

I: Inside the Gallo Probe

Ever since 1984 when he was hailed as the man who discovered the cause of AIDS, Robert C. Gallo has been under fire from critics who say he stole credit for his victory from scientists in France. The discovery has been the subject of countless news accounts and an unprecedented settlement signed by heads of state. But through it all, Gallo has never told his side of the story blow by blow.

Now, because of a new, and still unfinished, reexamination of all the issues by a panel of experts at the National Institutes of Health, Gallo is laying out his story for a jury of his peers. While the jury's verdict may take months, key elements of the Gallo defense are already emerging.

The new inquiry is driven by allegations published last November in the *Chicago Tribune* that Gallo, either by "accident" or "theft," claimed as his own an AIDS-causing virus first discovered by Luc Montagnier and his colleagues at the Pasteur Institute in Paris.

Now, 6 months into the panel's still secret deliberations, *Science* has obtained copies of hundreds of pages of documents Gallo has submitted to the NIH panel.

Science has also examined pages from laboratory notebooks of Gallo and his colleagues. We have reviewed documents obtained under the Freedom of Information Act (FOIA), as well as documents obtained by the well-known mechanism of the Washington leak. We have spoken to a number of persons close to the AIDS discovery—those who are on the "Gallo team" and those who are not.

What follows is an account of the ongoing NIH inquiry, where it stands, and what we surmise about its substance to date.

On 8 April, the NIH's inquiry panel, which has been conducting a "preliminary fact-finding" mission since December, held its first meeting with Gallo. The panel is being run out of the NIH's office of scientific integrity, with unusual oversight by an independent committee of scholars nominated by the National Academy of Sciences and the Institute of Medicine (see box, p. 1498).

At the end of the inquiry, the NIH panel must conclude either that there is no evidence of wrongdoing, and therefore the matter should be closed, or that there is sufficient reason to call for a full dress investigation by some procedure that remains a mystery to most of the principals involved. This may take a while, because, to date, the committee has reportedly only addressed—though in great detail—one of the principal areas of contention: the question of the AIDS isolates themselves. It is not clear right now how deeply it will probe other issues that have been laid before it (see box on p. 1497).

Gallo has said he welcomes the

inquiry and, in a prepared statement to the panel, said, "I am confident that this review body will learn that my co-workers and I have been wrongly treated, that there has been no wrongdoing in my laboratory, that there has been substantial misrepresentation in select press, and we hope that these evaluations will be able to help us rectify these misconceptions." This was his opening salvo at an hours-long session that began a series of interviews with the panel during the past 2 months.

Key documents given to the panel to support his contention detail the work in Gallo's lab on a variety of putative AIDS virus samples from 1982 through early 1984. It was in the 4 May 1984 issue of *Science* that Gallo and his colleagues published four papers that nailed down the evidence for virus causation and laid out the process for developing a test for detecting the AIDS virus in blood. In particular, Gallo highlighted data on viruses (named for the patients from whom they came) called CC, MoV, RF, MN, and SN.

These data are important to Gallo's case because *Tribune* reporter John Crewdson has suggested that the only AIDS virus that was yielding productive experimental data was the French virus, LAV, which Montagnier sent to Gallo for testing in July and, again, in September 1983. Gallo's contention is that these data should lay to rest any thought that he or his colleagues had any motive for "stealing" the French virus rather than using one of their own.

Is Robert Gallo's confidence justified? In an effort to get an independent yet expert reading of some of the data crucial to the dispute, *Science* asked a small number of senior scientists with no direct involvement in the issues to review the documents we have obtained. They agreed to do so off the record.

On the basis of what they have seen (admittedly only part of the evidence the panel has), their opinions are consistent on the matter of other viruses. One reviewer summed it up this way: "There's just no evidence of any fraud here. It is clear that Gallo's lab was working on other AIDS retroviruses extensively before they got LAV and simultaneously once they had it. Unless all these documents are forgeries in the greatest conspiracy since Watergate, you have to accept that there were other viruses."

Another concurs. "LAV was not the only virus being studied. They have a very serious and good argument for that."

The specifics in the indictment against Gallo are laid out in the *Tribune's* article of 19 November which has been widely circulated among biologists around the world. The article also caught the attention of Representative John Dingell (D-MI) and is the basis of his demand that NIH initiate an inquiry. To decide for themselves

THIS SPECIAL REPORT, in two parts, covers the ongoing controversy surrounding Robert C. Gallo, the National Cancer Institute's star AIDS researcher. The articles are based on dozens of interviews and on documents presented to the NIH committee investigating Gallo's role in the discovery of the AIDS virus.

Part I: *Inside the Gallo Probe* covers the NIH investigation, the Gallo defense, opinions of outside scientists about that defense, and a sketch of where the inquiry may go from here.

Part II: *HUT78, the Untold Story* is the tale of H9, the cell line Gallo's lab used to grow the AIDS virus. H9 turns out—after much confusion—to be HUT78, a line provided to Gallo long ago by colleagues at NCI. Did those colleagues get enough credit? This, too, will be part of the NIH investigation.

about the Gallo lab activities, the panel has been examining the chronology of events that surrounded the isolation of the AIDS virus. These events arise out of a day in April 1984 when former Health and Human Services Secretary Margaret Heckler called a press conference to announce that Gallo *et al.* had found the cause of AIDS and developed a sensitive test to show whether the AIDS virus is present in blood.

The clear implication of Heckler's press conference was that the National Cancer Institute had won the race. But the very day before Heckler's show, the *New York Times* ran a lengthy front-page article in which the head of the U.S. Centers for Disease Control (CDC) in Atlanta was quoted as saying that CDC researchers had evidence that the French virus was the cause of AIDS. Thus, dissension in the ranks of the U.S. scientific AIDS establishment became public and the stage was set for a conflict that has grown more inflammatory with the passing of years.

Gallo's position is that, yes, the French were the first to publish on LAV. In its 20 May 1983 issue, *Science* published a series of papers on AIDS, including two from Gallo and one from Montagnier. Montagnier's paper, whose publication Gallo endorsed, reports early data showing that LAV is a new virus but says "the role of this virus in the etiology of AIDS remains to be determined."

One of the crucial contributions from his lab, Gallo argues, came in making that determination during the course of the next year and developing a useful blood test which was patented by the U.S. government. Gallo's challenge now is to defend the claim for a second time. The first challenge came in 1985 when New York attorneys representing the Pasteur Institute alleged that Gallo had "misappropriated" LAV in developing the blood test. That conflict was settled by a negotiated agreement signed in 1987 not only by Gallo and Montagnier, but also by U.S. President Ronald Reagan and French premier Jacques Chirac. Like a referee holding up both prizefighters' arms, the agreement declared Gallo and Montagnier to be "co-discoverers" of the AIDS virus.

The patent fight was handled largely by the lawyers. This second round, however, will be adjudicated by scientists, and Gallo himself is playing a much more direct role in presenting data from his lab. Much of it, which has never been published, constitutes "supporting evidence" for data that have been reported in peer-review journals.

Among the first issues raised in Crewdson's article is whether Gallo's team was working on AIDS virus samples before receiving LAV from Montagnier. Montagnier got his sample LAV/BRU in December 1982.

A chronology Gallo submitted to the NIH panel, backed up by lab records, shows that the lab "had three new AIDS samples in culture" in May 1982, another in August, and five additional samples in October. Records show that the growth in culture was modest. Indeed, the real challenge on both sides of the Atlantic in the early research days was getting good viral growth.

"This was at a time when no one knew how infectious the causative agent might be," Gallo said in a statement to the panel, but he predicted in August that it was a retrovirus. Most likely, Gallo

thought, a variant of the first human retrovirus, HTLV-I, which he and his colleagues had discovered.

Then, in December 1982, from the hundreds of blood samples they received, Gallo's colleagues detected the presence of reverse transcriptase—the enzyme that is the telltale sign of a retrovirus—in two patients. These samples also tested negative for the p19 and p24 proteins that characterize HTLV-I. HTLV-I was used as a benchmark as researchers tried to figure out what they had in their cultures. In February 1983, two additional samples were found with the same profile: positive for reverse transcriptase but negative for

HTLV-I. It turned out that what they were seeing was, in fact, a new virus, but it was not fully appreciated at the time.

Looking at the data in retrospect, documents show that Gallo's lab was working early on with several virus samples that later turned out to be the AIDS virus—HIV. The earliest of those is in the history of the sample CC. In February 1983, according to the documents, a sample from an AIDS patient identified by the initials CC was established in culture by one of the lab technicians, Ersell Richardson. CC was tested for reverse transcriptase (positive), was examined by electron microscopy, and found to have "aberrant viral particles," suggesting particles that were not

HTLV-I. Yet, further analysis indicated the presence of HTLV-I proteins.

According to the documents, Gallo, Richardson, and retrovirologist Mikulas Popovic "noted and discussed the different kind of retrovirus present" in CC. The record also shows that by 13 May the growth of cells was "poor" and that by 16 May "cells are dying." Nevertheless, the viruses from the CC sample were kept in culture through August 1983, as the researchers puzzled about the cell death, further indication that something other than the HTLVs were involved: the human retroviruses known at the time—HTLV-I and HTLV-II—don't kill cells; they immortalize them.

Indeed, the ultimate solution to that mystery, discovered later, was that CC was in fact doubly infected, with both HTLV-I and HIV. Gallo's group did not publish these early data that hinted at a new retrovirus. Instead, their first papers focused on the possibility that the AIDS virus was a member of the known HTLV-I and HTLV-II family of retroviruses. Meanwhile, in Paris, Montagnier detected reverse transcriptase in LAV/BRU in February 1983 and asked Gallo to provide reagents so that his group could further distinguish the virus. Using Gallo's reagents, Montagnier showed that his virus was distinct from HTLV-I and HTLV-II. Montagnier did publish his data.

Not long after this, there was a key interchange between Gallo's lab and Montagnier's, which created the possibility that Montagnier's virus ended up in Gallo's own isolates.

Gallo has responded by detailing the exchange that brought LAV to his lab. According to the documents Gallo's team submitted, two key things happened shortly after the May publications in *Science*. In July, Montagnier sent Gallo a sample of LAV/BRU. At that time, Gallo said in his statement to the panel, Montagnier also announced he did not wish to have a collaboration between the two labs.



The Gallo lab meeting, 1988. Gallo and Montagnier (fourth and fifth from left) had buried the hatchet.

Collaboration or no, Gallo now had LAV/BRU. One question that is central to the running Gallo-Montagnier drama is this: What did Gallo do with the sample Montagnier sent him? Apparently, initial attempts to get virus to grow from that first sample failed. "It was just supernatant. We could not get any virus," Gallo has said.

In September, Gallo received a second sample of LAV/BRU. Popovic detected virus LAV/BRU in October. According to Gallo's statement to the panel, "Mika Popovic informed Montagnier of this, and that we confirmed its retrovirus nature." In October, Betsy Read, another key technician who is still in the Gallo lab, was trying to grow various viral samples in a human cell line.

At this time neither Montagnier's lab nor Gallo's had been successful in getting the new isolates from AIDS patients to grow in continuous, mass culture. Such mass culture was needed to produce the reagents required to "type" all the viral isolates, showing that they were all the same virus and thereby establishing the cause of the disease. Much attention in both labs was devoted to this search.

Betsy Read managed to get the LAV/BRU sample from Montagnier's lab into the human cell line known as HUT78. "The production of virus was transient," Gallo's statement to the committee says. "Low but continuous" growth of LAV was achieved shortly thereafter in another human cell line, Ti7.4.

Another crucial area of inquiry is what other, independent work on the AIDS virus was going on in Gallo's lab after LAV arrived from Paris. Part of the Gallo response has been the history of MoV, a virus which appeared to be a variant of HTLV-II, which came from patient Mo. Crewdson has suggested that MoV is an LAV contaminant.

By November, Gallo lab notes show, the MoV was in culture in HUT78 cells. On 29 November supernatant from that culture was used to infect a HUT78 clone designated H4. In December infected

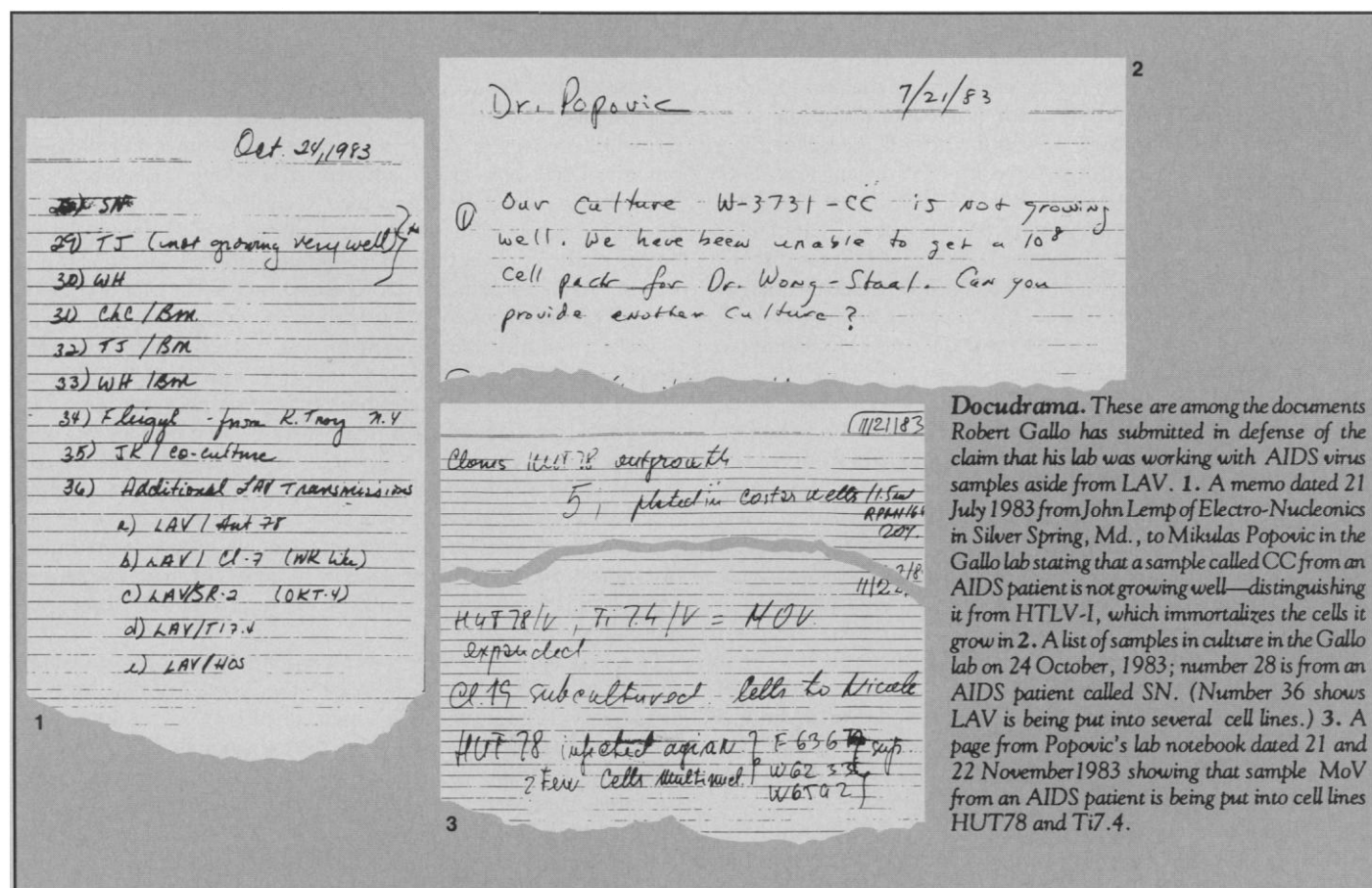
cells were sent to a contractor for electron micrographing. Micrographs showed virus particles that were consistent with what has turned out to be HIV. Further experiments through December 1983 and January and February 1984 suggested that MoV was neither HTLV-I nor HTLV-II. At the time, lab researchers were unsure whether MoV was a new virus or a contaminated culture.

Crewdson had reported that MoV may, in fact, be LAV, contaminating the culture. Even if MoV is LAV, the Gallo defense contends that MoV was not the only isolate brewing in the lab at the time. Another isolate that was ultimately very successful, Gallo records indicate, came from a patient known as RF. "On November 9, 1983, serum and frozen [peripheral blood lymphocytes] were received . . . from diagnosed AIDS or ARC (AIDS-related complex) patients. . . . On November 15, 1983, 11 samples [were] put into culture," notes say. One of them was RF, which Read nursed along until it was growing vigorously by April.

For a time, initial work going on in one lab with LAV and in Read's with RF might be described as similar. But in January, Gallo decided to put LAV in the freezer.

While Read was working on RF, the Gallo documents indicate, Popovic decided to take another tack in his efforts to get continuous viral growth in a human cell line. Popovic decided to pool viruses—first from three, and ultimately from ten different patients—into a single culture. The procedure has been described as "unusual" by other researchers who point out what Popovic says is "obvious"—it was not a scientifically "clean" experiment. "I was not trying to do a perfect experiment," Popovic has told *Science*. "I was trying to make a blood test." (He says he did not add LAV to the pool.)

Why pool the viruses? Popovic reasoned that the failure to grow might be tied to the fact that none of the viruses individually was producing high concentrations of reverse transcriptase. Maybe if he



dumped ten viruses into the same pot, the reverse transcriptase level would be enough to jolt one of them into action.

"The logic behind that is really crazy," says one of the scientists who has commented on the Gallo documents for *Science*. "But there is no doubt that he did it." And there is no doubt that from the pool came a virus named IIIB that grew like a charm—and was used for the work that led to the blood test. Yet subsequent genetic analysis has shown that IIIB and LAV are remarkably alike. Where most AIDS viruses seem to be cousins, IIIB and LAV appear, genetically speaking, to be almost as close as twins. But, Popovic says, "biologically they were not the same in the way they behaved."

The remarkable genetic similarity between LAV and IIIB has added much additional fuel to the controversy and bolstered the idea that Gallo might somehow have "stolen" Montagnier's virus. Is IIIB really LAV? Did LAV get into the pool by accident? Was it added deliberately but covertly?

Gallo has responded furiously to the idea that Montagnier's sample was consciously appropriated. "We emphatically deny this outrageous slander," Gallo told the NIH panel. "We would have had little reason to use LAV for the [AIDS] blood test. We had RF available, which could have been used instead of IIIB. Thus, again, the answer is 'no.'"

Yet even Gallo has consistently acknowledged that the similarity between the two implies that they could be the same isolate. "Could LAV have inadvertently contaminated our cultures and suddenly dominated the culture by rapid growth? This is certainly possible, since LAV was present in the same laboratory where some of our isolates were developed. Indeed, if this were the case, although it would not make me happy, I do not believe it would reflect negatively on our accomplishments, just as it would not add to the Pasteur accomplishments. Our work never depended on a single isolate."

One of *Science's* confidential reviewers has no trouble accepting this line of argument: an accidental contamination. "If you've ever

worked with vials frozen in liquid nitrogen, you'd know," our reviewer says. "A big cloud of smoke comes out when you open the door. You're wearing big gloves. In Gallo's lab, you're not dealing with just a few frozen samples but dozens and dozens. Labels fall off. Lots of people use that freezer. That's one of the arguments people have against big labs like his. [It has 36 members.] But it's also very creative. I don't know. Which is better? Perfect or creative?"

The defense is that the existence of other isolates argues against any motive for "theft." Yet if there were at least two other, independent, isolates in culture—MoV and RF—and, to top it off, IIIB came from a pool, why not use one of the others for the main scientific work and for the blood test?

The possibility that MoV was contaminated ousted that isolate as the one to be used for the blood test. And in past interviews with *Science* that took place before the controversy was resurrected, Gallo has talked about why IIIB was preferred to RF. The growth of IIIB was just a little more vigorous than RF, he has noted. Furthermore, IIIB had been growing a little longer. "RF was maybe a few weeks behind," Gallo says. And, IIIB was what Gallo calls an "American" virus—derived, he assumed, from an American AIDS patient, whereas RF was Haitian. Intuition, nothing more, Gallo says, made him think that there might be differences in the viruses related to geographic origin that were unknown but might be important in a blood test.

"Mika wanted to go with RF for the work on the blood test because it was a single isolate and worked nearly as well as IIIB," Gallo told *Science*, "but I said, 'No. IIIB looks good. Let's go with IIIB.'"

Now for the other question: Is IIIB really LAV? Conventional wisdom among virologists holds that the close similarity between IIIB and LAV argues in favor of their being the same—that LAV did in fact contaminate a culture in Gallo's lab and reemerged as IIIB. In 1985, the sequences of the genomes of each isolate were determined and, as Gallo told the panel, "They differed only by

What the Probers Want to Know



William F. Raub

The internal NIH panel that is conducting a fact-finding inquiry into allegations of misconduct in the laboratory of Robert C. Gallo has been instructed to "assemble and analyze" information on 14 points that were outlined by NIH acting director William F. Raub in a letter to Congressman John D. Dingell on 9 February. Raub's questions were triggered by a 50,000-word article by John Crewdson of the *Chicago Tribune*

in November of last year.

While the committee may eventually look at other aspects of the Gallo lab, for now it is focusing its attention on these key points:

1. Is there evidence that Gallo's lab was growing in culture AIDS virus isolates other than the French virus, LAV, in 1983?
2. When did Gallo's lab first get LAV to grow in culture? Was the growth successful? What use did Gallo's lab make of LAV?
3. One of the Gallo virus isolates used to develop the AIDS blood test is called IIIB. It was the strongest growing virus in a pool of ten separate viruses. What are the scientific details of the "pool" experiment?
4. Was there virus contamination in the lab?

These questions pertain to the central allegation: that the Gallo virus (IIIB) is really Montagnier's virus (LAV). But the scope of the inquiry goes beyond issues of possible fraud to questions of collegial

behavior. The scope is revealed here.

5. The origin of the cell line called H9 in which the AIDS virus grows permissively [see article, p. 1499].

6. In May 1983, Luc Montagnier published a paper on LAV which he transmitted to *Science* via Gallo. With Montagnier's consent, Gallo wrote an abstract for the paper, which had been sent in without one.

7. At a retrovirus meeting in Park City Utah in February 1984 Montagnier's colleague Jean-Claude Chermann gave a talk on LAV. Crewdson claims Gallo tried to prevent Chermann from speaking at the meeting.

8. In the fall of 1983 at a meeting at Cold Spring Harbor, Gallo presented data that were updated in the final manuscript published as part of the symposium proceedings.

9. Before the AIDS virus was clearly named, a technician used the French term LAV, plus an additional marker letter, to designate various virus samples that were being screened in Gallo's lab.

10. Questions about a genetic map of the virus.

11. Questions about an isolate in Gallo's lab called MoV.

12. Virus samples were sent to outside labs to be photographed by an electron microscope; there are questions about what they showed.

13. During the course of the patent dispute, memos about the identity of various virus samples were gathered from all labs and offices that had copies. In one case, an altered memo turned up. HHS lawyers say the altered memo did not come from Gallo's lab, but they do not know where it did come from.

14. Questions about the discovery of HTLV-1 in 1978. ■ B.J.C.

about 100 nucleotides (1%) whereas most other isolates differed by 5% or more." And, recently developed evolutionary trees of HIV also argue for the identity of IIIB and LAV, he said.

Yet new data—one published paper* and a report at a retrovirus conference this spring in Keystone, Colorado—are turning up evidence that viruses that come from the same cohort or population may be much more like each other than anyone has known, raising the possibility that LAV and IIIB are indeed different isolates. One of the people whom *Science* consulted is familiar with the information that is coming out on the subject and says, "Maybe we're not so sure we know what the situation really is any more."

This is where the inquiry stands so far. It seems to have zeroed in on the question of whether there were other isolates than IIIB in the lab at the time that virus was being grown. Gallo's defense, as contained in the documents submitted to the panel, is that there were many others, including at least two—MoV and RF—that were growing in cell lines. What the committee will decide about this information, and other evidence, however, is anybody's guess.

Where does the inquiry go from here?

The NIH inquiry panel is completing interviews with certain

members of Gallo's lab and is likely to meet with Gallo himself at least once more. Then it will present its conclusions to its own advisory committee—the one whose members were nominated by the National Academy of Sciences and the Institute of Medicine. Chaired by Frederic Richards of Yale, and made up of individuals who neither know Gallo nor have great prior familiarity with the case, the first task of this independent jury of peers will be to judge whether the NIH panel has done a good job.

If the committee is not satisfied that the panel has asked all the right questions and assembled all the right data to support its recommendation to drop the matter or proceed with an investigation, the committee is empowered to tell the panel to keep on working. If, on the other hand, the committee accepts the panel's recommendation, it will be incumbent on the committee to state its reasons unambiguously.

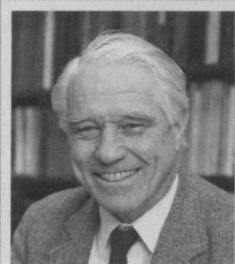
This is a very important issue for NIH. Gallo is not only a scientist but, because of his great celebrity, a symbol. NIH has to prove that it can handle investigations of misconduct or else the authority to inquire into allegations on its own may be taken from it. If the panel and committee exonerate Gallo, NIH will have to stand up to critics who have already made up their minds. If he is not exonerated, NIH will have to act decisively to right the situation.

Either way, the stakes are high for NIH and for Robert Gallo.

■ BARBARA J. CULLITON

*T. McNearney *et al.*, "Limited sequence heterogeneity among biologically distinct human immunodeficiency virus type 1 isolates from individuals involved in a clustered infectious outbreak," *Proc. Natl. Acad. Sci. U.S.A.* 87, 1917 (March 1990).

The Committees



Frederic M. Richards

The NIH inquiry into the case of John Crewdson v. Robert Gallo is special in many respects. First, the inquiry is entirely focused around allegations in a newspaper article. Second, it is the subject of unusual public interest because of Gallo's scientific prominence. And third, to ensure the independence of the inquiry, which is being conducted by a panel of federal scientists, NIH asked

the National Academy of Sciences and the Institute of Medicine to nominate an outside committee of expert but disinterested parties to oversee the activity of the internal panel.

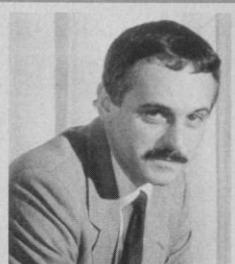
Yale University biochemist Frederic M. Richards, who is described by colleagues as a man of exceptional integrity, has agreed to chair the committee (*Science*, 30 March, 1533).

The Richards' committee—a jury of Gallo's peers—has met once to discuss procedures and will meet again on 27 June for its first substantive report from the NIH's fact-finding panel. Richards says it is vital to realize that his committee is an "advisory body. Contrary to what some people assume, we are *not* conducting the investigation." Sources say committee members have promised not to discuss their deliberations until they are complete. At that point, they expect to "speak out loud and clear."

The NIH panel includes biochemist Jules Hallum, new head of the institutes' Office of Scientific Integrity, and Suzanne Hadley, also in the Office of Integrity. The others are Richard H. Adamson, scientific director of the National Cancer Institute's division of cancer etiology (Gallo's lab is in Adamson's division); Paul Parkman, a virologist at the Food and Drug Administration; and NIH counsel Robert B. Lanman.

■ B.J.C.

Foreign Affairs



Maxime Schwartz

Scientists in the United States are not the only ones with a keen interest in the outcome of the current NIH inquiry into the affairs of Robert C. Gallo. The director of the Pasteur Institute, which has had a key role in the struggle over priority for the discovery of the AIDS virus and over the patent for the AIDS blood test, recently expressed hope that the NIH investigation would settle the matter quickly and cleanly—and made it

clear that, for now, the French are not interested in stirring things up further.

In April, Maxime Schwartz requested a meeting with the science attaché at the American Embassy in Paris to discuss the agreement signed in 1987 declaring Gallo and Luc Montagnier of the Pasteur to be "co-discoverers" of the AIDS virus. After the meeting, held on 19 April, the attaché cabled State Department officials in Washington to summarize what had been discussed. *Science* has obtained a copy of the cable.

"Schwartz began the meeting by stressing that it was the American press that had restarted the controversy and that the Pasteur Institute had no desire to re-open the question," the cable says.

The 1987 agreement was intended to resolve the dispute over conflicting claims to the AIDS test patent. Because it was signed by U.S. President Ronald Reagan and French premier Jacques Chirac, the current revival of the matter could have diplomatic implications.

"It is not a Franco-American problem at this point," Schwartz is quoted as telling the attaché, but "it may become one later." Schwartz said it would be "better for NIH to settle the matter clearly and quickly in order to forestall a possible congressional investigation that, he thought, would only fuel the controversy."

■ B.J.C.