disease in their hosts. This theory postulates that HIV has recently evolved from a non-pathogenic human ancestor lentivirus which would have had to be sufficiently different not to induce antibodies reactive in standard HIV tests or to have been confined until recently to small remote populations. These possibilities are not mutually exclusive. To date there is no evidence for such a "missing link." The serological and molecular techniques used to look for viruses like HIV in normal subjects may not, however, reliably detect even quite close ancestors. Occasionally antibodies to HIV core proteins are found in normal subjects,²¹ which might point to the existence of an unknown human lentivirus—but this is speculative.

If HIV was transmitted to man from monkeys how could this have happened? Transmission might have been possible through bites, scratches, medicines, or ritual preparations obtained from other primates. Irrespective of whether HIV was transmitted to humans from primates or whether it evolved from an ancestor lentivirus in man, when could this have happened? The earliest retrospectively identified cases of AIDS occurred in the 1960s,^{22 23} and a comparison of the genomic sequence variability among several strains of HIV-I, HIV-II, and SIV_{MAC} suggests that about 40 years would have been long enough for the differences observed between HIV-I and HIV-II to have evolved.^{24 25} It is therefore possible, but by no means certain, that HIV evolved towards becoming a pathogenic virus or spread into human populations, or both, within the past few decades.

Where did HIV come from? Very early cases of AIDS (retrospectively identified) seem to have originated in Africa.^{22 23} There have been unconfirmed reports that related viruses may occur in other parts of the world. The extent to which rapid political, social, and cultural changes that have occurred in African society during this century could have played a part in the spread of HIV is impossible to specify, although some of the features of the AIDS epidemic—for example, its spread through prostitution—are certainly linked to rapid urbanisation.

The origin of HIV remains a mystery. Attempts to solve it may disclose information about the evolution of lentiviruses in different species and, perhaps, lead to the discovery of as yet unknown lentiviruses in humans. The future prevention of AIDS is the real challenge, but understanding the origins of

HIV and the reasons why simian immunodeficiency viruses are not pathogenic in their natural hosts may eventually help in controlling HIV.

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Institutional review boards

Britain should consider the US example of more controlled ethics committees

The American counterpart to the British research ethics committee is the institutional review board. The principal function of these committees is to review proposals to conduct research in humans to assure conformity with ethical standards. Although the leading international code of research ethics, the World Medical Assembly's Declaration of Helsinki, charges these bodies to provide only "consideration, comment, and guidance," in both the United States and the United Kingdom they have the authority to approve or disapprove plans to conduct research.

Although the goals of ethical review in the United States and Britain are identical, there are some striking contrasts in the means employed to pursue them. In the United States, but not in Britain, ethical review and approval is required by national law for most types of clinical research; virtually all research institutions have negotiated agreements with the

federal government that extend the requirement for ethical review to all clinical research.¹ Federal regulations specify minimum requirements for membership, functions, and operations of the institutional review board.

The ethical criteria for approval of research by institutional review boards are set forth in considerable detail in federal regulations. The review boards have the authority to monitor the conduct of research to assure compliance with ethical standards; if they detect either non-compliance or "unexpected serious harm to subjects" they are empowered to suspend or terminate the research. By regulation, institutional review boards are required to report to institutional officials and to the federal government "any serious or continuing non-compliance by investigators" with the boards' requirements.

Applications to the United States Department of Health and Human Services for grants or contracts to support

research in human subjects must be reviewed and approved by the local institutional review board before the Department of Health and Human Services will even consider whether they should be funded. Nevertheless, by regulation, the Department of Health and Human Services is required to repeat some of the institutional review board's activities; for example, the department must repeat the evaluation of the relation between risks and benefits. The institutional review board does not have the authority to approve certain categories of research specified in the regulations—for example, research in children in which “more than minor increases over minimal risk” are presented by “an intervention or procedure that does not hold out the prospect of direct benefit” for the child subject. Research in these categories can be approved only by the secretary of the Department of Health and Human Services in consultation with a panel of experts and after an opportunity for review and comment by the public. To the best of my knowledge there are no similar activities at national level in the United Kingdom, although they have been advocated by Mary Warnock and others.²

Agents of the United States Food and Drug Administration conduct routine inspections of the institutional review boards and investigators engaged in the review or conduct of research on drugs, medical devices, and other “test articles” regulated by the administration. Inspections by officials of the United States Department of Health and Human Services may also occur in response to reports of “serious or continuing non-compliance.”

Federal regulations require that each institutional review board should have “at least one member who is not otherwise affiliated with the institution.” Many states require public institutions to open their meetings to the public, and some

private institutions similarly open their meetings. Though few “outsiders” seem to attend meetings of the institutional review boards, these policies serve to remind the members of their ultimate accountability to the public. Spokespersons for institutional review boards engaged in reviewing activities of great interest to the media—for example, the implantation of a baboon's heart in “Baby Fae” and of the first totally artificial heart⁴—have reported that the presence of journalists has been highly disruptive.

In response to apparent ethical improprieties in the conduct of clinical research several British commentators—for example, Byrne,⁵ Faulder,⁶ and Nicholson⁷—have called for reform in the British system of ethical oversight in research. In their view Britain should adopt a system similar to that in place in the United States. Elsewhere I have suggested that the American system of regulation reflects its unique recent social history and distinctively individualistic ethos.⁸ For this reason other societies may find some of the United States' policies and practices unsuitable for their needs.

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The contraceptive pill and breast cancer in young women

Evidence is still reassuring

Last week saw yet more press headlines about the contraceptive pill and breast cancer. Yet as the number of epidemiological studies on the effect of oral contraceptives on breast cancer has increased the picture remains far from clear. This lack of consensus contrasts with other studies on the contraceptive pill. For example, at least nine case-control studies have agreed that combined oral contraceptives reduce the risk of endometrial cancer, and at least eight case-control studies have shown a reduced risk of ovarian cancer.¹ A protective effect against uterine and ovarian cancers is biologically plausible because combined oral contraceptives abolish the rapid cellular proliferation that occurs every month in these organs.

An effect of combined oral contraceptives on the incidence of breast cancer is also biologically plausible. The fact that the risk of breast cancer is increased by an early menarche and by a late menopause¹ implicates ovarian steroids in the initiation or promotion, or both, of breast cancer. What is far from clear on theoretical grounds is whether combined oral contraceptives can be expected to enhance or to antagonise these harmful effects of ovarian activity. The ovary produces its hormones sequentially—first oestrogen then progesterone—but combined oral contraceptives provide them simultaneously. If unopposed oestrogen is a risk factor for breast cancer (as it is for endometrial cancer) combined

oral contraceptives should diminish breast cancer risk, but no such effect has been observed in epidemiological studies. Breast lobules do not proliferate during the menstrual cycle, but cell turnover increases in the second half of the cycle.^{3,5} The pattern of cell turnover in the breast is not affected by combined oral contraceptives.^{4,5}

The theoretical uncertainty has been reflected by conflicting results from epidemiological studies. Of the many studies published so far, none has suggested that combined oral contraceptives protect against breast cancer and most have failed to show any effect of combined oral contraceptives on the risk of breast cancer.⁶⁻⁹ Some have shown an increased risk associated with the use of the contraceptive pill early in life or before the first pregnancy while showing no risk associated with the use of combined oral contraceptives later in the reproductive years.^{6,10} Studies which have concluded that the use of combined oral contraceptives carries risks tend to have been scrutinised more critically than those with reassuring results, but in general both studies giving negative results and those giving positive results have been conducted with equal care and there is no obvious explanation for their different results.^{1,6,7,11,12}

Last week saw the publication in the *Lancet* of a case-control study in 11 areas of Britain of 755 women with breast cancer that had been diagnosed before the age of 36.¹³ Cases