1959 Manchester case of syndrome resembling AIDS

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Bailey and Corbitt’s letter to The Lancet about the 25-year-old man who died in Manchester Royal Infirmary, UK, in August, 1959, with a clinical syndrome resembling AIDS is welcome but it leaves several points unresolved, including some raised by a science journalist in March, 1995.†

A particular puzzle is that the original polymerase chain reaction (PCR) study was claimed to be of a randomised double-blind design. Properly applied, such a design makes it difficult for an interpretative bias to generate a false positive or negative result, and impossible for random contamination to do so. On application of Fisher’s exact test to the results of 1990, the probability that random contamination of the test and control samples would produce four positive results in six test samples and none in six controls is 1 in 33. Occurring in 1990, before the dangers were fully appreciated, accidental contamination in the first PCR study of a potential early case of AIDS would be understandable. However, the subsequent failure to address the statistical anomaly above and the neglect of other anomalies is not. We wish to highlight not only the mystery of how random contamination could have led to the results but also five more questions. For the third and fifth and partly for the fourth we suggest possible answers; the other two remain open. The questions are:

1. How did the original tissue samples from the patient come to be found HIV-1 positive by PCR when these results cannot now be repeated?
2. How have archival human tissues, which were apparently well preserved in 1990 to allow human and viral genetic analysis after 30 years in storage, apparently ceased to be so in the past five years?
3. Accepting contamination, what is its likely source?
4. How have four (and possibly five) different human genotypes been reported for HLA-DQα in tissue samples claimed to be from one cadaver?
5. What was the patient’s fatal disease?

Contrary to speculation mainly, but not wholly, in the non-medical press, investigations by EH have shown no evidence to suggest that “the Manchester sailor” (MS) was either homosexual or bisexual, or that he ever visited Africa. In early 1957 his ship did dock in Gibraltar for a fortnight. A day trip (well recalled by members of the ship’s company) was made by about a dozen sailors to Tangier in Morocco, but a member of that party has no recollection that MS was present. Even if he was, or there were other day trips to Tangier, and even if (as has been hypothesised) he had sex in a brothel during such a visit, this can hardly be characterised as a high-risk episode. HIV prevalence varies widely across Africa and the seroepidemiological evidence suggests that Morocco has always been among the least affected countries. The earliest evidence of HIV infection in the country pertains to 1984–87, when seven of 816 individuals (0·086%) tested positive, all from Casablanca. Six were in high-risk groups (gay men, male prisoners, and female prostitutes), the seventh was one of 3577 blood donors. None of 283 blood donors and pregnant women tested in Tangier in 1991 proved to be HIV-1 positive.‡

Questioning MS’ fiancée, family, friends, colleagues, and doctors suggests that he was neither sexually adventurous nor very experienced, and that he was not an intravenous drug user and had received no blood transfusions. Clearly one sexual encounter could have been enough, but everyone who knew him rates him as an improbable candidate for HIV infection. Those closest to him were saddened, indignant, and (rightly as it now appears) near to incredulous at the suggestion that he might have died of AIDS.

That incredulity is now borne out by Bailey and Corbitt, who have joined Zhu and Ho in concluding that the posthumous AIDS diagnosis was unsound, and that certain of the archival tissues made available to them may have been or have become contaminated with a modern (subtype B or “Euro-American”) strain of HIV-1. They suggest contamination “sometime from sectioning onwards”, and that the most likely source “would be from within our own laboratory”.§

The following scenario might go some way towards explaining the facts. The positive control used during the PCR work on MS was a CEM cell line infected with CBL-1.† In 1991, Weiss reported that CBL-1 had 98·0% identity with LAV-1 BRU (or, as it is now referred to, LAI) and 97·8% identity with HTLV-IIIB in env, tat, and nef. An accompanying commentary on this “remarkable similarity” cited laboratory contamination as the possible cause, and reported that Gerry Myers of the HIV Sequence Database in Los Alamos considered that up to 10% divergence in env usually indicated different isolates from the same person, whereas, at the other extreme, genuinely unlinked isolates usually diverged by more than 10% in the envelope gene.

The earliest versions of LAI are the French patent application sequences bearing the Genbank/EMBL accession numbers A04321 and A07867, and Fergal Hill, of the MRC Laboratory of Molecular Biology in Cambridge, has characterised A04321 as “apparently the most similar sequence to the Manchester isolate sequence currently known—at approximately 90% identity over large tracts, including the envelope gene”. Hill concludes that “this high degree of sequence similarity, and the fact that CEM/CBL-1 was grown in Manchester, strongly [his emphasis] suggest that the Manchester isolate is...
derived from LAI via its derivative CBL-1.\(^1\) Clearly Hill believes that repeated passaging of CBL-1 (for instance in Corbitt’s laboratory) could explain the 10% divergence between this positive control and the MS isolate. M yers is less convinced, considering that “the contaminant may have been a lab strain, or ... another patient sample”.

We have already mentioned that only M S’ tissues came to be contaminated in spite of their random interspersion with the controls. Thus conventional significance points either to earlier contamination, before the coding and dispatch of the samples to Corbitt’s laboratory (in which case considerations of the last paragraph suggest that the CEM cell line might also have been present in the source laboratory) or to error during the breaking of the codes. Sections were cut “with separate knives for case and control and with careful cleaning, with alcohol soaked swabs, of knives between blocks”.\(^2\) If we accept that the procedure was as stated, the best scenario at this point would seem to be that a knife cleaned neither before nor between section cutting happened to be contaminated with modern HIV-1-infected tissue and thus passed not only HIV-1 DNA but also appreciable human cell material to the first four sections, which happened to be from M S. By the fifth and subsequent cuttings the knife supposedly had wiped itself clean. As discussed below, however, there are still many problems.

The hypothesis of prior contamination might be clarified by a detailed description of the storage and location of the two sets of tissues, and of how and where sectioning was undertaken. EH learned from one of the doctors involved that for at least a part of the period of the PCR investigation the blocks were being stored in Williams’ home, and Williams later confirmed this.

Both Corbitt and Williams told EH that the code had been broken during a telephone call, in which Corbitt read through the list of numbered samples, indicating for each whether or not the presence of HIV had been demonstrated, and Williams then broke the codes, indicating which samples had come from M S and which from the control patient. Corbitt states that nobody else was in the room at the time; Bailey was waiting outside. A more appropriate method might have been an exchange of sealed envelopes and the presence of witnesses when the envelopes were opened.

Further examination of the original M S tissues and of the PCR products from Corbitt’s laboratory is needed. In the past, Williams has stressed that there was little tissue available and that he had been keeping a judicious eye on what remained to ensure that not all was used up.\(^4\) But he has less convinced, considering that “the contaminant may have been a lab strain, or ... another patient sample”. He acknowledges that about 40 blocks were taken at necropsy. These originated from a wide variety of skin lesions, together with bone marrow, heart, lung, and central nervous system, and abdominal viscera (including liver, kidneys, pancreas, and spleen), and even if most of the tissues are not ideal for finding lymphotropic virus, some DNA from an overwhelming virus infection should be detectable. Extraction of human DNA should be feasible from any of the samples. Perhaps the Central M anchester H ealth Care T rust but was neither acknowledged nor accepted.

Five human genotypes for M S have been mentioned.\(^1,6\) Zhu and Ho found that three HLA-DQ\(^\alpha\) genotypes had been sent to them, with traces of a fourth. In material from Corbitt they found type 1.2,4 “with traces of 2,3” in kidney and 1.2,3 in both marrow. In material from Williams, on the other hand, they found 3,4 in thyroid, liver and kidney. Bailey and Corbitt now report that, working on samples received from Williams in 1989 (those from 1995 having been found unusable), they detected 2,4 in liver and brain. They also found human type 2,3 in the CEM line that was their HIV-positive control in 1990. The frequency of 2,4 in Britain is likely to be well below 5%.\(^7\)

If Zhu and Ho’s interpretation of their bands was at all equivocal and “2,4 with a trace of 1.2,3” for kidney and bone marrow is a possible alternative to their stated “1.2,4 with traces of 2,3” the inconsistency of the New Y ork and M anchester accounts would be greatly lessened: 2,4 could then be due to the contaminating CEM cells, and Zhu and Ho’s technique, perhaps more sensitive than that of Bailey and Corbitt, could be revealing the underlying tissue type 1.2,3, exactly as found by Zhu and Ho in bone marrow which had seemingly escaped contamination.\(^8\) M S would then have a puzzle of only two genotypes; a third would be due to the CEM cells.

Perhaps both DNA and proteins of the wax block material were so degraded that they provided weaker and sometimes undetectable signals. Thus, provided by a recent cell contaminant, when present, T his is further suggested by the partial and wholly negative results obtained, respectively, by Bailey and Corbitt and by the UK Forensic Science Service.\(^1\) However, the idea that contaminant CEM cells explain all the genotyping and viral results since 1989 still involves many difficulties, whether that contamination arose in the laboratory where sectioning took place or in Corbitt and Bailey’s laboratory.

Turning to the nature of the patient’s disease, Bailey and Corbitt express themselves puzzled and reiterate that the symptoms were, retrospectively, very suggestive of AIDs. We believe, however, that the diagnosis has become the least of the problems of the case. It would be flippant to suggest that a patient with multiorgan HIV infection who died as a result of a wasting syndrome, P carinii pneumonitis, disseminated cytomegalovirus infection, and neurotoxoplasmosis. Apart from the Toxoplasma infection, the clinical profile matches that of M S. Dr T B Stretton, one of the M S physicians in 1959, now leans towards this retrospective diagnosis.
If M S did die from AIDS it is vital to our understanding of the early history of primate immunodeficiency viruses that an authentic sample of HIV DNA from such an archival case be made available for sequencing and phylogenetic analysis. Besides the controversial post-mortem tissues, biopsy specimens were taken from sternal marrow, scalene region (including a lymph node), and ulcers and skin lesions. Perhaps these are still available at the M anchester Royal Infirmary.

If, however, as we believe, this patient did not have AIDS, and if there was either substantial contamination with modern HIV DNA or tissue samples from other patients came to be included in the PCR investigations, then this man’s family and fiancée are owed an apology for the distress which this episode has caused them.

Unsourced information in this article is based on tape-recordings and notes of interviews between EH and the various scientists mentioned, personal letters from some of these scientists, and medical records of the patient, viewed with permission of his next-of-kin.

References
2 Connor S. World’s first AIDS case was false. The Independent (M arch 24, 1995).

Medicine and art

Untitled

Karl Gustav Sievers

There is little information about this untitled work (pencil and watercolours on flimsy paper, 19×26 cm) and the artist. We know only that Karl Gustav Sievers was a weaver with a diagnosis of schizophrenia, who was first recorded as being in Göttingen asylum, Germany, in 1909. It is one of the 6000 paintings, drawings, objects, and collages made by patients in psychiatric hospitals throughout Europe that were collected by the German art historian and psychiatrist Hans Prinzhorn (1886-1933), which is kept by the Psychiatric Institute of H eidelberg University. 200 of these works (created between 1890 and 1920), including Sievers’ cycle, will appear in an exhibition called “Beyond reason. Art and psychosis: works from the Prinzhorn Collection”. Themes include intricate drawings of mechanical inventions, engines, or hot-air balloons; religious images; sexual fantasies; repeated reworking of patterns, themes, or messages—on paper or in embroidery; anguished faces; and fantastic beasts. The exhibition can be seen at the Hayward Gallery, Royal Festival H all, London, from Dec 5, 1996, to Feb 23, 1997.