As it nears the final year of an unprecedented spending spree, the world's largest biomedical research organization has no permanent leader in sight

Who Will Be Custodian of the Crown Jewels?

THE FUTURE OF NIH

The lack of a permanent director, at a time when NIH's budget boom is about to end, is causing increasing concern. This special news package looks at the issues facing the next director of the world's leading biomedical research institute.

Before he resigned in December 1999 as director of the National Institutes of Health (NIH), Harold Varmus tried to pave the way for a successor. He asked his superiors to send the White House a list of names headed by Gerald Fischbach—a former Harvard University neurologist he had helped recruit in 1998 to lead the National Institute of Neurological Disorders and Stroke. Varmus reasoned that an internationally known scientist and an outsider with a vision of where NIH should be headed—a replica of himself—would be the best person to build upon his successful 6-year stint, which included a planned doubling of the NIH budget in 5 years.

But Varmus's cloning experiment ran afoul of politics. One powerful legislator said he wanted to continue working with Ruth Kirschstein, Varmus's deputy and a consummate insider (see profile). The Clinton White House—worried that any nominee might trigger a battle in Congress over the sensitive issue of embryonic stem cell research—did not act. As a result, this month marks Kirschstein's 18th as acting director of the $20 billion biomedical colossus, while Fischbach ended his short career as a civil servant last year and returned to academe as medical dean and health affairs chief at Columbia University.

With the rumor mill churning out the same stale names, researchers are beginning to ask how much longer the world's biggest and most prestigious biomedical research agency can thrive without a permanent chief. Their concerns coincide with NIH's need to chart a soft landing after the budget doubling ends in 2003 (see p. 1992). The transition from wildly inflationary to just moderate growth could reawaken some of the old tensions that wracked the community in the early 1990s, when competition for funds was intense. How well NIH is prepared for that new era has become a burning question for the biomedical community.

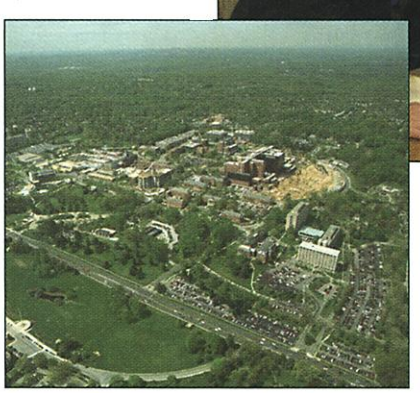
"NIH needs a leader who has a clear mandate from the White House to do the job," says oncogene researcher Michael Bishop, chancellor of the University of California, San Francisco, who shared a Nobel Prize with Varmus in 1989. The NIH chief is not just a spokesperson for biomedicine but a champion for all of science, says Maxine Singer, president of the Carnegie Institution of Washington in Washington, D.C., who finds it "discouraging" that no appointment has been made.

Apart from money, one of the touchiest subjects for the next NIH director will be the government's policy on human stem cell research. The Clinton Administration had planned to permit funding of some research on human embryonic tissue. But the Bush Administration, facing conservative opposition, is backing away. Future policy has been debated intensely at the White House in the past few weeks—all the way up to the president's office, according to disease advocacy groups involved in the talks. There was no decision at press time, but community leaders say that the uncertainty about stem cell policy could make it more difficult to recruit "the very best" scientist as NIH director.

Running on momentum

The NIH powered through the 1990s with a tremendous burst of energy. It was fueled by new money and a novel kind of leadership. Varmus brought an outsider's perspective to NIH, with the goal of making it seem less like a government agency and more like a hot-shot academic center.

A Nobelist in molecular biology, Varmus imported his lab from California and continued to oversee postdocs' research during his entire directorship. In public meetings, he affected the informal dress of an academic. And with the support of his boss, Health and Human Services (HHS) Secretary Donna Shalala, he took steps to make NIH more welcoming to other members of the academic elite. A series of administrative changes



$20 billion boardroom. NIH acting chief Kirschstein (second from left) oversees a weekly meeting on campus *(inset)* of institute and center directors and senior staff.

CREDITS: (TOP TO BOTTOM) MARTY KATZ; NIH

Ruth Kirschstein and Alan Rabson

Every institution has a hidden wiring plan. At NIH, the circuits all seem to connect to Ruth Kirschstein. For more than 4 decades, she and her husband Alan Rabson, both M.D.s and civil servants, have worked and lived on NIH's tree-shaded campus in Bethesda, Maryland. That's a lifetime of service as colleague, friend, and supervisor of the government's top biomedical scientists.

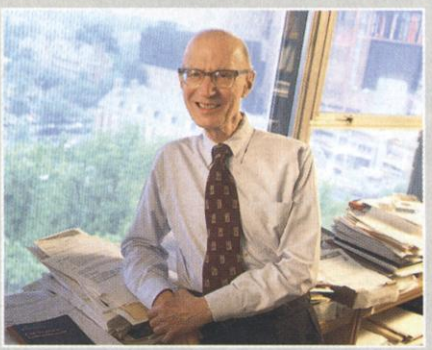
Kirschstein, 74, is NIH's acting director. She took on the job in January 2000, succeeding Harold Varmus, under whom she served for 6 years as deputy director. Rabson is deputy director of the oldest and largest part of NIH, the National Cancer Institute (NCI). Unofficially, Rabson also has been a troubleshooter for institute director Richard Klausner and counselor to scores of worried patients, including senators and celebrities. The secret of their long-lived success? Instead of making waves, Kirschstein and Rabson make friends and allies.

"I had always wanted to come to this place," says Rabson about the campus he first visited in 1952 during a sightseeing trip to the nation's capital. Three years later the couple moved to Bethesda from New Orleans, where Kirschstein had been teaching at Tulane University School of Medicine and Rabson had been a Public Health Service pathologist. Rabson went to a pathology lab at NCI, and Kirschstein became the first clinical pathologist at NIH's clinical center. A few years later they rented a house on the NIH campus—one of a handful then available to officers in the Public Health Service—in which they still live. Their son, molecular geneticist Arnold Rabson, grew up on the NIH campus, played in its labs, and is now an associate professor of molecular genetics and microbiology at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School.

"I love it," says Kirschstein about NIH. "This has been my whole life; I have never worked anywhere else." After completing her residency at the clinical center, Kirschstein moved into NIH's division of biologics, which later became part of the Food and Drug Administration. She helped identify a disease-causing batch of oral polio vaccine in trials and developed new tests which identified the Sabin vaccine as the best for public use.

In 1974, Kirschstein began climbing the NIH administrative ladder, becoming director of the National Institute of General Medical Sciences (NIGMS). The first woman to head any institute, she supported rapidly moving developments in cellular and molecular biology, says Maxine Singer, president of the Carnegie Institution of Washington in Washington, D.C. In 1990, while director of NIGMS, she also served as the first director of the women's health program.

At home. Kirschstein and Rabson have held high-level positions at NIH for 3 decades; they've also lived on campus since the 1950s.



As NIH's top official, Kirschstein stresses the importance of balance and stability. That contrasts with her predecessor, who encouraged turnover because "change is healthy." Kirschstein concedes that there's a risk of complacency "if people go a very long time." But she adds quickly, "I haven't seen that." **–E.M.**

CREDITS: KAY CHERNUSH

gave the NIH director more authority to recruit top staff and offer higher salaries.

Varmus also followed through on recommendations from a review panel that proposed changes to improve science on campus. Young scientists got a clear set of guidelines on how they could advance through the system to achieve "tenure" at NIH. For the first time, Varmus organized formal 5-year performance reviews of the institute directors. And he lobbied the institutes to kick in money from their own budgets for joint research projects on targeted initiatives, like sequencing the mouse genome, that no single institute could afford on its own. The value of such trans-NIH initiatives is open to question, however. National Cancer Institute (NCI) director Richard Klausner, for example, thinks joint projects work only when they arise from the "scientific grassroots"—in particular from the institute directors.

The first challenge for the next NIH director, some say, will be to win the cooperation of those directors and to fill vacancies with outstanding scientists. During Varmus's 6-year tenure, 16 new institute directors were appointed. Three have since left, and one major position—the directorship vacated by Fischbach—remains unfilled at the time of this writing. Recent years have been "good times for recruiting," Kirschstein notes: "Once you recruit one or two good people, others want to join." Although she believes that NIH has sustained the momentum built up under Varmus, one of his recruits says, "we're all waiting to see who's the next boss."

Varmus also wanted to boost the authority of the NIH director's office and cap the number of independent fiefdoms. During his tenure at NIH and after, Varmus decried the "proliferation" of NIH administrative centers, arguing that "having more institutes also means less flexibility, less managerial capacity, less coordination, and more administrative burden" (*Science*, 9 March, p. 1903). He proposed merging the current 27 centers and institutes at NIH into half a dozen and argued unsuccessfully against the creation that year of the National Institute of Biomedical Imaging and Bioengineering. More proposed institutes are "waiting in the wings," he warned, and should be resisted.

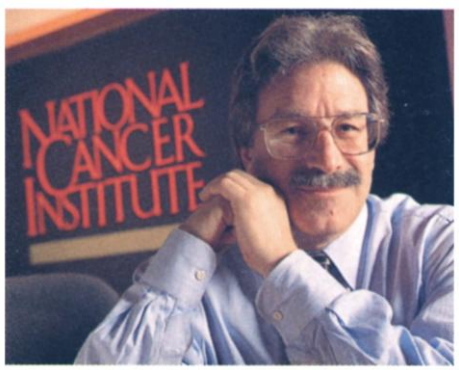
But the idea of streamlining NIH's structure is "not popular," says David Nathan, a former member of the NIH director's advisory committee and former president of the Dana-Farber Cancer Institute in Boston. Kirschstein isn't sure that proliferation is a problem, either, although she didn't respond directly to a question about it. "There was a time when people thought that if there were new institutes, every institute would gain," she says. "For a while that was true, but it remains to be seen if it is true now."

The NIH director's most important job, says one insider, is to express a vision "that can blow you away." Nathan believes that the NIH director "ought to be a good teacher, the kind of person who can really explain things." Shalala, now president of the University of Miami, emphasizes the need to instill a sense of trust: "You can't miss a beat.

THE BIG THREE

NCI's Richard Klausner

At 49, Richard Klausner is the youngest member of NIH's inner circle. He also has the largest portfolio. As director of the $3.74 billion National Cancer Institute (NCI), Klausner controls a budget some 150 times that of the NIH director, a job for which he has been frequently rumored to be a candidate. On the other hand, the NIH director possesses greater visibility and political clout, attributes that mesh with Klausner's reputation as a hard-driving and ambitious administrator. He also has an independent streak, as one high-level NIH staffer says, sometimes conveying the message that NCI might "secede from the NIH."



Moving the mountain. Richard Klausner seeks to redefine cancer in molecular terms.

Like the chiefs of other big NIH institutes, Klausner rose through the ranks of federal service, starting in 1979 at NCI's lab of mathematical biology. His transition from a cell biology branch chief to institute director was fueled by a reformist zeal. In 1992, he chaired an internal committee that found fault with NIH's intramural research program. The "Klausner report" sparked an external review, chaired by microbiologist Gail Cassells and oncologist Paul Marks, that called for radical changes in lab management, stronger scientific reviews, more open recruitment methods, and better training of young scientists. Harold Varmus began to implement the recommendations after becoming NIH director in 1993, and in 1995 he selected Klausner to lead NCI.

Klausner immediately announced that he wanted to "change the culture" by making NCI less hierarchical and more like a competitive university research center. Klausner says he wants to rebuild cancer research on the foundations of molecular biology and rely less on trial-and-error testing of drug compounds. Most of his peers seem to agree. "I think [Klausner] transformed the place," says David Nathan, former president of the Dana-Farber Cancer Institute in Boston. "He also has promoted critically important initiatives, like developing mouse models of human cancer. ... They're really going to help us predict what will happen in clinical trials." Observers also praise his support for new technologies and his skillful use of strategic planning.

As for the top NIH job, however, his prospects are less clear. Klausner was one of several people that the White House interviewed earlier this year for the post, although he declined comment. But in recent weeks biomedical lobbyists say that Klausner's name has dropped off the list. **–E.M.**

THE BIG THREE

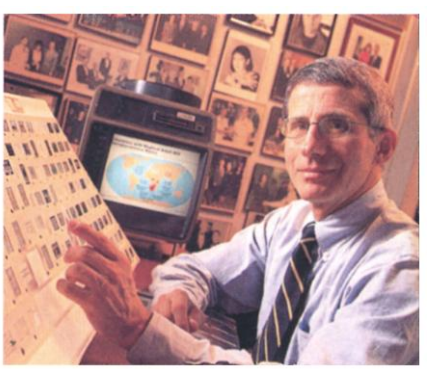
NIAID's Anthony Fauci

Tony Fauci may be the only scientist who has declined offers to run NIH by two different presidents—both named Bush.

Fauci, the 60-year-old AIDS researcher and director of the National Institute of Allergy and Infectious Diseases (NIAID), won't answer questions about his visit to the White House earlier this year. But another NIH official says that Fauci has fended off an offer because he doesn't want to give up his leadership post at NIAID, the third-largest NIH institute. An arrangement allowing him to wear both hats seems unlikely.

Fauci confirms that he was offered the NIH directorship before —in 1989, by former President George Bush (*Science*, 17 November 1989, p. 880). "I knew the president pretty well because I had briefed him many times on HIV-AIDS," says Fauci. That relationship made it easier for him to tell Bush père in person that he preferred to focus all his energy on fighting AIDS.

Still, Fauci's name keeps turning up on a list of candidates for NIH chief. Colleagues say he'd be ideal for this Administration: a Jesuit-educated Catholic with strong family connections to the Republican Party. He's a team player and a workaholic who routinely puts in 13-hour days, comes in on weekends, and sees patients every Wednesday and Friday in the clinical center. He also oversees the Laboratory of Immunoregulation, which includes five independent researchers and his own section, which studies the pathogenic mechanisms of HIV. His role as the leader of U.S. AIDS research gives him international recognition. And AIDS activists who once branded him a "murderer" during protests against government policy in the 1980s now embrace him.



Draft pick. Anthony Fauci's peers want him to become NIH director, but he likes his present job.

Fauci's credentials with his peers are no less impressive. He's a trusted NIH insider, a 32-year veteran of NIAID who began as a clinical investigator and moved up the ranks in two hops before becoming director in 1984.

So just how urgently does NIH need a permanent director? Fauci himself thinks that the problem is "more perception than reality." For one, he says, "the place isn't going to go to pieces." The director's main job—raising funds—has been solved by the doubling drive, he adds, and the House, Senate, and White House are "all on board." Although it would be "nice to have a permanent person" at the helm, he says, the current situation at NIH "is as good as it gets." **–E.M.**

... NIH has to continue to demonstrate that these extraordinary increases are going to be well spent." But all agree that it's difficult for anyone without the president's backing to design a grand strategy for NIH.

Holding the fort

For now, the responsibility of leadership falls to Kirschstein, a dedicated civil servant who has been in NIH headquarters, "Building 1," for the past 8 years. She and her husband, Alan Rabson, deputy director of the NCI, have worked—and lived—on the NIH campus since the mid-1950s. Their extraordinary tenure, combined with those of other long-serving institute directors and top administrators, provides an institutional memory that keeps the NIH on course.

In a recent interview, Kirschstein said she's very comfortable in the top job because "I have been here a long time ... and I know NIH." It would be "tempting," she added, "to be passive when you're in an acting capacity, but I have no intention of doing that; there's too much exciting science going on."

Still, Kirschstein seems likely to take her cues about scientific initiatives from other directors. And her own goals and methods of advancing them are more consensus-oriented than her predecessor's: "I would never dream of saying to an institute director that this is an initiative I want to

CREDITS: KAY CHERNUSH

do." Instead, she says, "we would sit down and talk about plans together."

Asked to cite an example of a new project that interests her, Kirschstein mentioned a "biomedical infrastructure network" called the Institutional Development Award (IDeA) program. A darling of Congress, which last year more than doubled its funding to $100 million, IDeA now funds special offices in 23 states and Puerto Rico to enable their researchers to compete more effectively in peer review. Its aim is to distribute NIH's largesse over a broader geographical area. The program, modeled after one at the National Science Foundation that began 20 years ago, languished during the Varmus era—and got a chilly reception last week when Kirschstein described it to the NIH director's advisory committee. But she likes it.

Kirschstein also stresses the importance of investigator-initiated grants, NIH's bread and butter. "The first commitment we all have is to the individual research grant," she says. An old assumption that one-third of applications deserve funding may understate the quality of the ideas being submitted, she adds, noting with approval the testimony of some NIH institute directors that the rate could rise to 40% or 45% without sacrificing quality. But more funding must also go into "shared resources," she notes, to improve access to data collections and expensive instruments like synchrotrons and imaging machines.

One area where Kirschstein seems to have been far ahead of the curve is in her concern about underrepresented groups in biomedicine: "I have been an advocate [for women and minorities] since the first day I came to NIH" in the 1950s. In 1974 she became the first woman appointed to run an institute—the National Institute of General Medical Sciences, the focus for basic science. The NIH's current lineup of three women and two African-American directors (out of 27) "is not enough," she says. Most recently, she supported the creation last year of the National Center on Minority Health and Health Disparities, bucking Varmus's no-more-institutes principle. Kirschstein is widely praised for her efforts on behalf of the disadvantaged and for preserving NIH programs in that area despite legal attacks on affirmative action.

But stability and collegiality are not necessarily enough to get NIH through uncharted waters. Although it would be an exaggeration to say NIH is on autopilot, it's in "a caretaker mode," says Gerald Rubin, the chief scientific officer of the Howard Hughes Medical Institute in Chevy Chase, Maryland. "We're pointed in the right direction, ... but the landscape is going to change, and you have to be concerned about whether we're going to run ashore."

The Bush White House has avoided any comment on potential candidates for permanent NIH director, and Bishop says the rumor mill "has never been quieter than it has been in the last month." Earlier in the year, it was filled with the names of several inside candidates—including Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), Klausner, and Steven Hyman, director of the National Institute of Mental Health. There were also reports that prominent Texans might be in line for the job, among them cancer researcher John Mendelsohn, president of the University of Texas M. D. Anderson Cancer Center in Houston, and Nobelist Michael Brown, a molecular geneticist at the University of Texas Southwestern Medical Center in Dallas.

But Mendelsohn and Brown have said they have not been formally interviewed by the Administration—and both say they're inclined to stay in their current jobs. Klausner was one of several interviewed by the White House but is rumored to be off the list. At this writing, Fauci remains the most visible candidate. But he also wants to remain in charge of his current portfolio at NIAID, an unlikely pairing. Current HHS Secretary Tommy Thompson hasn't said anything on the subject other than to grumble that the nomination process is so slow it's "ridiculous."

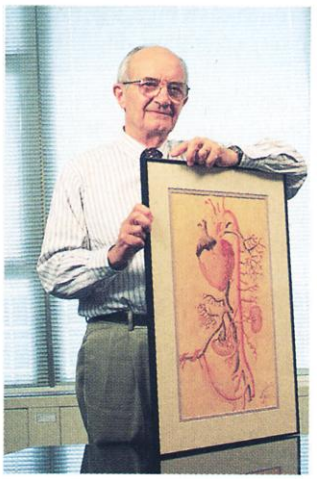
It took the Clinton Administration almost 9 months to get Varmus vetted and confirmed, and it may take at least that long to get the next permanent NIH chief in place even after a nominee is in sight. In the meantime, biomedical researchers are praying that NIH—steaming forward toward a budget that will have doubled within 5 years—doesn't run into any really foul weather. **–ELIOT MARSHALL**

THE BIG THREE

NHLBI's Claude Lenfant

The longest tenured NIH institute chief is Claude Lenfant, director for the past 19 years of the National Heart, Lung, and Blood Institute (NHLBI).

Lenfant, 73, trained to be a heart surgeon at the University of Paris in the 1950s and served on the first team that performed open-heart surgery in France. He patented an extracorporeal pump for blood circulation but says he "never made a penny" on it. He then refocused his work, studying blood-gas exchange and becoming a professor of physiology and biophysics at the University of Washington, Seattle. Lenfant came to NIH in the early 1970s to run its new lung research program after sending NHLBI a letter on how it should be organized. In 1982 he was promoted to director of NIH's second largest institute, which has a current budget of $2.3 billion.



Stalwart. Long-tenured NHLBI chief Claude Lenfant emphasizes public health and clinical research.

Lenfant is a champion of clinical research and somewhat uneasy about the 1990s gold rush in molecular medicine. Sometimes, he says, people at NIH act as though "if you don't talk about molecules, you don't do anything." But he believes that his philosophy fits squarely into NIH's mission: "My goal is to see that basic research is applied ... to the practice of medicine." He worries that "much of the research we do becomes an academic trophy. I don't like that. I am very interested in public health." He boasts that "one of my best investments" is a $15 million program to train ambulance crews and speed up treatment of heart attack victims.

Although he holds strong beliefs, Lenfant may owe his long run at the helm to his receptivity to new ideas. "I think he actually has gone with the flow," says Thomas Caskey, a molecular geneticist at Baylor College of Medicine in Houston and former Merck Co. executive, who says that there was a period in the early 1990s when NHLBI lagged in its support of molecular research on heart disease. When people pointed this out, the institute responded. "You might say he didn't move soon enough," Caskey notes, but the fact that Lenfant did move shows that he "has been a good administrator." The cardiovascular research community "thinks highly of him" and his skills as a manager, adds an NIH insider.

Lenfant seems to enjoy his seniority, and he's good at defending his status. "He's as territorial as hell," the staffer says. According to several sources, the two previous NIH directors—Bernadine Healy and Harold Varmus—took a run at Lenfant but backed off after realizing that he isn't easy to budge. **–E.M.**

CREDIT: KAY CHERNUSH