100 YEARS AGO

Our congratulations to the Leicester Literary and Philosophical Society. Stimulated into action by a paper on the disappearances of certain species of insects, by Mr. Frank Bouskell, a Committee was formed to formulate regulations for the protection of local species... When a collector now sees *Leucophasia sinapsis* (the Wood White butterfly), he must hold his hand and crush his sporting instinct, for none of this insect are to be taken. Of *Macroglossa fuciformis* only one specimen must be taken by each member in a single season, and only one specimen of *Sesia apiformis*. The penalties for breaking these regulations are drastic... The over-zealous collector will, indeed, be ostracised, and will find that no one will buy from him, exchange with him, or have anything to do with him entomologically. There may be a difficulty in carrying out the regulations, and one result will probably be that collectors will prefer to go out alone in the future. But it is hoped that entomologists will remember that they are not supposed merely to fulfil the functions of a fly-paper, but also to work for the advancement of their science.

From *Nature* 11 March 1897.

50 YEARS AGO

When Prof. Raymond Dart, of the University of the Witwatersrand, Johannesburg, announced in *Nature* the discovery of a juvenile *Australopithecus* and claimed for it a human kinship, I was one of those who took the point of view that when the adult form was discovered it would prove to be near akin to the living African anthropoids. [But] I am now convinced that Prof. Dart was right and that I was wrong; the Australopithecinæ are in or near the line which culminated in the human form. My only complaint now is the length of the name which the extinct anthropoid of South Africa must for ever bear... I have ventured, when writing of the Australopithecinæ, to give them the colloquial name of 'Dartians', thereby saving much expenditure of ink and of print... It is much easier to say there was a 'Dartian' phase in man's evolution than to speak of one which was 'australopithecine'. – Arthur Keith

From *Nature* 15 March 1947.

Xenotransplantation

Proviruses pose potential problems

Jonathan P. Stoye

Organ transplantation could save — or greatly improve the quality of — the lives of many people. However, there is a shortage of suitable donated human organs, so attention has turned to the possibility of transplanting primate or pig organs. Using transgenic animals designed to minimize the activation of human complement, considerable progress has been made in preventing immunological rejection of transplanted organs[1,2]. Yet clinical trials have been delayed, mainly due to fears that such procedures might facilitate the introduction of novel viruses, particularly retroviruses, to the human population[3]. This was largely a theoretical risk, at least in the case of pigs, as no such viruses had been described. But a report by Patience and colleagues[4] in the March issue of *Nature Medicine* indicates that there are grounds for practical concern. They provide evidence that at least one pig cell line produces a retrovirus that can infect human cells, and that a related virus is expressed in normal pig tissues.

If a retrovirus infects a germ cell, the resulting provirus can become part of the germ line. These retroviral elements are known as endogenous proviruses, and every vertebrate species will have picked up many such mementos of encounters with retroviruses during the course of evolution. Most seem to be harmless — over time they have accumulated mutations that destroy their ability to give rise to replicating virus, and they occur at the same location in the genome of all individuals of a species. But others are more recent; they show genetic polymorphism and potentially encode infectious virus.

In general, endogenous proviruses are not highly expressed, although occasional transcription can occur. Due to adaptations of host viral-receptor proteins, many otherwise intact endogenous retroviruses cannot infect cells derived from their current host. However, viral replication can take place in cells from a different species; that is, the viral host range is 'xenotropic'. So, if grown in apparently retrovirus-free mice, human cells will often show signs of infection by a mouse xenotropic virus[5]. A pig-to-human xenograft is conceptually similar, prompting fears that a porcine retrovirus from a transplanted organ might infect human recipients, with unknown consequences[6].

Until recently, porcine retroviruses received little attention: retrovirus production was seen from a number of pig cell lines, but these viruses seemed to be ecotropic in host range — they infected only pig cells[7]. Patience *et al.*[4] reinvestigated the infectivity of virus that was produced by two cell lines derived from pigs, MPK and PK-15. They confirmed that MPK cells make ecotropic virus; however, the PK-15 cells seemed to be making a mixture of ecotropic and xenotropic viruses. Moreover, the xenotropic virus could replicate, albeit very inefficiently, in a variety of human-derived cell lines (although primary cultures of human cells have not yet been examined in any detail).

Limited sequence-studies of the viral polymerase gene indicate that the ecotropic and xenotropic viruses are very similar to one another, and that they belong to the mammalian C-type family of retroviruses. Hybridization studies predict that the pig genome contains around 50 related proviruses, one or more of which is expressed in a variety of tissue types, including heart and kidney — the two organs most likely to be transplanted. Unfortunately no data are presented concerning the infectivity or host range of the spontaneously expressed virus. Also absent from the paper are sequence data from the region of the virus which determines host range, and information about the number of endogenous xenotropic proviruses in the pig genome. Indeed, although unlikely, it is still possible that none of the endogenous proviruses is xenotropic, and that the xenotropic PK-15 virus contains sequences derived from a non-porcine retrovirus.

Evaluating the risk posed by viruses of the sort described by Patience *et al.* is not simple. The first question is whether transmission can occur. It will be interesting to see whether studies using the polymerase chain reaction, with primers designed to the pig retrovirus, show any evidence for transmission in primates transplanted with pig organs, or in humans with occupational exposure to pigs or pig tissues. Frequent contact between pigs and humans has apparently never led to retrovirally induced disease, possibly because human complement can lyse retrovirus that is grown in animal cells[8]. But under the circumstances of a transplant — close proximity and long-term contact — this barrier to spread could probably be overcome, especially as the measures taken to prevent hyperacute rejection and permit xenotransplantation will reduce the efficiency of lysis. Patience *et al.* also show that porcine retrovirus grown in human cells is no longer susceptible to lysis by human complement, implying that once viral breakout occurs there will be no further barrier to spread by this resistance mechanism.

If a viraemic state is established, a number of outcomes are possible. Most endogenous xenotropic retroviruses are essentially non-pathogenic[9], so transmission of virus would