Prevention Research: A New Growth Area for NIH?

When the Clinton Administration took office 11 months ago, it quickly began talking up the merits of preventive medicine. Secretary of Health and Human Services (HHS) Donna Shalala said in February that the Administration's goal was not just to reform the finances of the health care system, but to push for early medical intervention. The Administration, she said, would launch a preventive medicine initiative, and other officials suggested it would lead not only to behavioral and clinical studies, but also to more funding for biomedical research—perhaps as much as an extra $1 billion a year.

But what is the prevention initiative really going to be? That question is causing uneasiness in the basic research community, since the National Institutes of Health (NIH) budget is already under stress and basic researchers fear that new money could wind up being put toward directed, rather than basic research. And adding to the nervousness is the fact that the anticipated funding for the initiative seems to be shrinking. Answers to questions about the scope and size of the effort won't be answered until next month, however, when a set of NIH proposals will be unveiled in the Administration's 1995 budget request.

In the meantime, the basic research community is trying to read the tea leaves offered by people like assistant secretary for health Philip Lee. Lee says: "We're looking at a spectrum from very basic research to applied interventions, and evaluation of the interventions." Lee estimates that 30% of what NIH does already falls within the category of "prevention," and he anticipates that the initiative would result in a "fairly broad-based expansion" of existing programs.

Despite such reassuring words, some researchers wonder whether the initiative will really provide new money for basic science or become just a new pro forma commitment—a requirement, as one Washington lobbyist put it, to pay for more "motherhood and apple pie." Says Keith Yamomoto, a molecular biologist at the University of California, San Francisco: "We always have concerns" about initiatives being turned into directed research projects. "We would like to keep the money as free as possible." Like many, Yamomoto takes comfort in knowing that "Harold"—his ex-colleague Harold Varmus who now runs NIH—is almost certainly making the same argument from his newly powerful position inside the government.

One reason that the basic research community is confused about the initiative is that the Clinton Administration has had trouble itself defining the project. Last spring and summer, NIH attempted to specify its needs for new funding on prevention research from the bottom up. The exercise quickly developed into an unwieldy and unrealistic wish list. A 17 May memo signed by Jay Moskowitz, a former policy planner at NIH and now deputy director of the deafness institute, listed scores of projects in 12 categories that would have required an *increase* in NIH's 1995 budget alone of $3.3 billion. This was twice the target aimed at in the memo itself as part of "a greatly energized prevention research effort." The memo was filed away, and this fall NIH has been taking another crack at the job.

As part of a priority setting exercise already under way, NIH held a large, 3-day meeting in October at its Bethesda, Maryland, campus titled, "Disease prevention and research at NIH: an agenda for all." The aim, according to NIH associate director for disease prevention William Harlan, was to invite outside comment. The roster of speakers included many well-known academic scientists—such as Gilbert Omenn of the University of Washington, Lester Breslow of the University of California, Los Angeles, John Groopman of Johns Hopkins University, as well as many NIH institute chiefs.

Each laid out proposals for preventive health care in the next decade, yielding a patchwork of recommendations (see sidebar). The effort, while it made for an impressive show, has not yet yielded consensus on what is needed in prevention research. But NIH's Harlan says he is drawing up an edited list of recommendations that will be passed along to NIH's deputy director Ruth Kirschstein in a matter of weeks. Harlan warns this will not lead to a crash program: "These are questions that need to be addressed over the next 5 to 6 years," he says.

Kirschstein says it's too early to comment on what will be in the new prevention plan, or even to say whether it will be an "add-on" to the NIH's regular budget. NIH's new director, Harold Varmus, declined to discuss the topic for the record in a recent meeting, noting that the size and shape of the 1995

No Shortage of Advice

While everyone seems to agree that disease prevention deserves support, there is no consensus on what belongs in NIH's budget and what does not. At a conference in Bethesda in October, public health officials and independent researchers made a variety of recommendations on what NIH ought to do in the future. A sampling shows that NIH is weighing a broad array of advice:

- David Rall, former director of the National Institute of Environmental Health Sciences, called for a systematic program to study people's exposure to toxic agents and other chemicals in the environment. He urged NIH to increase research on biomarkers of toxic exposure, on the pharmacokinetics of toxic and chelating agents, and on childhood asthma and neurological diseases.
- Ernst Wynder, president of the American Health Foundation, spoke of the big problem that afflicts all nutrition studies: People don't tell the truth about their diets. He urged NIH to look for biomarkers that will get around people's inherent dishonesty and reveal exactly they've been eating. Also near the top of Wynder's priority list were research on nutrition-related disease among the elderly and on the mechanisms of satiety.
- Gilbert Omenn, dean of the University of Washington School of Public Health, says the Public Health Service should be trying to answer major "questions that are important to medical practice and community public health." For example, like many others, he thinks the government should give high priority to developing a single-shot childhood vaccine. Omenn also emphasized the need to resolve major uncertainties, such as when and whether screening for breast and prostate cancer is worthwhile.
- John Kalberer, NIH coordinator for disease prevention and health promotion, reporting on the advice of a study group that looked at policy issues, recommended a thorough overhaul of NIH procedures. The group urged NIH to: increase the number of "prevention-related professionals" on study sections and advisory boards, eliminate barriers between NIH and other agencies such as the Centers for Disease Control and Prevention that inhibit collaboration, and consider new goal-oriented methods (other than investigator initiated models) for funding prevention research.

–E.M.

NIH budget have not yet been determined. Like many others, however, Varmus is concerned that any new assignments for NIH be supported by new funding and not carved out of its existing programs.

One of the few officials who seems eager to talk about the initiative is Lee. He told the NIH audience in October that prevention research "plays an essential role" in the president's overall health reform plan: It's expected to provide a rational basis for the benefits package that is to be guaranteed to every citizen, and it should help reduce the cost of health coverage. He mentioned specifically that NIH research has shown that only diuretic drugs and β-blockers have been proven to reduce death and morbidity from cardiovascular disease. If this knowledge were applied nationwide, Lee said, doctors might shift all patients from other, more expensive drugs and save "from $2 billion to nearly $4 billion" a year. Lee praised other NIH research that made it possible to measure bone loss noninvasively in older women, and development of the hemophilus B influenza vaccine.

In 1991 alone, according to Lee, the vaccine may have prevented 10,000 to 16,000 childhood infections, thereby lowering the risk of meningitis. In a telephone interview with *Science*, Lee specifically mentioned Alzheimer's disease, reproductive health, cardiovascular disease, cancer, diabetes, HIV infection, and childhood vaccines as areas that might benefit from the initiative. He insists, however, that decisions about what to fund will be left to NIH, and its peer-review process, although he adds the cautionary note that funding also depends on "congressional priorities as well."

The specific disputes about which types of prevention research should be included have been sharpened by the fact that funding for the initiative appears to be shrinking. The shrinkage began last summer. By late October, when the White House issued its health care reform proposal, the initiative had dwindled from $1 billion to an increase of about $400 million for NIH in 1995, and $500 million a year after that. All this is supposed to be "new money," an increase to NIH's regular budget.

By issuing hard numbers, the Administration appeared to give its plans focus. However, they still look blurry to some members of Congress—for two reasons. First, Clinton officials have not said where they expect to find the money to pay for it. Even though the cost of NIH's part of the initiative has shrunk, it would still require $400 million that's not accounted for in any official budget or appropriation bill. The financial uncertainty worries champions of NIH such as Senator Tom Harkin (D–IA). The current budget rules say that any increase in "domestic discretionary spending"—programs not funded in law by a formula—must be balanced by a cut in some other domestic program. And Harkin, who chairs the Senate appropriations subcommittee on health, says he sees no way of carving the sum promised for NIH out of other programs, each of which will be defended by lobby groups and advocates in Congress. Indeed, as Harkin told the recent meeting of the Society for Neuroscience in Washington, D.C.: "I'll be lucky to get [even] a cost of living increase for NIH" in the next 5 years, because caps on domestic spending are so tight.

And those financial constraints, coupled with the confusion over what research should be included, make the prevention initiative a fairly risky prospect in the already risky world of biomedical research funding.

–Eliot Marshall

VIROLOGY

Race to Grow Hantavirus Ends in Tie

Nothing gets the adrenalin flowing among virologists like a race to isolate a deadly virus. In the last few months, three groups—two supported by the U.S. Army in Frederick, Maryland, and the other by the Centers for Disease Control and Prevention (CDC) in Atlanta—have been trying to culture the pulmonary syndrome, or "Four Corners," hantavirus, responsible for 27 deaths in the United States since 1990 (*Science*, 5 November, p. 832). The race is now ending in a three-way tie.

A group of researchers at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), headed by Peter Jahrling, has reported isolation of the virus from a patient in New Mexico. And two other groups—one headed by Connie Schmaljohn of USAMRIID, who collaborated on the effort with her husband, Alan, and the other from CDC, headed by Clarence (C.J.) Peters—have isolated the virus from deer mice, its main reservoir. "This is a big step forward," says Schmaljohn. "Now we can really do some biology with the virus," she says, such as develop animal models and screen for antiviral drugs.

Like all hantaviruses, the Four Corners strain is notoriously difficult to grow in laboratory cultures. Although the three groups achieved initial success in the lab at different times, they all made their announcements within a few weeks of one another. Jahrling was the first to declare success. In a talk at a meeting of the American Society of Tropical Medicine and Hygiene in Atlanta on 3 November, Jahrling presented equivocal evidence for a hantavirus from a Mississippi patient, then later, his colleague Kurt Nolte of the University of New Mexico presented more convincing data—electron micrographs of virus particles isolated from a patient in New Mexico. The particles were tagged with an immune identifier called "immunogold," and genetic tests for hantavirus were positive.

Later that day, Schmaljohn presented data on a virus isolated from a deer mouse trapped near Mammoth Lakes, California. After her talk, she says, CDC informed her that CDC researchers were at a similar stage in isolating the virus from New Mexican deer mice. CDC virologists presented their data 2 weeks later, at a meeting organized by the University of New Mexico in Albuquerque, on 20 November. By then, CDC had put the virus through four "passages" from flask to flask. Says Brian Mahy, chief of the division of viral and rickettsial diseases: "We kept very quiet. We'd known for some time that we had something replicating, but we wanted to be quite sure we could reproduce it."

CDC/S. ZAKI AND C. GOLDSMITH

In the act. Pulmonary syndrome hantavirus replicating in monkey cells.

When CDC finally went public, it went all out. Bob Howard, CDC's public affairs chief, came to the meeting with glossy photos and slides of CDC's isolate for the press—one of which appeared in *The New York Times*. Schmaljohn joined CDC at the press conference, announcing that she, too, had isolated the virus. Schmaljohn says, "I have a feeling that if I hadn't happened to be [in Albuquerque], there would have been just one agency making the announcement." Jahrling wasn't in Albuquerque, and his human isolate didn't get mentioned in the news coverage.

Although the competition was intense, the Army and CDC seem ready to share the credit. Says Peters: "I'm not sure who had [the virus] first in cell culture, but that doesn't really matter....We've agreed to publish back to back articles."

–Eliot Marshall & Richard Stone