100 YEARS AGO

A note in the *Electrician* refers to a curious effect produced by severe thunderstorms upon the glow lamps on the circuits of the Calcutta Electric Supply Co. It appears that immediately following each lightning flash the brightness of the glowing lamps has been observed to increase suddenly, gradually returning to the normal incandescence. This phenomenon has so frequently been observed that the engineers of the company have sought every possible explanation of the curious phenomenon, but have been unable to find any defect in their circuits — which are on the overhead wire system — that might offer an explanation. Indeed, the only conceivable explanation is one which appears so extraordinary that many may find considerable difficulty in accepting it. It is well known that carbon, acting as a coherer in a wireless telegraph apparatus, undergoes the usual sudden decrease in resistance when subjected to electric radiation. It is suggested that the carbon filaments of a glowing lamp may undergo a similar change when exposed to the influence of a tropical thunderstorm in its immediate vicinity. This sudden decrease in the resistance of the filament would, of course, produce a correspondingly rapid increase in its candle-power, after which the gradual self-coherence of the carbon would account for the return of the lamp to its usual incandescence.
From *Nature* 6 September 1900.

50 YEARS AGO

In his presidential address to the tenth All-India Veterinary Congress held last April in Bombay, Dr. S. Datta, director of the Indian Veterinary Research Institute, Mukteswar, appealed for the creation of an Indian veterinary council, which should be a statutory body set up by Act of Parliament, with power to enforce a high standard of veterinary education in Indian veterinary colleges, to suppress quackery in the veterinary profession and to co-ordinate the work of the various State veterinary departments… He deplored the lack of interest shown by the State and the public in the welfare and improvement of farm stock, and rightly urged that veterinarians should not merely wait until disease occurs and then try to remove or prevent it… Quite apart from political or economic considerations, this reorganisation and development is urgently required for the sake of the farm animals themselves.
From *Nature* 9 September 1950.

et al. propose to knock out the gene encoding the enzyme α-1,3-galactosyl transferase, which catalyses the synthesis of a sugar in pigs. This sugar is the major molecule recognized by human antibodies that trigger xenotransplant rejection[4] (Fig. 1). This possibility seems to bring xenotransplantation closer to the clinic, but may also provoke worries.

Concerns about xenotransplantation stem mainly from the existence of porcine endogenous retroviruses (PERVs), which seem to be present (and harmless, if not useful) in the genome of all pigs. A retrovirus consists of a single RNA strand, enclosed in an envelope of glycoproteins derived in part from the membrane of an infected cell (Fig. 1). After infecting a cell, the RNA part of the retrovirus is copied into DNA, which inserts into the genetic content of the cell and is thus passed on to all of the cell's progeny. The DNA can also direct the formation of new viral particles. The worry is that PERVs might be transmitted first to a human transplant recipient and then more broadly in the population.

Humans have been in close contact with pigs for millennia, with blood products and tissues being exchanged by accident and, recently, by xenotransplantation[4]. Cultured human cells can be infected by PERVs released from cultured pig cells[2,5], but studies of 'control' humans and hundreds of patients who have received pig xenotransplants or blood plasma have not revealed even a single case in which PERVs infected human cells in the body[6,7]. There are three possible explanations for this. First, PERVs may lack the necessary 'equipment' that would enable them to enter and infect human cells *in vivo*. Second, human cells *in vivo* may lack a receptor to which PERVs need to bind in order to gain entry; alternatively, they might not have the machinery needed to allow PERVs to replicate. And third, humans may have natural defences against PERVs that cultured cells do not.

The first of these explanations may now be under threat. Van der Laan *et al.*[2] have transplanted pig pancreatic islet cells into immunodeficient mice, and found that PERVs infected several tissues — and can perhaps replicate — in these mice. Still uncertain, however, is whether human cells *in vivo* can be infected. Earlier results[6,7] suggest not, and one might conclude that xenotransplantation is safe. But such a conclusion would be premature, and would ignore the more important lesson to be learnt from van der Laan *et al.*'s work. Rodents carry a variety of viruses and retroviral elements, the genetic material of which can perhaps recombine with that of PERVs. This might give PERVs the equipment needed to for them to infect mouse cells — and perhaps even human cells — *in vivo*. The results reported by van der Laan *et al.* should serve as a warning: experimental xenotransplants in rodents could also present a risk for humans.

If PERVs have, or might acquire, the ability to infect humans, and so could be thought to pose some risk, then it becomes appropriate to ask whether we could eradicate PERVs from pigs. The method described by Polejaeva *et al.*[1] might offer a means of doing so. But this should not be undertaken unless the risk is certain and substantial, partly because it could have unforeseen effects on the pigs. And, because humans come into contact with pig tissues and blood in other ways (for example, through routine husbandry), the full protection of human society would require the eradication of pigs that were not modified in this way. In my opinion, the best way of determining the risk and consequences of

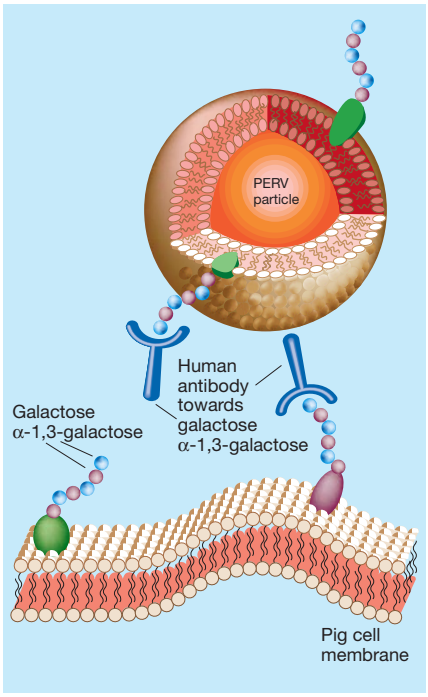

Figure 1 **The role of antibodies in the rejection of xenotransplants and in resistance to porcine endogenous retroviruses (PERVs). Most immunocompetent humans have antibodies that recognize galactose α-1,3-galactose, a sugar expressed on the surface of pig cells. The binding of these antibodies to pig cells is thought to trigger the rejection of xenotransplants. Similarly, PERV particles are coated by pig cell membranes, so they also express galactose α-1,3-galactose. So antibodies against galactose α-1,3-galactose might also inactivate PERVs. Some individuals, myself included, who have worked for many years with pigs have low levels of antibodies towards galactose α-1,3-galactose. Such individuals presumably lack the resistance to PERVs conferred by these antibodies. One way of measuring the importance of these antibodies in humans would be to find out whether such individuals are already infected by pig viruses.**