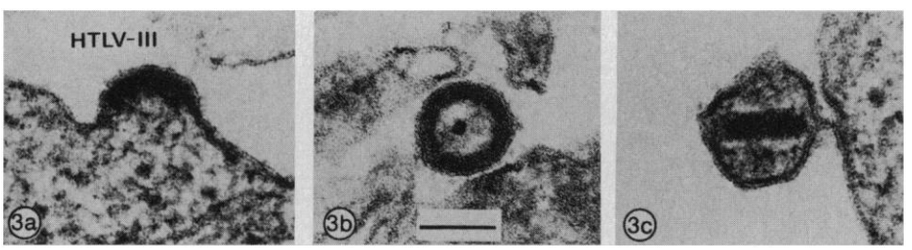
A New Twist in AIDS Patent Fight

A misidentified photograph published by U.S. researchers of a virus isolated by a group at the Pasteur Institute could be more than a little embarrassing

A correction to a figure legend published 2 years ago might seem a matter of no great significance. But the correction contained in a letter on page 307 from Robert C. Gallo of the National Cancer Institute (NCI) and his co-workers is likely to raise a few eyebrows. It could also have some legal ramifications.

The letter relates to electron micrographs in one of four key papers published by Gallo and his many collaborators in the 4 May 1984 issue of *Science*. The papers provided convincing evidence that AIDS is caused by a newly discovered retrovirus. The correction states that one set of electron micrographs depicted a virus isolated by a group at the Pasteur Institute in Paris and not, as the original legend stated, a virus isolated by Gallo's group.



HTLV-III/LAV. *These three electron micrographs were identified in Gallo's paper as pictures of HTLV-III. In fact, they were photographs taken of the Pasteur Institute's isolate, LAV. (They were originally the third row of a composite also showing HTLV-I and HTLV-II.)*

The correction has little scientific significance since electron micrographs of the two viruses are indistinguishable and that particular photograph had little direct bearing on the content of the paper. But, apart from being professionally embarrassing, the misidentification is likely to provide yet another complication in an already tangled legal dispute between the Pasteur Institute and the U.S. government.

The dispute centers on a patent held by the U.S. government on a test developed by Gallo's group for detecting antibodies to the AIDS virus in blood samples. Last December, lawyers for the Pasteur Institute filed suit against the U.S. government claiming that, in developing the test, Gallo's group used materials and information that were supplied by Pasteur researchers on condition that they be used only for research (*Science*, 4 January 1986, p. 11). The suit charges breach of contract and seeks to have royalties from the patent turned over to the Pasteur Institute.

The suit focuses on a sample of virus sent by the Pasteur researchers to Gallo's group in September 1983. Gallo has consistently maintained that there was little virus in the sample and that his group could not get it to grow in culture for more than a short time. The misidentified electron micrographs were pictures of virus from this sample. They were published along with pictures of two previously discovered human leukemia viruses as part of Gallo's contention that all three viruses belong to the same group; the Pasteur researchers have argued that the AIDS virus belongs to a different group known as lentiviruses.

According to James Swire, an attorney with Townley and Updike, a New York law firm representing the Pasteur Institute, the fact that several electron micrographs were taken of the virus "adds to the circumstantial evidence" that Gallo's group gained critical information from the Pasteur material. Gallo disagrees, arguing that the electron micrographs were taken simply to confirm that the virus was a retrovirus.

The Pasteur Institute's virus was first isolated early in 1983 from a patient with lymphadenopathy. The Pasteur researchers, headed by Luc Montagnier, Jean-Claude Chermann, and Françoise Barré-Sinoussi, published information on this new virus in May 1983, calling it lymphadenopathy-associated virus, or LAV. Because it was only a single isolation, few other researchers were convinced at the time that it was the cause of AIDS and some electron microscopists were skeptical that photographs published by the Pasteur group depicted a retrovirus.*

The Pasteur sample arrived in Gallo's laboratory at a critical period in the U.S. group's research. Virus isolated from AIDS patients would not grow for more than a few days in culture because it killed the cells it infected. (The Pasteur group, which recognized this effect early on, propagated LAV on fresh cells.) This problem was solved in November 1983 by Mikulas Popovic, a cell biologist in Gallo's lab, who developed a cell line, which he called the H9 line, that could be infected without being killed. To increase the chance of getting a productive infection, Popovic inoculated the H9 line with serum pooled from ten AIDS patients.

Popovic's breakthrough enabled Gallo's group to grow large quantities of virus, characterize it, and develop a test to detect antibodies to the virus in blood samples. They called the virus HTLV-III, for human T-cell leukemia virus type III. This work provided the basis of the four *Science* papers and it also led to the patent on the blood test. An application for the patent was filed on 24 April 1984 and it was awarded in May 1985.

Gallo said in interviews last year that his group infected fresh cells with the virus sent by Montagnier and detected reverse transcriptase activity—a characteristic sign of retrovirus infection. After a few days, however, the cells degenerated and stopped producing virus, and Gallo said they put the culture fluids in the freezer.

In fact, a few weeks after the sample arrived, Popovic thawed some of the material and used it to infect two cell lines, called HUT-78 and T-17.4. He sent samples of these cultures early in December to Matthew Gonda's laboratory at NCI's Frederick Cancer Center for electron microscopy. Gonda took photographs of virus particles and reported back to Popovic in a letter dated 14 December 1983, which contains the results of electron microscopy on 33 samples submitted by researchers in Gallo's laboratory during the previous few weeks. Gonda reported that only the two infected

*For a detailed account of the work of both the Pasteur and NCI groups, see *Science*, 1 November 1985, p. 518; and 8 November 1985, p. 641.

with LAV showed "productive lentivirus infection."

Swire, who says he has had a copy of Gonda's letter "for some time," alleged in the suit filed last December that Gallo's group had not successfully isolated the AIDS virus before December 1983. Gallo insists, however, that Gonda's letter should not be interpreted this way. "It can be conclusively documented," says Gallo, that he had electron micrographs, taken by a different laboratory, Electro-Nucleonics, well before the sample of LAV arrived at his lab. (Gallo's lab sent samples for electron microscopy to Electro-Nucleonics until September 1983, when they switched to Gonda's lab.)

Popovic says that the cell lines infected with LAV were killed by the virus in 2 or 3 weeks, and he again froze the material. However, he subsequently reexamined the cultures and on 13 February 1984, he sent five more samples to Gonda for electron microscopy. According to a letter from Gonda dated 22 February, all were negative for virus particles. Asked why he reexamined the LAV cultures in February, Popovic says he wanted to compare the susceptibility of the H9 line to infection with different isolates, including LAV. Gallo points to Gonda's results as confirmation that infection of the HUT-78 and T-17.4 lines was transient and that they could not infect the H9 line with LAV.

One of the allegations in the Pasteur suit is that HTLV-III "is, or is substantially identical to, the LAV strain . . . " The implication is that HTLV-III may be the French virus. Gallo indignantly denies this, pointing out that the genetic sequences of the two viruses differ by about 1.5%, a variation that, he argues, would not have come about by passage in culture. Gallo also points out that the patent application contained details of H9 cells infected with virus from single patients. Since he had these cultures, he asks, why would he sequence the virus from the culture he allegedly infected with LAV?

The electron micrographs of LAV were apparently mistakenly used instead of photographs of HTLV-III when Gonda's lab prepared a composite picture of HTLV-I, HTLV-II, and HTLV-III for Gallo's publication. The mistake came to light recently after a meeting between Gonda and Swire.

Gonda told Gallo and other U.S. officials that he was invited to a meeting to consult on some electron micrographs, but he did not realize until he got there that the meeting was with the Pasteur lawyers. Gonda declined to be interviewed for this article, but Swire admits that the lawyers did not identify themselves when they called Gonda. He says, however, that he told Gonda who he was at the start of the meeting, and Gonda "was free to leave at any time."

The lawyers showed Gonda copies of the letters he sent to Popovic and asked him about the electron micrographs in the Gallo papers. This prompted the U.S. group to check that the correct pictures were used, and to their embarrassment they found that one series was in fact pictures of LAV. ■

COLIN NORMAN

Tight Money Squeezes Out Animal Models

Certain animal models have been lost, in many cases because of funding priorities. Researchers think the issue warrants close scrutiny and careful planning

As Linda Cork of Johns Hopkins School of Medicine described her research on Rottweiler dogs at a recent National Institutes of Health meeting about diseases that affect nerve axons,* she gave no indication that the experiments would be her last with that particular genetic model. Later, in an interview, Cork explained that restricted funding had forced her to terminate not just one, but two, colonies of dogs carrying genes for degenerative neuronal diseases that are models for human diseases.

Cork is not the only researcher to lose animal models in recent years. Colonies of large animals, including cats, dogs, horses, and primates, are expensive to maintain and seem to suffer most often from the budget axe, but too little money is not the only issue. An increasing number of research scientists think that pressures from animal rights groups will jeopardize the use of certain animals in research.

Concern from scientists that valuable animal models are being lost recently prompted the National Research Council (NRC) to establish a new committee on the preservation of laboratory animal resources. Cork is a member of the committee, which met last month for the first time.

Not everyone agrees that important animal models have been squeezed out by the current funding crunch. James Willett of the Research Resources Branch at NIH says, "If you look at the number of projects NIH supports, or the dollars spent over the period from 1977 to 1984, research depending on animal models received a flat percentage of total support money. I find it hard, in light of that information, to see reductions in mammalian models during the past 7 years." Willett does not know what that means in terms of individual animal systems, but NIH is working with the National Academy of Sciences to see how specific models are being affected.

At least two general categories of animal models are used in biomedical research—genetic models for particular diseases and nondisease models used to study normal body functioning. Some researchers think that endangered models fall into both categories.

Cork describes the first group. "There are specific animal models which duplicate human disease in every respect. But more often, we are dealing with an animal model which replicates only certain aspects of human disease." The latter includes Cork's former colony of Rottweiler dogs which develop a movement disorder that worsens as they age. The dogs were a model for human neuroaxonal dystrophy, a group of inherited diseases in which nerve axons in the brain and spinal cord degenerate.

Although normal aging brain and spinal cord neurons show some signs of axonal dystrophy, the cellular changes in the disease state are more pronounced. Typically the end regions of axons swell first, forming spheroid structures. Ultimately the entire cell is affected. Cork and her colleagues at Johns Hopkins University School of Medicine showed that spheroids form in many different kinds of nerve cells, a finding that disspelled the theory that only a single population of neurons was at risk.

*"Neuroaxonal Dystrophy and Axonal Transport," 19–24 February 1986, National Institutes of Health, Bethesda, MD. The symposium was organized by the Fogarty Center and the National Institute of Neurological and Communicative Disorders and Stroke.