'Verdicts' Are in on the Gallo Probe

The final report of NIH's Office of Scientific Integrity and a critique of that report by outside scientists have been sent to top health officials for judgment

For two-and-a-half long years, a small cadre of scientists have been struggling to make sense of what has become one of the most complicated, contentious, and depressing scientific misconduct investigations ever: whether or not Robert C. Gallo and his colleagues were guilty of scientific misconduct for the way they conducted and then reported the crucial experiments that led to the development of a diagnostic blood test for HIV, the virus that causes AIDS. Now the "verdicts" of those scientists are in—in two forms: the final report of the National Institutes of Health (NIH) Office of Scientific Integrity (OSI) authored by one set of scientists, and a critique of that report authored by a panel of eminent researchers not directly associated with NIH.

"The investigators noted lapses of collegiality and seeming lack of proper recognition of the contributions of others."
–Bernadine Healy

© KEN HEINEN

In documents obtained by *Science*, both groups concluded that there is no evidence that Gallo "stole" a viral isolate provided to him by French scientists, but both criticize him for the way he conducted his research in the hectic months that led up to the crucial papers that demonstrated that the retrovirus HIV causes AIDS. According to a 119-page report of OSI's investigation—which has been passed up to assistant secretary of health James O. Mason for final action—although Gallo's behavior was "less than collegial" and "self-serving," it did not constitute misconduct. OSI did, however, recommend that Gallo associate Mikulas Popovic be found guilty of misconduct for errors and misstatements in a 1984 *Science* paper describing their early work.

The panel of outside scientists, drawn from members of the National Academy of Sciences and the Institute of Medicine and chaired by Yale biochemist Frederic Richards, were far more critical of Gallo than were those who wrote the final NIH report. They accused him of "intellectual appropriation" of the French viral isolate, and "essentially immoral" behavior for failing to make key cell lines freely available to other researchers. And they argued that for two counts of misconduct against Popovic, there was no clear reason why Gallo should not share the blame.

This marked divergence in views between the two groups of scientists bodes ill for hopes that the report would at last put the matter to rest. For Gallo, the least he can expect is disciplinary action. NIH Director Bernadine Healy acknowledged in an interview with *Science* that there will be some kind of administrative response for the way Gallo behaved. But, especially in light of the chasm between the scientists on the Richards panel and NIH's investigators, Representative John Dingell (D–MI), who has already declared his belief that NIH is incapable of investigating its own scientists and has mounted an investigation of his own, will almost surely hold new hearings—perhaps the kind that thrust David Baltimore and Thereza Imanishi-Kari into the public eye. And, if that weren't enough, two other investigations of Gallo are currently under way by the inspector general of the Department of Health and Human Services (HHS) and the General Accounting Office (GAO), which are focusing on whether Gallo made false statements relating to a patent for a blood test for AIDS.

For the scientific community, however, Gallo's troubles will be less important than NIH's public credibility. Was NIH's investigatory team competent in the end, and was the probe worth the effort? To let you judge for yourself how the investigation went and what was found, *Science* has developed tables from the key documents —OSI's final report, a letter from Healy to Mason accompanying the report, and the report of the Richards panel—that show just what was investigated and what conclusions were reached (see pages 736 and 738). In addition, the accused were invited to respond to the charges and have done so.

The origin of the virus

The most serious charge leveled against Gallo and his associates is that they knowingly grew up a viral isolate supplied to Gallo's lab by Luc Montagnier of the Pasteur Institute and passed it off as their own. The basis for this charge is that the virus Gallo grew and used to develop his blood test—a virus he called HTLV-III—is genetically virtually identical to Montagnier's strain, originally called LAV. Gallo now acknowledges that the viruses are the same but says the most likely explanation is that LAV contaminated his cultures.

OSI grappled with this issue in a preliminary inquiry conducted by OSI director Jules Hallum (a virologist), then deputy director Suzanne Hadley (a psychologist), virologist Paul Parkman, director emeritus of the Food and Drug Administration's Center for Biologics Research and Evaluation, and virologist Edmund Tramont of the Walter Reed Army Research Institute. According to OSI's final report, this panel concluded in October 1990 that "[t]he resolution of this question is not possible based on information available or obtainable by OSI." Gallo has consistently maintained that he had no motive to steal the French isolate because he had other isolates in his lab, and the inquiry team essentially agreed.

Does this mean that Gallo has been exonerated on this point? Both the Richards panel and Healy agree only that, as Healy put it in a telephone interview with *Science*, "There is no evidence that he stole the virus. All of the consultants said the same thing: that you are not going to be able to prove it and there is evidence that there were other viruses in his lab, and there's evidence that he thought that the virus he was growing in his lab in continuous culture was his isolate and not the French [isolate]." The Richards panel did conclude, however, that by failing to credit the French for providing an isolate that allowed them to "go to school" on the virus, the Gallo laboratory was guilty of "intellectual appropriation" of Montagnier's isolate.

The *Science* paper

Having dispensed with the larger issue of misappropriation in the preliminary inquiry, OSI in late 1990 launched a full-scale investigation* that focused on a series of errors that

*OSI investigators included Hallum and Hadley, and, later, physiologist Clyde Watkins, geneticist Barbara Williams, and biochemist Pamela Baker. They were aided by three extramural virologists: Kenneth Berns of Cornell, Priscilla Schaffer of Harvard, and Michael McGrath of UC, San Francisco. For Richards panel members, see p. 739.

appeared primarily in a *Science* paper (vol. 224, p. 497, 1984) detailing the first attempts to grow HIV in permanent cell culture. OSI's final report lists 16 "allegations" covering some 20 discrepancies between what was published and data contained in lab notebooks and other documents (see table below). A dozen of the allegations, though worrisome, didn't fit the definition of misconduct in the minds of the investigators, but four did and were blamed on Popovic, the first author on the *Science* paper, though not on his boss. This differential treatment mystified the Richards panel, which questioned why blame was assigned to Popovic and not Gallo with respect to two of the allegations (see page 738).

The issue of collegiality

The OSI investigation also looked into the matter of the cell line in which the Gallo team first grew the virus. In fact, the key advance described in the 1984 *Science* paper was the discovery of a "neoplastic aneuploid T-cell line, derived from an adult with lymphoid leukemia," that could be infected with HIV and produce large quantities of virus. The paper referred to this path-breaking cell line as HT, but it was actually developed from a cell line called HUT78 established by cell biologist Adi Gazdar. That raised a question first broached in detail in *Science* in 1990: Was Gazdar given appropriate credit

The Bottom Line of the OSI Report

The Office of Scientific Integrity (OSI) looked into 16 allegations of wrongdoing, virtually all of which were alleged errors and misstatements that appeared in a paper published in *Science* in 1984. The following are the allegations in the order they appear in OSI's final report, and OSI's findings for each one. The responses to the allegations are mostly taken from the report itself. Joseph Onek and Barbara Mishkin, lawyers for Robert Gallo and Mikulas Popovic, were given a chance by *Science* to review the responses and in some cases they amplified them. In each of the four cases where OSI concluded that misconduct had taken place, the finding applies only to Popovic, not to Gallo.

Allegations	Responses	Findings
1. Continuous culture. The legend for figure 2a describes a culture showing "continuous HTLV-III production," but this is misleading since the culture was repeatedly re-infected with virus and supplied with uninfected cells.	While culture conditions and times could have been presented more clearly, the culture was "continuous" in the sense that it was "self-replicating without supportive manipulations by the investigators (other than feeding and subculturing)." Usage is consistent with papers in animal retrovirology.	Clearly not a continuous culture in the classical sense, but a possible interpretation. NO MISCONDUCT.
2. Five months. The text says the culture was tested every 2 weeks for 5 months for particulate reverse transcriptase (RT) activity, but when the paper was submitted for publication, the culture had been in existence for only 4.5 months.	The culture had been growing for more than 5 months when the galley proofs were reviewed in April 1984. Also, Popovic originally wrote "over 4 months," which Gallo changed to "several months," which an unidentified author on the paper (most likely M.G. Sarngadharan) changed to "over 5 months" in the final draft.	Because it was true at the end of April doesn't explain why it was in a draft submitted at the end of March. This is misleading. NO MISCONDUCT.
3. Doubling time. No data exist to show that experiments to determine the doubling time for the culture were done.	Doubling time for the growth of the infected culture could be roughly determined despite adding fresh cells on two occasions. It was important to alert scientists that doubling time was longer than expected.	"Reader was not provided with sufficient information to reconstruct the experiment or understand its limitations," but no evidence that this was done with intent to mislead. NO MISCONDUCT.
4. Inconsistent methods. Data for RT activity in figure 2a were generated using two different methods that were not normalized and may not be comparable.	One method for RT activity, but two methods for sample preparation that were comparable to within approximately 20%, and since data were plotted on a log scale such a small change would not alter the conclusions to be drawn from the figure.	Minor differences should have been explicitly reconciled, but results of experiment "did not appear to have been misrepresented." NO MISCONDUCT.
5. Fluctuation. The apparent fluctuation in RT activity during the time the virus was grown in culture shown in figure 2a was either misrepresented or falsified.	Allegation arose from early inquiry when Popovic said he selected data to show RT fluctuations. Popovic explains he used "select" in the sense of to choose representative data points.	A legitimate scientific difference of opinion in how to "select" data. NO MISCONDUCT.
6. Density gradient. Data missing for the figure showing the sucrose density gradient used to generate figure 2b, and an implication that the same gradient was used in figure 2a, when it wasn't.	No indication that the sucrose gradient curve was not representative of experimental data on viral particle-associated RT activity. "Missing" data were discarded by contractors who generated it.	Figure could have been described more clearly, eliminating possibility that reader would be mislead, but not a misrepresentation of experiments. NO MISCONDUCT.
7. First shown. Text says that concentrated fluids used to create HTLV-IIIB pool were "first shown" to contain particle associated RT, when in fact they weren't.	True, possibly misleading. Popovic and Gallo assert that Popovic did not write the offending sentence. Gallo admits the statement was not accurate but asserts that it was an editorial error and that there was nothing to suggest deliberate misrepresentation or intent to deceive.	Misleading sentence appeared only in the final draft, suggesting a deliberate intent to deceive. Since Popovic wrote most of "methods" section, "more likely than not that Popovic was directly responsible for inclusion of the sentence." MISCONDUCT.

for his discovery, and did Gallo and Popovic conceal the origins of the cell line that had brought them success?

The OSI report concludes that if the Gallo team did not intentionally try to mislead other scientists, they did little to inform them, either. The report is particularly critical of Popovic for failing to do more to characterize HT—and in particular the H9 clone that was the best for growing the virus—which would have established that it was in fact HUT78.

As for suggestions that Gallo failed to make the cell line freely available to other researchers, OSI says he did send out uninfected cells, albeit with the requirement that prospective recipients sign an agreement that "work with these reagents will not be published without prior approval by Dr. Gallo." Gallo says this language was forced on him by his superiors at the National Cancer Institute, and was in effect for only 3 months. This apparently didn't wash with the Richards panel, which wrote: "We consider failure to distribute uninfected H9 cells freely after publication of the article...to be essentially immoral in view of the growing seriousness of the AIDS epidemic."

Healy says she accepted Gallo's defense—offered in a recent meeting that included Gallo and senior NIH officials—that he has sent uninfected cells to dozens of labs. But in her covering letter to Mason, Healy acknowledged that "the investigators noted lapses of

Allegations	Responses	Findings
8. Characterization of LAV. Text says it was not possible to compare HTLV-IIIB and LAV because LAV had not been successfully grown in permanent cell lines and therefore had not been produced in sufficient quantity to characterize. But Gallo's lab did successfully infect HUT78 and Ti7.4 cells with LAV.	Gallo says he wrote the passage about LAV. The lack of characterization was intended to refer to work done in France by Montagnier, not what the U.S. team did with LAV. Gallo says he and Montagnier collaborated on comparing the two isolates, but papers describing the results were never published.	Statement in paper is ambiguous, and could refer to French efforts only, although it therefore would not reflect well on French scientists. NO MISCONDUCT.
9. Serum mixup. Table 1 says immunofluorescence assays (IFA) were done with patient ET's serum, when in fact BRU's serum was used.	No evidence that this wasn't a simple error.	Apparently an inadvertent mistake. NO MISCONDUCT.
10. Meaning of N.D. Some of the results of the IFAs were reported as N.D. (not done) when in fact they were done.	Popovic says by ND he meant an experiment was "not finished, or not done properly, or not determinable." Popovic has published papers that used ND for "not determinable" and NT for "not tested," which he says demonstrate that ND did not mean that the test wasn't performed. He argues that ND as "not determinable" is common usage in many journals. Also, in one case, the experiment listed as ND would have supported the paper's conclusion.	In one other paper Popovic authored, ND seemed to be used in the more common sense of "not done." There should have been some broader explanation of why the experiments were not interpretable if that was the case. MISCONDUCT.
11. 10% versus "very few." An entry for clone H35 tested against rabbit antisera at 6 days in culture was reported as 10% positive, when an entry in the original lab notes shows "very few cells positive for rabbit antibody."	A technician who was a coauthor on the paper evaluated the assays and typically scored only those with more than 20% positive cells as positive. Popovic, who evaluated the assay personally, determined that 10% was the correct figure. Lab notes suggest that a key sentence should be read: "Very few cells. Positive for rabbit antibody."	Popovic could provide no primary data to support his assertion that 10% was a more accurate value. By selecting one individual's reading of a single data point (since the technician's values appeared in all the other entries in the table), the choice falls outside normal differences in interpreting data. MISCONDUCT.
12. RF and SN mixup. Electron micrograph (EM) data and RT activity data from patients RF and SN were switched.	Resulted from misunderstood editing instructions on the galley proofs.	Inaccuracy the result of honest error. NO MISCONDUCT.
13. RF's positive EM. Although reported as positive in the paper, there was a history of negative EMs for evidence of virus from patient RF.	Gallo argued that he had considerable experience with EMs, and that his conclusion that the EMs were positive was scientifically legitimate.	EMs have an inherently subjective component, and the conclusion that RF's data were positive is defensible. NO MISCONDUCT.
14. IFAs reported N.D. Similar to Allegation 10. Results in table 2 on isolation of HTLV-III from AIDS and pre-AIDS patients should have been reported "negative" not "not done."	Arguments are similar to those in Allegation 10.	Data appeared to be selected and misreported. ND was used for clearly negative results. MISCONDUCT.
15. Schupbach paper. Primary data for a second paper reported in the same issue of *Science* were missing.	Schupbach provided a detailed letter with his methods, as well as original artwork for figures 1-3 on the paper.	Information supplied adequate if incomplete. NO MISCONDUCT.
16. Ancestry of HT clones. Implication that the HT clones used to grow HTLV-IIIB were a new cell line, when they were actually derived from a well-established line called HUT78.	There was no attempt to mislead readers that HT was of an entirely different origin from HUT78. The issue didn't arise at all in the *Science* paper, and there was an attempt to clarify it in a subsequent article in the *Lancet*. It was more important to show that the cells were T4 positive, and that any neoplastic T4 positive line could be used.	Popovic should have done more to characterize the cell line he was using, if not before the *Science* paper was published, then certainly in time for the *Lancet* paper. But while this manifested "an unhealthy disregard for commonly accepted standards for responsible research," it did not merit charge of misconduct. NO MISCONDUCT.

collegiality and seeming lack of proper recognition of the contributions of others."

Recommended sanctions

Serious misdeeds? Or petty misdemeanors? OSI's scientists proposed three sanctions for Popovic: that he be prohibited from serving as a member or consultant to a Public Health Service (PHS) advisory committee for 3 years; that any grant or contract application he submits to PHS in the next 3 years be accompanied by a certification as to the reliability of the proposed research and procedures for monitoring his work; and during that time any PHS agency considering funding him be advised of the misconduct finding. Because the investigators did not find Gallo guilty of misconduct, it recommended no sanctions against him.

Healy, in her letter transmitting the report to Mason, urged leniency toward Popovic, citing as extenuating circumstances inadequate supervision and language difficulties. For Gallo, she wrote that "[O]ther problems that relate to Dr. Gallo's management of his laboratory...are being addressed by me and others within NIH." She told *Science* she was particularly concerned about the issue of collegiality, and said that this will have to be addressed by Gallo's boss, National Cancer Institute director Samuel Broder, and National Institute of Allergy and Infectious Diseases director Anthony Fauci.

What next?

Will Healy's actions satisfy skeptical congressional watchdogs? Dingell has already indicated that for him, the answer is no. Members of his staff have produced several internal reports detailing what they see as inaccuracies and shortcomings in the OSI report. And Dingell himself has issued a public statement charging that the findings have been "seriously watered down." The subcommittee is being aided by Suzanne Hadley, who was removed from the investigation by Healy (*Science*, 26 July 1991, p. 372). An aide says that Dingell may hold hearings on the matter once Mason acts on the final report, although this aide notes that hearings are difficult to schedule during an election year.

But as difficult as Dingell hearings could be to Gallo, he faces potentially still greater threats. According to Dingell's staff, investigators from the GAO and the HHS inspector general's office are looking into possible fraud in Gallo's patent for the AIDS blood test. These investigations are focusing on allegedly false statements in Gallo's 1985 blood test patent and in a sworn declaration he made in 1986 to defend against a challenge to the patent by the French.

Many scientists may feel less worried, however, about Gallo's future than about the damage this tragedy may be doing to the public trust, as it continues to produce acrimony within the scientific community.

–Joseph Palca

RICHARDS PANEL

Scientist-Consultants Accuse OSI of Missing the Pattern

They were supposed to provide a seal of approval on NIH's 2-year probe of Robert Gallo. The eight distinguished scientists nominated by the National Academy of Sciences and the Institute of Medicine were to monitor the investigation and reassure skeptics who doubted NIH's ability to investigate one of its own most prominent researchers. But now, in the closing days of the NIH investigation, the panel—known as the "Richards panel" after its chairman, Yale biochemist Frederic Richards—is not in much of a position to reassure anyone. Several members have ended up disgruntled and distressed with NIH, and the rest, including the chairman, believe the confidentiality agreement NIH forced them to sign precludes them from any public comment whatsoever. Worse yet, while Richards himself remains in frequent touch with NIH Director Bernadine Healy 2 months after submitting his report on NIH's findings—a report that was critical of a number of crucial conclusions concerning Gallo—the remaining panelists have been left out in the cold, where they read press reports that suggest to them that their advice has at best been ignored. As one angry panelist told *Science*: "Healy flipped us off, essentially—no question about it."

While the Richards panel report (of which *Science* has obtained a copy) generally applauds the thoroughness of the investigation conducted by NIH's Office of Scientific Integrity (OSI), it faults OSI's conclusions on several grounds (see table). In particular, the Richards panel noted that OSI tended to "trivialize" the significance of misstatements in a 1984 *Science* paper by Gallo and his former associate Mikulas Popovic by failing to place them in a "larger context"—a context that would reveal "a *pattern* of behavior on Dr. Gallo's part that repeatedly misrepresents, suppresses, and distorts data and their interpretation in such a way as to enhance Dr. Gallo's claim to priority and primacy."

According to the report, a "well-established" and "largely or entirely undisputed" sequence of events supports this charge: First, Gallo's lab established the "crucial" fact that the AIDS virus could be grown in HUT78, yet Gallo and Popovic wrote in their 1984 paper that LAV "has not yet been transmitted to a permanently growing cell line...." To the Richards team, this "constitutes intellectual recklessness of a high degree—in essence, *intellectual appropriation* of the French viral isolate."

Second, Gallo's lab changed the name of HUT78 to HT, obscuring the fact that its cell line was originally developed by Adi Gazdar, a National Cancer Institute scientist working under John Minna (a point first detailed in *Science*, 22 June 1990, p. 1499). And third, according to the OSI report itself, Gallo's lab slapped restrictions on the distribution of uninfected "H9" cells, or cells cloned from HUT78. Gallo disputes the Richards panel's interpretation of each of these events—see table.

The Richards panel also took issue with the way OSI accused Popovic, but not Gallo, of misconduct for two of the misstatements in the *Science* paper. As a result, the panel says, "[t]he public and/or the Congress will perceive a bias in the treatment of the two principals in the investigation."

Poor oversight. And the panelists complained that the OSI investigation failed to address the "overriding issue" of a lab chief's responsibility to oversee his personnel and "to pay particular attention to the accuracy of major publications which bear his name as author." Because Popovic "had an imperfect command of English and a known inadequacy in record-keeping," the report states, Gallo should have exercised "meticulous scrutiny" over his contributions to the 1984 paper—a failure the OSI report does not address.

"We thought our report was a reasonably serious document questioning the whole state of affairs [in the Gallo lab]," says one panel member. "We told Healy that if it had been our [investigation], we'd have recommended that Gallo be found guilty of misconduct." Instead, this member says, Healy has not acknowledged receipt of the report, and has since told *The Washington Post* that Gallo defended himself effectively against the Richards panel's charges. According to a 27 March Healy memorandum, she has endorsed the OSI report.

This has left a very sour taste in the mouths of some of the panelists. "We took a position we all agreed with, and I'd just as soon not be burdened with the notion that we've signed off on NIH's decisions," says one, adding: "I'd like it well known that we don't agree with NIH's decision." Another member puts the same point more succinctly: "It'll be a cold day in hell before any of us will consult for the U.S. government again."

But the worst aspect of the chasm between Healy and her independent consultants is likely to be the doubt into which the panel's report throws NIH's final conclusions—doubt which NIH adversaries such as Representative John Dingell (D–MI) are already moving to exploit.

–David P. Hamilton