

## Hints Emerge From the Gallo Probe

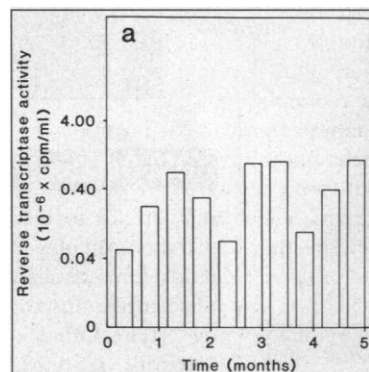
*NIH documents criticize Gallo, accuse Popovic of misconduct, and may even reopen the Franco-American patent dispute—but have come under fire themselves*

LIKE TINY RIVULETS OF WATER THAT PRESAGE the collapse of a dam, revelations in the 18-month National Institutes of Health (NIH) investigation of AIDS researcher Robert Gallo and his former colleague, Mikulas Popovic, have begun to trickle through the barrier of secrecy erected around the case by NIH's Office of Scientific Integrity (OSI). According to internal NIH documents and individuals familiar with OSI's draft report—completed nearly 2 months ago, and since circulated among the principals in the case for comment—the draft report accuses Popovic of scientific misconduct in the preparation of a 1984 *Science* paper he coauthored with Gallo. While the report does not similarly accuse Gallo, sources say it criticizes him sharply. Meanwhile, another recently surfaced OSI memorandum that could reflect on the validity of the U.S. government's patent rights to the HIV blood test developed in Gallo's laboratory has raised another set of intriguing questions.

The information on the Gallo case that has surfaced to date provides the deepest insight yet into one of OSI's most important, and most controversial, misconduct investigations. Because this case is seen as a bellwether of how thoroughly NIH can investigate its own scientists—particularly one as prominent as Robert Gallo—it has drawn close scrutiny and considerable criticism, especially in light of the events surrounding the departure of OSI investigator Suzanne Hadley from the case (*Science*, 26 July, p. 372). In recent weeks, OSI has been caught between Representative John Dingell (D-MI), who wants NIH to establish its credibility by conducting tough misconduct investigations, and NIH director Bernadine Healy, who has blasted the office for what she terms "horrendous management failures, sloppy performance, and failure to abide by [its] own guidelines" in conducting the investigation. More recently, lawyers for Gallo and Popovic have joined a rising chorus within the scientific community, complaining that OSI is unable or unwilling to protect the due process rights of its targets.

In such a volatile atmosphere, and with the investigation still officially unfinished, NIH officials have made a strenuous effort to keep the draft report under wraps—even

to the extent of forbidding a panel of consultants chosen by the National Academy of Sciences (NAS) to review the report outside the offices of the OSI. Despite such precautions, however, *Science* has pieced together some of the main charges in the draft report, which focuses on the 1984 paper in which Gallo and Popovic announced the discovery of the AIDS virus.



**Cast of characters.** Former OSI investigator Suzanne Hadley (right) authored a draft report that accuses former NIH researcher Mikulas Popovic (upper right) of misrepresenting data in a 1984 *Science* paper. Above, the disputed Figure 2a that allegedly described viral activity in a "continuous" cell culture.



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One charge centers on the paper's Figure 2a, which purports to show the reverse transcriptase (that is, retroviral replication) activity of the AIDS virus—then called HTLV-III—in a cell line named H4. The figure caption describes the HTLV-III production in H4 as "continuous" for a period of 5 months, and the paper's text states that H4 "consistently" showed reverse transcriptase activity "for over 5 months." The paper also reports figures on cell viability and doubling time calculated from the "continuous" culture.

OSI documents, however, state that this culture was reinoculated with additional virus samples as late as 2 January 1984—less than 3 months before Gallo and Popovic submitted the paper to *Science*. Such reinoculations "disqualify the culture as 'continuous,'" wrote OSI director Jules Hallum in a draft letter of 1 July to M.G. Sarngadharan, another coauthor of the paper who is now also under investigation (see p. 727). In addition,

the reported viabilities and doubling times are "meaningless" figures for which "no data exist," according to an internal OSI memorandum authored by former investigator Hadley. (This memorandum was first described last Sunday in *The Chicago Tribune*.) OSI considers Popovic at least partly responsible for these "misrepresentations."

OSI investigators have also attacked the paper's description of how Popovic created a cell line infected with HTLV-III by exposing it to a "pool" of supernatant fluids from ten AIDS patients. The paper states that the fluids were "first shown" to contain reverse transcriptase, suggesting that Popovic selected only supernatants he knew to contain retrovirus. But OSI has determined that only one of the ten supernatants had been shown to test positive for reverse transcriptase before Popovic created his pool. (Records from Gallo's laboratory also show that "several" of the samples used in the pool later tested negative for reverse transcriptase, sources say.)

A third charge in the draft report concerns the immunofluorescence assays performed on several clones of what the *Science* paper called HT—the first cell line infected with HTLV-III. One table in the paper reports that assays were "not done" (signified by the notation "ND") on a set of four clones. The OSI investigation, however, determined that for three of these clones, "the data show the experiments were done and the results were negative," according to Hadley's memo.

Popovic has not taken these and other charges in the draft report lightly. He provided a written statement to *Science* and followed it up with an exclusive interview. In his statement he asks OSI to withdraw its report, saying the draft betrays "a lack of understanding of the basics of retrovirology" and is flawed by "numerous procedural and factual errors." Popovic has also justified his creation of the virus "pool" and the "continuous" cell line (p. 730) and has explained

the misstatements in the paper as resulting from editorial changes he did not control (see story on this page).

While Popovic has issued the sharpest denunciations of the draft report, nearly everyone outside of OSI who has read it seems to have harsh words for it. Some members of the panel convened by the NAS—known as the “Richards Panel”—initially complained that the draft report was too harsh with Popovic and not tough enough on Gallo, although the panel has since accepted the substance of the report. But the panel remains critical of the report’s format, joining Healy in complaining that it is poorly written and that it undercuts its own points by failing to state clearly the issues, the findings, and the conclusions (p. 732). OSI is now drafting an Executive Summary for the report that will provide just such a concise statement.

In addition, Healy and the Richards Panel have accused OSI of committing technical violations of its policies and procedures while conducting the investigation. Mary Jane Osborn, a Richards Panel member, told *Science* that trying to figure out OSI’s guidelines for conducting investigations was “a continuing problem.” For instance, she said, OSI’s preinvestigation inquiry seemed to take far too long, but the panel was never able to obtain written guidelines for the conduct of intramural inquiries. “The business of seeming to operate in a vacuum has always been a major concern,” she said.

Whatever its faults, completion of the draft report signals that a new phase of the Gallo-Popovic affair is beginning. The investigation of the *Science* paper, which forms the substance of the OSI draft report, is only one of several ongoing probes into Gallo’s isolation of HIV. Other issues yet to be addressed include the validity of the U.S. patent on the HIV blood test and the question of whether or not Gallo actually misappropriated the virus he called HTLV-III<sub>B</sub> from French researchers at the Pasteur Institute.

An intriguing window into these two questions opened early this week when *Chicago Tribune* reporter John Crewdson published an article describing the contents of Hadley’s memo, which could affect the validity of the government’s patent on the AIDS test. (*Science* later obtained a copy of the confidential memo.) Written in early June, the memo lays out numerous contradictions between official statements in patent filings and legal declarations and the findings of the OSI investigation. While one NIH source sympathetic to Gallo insists that “the patent is solid” despite the OSI findings, other sources point out that willful false statements in a patent application can be grounds for invalidating the patent.

Perhaps the biggest surprise in Hadley’s

memo is the news that the first virus Gallo’s laboratory managed to grow in a continuous cell culture was none other than LAV—an isolate supplied by the Pasteur Institute. Gallo’s declaration states that while Popovic did attempt to infect two cell lines with LAV in mid-October 1983—at least a month before establishing the cell line that produced HTLV-III<sub>B</sub>—“both transmissions were only temporary in nature.” Hadley, however, notes in her memo that LAV continued to grow in Gallo’s laboratory until Gallo ordered Popovic to freeze the cultures away in January 1984. These transmissions

of LAV “were no more ‘temporary’ or transient than HTLV-III<sub>B</sub>, which was nurtured with fresh cells as well as virus to keep it alive,” Hadley wrote.

The future of OSI’s investigative work in this case remains uncertain, given the rough ride the misconduct office has taken in recent weeks. The controversy over the draft report and an ongoing administrative and management review at OSI seem likely to add considerably to the delay in releasing the final report. And even then, legal and procedural challenges will be waiting. OSI’s long trek is far from over. ■ DAVID P. HAMILTON

## Popovic Blasts Accusers, Demands Report Be Withdrawn

THE DRAFT REPORT FROM THE OFFICE OF Scientific Integrity (OSI) is particularly hard on Mikulas Popovic. Indeed, *Science* has learned that the report concludes Popovic is guilty of scientific misconduct as the result of false statements and data in the May 1984 *Science* paper in which he, Robert Gallo, and their colleagues at the National Cancer Institute reported that they had succeeded in growing the retrovirus that causes AIDS in permanently established cell cultures.

But Popovic isn’t accepting that verdict. Far from it. In a written statement and exclusive interview provided to *Science*, Popovic, along with his lawyer, Barbara Mishkin of the Washington, D.C. firm of Hogan and Hartson, argues that “there is absolutely no basis for any conclusions of falsification, fabrication or misrepresentation” in the *Science* paper. Furthermore, they add that “because of the numerous procedural and factual errors” in the OSI draft, “we have asked that the report be withdrawn.”

More is at stake than credit for isolating the virus. The 1984 paper was the first description of a crucial step in the development of a blood test for the AIDS virus: a technique for growing sufficient quantities of the virus to mass-produce the test. OSI investigators have questioned several claims made in the paper.

■ The draft report says that although the paper claims that a continuous culture was achieved in November 1983, in fact that did not happen until sometime in January 1984. In between, the report says, Popovic and his colleagues added fresh virus and cells to the culture to keep it going. In the interview, Popovic claimed that the dispute is purely semantic. He concedes he added fresh virus to cell cultures when the percentage of infected cells in the culture dropped below 10% to 30%. He did this to hasten the

development of cell lines continuously producing virus—and not because he worried that the virus would stop growing in the infected cultures. Popovic contends that he had used the technique of “refeeding” cultures in the past and that no one had ever challenged his subsequent use of the term “continuous production.” (See letter on next page for details.)

■ The OSI report points to an error in the paper when it says that the infected cell cultures continuously produced virus “for over 5 months.” When the paper was written the virus had been cultured for only 4 months (even granting the November starting date for continuous culture). Popovic says others in the lab are responsible for that error. He says his original draft read “over 4 months.”

Gallo has acknowledged that the draft of the paper submitted to *Science* on 30 March 1984 did read “over 5 months”—which, at the time of submission, was an overstatement. Gallo says he approved the change from Popovic’s language because he knew that by the time the paper came back to his lab in galley form, the virus would have been in culture for more than 5 months.

■ The OSI draft report also raises questions about whether the virus isolates used to create the continuous culture had been tested for the presence of reverse transcriptase (RT), an enzyme produced by retroviruses. The virus described in the paper was grown from a pool made from viral samples from ten different AIDS and pre-AIDS patients. OSI investigators say that by using the words “first shown” to have RT activity, the paper implies that each of the ten samples had been tested individually for the presence of RT. Popovic says that, once again, imprecise language is to blame: All the samples were tested serologically for the