum Natura



Fran Pollner

Lee Mack on assignment

Lucretius probably didn't have pre-IRTAs in mind when he wrote this, but at moments, in a certain light, these words could very well describe the station at which I and others like me have arrived: the pre-IRTA program at NIH and, more specifically, the postbac slot, that place between college and the Great Beyond where we haunt the labs of NIH looking for the meaning of life.

What is the postbac? The answer will depend on who you are. To a seasoned principal investigator at NIH, a postbac might be a much-needed breath of fresh air. To a newly minted investigator, a postbac may be a critical pair of hands and a junior colleague of a

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BAC-TRACKING AND OTHER DATA GATHERING: NEW HANDLES ON THE NIH TRAINING POT

by Fran Pollner

An online application system launched the first week of calendar 1998 will bring to an end speculation about who applies for and receives postbaccalaureate training slots at NIH. Their numbers, their demographics, their success in being placed in their institute of choice, and other relevant data will be maintained in a central database in the Office of Education (OE), with certain unlinked, anonymous demographic statistics available by password to EEO officers.

And an intramural scientist database to be launched by the Office of Intramural Research (OIR) before the end of fiscal year 1998 will end speculation about where the postbacs go and what they do after they leave NIH, information central to evaluating the success not only of the postbac but all NIH training programs—all of which and more this eagerly anticipated database is being designed to capture.

It may seem inconceivable that tracking systems like these are only now materializing when few would dispute that NIH has been training new generations of biomedical scientists since its beginning over a century ago. But it wasn't until October 1986 that the IRTA program, per se, was born.

IRTA stands for Intramural Research Training Award, an authority conferred by Congress in the Health Research Extension Act of 1985. Until then, recalls OIR Executive Director Richard Wyatt, "we had no targeted way to bring U.S. postdocs here for training." The main mechanism was to hire them as government employees.

Lee Mack

Several among about 70 postbac IRTAs brought together for the first time last fall

In contrast, foreign postdocs had been training at NIH under the auspices of the Fogarty visiting fellows program since the 1950s. There were 736 visiting fellows on campus the first IRTA year, when 103 U.S. postdocs set foot on NIH soil. "We aspired to parity between foreign and U.S. nationals," Wyatt said in an interview, "and today there are roughly equal numbers in postdoctoral training programs here—about 1,000

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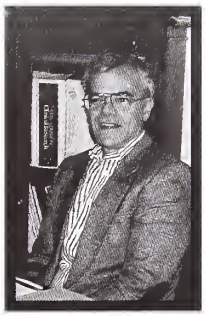

Michael Gottesman


Richard Wyatt

Our commitment to improve the environment for clinical research at NIH is beginning to catalyze change across campus. This column is a progress report on accomplishments in this realm—realized and projected.

NIH Director's Clinical Research Panel

In the spring of 1995, NIH Director Harold Varmus empaneled a group of extramural clinical researchers and academic and industry leaders to recommend measures to stimulate and support clinical research in the United States. The panel's report, presented to the Advisory Committee of the NIH director, includes some major new initiatives NIH is undertaking, such as enhanced clinical research training awards for young investigators and support mechanisms for midcareer investigators, a loan repayment program for clinical researchers, and an NIH-based clinical research training program for medical students (see below).

Clinical Research Training Program

Responding to the director's panel, NIH now has a Clinical Research Training Program for medical students who have completed their principal clinical rotations (usually third year). This year, we welcomed the first class of CRTP fellows—nine students, some living in a group house on campus (formerly the director's residence) and all working on clinical research projects (under the supervision of some of our most outstanding clinical researchers (see <http://www.training.nih.gov/student/crtp/index98.html> for a detailed program description). With partial support from the National Foundation for Biomedical Research, these students have their own journal club, attend Monday night lectures and dinners with HHMI research scholars, and take the Core Curriculum in Clinical Research. Given the enthusiasm for the program, we expect to expand to as many as 15 to 20 students in the class that arrives this summer.

NIH Committee on the Recruitment and Career Development of Clinical Investigators

In early 1996, the Scientific Directors concluded that recruiting new and outstanding clinical researchers to NIH was both a great challenge and crucial to efforts to enhance clinical research activities. Steve Straus, chief of the Laboratory of Clinical Investigation, NIAID, chaired the interinstitute committee that came up with ways to attract and maintain our talent pool (see "Clinical Research Action Plan," September-October 1997, page 1). Among those being implemented are increased salary scales for tenure-track and tenured clinical researchers, a longer tenure track for clinical investigators, establishment of a clinical research advisory committee (chaired by NCI's Tom Waldmann) to the Central Tenure Committee, enhanced status of NIH clinical directors, and creation of a Clinical Research Revitalization Committee to pursue the more general concerns of the original Straus Committee (see below).

Clinical Research Revitalization Committee

Steve Straus chairs this new standing committee. It is exploring innovative ways to improve clinical research support services and patient care in the Clinical Center (CC) and setting standards (with the Medical Executive Committee) for staff clinician promotion. Recommendations will be acted upon as they arise.

Clinical Research Center Activities

John Gallin, associate director for clinical research and CC director, has taken the lead in a series of recruitment, training, and management activities that have fostered clinical research at the NIH CC. The recruitment of Nick Bryan as CC radiology chief and associate director of radiological imaging is one key appointment. A CC Board of Governors, constituted by the HHS secretary and working with Gallin, has been examining CC management and budget for the past year and has helped keep CC costs stable. A CC Advisory Committee (CCAC), chaired by Steve Hyman, NIMH director, and Ed Liu, scientific director of NCI's Division of Clinical Sciences, now exists to consider such programmatic and scientific issues as the organization of the patient care units in the new Clinical Research Center (CRC) and the dispersal to the Institutes of carryover funds from CC savings. The CCAC, with the scientific directors and institute directors, will also shape the process to allocate CRC laboratory space. Ultimate decisions on lab assignments will be made by the NIH director, with the advice of a committee representing clinical investigators, clinical directors, scientific directors, and institute directors.

The Mark O. Hatfield Clinical Research Center

Groundbreaking for our new CRC occurred on November 4, 1997. Special guests, including Senator Hatfield, Vice President Gore, and two NIH patients, spoke glowingly of NIH contributions to basic science and clinical research (see "Clinical Research Center Moves from the Drawing Boards . . ," November-December 1997, pages 6–7). Site preparation began with demolition of the apartment building (Building 30), amidst the well-publicized, if only partially effective, effort to save venerable trees on the site. We expect excavation to start in October 1998 and the building to be complete by the end of 2001. This state-of-the-art facility will offer a dramatically improved physical environment for conducting clinical and translational research.

Other Clinical Research Activities

Building on last year's impressive and morale-boosting Clinical Research Day, at which many of our top researchers showcased their work, this year's NIH Research Festival will highlight clinical research activities. Scott Whitcup, NEI clinical director and incoming chair of the Medical Executive Committee, will help organize the festival with Art Levine, NICHD scientific director, and Story Landis, NINDS scientific director. A recent generous gift pledged by NCI scientist emeritus Robert W. Miller and his wife Haruko Miller, a retired NCI research technician, will establish an NIH Director's Lecture to honor astute clinical observations that led to important laboratory research. And, finally, NIH Clinical Center protocols can now be accessed by all via a fully searchable Web site at <http://www.cc.nih.gov/nihstudies/>, a development that will greatly simplify the patient referral process (see "Just Ask," page 3).

As always, we welcome your suggestions for further improvement. ■

—Michael Gottesman, DDIR
Richard Wyatt, Executive Director, OIR

Just Ask!

Dear Just Ask:
From time to time I receive requests for information from individuals on the outside about ongoing treatment protocols here at NIH. Is there any single source of information I can query about such protocols, or does each institute deal with these through an information officer? Thanks.

—Jack London, NIDR

Dear Jack:
In answering this question, I must point out I am not an expert on this subject, but I do have a good sense of where most major NIH online resources reside. Here's what I know about online information for clinical studies.

The best source of in-house data on clinical studies can be found at the Clinical Center's Web site at <http://clinicalstudies.info.nih.gov/>. This online database can be queried in several ways and provides details on each protocol, including a summary, the sponsoring institute, recruitment details, and population exclusions. According to Jerry King, who heads the CC medical record department, each principal investigator chooses whether to be included in the database. He estimates the database encompasses about 78 percent of the intramural studies. If you have questions about this resource, I suggest you contact Sara Byars, deputy chief, Office of Clinical Center Communications (594-5788).

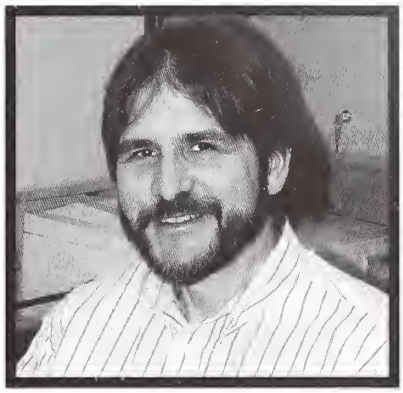
Several ICDs also use their own Web sites to carry information on their own intramural clinical studies; however, these resources appear to be subsets of the data found in the CC database.

There are other online databases of NIH-supported clinical studies that also include extramural trials. If you search one of these resources, I would imagine it would be relatively easy to sort your results to show only those studies that are being conducted here at the Bethesda campus.

First, we have NCI's PDQ: <http://cancernet.nci.nih.gov/trials/h_clinic.htm>. Here's how this information resource is described:

"PDQ contains the world's most comprehensive cancer clinical trial registry—more than 1,600 summaries of trials that are open or approved for patient accrual, including protocols for cancer treatment, supportive care, screening and prevention. In addition, you can reference more than 8,000 summaries of protocols that have been completed or are no longer accepting patients.

"For each trial, detailed summaries are prepared from the original protocol document, ensuring uniformity and accuracy of the content. You can retrieve protocols by diagnosis, treatment modality, phase, locality or drug name, or a combination of these parameters.



Fran Pollner

Dennis Rodrigues

"All protocols supported by the NCI are listed in PDQ. Clinical trials not sponsored by the NCI, including foreign protocols, are included in PDQ after review and approval by the PDQ Voluntary Protocol Review Board."

Another place to look is the NIH Office of Rare Diseases, which describes its clinical trials database in these words:

"The NIH Office of Rare Diseases has developed a clinical research database to assist researchers and the public in identifying ongoing or planned clinical research projects related to rare diseases or conditions. The Rare Diseases Clinical Research Database (RDCRD) is located at <http://rarediseases.info.nih.gov/ord/wwwprot/index.shtml>.

"The purpose of the database is to match potential research participants with current clinical research projects supported by NIH by making information about rare disease clinical research studies available to the rare disease community. The database also provides a directory of information on voluntary organizations and support groups.

"The Rare Diseases Clinical Research Database contains protocol summaries of clinical studies currently accruing patients. Each protocol summary includes the study objectives, patient entry criteria, and the details of the treatment regimen. Also included in the database are the names of the research investigators and the geographical locations of the studies. The RDCRD contains names, addresses, telephone numbers, and voluntary patient support organizations that provide information concerning rare diseases."

For more information about the RDCRD, contact Steve Groft at 402-4336 or e-mail <grofts@od31em1.od.nih.gov>.

The Office of Rare Diseases page also provides some tips on searching for information on clinical studies. For example, it points out that you can use the NIH CRISP Database to try to identify studies using search terms such as "clinical trials" or "clinical studies." CRISP is located at <http://www.nih.gov/grants/award/gophercrisp_t.htm>.

You can find information about AIDS Clinical Trials at the National Library of Medicine. Go to <http://www.nlm.nih.gov/pubs/factsheets/aidstdfs.html>.

Finally, you may want to note that NIH is exploring the creation of a trans-institute database that would provide information on all NIH-sponsored clinical studies; however, this initiative is in an early stage of development.

Hope this helps.

—Dennis Rodrigues
Office of Communications

Interest Group Gazette

The **Mitochondria Interest Group** (MIG) and NCI's Laboratory of Cell Biology are hosting a lecture on "Cytochrome oxidase in neuronal metabolism and Alzheimer's disease," by Francisco Gonzalez-Lima, of the University of Texas at Austin. The meeting will be held February 5 at 3:00 p.m. in Wilson Hall (Building 1) and teleconferenced to NIEHS in North Carolina and NIA in Baltimore. (The videotape will be archived on the MIG web site <http://www-lecb.ncifcrf.gov/~zullo/migDB/>.)

Flash: This will be the first MIG meeting with CME credit available; CME credit can also be obtained for all subsequent 1998 MIG meetings, as well as and the first (and the second, if it falls before February 6) in 1999. For information, contact Steve Zullo at 435-3576 or <zullo@helix.nih.gov>.

The **Cytokine Interest Group** has a new co-chair: Warren Leonard has replaced Howard Young; Sharon Wahl continues as the other co-chair. ■

Seminar Highlights

Contemplating Triplex DNA As Explosive Gene Therapy

By Ronald Neumann, M.D., Chief, Nuclear Medicine, Clinical Center. Neumann presented this November 12, 1997, at the Stone House at a joint DOE/NIH workshop to assess isotope-based medical research in the post-genome era. These Seminar Highlights were prepared by Celia Hooper.

ABSTRACT

Triplex-forming oligonucleotides (TFOs) labeled with radionuclides that are Auger electron emitters could prove to be ideal vehicles for delivering radioactive decay energy to specific DNA sequences, causing local DNA breaks and subsequent inactivation of genes containing the target sequences. In a DNA triplex, the TFO, a short oligonucleotide generally 15–20 base pairs (bp) in length, occupies the major groove in a DNA double helix. Hoogsteen bonds are formed with the purines of the Watson-Crick base pairs in a sequence-specific fashion. In general, stable triplexes can be formed between polypurine-polypyrimidine duplexes and polypurine or polypyrimidine TFOs. Such sequences are widespread in eukaryotic genomes and are often found in regulatory regions. We have shown that TFOs can serve as suitable vehicles to deliver iodine-125 (^{125}I) to a specific sequence in a DNA target (1).

The radiodecay of certain radionuclides produces a cascade of low-energy electrons, named after Pierre Auger, who first described this process in 1929. For example, radiodecay of ^{125}I results in the emission of approximately 20 electrons of varying energy. Most of these Auger electrons have initial energies of less than 1 keV and a maximum range of only a few nanometers. The radiodecay of incorporated ^{125}I from a TFO in a triplex structure with a targeted sequence in duplex DNA produces strand breaks located within 10 bp of the decay site with an efficiency close to one break per decay (2). Therapeutic applications of Auger electron emitters depend on developing methods for radionuclide delivery to the intranuclear genome of target cells, for example, cancer cells or perhaps even virally infected cells (3).

The promise of TFOs carrying Auger electron-emitting radionucleotides may be gene-specific radiation therapy if the complexities of triplex formation in vivo can be resolved.

Fran Pollner

Ronald Neumann

QUESTIONS

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

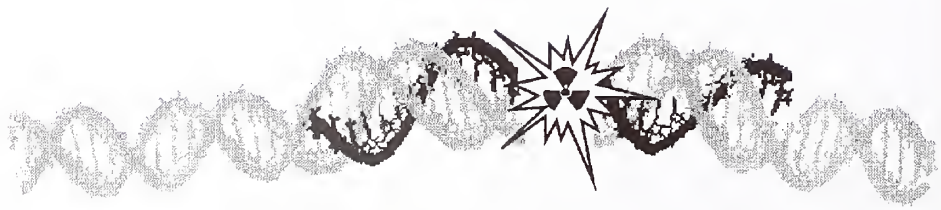
A: My initial puzzle was how to position the Auger electron-emitting radionuclides sequence specifically and in close proximity to genomic DNA. Fortunately, I went to a lecture in Masur by a visiting Russian DNA chemist, Maxim Frank-Kamenetskii, where I first learned of triplex-forming oligonucleotides, short DNA fragments that incorporate themselves into the major groove of duplex DNA in a sequence-specific fashion. Ironically, the existence of triplex nucleic-acid structures was first demonstrated in 1957, here on campus by Gary Felsenfeld, David Davies, and Alex Rich.

Our first task was to demonstrate triplex binding by radiolabeled TFOs. My colleague, Igor Panyutin, devised a plasmid model system in which we showed DNA double-strand breaks could be produced by TFOs carrying ^{125}I. Next, we measured the frequency and distribution of the breaks to show the small (± 5 bp) zone of DNA damaged by Auger electrons emitted during ^{125}I decay. We then asked gene therapists how best to deliver DNA to specific cell nuclei. We chose cationic liposomes for the in vitro plasmid-model experiments, and demonstrated delivery into cultured cell nuclei by autoradiography and confocal fluorescence microscopy, effected by our visiting fellow, Olga Sedelnikova, in collaboration with Alain Thierry, who was then in Robert Gallo's lab. By attaching chemical linkers to the TFOs, other Auger-emitting radionuclides can now be used. This is work by Valeri Karamyshev, a visiting fellow, and our collaborators at Epoch Pharmaceuticals, Bothell, Washington.

Once formed, the triplexes are quite stable. One that we studied has a melting temperature of 65 °C at conditions close to physiological. Double-strand breaks produced by decay of ^{125}I incorporated into genomic DNA are highly radiotoxic and hardly reparable. Their repair usually results in deletion of large (>100 kbp) fragments of DNA.

Nanonuclear explosion produces sequence-specific DNA breaks

A. Triplex-forming oligonucleotide carrying Auger electron emitter binds in the major groove of the target duplex sequence.



B. Decay of Auger electron-emitting radionuclide producesDNA strand breaks within five nucleotides from the decay site.

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

A: Our biggest and most pleasant surprise was finding that ^{125}I-TFOs that do not form triplexes with genomic sequences, yet are present in the nucleus, caused very little radiation damage. These nonbound oligos are nearly 1/300 as toxic to the cell as ^{125}I-5-iododeoxyuridine, a precursor of DNA synthesis that is incorporated into genomic DNA. This gives us some hope that we can produce breaks in targeted gene sequences without causing excessive nonspecific radiation damage. The half-life of phosphodiester TFO in cell culture is hours and even shorter in vivo. For this reason, we have to freeze the cells after TFO delivery to accumulate DNA breaks and are now developing labeling procedures for phosphoramidate TFOs that are considerably more stable in vivo. Of course, for the therapeutic application we will need radioisotopes with a shorter half-life than ^{125}I.

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

A: Our current experimental focus is to demonstrate that TFO-mediated Auger breaks in a tumor model have therapeutic benefit. We hypothesize that manipulation of the genomic DNA–nucleosome complex may affect triplex formation, and we would like to better understand those manipulations to improve the ability of TFOs to find their targets in vivo and to increase the specificity of such targeting.

Q: In which areas do you see this research having the greatest use for clinical scientists? In which areas of basic research will it be most illuminating?

A: Clinically, treating cancers containing amplified genes or viral-derived "foreign" sequences may be the best application of this technique should it be proven to work in vivo. Our chances of hitting a target gene increase if the gene is amplified, as happens in some cancers.

For basic scientists, this method may be useful to probe nucleic acid–protein complexes because the Auger electron damage is so focal and is distance-related. Igor Panyutin and collaborators in NCI and NIDDK laboratories took this approach recently when they analyzed decay-induced DNA breaks to successfully examine nucleic acid conformations.

Q: How are you following up on this work?

A: Beyond the specific cancer genes we're studying now, we would like to explore the application of our techniques in other genetic diseases and are thus in search of collaborators with amplified-gene models of disease in which to test other radiolabeled TFOs for gene-specific radiotherapy.

References

1. I.G. Panyutin and R.D. Neumann, "Sequence specific DNA breaks produced by triplex-directed decay of iodine-125," *Acta Oncol.* **35:** 817-823, (1996).

2. I.G. Panyutin and R.D. Neumann, "Radioprobing of DNA: distribution of DNA breaks produced by decay of ^{125}I incorporated into a triplex-forming oligonucleotide correlates with geometry of the triplex," *Nucleic Acids Res.* **25:** 883-887 (1997).

3. O. Sedelnikova, I.G.Panyutin, A. Thierry, and R.D. Neumann, "Delivery of triplex-forming oligonucleotides into cells: Comparison of different liposome compositions." Genetherapy poster session, NIH Research Festival (1997).

Catalytic Reactions

On the New Clinical Research Center

Please allow the beautiful trees around the NIH campus to be cultured and not destroyed. I write specifically to preserve several trees marked for cutting to make way for construction of the new Clinical [Research] Center and Center Drive. The awe-inspiring white oak tree marked number 154 and several other majestic oaks in the vicinity of number 154 as well as several stately tulip-poplars along the proposed swath of cutting should remain standing. Their beauty stimulates the imagination and is, therefore, part of what makes the NIH campus a unique and valuable site to conduct biomedical research. They provide an irreplaceable natural sanctuary for quiet reflection. These trees symbolize the power of life and inspire us to solve problems with the living. The trees, furthermore, imbue pride and honor in the wider community.

In the final tally, these trees may provide more immeasurable value for the NIH mission than the structures that replace them. Please revisit the trees and make every effort to allow their survival. I hope that you will inform the NIH community of plans to cut the trees so that they may offer further input to what I see as a proposed diminution of our NIH.

—Brian Lowe, NHLBI

On Training Scientists at NIH

I would add to Dr. Michael Gottesman's extensive list of the necessary components of research training the availability of formal courses that last from a few hours to entire academic years. More and more components of the NIH, such as DCRT and the Building 10 Library, offer research-related training programs. The Clinical Center offers a highly successful Core Course in Clinical Research., and the Foundation for Advanced Education in the Sciences (FAES) Graduate School offers a rich menu of courses that can fill gaps in a fellow's training, bring him or her up to date in areas that have emerged or developed quickly since graduate school, or give a fellow background in a broad range of areas he or she may be curious about, helping in formulating new areas of research for an evolving career. These various educational programs are important complements to the less formalized training that takes place in the laboratory setting itself. For FAES course offerings, call 496-7476.

—Alan Schechter, FAES Graduate School

How about getting a job and finding a good mentor? Also, it's not all just from the trainees' perspective: How about rewarding mentoring and teaching mentors how to do a good job?

—Anonymous

Bac-Tracking
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Fran Pollner

Richard Wyatt

each—which seems to be a steady state."

The first "predoctoral IRTA" fellows, doctoral candidates, arrived in 1989 to do thesis work. There were 13 the first year; today, the census is around 250. (Medical students are another constituency, slated for treatment in a future issue of *The NIH Catalyst.)*

And it was only less than four years ago, in April 1994, that the "postbac" program—extending the pre-IRTA umbrella to fledgling owners of baccalaureate degrees with a proclivity for science—emerged. Their numbers doubled in the last year to about 200, according to Michael Gottesman, deputy director for intramural research, but should level off, if for no other reason than that tenure-track scientists are the mainstays of postbac preceptorship, and there are about 250 of them on campus.

With few exceptions, postbacs are here for one or two years, immersed in research and applying to schools of ever-higher learning. Until this fall, they were largely isolated from one another. Now they are linking up by e-mail, an interest group, and an OE-organized lecture series (see companion story, "Postbac to the Future," page 1).

Postbac Program Rationale

Created to give recent college graduates exposure to research and additional time to apply to graduate or medical school—and to "entice" them into research careers, as Wyatt puts it—the postbac program was also conceived in the language of affirmative action. Of the five types of IRTA programs (postdoc, predoc, postbac, technical, and student), the postbac is ideal for attracting disadvantaged students for whom access to biomedical research careers might otherwise be limited, including "minorities, women, and persons with disabilities."

Mindful that there appear to be fewer research jobs than research scientists these days, Wyatt does not see this IRTA cohort as a means to increase the ranks but rather to diversify them, not only in the fields of basic and clinical research but also in the related professions like tech transfer or communications that trainees may enter.

Not only will the central electronic application system keep track of how the program is meeting its goals, it may also serve to further them. According to Debbie Cohen, OE training program coordinator, applicants will specify as many as three institutes of choice; the institutes will have one month to decide on the candidate. If the response is negative, the application will circulate in the general pool for another month, providing more opportunities and a more equitable review among all the institutes of candidates closed out of sites with long lines. This mechanism was unanimously approved by the scientific directors (SD) in December. NIH's desire to improve the postbacs' lot in life is also reflected in the stipend increase from $16,000 to $17,600 that went into effect January 1.

Today's Patchwork Data-Quilt

Data on the composition and post-NIH whereabouts of program participants thus far are incomplete. At a July 1996 SD meeting, Gottesman presented data from about two-thirds of the institutes covering the first six to nine months of the program. Of the 53 postbac awards made during that period, 55 percent were to women and 36 percent to minorities; 17 percent were underrepresented minorities—seven African-Americans and two Hispanics. He called this record a "good beginning." Cumulative data since then are lacking.

Questions posed by *The NIH Catalyst* to a few institutes elicited a mix of responses reflecting different degrees of tab-keeping.

NCI's Jan Romanoff provided a chart tabulating 1996 data on race, national origin, and gender for 16 categories of NCI trainees. In those categories that include postbacs, race and national origin are "not specified" for more than half; underrepresented minorities account for 13 percent of the remainder.

NIDDK's Allen Spiegel dispatched the results of a recent survey of lab and branch chiefs on the destinations of "pre-IRTAs who have left in the past year or so." Of the 50 or so persons accounted for, slightly more than half were female and more went to medical school than other graduate programs. There was no data on racial or ethnic composition or disability status.

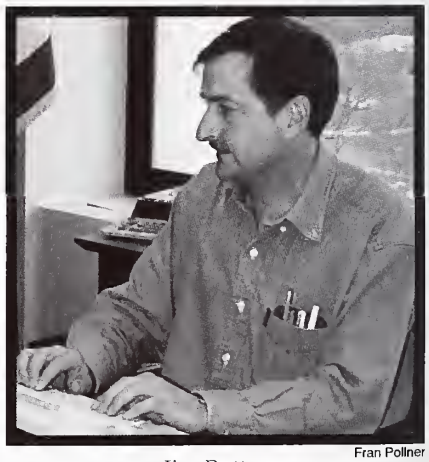
NIAID's Richard Asofsky reported that 67 postbacs have passed through NIAID's doors since the program's inception, 32 of whom are currently on campus. Plumbing his institute's databases, he surmised (on a first-name basis) that 28 of the total 67 and half of those now present are female. As for racial and ethnic compositions, the anonymous tallies provided by his institute's EEO office are incomplete for IRTA postbac positions.

NIDCD's Jim Battey could supply more details about his postbac population because "it's a small program, and I know them all."

According to data he compiled on 50 student NIDCD trainees since 1994, 10 appear to fall under the postbac IRTA umbrella, by virtue of the duration of their tour at the institute. Six of these are female, and all but one are minority. Most went on to medical school.

It's Battey's impression that the IRTA program is not perceived to be used exclusively for recruiting underrepresented scientists into biomedical research, unlike the minority outreach training program organized through the Office on Research and Minority Health, a door through which many NIDCD predoctoral trainees enter.

Who enters through which portal and the road they follow after will soon be a matter of more complete record. But according to an accolade by the late Lewis Thomas, which Wyatt is fond of citing, NIH trainees are the "youngest and brightest candidates for careers in biomedical research" who "deploy out to universities" to become "this country's leaders of academic science." ■



Fran Pollner

Jim Battey

Postbac to the Future
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sort, who likewise feels a bit alone in the shark tanks. To another postbac, the postbac may be a co-conspirator, a future collaborator, a rival, or a friend. A postbac may look into the mirror of the soul and see Lucretius' sailor: a little bit alone, a little bit intimidated, a little stranded on a seemingly deserted isle of science but possessed of remarkable perseverance and ingenuity.

As a postbac myself, I am close to the question at hand. *The NIH Catalyst* charged me with taking the pulse of this burgeoning population. All well and good, I thought. But from my first question—who are the postbacs, anyway?—I found that my own experience reflected only a fraction of the full range of what a "postbac" may be.

For instance, one of my fellow postbacs has been at NASA and aspires to go into outer space some day. Another grew up on a socialist farming commune in Israel and teaches Hebrew school. Another had just gotten back from a Peace Corps stint in the islands of Tonga. Another knows the East Coast rave scene inside and out. Another is a certified massage technician. More than a few I found were aspiring musicians as well as dedicated researchers. Quite a bunch! So, armed with a tape recorder, a notebook, curiosity, the deductive powers of a mathematician, and about five dollars in cash, I set forth.

The fiver was put to immediate use at the Capitol City Brewery in Bethesda, to which I was summoned by a fortunate e-mail exchange with a fellow postbac by the name of Ary Shalizi, a '96 Oberlin grad working in NIDR. Shalizi and I had two things in common: we'd both been haunting the NIH subterranes for over a year and we were both itching to find out whether there were more of our kind.

A few months back, Shalizi had gotten fed up with knowing only one other postbac on campus and posted a plea for interested postbac homebodies to identify themselves. Over the ensuing weeks, a wave of responses poured in. An amorphous group evolved around a weekly social gathering anonymously christened D(rinks) W(ith) S(cience), where postbacs would meet and greet in a vaguely proletarian spirit.

From this nucleus, word spread quickly round the campus until it became clear there were enough postbacs here to fill a fleet of Volkswagen buses—and yet, no one knew exactly how many there were, where they were, what they were doing, or how to get in touch with them. No one knew the history of the program; no one knew, in any general sense, why the postbacs had even been summoned to this mecca of biomedical research in the first place. True to their scientific nature, they wanted some answers, and so did I.

Lee Mack

Michael Gottesman, deputy director for intramural research, has the floor at precedent-setting gathering of postbacs last fall. OE's Debbie Cohen (foreground) takes notes.

I paid a visit to Debbie Cohen, a harried warrior in the Office of Education who somehow manages to juggle the myriad intramural research fellows on campus. Cohen organized a precedent-setting gathering of postbacs at FAES house on October 23rd with Michael Gottesman, deputy director for intramural research,as keynote speaker. The postbac program was his baby, anyway, and he came to lend a supportive ear to the 60 or 70 of us who had been alerted via the e-mail list Shalizi had compiled. The October meeting marked the first formal postbac gathering and set a trend Gottesman says he would like to see perpetuated as a means of staying abreast of evolving concerns of the postbac population, which, he says, could easily be marginalized by its intrinsic transience.

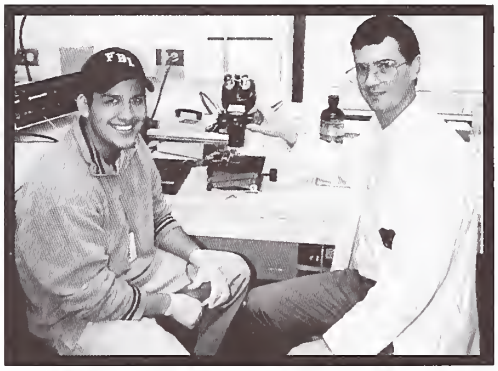
The event was a chance for these strange and furtive beings to get to know each other, share their tales, compare MCAT scores, eat free pizza, and vent all that frustration that had been building for the past three years, since the first postbac had strolled onto the NIH campus. Later, Gottesman reflected that he felt a definite "chemistry" among the participants, which has carried over into several projects now off the ground, including an Internet mailing list for the postbac population, a lecture series aimed at the postbac level, and workshops with med students.

The linchpin of the postbac program is the interaction between the trainee and the teacher. Not surprisingly, the more postbacs I talked to, the greater the variety of experiences I heard about. People's experiences varied widely, from institute to institute and even lab to lab: Some felt they were being used as cheap labor in place of technicians, and others felt they were treated as colleagues; some felt a little lost and overlooked in the lab, and others like they were part of a family.

PIs whom I spoke with gave an equally diverse picture. Some, like NCI's

Elise Kohn, accentuated the efforts and accomplishments of their postbacs, some of whom, she says, will "take my job and run with it" into the next millennium; others like NICHD's Tom Sargent and NIDDK's Debbie Hinton reported mixed results.

I began with the question: Why have postbacs anyway? Hadn't things been running smoothly without the injection of another variable into the research equation?



Lee Mack

NICHD's Tom Sargent (right) and "ace injector" postbac John Sandoval

Consensus held that postbacs add a dimension of vivacity to a laboratory setting. "They make life in the lab more interesting, more fun," Hinton says. She recalled a postbac who wasn't much for the nuts and bolts of research but proved to be quite a character to have around the lab, anyway—until leaving to pursue a law career.

According to Gordon Guroff, NICHD deputy scientific director, postbacs serve as surrogate grad students for NIH. Although some investigators come to NIH specifically to avoid graduate students, many—especially the younger ones—feel they are missing out on an opportunity enjoyed by their academic counterparts, according to Jim Hurley, a PI in NIDDK. Judah Rosner, another NIDDK PI, appreciates the tinge of the university atmosphere he thinks postbacs bring to the NIH campus: "Young people asking young people questions. . .blank slates."

Having a postbac in a lab presents an opportunity for a PI to learn some things as well. Hinton, an NIH veteran of 15 years who'd been skeptical about the teacher role for herself, learned she actually liked it after she'd had several postbacs in lab. And Kohn says she learns "a lot about myself, science, and life from my younger colleagues." Hurley adds, "They bring in a wonderfully fresh perspective, having yet to learn about the 'externalities' of science," a perspective, Hinton observes, that often translates into questions more experienced people may have lost sight of.

This assumes, of course, that a PI is open to such ostensibly amateurish inquiry, a condition most PIs I talked to seemed more than willing to fulfill. Shalizi, the NIDR postbac who got the mailing list going, says his preceptor is very receptive to a new idea "if I can make a good case for it."

"Ultimately," says Rosner, "it boils down to science." In that spirit, postbacs are often treated as junior colleagues. "It's a collegial concept," he explains. "If you're a scientist, you're a scientist."

And being a scientist means you have to meet certain expectations. Kohn, for example, meets personally with everyone in her lab at least once a week, from postdocs on down, in addition to holding a weekly lab meeting at which everyone is expected to present a journal club article and project update on a rotating schedule. Similarly, Gottesman expects that the postbac in his lab, John Gribar, will give a seminar of his work before he leaves.

Among PIs and postbacs who report positive experiences, this level of expectation and reciprocation seems ubiquitous. Hakim Morsli, unusual as a third-year postbac in NIDCD, reports that after an initial six-month training period he was let loose with his own project. As a result, he has submitted a paper to the *Journal of Neuroscience* and will be giving a talk in February. Michael Dedekian, only five months into his term at NICHD, has already produced results that were partially presented by a labmate at a meeting in Japan. Stuart Hicks, fellow NCI postbac, is a coauthor of a paper appearing in the January 1998 issue of the *Journal of Immunology.*

Lee Mack

NCI's Elise Kohn (left) and postbac Chris Gasbarre collaborate over a tissue culture flask

Postbacs are involved in many different types of research in almost every institute, ranging from the experience and expression of emotions in adolescents (Laura Mielcarek, NIMH), to cognitive-behavioral studies in rhesus monkeys (Gena Pixley, NIMH), to the embryogenesis of zebrafish (Michael Dedekian, NICHD), diabetes (Alison Cotrell, NIDDK), gene transcription in mammalian cells (Farhang Amini, NICHD), gender differences in pain response (Julie Miller, NIDR), complications in Parkinson's therapeutics (Christina Vaughan, NINDS), and on and on and on. My NCI research (under the direction of Carl Baker, cellular regulation and transformation section) is on the life cycle of papillomaviruses.

Research training is one thing, and providing technical services is another. I got mixed messages about the extent to which postbac naiveté and enthusiasm make us susceptible to excessive demands from overworked mentors.

"The idea is *not* to use [postbacs] as cheap labor," Sargent says, "[but] when I first heard about the program, I was afraid it could be used in an exploitative way. I think it's a danger." One particularly frank PI said he thought some people viewed the postbac program as another hiring mechanism. Two postbacs from the same lab who have since left NIH and wished to remain anonymous told me their sole responsibility in lab was to run sequencing gels day in and day out.

While limited technical work may expose a student who has no previous relevant lab experience to the methods needed to carry out a project, postbacs who were not brought in under the techni-

cal postbac tag are definitely not technicians, according to Gottesman.

In fact, my sleuthing revealed that the use of postbacs as glorified dishwashers is uncommon. Most PIs seem to realize that the goal is to introduce a group of potential future researchers to the culture of biomedical research and to propagate the high standards they themselves inherited from their predecessors. The emphasis across the board was on a holistic research experience. Most postbacs reported being encouraged to sample from the sometimes-exotic NIH platter by going to seminars, taking classes through FAES, volunteering, setting up collaborations with other groups, and really rolling up their sleeves and getting their hands dirty in the lab. "It's what you should expect when you go into science," says Guroff.

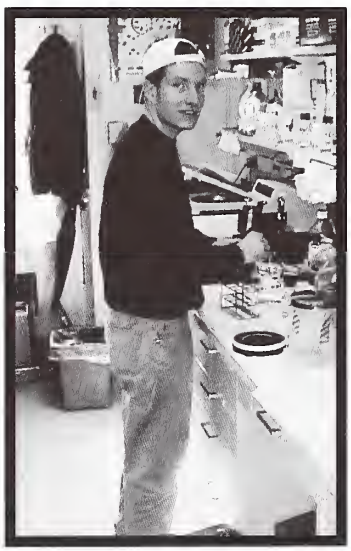
Lee Mack

NIDR postbac Ary Shalizi—e-mail wizard and Nobel aspirant

Aside from all the obvious benefits to the arrangement, problems do crop up occasionally, and anomalies often get more attention than everyday successes. The anomalies have led some interest in developing NIH-wide guidelines for postbacs and their mentors. But, as NIDDK's Rosner points out, "It is easy to envision hierarchy and structure, but problem solving is the real mechanism."

Rosner himself is the first official liaison between postbacs and the powers that be in his institute. He serves as a contact person for postbacs with questions or concerns falling outside the scope of a busy PI. The impetus for the creation of this position was NIDDK's Ira Levin, who explains that "in order to ensure that these junior scientists have the best possible experience in the short time they are here, we felt that a contact or liaison individual that they would feel comfortable with would be a useful adjunct for this group. . . .it seemed a natural extension of the mentoring concept." Such a liaison would serve as a facilitator of student-mentor dialogue and an external mediator if irreconcilable differences prevent resolution of a conflict. Of the many postbacs who have come through his institute, he has been faced with only one instance in which a change of scenery was necessitated.

At NICHD, Guroff performs a similar function for postbacs. A position like his is needed, he says, because "out of a group of 50 to 70 postbacs, a couple of people are bound to get lost." His responsibilities in this capacity include contacting postbacs before they begin their term of fellowship and advising them on the corollaries of the program, such as paying taxes, mentoring, social contacts, etc. He doesn't fault the PIs—who "daily have to deal with ethical, chemical, animal, radiation safety, and budget concerns"—for the fact that such a liaison is needed.

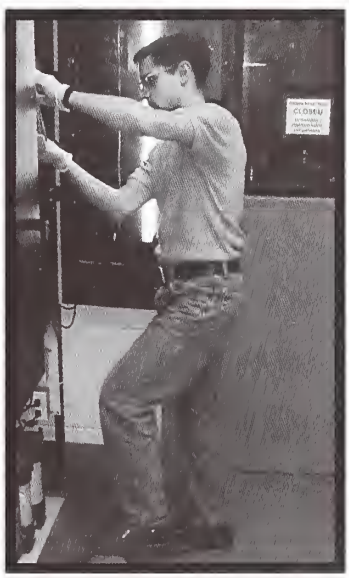


Lee Mack

NCI postbac Stuart Hicks—in it for the long haul and already published

To date, these are the only two institutes that have designated postbac contacts, and the results speak for themselves. Of all the postbacs I canvassed, NICHD and NIDDK postbacs seemed most comfortable and excited about their experiences. In fact, Guroff mentioned a small diaspora of NCI postbacs into the NICHD ranks.

The key to the continued success of the postbac program is mentoring. As Rosner points out, the "stated purpose of the program is to provide training and encouragement to follow a career in the biomedical sciences." Nevertheless, mentoring is a touchy issue in the trenches, given the conflicting pressures on PIs to run a smooth, productive research organization while also finding the time to be, as a recent mentoring pamphlet published by the National Academy of Sciences puts it, "adviser, teacher, role model, friend" to trainees. One person I spoke with made a clear distinction between the idealistic mentoring "party line" and the everyday reality of competing demands.



Lee Mack

NICHD postbac Michael Dedekian—stirring up zebra fish and interest groups

As NIH tries to push improved mentoring from the realm of rhetoric into reality at all levels, most postbacs view mentoring as basic to whether their training program works or not. Hicks looks at his PI as his teacher, but Shalizi wryly notes that "to be a postbac implies certain minimal qualifications, but there really are no minimal qualifications to *hire* a postbac."

In some cases, exemplary mentoring is taking place, as with Morsli, who describes his PI as a "mind-bogglingly good teacher. She made expectations clear from day one and has always been up front with me." No surprise that Morsli says his postbac experience has literally shaped his life and he still gets the chills coming to work every day.

Others have been not as fortunate. One postbac I talked to had been brought on board by a branch chief and then was immediately and haphazardly pawned off to another PI. Although there are few institutional rewards set up to encourage good mentoring, Guroff notes that poor mentoring does

not go unnoticed and good mentoring often leads to good research. Furthermore, according to Gottesman, mentoring is often incorporated into promotion evaluation and quadrennial site reviews.

Different PIs have different ideas about what mentoring entails. For example, Kohn keeps in touch with former postbacs and takes an active role in career counseling. She sees a mentor as "guide, teacher, listener, partner, friend, soft shoulder, punching bag, always available, tries to be objective, committed."

Lee Mack

NEI postbac Maya Shalev enjoying the gathering of her peers in this "world unto itself"

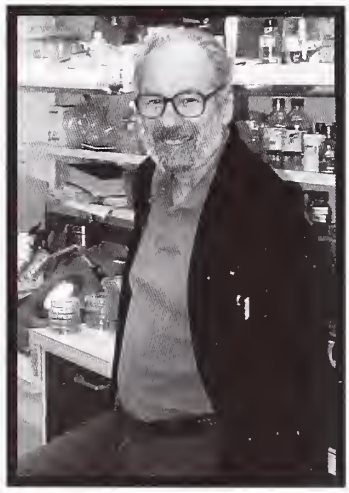
Furthermore, she makes the point that "it is a good mentor who can recognize when s/he cannot provide a nurturing and educational environment. It is someone with good introspection who can admit they have not succeeded and seek guidance to bring an unsuccessful partnership around, whether that means finding the other person another scientific home or improving the current one. Not every pairing is perfect."

Sargent agrees. As a Ph.D. and an adjunct professor who teaches genetics and molecular biology at a local university, his mentoring and career counseling can be more relevant to postbacs in his lab who are thinking of going on to a doctoral program or a career in basic research. But for those applying to medical school, his involvement in career advancement, he says, doesn't go much beyond giving general advice, writing recommendations, and referring them to clinical associates more familiar with internships, residencies, and specialization.

Not every postbac is cut out for a research career. Hinton explains her philosophy and expectations at the outset of the fellowship and is as straightforward as possible.

Recently, she sat down with a postbac who had displayed inadequate commitment to the research. Together they set up a schedule, and when the postbac failed to follow the schedule, she advised him that perhaps he was not suited to a career in research science. Such a confrontation is difficult, she says, but necessary.

Similarly, Guroff observes that the program makes a contribution to the human being, whether a student is inspired to go on to grad school or med school or finds out that he or she never wants to see the inside of a laboratory again, as in the case of NICHD postbac Heather Contaxis, who has decided she will not pursue a career in research science.



Lee Mack

NIDDK's Judah Rosner values being his institute's liaison to "junior colleagues"

Other postbacs who have pretty much concluded they're in it for the long haul aren't Pollyannaish. Hicks says that for the neophyte postbac, "a lot of preconceptions are shattered, such as you're going to have fun all the time and you're going to like everyone. You just don't realize how much work goes into science."

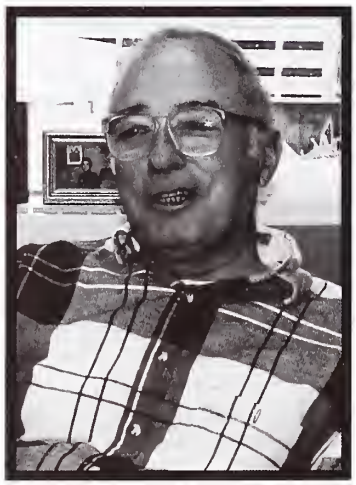
Maya Shalev, an NEI postbac, says that "being at the NIH is like being in a foreign country and learning the language of that country. Without the NIH, I don't think I could have lived science and learned science and learned how to be a scientist. . . . It's a world unto itself."

Morsli, a recipient last summer of an NIDCD award for research excellence, says his research experience has been a roller coaster of emotion, and Hicks speaks of his feeling upon arriving here that "there was no one else here like me."

This feeling is not uncommon but seems to be dissolving as the postbac contingent gains momentum and coherency. The initiative of postbacs like Shalizi and Dedekian has helped postbacs locate each other and end feelings of isolation and powerlessness. Dedekian is also organizing a postbac interest group, inspiring some veteran NIHers to question whether collectivization is in the best interests of the postbac community. But most postbacs are pleased that NIH is beginning to take notice and, as Morsli maintains, "we are here to learn research, not unionize."

The goal of Dedekian's group is to provide a regular forum for postbacs to gather and present their research and talk about their experiences, allowing them to learn from one another and cultivate communication skills.

At the first organizational meeting late last year, nearly every one of the two dozen attendees wanted to present their research at the next meeting. Many foresee a day when the group will be a forum for the dissemination of consistently topnotch research that is attended by postbacs and PIs alike.



Fran Pollner

NICHD's Gordon Guroff—there to answer the hard and odd questions

If there is a take-home message on the nature of what NIDDK postbac Meredith Korneff calls "pre-IRTA-tude," it is that postbacs do much more than is summed up by one postbac's e-mail signature line—"put the labor in laboratory."

We may do that, and doubtless do it well. But to make the program best serve its growing numbers of trainees and mentors, both sides need to vocalize and communicate intelligently and sensitively, and if we do, "it'll work itself out," as Guroff says. ■

LEARNING EVERY MINUTE: ONE POSTBAC'S EXPERIENCE

by Moneera Islam

Moneera Islam won a fifth-grade science fair prize and has been immersed in science ever since. She's worked at NIH and other labs since her sophomore year in high school, was an NIH MARC scholar during her college years at Howard University, from which she graduated summa cum laude *with a degree in biology and anthropology in June 1996. She is now in her second postbac year in the laboratory of NCI's Luigi De Luca and pursuing a master's degree in health policy at Johns Hopkins. She's intent on an M.D./Ph.D. program—what she calls the "best of both worlds."*

Claude Bernard said that "man can learn nothing except by going from the known to the unknown." This reigning paradigm is what attracted me to do research at NIH. Working here through different programs since high school, I have found that NIH offers an optimal setting for students to thrive. The intellectual forces that interconnect mentors and students often spark new methods of attacking problems and interdisciplinary concepts enormously valuable to society.

I have been profoundly lucky. In my two years as a pre-IRTA, I have had as my mentor and role model Luigi De Luca, chief of the Differentiation Control Section at NCI's Laboratory of Cellular Carcinogenesis and Tumor Promotion—and *the* world-renowned expert in retinoid research. De Luca personifies the traits of the ideal mentor. He respects my cumulative knowledge enough to give me the responsibility to design my own project; he sends me to conferences, allows me to review papers, shares a genuine interest in my goals, encourages oral presentations, always has time to hear my ideas despite his demanding schedule, offers me the opportunity to take Bio-Trac and FAES classes (of which I have availed myself), and continually makes me feel like an integral part of the lab and the research process. Naturally, everything is not always peachy, but, in the end, my mentor augments my experiences.

De Luca has walked me through the many steps that comprise medical research, from the conception of a hypothesis to the publication of results. He may not realize how exciting it was for me to see my first publication (M. Isogai et al., "Expression of a dominant-negative retinoic acid receptor construct reduces retinoic acid metabolism and retinoic acid-induced inhibition of NIH-3T3 cell growth," *Cancer Res* **57**:4460–4464, 1997). Coauthoring this study also gave me a sense of worth in that I may have contributed to an increased understanding of medicine.

The research in my section of the lab is focused on vitamin A and its metabolites, which play a crucial role in regulating the differentiation and proliferation of epithelial cells, act as signaling molecules in embryogenesis, and are potent inducers of apoptosis. Vitamin A is an important factor during gestation, and one of its metabolites, retinoic acid (RA), is a potent teratogen. The effects of retinoids are thought to be mediated through RA, which binds to nuclear RA receptors that then interact with specific RA response elements. The potency of retinoids as differentiation agents has led to their successful use in treating some forms of cancer. My research examines the effects of retinoids on prostate and breast cancer.

Fran Pollner

NCI postbac Moneera Islam

As my research experiences have expanded, so have my thought processes slowly begun to change. Research requires the composure to gather the data and the creativity to interpret them correctly. Classroom concepts come alive in the laboratory, where research promotes learning by a process I call "creative playing," rather than by rote. Research has sharpened my observation skills and my ability to persevere; presenting my research at meetings and convincing others of my data have surely contributed to the development of my own communication and persuasion skills. I have also gained insight into the relationship between basic science and health care and how scientific research can be used to study clinical problems.

Of course, the laboratory is also the setting for honing one's tolerance for frustration and disappointment. I have sensed some of the helplessness one feels when an experiment just will not work or when the actual results do not match what were reasonably foreseeable and expected. I have learned to value the explorative process as much as any "answer" I find. I have also begun to realize how research on a day-to-day basis evolves rather than explodes.

Learning is a privilege. Being surrounded by distinguished scientists and able to take advantage of lectures, seminars, and conferences at which such luminaries as Bert Vogelstein, Ian Wilmut, and David Baltimore have spoken is a privilege. Reading the publications of the scientists I have been working with, observing how their results and conclusions evolved, and discussing where their research is heading is a privilege.

Truly, NIH is the only enterprise in which one can pursue cutting-edge research, line dance with HHS Secretary Donna Shalala, hear a potpourri of languages from around the world, drop off receipts for "Apples for the Students," pray at the interfaith room, play volleyball on Wednesday nights, volunteer during lunchtime, order Kings Dominion tickets from the R&W, watch people go through e-mail withdrawal symptoms, see awesome pandas at the Children's Inn, have a friend who is a "normal" volunteer in a study, hear a Nobel laureate speak, realize you are not the only one who needs a life when you are looking for parking at midnight, wonder whether the shuttle you are riding is heading for any of the many construction ditches, and see NIH Director Harold Varmus with his L.L. Bean backpack riding his bike....should I go on?

I have come to regard NIH as my second home. I have adopted my colleagues as family. I even speak with an Italian/Japanese/Hungarian/Sri Lankan/Chinese, and, oh yes, an English twang. I have been nurtured and challenged here, but soon it will be time to "[go] from the known to the unknown," to go through NIH's exit door and into that other "real" world. ■

Recently Tenured

Peter Shields *received his M.D. from the Mount Sinai School of Medicine in 1983 and did an internal medicine residency and hematology/oncology fellowship at the George Washington University Medical Center. He did his research training at the Laboratory of Human Carcinogenesis of NCI, and has remained there. He now is the acting section chief of the Molecular Epidemiology Section.*

My research in molecular epidemiology is aimed at developing, validating, and applying biomarkers of cancer risk in order to enhance human cancer risk assessments, focus cancer-prevention strategies, and elucidate mechanisms of carcinogenesis. These studies are based on known complexities in carcinogenesis, interindividual variation in carcinogen metabolism, and a priori mechanistic hypotheses.

Fran Pollner

Peter Shields

My most recent objective has been to identify gene-environment interactions, using tobacco smoking as a model for cancer risk. Initially, I had developed methods for the detection of carcinogen-DNA adducts resulting from exposure to polycyclic aromatic hydrocarbons and *N*-nitrosamines. Using these methods, I then assessed the association between inherited susceptibilities for carcinogen metabolism and the formation of these adducts. In a study of lung tissues from 90 people, I found that the *GSTM1* null detoxification genotype was associated with polycyclic aromatic hydrocarbon–DNA adducts and that variants in cytochrome P450s (*CYP2D6* and *CYP2E1*) were associated with 7-methyl-dGp adducts, the latter of which varied by smoking exposure.This in vivo data from a target tissue is consistent with other laboratory findings, and I am now using these methods to study differences in cancer risk by gender and race.

Using methods developed for studying tobacco smoking and lung cancer, my collaborators (Drs. Christine Ambrosone [now at the National Center for Toxicology Research, Jefferson, Arkansas] and Jo Freudenheim [University of Buffalo]) and I set out to study breast cancer risks. We took up this challenge because currently known risk factors do not adequately explain breast cancer risk and there is limited evidence for chemical etiologies. Use of tobacco, for example, is not commonly considered a breast cancer risk factor.

But in a case-control study, we developed the hypothesis that exposure risk factors can be identified by classifying women based on genetic susceptibilities. Indeed, we found that postmenopausal Caucasian women who are NAT2 slow acetylators (involved in the detoxification of aromatic amines) had an increased risk of breast cancer from smoking. For women genotyped for cytochrome P450 1A1 variants, there was a small breast cancer association for smoking less than 29 pack-years. There also was an increased breast cancer risk for smoking in women who carried one variant of *CYP2E1*. Thus, taken together, these studies suggest that smoking may be a risk factor for breast cancer in susceptible women. Most recently, in this same group of women, we have found that the breast cancer risk of alcohol drinking is modified by metabolism through the alcohol dehydrogenase gene.

While the identification of smoking-related cancer risk is an important goal, determining the risks of becoming a smoker may be more important from a cancer prevention perspective. In collaboration with Drs. Caryn Lerman (Georgetown University) and Neil Caporaso (DCEG, NCI), we have done a study of 466 smokers and nonsmokers to explore genetic-"neurobehavioral" risk factors for smoking. It is known that nicotine stimulates the secretion of dopamine into neuronal synapses, which in turn stimulates dopamine receptors involved in reward pathways.

In our study, a genetic polymorphism in the dopamine transporter gene was associated with smoking risk, attempts at quitting, and duration of successfully quitting. Further, there was an interaction for this gene and a polymorphism in the dopamine D^2 receptor gene. Separately, we studied a genetic polymorphism in the dopamine D^4 receptor, and, although there was no direct relationship to smoking, one variant was associated with subclinical depression and the risk of smoking in Caucasians, while another variant was associated with smoking in African-Americans. The latter data were particularly striking because the chances of successfully quitting two months after counseling was zero for African Americans with the "at-risk" allele but 35 percent for those without it.

In future work, we will look beyond carcinogen metabolism to interindividual variation in DNA repair, apoptosis, and cell cycle control. ■

Symposium: Accelerated Drug Screening

A symposium entitled "From Good Ligands to Good Drugs: Optimizing Pharmaceutical Properties by Accelerated Screening" will be held February 19-21, 1998, in the Natcher Conference Center (Building 45). Cosponsored by NIGMS and the American Association of Pharmaceutical Scientists (AAPS), the meeting will explore ways to optimize the pharmaceutical properties of candidate compounds through accelerated screening early in the discovery phase, rather than later in the drug development phase.

Early assessment would alleviate what is becoming a drug development bottleneck. For instance, rational drug design coupled to crystallographic visualization of the target site can lead to the development of drug candidates with potent biological activity, but many of these are subsequently shown to have poor solubility or poor bioavailability, or to be extensively metabolized..

The meeting will begin with an overview of important screening processes, including combinatorial chemistry, genome databases, robotics, and spectroscopic techniques. The next sessions will then focus on important pharmaceutical properties and predictive models in vivo and in vitro. The final session will deal with emerging fields that are likely to affect screening strategies for pharmaceutical properties in the future.

Check the AAPS home page at <http://www.aaps.org/edumeet/workshops/nigms/index.html.> for more information. Advance registration is encouraged to guarantee admittance, but the **registration fee will be waived for all NIH employees**, and walk-ins will be welcome, space permitting. ■

SCIENCE WRITERS ENTERTAINED BY HIGH-POWER BATTLE OF THE BANDS

(IF MUSIC BE THE FOOD OF SCIENCE, PLAY ON)

Scientists are often amused by the artistic struggles of the Washington science press corps as they try to make science "sing" through their prose. In December, the tables were turned as members of the D.C. Science Writers' Association (or "Duck-Swa") were entertained by a battle of the biomedical bands. Opening the evening was NIH's (scientific, if not musical) all-stars: "The Directors," with Francis Collins (guitar and vocals; day gig: director, NHGRI), Chuck Ellerson (drums; postdoctoral fellow, NICHD), Steve Katz (guitar and vocals; director, NIAMS), Rick Klausner (guitar and vocals; director, NCI), John O'Shea (bass guitar and mandolin; research scientist, NIAMS), and Tracy Rouault (keyboard; research scientist, NICHD). High points of "The Directors" performance were bio-political rewrites of popular folk, gospel, and rock tunes, including "Will our Funding Keep on Growing?"— a take-off on "Will the Circle Be Unbroken?"—and "Clone-away," based on "Runaway."

Following this warm-up act was the rock band "Wild Type," led by keyboard player (and Johns Hopkins cancer geneticist) Bert Vogelstein. Other members of "Wild Type" are Pat Morin, (guitar and postdoc in Vogelstein lab), Ellie Carson Walter (vocals and postdoc in Vogelstein lab), Ken Kinzler (drums and codirector of Vogelstein lab), Chris Torrance (guitar and postdoc) and Bob Casero (base and toxicology lab chief).

Outcome of the Battle of the Bands: "Wild Type" is phenotypically stronger for true rock traits; the more folksy, clever "Directors" would be well advised to keep up their day jobs.

—ch

The Dueling Bands: *"The Directors" (left) brought back the old days (and nights), singing their hearts out with great spirit (and even decent voices), faithful to the beat and in sync with each other and the admiring crowd, but it was "Wild Type" (below) that really got the joint jumping till the wee hours (wee hours for the National Academy of Sciences, that is).*

Getting Down and Wigging Out: *"Directors" guitarist Francis Collins (above, foreground) breaks loose to "Wild Type" (as does another NIH notable [deep background, cleverly disguised by his necktie]—as "Wild Type" keyboardist Bert Vogelstein (right) lets it all hang down.*

Photos by Fran Pollner

Arthur Andersen Delivers Mixed Review Of NIH Administrative Acumen

After seven months of data gathering and analysis, including focus groups, surveys, and site visits, the Arthur Andersen reviewers have concluded that the quality of NIH administrative services is "uneven."

"Brilliant minds" notwithstanding, NIH "nevertheless has to attend to the necessities of managing its vast enterprise," the reviewers noted in an intro to their report, undertaken at the behest of Rep. John Porter (R-Ill.), chairman of the House Appropriations subcommittee that oversees the NIH budget.

"The closer a given function is to the scientific mission," they observed, "the more likely it is to mirror the excellence of the scientific work." They cited extramural and intramural management as examples of this good news.

But the bad news is that the farther away from the scientific core an administrative function is, the "more recognizable" it becomes as a "normal federal bureaucracy."

To remedy the latter, the Arthur Andersen team offered 80 recommendations based generally around four strategies:

1. Decentralizing routine administrative service delivery and streamlining OD operations

The authors suggest NIH conduct such business in the manner of a "holding company," with the OD providing leadership and oversight in uniform administrative performance standards, professional requirements and criteria for service, and "best practices," while the ICDs carry on with their individual appropriations and internal management structure so that "routine service is performed as close to the user as possible."

Regarding procurement, strategy is best articulated by the OD, whereas operational procurement units should reside in ICDs or service centers; regarding personnel, the Office of Human Resource Management should be reorganized to better provide the ICDs with advisory services; and regarding property, effective management requires a more user-friendly centralized, integrated administrative database, whereas property accountability and transactions should be ICD-based.

2. Generating a "culture of partnership" between scientific and administrative components

The idea that administrative and scientific operations of NIH can be separated is false, the reviewers say, because scientists cannot perform well in a poorly run institution and administrators who feel removed from the work of NIH may not be moved to greatest efficiency.

Technology transfer and extramural research management are two realms in which a partnership is particularly relevant. Regarding the former, the reviewers note that the Office of Technology Transfer has plans to educate scientists in reporting new technologies by making this subject the "centerpiece of orientation for newly hired scientists"; regarding the latter, the reviewers call for teamwork to replace the bureaucracy that often characterizes the interactions between the review, program, and grants management groups within the institutes.

3. Enhancing administrative accountability by elevating key administrative leadership positions and establishing performance measures

Different Strokes for Intramural Research Management

Following are excerpts from some key Arthur Andersen findings and recommendations regarding intramural research management.

◆ **"Seek to establish a separate NIH personnel system."**

"Scientific staff are frustrated by the federal personnel system's inflexibility and intramural research's unique requirements. The following two mjaor findings arose from the intramural focus groups:

■ "Limitations of personnel system recruitment requirements and the inability to deal effectively with poor performers are "thorns in the side" of the intramural scientific community.

■ "A rule-bound government personnel system is probably more antithetical to the scientists than to federal employees in general. . . .

"Although personnel authorities—the Senior Biomedical Research Service and Title 38—have provided increased flexibility in hiring scientists and medical doctors, their presence have further complicated a very complex administrative function.

"NIH is one of very few agencies to have planned turnover. Training postdoctoral students, a large portion of the scientific staff, and accommodating the large summer influx of student interns, create an unusually large volume of personnel transactions.

"Accommodating the cumbersome federal personnel system for this volume of personnel actions propels NIH far beyond the demands of a typical government agency.

"Arthur Anderson strongly recommends a separate personnel system to meet NIH's own needs. The extra efficiency and reduction in the valuable time scientists devote to administration would greatly enhance NIH's ability to carry out its research mission."

◆ **"Encourage the rapid adoption of the purchase card and IntraMall approaches."**

"Procurement is a vital support mechanism for the intramural research effort at NIH. Despite relatively low satisfaction levels for procurement, most ICDs have managed to make the procurement system work adequately for them. The results are far from optimal. Timeliness is the predominant issue. . . . Vendors of critical scientific supplies and equipment have sometimes refused to ship to ICDs because of slow payment.

"Procurement-function decentralization to date is at least partially responsible for [some] improvement. Further decentralization and accelerated use of purchase cards should bring additional improvements.

"A major perceived impediment of purchase card use is concern about the time necessary to reconcile the statement at month's end. Some ICDs have overcome these issues. the proposed function for intramural research administration (see below) could serve as a catalyst in promulgating the best practices.

◆ **"Establish a senior administrative leadership intramural research function."**

"The DDIR has sole responsibility for scientific intramural functions, including the administrative functions. The amount of the DDIR's time necessary to deal with administrative issues is often substantial, with one of two undesirable outcomes likely—either the DDIR is stretched too thin and the problem does not receive adequate attention, or the DDIR's time is subtracted from pressing scientific matters.

"The establishment of a new senior leadership intramural research function could provide improved communications linkage at the OD/HQ level as well as an improved communication path at the ICDs. Intramural research AOs need a communication liaison between the scientific directors and the various administrative services provided under the deputy director for management. . . .

"To foster a continuous-improvement culture, this new function should hold periodic meetings among the intramural research AO community to include a process for identifying and resolving common issues. If additional resources are needed, this new function should act as the ombudsman." ■

The reviewers "strongly recommend" that the NIH CFO move up in the hierarchy and oversee finance, procurement, and logistics the better to solve "longstanding problems" in these areas.

They advise that NIH carry out an intended reshaping of the chief information officer position so that the CIO heads the Division of Computer Research and Technology, the Office of Information Resources Management, and Telecommunications.

They recommend that the principal official responsible for acquisition (PORA) have jurisdiction over all procurement policy. The Office of Management Assessment, similar to an inspector general, could also be elevated to report directly to the NIH director.

4. Identifying and tracking costs and benefits by core function, the better to budget and the better to present NIH activities to Congress

NIH ought to refashion its budgetary and organizational chart around three core functions: extramural research, intramural research, and health information and education, with the current administrative budget "disaggregated to the greatest extent into the core functions" and the remainder left in administration.

The health information and education budget should reflect the NIH focus on education rather than public affairs. Tracking costs by core functions, the authors reason, would enable NIH to better assess costs and benefits for its own as well as Congress's edification.

Should NIH follow through on the Arthur Andersen recommendations, the authors conclude, it "could very well become a model for efficiency for other complex government agencies." ■

NIH Committee Reviews the Andersen Review

In the time-honored tradition of one committee leading to another, an advisory committee of NIH senior managers was formed to respond to the Arthur Andersen assessment and advise the NIH director on the feasibility, desirability, and order of priority of implementing the recommendations.

The committee response was delivered by Tony Itteilag, NIH deputy director for management, at the meeting late last year of the Advisory Committee to the NIH Director. The 15-member group of administrators and scientists endorsed the first three Arthur Andersen "themes" but advised that the fourth—the proposed new "budget/organizational paradigm," which would disaggregate the budget into extramural research, intramural research, health information/education, and general administration categories—be deferred for further study.

The committee set priorities for recommendations related to the other three themes, designating as "Priority I (short term)" those that could be implemented quickly or required a brief (though intensive) effort to remedy a long-standing problem, as "Priority I (long term)" those addressing complex issues that would require more time to implement, and as "Priority II" those addressing less serious problems and those that could be implemented without NIH-wide oversight.

Among those recommendations accorded "highest" priority within the short-term Priority I items were:

√ Eliminating payment backlogs and paying bills promptly
√ Elevating the chief financial officer position
√ Pursuing IntraMall technology
√ Streamlining the property management system
√ Creating an accurate NIH personnel database

Other short-term Priority I items included reorganizing OHRM to be a policy and problem-solving organization; being aggressive in recruitment and accountability, according to Equal Employment Opportunity guidelines; enlightening scientists about technology transfer and the outcome of negotiations; requiring supervisors to collect badges and keys at separation; and establishing an administrative leadership function to expedite intramural research management.

Among those recommendations accorded "highest" priority within the long-term Priority I items were:

√ Creating an information technology organization under a chief information officer
√ Decentralizing procurement service delivery
√ Financing policy functions through direct appropriations
√ Investigating a new personnel system
√ Developing performance standards for administrative functions

Among those issues the advisory committee accorded Priority II status were consideration by ICDs of creating a chief financial officer function, consideration of outsourcing police and locksmiths, designating an individual to serve as congressional liaison on cross-cutting legislative issues, and changing the title of "Public Affairs" to better reflect NIH educational activities. ■

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: clinical research at NIH, the postbaccalaureate IRTA program, story leads, and the need for an electronic *Catalyst* .

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

In Future Issues...

- MediaSpeak For Scientists
- First-Class Clinical Research Trainees
- Fogarty Scholars Program Evolves

1) Do you think changes in the working environment for clinical research are beginning to have any effect? Are morale and productivity improving? What additional changes are needed?

2) Is the postbaccalaureate program an asset for NIH? Does it serve the participants well? How big should the program be? How could it be improved?

3) Give us your ideas for stories you'd like to see in *The NIH Catalyst*. What is the hottest research coming out of your institute? What's Topic One in your lunch room?

4) URGENT: We really need to know your feelings about electronic versus hard-copy issues of this publication. Do you have use for *The NIH Catalyst* on-line (<http://www.nih.gov:80/campus/irnews/catalyst/>)? Would you if it were up-to-date?

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

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