

New twist in the long saga of HIV

Nucleotide sequence data from Robert Gallo's laboratory now show that neither the French nor the US samples of virus isolated in 1983 correspond to the French LAV strain whose sequence appeared in 1985.

THE origin of the first AIDS virus has been a pervasive and somewhat destructive theme in AIDS research since French and US researchers got into a row about it eight years ago. Now, data from the laboratory of one of the principals — Robert C. Gallo of the US National Cancer Institute — add a curious twist to an old story (see *Scientific Correspondence*, page 745).

The new data cast doubt on the widely accepted view (some say canard) that the virus Gallo showed to be the cause of AIDS — called IIIB — is really a French virus in disguise. Spurred in part by a continuing NIH investigation of the integrity of his AIDS research, Gallo's colleagues, headed by Marvin Reitz, took advantage of modern polymerase chain reaction (PCR) techniques to go back to the freezer and sequence for the first time samples of viral isolates they received from Luc Montagnier and Jean-Claude Chermann of the Pasteur Institute in 1983.

The question was simply this: How does the sequence of IIIB, published in 1985, compare to that of the 1983 samples derived from a French male homosexual identified by the initials BRU. The expected answer would be that BRU and IIIB correspond. In fact, they do not. More surprising still, the data show that the BRU sequence, representing the first putative AIDS virus, does not correspond to the sequence the French published in 1985 for their own virus, then known as LAV/BRU, where LAV stands for lymphadenopathy virus.

From the nucleotide sequences of several BRU samples that verifiably came from the Pasteur Institute in 1983, the new data add a new layer of mystery to the case, while providing strong circumstantial evidence that Gallo's IIIB did not come from the Pasteur Institute. As Gallo notes, the fact that LAV and IIIB were shown by 1985 sequence analysis to be nearly indistinguishable molecularly has led most AIDS researchers to conclude that they are, in fact, one and the same.

Assuming that the provenance of the viral isolates is correct (and there is no reason to doubt it), the new molecular analysis, and unpublished serological data, indicate that neither LAV nor IIIB (as published in 1985) is present in samples from the patient BRU. (The presence of Chermann among the signatories of today's correspondence bears on the authenticity of the 1983 French samples now analysed.)

Virologist Howard Temin of the McArdle Laboratory for Cancer Research at the University of Wisconsin, who is familiar with the new data, but who was not one of the referees of the correspondence, summarizes the situation this way. "We now do not know where LAV or IIIB came from. Therefore, we can't accuse anyone of anything. Do we care further? No, This is a non-issue as far as the AIDS epidemic is concerned. Now it is a non-issue as to the character of Dr Gallo. Let's get on with it." Temin also wonders why, in this case, people were so ready to assume chicanery, when science is full of examples of researchers doing parallel yet independent work."

A word on the nomenclature may help in making the outline of this story clearer. The virus that causes AIDS, now known as the human immunodeficiency virus (HIV) varies in molecular sequence from patient to patient. Even the few isolates described in Gallo's correspondence have separate designations. For simplicity in what follows, the viruses are referred to by only three terms: BRU refers to all the samples reported here to have come from the patient BRU; LAV refers to the Pasteur Institute isolate whose sequence was published in 1985; IIIB refers to the isolate from Gallo's laboratory whose sequence was also published in 1985, and which bears the uncanny likeness to LAV (or *vice versa*).

When Montagnier published the sequence of BRU in 1983, he suspected, but could not prove, that it might be the cause of AIDS. An inability to grow BRU in quantity limited possibilities for developing further data. Montagnier sent samples of BRU to Gallo, where cell biologist Mikulas Popovic was busy trying to get one of the laboratory's many isolates to grow in culture.

After repeated attempts with single isolates, Popovic, in November 1983, took isolates from ten different patients whose identity is known and, unconventionally pooled them to create a viral soup. His gamble paid off when IIIB emerged from that soup as an isolate that could be grown in quantity. By the spring of 1984, Gallo's laboratory had developed and patented an AIDS blood test based in part on IIIB.

Recently, NIH contracted with independent scientists to do molecular analyses of available samples of the isolates in Popovic's viral pool — at least seven of the ten have been retrieved — together with other isolates from Gallo's

laboratory. The committee now also has the material from the 1983 samples described in the correspondence. One goal is to find the patient who was the source of IIIB. Now it would also be interesting to find the patient who was the source of LAV.

Gallo's laboratory received five samples of BRU in 1983. One, called MT2B, cannot be found. One sample, called RUB, was apparently used up. Is it possible that either of them was LAV? Perhaps, but Chermann, who was working with Montagnier at the time, avows that they, too, came from BRU.

Is it possible that BRU was doubly infected, by the isolate called BRU and by LAV? No such case of double infection by two widely different isolates of HIV has been reported, but an experiment can be done to test that possibility.

Yet another possibility is that Montagnier and Gallo each received viral isolates from the same patient. Gallo has records of the samples received from physicians in the United States and abroad. Presumably the Pasteur Institute does as well. Were the Institute to open its notebooks, it would be easy enough to see whether the French and US scientists received material from the same source.

Finally, it would be interesting to analysis by PCR any original 1983 viral samples that may still be frozen at the Pasteur Institute. A number of attempts to retrieve this tissue have been made, not only by Gallo and his colleagues, but also by NIH officials who are hoping to find the patients from whom these viruses are derived. But, so far as is known, no one has as yet received 1983 Pasteur Institute isolates either from the institute itself or from the official French national cell repository.

If Gallo's sequence data for BRU are indeed correctly attributed to the initial French isolate, it means that for the present, the origin of LAV is as much a mystery as the origin of IIIB. Although the value of the missing data is more historical and political than scientific, the issue has created an unhealthy diversion from the important business of stopping a deadly epidemic. All of Gallo's laboratory records, and now samples of viral material, have been opened to independent scrutiny by lawyers for the Pasteur Institute and committees of the NIH. Perhaps it is time for the French to come forward with its own records and early isolates.

Barbara J. Culliton