Verdict in Sight in the "Baltimore Case"

Congressional and NIH investigators have been sifting through forensic analyses of Thereza Imanishi-Kari's notebooks for nearly 2 years; at least two sets of data are in doubt

WHEN A TEAM OF RESEARCHERS PUBLISHED A paper in *Cell* in April 1986,* they probably expected to generate scientific controversy, for they were reporting results that challenged the conventional wisdom about how immune responses are regulated. But they surely didn't expect the attention to which their paper has been subjected over the past 5 years: two university reviews, a congressional inquiry, and two investigations by the National Institutes of Health.

What began as a laboratory dispute between Tufts immunologist Thereza Imanishi-Kari and her then postdoc, Margot O'Toole, has escalated into one of the more celebrated cases of alleged scientific fraud in years. Congressional investigators working for Representative John Dingell (D–MI) have privately accused coauthor and Nobel laureate David Baltimore of using his prominence to "cover up" error and possible fraud; defenders of the paper's authors have depicted Dingell's inquiry as a political assault on the foundation of science. No matter whose side you've been on, the affair has been an ugly one. Rightly or wrongly, everyone has been impugned: the authors for, at best, doing shoddy science; O'Toole for blowing errors out of proportion; the congressional investigators—who have been assisted by unofficial NIH fraudbusters Walter Stewart and Ned Feder—for conducting a witchhunt; and the official investigative bodies, including Tufts University and the Massachusetts Institute of Technology, for carrying out a series of botched inquiries that had the effect of derailing O'Toole's career. And the accused have all been left in a form of purgatory, their reputations tarnished for years, with neither final condemnation nor vindication. Until now, perhaps.

After 22 months of investigation, an NIH panel is expected to deliver its verdict in the case within the next few weeks, assuming that a recent court challenge to NIH's Office of Scientific Integrity (OSI) doesn't derail the investigation (*Science*, 11 January, p. 152). A draft reportedly is circulating among the committee members and will eventually be sent privately to all parties concerned. Once the OSI has considered any comments the authors and institutions may wish to make, the report will be made public. Although neither NIH panel members nor OSI officials will comment publicly on the ongoing investigation, *Science* has assembled an account of the main issues with which the NIH panel is wrestling, based on a months-long examination of testimony given at two bruising public hearings by Dingell's subcommittee, additional unpublished documents, and in-depth interviews with Imanishi-Kari, congressional investigators, several independent immunologists, and sources close to the NIH investigation. (Baltimore declined to be interviewed for this article, pointing out through a spokesman that he has not been accused of misconduct and is not a target of the investigation.)

Facing the heat. *The now infamous 1986* Cell *paper; Thereza Imanishi-Kari at Dingell's 1989 congressional hearing.*

The central charge facing the NIH committee is the one raised by O'Toole almost 5 years ago: that Imanishi-Kari's original laboratory data do not support the authors' published contention that a gene transplanted into a line of mice indirectly changed the repertoire of antibodies produced by the mouse's own genes—the *Cell* paper's main thesis. The evidence available to *Science*—especially Secret Service forensic analyses of ink, paper, and dates in Imanishi-Kari's laboratory notebooks, as well as of paper tapes produced by radioactivity counters—casts doubt on the authenticity of one key set of data. And the recent emergence of contradictory original data in a grant application raises questions about a second.

Investigative panels at MIT and Tufts found O'Toole's charges unwarranted in 1986, and an NIH panel concluded in February 1989 that there was "no evidence of fraud, manipulation or misrepresentation of data." But when Dingell scheduled hearings in May 1989 to present forensic evidence in the case developed by the Secret Service, then NIH director James Wyngaarden added two new members to the original panel,† reopened the NIH investigation, and announced that he, too, was calling in forensics experts. It is this second panel whose report is expected soon.

What follows is an explanation of the most conclusive and—given the complexity of the immunological science under investigation—easily understood evidence that *Science* has uncovered.

■ ***Unauthentic data.*** Potentially the most damaging evidence investigators are examining involves allegedly unauthentic data. Even the first investigatory panel, while validating the science and clearing the authors of misconduct, uncovered a number of troubling inconsistencies in the data underlying some parts of the *Cell* paper, especially those data presented in Table 2. This table purported to show that nearly 76% of certain monoclonal cell cultures demonstrated the indirect effect of the transplanted gene, or "transgene." These results seemed to provide striking support for the paper's main thesis that the transgene had influenced antibody production by the mouse's own genes (see box, "Deciphering the Science"), but the panel noted that the raw data taken from 340 of these antibody-producing cell lines, or hybridomas, seemed in some cases to contradict the results published in the table.

*D. Weaver *et al.*, "Altered repertoire of endogenous immunoglobulin gene expression in transgenic mice containing a rearranged Mu heavy chain gene," *Cell* **45**, 247 (1986).

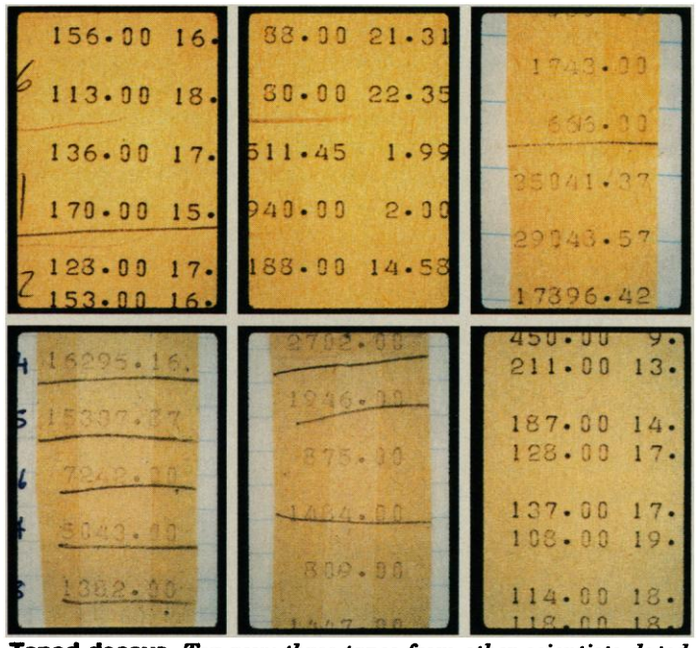
†The first panel included chairman Joseph Davie, vice president of Searle; Stanford immunologist Hugh McDevitt; and University of Chicago immunologist Ursula Storb. Carnegie-Mellon biologist William McClure and University of Texas biologist Stewart Sell joined the panel when the investigation was reopened.

When the first group of NIH investigators asked Imanishi-Kari to account for the discrepancies, she had a simple, if surprising, explanation: The 340 cultures weren't necessarily monoclonal cultures at all—though the paper had stated this fact explicitly—but merely "wells," or cultures that might contain several different strains of antibody-producing cells. The committee was worried by this explanation. As NIH panel chairman Joseph Davie told *Science* in a recent interview: "Unless you have a clonal population where each [recorded] value represents the product of a single cell, it's impossible to calculate [such] antibody frequencies."

The next day, however, Imanishi-Kari reassured the committee by presenting it with several pages of unpublished data from a "subcloning" analysis of these Table 2 wells. Subcloning involves growing, or "cloning," hybridomas from a single cell extracted from a polyclonal culture. The NIH panel was convinced, as member Hugh McDevitt told the paper's authors later at a tape-recorded meeting on 3 May 1989. (*Science* has obtained a partial transcript of that meeting.) McDevitt said that until Imanishi-Kari presented it with the unpublished subcloning data—which confirmed, albeit less strongly, the Table 2 claims—the panel had decided "the whole [study] should be thrown out the window." The subcloning data "convinced us that maybe there was something to the thesis [of the paper]," he continued.

In a recent interview with *Science*, Imanishi-Kari said these critical subcloning experiments were performed on 20-22 June 1985. But Secret Service agents testified in a Dingell hearing on 14 May 1990 that their forensic analysis is at odds with her account. The clearest evidence of discrepancies in Imanishi-Kari's claim presented by the Secret Service comes from an analysis of radiation counter tapes that are fixed to Imanishi-Kari's laboratory pages along with the subcloning data. When biologists want to ascertain the quantity of antibody present in a given solution, they often perform a radioimmunoassay (RIA) in which they "tag" another antibody that specifically recognizes the first with a radioactive label such as iodine-125, then measure the radioactivity with a counter that prints the number of gamma decays on paper tapes. By comparing the paper color, ink composition, and print density on these tapes with those produced by other scientists who used the same counter, forensics experts can date them relatively easily. And since the tapes are produced as an experiment is performed, they should be an accurate indicator of when the work was done.

Such dating is exactly what the Secret Service did at Dingell's behest in the spring of 1990. According to the Secret Service report to the congressional committee, the agents concluded that these particular subcloning tapes "are not consistent with experiments having been performed by other researchers on or around [June 1985]." In testimony at the hearing last May, Secret Service chief document examiner John Hargett explained that Imanishi-Kari's tapes were produced at a time "several months and probably years" earlier or later than Imanishi-Kari had claimed. Because her subcloning tests are one link in a tight chain of experiments recorded in the notebook, a date discrepancy of this magnitude could cast a large portion of the notebook into doubt.



Taped decays. *Top row: three tapes from other scientists dated June 1985. Bottom row: two tapes from Imanishi-Kari's Table 2 subclones; a 1983 tape from Charles Maplethorpe's notebook.*

Sources close to the NIH investigation have also revealed that at the request of OSI, Secret Service agents have compared the ink and paper color of these tapes with samples taken from the notes of other scientists who used the same counter in order to date them more precisely. In these analyses, agents reportedly have matched Imanishi-Kari's tapes to tapes in the notebooks of former MIT graduate student Charles Maplethorpe, who performed his experiments in the early 1980s—at least one and possibly several years before the mice used in Imanishi-Kari's experiments had even been delivered to her laboratory.

Imanishi-Kari declined to testify at Dingell's hearing last May, saying later that she didn't know the specific charges brought against her. But she has willingly discussed the matter of the Table 2 subcloning tapes with *Science* and expresses bafflement about the Secret Service results. "Things did happen all the time at those [counters]," she said. "I mean, papers were changed, ribbons were changed....There are a thousand and one different [explanations], and I am not the one who can tell exactly why it is different—I have not the faintest idea."

To NIH and congressional investigators, there are still other indications that these subcloning data may not be authentic. For instance, Imanishi-Kari told *Science* that while she pasted some of these tapes into her notebook, she copied radiation count data from others by hand. If the data were generated by a radiation counter, however, digits in the tens columns of Imanishi-Kari's recorded counts (the unit column was rounded off) should be random, yet there is an unusual abundance of 1s and 3s among these digits, and a scarcity of 2s and 9s (see table, p. 1171). When *Science* subjected this distribution to a chi-squared statistical analysis, the result suggested that such a skewed distribution has only one chance in 10^{32} of occurring randomly. Imanishi-Kari admits that she doesn't have a ready explanation for these nonrandom numbers: "I can come up with ad hoc explanations, but I cannot tell if any one is right."

■ ***Patterns of changed dates and misordered pages.*** Much of the press accounts of the first hearing by Dingell's subcommittee, in May 1989, focused on the testimony of Hargett, the document examiner for the Secret Service. At that time, Hargett had only done a preliminary analysis of the counter tapes, but he had subjected Imanishi-Kari's notebooks to forensic analysis and concluded that they contained at least 25 pages "which raised some question in our minds regarding the authenticity of these pages." Hargett revealed numerous instances where the dates on laboratory pages had been altered and where pages had been backdated, such as a page dated 1984 that was shown through forensic analysis to have been written after a page dated 1986.

But Hargett's testimony raised almost as many questions as it answered. First of all, from the way Hargett presented his findings at the hearing, it was impossible to tell how these alterations affected the scientific conclusions of the paper, if at all. Second, Balti-

Deciphering the Science

A standard joke among immunologists is that they don't understand much about immunology themselves. So it may come as no surprise that even the various scientific investigators—not to mention reporters and congressmen—have had a difficult time coming to grips with the science underlying the so-called Baltimore case. In fact, the mind-numbing complexity of the science has been one of the chief obstacles to resolving this affair. What follows is an attempt to clarify Thereza Imanishi-Kari's work in order to present a road map to the major issues in dispute.

In the April 1986 issue of *Cell*, authors Imanishi-Kari, David Weaver, and David Baltimore presented a study designed to help answer a hot question in immunology: How does the immune system figure out how much and what types of antibody to produce in response to antigens? Most theories have involved complex interactions between all parts of the immune system. But for nearly 20 years, a small group of immunologists has clung to the idea that some responses might be governed in a very different manner.

First advanced by the English–born immunologist Niels Jerne, who won the Nobel Prize for his ideas in 1984, this "network theory" holds that antibody surface characteristics known as "idiotypes" act as antigens, like any foreign protein. Idiotypes stimulate B cells to produce other antibodies with "anti-idiotypes," which in turn elicit a third set of antibodies, and so on, linking every kind of antibody to other antibodies in an "idiotype network." Because idiotypes are also found on B cell surface antibodies, each anti-idiotype could regulate the cells producing its target antibody. Immune function as a whole might be controlled by a vast idiotype network. The effect of any new idiotype should ripple through the network, affecting the production of other antibodies.

Although a considerable body of research indirectly suggested the existence of idiotype-anti-idiotype interactions, no one had ever advanced clear evidence—much less solid proof at a molecular level—that such interactions actually take place on a large scale. Until, that is, Imanishi-Kari entered into a collaboration with Baltimore's laboratory in early 1984.

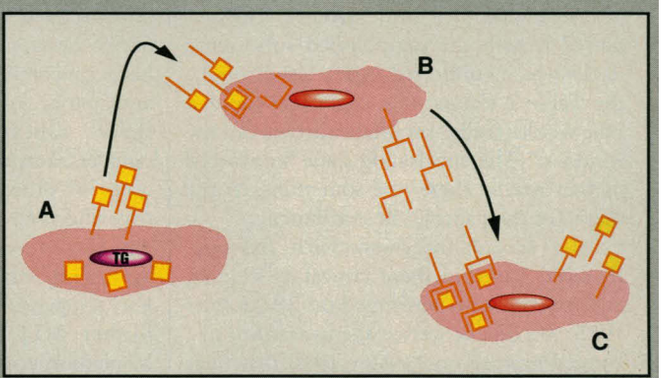
The experiments described in the *Cell* paper were intended to explore just such large-scale interactions. The researchers inserted a gene responsible for producing a specific idiotype into a line of mice and then examined its effects on the antibody population. If the traditional view won out, the mice should have expressed their normal complement of antibodies plus, perhaps, the antibodies generated by the transgene. On the other hand, if the new idiotype encoded by the transgene triggered network interactions, the natural—or "endogenous"—repertoire of mouse antibodies would reflect these interactions. The most spectacular evidence of network interactions would be B cells lacking the transgenic DNA but producing antibodies with the foreign idiotype.

To the surprise of most cellular immunologists, the experiments reported in *Cell* seemed to suggest that the transgene did indeed indirectly affect the production of endogenous antibodies. Two parallel lines of experimentation supported this view. In one, the investigators used a variety of biological reagents to probe the antibodies produced by single-cell cultures. In the second, they looked at the RNA within the cells, which carries the genetic messages directing antibody production. After describing the results of these experiments, the authors wrote that network theory "appears more appropriate in most cases" than alternative explanations for the data.

The serological analysis provided the most striking evidence in support of this thesis. First, Imanishi-Kari obtained a strain of mice from the laboratory of Columbia immunologist Frank Costantini that carried the gene for an idiotype known as 17.2.25. Next she created a number of cellular "hybridomas"—monoclonal cultures made by fusing a single B cell line from these mice with immortal tumor cells. Then she examined each hybridoma for two important features: to see if it was expressing antibodies with the 17.2.25 idiotype, and then to see if the idiotype resulted from the transgene's action. Summarized in the paper's all important Table 2, her tests showed that 68% of lymph node hybridomas and 28% of spleen hybridomas produced antibodies with the transgenic idiotype, compared to less than 1% of hybridomas from normal mice. And of the idiotype-positive hybridomas, nearly 76% showed no sign of antibodies produced by the transgene itself.

The obvious conclusion was that large numbers of B cells were producing endogenous antibodies with the same idiotypes as those produced by the transgene. The implication seemed to be that the transgene's antibodies had triggered the mouse's own genes to produce antibodies with an anti-idiotype, which then prompted B cells to produce endogenous antibodies with an anti-anti-idiotype—or the same idiotype as the transgene's antibodies.

Because serological reagents are often difficult to work with—there is always a possibility that a monoclonal antibody used to identify one particular molecule might accidently pick out another—the authors also performed a separate analysis using the tools of molecular biology. David Weaver, then a postdoc in Baltimore's laboratory at MIT, examined the DNA and RNA present in 34 of Imanishi-Kari's hybridomas, summarizing his results in the paper's Table 3. He determined that a majority of the cultures didn't show any transgene RNA—seemingly clear evidence that any 17.2.25 idiotype in these hybridomas had not been produced by the transgene. And a few hybridomas which transcribed RNA corresponding to the 17.2.25 idiotype seemed to have lost the transgenic DNA altogether, apparently ruling out the possibility that the transgene had produced the idiotype directly. Even today, immunologists who question the validity of Imanishi-Kari's serological analysis consider Weaver's molecular work, in combination with the asumption that these hybridomas were positive for idiotype (see below), compelling evidence that at least some endogenous genes were producing transgenic idiotype.



Networking. *A transgenic B cell produces idiotypic antibodies (A), triggering the production of antibodies with endogenous anti-idiotype (B) and then endogenous idiotype (C).*

Enter former Imanishi-Kari postdoc Margot O'Toole. Shortly after the paper was published, O'Toole happened across the raw data underlying Tables 2 and 3. After xeroxing it for study, she became convinced there were serious problems with how the data had been presented. Her analysis of Table 2 led her to believe that nearly all the idiotype detected in these hybridomas was

due to antibodies produced by the transgene, not by the endogenous genes—a fact obscured, she said, by inadequate specificity and varying sensitivity of Imanishi-Kari's reagents.

Similarly, O'Toole claimed that Weaver's probes were not sensitive enough to detect low levels of transgene RNA, which O'Toole said would be enough to account for the presence of idiotype. And she challenged the manner in which these hybridomas were tested for idiotype.

Interestingly enough, the paper itself is not explicit in linking the molecular and serological analyses since nowhere does the paper state that the Table 3 hybridomas were producing antibodies with the transgenic idiotype. "It was not explicitly stated in the paper, and it kind of surprised us," says NIH panel chairman Joseph Davie, an immunologist and vice president for research at the G. D. Searle Co. "Frankly, we think this was just an oversight."

Four years later, no one has published a study replicating the results reported in the *Cell* paper. Some immunologists, like Eric Selsing at Tufts, tried—and failed—to find similar effects in a different line of transgenic mice. (Selsing points out that his results don't prove Imanishi-Kari wrong.) Others, like Columbia's Alan Stall, think that Imanishi-Kari's conclusions could have been distorted by either of two effects unrelated to network interactions: by the fact that her transgenic mice could have developed B cells that produced both endogenous and transgenic antibodies; or by an unanticipated side effect of the transgene that Stall says alters the balance of certain B cell populations, skewing the resulting array of antibodies. And some, like John Kearney of the University of Alabama at Birmingham, say that many researchers have moved away from "fundamentally interesting" immune regulation experiments using transgenic mice to study problems that are more quickly and easily solved—at least partly, perhaps, because of the controversy associated with the *Cell* paper.

Yet there is one claim to have replicated Imanishi-Kari's experiments, which surfaced in hearings held by Representative John Dingell's subcommittee in 1989. Immunologist Henry Wortis, one of three Tufts scientists who originally examined O'Toole's concerns, testified: "[I]n fact, the central conclusions have been confirmed. Those have not yet been submitted for publication, however." When recently contacted by *Science*, Wortis said these results are still unpublished, nearly 2 years after he testified to their existence. He refused to disclose the name of the scientist who conducted these experiments, claiming that it is up to this researcher to come forward with his or her results. ■ **D.P.H.**

more, in his prepared testimony before the subcommittee, suggested that the alterations were irrelevant: "[T]he pages which concerned [the Secret Service] contained none of the data that actually contributed to the *Cell* paper." And third, Imanishi-Kari came up with what observers dubbed her "sloppiness defense." She testified that she sometimes didn't date experiments on the days they were performed, that she often recopied old notebook pages, and that she frequently kept counter tapes stuffed in a desk drawer for months before cutting them up and pasting them down on notebook pages.

NONRANDOM NUMBERS

Frequency of digits in Imanishi-Kari's Table 2 subcloning data:

0	14
1	71
2	7
3	65
4	23
5	19
6	12
7	45
8	53
9	6
N =	315

These Secret Service findings have turned out to be important to the investigation, however. What was not made clear at the 1989 hearing was that some of the data on those notebook pages concerned the subcloning experiments that had played a critical role in convincing NIH's initial investigators to accept the paper's conclusions. Moreover, as OSI deputy director Suzanne Hadley testified a year later before Dingell's committee, in the May 1990 hearing, the Secret Service had questioned the authenticity of some data published in Table 2 that described certain control experiments. As for the sloppiness defense, when Representative Ron Wyden (D–OR) asked Hargett to evaluate it at the 1990 hearing, he testified that "we believe [Imanishi-Kari's] testimony [regarding her explanations] before the subcommittee last year was not accurate."

■ ***Inconsistent data.*** Worrisome as these assaults on Imanishi-Kari's integrity might be, they do not invalidate all the supporting data for the paper's conclusions. Indeed, to many immunologists, the strongest evidence demonstrating indirect effects of the transgene on the endogenous mouse antibody repertoire presented in the *Cell* paper was not the serological evidence in Table 2 but the molecular analysis of 34 hybridomas listed in Table 3 (see "Deciphering the Science"). There, among other findings, the authors reported that several hybridomas produced antibodies with a particular characteristic known as idiotype related to the transgene—even though the cells lacked the transgene itself. So even if Table 2 fell apart completely, Columbia immunologist Alan Stall told *Science*, the evidence presented in Table 3 "is [still] very striking." But the serological data apparently used to demonstrate that the Table 3 hybridomas were producing the transgenic idiotype have also been questioned by congressional and NIH investigators.

A surprising bit of evidence surfaced late last year when these investigators unearthed an NIH grant application submitted on 2 February 1985 by MIT researcher Herman Eisen, Imanishi-Kari, and three other biologists. Imanishi-Kari's data in the application includes a description of the same set of hybridomas from which the Table 3 hybridomas were taken. The characteristics of the hybridomas in the application differ from those in Imanishi-Kari's laboratory notebook, however—and in crucial ways.

For instance, the notebook records that on 12 December 1984 a full 119 out of 147 hybridomas tested positive for the transgene's idiotype, suggesting that the transgene was influencing the mouse's antibody production. But in the grant application, only 60 of 150 are said to have tested positive.

The grant application, whose existence was first reported by *Nature* last September, provides an independent check on the data in the notebooks, and the contradiction would therefore seem to be damaging. But the issue is not clear-cut. Imanishi-Kari told *Science* that the discrepancy resulted from using two different tests for idiotype—a radioimmunoassay in the grant application, and a more sensitive enzyme-linked assay known as an ELISA in the notebook. Immunologists say it is difficult to determine whether this discrepancy could be reasonably attributed to differences in the assays. For instance, the underlying distribution of positives and negatives in the data could have a strong effect on the obtained results, Stall told *Science*:

A direct comparison between the two sets of data might help clear up the reasons for the discrepancy, but Imanishi-Kari told *Science* that she can no longer find the raw data from the RIA. "Very often, at that time, when I made a pile of data, I threw the original data away," she said.

In any case, why didn't Imanishi-Kari submit the ELISA data in the subsequent grant application since they offered stronger support for the notion that the transgene was influencing the mouse's endogenous genes? She told *Science* that the transgenic project was a "minor part" of the grant application, adding that because other tables in the application contained data taken from RIAs, submitting the RIA-generated idiotype data was "a matter of choice—it was the easiest in the context."

In a 10 January 1990 memo to NIH's

Office of Scientific Integrity obtained by *Science*, however, O'Toole challenges this explanation. She alleges that Imanishi-Kari did not use an ELISA to test hybridomas for idiotype at all, as the notebook indicates. In her memo, O'Toole claimed that Imanishi-Kari told her in 1986 that she had performed the ELISA recorded in the laboratory notebook to test only for a characteristic known as isotype. O'Toole charged that the reagents used in the isotype assay could not have detected the presence of idiotype.

This dispute essentially boils down to a question of which reagents Imanishi-Kari used in the ELISA, and there appears to be no definitive way to check it. Dingell's committee staffers did, however, have the Secret Service examine Imanishi-Kari's notebook pages containing the ELISA data. The first page contains a handwritten statement that an idiotype-detecting reagent was used to screen the hybridomas, but the forensic analysis indicated that this statement was added in a different ink from the rest of the page after the data themselves were recorded.

Such issues have kept members of the current NIH panel occupied for an inordinate amount of time. Their "employer," OSI deputy director Hadley, estimates that the scientists have each put in "hundreds of man-hours." And that time is almost purely advisory: unlike the first NIH investigation, which was conducted entirely by the three immunologists convened by NIH, the new five-member scientific panel defers line duties to OSI staff members. "We do all of the heavy-duty interviewing and data review," Hadley told *Science*. "We do the legwork and present it to the panel. They look, and say, 'You haven't done X, Y, and Z.' "

Will this incredible effort be worth it, if only because it finally puts matters to rest and allows the principals to go on with their lives? Perhaps not. According to Hadley, OSI is already planning a "phase two" of the investigation—dubbed by Dingell aides the "who-knew-what-when" investigation. OSI has passed on responsibility for this follow-up to the inspector general's office within the Department of Health and Human Services.

Whatever the final result of the NIH and other investigations, the Baltimore case has already given some of science's most prominent members and institutions a black eye. And there is little question in the minds of many prominent scientists that the damage has been partly self-inflicted. As Harvard molecular biologist Walter Gilbert, who has watched the case closely, says: "Everyone could have walked away after making a public retraction.... I'll never know why David [Baltimore] defended the paper down the line like that. There was no reason to defend the paper that way." ■ DAVID P. HAMILTON

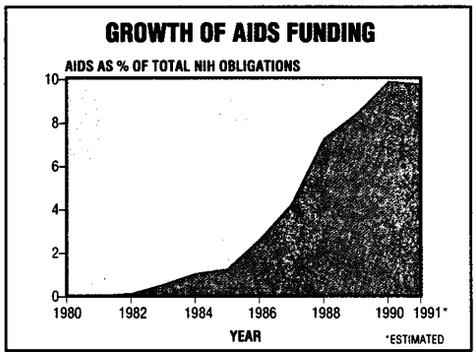
Putting AIDS Research in Perspective

In 1985, the National Institutes of Health was spending a mere $64 million a year on AIDS research and activists were pounding on Congress's doors demanding big increases. They got their way: NIH is now spending more than $800 million a year on AIDS-related research, nearly 10% of its total budget. But is all this money being spent on the right things?

"Mostly yes" is the perhaps unsurprising answer from the biomedical research establishment: a committee of the Institute of Medicine chaired by Washington University Chancellor William H. Danforth, which was asked by NIH to look into the question. But, in a report released yesterday,* the committee identifies segments of NIH's AIDS activities that need strengthening, as well as programs that might be cut back without harming the overall effort.

Take epidemiology research. The populations most affected by AIDS have changed dramatically in recent years. Women, children of infected mothers, and intravenous drug users have emerged as important populations to study in order to understand the spread of AIDS. The report suggests that NIH take a hard look at some of its long-term studies composed largely of homosexual males and decide whether the data these are producing are still worth the investment.

Also, the committee says it is time for the AIDS Clinical Trials Group (ACTG) to narrow its focus. ACTG has overextended itself, the report says, trying to do too many trials. ACTG should focus on drugs for opportunistic infections and trials of drugs or drug combinations that are unlikely to be conducted by the pharmaceutical industry.



Reaching a plateau. *AIDS research will account for 9.7% of NIH's $8.3-billion budget in 1991.*

In contrast, basic biological research, basic behavioral research, nursing research, and research on opportunistic infections associated with AIDS are all in need of increased support, the panel says. In particular, the committee argues that NIH should devote more attention to vaccine research and step up planning to test vaccines in humans. This will also mean that NIH will have to ensure an adequate supply of primates for vaccine development.

NIH's point man for AIDS, Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases and the associate director of NIH for AIDS research, says most of the criticisms the panel came up with are already being addressed. The report, says Fauci, "represents a static evaluation of a process that is dynamic.... A lot of what they're recommending has been done, is being done, or is being planned to be done." For example, Fauci says ACTG's structure and direction is being reviewed, and ACTG members will be given financial incentives to do a better job recruiting women and minorities to participate in trials. And he says several epidemiological studies are currently being reevaluated, and older studies like the multicenter AIDS cohort studies may be cut back. As for a 5-year plan, Fauci endorses it in principle, but "you have to be careful," he says. "Science doesn't always work by plan." Still, Fauci admits that it is unlikely that AIDS budgets will expand dramatically in the future, so planning will be that much more important.

Although it was not part of its charge, the committee leveled a blast at shortcomings in health care for AIDS victims. NIH's job is to facilitate discovery and evaluation of "therapeutic, diagnostic and preventive agents, and not to assure health care," the report notes. At $164 million, the NIH clinical research budget is not nearly enough to care for the more than 60,000 AIDS patients in this country. If NIH is asked to shoulder this clinical care burden, the report warns, it will threaten the institute's ability to conduct clinical research. ■ JOSEPH PALCA

* *The AIDS Research Program of the National Institutes of Health* (National Academy Press, Washington, D.C. 1991).