Conflicting Agendas Shape NIH

In Part II of a probe of NIH, *Science* finds many constituencies—including disease activists and basic researchers—struggling for control of the institution's direction

Two decades ago, during the halcyon days of the National Institutes of Health (NIH), almost every worthy grant application from an outside researcher was funded, the in-house intramural program attracted the finest investigators in the land, and Congress was a generous, unobtrusive benefactor, always willing to pick up the check today for the promise of curing deadly diseases tomorrow. "Almost by definition, biomedical research is a beast that has unlimited aspirations, but in the 1960s, the aspirations were exceeded by the resources. We called people and said, 'Send in your grants,'" recalls Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases, who has been at NIH 25 years. Now, says Fauci, the situation is reversed: Aspirations far outstrip resources.

One measure of the disparity is that the percentage of investigator-initiated grant proposals receiving funding has dropped sharply: from 49% of all submitted proposals in 1965 to 27% in 1992. And that trend is likely to continue, which means "we're going to have to prioritize in a way that we've never had to before," says Fauci. As a result, he adds, "tensions start growing."

What is more, Congress no longer is willing to play the role of unquestioning benefactor. Staffers on Capitol Hill are beginning to demand tangible returns in place of promises of future cures for the $11 billion in taxpayers' money NIH consumes each year. A congressional staffer who insisted on anonymity says that, after investing billions of dollars, decade in and decade out, "the public should be realizing some very specific improvements affecting its health." In fact, the same staffer argues that "it's time to cure a disease. A major disease. Dramatically alter the course of a major, disabling disease. For $11 billion a year, they ought to be doing it.... They've given us building blocks, stepping stones, elegant basic science. Those are important steps—but they aren't the final products that the taxpayers are investing in."

Many highly respected extramural researchers, however, argue that the Congressional staffer's opinion is wide of the mark. Among many examples, they point out that NIH-sponsored research has made it possible to cure some childhood leukemias. They note that NIH research led to screens for hepatitis B and HIV, dramatically increasing the safety of blood transfusions. NIH also helped develop positron emission tomography and magnetic resonance imaging, technologies that have fundamentally altered our understanding of the brain and its disorders. Furthermore, they argue, the large investments made in oncogene research and research on heart disease may be on the verge of enormous clinical payoffs for the "major diseases" the Congressional staffer is concerned about.

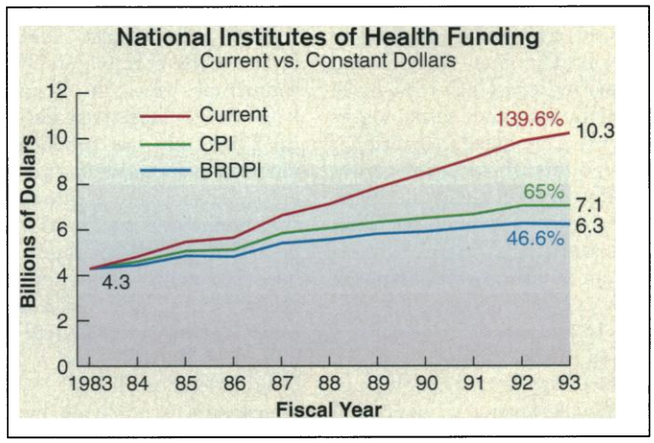
Nevertheless, NIH is clearly under pressure to produce, and as it considers how to achieve maximum productivity, it must face some fundamental ambiguities in its mission. One ambiguity lies directly in the center of the NIH franchise: progress against disease. The basic research community argues that cures and vac-

NIH: A House Growing Rapidly, But Without a Blueprint

Every year, NIH crafts a statement of mission for its congressional overseers. The latest version, written for the fiscal 1994 budget hearings (held last spring), says that "through the conduct, support, and promotion of biomedical research, NIH pursues science to expand fundamental knowledge about the nature and behavior of living systems, to apply that knowledge to extend the health of human lives, and to reduce the burdens resulting from disease and disability." Such a statement suggests an institution in the process of being constructed from a clear blueprint, but in reality NIH is more like a spacious Victorian house to which rooms have been added, one after another, with the needs of the present, rather than any carefully thought out design, guiding construction.

That trend has been visible from the beginning, in 1887, when the federal government allocated $300 for a one-room Laboratory of Hygiene in the attic of the Staten Island Marine Hospital. By 1938, NIH (at that time the singular National Institute of Health) had broken ground at what is now a 300-acre campus in Bethesda, Maryland, and the National Cancer Institute (NCI) had been formed. The pattern of growth without clear central direction continued in 1945, when the extramural program was created by Congress with little discussion or definition. This led to the formation of study sections to review investigators' proposals for funding, study sections that remain the backbone of the extramural program (see sidebar on page 1678).

When Congress launched the National Heart Institute in 1948, NIH became the plural National Institutes of Health, and new individual branches followed quickly. The institutes were named after diseases and organ systems, a "literary device," in the words of NCI director Samuel



Going up. Even when adjusted for inflation by the Consumer Price Index or the more liberal Basic Research and Development Price Index, NIH funding increased substantially in the last decade.

cines can come only from undirected fundamental science and bristles at any attempt to impose targets on its research. Yet the increasingly vocal groups of people with AIDS, say, or breast cancer are calling for research to be organized and directed from the top—because they want cures now. The tension between these views is present in every debate over the research agenda of NIH. Until recently, a growing financial pie has made it possible to give increasing amounts to both basic and targeted research. In an era of financial constraints, however, it isn't possible to keep everyone happy that way.

Another ambiguity in the charter of NIH is the ongoing struggle to define the specific functions of the intramural and extramural programs. The first part of *Science*'s probe of NIH centered on the intramural program and the concerns, expressed by many leading researchers, that this jewel in the biomedical research crown may be losing its luster (27 August, p. 1120). But the intramural program is overshadowed in numbers and funds by the extramural program, which supports 50,000 researchers at 1700 institutions—and consumes about 80% of NIH dollars. Although some researchers argue that the two have distinct functions, others disagree—and, in fact, no precise division of labor has ever been worked out between them.

DONNA BINDER/IMPACT VISUALS

Storm over Bethesda. AIDS activists protest on the NIH campus, demanding participation in designing clinical trials.

In the decade to come, the endemic tensions between basic and directed research, between intramural and extramural programs are likely to grow, and so far no one has been able to synthesize these competing agendas. Former NIH director Bernadine Healy tried to strike a balance in her "strategic plan" for the institution's future. But her efforts displeased many basic researchers, who thought that it oversold the direct health benefits of NIH and shortchanged the importance of investigator-initiated science. "The best place for [Healy's strategic plan] would be at the bottom of a desk drawer," says Harold Schachman, a University of California, Berkeley, biochemist.

That kind of reaction puts Harold Varmus, nominated to succeed Healy, in a difficult position: Without a strategic roadmap for producing clinical results, NIH may not be able to maintain its political support; yet the notion of such a roadmap is anathema to Varmus' peers in the basic research community. Therefore, eager as Varmus may be to push NIH in the direction of more funding for basic science, he will have to deal with the pressures from activists and from Congress for cures—soon. He will also have to address Congress's stated demands for a careful review of the relationship between the intramural and extramural research programs. Like Healy, Varmus will be forced to try and define how the parts of the NIH mission fit together. And he will have to do so within the limits of an NIH directorship that many insiders say has been losing power since the 1960s.

These issues are the subject of the second part of *Science*'s probe of NIH. Over the past 6 months, *Science* has discussed the tension between basic and directed research and the functions of the extramural and intramural programs with more than 100 researchers, congressional staffers, scientific administrators, and disease activists. Interviews with these knowledgeable players show they have widely varying ideas, and as Varmus defines his vision, he'll have no shortage of input from this increasingly aggressive group. How he reconciles their conflicting priorities will have a lasting influence on the future health of a program intended to ensure the future of the nation's health.

Broder, that enables the lay public and Congress to identify with the goals of NIH research that often have little direct relation to diseases or symptoms.

This unplanned, politically driven genesis had three significant effects on the character of NIH. The first is that the institution, according to many insiders, including those who have led it, has become a group of largely independent fiefdoms: institutes led by directors who consider themselves the final authority on matters affecting their programs. The second is that the intramural and extramural programs, though perhaps initially distinct, have tended to overlap as the decades passed. Finally, the "literary device" of justifying basic research under the umbrella of diseases has become a double-edged sword: Although it encourages the public to offer generous support to biomedical research, it also encourages lay people to think they should have a significant role in setting the research agenda. The rest of this story spells out the costs—and benefits—of these three fundamental characteristics that define NIH.

The Role of the NIH Director: Can the Center Hold?

"I've always referred to [NIH] as a federation," says William Raub, who spent 25 years there, including 2 as acting director. According to Raub and other NIH insiders, the powers that make up the federation are the institute directors (see table on page 1676). As NIH has grown, the institute directors have gained power, while the authority of the NIH director has decreased sharply.

By most accounts, the NIH director had real clout until the late 1960s. It was then that the institute directors started down a road that led to their becoming independent powers, able to challenge the NIH director when they feel they need to. Many insiders say the shift began in 1967, when the National Institute of Mental Health split from NIH. Then, in the early 1970s, a campaign led by an influential medical research advocate, Mary Lasker, further weakened the director's power. Lasker convinced Congress to boost NCI's budget and give it special powers, including a budget that—unlike the budget of the other institutes—bypassed the NIH director and went directly to the president. "Cancer really led to the disintegration of NIH," says Donald Fredrickson, who headed NIH from 1975-81. "There was an attempt to separate cancer from the rest of biology."

NCI's new powers created what one official NIH historian refers to as "organizational envy." In 1972, the heart institute convinced Congress to change its designation as an institute to the more powerful "bureau" (a title since done away with). "The net effect [of these changes] was to strengthen the role of institute directors," says Wyngaarden. "Every one of those moves took something away from the authority of the NIH director."

Former director Bernadine Healy, who clashed frequently with some of the institute directors, says she was outraged at what she sees as a lack of accountability on the part of institute directors. "They don't think they're accountable to anybody," says Healy. "In

fact, they don't even think they're accountable to the NIH director." She says the imbalance of power stems from the fact that "NIH directors are turned over every couple years, and the institute directors seem to be tenured for life."

That lifetime tenure, in her opinion, reflects the fact that the institute directors are not rigorously enough evaluated. In an interview with *Science* earlier this year, Healy said she thinks institute directors should have renewable contracts that are evaluated every 5 years by an outside panel. "Anybody in an administrative leadership position where they don't have rigid accountability, where their job isn't on the line—it just isn't healthy. There are some NIH directors who are fabulous and there are some who aren't so hot, and that needs to be looked at," she adds.

Acting NIH director Ruth Kirschstein, who served as director of the National Institute of General Medical Sciences for 18 years, disagrees sharply with Healy's assessment. Kirschstein points out that the NIH director does performance reviews on all institute directors, each year, and she says the system "is working quite well." Healy concedes that the NIH director is charged with reviewing the institute directors but argues that since the directors are appointed by the Department of Health and Human Services—not the NIH director—the relationship is ambiguous. She adds: "Someone will challenge me and say 'What do you mean, we have a rigorous SES [Senior Executive Service] evaluation.' Baloney! It's perfunctory. It should be changed."

Eugene Braunwald, an NIH alumnus who is now chairman of medicine at Brigham and Women's Hospital, agrees that the NIH director needs more authority. "There's so much overlap between the institutes in terms of interest and what they support that they often require coordination," he says. "Science and medicine are overarching and there should be a central or corporate power. [At NIH], the right hand sometimes doesn't know what the left hand's doing." He adds that the NIH director has "very little budget authority" because each institute has its own line item budget.

Kirschstein disagrees. She thinks there is a good power balance between the NIH director and the institute directors: "I really believe this is a partnership, and I think that's what Congress had in mind when—in what I consider a stroke of genius—it set up the budgets separately." Furthermore, Kirschstein doesn't think the institute directors are subordinates of the NIH director: "As far as I'm concerned the institute directors are the board of directors, if you want to use corporate terms, for the NIH director."

MEMBERS OF THE FEDERATION: NIH INSTITUTE DIRECTORS

Institute Director	Research Institute	FY93 Budget (millions)	Years in Job
Samuel Broder	National Cancer Institute	1978	4
Carl Kupfer	National Eye Institute	276	23
Claude Lenfant	National Heart, Lung, and Blood Institute	1215	11
Anthony Fauci	National Institute of Allergy and Infectious Diseases	988	8
Lawrence Shulman	National Institute of Arthritis and Musculoskeletal and Skin Diseases	212	6
Duane Alexander	National Institute of Child Health and Human Development	528	7
Harald Löe	National Institute of Dental Research	161	10
Phillip Gorden	National Institute of Diabetes and Digestive and Kidney Diseases	681	7
Kenneth Olden	National Institute of Environmental Health Sciences	251	2
Marvin Cassman*	National Institute of General Medical Sciences	832	<1
Richard Hodes	National Institute on Aging	399	<1
Murray Goldstein	National Institute of Neurological Disorders and Stroke	599	10
James Snow	National Institute of Deafness and Other Communication Disorders	155	3
Donald Lindberg	National Library of Medicine	113	9
Ada Sue Hinshaw	National Institute of Nursing Research	48	6
Philip Schambra	Fogarty International Center	20	5
David Rodbard	Division of Computer Research and Technology	49	2
Saul Rosen*	Clinical Center	221	3
Jerome Green	Division of Research Grants	36	7
Judith Vaitukaitis	National Center for Research Resources	313	<1
Francis Collins	National Center for Human Genome Research	106	<1
Frederick Goodwin	National Institute of Mental Health	583	1
Richard Millstein*	National Institute on Drug Abuse	404	1
Enoch Gordis	National Institute on Alcohol Abuse and Alcoholism	176	7

*Acting

Extramural vs. Intramural: Is There a Difference?

Given the disparity of opinions on whether the NIH director needs a stronger hand, Harold Varmus is going to have a tough time getting a consensus on whether his own authority needs beefing up. And that isn't the only subject on which the institution seems to be lacking in consensus. Another is the vexed question of whether the intramural program ought to have a different function from the extramural program.

Little help on this problem is likely to come from official documents. The 1993

mission statement, like most of its predecessors, makes no mention of such a distinction. To be sure, many proponents of basic research don't see a problem in this blurry border: They contend the two programs have the same aim—supporting the best science, wherever it is. Others, however, believe the intramural program has a unique mission: moving research into the clinic quickly and supporting risky research that wouldn't otherwise get funded. These researchers, many in the intramural program, think the lack of a clearly drawn distinction is a serious shortcoming.

Among those who believe the functions of the two programs should be clearly delineated is Congress. As members of the House appropriations committee wrote this past June in a report accompanying the fiscal year 1994 budget, they are concerned that there is no "well thought out division of labor" between the intramural program on the Bethesda campus, which receives 11% of the budget, and the vastly larger extramural program that supports biomedical research across the country.

"BY TARGETING TOO CLOSELY WHEN WE'RE NOT REALLY READY, WE SLOW DOWN BASIC RESEARCH."

BERNARD FIELDS

One researcher who supports the notion of a clear difference between the two programs is Carl Kupfer, head of the National Eye Institute and a 23-year NIH veteran. For Kupfer, the distinguishing feature of the intramural program is the Clinical Center, with 540 beds. He argues that the intramural program's mission is to exploit this resource by moving basic research to the bedside quickly. "The intramural program should be doing things that can't be done on the outside," says Kupfer. This function, he says, ought to be supplemented by research in areas where the extramural community isn't doing vigorous enough work to "really make an impact"; as an example, he cites cataract research.

Yet many researchers—including some in the intramural program—do not believe the intramural program operates this way. "In the area I work in, there aren't things that could only be done in the intramural program being done here," says Igor Dawid, a developmental biologist at the National Institute of Child Health and Human Development. "No basic biology anywhere is unique. It's different in physics if you only have one cyclotron." When asked whether he thinks the intramural and extramural programs have different missions, Frank Fitch, president of the Federation of American Societies for Experimental Biology, says, "I must confess, I do not." Stanford immunologist Irving Weissman goes a step further: "The intramural program sometimes pretends to be different, but I think it's almost exactly the same as the extramural program."

But if the intramural program does the same thing as the extramural program, many extramural researchers ask why the $1 billion a year bestowed on the intramural program shouldn't just be given to academic researchers. Many of those asking the question are hardly disinterested, but others with less obvious self-interest agree that something is wrong if the programs are identical. Healy says that if the intramural program "is a clone of the extramural program, then we should close it." But, she adds, "I don't think it is." Healy's strategic plan echoes Kupfer's view in saying that the intramural program should foster "innovative, risk-taking science" and, in its clinical facilities, provide "a proving ground for the entire biomedical research enterprise."

But when intramural scientists do take risks, they can find themselves in an uncomfortable position. Take a senior researcher at the National Institute of Neurological Disorders and Stroke. The researcher, who insisted on anonymity, strongly believes that because intramural researchers don't have to apply for grants, they should take scientific risks. He says he's followed his own advice and picked several projects without guaranteed payoffs. As a result, he says, he's gone 4 years without publishing. "I'd be dead in the extramural community."

Yet this researcher (whose overall publication record shows he's quite reputable) says the extramural researchers on his institute's board of scientific counselors who reviewed his work didn't look kindly on his projects. "I got a lot of flak from some of the scientific counselors," for not publishing frequently enough, he says. His conclusion is that extramural types "want the intramural program to be like the extramural program."

Clearly, there are those who think the intramural and extramural programs are the same and others who think they are quite different. Still others believe that the two should be different—but not completely. Phillip Sharp of the Center for Cancer Research at the Massachusetts Institute of Technology cautions that while the intramural program has unique capabilities, he would not like to see the program be limited to work that cannot happen outside Bethesda. "I think it would be very counterproductive if those lines were drawn too rigidly," says Sharp, stressing that the intramural program needs overlap with the extramural program to keep both communities communicating.

A carefully nuanced position like Sharp's may or may not please Congress, which says it wants a clearly thought out "division of labor" between the programs. Even before Varmus arrives, the process of heeding congressional wishes has begun. Kirschstein told *Science* she has convened a group of intramural scientists and extramural advisers to consider the functions of the two programs. Their report, she says, should be ready by next spring when Congress holds appropriations hearings.

From Costumes to Rolodexes: The Activists March In

Although the issue of whether the intramural program and the extramural program should be the same or different is important, it pales beside a more fundamental question that affects NIH as a whole: How much emphasis should be put on basic research and how much on targeted research aimed at specific vaccines and cures?

That question has been put at the top of the NIH agenda by the action of the people most directly affected by NIH research: those with diseases such as AIDS or breast cancer. In the spring of 1990 their actions came home to the Bethesda campus. In May of that year, hundreds of AIDS activists, some costumed as the Grim Reaper or as court jesters, held a protest they called "Storm the NIH." Their demand: participation in designing clinical trials and speedier testing of new treatments.

As the AIDS activists became more sophisticated, they traded street theater for fat Rolodexes. Earlier this year, some of the same activists who participated in the 1990 protest were back in a different guise. This time, wearing ties and sports jackets, they stalked Congress, buttonholing key staffers. Their goal was legislation that would radically alter how NIH distributes its $1 billion AIDS budget by funneling it through the Office of AIDS Research (OAR), which, the activists hoped, would direct AIDS research more quickly toward a cure.

The NIH institute directors were strongly opposed to the legislation, which they feared would add a layer of bureaucracy to NIH. But they were in an awkward position because the Clinton Administration backed

the bill. Rather than speaking publicly, the institute directors spread the word to leading extramural researchers and scientific societies to weigh in against the legislation—and they spoke to Congress on the quiet. They also wrote a letter detailing their objections to Healy, who forwarded it to Health and Human Services. In spite of protests from many scientific voices—including that of Harold Varmus—the OAR restructuring passed Congress and became law.

The success of the OAR legislation illustrates the clout AIDS activists now have in shaping NIH research policies. And people threatened by other diseases are following their lead. Most notable is the National Breast Cancer Coalition (NBCC), which, by flooding Congress and the White House with letters and staging demonstrations, convinced the government to boost the breast cancer research budget by a whopping $210 million (*Science*, 29 January, p. 616). (Much to NIH's chagrin, the money ended up going to the Defense Department, because, unlike NIH, Defense doesn't face discretionary spending caps.) "This is democracy in action," says NBCC member Kay Dickersin, an epidemiologist—and breast cancer patient—who works at the University of Maryland Medical School.

Dickersin says her group is not trying to undermine basic research. Instead, NBCC would like to organize research for quicker payoff. "Researchers belong to certain fiefdoms and act independently of a plan," says Dickersin. "Somehow we've got to come together and get some strategic plans and decide where we should be focusing our attention and spending our money." Lack of direction is the main reason Mark Harrington and other AIDS activists lobbied to give OAR the final say about how AIDS money is spent by NIH. "The agenda is set by the person who holds the pursestrings," says Harrington.

Many researchers and scientific administrators argue that the activists are sorely misguided and that by pressing for directed research they could undermine the ends they seek. Harvard's Bernard Fields, author of a respected text on virology, concedes that "patients have to have input" into the research agenda but cautions that "it's a delicate balance" and worries that too much is expected too soon. He warns that "by targeting too closely when we're not really ready, we slow down basic research."

James Darnell Jr. of Rockefeller University agrees with Fields that political pressure doesn't make for good science. In fact, Darnell singles out the billion-dollar AIDS budget as an excellent example. That much money "can't possibly be spent on good research," argues Darnell. "You have to understand what a narrow problem it is scientifically: It's one retrovirus." Though he acknowledges that HIV is "affecting people cataclysmically," he contends that the research questions "make room for a few dozen research groups, not a few hundred."

Wyngaarden, though he also professes sympathy with the plight of the disease activists, says that "only rarely can you really accelerate" basic research. He thinks pressure from AIDS activists has distorted the NIH research agenda: "There's too much pressure to get to cure and application before there's a body of knowledge that will get you there."

Study Sections: Does a Superb System Need a Tune-Up?

Ask any scientist what makes the biomedical research enterprise in the United States the envy of the world, and the answer will almost certainly include a rigorous system of peer review. But in the next breath, you may also hear that the peer-review system at the heart of the National Institutes of Health (NIH) extramural program could use some fine tuning. This system, set up in 1946, has been praised for objectivity, integrity, and efficiency. But extramural researchers interviewed by *Science*—who, to a person, strongly support the system—worry that as the system has aged, the quality of reviewers has diminished. They also question the rating system for grant proposals, the way proposals are categorized, and the difficulty innovative, high-risk work has in getting funded.

It's no surprise that concerns about the system have intensified, given the current climate of increasing financial constraints and clashing research agendas (see main story). A 1992 review of the peer-review system by eight top NIH administrators acknowledged that NIH "faces a new era of increased accountability to both the American people and the Congress and of intense competition for new dollars. Thus, the pressure to improve the effectiveness of peer review will continue."

Efforts to improve the system will undoubtedly zero in on the "study sections" that NIH uses to rank the merits of more than 20,000 grant applications sent in each year by researchers. Run by NIH's Division of Research Grants (DRG), the 105 study sections mostly focus on such basic research topics as virology, neurology, and immunology, though 17 are clinical. Each has a DRG scientist as an administrator who nominates 16 or so "respected" investigators from different locations and institutions for 4-year terms.

After a screening, grant applications are rated by the study sections and assigned a "priority score." Applications are also ranked by percentile to reflect how well each fared in relation to others in the same section. The percentile ranking was instituted after a 1988 peer-review committee found that priority scores were "creeping" higher as study sections attempted to increase the likelihood that "their" area of research got enough funding. Rankings and a summary for each proposal are sent to advisory councils of NIH institutes and institute staff, who make funding decisions based on study section input and the institute's needs.

Praise for the study sections is widespread. "Anybody who has served on a study section or been chair of one, as I have, has been impressed by the objectivity and surprising lack of politics because in that format, politics are easily exposed and embarrassing," says Marc Kirschner, chair of cell biology at Harvard Medical School.

Yet even Kirschner concedes that "it's not a perfect system." One imperfection mentioned by several extramural researchers is that each study section depends on the willingness of leading investigators to spend 2 months a year doing study section work—and submitting their own proposals to a different, perhaps less appropriate, section. The result, say some top extramural researchers, has been a drop in quality. "The single most problematic area in terms of NIH research funding is the composition of the study sections," asserts Stanford's Irving Weissman. "You expect study sections not to represent the mediocre in your field, but the best in your field."

When the system was established 47 years ago, it wasn't hard to inveigle the cream of the crop to make these sacrifices. DRG's director, Jerome Green, says that "if you look at those rosters, it's absolutely wonderful. Mind you, nobody had served before, and you were able to go out and get the greatest names." Now, says Green, most "top echelon" scientists have served; many feel once is enough. His concerns are backed up by NIH data showing that from 1981 to 1991, while the average age of study section members increased from 44.6 to 46.3 years, the fraction who were full professors dropped from 71.4% to 61.7%, suggesting current members may be less distinguished than their predecessors.

Several ideas have been floated to persuade accomplished

As a highly respected basic researcher, Harold Varmus no doubt agrees with those who put tremendous faith in undirected fundamental scientific investigation. Yet, as NIH director, he will not have the luxury of ignoring the politically powerful voices being raised in favor of targeted research. How successfully he bridges the gap between his research peers and those who stormed the Bethesda campus and are storming Congress with their Rolodexes may be a key measure of his tenure as NIH director.

After Healy: Planning Strategies For the Future

If Harold Varmus wants clues about how others have tried to deal with the pressure to justify research on the basis of its clinical payoffs, he need look no further than the tenure of Bernadine Healy. Healy's "Strategic Plan" was an attempt to show that basic research and clinical benefits can readily be packaged in the same program. After soliciting input from 2000 scientists, physicians, and government officials over 2 years, Healy unveiled the 118-page "Investment for Humanity" as a "strategic vision" for NIH.

Healy's plan included a "commitment to scientifically meritorious investigator-initiated research." But she also has favorable things to say about targeting science. "I don't believe you blindly stumble onto a nugget," she told *Science* before stepping down. "It baffles me. It's a bizarre, outmoded, anachronistic, and damaging attitude, and sadly it's celebrated. It'll be a tragedy for NIH if NIH doesn't wake up on that one. The scientific community is afflicted with an immunosuppressive disease, and they don't know it."

Healy's extramural critics bristle at the idea of directed research. Howard Schachman of the University of California, Berkeley, calls her strategic plan "a colossal blunder" that exaggerated the benefits of targeted research efforts. Thressa Stadtman, a prominent biochemist at the National Heart, Lung, and Blood Institute who has been at NIH for 43 years, says Healy's document "was an attempt to turn NIH into something more practically oriented, something the legislature would appreciate." That, says Stadtman, is no way to run what she calls "a basic research institute."

Some researchers are afraid that justifying research in terms of tangible payoff leads to overselling; then, if the results don't measure up to the hype, disillusionment sets in. Says Phillip Gorden, a 27-year NIH veteran and director of the National Institute of Diabetes and Digestive and Kidney Diseases: "We're at this interface where we've created an expectation that we can't deliver on, and we're forced to do it more and more. We have to be careful that the gap doesn't become wider."

Varmus may agree that Healy's plan raises impossible expectations. He could simply deep-six "Investment for Humanity," since he is under no obligation to consult it. He is, however, under an obligation to develop a strategy for reconciling NIH's conflicting constituencies and agendas. Unless, that is, he is willing to see NIH's budget—and the public's faith in medical research—dwindle away.

–Jon Cohen

senior researchers to participate. One is adding a year's extension to an existing grant in exchange for serving. Others suggest instituting a jury duty-like requirement that everyone who receives NIH funding must occasionally serve. But acting NIH director Ruth Kirschstein worries that this might backfire. "My concern about compulsion is they might not do a good job," says Kirschstein.

Aside from the quality of reviewers, many researchers are disturbed that the study sections don't reflect the scientific importance of areas of biology. Areas that are no longer hot get the same treatment as areas that are on the cutting edge, says Kirschner. "Some areas lag behind the current nature of the scientific enterprise," says Kirschner. "If [peer review] had a larger scope, you'd be asking, 'Should funding still be going to that area?'...I don't think that review is happening now to the extent that it should."

NATIONAL INSTITUTES OF HEALTH

Golden section. Members of an NIH study section deciding which of many worthy research proposals should be funded.

DRG's Green says the system is not nearly as static as Kirschner and others think. "People say, 'My goodness, some study sections have been in existence for 30 years. The system seems to be ossified.' The name of the study section may be the same, but in terms of what the science is and the competency of the membership, those have changed tremendously." Furthermore, he says, sections spawn new sections as science changes: The molecular biology section splintered from cell biology and surgery became surgery and bioengineering.

Yet even DRG concedes that the system is not ideal. DRG's Green says ranking by a percentile system assumes that "the quality of the applications submitted to all sections are essentially equivalent. I know that's not true." Green says the people who use the percentile rankings to make funding decisions can compensate for the system's weaknesses by carefully considering priority scores and summary statements. But do they? "Not enough," admits Green. "Institutes tend to follow too slavishly the percentile."

In the 1992 review of the system, the panel suggested establishing a permanent group, called Peer Evaluation of Extramural Research (PEER), to test new ways of evaluating applications more effectively. PEER also would routinely recommend forming or discontinuing study sections.

Those changes, however, wouldn't overcome another problem that some researchers say plagues the study sections: their aversion to risky proposals. Stanford's Weissman, who helped develop the SCID-hu mouse (an animal with a human immune system that is now an important model for many diseases), says he did the work without applying for an NIH grant because "we knew with study sections, I wouldn't be in." Says Weissman, "You better have gotten your work done before you put in a high-risk proposal." DRG's Green counters that, "When you have limited financial resources, it's only natural to look askance at something that looks like a flier." To reconcile risk and responsibility, the 1992 panel suggested setting up a special fund for risky projects.

Whether these proposals rise or fall depends largely on Harold Varmus. Judging by an article Varmus wrote in *Science* in January (with Kirschner and J. Michael Bishop), Varmus seems interested in giving the system a tune-up. "Many of the NIH study sections," he wrote, "are now organized according to outmoded...categories." To solve this problem, Varmus and his co-authors called for instituting a PEER-like review. But calling for reform in a journal article is one thing; actually tuning up a system that has met with great success is another.

–J.C.