As politicians square off for another fight over social spending, Harold Varmus discusses how NIH has achieved exceptional growth recently, and how its organization could be improved in the future

View From the Top of a Biomedical Empire

Six years ago, Harold Varmus arrived in Bethesda, Maryland, a very green new director of the National Institutes of Health (NIH). Although he had achieved distinction as a basic scientist—sharing a Nobel Prize in 1989 for research on genes that cause cancer—his administrative skills were largely untested. He had never run an organization bigger than his 20-person lab at the University of California, San Francisco. The challenges would be immense even for a seasoned administrator. Bureaucratic and fraught with internecine rivalries, NIH is the world's largest basic research center. In 1993, when Varmus took over, it employed more than 17,000 people and boasted a budget of $11 billion—and it was clearly in distress.

The NIH research hospital, the Clinical Center, was falling apart. The building had long been slated for replacement, but Congress was wary of releasing the hundreds of millions of dollars the new construction would cost. Hampered by a tight budget, NIH was pinching its funds to support extramural grants. At the same time, many of NIH's best and brightest intramural scientists were fleeing the Bethesda campus for jobs in academe and industry. Varmus himself and two colleagues wrote in 1993 that they were concerned about "outmoded procedures" at NIH and threats to the "long-term viability" of U.S. biomedical research (*Science*, 22 January 1993, p. 444). Given the many problems, observers wondered whether it made sense to tap Varmus, a devotee of "pure research" and a novice in politics, to lead NIH in this difficult period.

Today, the record suggests that such worries were exaggerated. NIH's reconstructed Clinical Center is on course for completion in 2002. NIH is enjoying in 1999 not only the largest federal appropriation ever, but also the largest 1-year increase—a boost of $2 billion, for a current budget of $15.6 billion. The overall "success rate" for extramural grants—the percentage of approved investigator-initiated applications that get funded—is as high as it has ever been, heading toward 33% this year, up from 23.6% in 1993. Many small but destructive "brush fires," as Varmus called them in an interview with *Science* in 1993—controversies over employment discrimination, sexual harassment, scientific misconduct—seem to have fizzled out. New leaders have taken over key posts, like the long-vacant directorship of the National Institute of Mental Health, now filled by former Harvard professor Steven Hyman. Whether all this makes Varmus the Clinton Administration's "most effective backstairs politician," as a *New Yorker* article called him in June, or the lucky heir to favorable politics is debatable. But the record suggests that at least part of the credit is his.

At a meeting last month, *Science* invited Varmus to reflect on what he sees as his major accomplishments at NIH, his disappointments, and some ideas about NIH's future. A condensed version of his conversation with *Science*'s news and editorial staff, edited for clarity and concision, follows.

Reviewing NIH's budget, Varmus argues that his decision to seek modest growth in the mid-1990s established the agency's credibility. This, he says, paid off handsomely in larger appropriations when the U.S. budget deficit began to fade in 1999. He's also proud of his record in recruiting new scientists to NIH, including 12 institute directors. His concerns include the fragmentation of NIH's administrative structure, now divided into 25 major institutes and offices. He also regrets that the NIH director does not have adequate authority to launch major scientific initiatives on his own. And he wishes his efforts to rationalize the scientific jurisdictions of the review panels that rank grant applications for NIH had moved along more rapidly.

The only subject Varmus placed off limits was his own future. He declined to talk about the rumor that he is being considered for the presidency of the Memorial Sloan-Kettering Cancer Center in New York City. When asked about his plans, Varmus would only say, as he has many times before, that his tenure is determined by the president. However, he also said in the past that he considered a term of "about 6 years" about right for NIH director.

–ELIOT MARSHALL

Q: *NIH got a 2% increase in the president's 2000 budget. Are you expecting more?*

A: I think it's not unreasonable to envision an increase of approximately 10%. But at this point, it is very dangerous to make that kind of prediction. ... It's obvious that the committees that are responsible for paying us are short of cash. ... We don't want to see social programs and educational programs that are supported by those committees suffer just to pay us. ... I think the mood of the country is to support science, and when push comes to shove, there will be some kind of omnibus, emergency appropriation that allows NIH to be reasonably supported, and, hopefully, other science as well.

Q: *Is there an upper limit on NIH's budget in your mind?*

A: If we turn our attention to neglected areas [undersupported grants, infrastructure, instrumentation] and exploit new opportunities ... we would accommodate very well a doubling over a period of about 5 years. ... What concerns me more is the structure of NIH. NIH has prospered in part because of the strong advocacy we've enjoyed from members of Congress and the public. ... On the other hand, this has been responsible for making an institution that has become much more complex over the years. ... It makes me think that at some point there will have to be a moment [when everyone says]: Whoa, let's have a look at how NIH is organized. Let's try to simplify that organization, make it more rational, more manageable.

Q: *What would the ideal NIH look like?*

A: The proposal I threw out for the sake of argument [at Jackson Laboratory in Bar Harbor, Maine] was one in which there were roughly six institutes, of roughly comparable size [embracing internal medicine, cancer, environment and infectious diseases, human development and aging, brain and behavior, and an NIH central]. The central component would be the home of the NIH director and would include the clinical center and the review groups. It would also undertake special initiatives that do not be-

come part of the commitment base but are expected to come and go. And it would provide also a little more scientific authority for the director. One of the things we have to be concerned about in the future is what kind of authority and leadership the NIH director can command. So much goes on in categorical institutes that there is a danger of having ... very little for the NIH director to do but maintain conformance with broad policy issues. ...

Q: *How would that structure improve things?*

A: It would allow more flexibility in budget formulation. Priority setting wouldn't be quite as focused on what percentage increase each institute gets each year. Movement between fields would occur more effectively.

Q: *Is the NIH director's authority more limited than you expected?*

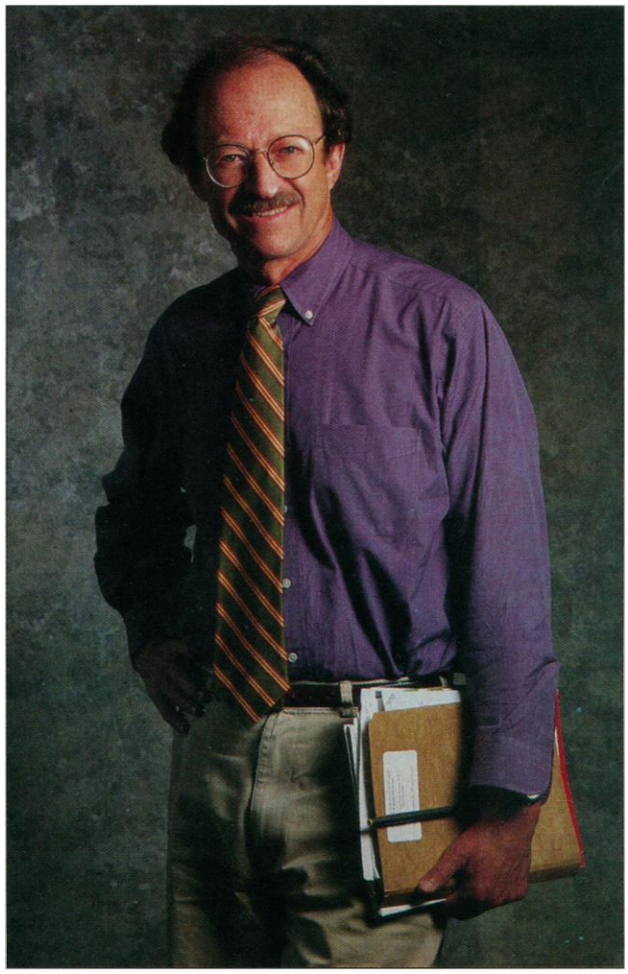
A: It's mixed. ... There is inevitably a kind of tension, because the institutes have independent authorities and independent budgets. I certainly have had the sense that it is difficult to follow through on scientific initiatives that I try to get under way myself. A good example might be malaria, where I've tried to push funding and develop international consortia. ... It is a slightly frustrating experience. Without a laboratory of my own I think I would feel pretty starved for scientific conversation.

Q: *What accomplishments have given you the most satisfaction?*

A: One is surviving a period in which the budget prospects looked very bleak. There was much amusement about my early speeches in which I emphasized living within a "steady state." But I do think that was a useful position to take. It was realistic. I think it gave NIH credibility. We were willing to say: Look, the budget situation is tough; if you can give us some reassurance of stability, that we're not going to get cut, we will try to live within reasonable means. I think that was a smart approach. With that reasonably high level of credibility within Congress and the Administration, we prospered when the economic status of the country improved.

Second, I would point to recruitments. I think I've been incredibly successful, and lucky, in not just attracting some good talent, but imbuing the scientific community with a sense that public service is something that people should look forward to in their career. A good scientist should say at some point, there is an opportunity here to pay back the federal government. And you can have a tenure in public office that is enjoyable, not inconsistent with thinking about science, and not even inconsistent with practicing some science. ... All those things have affected my ability to recruit institute directors, scientific directors, lab chiefs. ... We have had some colossal successes. ... The spirit in Bethesda is quite different.

We've also had success in trying to cope with the erosion of support for clinical research. One of the biggest issues that faced me when I came to NIH was the dilapidated condition of the clinical center, a sense that clinical research had had its day. ... Well, as you can see, we are building a wonderful new building. Clinical research has been given important lifts from new training that affects the extramural community and from a number of programs we've started intramurally.



PHOTOS BY SAM KITTNER

Q: *Is it healthy for a person to be director of an institute for 20 years?*

A: Not necessarily. [But] it may not be wrong. One of the things that I've done that may not have gotten as much attention as it should is that I've instituted 5-year reviews. I have a group of five or six people who go out and solicit opinions from a very broad swath of people who are affected by the institute and then I and the chair of the committee get back to the institute director the opinions that have been collected. Those opinions have made a difference. ... My personal feeling is that institute directorships should not be considered lifetime entitlements. The most healthy situation would be for people to come and do those jobs for 5 or 10 or 12 years. Less than 5 years is probably too short a time to have an imprint. As in any way of life, change is usually a good thing.

Q: *How substantial are the changes you've made in peer review?*

A: We have made some big improvements. Looking back on what I thought was important 5 or 6 years ago, there's no doubt that we've streamlined peer review in at least two important ways. First, by doing triage. On the whole, in 98% of the cases, it's been a very successful enterprise. Second, by implementing a modular grant formula so that you don't have to be so precise about your budget. You can submit your budget in $25,000 increments. That's clearly the wave of the future. It's essentially going to be implemented across the board. We've had some improvement in setting criteria for review, especially in putting innovation—novelty—into the review process. ... We've made a limited effort to incorporate the public into the review process. I started with a degree of skepticism. But in certain areas—for example, clinical trials—it's quite appropriate to have people who represent health care consumers. ...

Q: *What about unfinished work?*

A: There are a couple of areas where I think things have happened more slowly. Reorganizing the peer review study sections. That's now coming along. [National Academy of Sciences president] Bruce Alberts and his colleagues are doing the "boundaries report" [remapping the scientific jurisdiction of panels] and have published

a policy forum in *Science* (*Science*, 30 July, p. 666). I think we're on the right track. ... The other thing that's been disappointing to me is electronic review of grant applications. I thought we could get electronic submission and review into practice much more quickly than we have.

Q: *The Administration's computing initiative has fallen flat with Republicans on the Hill. Are you concerned that the NIH computing initiative could have similar problems?*

A: No ... I think we are prepared to make the case, and would be listened to by our appropriators, that computer science is undersupported, and that the flood of new genomic data and from imaging and other new fields of biological science demand personnel and software and hardware that we don't have. The competition from industry for talent and the undervaluing of computer scientists by our grantee institutions are problems that we need to rectify. ... This requires at least bidisciplinary training in computer science and biology. ... I'm reluctant to say, here is a request for $100 million. What we are saying is that [the computing initiative] is a consortium of many institutes—at least 10, maybe 15 new centers—to train and support computer scientists who know biology. It's a little bit here, a little bit there. There isn't going to be one package that can be cut.

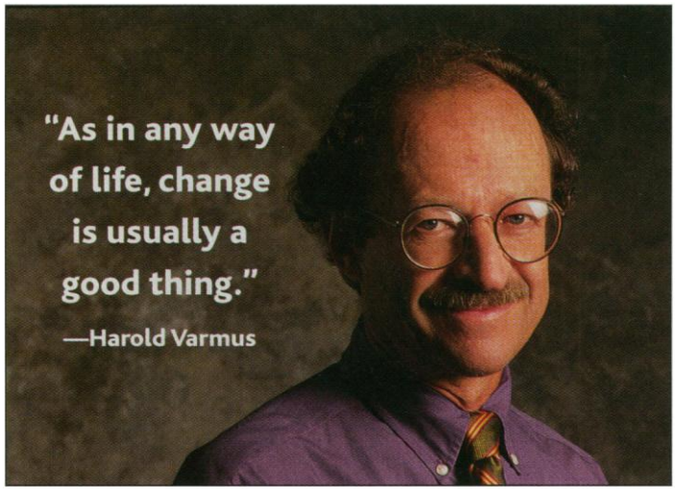
Q: *The Defense Advanced Research Projects Agency (DARPA) gives program chiefs great latitude to create new initiatives. People suggest that NIH and the National Science Foundation should adopt a DARPA-like philosophy. What do you think?*

A: I've been advocating that myself the last few years. ... The initiatives we're thinking about are much more expensive than the traditional grant and would be undertaken by teams. One novel effort is being made by the National Institute of General Medical Sciences where [director] Marvin Cassman has come up with "glue grants" in which investigators who work on a single problem—in one case G proteins—form a complex network and ask for money to support the whole endeavor. This group then identifies common needs and asks for money to help support building databases, getting certain structures done.

Q: *NIH plans to distribute scientific articles through PubMed Central. Suppose publishers went to Congress and complained that NIH is trampling on private enterprise: How would you explain the policy?*

A: We support the research; we want the research findings to be available to our communities in the easiest, most searchable way. If technology has given us the tools to promote the dissemination of the information, I think we should use them. ... We have an opportunity here to put anybody who has a desktop computer in contact any time day or night with the current scientific literature. That seems to me a very important public service.

Q: *Early this year, NIH enunciated a controversial policy of supporting the research use but not the derivation of human embryonic stem cells. If you could do it over, would you handle that policy any differently?*



A: No ... I solicited a legal opinion [from the Department of Health and Human Services] on what we could do legally. It is not my view necessarily of what should happen. ... I think we should be supporting research with embryonic stem cells. I also think we should be supporting research on the derivation of stem cells from spare embryos. It may not be politically appropriate to do that at this point. But that is my view, and it is a consistent view. ... I think any ethical evaluation has to take into account the consequences of not doing research that would benefit living people who have serious diseases now or in the future. I take that responsibility very seriously.

Q: *How useful is the Council of Public Representatives (COPR, a consumer advisory group created this year at Congress's urging)?*

A: That's hard to evaluate, because it has only met once. ... When we advertised the positions on the council, we got hundreds of applications from interesting and energetic people. Rather than say you're in, you're out, I said you're all in. Just 20 of you are on the council and the rest of you are COPR associates. And I would like to build on that cadre. ... They are our advocates out there in the community, and sometimes our critics. That's all right. I would like to expand the COPR associates to thousands, hundreds of thousands. Why not? It's a way of building an advocacy community that's really paying attention to the details.

Q: *On AIDS research: The field seems to have plateaued. Is it being funded well enough?*

A: I would say it's not a static situation. We are increasing our investment in vaccine development tremendously. And that also involves a very serious investment in immunology. I think we have here a novel problem in immune response, but one that will be applicable to vaccines against tuberculosis, malaria, hepatitis C, other organisms that coexist with a host even though there is a partial immune response. Secondly, we are making a greater effort in behavioral research in AIDS. Right now the emphasis has got to be on prevention. ... At the same time we are recognizing that there are serious deficiencies in even the quite good drugs that have been developed. There is much more interest in drug design than there was a few years ago, in understanding the nature of viral resistance to drugs and how drug combinations work together. It is a changing field; it's not static at all ... although the AIDS budget is no longer rising faster than the overall NIH budget.

Q: *How long will you stay in this job?*

A: I'm a presidential appointee. ...

Q: *Any regrets about what you were not able to do because you were in Washington?*

A: My [scientific] productivity probably could have been greater. Actually I've had a very good lab experience. ... I would rather have a little more time to read scientific literature.

Q: *Has it affected your physical training?*

A: Washington has been great for my physical training, because I live 12 miles from NIH. I ride [my bike] to work almost every day. I've also taken up sculling. The ideal day begins for me with a ride to the boathouse, about 4 miles, then I row for 45 minutes, then I ride my bike out to [NIH], then ride home after work through Rock Creek Park. That's a beautiful day.