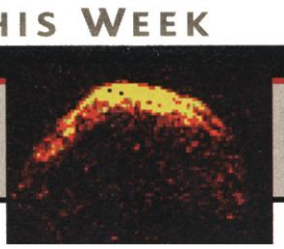
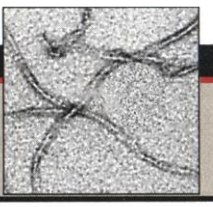


PAGE 27
Beware 16 March 2880



28
Proteins in a twist

NIH DIRECTOR-DESIGNATE

Money, Mission, Management Top Zerhouni's Agenda

Elias Zerhouni has spent 27 years at Johns Hopkins University in Baltimore building a reputation as a creative thinker and adept manager. Those skills will be sorely tested as the Algerian-born radiologist, nominated last week by President George W. Bush to be the next director of the National Institutes of Health (NIH), prepares to lead an agency nearing the end of an extraordinary 5-year run, during which its budget will have doubled to a projected $27.3 billion in 2003. "The thing staring the new director in the eye is explaining what has been done with [the budget] and what's to come," says Harold Varmus, who stepped down as NIH director in December 1999 to lead the Memorial Sloan-Kettering Cancer Center in New York City.

Looking ahead. Elias Zerhouni faces many contentious issues as he awaits confirmation as NIH director.

The first step for 51-year-old Zerhouni is a confirmation hearing before the U.S. Senate, which is expected to press him on his views about research involving human embryonic stem cells. But because Bush has already laid down the Administration's policy on that issue, the biomedical community is probably more anxious to hear what he thinks about the federal crown jewel with which he is being entrusted. "As someone who's less widely known, he's going to have to really establish what his values are as the leader of NIH," says Harvard provost Steven Hyman, who was director of the National Institute of Mental Health until last December. (Zerhouni has declined to give interviews until after he is confirmed.)

One early test for him will be shaping the newest of NIH's 27 institutes and centers, the National Institute for Biomedical Imaging and Bioengineering (NIBIB). Championed by radiology and bioengineering groups—including the Academy of Radiology Research, on whose executive committee Zerhouni sits—the institute was created by Congress in December 2000 over the objections of Varmus and others, who felt that creating more entities undermined good management practices.

Congress allocated $112 million to NIBIB this year, including $67 million in existing extramural grants from other institutes to develop new imaging and bioengineering technologies that cut across organ systems and diseases. But in a bid for a larger pot, lobbyists persuaded Congress to order NIH to set up an advisory group to examine the entire NIH portfolio. Preliminary criteria from the working group have sparked heated debate, however, with some NIH staff and outside researchers saying that many of the grants flagged by the panel lie outside NIBIB's territory.

Zerhouni also inherits a proposal for an imaging center at the University of Mississippi Medical Center in Jackson. Research director David Dzielak says that the center would enhance ongoing campus projects as well as the work of scientists at nearby NASA Stennis Space Center. The university has talked with top NIH officials about its plans, Dzielak acknowledges, but he says it is not trying to sidestep peer review. "We don't want to see the NIH [budget] earmarked even if it would benefit us," Dzielak says. "We just think this is a good idea, and we're testing the waters to see how it could be done." Although submitting a proposal may be standard practice, Mississippi legislators have upped the stakes by claiming that the peer-review system discriminates against their state and informing NIH that they are keenly interested in the project's fate.

The imaging institute isn't the only political hot potato in the NIH budget. Another is the first-ever request by a president for a specific total for cancer research. The amount encompasses more than the recommended funding for the National Cancer Institute. Special-interest groups have pushed Congress to adopt similar language for their particular cause, a step that some feel would limit NIH's ability to pursue the most worthy science. "NIH would have to spend no less than $5.1 billion" on cancer, says Richard Turman of the Association of American Universities. "Our biggest worry is that it would create me-too's" from other disease groups. Several lawmakers have also raised questions about the president's request.

That debate is part of a broader discussion of how NIH will cope with budget increases that are expected to be much smaller than the 14% or 15% received each year since 1999. In particular, lobbyists can't see how NIH can maintain its current annual pace of 9377 new grants and allow for growth in the size of existing grants with budget increases as small as 2.1%, the figure projected for 2004 in the president's budget. NIH acting director Ruth Kirschstein told legislators last month that she is working on various "models." One key variable is the $770 million in the 2003 request for bioterrorism funding to build facilities and buy a new anthrax vaccine, an NIH official says. Although all the money would go to those two activities in 2003, officials hope that an equivalent amount might be put into the 2004 NIH budget, allowing them to use some of it for regular grants.

However, if Zerhouni pushes for increases that outpace inflation—7% to 10% is most often mentioned—he will bump up against intense lobbying by nonbiomedical groups that argue that the physical sciences have been shortchanged during NIH's recent budget spree. "He's going to have to figure out the right balance," says Varmus. Zerhouni will also have to map out a plan for spending the $1.5 billion for bioterrorism in this year's budget, nearly all of it to the National Institute of Allergy and Infectious Diseases (NIAID). "Many of us were surprised by the large size of the bioterrorism alloca-

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tion," says Varmus. "[Zerhouni] will need to work out with [NIAID director Anthony] Fauci where it's going to be invested."

Another looming task is finding top-quality institute directors. Varmus recruited several talented people, such as Hyman and Gerald Fischbach, head of the National Institute of Neurological Disorders and Stroke, who have since moved on. Six directorships—of the imaging, mental health, neurology, mental health, general medical sciences, and alcohol abuse institutes—are or will soon be vacant. "The recruitment process is hard," Varmus says.

In the larger picture, the new NIH director will be expected to explain the importance of bench biology to a public that hungers for cures. The race to sequence the draft human genome "made it a little easier," says MIT molecular biologist Phil Sharp, a member of the National Cancer Institute advisory board. But explaining how those discoveries will help vanquish disease is a huge challenge, he adds.

Edward Benz, president of the Dana-Farber Cancer Institute in Boston and former chair of medicine at Hopkins, thinks that Zerhouni is up to the task. "Varmus is a hard act to follow," he says. "But I think [Zerhouni] has all the tools to do it. He has the intellectual capability, he's an outstanding manager and consensus builder, he's extremely fair, and he has a lot of integrity."

–JOCELYN KAISER

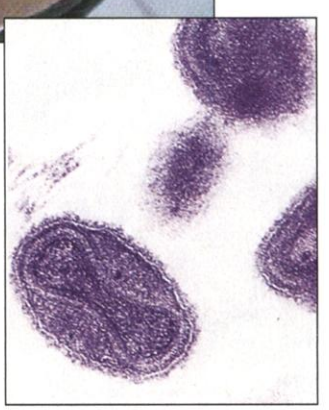
SMALLPOX VACCINES

New Cache Eases Shortage Worries

Since 11 September and the spate of anthrax attacks, the U.S. government has been scrambling to prepare for an even worse scenario: a bioterrorist attack with the variola virus, the cause of smallpox. Now, the nation can breathe a little easier. A new study has found that the 15.4 million doses of aging smallpox vaccine currently in the U.S. stockpile—an amount considered woefully inadequate—can be safely diluted by a factor of 5 or 10 without losing their potency. And, in another unexpected windfall, Aventis Pasteur, the vaccines business of Aventis Pharma with U.S. headquarters in Swiftwater, Pennsylvania, has just announced that it plans to donate to the government about 85 million additional doses of a similar vaccine that have been stored in its freezers for about 40 years.

Although the Aventis vaccine still needs to be tested for safety and efficacy, "this ratchets back our anxiety meter quite a bit," says Peter Jahrling, a smallpox researcher at the U.S. Army Medical Research Institute of Infectious Diseases in Fort Detrick, Maryland.

The Aventis vaccine may offer the U.S. government an extra "insurance policy" until new vaccines are ready for use, Tommy Thompson, secretary of the Department of Health and Human Services, said last week. Last November, the U.S. government placed a rush order for 155 million doses of a brand-new smallpox vaccine with a British-U.S. company called Acambis—in addition to the 54 million doses it had ordered from Acambis a year before. Clinical trials with the Acambis vaccine started last month; the entire batch is to be delivered before the end of 2002.



Shot in the arm. Dilutions of the smallpox vaccine, administered to volunteers (*top*), appear to be just as protective against the smallpox virus (*right*).

The dilution studies were launched last fall. The National Institute of Allergy and Infectious Diseases (NIAID) funded Sharon Frey and her colleagues at St. Louis University to test whether Dryvax, the vaccine currently in stock, could be stretched to protect more people if needed. Wyeth produced the vaccine, an attenuated virus called vaccinia, before routine smallpox vaccination was halted in 1972.

The study of 680 volunteers, released online last week by *The New England Journal of Medicine*, showed that more than 97% of the participants who received undiluted vaccine developed a "take"—a localized skin infection at the site of the shot, known to reliably indicate protection. So did 100% of those in the group given a vaccine diluted fivefold and 99% of those who got a 10-fold dilution. The slight variation in numbers, the researchers suspect, probably means that some of the volunteers were vaccinated earlier in life.

Few people knew of the cache of old vaccine in Aventis's freezers until *The Washington Post* reported it last week. But Aventis Pharma CEO Richard Markham denied that the company recently "discovered" the supply, as the *Post* reported. The company knew about the vaccine, which had been produced at the request of the U.S. Department of Defense, all along, he says, and had in recent years discussed with the government what to do with it. But the issue was never urgent—until last fall, when the company offered the vaccine to the government for free.

The company, which is hoping to be reimbursed for repackaging and other costs, has transferred the vaccine—stored in about 60 2-liter bottles at –20°C—into standard vials containing about 100 doses each. Like Dryvax, it consists of a vaccinia strain dubbed "New York City Board of Health." Thompson says the government decided to keep the huge cache a secret while awaiting the results of preliminary tests of the vaccine's viability and potency. Those test tube experiments, completed recently, suggest that the vaccine is about as potent as Dryvax, the company says.

NIAID will test the Aventis vaccine in human volunteers over the next 6 to 8 weeks. Researchers will also test whether it can be diluted, like Dryvax. If so, the U.S. government could soon have more than half a billion vaccine doses at its disposal, more than enough for the country's 286 million residents.

With the acute shortage most likely solved, the government also plans to address the needs of millions of infants, the immuno-

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