Varmus: The View From Bethesda

The Senate finally confirmed Harold Varmus as the new NIH director last week. In an interview with *Science*, he spells out his initial thoughts and ideas about his new job

In the past 3 months, Harold Varmus has had an inside view of how the government works: glacially slowly. President Clinton announced that the Nobel Prize–winning virologist would be his nominee for director of the National Institutes of Health (NIH) on 3 August. Ten weeks passed before the White House sent Varmus' paperwork to the Senate, and another 5 weeks passed before the Senate was ready to vote. The nomination then ran into a final snag on 18 November. Charles Grassley (R–IA) threatened to block the vote because the Department of Health and Human Services (HHS) had not responded to questions he had raised about the attempted dismissal of NIH fraudbusters Walter Stewart and Ned Feder. HHS rushed a response to the Senate, and Grassley relented. On 19 November, the Senate finally approved the nomination, and Varmus has taken the helm at NIH's campus in Bethesda, Maryland.

"We need to make study section service more palatable."

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As the bureaucracy ground away, Varmus took the opportunity to survey his new domain. He has visited nearly all of NIH's 24 institutes and centers, consulted on personnel changes, met with senior staff, lunched with trainees, and learned "about problems at every level." In an interview with editors and reporters from *Science*, Varmus discussed some of these problems.

One of Varmus' main goals is to re-energize the NIH intramural research program. Internal and external review committees are now examining the $1.2-billion-a-year enterprise, and Varmus expects to have concrete proposals to take to Congress early next year. He made it clear, however, that he is not planning to create a sharp distinction between the kinds of research conducted on NIH's Bethesda campus and in university labs, as some have suggested (*Science*, 24 September, p. 1674). "I don't feel that the intramural program has to be profoundly different from what goes on outside," Varmus said. "I just don't see any rationale for that."

Another Varmus priority is to improve the peer-review system. He says he is already planning tests of electronic submission and review of proposals, and he may try an experiment in triage, in which the least competitive proposals would be quickly eliminated to give reviewers more time to concentrate on the better ones. These experiments, he said, would run in parallel with regular reviews to see if they produce good results.

During his 3 months of before-the-job training, Varmus has evidently developed a distaste for bureaucracy. He praised the Administration's "reinventing government" drive, saying he wants to invite Vice President Al Gore to the campus for a session on how to improve NIH by removing "completely ridiculous" regulations. "Science as a culture is fundamentally chaotic, ought to be chaotic," he said. "And, of course, government runs exactly the opposite way. It's all ordered. The word I've come to hate most is the word 'chief.' When I hear someone tell me, 'I'm the chief of the section, something, something. That to me is not what the scientist should think about."

Here, in Varmus' own words (edited for brevity), are his thoughts on some issues he will face:

Intramural program

[Deputy Director Ruth Kirchstein has] put together three committees composed of intramural scientists to assemble all the facts about what we do and how we do it in clinical research, in basic research, and what goes on in the organization—the infrastructure, the buildings, and procedures....Now, we always felt that [the information assembled by these committees] has to be judged by people on the outside....So with some advice from me, we've put together a group of extramural people, and this is an outstanding group....* They're looking at every aspect of how the intramural program works...on how appointments are made, how promotions are determined, how space is allocated, how reviews are done, how the recommendations of the review bodies are carried out....They are looking carefully at the clinical center and its role in campus life and, of course, giving some advice about the inevitable issue of how we replace the clinical center....I expect by March to have a list of recommendations. I am not going to appear in front of the Appropriations Committee next year without having the detailed report from this group.... I hope to have evidence that some of the things that are recommended are actually moving forward.

Improving peer review

What troubles me...about the review process right now is its cumbersome nature—the large number of grants we're trying to review under circumstances that are made very difficult by the low success rate, the high number of resubmitted applications, the unwillingness of talented people to serve on study sections. They're making distinctions between grants that are equally excellent. It's very, very demoralizing to do that kind of reviewing. Then there's the massive paperwork that's always been involved and the intensity of the meetings and the amount of time spent on applications that never stood a chance.... There are opportunities created by computers and e-mail [to make the process friendlier and more efficient]. Jerry Green [director of the Division of Research Grants], Wendy Baldwin [acting deputy director for extramural research], and I are talking about some experiments we might do on a small scale, look at a few study sections and have them look at a bunch of applications with the triage process and take the applications and do them in the conventional way and see if there are any significant differences. We need to think about ways we might make study section service more palatable.

Intramural peer review

One of the inherent difficulties in the evaluation process and making it stringent is [that] the boards of scientific counselors, of course,

* Gail Cassell, University of Alabama, Birmingham (co-chair); Paul Marks, Memorial Sloan Kettering Cancer Center (co-chair); Michael Brown, Southwestern Medical Center; Elizabeth Neufeld, University of California, Los Angeles; Lucille Shapiro, Stanford University; Maxine Singer, Carnegie Institution of Washington; Gerald Fischbach, Harvard Medical School; Arthur Rubenstein, University of Chicago; Kenneth Shine, Institute of Medicine; P. Roy Vagelos, Merck; James Wyche, Brown University.

are appointed by the scientific director of the institute. So already...it's less anonymous than the study section method. The other issue is a tricky one, and that is that when you review someone in the intramural program, you are not just reviewing a grant application. You are reviewing a person's life, his whole career, and that doesn't mean that you shouldn't be stringent but it is a little different....One of the things I'm looking forward to hearing from those who review the NIH program in the next couple of months is the extent to which we can strengthen the review process and still be humane....When someone receives a negative review, does that mean that the space should be taken away? Does it mean that person should be working on something else? That could be something that varies from case to case.

NIH's independence

The NIH director has traditionally been a somewhat difficult position because you're not the top of an agency. There are people above you, and that in the past has been detrimental to the actions or the aspirations of NIH directors. Right now I feel incredibly fortunate. Phil Lee [the assistant secretary for health at HHS] is my buddy. He's very easy to work with. He's remarkably accessible. He's happy to be called at 11:00 at night if you've got a complaint. I can see him whenever I want to see him. I've only met a few times with [HHS Secretary] Donna Shalala but this is only through want of trying....

There is an issue that Donna Shalala talked about in her interview here [*Science*, 2 July, p. 20]: Some of the authority that allows the NIH director to make appointments on campus could be returned to my office. Now those powers are ultimately found in the department. The department generally ultimately endorses appointments that are suggested by the director but can take 6 or 9 months before you have all the papers signed and stamped and the appointments actually made.

We have some proposals that Ruth [Kirschtein], as acting director, sent downtown asking for new authorities for the director. Now, if I get those authorities that's going to help me, I hope, with my institute directors who will be happy that I have those authorities and will see the trust invested in me by Donna and others as evidence that I really can do some things. [Shalala] is very supportive of our doing that. Now, there are a few bureaucratic hurdles as there always are, but I think that it could all come to pass.

Institutional politics

NIH is a confederacy, and it's a confederacy with some very strong components, each of which has its own strong leadership. The ability of the NIH director to make things different...is going to depend a lot on moral suasion, on my having some discretionary funds that I can use to make things that may not be palatable more palatable. It will depend upon my having good relations with [the institute directors], and one of the things I've tried to put my months of special volunteer status to use doing is going around to all these institutes and meeting a lot of people and making it clear that there is not a trench between Building One and the rest of the campus. That's been the perception for the last couple of years—that Building One is a fortress of central administration and the rest of it is the research, you know, the geeks out there in the trenches. But, no, I'm a geek, too....

"In 3 or 5 or 10 years...I don't want to go on to a foundation presidency. I want to go back and do research."

The institute directors have been advertised to me as cold-blooded, hard-hearted individuals who are going to give me all kinds of [trouble] for the rest of the time I'm there. But so far relations have been extraordinarily amicable.

AIDS and breast cancer research

[Varmus was asked why he calls the quasi-independent Office of Aids Research, which he once opposed, a "good idea."]

The way it was proposed changed. For example, at one point it was argued that the discretionary fund for that office could be as high as $250 million. The way in which the budgetary negotiations were to take place wasn't as clear as it is now. At this point, what's going to happen is there will be a coordinated budget. They have the option of having a by-pass budget that goes directly to the president....But I think in the realpolitik of things, unless there's some extraordinary reason not to abide by the AIDS components that are defined by each institute, it's very likely that there won't be a major squabble over who sets the budget for AIDS.

....I take the view that we should be defining money like AIDS money or breast cancer money as broadly as possible...not by putting out a definition but by saying that if you want money from this pot, you tell us, you convince us that what you're doing is related to breast cancer. And that's really good. It brings people in. It makes them think about their research in relation to this major clinical problem. You also set up a program so that people get trained in this area. And a lot of the money that the Army will spend in this area [through a $210 million appropriation for breast cancer in last year's defense bill] will be spent on what could be called training. It could be called recruitment to a way of thinking about one's work in relation to breast cancer.

Gene patents

[Moving forward on gene patents] is not my highest priority, but I do think it's extremely important that we know whether this stuff is patentable, because private companies have gotten into this in a big way. Francis Collins [director of the National Center for Human Genome Research], tells me that there may be as many as 130,000 sequences for which there are patent applications in the private sector, and most of these sequences are not yet available. So there is a potentially difficult situation emerging....

I'm not opposed to patenting the fruits of biological research. In many cases it undoubtedly fosters industrial development, which is what we're trying to do in many cases....But the thing I feel most strongly about is that we don't end up impeding the research process by patenting things that were paid for by public money....I'm particularly concerned about inhibitory influences of patenting of mice on the new genetics ....But I think it's probably a mistake to make blanket statements about whether the products of federally funded biological research should be patented.

Plans and "missions"

Strategic planning on the grand scale [of former NIH Director Bernadine Healy] had some virtues, but I think the goals were not my goals....I think what had some energizing effect was the process of getting people together in a room talking about what we ought to do in molecular medicine for the next 10 years. I think it affected the way all of us thought about how we'd be spending money in the future. I didn't think the process of writing it all down and putting it in a book was all that helpful....If I read another mission statement, I think I'll pass out....

One problem I've had is, when I ask people what they do, they give me a mission statement which says they communicate, facilitate, coordinate—I don't know what the hell they're talking about. I want to know what do you do, what ideas you have, what experiment you're doing, what real thing you're trying to do. So I think to be able to say to Congress: The mission of NIH is to do great science to further human health—that's fine. A more detailed mission statement I don't think is all that useful.

Varmus' own lab

I knew from day one that I couldn't take this job if I didn't have a lab. First of all, I couldn't just close down my lab. There are 20 people in it. Number two, I don't expect to do this job forever. In 3 or 5 or 10 years from now when I stop doing it, I don't want to go on to a foundation presidency. I want to go back and do research. So I had to keep something up. And one of the pivotal moments in the recruiting process here was saying to Phil Lee and Donna Shalala, "I can't do this job unless I have a small lab." And they're saying, "Great!" So I had to decide whether this is realistic. And I went around and talked to a lot of people who had seen other directors in action. I talked to other directors, and I found that everybody had something that was fairly time consuming that I probably wasn't going to do.... Dr. Healy had a family back in Cleveland. She traveled to Cleveland every weekend. I don't have to do that.... I'm going to spend an hour or two every day, perhaps more time on weekends, looking after my lab group.

Conflict of interest?

[Varmus was asked whether his running a lab within NIH could pose conflict-of-interest problems. His eight-person lab, focusing on oncogene research, will be housed in a division of the National Cancer Institute.]

There's no way to avoid that entirely. I've tried to protect myself as much as possible ....[NCI's board of scientific counselors] will look at my lab. They will write a report. I don't have control over those reports. If my lab's doing poor work and is not productive and they say they want to shut it down, they can shut it down. That's fine with me. If I'm not producing, it should be shut down.

How long a term?

It's a little hard for me to say at this point, but I do think an argument can be made for a fixed term, a 6-year term, I would say would be the way to go. Uncouple it from the election....How long I do it I think will depend in part, of course, on whether I enjoy the job, but also on whether I'm able to continue to do some research while I'm doing this job.

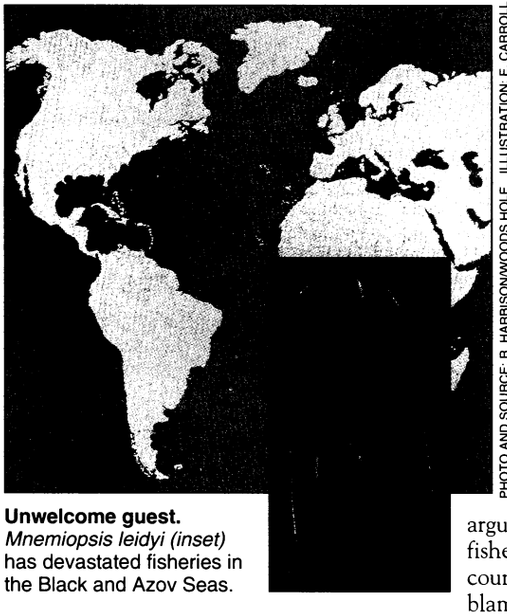
–Eliot Marshall

ENVIRONMENTAL SCIENCE

Invader Threatens Black, Azov Seas

The invasion began in 1982. Stowaways lurking in the ballast water of a ship traveling from the coast of the Americas disembarked at a port somewhere in the Black Sea. The alien intruders lay low, vigorously reproducing in their hospitable and enemy-free new home. Then, in the late 1980s, the aquatic army emerged in force.

The invaders, jellyfish-like, tentacled creatures called ctenophores, provide a dramatic example of how damaging intruding exotic species can be: The creatures appear to have devastated local fishing. "This is clearly one of the most outstanding global invasion stories in the last 50 years," says invasion expert James Carlton of Williams College in Connecticut (*Science*, 2 July, pp. 34 and 78). The presence of the ctenophore, called *Mnemiopis leidyi*, is now prompting affected countries to look at strategies for controlling the invader—and it has touched off a debate over whether they should risk trying. "*Mnemiopsis* is one of the hottest issues that has broken out in the last few years in marine biology," says John Caddy of the Mediterranean Fisheries Commission in Rome.



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Unwelcome guest. *Mnemiopsis leidyi (inset)* has devastated fisheries in the Black and Azov Seas.

While there's still doubt about whether an effort can or should be mounted to control *Mnemiopsis*, there's no question that the ctenophore has taken over in the Black and Azov Seas. Russian fishery experts have documented that at times 95% of the Black Sea's wet weight biomass can be attributed to this ctenophore, notes David Aubrey of the Woods Hole Oceanographic Institute (WHOI), who directs the international Cooperative Marine Science Program for the Black Sea. "That's a huge domination," he says. So huge that it may have led to the precipitous decline of fishing catches in the Black and Azov Seas during the past 5 years. Although many local fisheries had already been flagging for two decades because of severe pollution problems, they have plummeted since *Mnemiopsis* emerged as a pest. In the Azov Sea alone, catches have dropped by an estimated 200,000 tons.

The voracious ctenophore is the leading suspect. It devours—even beyond its capacity to digest—huge quantities of zooplankton, small crustaceans, and the eggs and larva of fish. In short, it not only kills fish directly, but also indirectly by depriving them of food. The cost to Black Sea fisheries from *Mnemiopsis* is estimated at $250 million; in the Azov, fisheries have simply shut down.

The decline has brought local fishery experts and ecologists together with colleagues worldwide to try to find a solution to the problem. For example, the United Nations Environment Program has formed a working group to study *Mnemiopsis*. But any effort to control the pest faces formidable political challenges as well as scientific ones. For instance, six countries—Bulgaria, Turkey, Rumania, Russia, Georgia, and Ukraine—border the affected waters, and in Russia alone, there is little harmony on the issue, says WHOI ctenophore expert Richard Harbison. Members of the Russian Academy of Science argue that pollution is the chief cause of the fisheries decline, he explains, while the country's Committee of Fisheries places the blame for their woes squarely on *Mnemiopsis*.

Even the United Nations has been slowed by internal bickering over which programs or agencies should take the lead. Adding to the pressure is the prospect that any campaign mounted against *Mnemiopsis* may serve as a model for repelling future aquatic invaders affecting multiple countries. "It's an interesting test case in terms of the biopolitical decisions of pursuing [a control] strategy. This is not the last [ctenophore] invasion in the world," explains Carlton.

To combat this particular invasion, there are four options—none of which are particularly appealing or risk-free. One is to use pesticides, an unlikely alternative since they could cause greater harm than good by killing other species. Another notion is the introduction of a *Mnemiopsis*-specific disease. The problem: Very little is known about ctenophore illnesses. Parasites are a third option, but the one known parasite, an anemone that feeds off *Mnemiopsis*, causes little harm to the ctenophore and can bloom it-