and Egger *et al*¹¹). Although most data come from less than optimally designed studies or ones not specifically undertaken to address this issue, this great mass of negative results cannot simply be dismissed. Moreover, two recent double blind crossover trials in 67 patients with insulin dependent diabetes found no difference in the frequency of hypoglycaemia during treatment with porcine and human insulins. The study by Colagiuri *et al* had the statistical power to detect a 20% increase in frequency.¹⁵

Thus, viewing the scientific literature as a whole, there seems no rationale for supporting the hypothesis that human insulin has the intrinsic ability to reduce the awareness of hypoglycaemia, and there is no convincing evidence that its use intrinsically increases the risk of severe hypoglycaemia.

Despite this, considerable concern still exists among patients and doctors. Excluding a specific effect in a small subpopulation of patients or a small increase in risk (for example, less than 20%) is not possible on the basis of current published studies. An additional study with a design identical with that used by Colagiuri *et al*¹⁵ would alleviate this concern if both studies' results were the same, as their combined power could exclude a clinically important effect. Such a study, rather than an expensive large scale multicentre study, would therefore seem indicated.

At present, the following recommendations seem reasonable: concerned patients and doctors should be informed of the current status of evidence against human insulin, patients satisfactorily treated with porcine insulin should not routinely be transferred to human insulin, patients who want to transfer from human insulin should be able to, and preparations of

animal insulins should remain available until the appropriate study has put this issue to rest.¹⁶

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“AIDS” without HIV: fire without smoke

Claims of a new strain of HIV are premature

Delegates returning from the international conference on AIDS in Amsterdam were surprised to find that press coverage in both the United States and the United Kingdom had been dominated by an issue that had been ignored during the formal scientific sessions and had received only cursory mention during the conference summaries. The stories at home were dominated by a few patients who seemed to have AIDS but no HIV.

Press attention had been directed to an additional scientific session and subsequent press conference at which Dr Jeffrey Laurence from Cornell University announced first details of an investigation of five patients from a large HIV practice who had signs or symptoms consistent with AIDS or AIDS related complex but from whom HIV-1 and HIV-2 had never been detected by antibody testing, virus isolation, or molecular detection techniques, including the polymerase chain reaction. Four patients had risk factors for the acquisition of HIV, and infection with human T cell leukaemia/lymphoma virus types I and II had been excluded by immunoblotting.

At the same session Dr James Curran, head of the AIDS section at the Centers for Disease Control, Atlanta, reported that the centres had received information on a further six cases, which were now under investigation. In the following discussion scientists representing several research groups, including Professor Luc Montagnier, who discovered HIV, reported brief details on a few additional cases at various stages of investigation.

At this point the world's press proposed a series of emotive

questions quite out of proportion with the limited clinical data presented. These included the safety of national blood supplies and the extent of risk to those in high risk categories for HIV infection but who remained negative for HIV antibody. Although not raised two weeks ago, further questions of the more general relevance of HIV to the pathogenesis of AIDS will no doubt soon follow.

One week later the *Lancet* carried a brief report of the cases in New York City, which contained little further documentation.¹ Indeed, one of the patients had no clinical indication of immunodeficiency other than infection with *Mycobacterium tuberculosis* and two slightly low CD4 counts, which could have been secondary to his acute illness.² Preliminary information about reverse transcriptase activity in cultures of lymphocytes from two patients will require further confirmation, and no viral isolates were reported.

In many ways the limited scientific debate in Amsterdam was reminiscent of that in the early days of the AIDS epidemic. In 1981-3, before HIV had been isolated and identified, the cause of the new syndrome aroused widespread speculation and investigation, which ended with the description of the new virus and the development of a highly sensitive and specific diagnostic antibody test. The driving forces then for a scientific search for a transmissible cause were the epidemic rise in numbers of newly identified and reported cases and the careful early epidemiological studies that suggested a pattern of spread similar to that of known viral infections such as hepatitis B. These epidemiological studies

allowed cases of what later became identified as HIV infection to be distinguished from rare sporadic cases of primary or secondary T cell immunodeficiency.

Emotional reactions seem to have clouded the fact that at the moment none of the epidemiological criteria pointing to a new transmissible agent have been met by these most recent cases. The null hypothesis remains that they may represent merely the increasing ascertainment of cases of rare spontaneous primary or secondary immunodeficiency disease by doctors whose awareness has been sharpened by extensive experience of HIV. Despite a number of sporadic cases over the past few years,^{3,6} the total number of reported cases remains low and insignificant when compared with the total of 250 000 cases of AIDS reported so far in the United States. There is no suggestion of case clustering or of a pattern of sexual or vertical association of cases, in contrast with what was apparent in AIDS studies at an early stage. The number of cases reported has not seemed to be increasing, although a rapid rise can now be expected as clinical teams report additional isolated cases for the first time.

Even if epidemiological support appears for a transmissible agent, its isolation and identification may prove difficult. Preliminary work suggests that currently classified human retroviruses have been excluded. The sensitivity and specificity of the assays used could, however, result in even relatively closely related strains being missed. Full published data on attempts at isolating cell lines and reverse transcriptase activity in cultures are awaited with interest. Reports of viruses isolated from individual patients will need to be interpreted with caution in view of previous experience of cross contamination of laboratory cultures and the difficulty of assigning pathogenicity to any isolates obtained from immunodeficient people.⁷

The cases already under investigation probably represent a heterogeneous group with mixed aetiologies. These will include some cases of primary immunodeficiency not yet appropriately classified and also some of immunodeficiency secondary to occult illness such as lymphoproliferative disease or malignancy. Even cases of primary immunodeficiency presenting in adults can show evidence of clinical and immunological progression similar to that described by Laurence in Amsterdam. Careful collection of epidemiological and clinical data on reported cases will be required to

assess the results of laboratory investigations under way. The proposal of the Centers for Disease Control and the World Health Organisation to coordinate reporting and classification of cases is welcome since any preliminary laboratory findings must be rapidly confirmed or refuted on the basis of a larger series of cases.

Answers to questions such as the wider relevance of any preliminary findings for the safety of national blood supplies will have to await the full evaluation of work already under way and the development of sensitive and specific detection systems for any new pathogens that may eventually be identified.

It seems that press hunger for a story from a conference on AIDS that otherwise reported steady slow progress against a problem of immense dimensions has resulted in renewed pressure to publicise claims before the peer review system has established that they are soundly based. Press interest raises public concern at a stage when objective scientific appraisal is not possible and results in independent researchers appearing flat footed and defensive. One lesson that should be learnt from this experience is the need for the media to understand the nature and importance of scientific method and to appreciate that premature exposure of an incomplete investigation is not in their long term interests or those of the general public or the scientific community.

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Vitamin K and childhood cancer //

The risk of haemorrhagic disease is certain; that of cancer is not

Many events in early life have been reported to be associated with the development of cancer in childhood.¹ One unexpected finding was the association with vitamin K given after birth among the 33 children from the national cohort of children born in April 1970 who developed cancer by the age of 10.² In this issue Golding and her colleagues, who found this association, report a further study, in which they identified a group of children who developed cancer and compared them with a larger group born in the same hospitals but who had not developed cancer.³ Again they found an association between administration of vitamin K and childhood cancer, with a relative risk of around 2.0 when the vitamin K was given intramuscularly. Can this be true, and, if it is, what does it mean?

The design, method, and conduct of epidemiological

studies all need close scrutiny before their findings can be used to drive clinical practice. Moreover, epidemiological associations do not establish causation; the association may mask another cause. In this case Golding *et al* looked for confounding factors but did not find any. An association also demands more attention if it persists in many studies, and no doubt this report will provoke such inquiries.

If the association holds it has major implications. Biologically it means that a single injection of a drug at a vulnerable time doubles the risk of a child developing cancer. The clinical implications are also considerable. In those countries where vitamin K is given by injection to all children a relative risk of 2.0 means that the rate of cancer would be halved if vitamin K prophylaxis was withdrawn.

In their first study, on the national cohort, Golding *et al*