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CLINICAL RESEARCH ACTION PLAN

This implementation plan, under consideration by the ICD directors, includes components derived from recommendations of a working group of ICD personnel officers, senior staff of the Office of Human Resource Management, the Office of Intramural Research, the Board of Scientific Directors, and the Office of the Associate Director for Clinical Research.

The NIH leadership is pleased to respond in detail to the recommendations of the NIH Committee on the Recruitment and Career Development of Clinical Investigators. All the recommendations have been carefully considered, and each is judged to be meritorious. The following implementation plan addresses the more specific ones.*

PERSONNEL MECHANISMS AND FUNDING

We concur that the existing personnel salary and funding mechanisms in some cases do not support the special needs of clinical researchers and in other cases are disincentives to the recruitment and retention of

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CLINICAL RESEARCH AT NIH IN THE SPOTLIGHT

The following account of IL-2 therapy trials in HIV-infected people marks the debut of our promised occasional feature on "bot new clinical trials" at NIH and is based on published material and interviews with two of the principal investigators, H. Clifford Lane, NIAID clinical director, and Joseph Kovacs, a senior investigator in the Critical Care Medicine Department at the NIH Clinical Center.

IL-2 IMMUNE BOOST IN HIV-INFECTED PATIENTS TO BE TESTED IN THOUSANDS WORLDWIDE

by Janet Yee and Fran Pollner

The most conspicuous excitement lately in the HIV-AIDS arena has been generated by the clinical success of protease inhibitors, which, used in combination with other antiretroviral agents, have yielded stunning results in decimating viral burden in HIV-infected individuals.

But attacking the virus directly is but one part of a two-fisted strategy in dealing with the ravages of HIV infection. The partner of antiviral therapy in the battle against AIDS is immune system reconstitution, the focus of an NIH team of investigators that has been conducting clinical trials of a recombinant version of interleukin-2 (IL-2), an endogenous immune system stimulator. This cytokine would be used in conjunction with any antiretroviral regimen deemed appropriate for any given patient and, unlike the therapeutic agents whose action is HIV-directed, is unperturbed by the virus' capacity for mutation and resistance.

Begun in earnest in 1991 with open studies involving handfuls of patients, IL-2 research has progressed to the point where plans are being finalized for a Phase III clinical trial that will involve nearly 4,000 HIV-infected people in about a dozen countries.

According to H. Clifford Lane, NIAID clinical director and a principal investi-

gator, the protocol for the randomized, controlled trial was completed this summer and recruitment will likely begin early next year.

Eventually, more than 3,700 HIV-infected individuals from the United States, Canada, Argentina, South Africa, Thailand, Australia, the United Kingdom, Spain, Italy, The Netherlands, Belgium, and Germany (and possibly Switzerland and France) will be enrolled.

The goal of the study is to determine whether the increases in CD4+ T cells induced by IL-2 seen in preliminary studies translate to fewer AIDS-related complications and improved survival for HIV-infected patients. All patients will

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The life and times of 'Joe Postdoc': Interview with Catalyst cartoonist Alex Dent begins on page 8.

CONSTRUCTING NIH'S FUTURE



Michael Gottesman

We have an unprecedented amount of construction occurring at NIH today, and more is coming soon. Although it may cause some temporary inconvenience to us all, we are building the infrastructure that will be vital for NIH's ability to conduct state-of-the-art research in the 21st century. This construction is giving birth to NIH's future, and the birthing process is innately messy.

These projects have two primary purposes: 1) to bring the utility capacity of our existing facilities up to current, safe standards and 2) to provide modern research laboratories to support future research initiatives at NIH. Many of the projects fulfill both purposes. The utility-tunnel project, which we all dodge as we walk around campus, is providing needed current utility capacity—such as electricity, water, chilled water, steam, communications, and sewage disposal—and the means to distribute additional future capacity. Building 50 and the Clinical Research Center (CRC) together will replace outdated facilities in Buildings 2, 3, 6, 7, and 10 and create state-of-the-art research labs and accommodations for shared instruments.

Much of this construction is necessary because the nature of biomedical research and the technology needed to support it have changed since many of the laboratories on the NIH campus were built. For example, Building 50 is being designed to house a 1-gigahertz NMR research instrument, which does not yet exist! The required amount and reliability of electrical power to run our centrifuges, air-flow hoods, incubators, and cold rooms has increased dramatically, and the cooling required in the rooms containing the equipment has also skyrocketed. Computers were not standard research tools when most of our facilities were built—now they are intrinsic to biomedical research and accommodating them necessitates major changes in building design. The increase in computers even dictates changes to the standard NIH postdoc's desk. The old 3.5-ft desk is no longer big enough to hold a computer, a telephone, and a piece of paper, so desks are increasing in size. And now computers must be interconnected by LANs and internets. Building 49 was the first facility with a combined communications system, which included phones, computers, LANs, faxes, and other such items. Integrated communications are now just assumed to be standard in all new facilities.

Other changes are more subtle. Laboratories used to be defined predominantly by the techniques they used. Organic chemistry or electron microscopy labs attacked projects that could be addressed with those

techniques. Now labs are more apt to be defined by the problems they address, and most attack their research questions by using multiple techniques at the same time. This means that groups of scientists with different backgrounds must meet to share data, creating a need for small, informal conference spaces and large, formal meeting rooms within laboratory buildings. Many groups also want to encourage this communication between scientists by having larger, more open labs rather than the old single-lab modules, while still providing for containment of noise and hazards. These open labs also rely on small conference spaces to give scientists a quiet spot where they can think, read, and draft papers.

This need for communication between scientists has also reemphasized the surprising fact that scientists are people. Architects are trying to humanize these increasingly high-tech spaces with materials, colors, and, most importantly, daylight. Building 50 and the CRC will both have views of the outside world from most of the labs and offices.

If nothing else, our experience constructing research facilities has taught us that the one thing that is predictable is change. Because we can't predict the direction of that change, we need to design our research facilities to be as adaptable as possible. If we begin a design for a new building by customizing spaces to meet a scientist's current research needs, the labs will no longer be suitable when he or she moves in—perhaps five years later. We learned this the hard way in Building 4, which was uniquely defined five years before it was occupied and so had to be redone while scientists were moving in.

As we did with Building 49, a better approach is to create buildings with the utility capacity to support potential changes but to defer defining the nitty-gritty details as long as possible. In Building 50, we have a standardized "kit-of-parts" for each lab space assigned to the ICDs that will be occupying the building, but substitutions can be made in these standard components, allowing for program changes and further detailing to occur during construction. In the CRC, we are designing good, safe, generic, flexible labs without assigning space to the individual intramural programs. Customization will occur only after final occupants are identified.

In all these projects, the input from the scientific community is essential, and your involvement will yield benefits that extend well beyond your own lab plans. So . . . continue to watch your step as you dodge construction sites, and send your advice and opinions to the DDIR or the Office of Research Services as we all prepare for the future of research at NIH. ■

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Cyrena Simons

Research Festival Beckons, October 6-10

The 11th annual NIH Research Festival arrives on the Bethesda campus October 6 and will run through October 10. This year's festival will feature more than 20 workshops and 300 posters, with several symposia showcasing intramural research. Scientific sessions will be on Monday and Tuesday in the Natcher Center, including two major symposia hosted by the Structural Biology and Immunology Interest Groups. Monday's immunology symposium will discuss activation of the T-lymphocyte response, from basic cell biology to clinical applications. Tuesday's symposium will address the structural biology of viral diseases, including antiviral-drug design.

On the evenings following these symposia, the Technical Sales Association will sponsor picnic dinners. Wednesday's program includes a job fair for postdocs, organized by the Office of Education and co-sponsored by the National Foundation for Biomedical Research, and a special symposium honoring 60 years of intramural NIH research, co-sponsored by the DeWitt Stetten, Jr., Museum of Medical Research. Several distinguished current and former NIH investigators will speak at the Wednesday symposium.

On Thursday and Friday, the festival will conclude with the Technical Sales Association's Exhibit. Allen Spiegel, scientific director of NIDDK, chairs this year's festival. Details are available on the web at <<http://pubnet-mac.nih.gov/festival97/>>.

In Vivo NMR Research Center Celebrates 10th Year, October 7

The In Vivo NMR Research Center will celebrate its 10th anniversary on October 7, in conjunction with the NIH Research Festival. The program at the Mary W. Lasker Center (the Cloister) will feature lectures on in vivo NMR spectroscopy and functional neuroimaging by Jeffrey R. Alger (UCLA), Chrit T. W. Moonen (University of Bordeaux), and Robert Turner (University of London), all of whom worked previously as investigators in the NMR Center.

Activities will begin at 12:30 p.m. with short talks commemorating the founding and development of the center, followed by the three lectures. A poster session (including refreshments) is scheduled from 3:30 to 5:30 p.m.

Since its inception in 1987 with financial support from all ICDs with intramural programs on the NIH campus, the center has provided state-of-the-art facilities for carrying out in vivo NMR research on humans and animals. The center's building has been expanded to accommodate independent ICD NMR research programs, and further expansions are planned as the center is organizationally relocated in NINDS.

For more information on the October 7 program, contact Daryl J. DesPres, Building 10, Room B1-D125; e-mail: <depres@helix.nih.gov>.

WALS Starts Fourth Year

The Wednesday Afternoon Lectures (WALS) have jumped into their fourth year with an outstanding slate of speakers. On September 10th, the speaker was Stanley Korsmeyer of Washington University, presenting the NIH Director's Dyer Lecture. On September 17, it was Lee Limbird of Vanderbilt University, presenting the Director's Pittman Lecture. And September 24 brought Jean MacCluer of the University of Texas in San Antonio, presenting the Gordon Lecture. The lineup for the rest of the fall and winter, and for the spring of next year, looks equally stellar.

The WALS series was launched as NIH's foremost campus-wide scientific lecture series in October 1994. The premier lectures—the NIH Director's Lectures—were scheduled for a uniform time and place: Wednesday afternoons at 3:00 in Masur Auditorium, Building 10. These lectures were augmented by with speakers nominated and hosted by NIH's interinstitute interest groups. To make the series even more irresistible, NIH's intramural institutes, centers, and divisions agreed to sponsor postlecture receptions outside the Clinical Center's Visitor Center. The receptions then become a good venue for poster sessions. This year, winners of the NIH Fellows Awards for Research Excellence will be displaying their prize-winning work at the Wednesday receptions.

Hosts of WALS speakers also sched-

ule an informal meeting with postdocs and students—typically a brown-bag lunch. So block off your calendars for Wednesdays at 3:00 from now through June. For more information, visit the WALS Web site at <<http://www1.od.nih.gov/wals/index.html>>.

October 1: Peter Walter, University of California, San Francisco. "Intracellular signaling from the endoplasmic reticulum to the nucleus." Hosted by the Cell Biology Interest Group; sponsored by NCI.

October 8: No lecture—Research Festival (see box, this page).

October 15: Don C. Wiley, Harvard University. "Structure/function studies in MHC/antigen recognition and in viral entry mechanisms." Hosted by the Crystallography, Structural Biology, and Immunology Interest Groups; sponsored by NIAID.

October 22 (the Stetten Lecture): Jacqueline Barton, California Institute of Technology. "DNA-mediated electron transfer: chemistry at a distance." Hosted and sponsored by NIGMS.

October 29: Jonathan Beckwith, Harvard Medical School. "Making, breaking, and shuffling protein disulfide bonds in vivo." Hosted by the Lambda Lunch and Molecular Biology Interest Groups; sponsored by NLM.

November 3 (Special Monday Lecture): Peter Dervan, California Institute of Technology. "Molecular design for DNA recognition: an approach toward gene-specific transcription." Hosted by the Chemistry Interest Group; sponsored by NIGMS, NIDDK, and the American Chemical Society.

November 5: James Hildreth, Johns Hopkins

University. "The role of host adhesion molecules in the biology of retroviruses." Hosted by the Trans-NIH AIDS Interest Group; sponsored by NIAID.

November 12: James Wilson, University of Pennsylvania. "Cystic fibrosis: pathogenesis and treatment." Hosted by the Clinical Research Interest Group; sponsored by NIA.

November 19. (the NIH Director's Lecture): Judah Folkman, Harvard Medical School. "New directions in angiogenesis research." Hosted by the Clinical Research Interest Group; sponsored by NCI.

November 26: Kai Simons, University of Heidelberg. "Sphingolipid-cholesterol rafts in membrane trafficking and signaling." Hosted by the Cell Biology Interest Group and the Fogarty International Center; sponsored by NICHHD.

December 3: Wolf Singer, Max Planck Institute for Brain Research. "The putative role of response synchronization in cortical processing." Hosted by the Integrative Neuroscience Interest Group and the Fogarty International Center; sponsored by NINDS.

December 10. (the Khoury Lecture): David Baltimore, California Institute of Technology. "Cell life and cell death." Hosted by the Virology and Trans-NIH AIDS Interest Groups; sponsored by NIAID.

December 17: Michael Geoffrey Rosenfeld, University of California, San Diego. "Mechanisms of transcriptional control of neural and endocrine development." Hosted by the Neurobiology, Molecular Biology, and Transcription Factors Interest Groups; sponsored by NIMH.

December 24: Holiday break.

NIDA REVIEWERS ATTACH SOME STRINGS TO JUST SAYING 'YES'

The intramural research program of the National Institute on Drug Abuse originated before NIDA was born—as the research unit of a prison-affiliated PHS hospital in Lexington, Kentucky, where addicted prisoners were treated and studied. It was renamed the Addiction Research Center and attached to NIMH before it relocated to NIDA and its current Baltimore location on the Johns Hopkins Bayview Research Campus about 40 miles from Bethesda. In June, NIDA's IRP became the third (after NCI and NIMH) to complete a detailed appraisal by outside reviewers. A panel chaired by Stanley Watson, professor of psychiatry and codirector of the University of Michigan Mental Health Research Institute, studied the program for six months. A summary of its findings follows.

Though criticisms of the program's recent lack of leadership, mentoring, spirit, and scientific vision were pointed, they were offered within the context of two fundamental conclusions, neither of which had been foregone: that the program remain in existence and that it remain in Baltimore. Both issues were on the table in the panel's deliberations, and these two conclusions reflected the belief that the IRP could and would set the country's pace for drug-abuse research once certain recommended changes were implemented.

"The pivotal issue in the decision to keep the intramural research division open was the opportunity . . . to produce an integrated view of drug use and substance-abuse biology across species, including humans," the panel stated. Not least among the panel's reasons for optimism was the recent recruitment of Barry Hoffer, "a superb scientist, admirable mentor . . . and a person of vision and administrative experience" to fill the long-vacant scientific director slot. "His strong reputation in neuroscience will bring much-needed stature and scientific credibility to the IRP," the panel said.

Conversely, the more than four-year absence of a permanent clinical director—and the resulting deterioration in the quality of clinical research, characterized by "mediocre protocols . . . and poor integration of clinical and basic studies"—remains to be corrected, the panel said.

Also to improve the clinical research climate, the panel recommended involving clinical investigators in study-partici-

pant recruitment, and recruiting more African-American clinical scientists to enhance the "ethnic match" between the researchers and a large proportion of study volunteers.

THE BLESSINGS OF BALTIMORE

In the matter of facilitating connections between basic and clinical research, the reviewers viewed the Baltimore facility in an especially favorable light, calling one of its "most valuable features" the "housing of its entire scientific operation [including] basic, translational, and clinical research and researchers . . . within that one site." They considered this arrangement a strong

argument against moving any part of the IRP to Bethesda, despite the fact that their review had revealed "virtually no significant information flow between basic and clinical programs" and an "almost universal lack of communication between groups," especially between branches, whose interactions they found to be marked by secrecy and fierce competition for resources.

Consequently, they recommended incentives for collaboration, such as

- ✓ Allocating budget and space resources contingent on active collaborations.
- ✓ Tying funding for new basic science models to plans for shared use, either with other intramural labs or the

New Scientific Director On the Move—and Here to Stay

"I was sufficiently new to have had no opportunity to do anything wrong" is how Barry Hoffer, NIDA's new scientific director explains the praise accorded him by the independent panel that reviewed NIDA's intramural research program.

Not only did the reviewers deem him a "superb scientist" and an "admirable mentor," they also predicted his leadership would position NIDA to be the "premier substance-abuse research center in the world, in both the basic and clinical arenas."

But they also put forth an extensive "to-do list" to overcome the deficiencies that have kept that potential from being realized. It's a list that Hoffer embraces.

"Virtually all the recommendations are being implemented, or will be," Hoffer said in an interview with *The NIH Catalyst*.

The most crucial of the panel's directives, he said, are to inspire NIDA intramural research groups to communicate with one another, to strengthen the clinical research program, and to "protect and develop younger investigators and staff scientists."

Hoffer came to NIDA last September from the University of Colorado School of Medicine in Denver, where he was a professor of psychiatry and pharmacology. The reviewers began their work in December and issued their report and recommendations in June, but the new SD began fixing

things as soon as he unpacked. "Many of the needs [the panel addressed] were obvious" at the start, he said, citing especially a "clear need for mentoring."

ACTIONS

Hoffer selected Roy Pickens to be associate director for training and education. "I have a short institutional memory, but to my knowledge, no one previously was charged with mentoring fellows and postdocs," he said, noting that there is now a written document to guide the mentoring process. A weekly seminar series is also in full swing.

In the realm of improved communication among the branches, Hoffer has "called in people from different branches to talk and also to let it be known that I have a modest director's reserve fund, a little extra to prime the pump for projects, particularly those with collaborative components. They're writing proposals to me," he said, crediting NIDA director Alan Leshner with having provided him with the discretionary funds.

A direct funding line from the SD to independent investigators, another panel suggestion to which Hoffer subscribes, is actually also in line with "new winds blowing through all of NIH that independent investigators ought indeed be independent, free to work on projects of their choosing." Scrutiny by the Board of Scientific Counselors, he added, is the quality-control mechanism for their research. "We formed an implementation committee, to which the branch chiefs will have input, that will report to Dr.

extramural community.

✓ Establishing team projects in such areas as translational research and drug development.

The panelists counted among other advantages of the Baltimore site its spaciousness, its "potential linkages" with Johns Hopkins and other academic institutions, and its shared location and increasing collaboration with components of the National Institute on Aging (NIA) and the National Human Genome Research Institute (NHGRI). They lauded NIDA's collaborative project with NHGRI's Center for Complex Heritable Diseases on the human genetics of substance abuse and its plans to share core

facilities with NIA, including DNA sequencing and space for nonhuman-primate studies. The panel encouraged NIDA-NIA collaboration in "constructing a new shared facility."

ON MONEY AND MORALE

The panel noted that NIDA's intramural research budget in proportion to its total budget is only half that of other institute allocations, accounting for 5.6% (of NIDA's \$489 million), compared with the 11.3% slice accorded NIH intramural research programs overall. It did not, however, suggest any change in the amount but instead recommended changes in the way the money is divvied

up within the IRP.

Each independent investigator's lab should have its own budget, the panelists advised, with the scientific director—not the branch chiefs—making budgetary decisions based on each lab's past productivity and future plans and NIDA's research priorities. This change, the panel reasoned, would minimize competition at the branch level, raise investigator morale from its current low level, and foster investigator independence from the branch chief.

Currently vacant branch chief slots should be filled promptly, the panelists said, with fine scientists who are also accomplished mentors. ■

Leshner and Dr. Michael Gottesman [deputy director for intramural research] by October 1."

Hoffer also responded with alacrity to the panel's exhortation that a permanent clinical director be found to replace the nearly five-year rotating directorship that had left the clinical research arm of the intramural program dangling. "Jean-Luc Cadet, a clinician-scientist and intramural section chief,

is our new clinical director," he said, adding that filling the two branch chief vacancies awaits "overall restructuring" of the IRP that targets more collaborative and translational research. "We don't know yet how those two branches will fall out," he said. He estimated that the reorganization would take six months to a year.

He and Cadet, Hoffer said, are working to draw together another extramural panel to evaluate exclusion and inclusion criteria for clinical trials. He expressed uncertainty regarding the wisdom of the review panel's suggestion that clinical investigators be involved in recruiting for their own trials. Regarding the panel's observations on the ethnic mismatch of NIDA clinical investigators and the 80% African-American study population, Hoffer noted that the

study population reflects the demographics of the Baltimore area, where

NIDA's Addiction Research Center is located, as well as the demographics of that segment of the population willing to participate in research—not the demographics of addiction in this country. "I am committed to diversity in the patient and investigator pool," he added, noting,

however, that there is currently only one other African-American clinical investigator in the IRP in addition to Cadet.

PROJECTIONS

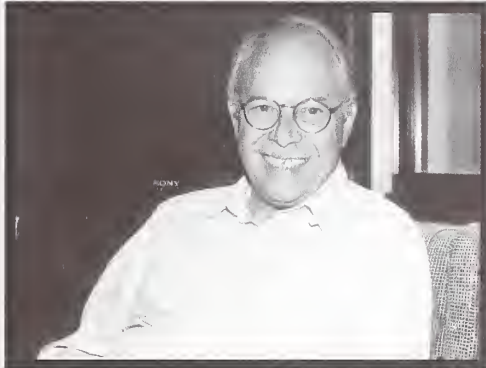
Staying in Baltimore seems not only inevitable—"Bethesda is very crowded"—but also desirable. "We have good space here, and we're planning research on the genetics of drug abuse with NHGRI's Center for Complex Heritable Diseases, which is right here." The recommendation that NIDA and its other Baltimore neighbor, NIA, share resources is especially appealing to Hoffer. "My background is in aging research, and NIA's scientific director, Dan Longo, and I have started a series of discussions with the directors of our institutes and with Dr. Varmus. I'm not sure where it will all go, but I'm certainly enthusi-

astic. NIDA and NIA have common interests in molecular biology and gene sequencing, in animal research—and a common vivarium makes sense—and collaboration with NIA scientists only 50 paces away would be even better than the short walk we now have."

He hesitated to stipulate scientific objectives for NIDA's IRP, explaining that he's a "firm believer in investigator-initiated research." He sees a general need for more translational research in treatment and prevention—especially in cocaine-addiction therapies and methamphetamine-addiction prevention—and more collaborative research with other neuroscience institutes. "Addiction is a brain disease, like schizophrenia and Parkinson's disease," he said. He pointed to the need for more research in fundamental neuroscience—a field with which he has more than passing familiarity.

Hoffer's *Catalyst* interview was by phone at the end of one of the days of the Gordon research conference on catecholamines, where he presented a talk on his research on dopamine neuronal plasticity and development and was a discussant at another session on neuroimaging applications in addiction research. He fully intends to continue his research. "I would not have taken this job otherwise," he said, adding that he's "hoping to stay at NIH indefinitely, as long as the Board of Scientific Counselors is happy with me." ■

—Fran Pollner



Barry Hoffer

"Addiction is a brain disease."

IL-2 ON PHASE III THRESHOLD continued from page 1

be on antiretroviral therapy, with half randomly assigned to a group that will also receive IL-2. Patients will adhere to protocol for two years, with follow-up monitoring of CD4 counts, viral burden, and incidence and severity of opportunistic infections continuing for another four years.

Patients assigned to the IL-2 treatment arm will self-administer the cytokine by subcutaneous injection twice a day for five consecutive days every two months, initially at a standard dose but with adjustments within upper and lower limits, according to individual tolerance of side effects. (Patients not suited to this mode of administration will receive IL-2 by infusion for five consecutive days every two months. Dosages and routes of administration were established in earlier trials.)

The trial is limited to HIV-infected patients with CD4 counts above 350/mm³, the "most practical cutoff," Lane said, because it best reconciled "two competing forces: the lower the CD4 count, the poorer the response to IL-2; the higher the initial CD4 count, the longer it would take to reach an endpoint. Thus, 350 was picked as the lowest count that would still be able to give an acceptable response rating at some degree of disease progression."

Early Trial Results

In initial dose-escalation studies, IL-2 therapy proved capable of elevating CD4

counts in HIV-infected people, but only in those who had baseline CD4 counts above 200/mm³ at the start of the study; those whose initial counts were lower showed little response to IL-2 (J. A. Kovacs *et al.*, "Increases in CD4 T lymphocytes with intermittent courses of interleukin-2 in patients with human immunodeficiency virus infection: a preliminary study," *N Engl J Med* **332**:567-75, 1995).

"The idea is to come in while the immune system is still intact, so as to expand and protect it. Once the immune system declines too far, it is difficult to reconstitute," Lane said.

In 1993, 60 HIV-infected individuals with baseline CD4 counts above 200 were enrolled in a controlled, randomized (Phase II) study of IL-2. All patients received standard antiviral therapy, but half also received IL-2 by intravenous infusion for five days every two months.

At the end of one year, CD4 counts in the IL-2-treated patients had doubled; the counts in those treated with antiviral drugs alone had declined. The increase was sustained for more than two years by continued IL-2 administration, and in five patients, counts remained above 1,000 for at least 18 months after IL-2 was discontinued.

"To date, no combination of antiretroviral agents has been shown to be capable of inducing increases in CD4 counts of this magnitude or duration," the authors wrote in their second *New England Journal of Medicine* article on

the ongoing research (Kovacs *et al.*, "Controlled trial of interleukin-2 infusions in patients infected with the human immunodeficiency virus," *N Engl J Med* **335**:1350-1357, 1996).

During the course of these trials, patients experienced varying degrees of flu-like symptoms as well as transient increases in their HIV levels. Consequently, the IL-2 dosage was adjusted for each patient, within the range of 3 million to 18 million IU.

Although the bursts of HIV production observed after each IL-2 treatment were worrisome, investigators found no long-term increases in viral levels, as measured by blood levels of HIV RNA and p24 antigen. Similar trials by two other research centers have confirmed these results.

Among the 10 or so IL-2-related protocols conducted at NIH was one led by NIAID's Richard Davey, another co-author, which evaluated the effectiveness of self-administered subcutaneous IL-2 injection as an alternative to the more complicated and costly infusion route.

The finding that self-administration was an acceptable and effective method enhanced the feasibility of clinical use of IL-2 therapy and served as the basis for the route of administration that is the mainstay of the Phase III protocol design (R. T. Davey *et al.*, "Subcutaneous administration of interleukin-2 in human immunodeficiency virus type 1-infected persons," *J Infect Dis* **175**:781-89, 1997)

Scientific Rationale

HIV-infected individuals become increasingly vulnerable to infections by other pathogens as their immune systems become progressively damaged by the replicating virus. These secondary, or opportunistic, infections are the main cause of health complications and deaths associated with AIDS. The decline in the level of CD4+ T cells, a major immune component in the patient's bloodstream, is indicative of advancing disease. Since IL-2 can stimulate the production of CD4+ T cells, this cytokine may be effective in boosting the immune system of HIV patients. Scientists at the NIH Clinical Center, NIAID, and FCRDC have been collaborating with Chiron Corporation of Emeryville, Calif., to evaluate the long-term effects of treating HIV-infected individuals with recombinant IL-2. ■

Interpreting the Numbers

CD4+ levels in normal, uninfected adults typically range from 800 to 1,200 cells/mm³ but can be as low as 600 in some healthy people. HIV-infected individuals who have not developed AIDS and are in relatively good health typically have counts above 500. Patients with cell counts between 200 and 500 commonly exhibit some HIV-associated conditions, such as thrush. Major, life-threatening illnesses, such as mycobacterial infections and pneumocystis pneumonia, are typically found in patients with cell counts below 200. Counts approach 800 and above in long-term HIV-infected individuals who remain symptom-free—the "nonprogressors," whose evasion of disease has recently been connected to the absence of a T-cell co-receptor. ■



The IL-2 Crews: (above) outside the NIAID/CCMD HIV Outpatient Research Clinic (Clinic 8), Bethesda, Maryland; (left) from the Clinical Services Program, AIDS Monitoring Laboratory, Virus Isolation and Serology Laboratory, and the Laboratory of Molecular Biology, SAIC-FCRDC, Frederick, Maryland. These group photos, says Cliff Lane, a PI in the IL-2 studies, epitomizes "what intramural research at NIH is all about—a collaborative effort involving many people, all of whom play very important roles."

Outlook

Follow-up of Phase II study patients has continued for more than two years, with monitoring of CD4 counts and health status. Patients whose counts drop below 1,000 get another cycle of IL-2 treatment. Individualizing the regimen has enabled the researchers to keep counts up in this "extension" phase of the Phase II trial, while minimizing patient discomfort and inconvenience, according to lead author Joseph Kovacs, of the Clinical Center Critical Care Medicine Department. Increased CD4 levels have also been achieved in patients originally in the control group who started receiving IL-2 during the follow-up period.

At this point, increases have been sustained for more than five years in some patients, Lane said, and there's at least one patient whose high levels have persisted in the absence of additional IL-2 therapy.

Judy Falloon, an NIAID scientist in the Laboratory of Immunoregulation and coauthor in the earlier studies, recently completed another study that showed

that CD4 response to IL-2 can be improved in patients with more advanced disease if a protease inhibitor is added to their treatment.

Falloon's findings are the basis of an AIDS Clinical Trial Group multicentered IL-2 trial involving HIV-infected patients with CD4 counts between 50 and 350—the cohort with poorer or no response to IL-2 in the earlier trials conducted at a time when nucleoside analogs (like AZT) were the only available HIV therapies, Kovacs noted.

Kovacs' "guess," based on early observations from ongoing studies, is that any benefits from IL-2 will be potentiated in the presence of today's "supercompetent" antiviral combinations—both in patients with more advanced disease and in the cohorts of the upcoming Phase III trial. ■

For more information about the Phase III IL-2 trial and other AIDS trials, call 1-800-AIDS NIH and 1-800-TRIALS A.

Principal Investigators

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Norman Salzman
Randy Stevens

ALEX PUTS A DENT IN THE POSTDOC BLUES: AN INTERVIEW WITH THE CATALYST'S CARTOONIST

by Janet Yee

National Institutes of H. E. Double Hockey Sticks



IDEAL LAB ENVIRONMENT



NIH LAB ENVIRONMENT

Walk the corridors and labs of NIH and you're bound to make multiple sightings of the cartoons of Alex Dent. Devotees of The NIH Catalyst's cartoon strip—especially postdoctoral fellows—are even sending copies to friends and colleagues outside NIH, spreading the adventures of "Joe Postdoc," the strip's protagonist, to research labs throughout the world. Last month, Dent was awarded a "Quality of Work Life Award" for his cartoon contributions to NIH. Janet Yee, a postdoc in NICHD recently on detail for The Catalyst, set out to find out more about the man behind the strip.

Alex Dent is originally from California, where he received his BS in biochemistry at UCLA and his PhD in biology at UCSD. He has been a postdoctoral fellow in the lab of Louis Staudt at NCI since 1992 and is currently looking for an academic research position. He and his wife, who is also a biomedical scientist, have an eight-month-old son. Alex has published 21 cartoons (counting the one in this issue in its usual spot on page 15) in *The Catalyst* since 1994. (He missed two issues—the last one of 1996 and the first one of this year. His excuse was something about having a baby.)

One of the first things that strikes you when you meet Alex Dent is his resemblance to Joe Postdoc, and Dent admits that he used himself as a model for the cartoon character. But unlike Joe, Dent is not glued to his safety glasses and lab coat. In fact, he searched the nooks and crannies of several labs to find a relatively clean and intact garment to pose

in for a photo (see page 11).

Alex credits his sense of humor with helping him cope with the stresses and demands of research at NIH, not the least of which are the dark and cramped labs here that stand in stark contrast to his doctoral digs at UCSD, which was partly the model for the ideal lab environment depicted in his cartoon "National Institutes of H.E. Double Hockey Sticks" (July-August 1996).

But he admits that the availability of resources, expertise, and funds to perform basic biomedical research were factors that attracted him to NIH and that he continues to appreciate (as do most

at NIH, fondly referred to as "Nerds in Heaven" by outsiders).

Our starting point in the interview was the Dent cartoon that sparked the greatest controversy among readers—one in which Joe shows his parents his unkempt desk—just like Alex—in an overcrowded lab ("The National Institutes of the Dungeon Gnomes," September-October 1995). One reader wrote to say that Joe's mother's comment about the lab's resemblance to "a messy kitchen" was sexist, and a couple of readers objected to Joe's invidious suggestion that MDs get more spacious quarters at NIH than do PhDs. The second most controversial Dent cartoon was about Joe's suspension by a radiation safety officer in the "National Institutes of Radiation Safety Blues" (January-February 1996), which prompted complaints from NIH radiation safety officers. As it turns out, the published version of the cartoon was toned down from the original, which showed Joe choking the radiation officer in the last frame. This pre-publication alteration prompted the first question.

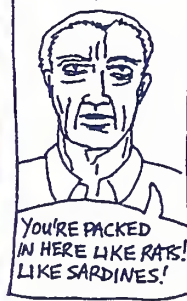
Q: Besides the cartoon about radiation safety, how many of your cartoons have been edited?

Dent: I had three other cartoons censored. One cartoon was entitled "The National Institutes of Not Exactly the Opposite of Not Unhealth" (January 1994; Dent's debut), which showed Joe

The National Institutes of the Dungeon Gnomes



FIVE YEARS OF COLLEGE, SIX YEARS OF GRADUATE SCHOOL, AND FOUR YEARS OF POST-DOCTORAL WORK—AND THAT'S ALL THE SPACE YOU GET? IT'S LIKE A MONK'S CELL! WHY HAVEN'T THEY GIVEN YOU MORE SPACE?



WELL, IT'S NOT LIKE I'M AN M.D.! I'M JUST A LOWLY POST-DOC. I'M JUST A GRUNT—A FOOT SOLDIER IN THE WAR ON CANCER. I'M DOWN IN THE TRENCHES! I'M DOING THE DIRTY WORK THAT NOBODY CARES ABOUT. I DON'T ALWAYS LIKE IT, SOMETIMES I HATE IT. BUT IT'S MY JOB—MY DUTY TO MY COUNTRY!



DENT

OK STEVIE— YOU HEAR THAT? YOU'RE GOING TO MEDICAL SCHOOL!

YES, MOM

YOU DON'T UNDERSTAND, I'M THE LAST LINE OF DEFENSE! YOU KNOW, THERE ARE STRANGE FORCES OUT THERE. CAN YOU SMELL THE CHAOS?... MOTHER, DON'T LET YOUR SONS GROW UP TO BE POST-DOCS!

National Institutes of Radiation Safety Blues

Dent

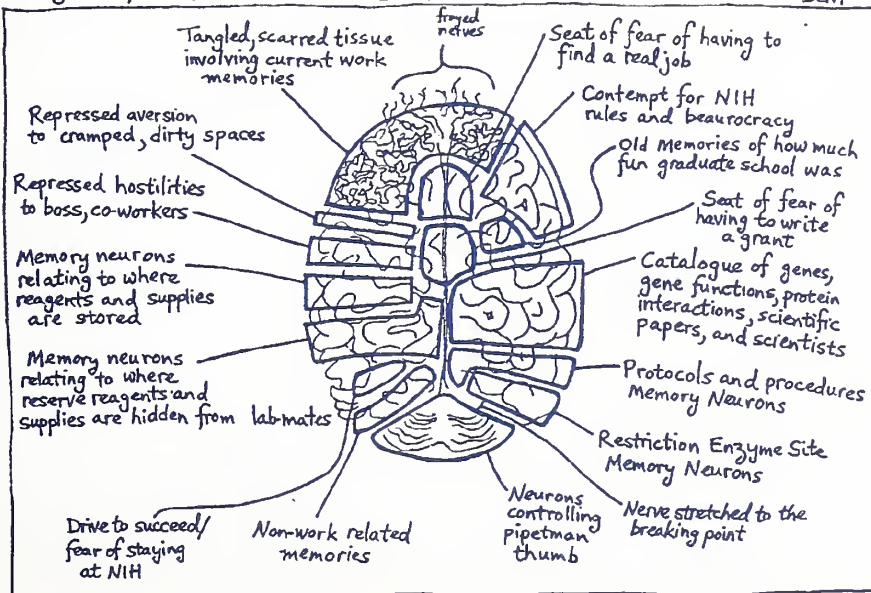


chanting a series of DNA triplets. I casually remarked to a *Catalyst* staff member that I had hidden a message in the DNA sequence, which, unfortunately, resulted in its removal from the cartoon. I would probably have gotten away with it if I hadn't said anything. My most popular cartoon, about the evolution of an NIH postdoc (May-June 1995), was also censored. In the original version, the postdoc, by his fifth year at NIH,

considered each of his experiments "a waste of [sorry, Alex, still censored]," which was changed to the more subtle phrase "worthless phenomenology." My last cartoon censored was the "Diagram of an NIH Post-Doc's Brain" (September-October 1996), which showed a part dedicated to "remembering not to bring a gun to work." This part of the brain's memory was erased at the direction of *The Catalyst's* editorial board.

Diagram of an NIH Post-Doc's Brain

DENT



Q: I heard that you had drawn a cover for *The Catalyst*; what happened to it?

Dent: The cover was supposed to be for *The Catalyst* issue about postdocs at NIH (November-December 1995). I did a drawing of a nude Joe Postdoc holding a pipetman and a lab coat and in the same pose as Michelangelo's statue of David. I think some of the higher-ups at NIH thought this cartoon was too risqué. Although *The Catalyst* had considered printing this picture with Joe's genitals covered [by the Table of Contents box], it was decided not to use any of this drawing in the end.



Q: When do you get the best ideas for the Dent cartoons?

Dent: Usually, the night before the deadline for completing an issue of *The Catalyst*. Sometimes, I stay up fairly late at night to work on the comic strip.

Q: It's obvious that you based Joe Postdoc on your own experiences. Do your colleagues recognize themselves in the characters you portray?

Dent: I got a number of comments from other postdocs that they liked the cartoon about the evolution of an NIH postdoc. Most of them identified with the "fifth-year postdoc." When my cartoon about "the nine types of principal investigators" appeared (November-December 1995), my boss asked me which type he was.

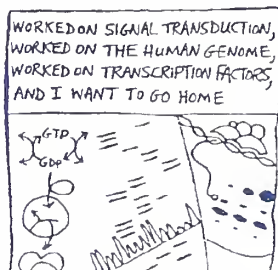
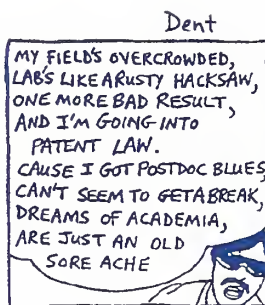
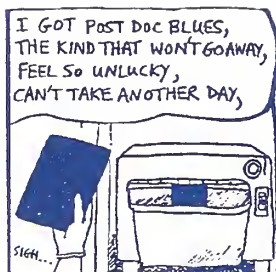
Q: Uh oh, what did you say?

Dent: I said he was a combination of all the different types.

Q: That's very diplomatic. Have you considered trying to make some money from your cartoons? I'm sure there would be some buyers for Joe Postdoc T-shirts.

Dent: No, I have never considered it. Probably because I have no business sense—I'm terrible about money matters. I don't get paid for any of the cartoons I draw for *The Catalyst*—not even

National Institutes of the Post-Doctoral Blues



reimbursement for supplies, such as markers and paper.

Q: Have you ever considered becoming a professional cartoonist?

Dent: I wanted to when I was a kid, but my parents weren't too thrilled by the idea. I got interested in science when I took an advanced placement course in biology in high school. I drew a few other comic strips in high school and college, such as "Stoner Commandoes," and "The Sorcerer and I."

I didn't do any cartooning in graduate school, although I liked to play practical jokes, such as making humorous drawings and articles about my friends and colleagues.

The major target of these jokes was my PhD advisor (in fact, he was the model for one of the nine types of principal investigator—the "Laid-Back" one—in that cartoon). Luckily, he has a good sense of humor.

Q: Which of the Dent cartoons is your favorite?

Dent: My three favorites are "National Institutes of the Post-Doctoral Blues," "Evolution of a Postdoctoral Fellow," and "Diagram of an NIH Post-Doc's Brain" (July 1994, May-June 1995, and September-October 1996).

Q: Which "professional" cartoon strip do you like the most?

Dent: I read the comics in *The Washington Post*. My favorite cartoon is "Big

Nate" because I like both its humor and artwork. I also like "Baby Blues," especially now that I'm a father. There's one more strip I like, although I don't like to admit it.

Q: Which cartoon is it? Cathy?

Dent: No, no, no. It's "For Better or For Worse." The strip is not always funny, but you become familiar with the characters, and you want to know what's happening to them. I guess it's like being addicted to a TV soap opera. "Cathy" is pretty annoying. . . . I'm not really a big fan of "Dilbert" because I feel that the timing of the jokes tends to be

slightly off. My least favorite cartoon is "Family Circus." It's horribly saccharine.

Q: Perhaps you would appreciate "Family Circus" more when your son gets a little older?

Dent: I hope not.

Q: Which piece of equipment in your lab do you feel most possessive about?

Dent: The tissue-culture hood. I hate it when people make a mess there and don't clean up. I also get upset when someone uses up all the supplies stored in the hood, such as pipettes and tips, but doesn't bother to restock it.

Q: If you were stranded in a lab on a desert island, which three pieces of equipment would you like to have?

Dent: My pipetman, of course. An agarose gel electrophoresis apparatus would be nice and, perhaps, a PCR machine.

Q: Do you have a lab superstition—like, do you routinely do something that you know is not necessary or reasonable, but you're compelled to continue doing it because you fear the wrath of the lab gods?

Dent: I have several lab superstitions. One of them is to avoid the number "13."

For example, I try not to use slot number 13 in the microfuge, and I avoid loading 13 samples on any type of gel or leaving 13 pipet tips in a rack.

	1 st YEAR POST-DOC	3 rd YEAR POST-DOC	5 th YEAR POST-DOC
National Institutes of the PostDoc Meat Grinder - or - Evolution of a Postdoctoral Fellow			
General Demeanor:	GUNG-HO	BATTLE HARDENED	SHELL-SHOCKED
Motto:	BONZAI!	Slow and Steady Wins the Race	Another day, another chance to change careers
Career Aspiration:	Tenure Track Faculty Ivy League School	Biotech Company	Manager at Radio Shack
Relationship with Advisor:	Congenial	Guarded	Hostile
Each Experiment is:	A potential Nature paper	A possible prelude to a bigger result	Worthless Phenomenology
The Night Before a Big Result:	Can't Sleep	Doesn't expect experiment to work anymore	Forgot what the experiment was


-Dent

➔ Don't let this happen to you!

National Institutes of...

THE NINE TYPES OF PRINCIPAL INVESTIGATORS


Big Talker



These results have clear implications for the cure of cancer in our lifetime

(+) Makes your data seem really important
(-) Doesn't really understand what you do


Slave Driver



You know, 60 hrs a week just isn't going to cut it in this lab


(+) You get lots done
(-) You forget your spouse's name

Demi God



(+) Power, prestige, better job prospects
(-) You never see them

Control Freak



Why didn't you use 25mM NaCl in the second wash?

(+) Knows exactly what experiment you're doing
(-) Knows exactly what experiment you're doing

Science Wonk



Why don't you try this new reverse gyropismatic amplifying DOR technique?

(+) Knows everything about science
(-) He's a total geek


Laid-Back



Make it quick, I've got a 2:00 tee-time

(+) Leaves you alone
(-) Doesn't care about your results


Psycho



WHAT DO YOU MEAN YOU MADE A MISTAKE!?


(+) Keeps you on your toes
(-) Scary

Small Town Grocer



(+) Happy with his own little niche
(-) Little Ambition

Rising Star



(+) Exciting Ride
(-) Not much room for you

Q: You count the number of tips left in a rack?

Dent: Yes. I like to keep a tally of the tips left in the box I'm using. Furthermore, I like to remove pipet tips in an ordered, rather than random, sequence.

Q: Would you rather have a paper in *Cell* or a million dollars?

Dent: A million dollars.

Q: Why?

Dent: If I had a million dollars, I could do science as a hobby. I could become a gentleman-scientist like Charles Darwin so I would be able to work on whatever I like, without worrying about research grants. However, I might choose the *Cell* paper if the money offer was for an amount significantly less than a million, such as \$100,000.

Q: Would you rather be the president of the United States, Bill Gates, or a Nobel Prize laureate?

Dent: I guess I would choose the president of the United States.

Q: How would you rate your lab coffee on a scale of one to 10?

Dent: Zero. It's so bad that I don't drink it.

Q: Do you have a secret parking space at NIH?

Dent: Yes. In desperate situations, I park in an unmarked space in the corners of the MLPs (multilevel-parking buildings). Of course, I'm only telling you this because lately I've been walking to work.

Q: Since it's possible you may be leaving NIH within the next year for a job, would you continue to provide cartoons to *The Catalyst*, or do you have an heir apparent at NIH?

Dent: No, I'm not aware of any potential replacement. I have been asked by *The Catalyst* if I would consider continuing the comic strip, but I haven't decided yet. ■



Alex Dent with three treasured lab tools



Today the Quality of Life Award (for lifting NIH spirits), tomorrow the Nobel: Alex Dent displays the award he received in May; also standing is Michael Gottesman, deputy director for intramural research, who nominated him; and in front are Celia Hooper, NIH Catalyst scientific editor, who received her own award; and Sam Hooper (definitely a relation).

RECENTLY TENURED

Leonid Chernomordik received his Ph.D. from the Frumkin Institute of Electrochemistry of the Russian Academy of Sciences in Moscow in 1979. He did postdoctoral work and then led a research group there before joining the Laboratory of Theoretical and Physical Biology (now the Laboratory of Cellular and Molecular Biophysics) of NICHD in 1991. He is now a senior investigator in this laboratory and heads the Unit on Lipid Intermediates in Fusion.

Exocytosis, protein trafficking, and viral infection have in common the process of membrane fusion. Whereas the majority of scientists working on fusion are concentrating on identification and characterization of the proteins involved in diverse fusion reactions, my research goal is to characterize the fusion pathway and to uncover the physical forces that drive the rearrangement of two membrane lipid bilayers into one.

To understand how lipid bilayers fuse, my colleagues and I in the Frumkin Institute studied fusion of protein-free lipid bilayers. The specific dependence of different fusion stages on the lipid composition of bilayers led us to develop the "stalk-pore" model of membrane fusion. This model is based on the fact that two pairs of membrane monolayers, contacting and distal, must each bend during fusion. We hypothesized that first the contacting monolayers of membranes bend toward each other to form a stalk—a local connection between membranes. Then distal membrane monolayers come together and bend in the direction opposite to the stalk, which opens a fusion pore whose expansion concludes fusion. The monolayer's propensity to bend depends on the molecular shape of the lipids forming the monolayer. By adding lipids of different molecular shapes to different monolayers, we can manipulate different fusion stages. For instance, inverted-cone-shaped lysophosphatidylcholine, which cannot bend into the curvature of a stalk, inhibits stalk formation when added to contacting membrane monolayers. The same lipid promotes pore formation when present in the distal membrane monolayers. The effects of cone-shaped lipids such as phosphatidylethanolamine and arachidonic acid are opposite to those of lysophosphatidylcholine.

To test the relevance of this model to protein-mediated fusion in biological membranes, our group at NICHD has focused on fusion of the influenza virus and baculovirus envelope membranes with the endosome membranes of their host cells at the early stages of the viral infection. If the proteins that mediate these reactions—influenza hemagglutinin and baculovirus gp64—bend the fusing membranes to form stalk intermediates, we can make it easier or more difficult for these proteins to act by altering the lipid composition of membranes. We have now

identified an early fusion stage that is dependent on the composition of contacting membrane monolayers. As suggested by our hypothesis, lysophosphatidylcholine inhibits, and arachidonic acid promotes, fusion at a stage after the refolding of viral glycoproteins into a fusion-competent conformation but before lipid mixing and fusion-pore opening.

In addition to the gp64- and hemagglutinin-mediated fusion reactions triggered by acidification of the endosomal contents, the same lipid, lysophosphatidylcholine, inhibits Ca⁺⁺-triggered exocytosis in sea urchin eggs, GTP-gamma-S-triggered mast-cell degranulation, and GTP-dependent microsome-microsome fusion. Thus, while these different fusion processes use different triggers, they apparently share a common trigger-independent step involving membrane merger. At this lipid-sensitive stage, fusion proteins may promote fusion by decreasing the elastic energy of stalk-like fusion intermediates.

Altering the lipid composition of membranes to be nonpermissive for fusion allowed us to isolate the "activated" fusion state, in which the fusion proteins remain frozen for hours in a fusion-competent conformation. We plan to characterize this conformation, find out the number of viral fusion proteins required for a functional fusion machine, and identify fusion intermediates downstream of stalk formation. I hope these studies will help us to better understand how membranes fuse.

Ezekiel Emanuel received his M.D. from Harvard Medical School in 1988 and his Ph.D. in political philosophy from Harvard in 1989. He completed a fellowship in ethics at Harvard's Kennedy School of Government, an internal medicine residency at Boston's Beth Israel Hospital, and an oncology fellowship at the Dana-Farber Cancer Institute. He has served as a senior consultant in bioethics to the NIH Clinical Center and is the director-designate of the Clinical Center Department of Clinical Bioethics, as well as an associate professor of medical ethics at Harvard.

For more than a decade, my research has focused on care for patients at the end of life. During the first phase of this, which concentrated on living wills and advance-care directives, my wife, Linda Emanuel, and I designed and clinically evaluated an advance-care directive, called *The Medical Directive*, which enables an individual to stipulate medical-care choices in the event of mental incompetency.

My research then focused on requests for euthanasia and physician-assisted suicide. Surprisingly, we found that cancer patients

experiencing pain were not likely to be interested in either of these interventions; indeed, they tended to find them unethical. Cancer patients with depression and psychological distress, on the other hand, were much more inclined to consider these measures.

I am now interviewing about 1,000 terminally ill patients and their family caregivers to see what factors make the dying experience easier for patients and their families and what factors make it worse. Thus far, it appears that high caregiving demands on the family—the need to provide transportation, nursing care, homemaking services, and the like—are associated with poorer outcomes, including increased depression of the patients' caregivers. Home-health-care services seem to improve the situation, especially reducing rates of caregiver depression.

On a more theoretical plane, I've been defining and elaborating important characteristics of the physician-patient relationship, such as choice, compassion, and continuity. This work has proceeded in two directions: first, I've defined different ideal types, or models, of the relationship based on different ways of relating to the patient; second, I'm considering how changes in the health-care system, especially increased managed care, are likely to affect this relationship.

This last-mentioned topic complements the most recent focus of my research: organizational and institutional ethics. With the shift of medicine from solo practitioners to organized managed-care systems, the major medical-ethical issues revolve not so much around an individual physician's problematic cases as the need to develop overarching institutional policies and procedures.

Therefore, I have been working on different types of accountability that might exist and how to enhance ethical performance of managed-care organizations. Some areas I am now working on relate to the just allocation of health-care resources within managed-care organizations and to identifying ethical criteria for physicians' financial incentives.

With respect to my work at the Clinical Center, the Department of Clinical Bioethics is launching several clinical research projects that will explore advance directives for research

(for example, indicating beforehand a willingness to participate in research in the event of mental incompetence), motivations for people who participate in Phase I studies, and incorporating respect for communities into considerations of the ethics of research. Another major endeavor is to better define the ethical values at stake in medical privacy and confidentiality. We will also be looking for ethical issues affecting patient care and research that arise in the daily work of clinicians and researchers at NIH, with a view toward entering into collaborative theoretical and empirical research focusing on these issues.



Leonid Chernomordik

Fran Pollner



Ezekiel Emanuel

Janel Yee

Allan Weissman received his M.D. degree from the Albert Einstein College of Medicine in 1981 and trained in internal medicine at Barnes Hospital in St. Louis before coming to the Cell Biology and Metabolism Branch of NICHD in 1984 as a medical staff fellow. He joined the Experimental Immunology Branch of NCI in 1989 and is now a senior investigator in the Laboratory of Immune Cell Biology, NCI.

The ability of a cell to maintain homeostasis and respond to external stimuli requires acute regulation of protein levels. Although the importance of regulated protein synthesis is taken for granted, the significance of regulated and specific protein degradation is just now becoming fully appreciated. The conjugation of proteins with ubiquitin and their degradation in the multicatalytic 26S proteasome plays a central role in this process. A major focus of our laboratory is the ubiquitin-conjugating system and the consequences of this modification, particularly on membrane-bound proteins.

Ubiquitination involves a cascade of enzymes known as E1 (ubiquitin-activating enzyme), E2s (ubiquitin-conjugating enzymes), and E3s (ubiquitin-protein ligases). E1 activates ubiquitin in an ATP-de-



Fran Pollner

Allan Weissman

pendent manner. Substrate specificity for ubiquitination is conferred primarily by E3s and, to a lesser extent, by E2s.

We became interested in ubiquitination when we discovered that T-cell-antigen receptor (TCR) components are ubiquitinated in response to receptor ligation. At that time (1992), few naturally occurring ubiquitination substrates had been identified. Until our studies on the TCR, it was generally accepted that only one specific lysine within a protein is modified with ubiquitin. We demonstrated that ubiquitination occurs on multiple lysines within TCR subunits, and we recently established that this TCR modification is tyrosine kinase dependent. However, we now know that lysosomal rather than proteasomal degradation is the major route by which assembled cell-surface TCRs are degraded in response to ligand; thus, the role of ligand-induced ubiquitination is not obvious. Findings in yeast suggest that ubiquitination of cell-surface receptors serves as a targeting signal for internalization and lysosomal degradation, a possibility we are actively investigating for the TCR.

Although proteasomes do not play a substantive role in the degradation of cell-surface TCRs, ubiquitination and proteasomal degradation play an important function in

determining the fate of unassembled TCR components. It has been known for some time that TCR components that are not assembled into complete receptors are degraded by an ill-defined process that has been referred to as "ER degradation," which ensures that only fully assembled receptors reach the cell surface. We recently determined that the TCR CD3- δ subunit, which is largely disposed of by ER degradation, actually undergoes ubiquitination and is extracted and degraded from the ER by a coupled process that requires the catalytic activity of proteasomes. Interestingly, and unexpectedly, ER degradation of CD3- δ is dependent on trimming of N-linked sugars in the ER. Our findings should provide new insights into the molecular bases by which quality control in protein folding and assembly is regulated within the central secretory system.

We have cloned and characterized a family of closely related E2 enzymes that function in the human papilloma virus' E6-mediated ubiquitination of p53, and we have characterized an E3 enzyme, Nedd-4. Also, using the yeast two-hybrid system, we have begun to identify novel binding partners for E2s and E3s in lymphocytes. Among the binding partners being characterized are a protein previously identified as a tumor suppressor and a novel E3 enzyme unrelated to any other known E3. Finally, with Michael Kuehn, NCI, we are studying the ubiquitin-conjugating system during embryogenesis. ■

In Memoriam

In memory of Linda S. Dorman, a member of the Laboratory of Experimental Immunology, National Cancer Institute-FCRDC, whose death on June 22, 1997, was due to complications following a bone marrow transplant. This tribute was written by co-worker Howard Young.

Our co-workers aren't supposed to die. Oh, some may come and go, but the core—those like Linda who are here year after year—they're not supposed to die, for their presence brings stability to our lives. We know as the workday begins that we will see familiar faces, hear familiar voices, and that is somehow calming in this frantic world.

No, these co-workers of ours aren't supposed to die because they are us, and we're not ready to die. We know more about their lives than their parents and relatives. We hear about their triumphs and their sorrows, their dreams and their realities. We know when their car breaks down because they call us to bring them to work. We know when their kids are sick because they call us to let us know they'll be late. We laugh with them, we sing

with them, and sometimes we cry with them, but we never cry for them because our co-workers aren't supposed to die.

Our co-workers aren't supposed to die because their children are still growing, still learning, still chasing their dreams. We hear about their children's births; we see their children grow. As days and years go by, we know when their children start to drive, have their first date, go to the prom, and leave for college. No, our co-workers aren't supposed to die because if they die, they might miss these things, and we don't want them to miss these things because we wouldn't want to miss these things.

Sometimes our co-workers leave us as they take new jobs or begin their retirement. But these are happy events as new worlds are being explored. We wish them well because we know that they can still be part of our life if we want them to be. We can always call and say hello, and with some, we often do. But die? No, they're not supposed to die because that separation is forever, and we can't imagine that.

As I sit here in my sorrow, I become angry and I want to shout at Linda and say, "How could you leave us! Don't you know that there are too many experiments yet to do, too many reagents to be or-



The lab family of Linda Dorman (seated, far left); author Howard Young is standing, above, second from right.

dered, too many students still to train? You had no right. . . it isn't fair. . . you had too much of a life yet to live! Don't you know our co-workers aren't supposed to die!"

And yet now I realize that although Linda may be physically gone, she will forever be part of us. When we hear Bruce Springsteen sing, we will think of her; when we watch the Redskins play, we will remember her; when we share a box of chocolate, she will be in our thoughts; when we have a lab lunch, she will be there with us. Our co-workers aren't supposed to die, and with our memories of them, they never will. ■



CLINICAL RESEARCH ACTION PLAN
continued from page 1

clinical researchers. Therefore, we support the recommendations of the committee as follows.

1. The authority to pay tenure-track clinicians (investigators) under Title 42 up to a maximum of \$115,700 (or the equivalent Executive Level IV salary) is hereby delegated to the ICD directors. They may redelegate this authority to scientific directors, who must exercise it in consultation with the clinical directors. All re delegations must be in writing. For salaries between \$115,700 (or the equivalent Executive Level IV salary) and \$133,700 (or the equivalent Executive Level II salary), review by the Medical Executive Committee will be required, with concurrence by the associate director for clinical research and approval by the DDIR. For salaries between \$133,700 and \$148,400 (or the equivalent Executive Level I salary), or increases in excess of \$20,000, review by both the Medical Executive Committee, with approval by the associate director for clinical research, and review by the Title 38 Policy Board, with approval by the deputy director for intramural research (DDIR) and the NIH director, will be required. The Office of Human Resource Management is charged with the development of a specific review and approval process, publicizing the new pay caps, keeping track of comparable private-sector pay scales, and evaluating the role of pay in affecting recruitment and retention of clinical researchers at NIH.

2. There is no guarantee that nonfederal employees are covered under the federal Tort Claims Act. Therefore, NIH has decided that each clinical researcher in training, while caring for patients, should occupy an FTE. However, during training in laboratory investigation, there is no need for Tort Claims Act coverage, and, in fact, a stipend to support this aspect of training could be provided under NIH training authority (or equivalent for NCI). In addition

to their status as postdoctoral fellows supported under NIH training authority, such individuals could also be appointed intermittently as clinical fellows under Title 42. Total pay (IRTA stipend plus salary) should not exceed established salaries for full-time clinical fellows.

3. The NIH director has established an advisory group, led by a subcommittee of the Clinical Center Board of Governors, to make recommendations on stabilizing the budget of the Clinical Center so that there is no financial incentive to decrease clinical research activities. A mechanism to provide incentives to ICDs to recruit new tenure-track clinical investigators is also being pursued. These recommendations will be reviewed by the ICD directors and acted upon by the NIH director.

Staff Clinicians

4. The staff clinician appointment has been used at NIH to fulfill a variety of clinical research needs: primary patient care, oversight of research protocols, and, as noted in the report, some staff clinicians have controlled independent research resources and managed their own clinical protocols. It is the intent of NIH to preserve as much as possible the flexibility of this appointment mechanism, which has supported clinical research at NIH so well for many years, while at the same time assuring proper oversight of resources and providing the possibility of career development for our staff clinicians. With these goals in mind, the following steps will be taken.

a. Staff clinicians whose primary responsibility is patient care:

Appointments will stay as they are. Some of these staff clinicians may exercise considerable judgment regarding the design and execution of projects decided upon within their ICDs and branches, including serving as principal investigators on clinical protocols. However, a scientist within the ICD should supervise the staff clinician in this work and report on it to the Board of Scientific Counselors (BSC). Occasionally, a staff clinician with primary clinical responsibilities conducts independent research as well. All such clinical research must be reviewed by a BSC.

b. Staff clinicians whose primary responsibility is clinical research:

At the discretion of the ICD, such staff clinicians may be offered the opportunity to enter the tenure track, without loss of general schedule (GS) position and salary. The "grandfathering" process will be modeled after that established in 1994 for bench

scientists. No one hired after June 1, 1997, will be considered for "grandfathering" into tenure track. The candidate must receive a positive scientific review by the BSC, must be nominated by the clinical director and scientific director, must already have been engaged in significant and meritorious independent clinical research prior to June 1, 1997, and must receive the approval of the DDIR before Dec. 31, 1997. If such a tenure-track investigator fails to achieve tenure after eight years, that person must give up independent resources and return to the position of staff clinician. In exceptional cases, a staff clinician who has a substantial record of achievement in independent clinical research may be considered for tenure at NIH following discussion with the DDIR, scientific review by the BSC, a letter of nomination from the scientific director, and review and recommendation for approval by the Board of Scientific Directors, with final approval by the DDIR.

c. New hires of staff clinicians after June 1, 1997:

The rules that govern staff clinicians, as specified in 4a above, will apply here; a staff clinician is responsible primarily for care of patients and will not be allocated independent resources by the scientific or clinical director. Any such resources must be provided under direct supervision by a supervisor who is reviewed by a BSC.

PROMOTION AND TENURE

NIH recognizes the additional responsibilities of clinical investigators compared with laboratory-based researchers and concurs that they should be weighed into promotion and tenure decisions. The following recommendations deal with how this can be accomplished.

1. The Clinical Research Revitalization Committee* should review existing standards for promotion of staff scientists and senior investigators. Recommendations to augment these standards to account for the additional training and clinical service roles of clinical investigators and staff clinicians should be developed for review by the Medical Executive Committee and the Board of Scientific Directors and approved by the associate director for clinical research and the DDIR.

2. Each BSC of an ICD that conducts clinical research should include at least one recognized clinical researcher who conducts patient-oriented research and has

been approved for inclusion by the DDIR and the NIH director. When NIH clinical investigators are reviewed by the BSC or by site visitors, there should be at least two reviewers present who are expert in patient-oriented research. Those members of the BSC who are clinical investigators should be asked to provide names of potential ad hoc reviewers of NIH clinical researchers. Either the scientific or the clinical director, or both, must ensure that each institute's promotion and tenure committee includes clinical researchers.

3. The five-to-eight-year rule should be utilized to encourage career development of potential clinical researchers. After five postdoctoral years, those candidates judged likely to succeed as independent clinical investigators can be offered an appointment as a clinical fellow for another three years. A memorandum to the fellow explaining the reason for this extension—to allow career development as a clinical researcher—should be sent, with a copy to the Office of Intramural Research.

The tenure track for a clinical investigator shall last up to 8 years, especially for outside recruits, with the usual requirement for a midterm review and a pre-tenure review by the BSC. As recommended by the committee, the total length of stay for a clinical researcher in a nontenured position at NIH should not exceed 14 years.

4. The tenure-review process for clinical investigators will be the same as that for laboratory-based investigators. The DDIR, in consultation with the associate director for clinical research, will ensure that the NIH Central Tenure Committee has members who are active in patient-oriented research. In addition, a Committee on Clinical Investigation has been appointed by the DDIR in consultation with the associate director for clinical research to re-

view the application packages of candidates for tenure who are clinical researchers and make recommendations to the Central Tenure Committee. This is currently standard practice for the review of epidemiologists, computer scientists, and engineers.

RESEARCH SUPPORT AND TRAINING

NIH acknowledges that the quality of clinical research and training at NIH is dependent on the environment and resources that are brought to bear in these areas. The following recommendations are aimed at improving the overall support for clinical research activities at NIH.

1. A subcommittee of the NIH Medical Executive Committee is developing a new policy statement on consultative services. This policy will provide a mechanism for evaluating the consultation services and assure that appropriate authority is vested with the Clinical Center director, who is ultimately responsible for the quality of consultative services.

2. The Clinical Research Revitalization Committee,* with the assistance of appropriate Clinical Center staff, is charged with working with individual clinical directors, scientific directors, and ICD directors to review support resources for clinical research provided within each ICD, especially resources for outpatient care. The committee will direct its recommendations to individual ICDs. Data and recommendations about Clinical Center-supported activities will be given to the Clinical Center director for presentation to the Clinical Center Board of Governors.

3. The associate director for clinical research is pursuing bringing advanced-degree programs (Ph.D. and Masters degrees) to NIH through partnerships with

existing universities. In addition, NIH is considering the development of a degree-granting program in translational research.

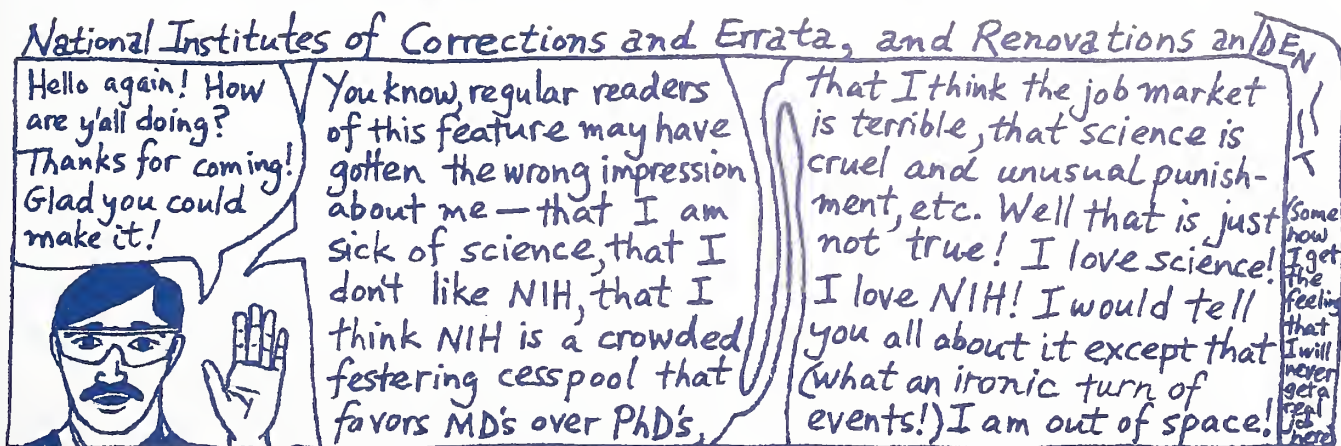
4. The Clinical Research Revitalization Committee* is charged with recommending ways to facilitate involvement of clinical researchers at NIH in extramural research activities, including examinations of current rules that limit such activities and stringent restrictions on extramural involvement imposed at the ICD level.

In addition, a Committee on Extramural/Intramural Investigations in the Clinical Research Center has been established, chaired by Ed Liu, scientific director, Division of Clinical Sciences, NCI. This committee is exploring ways for extramural investigators to work in the Clinical Center.

Status of Clinical Directors

During discussions related to the preparation and implementation of this report, it was recognized that an enhanced role for clinical directors is a prerequisite to establishing an environment for outstanding clinical research, including the recruitment of the highest-quality clinical researchers. The institute director is charged with determining how to enhance clinical director status. Possible measures include having clinical directors, along with scientific directors, report directly to institute directors and assigning to clinical directors specific resources for clinical-research portfolios and support. Because such changes in the status of the clinical director involve a substantial change in job description, the ICDs may need to initiate national searches to identify the best-qualified candidates for these positions. ■

*Those recommendations more general in nature and requiring more detailed analysis have been forwarded to a newly established committee—the Clinical Research Revitalization Committee, consisting of scientific directors, clinical directors, and other NIH clinical researchers.



CALL FOR CATALYTIC REACTIONS

In this issue, we are asking for your reactions in four areas: the Clinical Research Implementation Plan, Alex Dent's cartoons, NIDA's review, and construction at NIH.

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:
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In Future Issues...

- Nursing's New Scientific Director
- Laser-Capture Microdissection
- NIH's Vanity Fare

1) What are your reactions to the Clinical Research Implementation Plan? Will these measures be sufficient to revitalize clinical research at NIH?

2) What are your picks for Alex Dent's best (and worst?) cartoons? What NIH subjects would you like to see "Joe Postdoc" tackle before his creator moves to more commodious pastures?

3) Do you think NIDA's reviewers were on the mark in their criticisms and recommendations for the institute? What suggestions or comments would you add?

4) Do NIH's building plans lay the right foundations for research in the 21st century? What other considerations should NIH be taking into account?

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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