Patent Dispute Divides AIDS Researchers

A tussle between the Pasteur Institute and the U.S. government over rights to blood test kits rests on issues of scientific priority

In April 1984, rumors began circulating around the scientific community that Robert C. Gallo of the National Cancer Institute (NCI) had made a major breakthrough in the search for the cause of acquired immune deficiency syndrome (AIDS). Gallo had in fact been playing his cards close to his chest since early November, as he and his many co-workers accumulated a mass of data firmly implicating a newly discovered retrovirus as the cause of the disease.

Gallo was about to report, in four papers in *Science**, that his group had isolated a virus, which he called HTLV-III (for human T-lymphotropic virus type III), from 48 patients with AIDS and AIDS-related symptoms. The papers also described a system for mass-producing the virus—something that had eluded researchers for more than a year—and reported the detection of antibodies to HTLV-III in the blood of the vast majority of AIDS patients he tested, but in only one of 186 healthy controls.

To most people, the evidence was convincing, and Secretary of Health and Human Services Margaret Heckler scheduled a press conference on 23 April to tell the world.

The day before Heckler's big announcement, however, an article appeared on the front page of the *New York Times* stating that a team of researchers at the Pasteur Institute in Paris had discovered the cause of AIDS. The article was based largely on an interview with James O. Mason, the head of the Centers for Disease Control (CDC) in Atlanta, which had been cooperating closely with the French group. Mason said that data gathered over the previous few weeks had provided strong evidence that a virus first isolated by the Pasteur group early in 1983 was the AIDS agent. The French called their virus lymphadenopathy-associated virus, or LAV.

To Gallo and his colleagues, Mason's announcement looked like a deliberate attempt by CDC and the Pasteur group to steal his thunder. Relations between Gallo and CDC were already strained, and Gallo was competing with the French researchers to nail down the cause of AIDS. Mason says, however, that he had not seen Gallo's papers when he spoke with the *New York Times*, and Pasteur officials deny any part in Mason's announcement.

The Pasteur group, which was headed by Luc Montagnier, Jean Claude Chermann, and Françoise Barré-Sinoussi, were annoyed when they subsequently read Gallo's papers, however, because they felt he had slighted their contributions. Gallo noted that the French team had reported isolating LAV, but said that the virus had not been sufficiently characterized to know whether it was the same as HTLV-III. "I was shocked by the way he presented our data," Montagnier says.

The Pasteur group, working with limited quantities of LAV, had done considerable characterization of the virus, found that it selectively infects a class of lymphocytes known as T4 cells—key components of the immune system that are missing or severely depleted in AIDS patients—and developed a test to detect LAV antibodies in blood. Their research had, however, been hampered by the fact that they could not grow the virus in quantity because it killed the cells it infected.

Gallo had solved this problem by infecting a line of T cells established from a leukemia patient with virus he had isolated from AIDS patients. The cells produced large quantities of virus but did not die off. This break-through enabled Gallo's group to mass produce the virus, characterize it in detail, and develop a sensitive assay to detect HTLV-III antibodies. It also led directly to the commercial development of a test for mass screening of blood donations. (For a detailed description of the work of both groups, see part 1 of this article in last week's issue.)

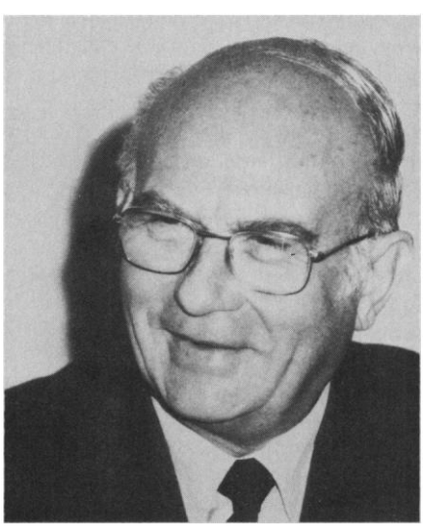
The ill feeling surrounding the publication of Gallo's papers exacerbated a scientific dispute that was already dividing the two groups over the name and classification of the AIDS virus. The dispute gathered momentum early this year when the genetic sequences of HTLV-III, LAV, and a third virus isolated by Jay Levy of the University of California at San Francisco, were published. All three isolates are clearly variants of the same virus, but they differ substantially from other members of the HTLV family (see box on p. 641).

In addition to the contests over priority and nomenclature, another issue has come to dominate relations between the two groups. It involves patent rights on kits that are being used commercially to test blood samples for antibodies to the AIDS virus. Although the dispute is formally between the Pasteur Institute and the U.S. government, it is intricately linked with the question of priorities.

At issue is a patent, applied for by the U.S. government on 23 April 1984 and awarded on 28 May 1985, covering a method of detecting HTLV-III antibodies by exposing serum samples to proteins from the virus. If antibodies are present in the serum, they will bind to the viral antigens to form complexes that can be detected by various techniques,

The War on AIDS

This is the second part of a two-part article on the discovery and identification of the AIDS virus, and the third piece in a series on AIDS research.† *Future articles will examine the epidemiology of the disease and research on vaccines and therapy.*



Raymond Dedonder

"If there is no solution, then we will have to go to court."

**Science*, 4 May 1984, pp. 497–508.

†Previous articles in the series were published in *Science*, 25 October, p. 418, and 1 November, p. 518.

including a simple test known as enzyme-linked immunosorbent assay, or ELISA.

On the basis of this patent application, the federal government has licensed five companies to develop and mass-produce ELISA test kits to screen blood donations for HTLV-III antibodies. The license agreements were initially a means of limiting the field to ensure that each company would have sufficient quantities of HTLV-III to produce test kits as quickly as possible. According to Lowell Harmison, science adviser to the assistant secretary for health, the licensees are required to pay the government royalties amounting to 5 percent of their profits from sales of the kits. Some estimates suggest that total royalties could reach $5 million a year for the U.S. market alone.

At the time they filed their patent application, federal attorneys were unaware that the Pasteur Institute had already filed for a patent on an ELISA test to detect antibodies to LAV. Although this application was filed in Europe in September 1983 and the United States in December, it has not yet been dealt with. The delay in handling the French application is not unusual. What is unusual is the speed with which the government's patent was issued.

There is, however, another potential complicating factor in all this. In August 1983—before either the Pasteur Institute or the federal government applied for their patents—Biotech Inc, a small biotechnology company based in Rockville, Maryland, filed for a generic patent on ELISA test kits to detect antibodies to human retroviruses.

According to Robert Ting, Biotech's president, the patent, which is still under review at the Patent Office, is derived in part from work in Gallo's lab. Gallo's group developed an ELISA test to detect antibodies to HTLV-I using a method that was fine for laboratory work but which could not be mass-produced and used for widespread screening. Biotech modified the technology and patented it. The application, according to Ting, focused on HTLV-I, but was broadly worded to cover other human retroviruses, including HTLV-III.

Pasteur officials believe their application has been unfairly treated and are preparing to challenge the U.S. patent, if necessary by taking legal action. The issue is likely to come to a head in the next few weeks. A blood test kit, manufactured under license to the Pasteur Institute by Genetic Systems Corporation of Seattle, Washington, is currently under review by the Food and Drug Administration and is expected to be approved soon. When it reaches the market, it will technically be in violation of the U.S. patent.

In an attempt to head off a legal confrontation with the U.S. government, Raymond Dedonder, the head of the Pasteur Institute, Robert Nowinski, president of Genetic Systems, and Gerard Weiser, a Philadelphia attorney, met with top officials of the Department of Health and Human Services (HHS) on 6 August to try to negotiate a settlement. Dedonder, in a recent interview with

What's in a Name?

For the past several months, a committee headed by Harold Varmus of the University of California at San Francisco has been struggling to come up with an acceptable name for the AIDS virus. It is not a simple matter, for the name of the virus is a major item of contention between French and American research groups. At least five names have so far been used. Part of this contest is symbolic: whoever gets to name the virus will be broadly identified as its discoverer. But a legitimate scientific issue is at stake as well in determining how the virus should be classified.

One one side is a group headed by Robert C. Gallo of the National Cancer Institute (NCI). Gallo originally thought that the AIDS virus would turn out to be a variant of a leukemia virus that was discovered by his lab in the late 1970's. Known as HTLV-I, for human T-cell leukemia virus type I, it causes proliferation of T4 cells, the same cells that are killed by the AIDS virus. When he isolated and identified the AIDS virus, Gallo argued that, although it appeared to differ from the other HTLV's (a second virus was isolated from a leukemia patient in the early 1980's and called HTLV-II), they shared some characteristics. He therefore christened his virus HTLV-III. But, because the leukemia viruses lead to proliferation of T4 cells while HTLV-III has the opposite effect, Gallo argued that the name of the whole family should be changed to human T-*lymphotropic* virus.

The French group, headed by Luc Montagnier of the Pasteur Institute, isolated a virus from a patient with lymphadenopathy syndrome early in 1983. Although in their first publication on the virus they said it appears to be a member of the HTLV family, the Pasteur researchers reported that it was different from HTLV-I and HTLV-II. Shortly thereafter, however, they began to argue that their virus appeared not to be related to the HTLV's at all, but was more like viruses that belong to the so-called lentivirus family. To distinguish their virus from the HTLV's, they christened it lymphadenopathy-associated virus, or LAV. However, when they subsequently isolated viruses from other AIDS and lymphadenopathy patients, they called these isolates immune deficiency–associated viruses, or IDAV's, because they were not sure that they were always dealing with the same virus. Finally, when it became clear that all their isolates were variants of the same virus, they settled on lymphadenopathy/AIDS virus, which happens to have the same acronym as their original choice.

Yet another candidate has more recently been put forward by a third group, headed by Jay Levy of the University of California at San Francisco. Levy, who isolated virus from AIDS patients last year, christened his AIDS-related virus, or ARV.

The nomenclature dispute gathered momentum early this year when the precise genetic structure of the AIDS virus was determined. The AIDS virus genome turns out to be very different from those of the other HTLV's. Gallo still maintains that it should be placed in the same family, however, because they are the only known human retroviruses, they all have a propensity for T4 cells, and some of their genetic mechanisms are similar. The Pasteur group argues, on the other hand, that the structure of the AIDS virus genome places it squarely in the lentivirus family. This classification, they argue, is strengthened by recent findings that the AIDS virus, like a sheep lentivirus called visna, infects brain cells.

Varmus says that his committee, which is sponsored by the International Committee on the Taxonomy of Viruses, is discussing a list of alternatives to HTLV-III, LAV, and ARV, and he hopes it will reach a decision by the end of the year.—**C.N.**

Science, said they asked for three things: reissuance of the patent, with the Pasteur Institute as a coholder; recognition of the fact that the Pasteur group was the first to discover the virus and apply for a patent; and an agreement that the Genetic Systems test kit could be marketed without hindrance.

The HHS officials asked Dedonder to supply details of the Pasteur Institute's version of the events. This was done in a memorandum dated 16 August, which laid out the institute's case for declaring the U.S. patent invalid. According to Dedonder, "HHS said that the documents are not sufficient to change their position."

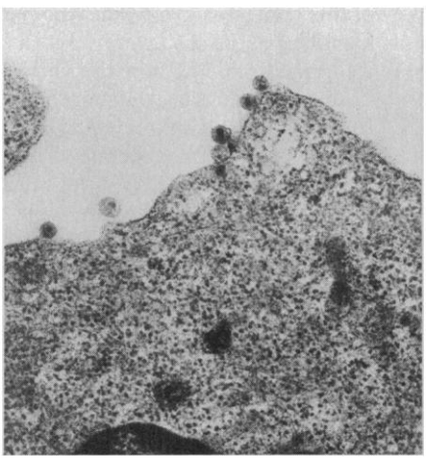
The Pasteur Institute has therefore been pursuing its case directly with the Patent Office. According to Dedonder, the institute is seeking what is called an "interference," which, if granted, would essentially mean that the Patent Office would reopen consideration of the U.S. patent and the Pasteur Institute would be given a year to prove its case. During the interference period, the patent would not be enforceable and thus Genetic Systems would be able to market its test kit. Failing that, "If there is no solution, then we will have to go to court," says Dedonder.

The Pasteur Institute's memorandum, a copy of which has been obtained by *Science*, sets out two chief grounds on which the institute is likely to challenge the U.S. patent. First, "the Institut Pasteur can establish that its team had all the essential elements of the subject matter of the Gallo *et al.* patent, prior to any patent filing of Gallo." Second, "the subject matter of the Gallo *et al.* patent was obtained or derived from the Montagnier team."

The first argument rests on the fact that the Pasteur group had isolated a retrovirus early in 1983 and determined that it was different from HTLV-I and HTLV-II, the only other known human retroviruses. A paper describing this work was published in the 20 May 1983 issue of *Science*. The Pasteur group had also constructed an ELISA test using proteins from this viral isolate as antigens, and employed the test in serological studies establishing a link between the virus and AIDS. "There is a prima facie case that the Montagnier team was 'first,' " the Pasteur memo states.

The basis for the second argument is a series of exchanges between the Montagnier and Gallo groups, through which, the Pasteur memo contends, Gallo gained an advantage. These include the fact that Montagnier sent Gallo a prepublication copy of a his *Science* paper, a presentation Montagnier made at a meeting at NCI in July 1983, and a paper Montagnier delivered at a meeting at Cold Spring Harbor in September, which included preliminary serological findings from use of the ELISA test.

The messiest part of this second argument concerns a sample of supernatant containing a small amount of LAV that Montagnier sent to Gallo on 23 September 1983. The Pasteur memo notes that when the precise genetic sequences of HTLV-III and LAV were determined early this year, the two were remarkably similar, while the sequences of other isolates have turned out to be quite different.



The French virus

Reagents supplied by Gallo helped determine that it was not HTLV-I or HTLV-II.

By implication, the memorandum suggests that Gallo's group somehow grew the French isolate. "The Institut Pasteur can establish a prima facie case of breach of contract in that the retrovirus given to [Gallo's group] or one derived therefrom to the best of Institut Pasteur's knowledge, was used in contravention of the terms of the letter agreement," which restricted use of the isolate to research purposes, the memo states.

Gallo indignantly disputes this allegation on several counts, including the fact that the viruses are not identical and that the amount of virus Montagnier sent would not have been sufficient to infect a cell line (see box on page 643).

Although federal officials are reluctant to discuss in detail the legal aspects of the dispute with the Pasteur Institute, they challenge some of the scientific claims. For example, they point out that although it is certainly true that the Pasteur group was the first to identify the correct virus in the literature, Gallo's group was also getting glimpses of a new retrovirus as early as December 1982 but could not grow it or properly characterize it.

Many scientists also found the Pasteur group's serological studies less than convincing in demonstrating that LAV is the cause of AIDS. In their patent application, for example, the Pasteur researchers note that they detected LAV antibodies in only 20 percent of serum samples of AIDS patients, and early in 1984, they reported that this figure had risen to only 37.5 percent. Moreover, federal officials point out that the Pasteur Institute's patent application specifically states that LAV's "envelope proteins are not detected immunologically by the sera of LAS [lymphadenopathy syndrome] and AIDS afflicted patients." The envelope protein is, in fact, the most immunogenic viral antigen.

Federal officials also point out that the flow of information and materials was not all one way. For example, the Pasteur group would not have been able to determine that their first isolate was different from HTLV-I without reagents from Gallo. Finally, they argue that it was Gallo's breakthrough in mass-producing the virus that enabled ELISA tests to be produced on a scale large enough to be useful for monitoring blood donations.

The unfortunate aspect of this patent dispute is that it is being cast as a winner-take-all contest. In fact, both groups, although moving along somewhat separate tracks, made important contributions.

For example, it was largely the prior work of Gallo and his many collaborators that laid the groundwork for searching for a retrovirus and, when it was isolated, determining that it was different from previous human retroviruses. As one of Gallo's collaborators puts it, "If this disease had appeared 10 years ago, we would be completely lost." Gallo's group also achieved the key breakthrough of finding a cell line that would produce the virus without dying off, which in turn led to the rapid development of a sensitive ELISA test and convincing serological evidence that the virus is the cause of AIDS.

The Pasteur group was the first to identify the correct virus in the literature and to recognize the virus's propensity for killing the cells it infected. By careful work with small quantities of the virus, they were able over the following year to link their virus more firmly to the disease. And they also have the advantage of being the first to file for a patent on the ELISA test.

As Nowinski of Genetic Systems puts it, "It is pretty remarkable what both Montagnier and Gallo have done."

—COLIN NORMAN