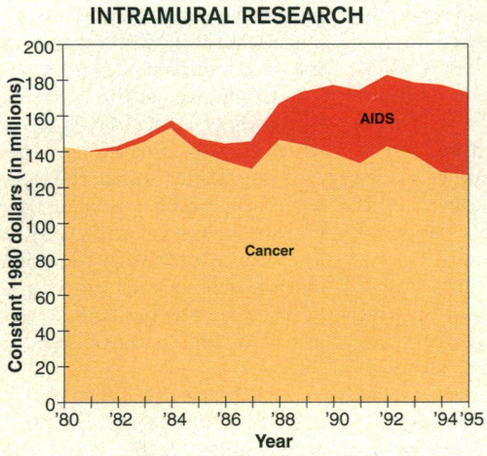
A New Phase in the War on Cancer

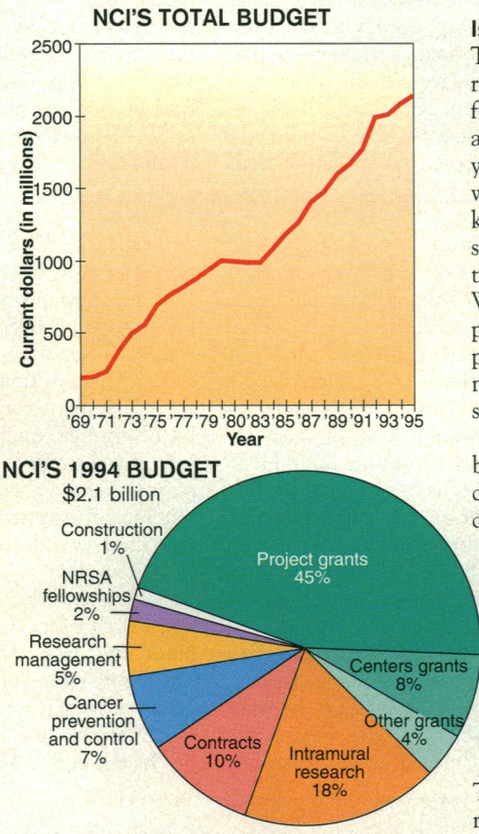
NIH Director Harold Varmus has launched a review of the National Cancer Institute, which is facing budget shortfalls and is losing several top officials, including its director

Samuel Broder has spent his entire professional life as a soldier in the war on cancer: "I started as a private, and now I'm a general," he said in an interview with *Science* a few days before celebrating his 50th birthday and ending a 23-year career at the National Cancer Institute (NCI). But even old soldiers finally fade away. On 1 March, Broder stepped down as NCI director, quitting public service to join a small drug company in Florida. "I'm doing my part to downsize government," he jokes—"downsizing myself out of it." Jokes aside, Broder's departure signals a dramatic change for NCI.

Broder's history is intertwined with that of the institute. He came to NCI from Stanford University in 1972, arriving just months after President Nixon launched the war on cancer and gave NCI special status within the National Institutes of Health (NIH). He's been NCI director for the past 6 years. But he is leaving just as some bloody battles are shaping up—over NCI's budget, organization, and priorities. After two decades of budget growth, economic changes are converging on NCI, compelling its leaders to find a new strategy. "I don't look forward to the level of extreme budget austerity which I think is coming," Broder said last fall. NCI intramural program chief Edward Tabor puts it succinctly: "The NCI you see 6 months from now is going to be very different from the one you see today."



Even before Broder announced in December that he was leaving, NIH Director Harold Varmus had ordered a stem-to-stern review of NCI. Last October, in a move some NCI officials resented, Varmus persuaded Broder to create an "ad hoc working group" of outside reviewers under the National Cancer Advisory Board. Their assignment from Varmus: "To evaluate the intramural program in a more organic way" than is possible in individual reviews of labs or investigators. Varmus chose NCI to be the first NIH institute to undergo large-scale scrutiny because of its size and complexity, and because it seemed "opportune" in view of the impending departure of two division chiefs. With Broder's departure, the review could provide a blueprint for his successor.



Three views of the budget. NCI's budget has grown rapidly *(top)*, but the cost of biomedical research has grown almost as fast, and new priorities are claiming a growing share of intramural funds *(above, left)*. NCI spends 18% of its funds on intramural research, a larger proportion than other institutes *(above, right)*.

This panel, whose final report is due in May, is widely respected within NCI: It is co-chaired by clinician Paul Calabresi, professor emeritus of Brown University, and by Michael Bishop, Varmus's friend and co-winner of the 1989 Nobel Prize, a virologist from the University of California, San Francisco.

Four issues are expected to dominate the panel's deliberations: the size and structure of NCI's intramural program, low morale and the problems of recruiting top scientists, peer review and priority-setting in the intramural program, and the growing inflexibility of NCI's budget as Congress singles out specific areas for funding.

SOURCE FOR GRAPHS: NCI

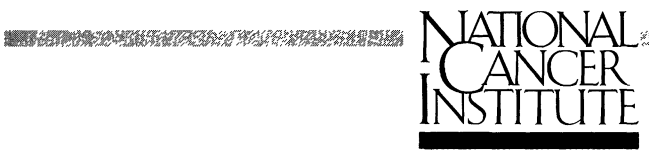
Issue I: Dealing with duplication

The public expects a lot from NCI, and, until recently, Congress responded by giving more funds each year, creating the largest, richest, and most complex institute at NIH. After 57 years of growth, however, NCI is hitting the wall. Its budget, now $2.1 billion, is not keeping up with inflation, and its favored status is unlikely to provide complete protection from the icy fiscal winds now blowing in Washington. If NCI is to explore new projects in these austere times, it must prune programs and consolidate activities. Yet much of the staff, one harried NCI manager says, is in a "psychological state of denial."

Broder says he saw how the wind was blowing 2 years ago. In mid-1993, he endorsed a project led by Michael Friedman, director of the Clinical Trials Evaluation Program, to find ways to tighten up operations. A group of eight extramural program leaders delivered a 38-page memo in January 1994—now called the "Hard Times Report"—recommending "a comprehensive process of analysis and evaluation to define and prioritize the problems confronting NCI."

The basic problem at NCI, the Hard Times authors wrote, is that each of its four research divisions "exists as a separate administrative and scientific structure," like four "individual cancer institutes." Intramural research gets 18% of NCI's funds and 74% of its personnel, but unlike any other NIH institute, NCI mixes intramural and extramural research within each division. The report noted that divisional leaders are chiefly drawn from labs on campus, and that they "retain their deep interest and affection for intramural activities." This creates two problems, the panel found: redundancy between divisions and, in some areas, competition within divisions between intramural and extramural projects.

The Hard Times panel tagged several pro-



Acting Director: Edward J. Sondik
Deputy Director: vacant

Research Divisions

SOURCE: NCI

Division of Cancer Biology, Diagnosis, and Centers
Director: Alan S. Rabson
1994 budget: $307,373,000
13 labs, 7 branches
1 top position vacant
Biggest lab: Laboratory of Pathology; Lab chief: Lance Liotta; 1993 budget: $10,225,000

Division of Cancer Treatment
Director: Bruce Chabner (leaving)
1994 budget: $231,011,000
9 labs, 25 branches
6 top positions vacant
Biggest lab: Laboratory of Experimental Immunology; Lab chief: John R. Ortaldo; 1993 budget: $3,447,000

Division of Cancer Etiology
Director: Jerry Rice (acting)
1994 budget: $105,385,000
14 labs, 10 branches
10 top positions vacant
Biggest lab: Laboratory of Tumor Cell Biology; Lab chief: Robert Gallo; 1993 budget: $7,382,000

Division of Cancer Prevention and Control
Director: Peter Greenwald
1994 budget: $161,584,000
1 lab, 14 branches
6 top positions vacant
Lab: Laboratory of Nutritional and Molecular Regulation; Lab chief: James M. Phang; 1993 budget: $1,809,000

grams as duplicative and candidates for merging. For example, each division carries on its own preclinical evaluations of new anti-cancer agents. This work could be combined, the report said, streamlining management and creating a single point of contact for companies that want to develop commercial products. Other areas that might benefit from tighter coordination, according to the report, are clinical trials, tissue banking, animal model research, work on gene transfection vectors, and programs that deal with carcinogenesis and basic biology. "Too many activities remain separated artificially by divisional administrative structures," the authors concluded. They wondered, for example, why NCI supports intramural work on oncogenes in three divisions, when everyone is working on the same genes and the same concepts.

Broder did not act on the Hard Times report. Just after he received it, Congress began investigating fraud in an NCI-sponsored breast cancer clinical trial (*Science*, 25 March 1994, p. 1679). That furor and other controversies kept NCI busy putting out fires most of the year. "We've had one commission after another" looking over NCI's shoulder, and "you can OD on oversight reviews," explains Broder.

NCI division chiefs were not asked to respond formally to issues raised in the Hard Times report. If you ask them today, they disagree with many of its conclusions. For example, Peter Greenwald, director of the Division of Cancer Prevention and Control, would not want to merge traditional research on cancer drugs with his own division's search for "chemopreventative" agents, mostly nontoxic food derivatives, because the regulatory problems entailed by the two kinds of research are so different. Bruce Chabner, director of the Division of Cancer Treatment, who will soon leave after 26 years at NCI, spoke out on 27 February against the view that all intramural research should be merged into one office. Chabner told members of his advisory council that it would demand too much of any individual to oversee all of NCI's intramural projects, as NCI's clinical research alone is twice as large as any other institute's. He argued that NCI's extramural programs are better run because their chiefs work side-by-side with clinicians and bench scientists.

In spite of this apparent internal resistance, Broder says he is "proud" that NCI itself was the first to raise the question of program overlap, adding that the Hard Times report shows "we were ahead of the curve." And he's annoyed that Varmus plunged ahead with the Bishop-Calabresi panel before checking to see what NCI had done on its own. "It would be helpful sometimes if people in the chain of authority would ask us, rather than simply asking for another review," says Broder. One top NCI manager warns that the agency may begin to "fibrillate" from all the reviewing. For example, this official says, Bishop is running staffers ragged; last week he demanded data on a division's tenure decisions and lab allocations for a 6-year period, to be delivered in a few days.

Issue II: Room at the top

NCI's top priority in 1995 may be to rebuild and reorganize, but before it can do that, it must recruit several top officials and stem a hemorrhage of scientific talent to outside organizations. NCI needs both a director and a deputy director. The former deputy, Daniel Ihde, left in early 1994 for Washington University in St. Louis and hasn't been replaced. Two of four division heads, Richard Adamson of cancer etiology and Chabner of cancer treatment, are gone or about to go. Below them, 17 lab and branch chiefs and five associate directors have departed or announced plans to go. NCI is now being run by Edward Sondik, deputy director of the Division of Cancer Prevention and Control. James Watson of the Cold Spring Harbor Laboratory says, "Twenty-five years ago, when viruses were the center of attention, NCI was more than any other place the center of an enormous amount of talent. Most of that talent has moved out."

The exodus, Broder says, is part of a "natural cycle of renewal." He thinks NIH is an ideal place for young scientists because it offers lots of responsibility and lab support at an early age. But "if you're a superstar, this is a bad place, because you can't get ... the resources you would get at a university." Ironically, NCI's own efforts have contributed to its current straits. The main reason good academic jobs are available is that for two decades NCI has been pumping billions of dollars into a network of cancer centers. When the war on cancer began in 1972, there were only three independent cancer centers in the United States; NCI now funds 55. As the relative importance of cancer rises—it's likely to replace heart disease as the leading cause of death in the United States—hospitals are raiding NCI's top talent to build up oncology staffs.

But it's not just the pull of outside jobs that has caused the intramural program to slide. NCI's deteriorating environment may also be providing a push. The Hard Times authors complained a year ago about the agency's "exaggerated efforts to respond to political imperatives," the role of "powerful advocacy groups," hierarchy, and bureaucracy. These problems worsened last year when Congress zeroed in on allegations of fraud and mismanagement in NCI studies. Chabner spoke of the "extraordinary pressures" some staffers have experienced. A hiring freeze has hit NCI hard, and many staffers

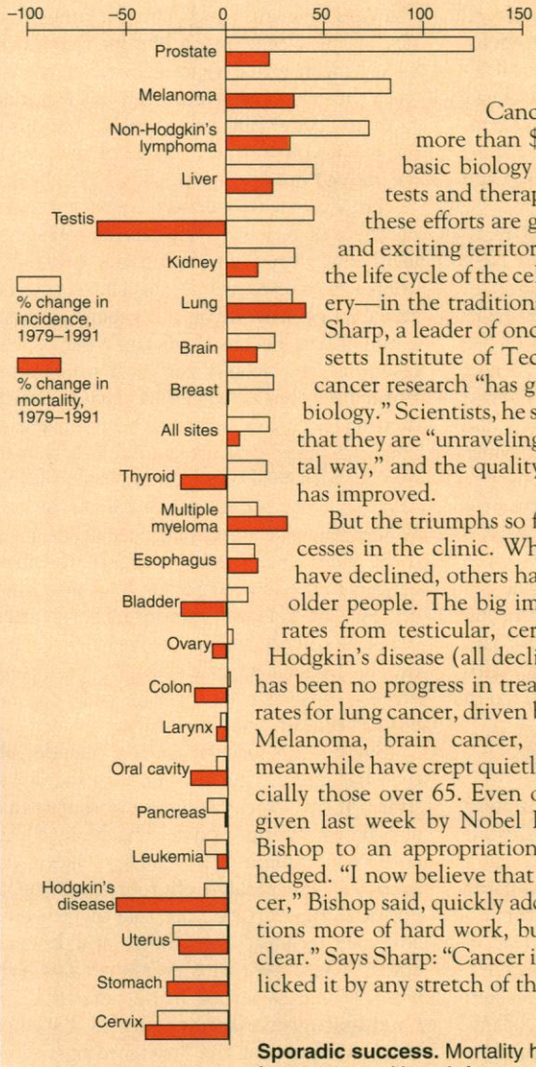
were overworked before the big exodus began. He also noted that scientific directors have "lost authority and independence" under the new regime, which relieves them of control over tenure, lab space, and decisions on AIDS research. Clinicians feel particularly left out, Chabner said, because "they have the sense that their research is less important than laboratory-based investigations" in genetics and molecular biology (*Science*, 27 January, p. 448).

One final factor adding to clinicians' uncertainty is the future of the NIH clinical center. This 450-bed hospital on the NIH campus is overdue for repairs. But even if it is rebuilt at half the size, as has been proposed, it will be an expensive project, and Congress is hesitating. The cancer institute, with 40% of the inpatients, has a lot at stake: Without a new center, NCI could find it even more difficult to compete with academic medical centers for top clinical researchers.

Broder accepts some responsibility for the malaise on campus. But he feels morale would be better if NCI's staff—people of "character, depth, high integrity"—had been defended in recent months by those above him. "It is quite important for the chain of authority not simply to do political calculations but to stand up; that's the most important aspect of leadership," Broder says. "You need to have people [at the top] express faith, not silence or a vague undertone of bewilderment."

NCI staffers are hoping morale will improve when the institute gets a new chief and new marching orders. Donna Shalala, secretary of Health and Human Services, has named a 14-member search committee under Paul Marks of the Memorial Sloan Kettering Cancer Center to recruit a director. Shalala said: "We are looking for an individual ... who has vision to explore new directions in the field and leadership qualities to mobilize researchers ... in the basic and clinical areas." The committee's choices will be submitted to the president, who will make the final selection, as provided for in the 1971 National Cancer Act.

Reports From the Front



Since President Richard Nixon signed the National Cancer Act in 1971, the National Cancer Institute has spent a total of more than $27 billion trying to unravel the basic biology of the disease and develop new tests and therapies. Ask cancer researchers how these efforts are going, and they will point to new and exciting territory opening up for cancer genetics, the life cycle of the cell, and even—with taxol's discovery—in the traditional field of chemotherapy. Phillip Sharp, a leader of oncogene research at the Massachusetts Institute of Technology, notes that support for cancer research "has given rise to much of modern cell biology." Scientists, he says, are more confident than ever that they are "unraveling a disease process in a fundamental way," and the quality of life for many cancer patients has improved.

But the triumphs so far have led only to sporadic successes in the clinic. While death rates for some cancers have declined, others have increased, particularly among older people. The big improvements have been in death rates from testicular, cervical, and stomach cancer and Hodgkin's disease (all declining by 30% to 70%). But there has been no progress in treating pancreatic cancer. And the rates for lung cancer, driven by tobacco use, have skyrocketed. Melanoma, brain cancer, and non-Hodgkin's lymphoma meanwhile have crept quietly up the charts, threatening especially those over 65. Even optimistic forecasts, like the one given last week by Nobel Prize–winning biologist Michael Bishop to an appropriations committee (see p. 1415), are hedged. "I now believe that we will eventually conquer cancer," Bishop said, quickly adding, "It may take several generations more of hard work, but the strategies for conquest are clear." Says Sharp: "Cancer is still a major disease. We haven't licked it by any stretch of the imagination."

–E.M.

Sporadic success. Mortality has declined dramatically for only a few cancers, although for most, incidence is increasing faster.

Issue III: Setting research priorities

The Bishop-Calabresi panel has spent a lot of time so far focusing on one question: How does NCI plan and review its intramural program? Intramural studies are getting attention for several reasons. For one, panel members find NCI's method of setting in-house priorities obscure. Each NCI division steers an independent course, guided by its scientific advisers. While all the divisions use the same method of evaluating research—site visits at 4-year intervals—the peer comments are private, not binding, and, according to Bishop, mild. This disconnection between reviews and intramural funding decisions is pervasive at NIH, some say (*Science*, 27 August 1993, p. 1120).

Another reason for focusing on the intramural budget is its size. In 1994, NCI spent more than $374 million on in-house research, 18% of the total NCI budget, a fraction far higher than the NIH-wide average of 11%. In addition, according to NCI's budget chief John Hartinger, the agency spends about 10% of its total budget, $205 million, on R&D contracts. Much of this work is done in support of intramural objectives, and about half the sum supports a dedicated laboratory at the Fort Detrick Army base in Frederick, Maryland, where NCI and contract staff screen anti-cancer agents and design new drugs.

At Varmus's request, the Bishop-Calabresi panel is trying to learn how NCI evaluates its internal projects and how it decides which should be expanded or shrunk. This line of inquiry follows the lead of a blue-ribbon committee, co-chaired by Marks and Gail Cassell of the University of Alabama, that made a strong plea last year for rigorous peer review and priority-setting throughout NIH's intramural programs (*Science*, 13 May 1994, p. 896). A few institutes, the Cassell-Marks report said, plan aggressively, but others allow historical patterns to become "a rationale for current decisions."

Is NCI's intramural program one of those run by inertia? Broder says it is not. "We have tried to develop a system where young people are given very substantial opportunities, ahead of schedule if you will," he says. Acting NCI Director Sondik told the Bishop-Calabresi panel at its 16 February meeting that recent "scientific advances" have the "biggest influence" on setting the intramural agenda. Sondik then described a complex process used by NCI to incorporate new sci-

ence into its budget plan. Staffers talk with lab chiefs; lab chiefs negotiate with division chiefs; and division chiefs huddle with administrative officers in retreats to discuss a document called the bypass budget. This annual statement of NCI's scientific goals, and the funds it needs to meet them, is drawn up by the NCI director and his executive committee. As stipulated by the 1971 Cancer Act, it goes directly to the White House, offering the executive branch scientists' judgment on what must be done to fight cancer. Later, the Health and Human Services Department and NIH submit a "real" budget request to the White House, which is revised and sent to Congress.

The bypass budget—some refer to it as NCI's "wish list"—bears little relation to the budget that is finally submitted to Congress. The 1996 bypass budget, for example, called for a total of $3.6 billion for NCI—a whopping $1.4 billion more than the Clinton Administration requested. Clearly, NCI has to do a lot of squeezing to shape its wish list to fiscal realities, but how that shaping is achieved isn't clear even to many on the inside. The Bishop-Calabresi panel seems ready to recommend that the next NCI director create a more comprehensive and transparent system for setting priorities.

Issue IV: Loss of flexibility

NCI's priorities are not all set from within. Patient advocacy groups, professional societies, and disease lobbies all have a hand in shaping the agenda, mainly by asking Congress to earmark certain tasks for funding. One example: research on cancer prevention and control. The 1993 bill authorizing NIH specified that NCI must devote a fixed percentage of funds to this area, reaching 10% this year. NCI is having trouble hitting that target, however, and is asking Congress to drop the requirement.

Perhaps the most striking earmark is for breast cancer research, for which funding at NCI has increased 236% since 1991, when cancer patients began lobbying hard. Broder says he agrees that breast cancer and prostate cancer research were due for an increase. But he warns that "we have to be cautious that we don't overcompartmentalize the process" by creating "scientific entitlements."

Broder doesn't think earmarking has unbalanced cancer research—at least not yet. But he worries that the process could become unbalanced if a set-aside for AIDS research (also part of the 1993 NIH authorization bill) isn't handled carefully. AIDS-related research already consumes 26% of the NCI intramural budget, and Chabner told the Bishop-Calabresi panel that all intramural growth in his division since 1992 has gone into AIDS, while funding for cancer "headed south." The result: "We shift research," and people change what they do.

But when it comes to predicting what the NCI itself will look like a year from now, nobody is ready to make a guess. Varmus is waiting for the Bishop-Calabresi report, and he says he wants to hear the views of the new NCI director—whoever that may be. "I would be surprised if there weren't some changes," says Varmus, but beyond that, "I don't know enough to say what they should be." But Varmus is certain of one thing: The Bishop-Calabresi review won't be the last of its kind. He says he will soon order up a similar review of the National Institute of Mental Health, which is also looking for a new director, and other institutes will get their turn.

–Eliot Marshall

With reporting by Antonio Regalado.

BIOMEDICAL FUNDING

Nobelists Make a Plea for NIH Budget

Six Nobel Prize winners who went to Capitol Hill last week to make a pitch for biomedical research themselves came away with an unsettling message: Prospects for funding this year are more uncertain than at any time in recent memory.

The Nobelists had been invited to testify before a key panel—the House appropriations subcommittee for Labor and Health and Human Services, author of the appropriation bill for the National Institutes of Health (NIH). But before they even began, the panel's most senior Democrat, David Obey of Wisconsin, rattled them with a warning that a fiscal "train wreck" lies ahead for basic research if a federal tax cut—promised by the Republican leadership in Congress and by the White House—is enacted. He predicted such a tax cut would lead to a 30% reduction in all domestic spending, including funds for NIH. Another panel member, Louis Stokes (D–OH), agreed that a tax cut would be devastating, but doubted it would be approved.

It fell to the subcommittee's Republican chair, John Porter (R–IL), to provide some reassurance. Torn between his party's plan to cut spending and his own support for NIH, he reiterated his own opposition to the tax cut: "I believe in the end we will not cut taxes," Porter said, suggesting that his colleagues are "wise enough" to avoid the governmental crisis it would create. And Porter said he would do his best to support biomedical research in what will be a tough budget year, with or without a tax cut. Another Republican member, Dan Miller (FL), also noted that House Speaker Newt Gingrich (R–GA) is "a very strong supporter of basic research" and not one to abandon biomedicine. However, the most junior Republicans on the subcommittee—members who favor stringent spending cuts—didn't show up for the hearing and have not yet indicated how they will vote on research funding.

SAM KITTNER

Show and tell. Phillip Sharp demonstrates for House appropriations committee members how cancer genes are spliced and expressed.

Only then did the scientists get to talk about their own experiences and the importance of federal support for research. Michael Bishop, friend of NIH Director Harold Varmus and co-winner with Varmus of a Nobel in 1989, orchestrated this part of the hearing. Bishop described his own work on retroviruses and the progress since 1970 in understanding the causes of cancer, declaring that a strategy for conquering the disease is now in hand. Other speakers included Michael Brown of the Southwestern Medical Center at the University of Texas, Dallas, on heart disease; David Hubel and Joseph Murray of the Harvard Medical School, on brain research and organ transplantation, respectively; Phillip Sharp of the Massachusetts Institute of Technology on oncogenes and biotechnology; and James Watson of the Cold Spring Harbor Laboratory on the Genome Project.

Murray's presentation, illustrated with a photo of the "oldest living organ transplant recipient"—one of his patients, now living in Oklahoma, not far from the home town of one of the House panel members—was especially powerful, in the opinion of one longtime observer of these hearings. But some of the other discussions, he said, verged on "whining" about the hardships associated with applying for federal grants, which is unlikely to evoke sympathy from the subcommittee. The "real question" facing biomedical funding, this observer says, is: What if funding decisions get entirely "out of Porter's control?" In this topsy-turvy year, it could happen.

–Eliot Marshall