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Introduction

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Hetero transplantation, or xenotransplantation, is no exception to the axiom that history repeats itself. The first attempts at whole organ transplantation were made between 1906 and 1923 using pig, sheep, goat, and subhuman primate kidney donors, and are summarized by Groth[3]. The first of these efforts were in France and Germany, and in some the blood vessels coming to and leaving these organs were sewn to recipient blood vessels in much the same way as today[8,22]. None of the kidneys functioned for long, if at all, and the human recipients died from a few hours to 9 days later.

No further trials were made until the surge of enthusiasm caused in 1963 by the repeated success of renal allotransplantation (using predominantly living related donors) with combined azathioprine–prednisone therapy[18]. Brain death as a condition for cadaveric donation was 5 years in the future, the supply of living donors was limited, and desperate potential kidney recipients were piling up faster than places could be found for them in the few existing dialysis programmes.

At the height of the crisis, heterotransplantation was re-explored. On 16 February 1963, Claude Hitchcock of Hennepin County Hospital, Minneapolis, transplanted the kidney of a baboon into a 65-year-old woman. The organ functioned for 4 days before its artery clotted[6]. The case was not made public until it was learnt, later in the same year, of a far more encouraging experience by Keith Reemtsma of Tulane University using the closer-to-human chimpanzee donor[14]. One of Reemstma's chimpanzee kidney grafts functioned for 9 months. Reemstma also transplanted a rhesus monkey kidney which was fiercely rejected.

Subsequently, Cortesini *et al.*[2], and probably others who did not report their cases, accumulated chimpanzee heterotransplantation experience, generally confirmatory of Reemstma's, and Hardy attempted a chimpanzee-to-human heart transplant which failed peri-operatively[5]. Liver heterotransplantation with chimpanzee donors was attempted three times by us, 19 or more years ago, with maximum survival of 9 days, summarized in[15]. The histopathological findings at autopsy were not distinguishable from those in allografts at comparable times. No further attempts have been made using modern immunosuppression (with cyclosporine), and are not likely to be, because of the endangered status of chimpanzees and their increasingly recognized humanoid qualities[4].

Much is also known about baboon to human transplantation. In December 1963 and January 1964, six patients were given baboon kidneys at the University of Colorado[17]. All the organs functioned promptly and maintained their function for 10 to 60 days. However, the necessary doses of azathioprine and prednisone were very high, and eventually the grafts were rejected. The rejection was midway in severity between that of the chimpanzee and rhesus kidneys but not qualitatively different from that observed in some homografts in which there was a humoral component[13]. The same events were recapitulated two decades later in the Baby Fae baboon-to-human heart transplant in spite of

heavy cyclosporine-steroid immunosuppression[1]. It was clear that the use of baboon organs would have to wait for better and possibly fundamentally different immunosuppression, assuming that baboons, more plentiful and with a seemingly more distant anthropomorphic separation, might be a socially and ethically acceptable donor. This latter issue is certain to be hotly debated even if clinical trials are successful.

All of the baboon kidneys (and Baby Fae's heart) developed spotty necrosis or uneven regional infarctions. It was unfortunate that there were not better humoral antibody studies in these early days. The technology for this was not then developed and lymphocytotoxic antibodies as a cause for humoral allograft rejection were not recognized until 1964[21]. However, even in early 1963, we measured heterospecific antibodies that may or may not have been relevant to the eventual destruction of the baboon kidneys. It was evident from declines in their titres and confirmatory electron micrographic studies that heteroagglutinins bound to the grafts[17]. K.A. Porter, the London pathologist who was working with us, concluded: 'In the resulting rejection process, cellular infiltration and peritubular capillary destruction are prominent early pathologic features, but in nine days the vasculonecrotic element is marked. There is circumstantial evidence to suggest that, whereas the peritubular capillary damage is mediated by cell-bound antibody, the fibrinoid necrotic vascular lesions are caused by circulating antibodies.'[13].

The serological and histopathological indictment of antibodies was prophetic. The humoral component of rejection has been the central topic for any discussion of transplantation between species since that time[19]. In fact, xenograft models have been used to evaluate treatment of hyperacute rejection of allografts in sensitized recipients with the assumption that the mechanisms of destruction of xenografts is by the same process. Such techniques to prevent humoral rejection have been summarized elsewhere[19] (see also Part II) and include plasmapheresis, antibody removal with a Staph A column to reduce the antibody titre; infusion of citrate, a chelating agent and anticoagulant – which is also very efficient in preventing complement activation – and the use of prostanoids and other inhibitors of the inflammatory response. Of these approaches, it is curious that the most promising, i.e. prostaglandin (PG) therapy has received the least attention. PGE_1 can unequivocally mitigate the xenograft rejection of cat to dog[11], hamster to rat[9] and pig to dog[10]. In FK–506-based drug cocktails, PGE_1, in combination with steroids, converts the prognosis of lymphocytotoxic crossmatch-positive liver allograft recipients to the same as those given crossmatch-negative organs[20].

Generally speaking, the humoral antibody barrier becomes more extreme, roughly in proportion to the degree of species disparity, so that with widely divergent species, humoral rejection usually occurs within a few minutes. However, trial and error has been the only way to rise above speculation with any given animal to human combination. Thus, dwelling on the historical experience with clinical heterotransplantation reflects more than an idle preoccupation. Each of these transplant efforts has yielded information about the extent of the human barrier to the particular species used.

Success was tantalizingly close with the chimpanzee, baboon, and rhesus monkey, in that order. Because the pig is often mentioned as a possible clinical organ donor, it is important to recount an unreported attempt by René Kuss, the pioneer French transplant surgeon, at a pig-to-human renal transplant in the early 1960s under azathioprine and prednisone (personal conversation in November 1990 with René Kuss and Jacques Poisson). The kidney functioned well for approximately 30 min but then underwent hyperacute rejection. The dominant finding was widespread thrombosis of the microvasculature, concentrated in the venules. Kuss' willingness to share this experience almost three decades later was important because it would be difficult, in the climate of today, to acquire this kind of vitally needed information. The pig will not be easy.

Those who were driven by an organ shortage in the early 1960s to attempt renal heterotransplantation found an abandoned camp fire left by workers at the turn of the century, and in turn were forced themselves to give up their bivouac. Now the cycle has begun again with the stimulus of an impending or actual shortage or organs for transplant procedures (kidney, liver and heart) which if successful provide the best and sometimes the only treatment for end-stage diseases of these organs.

This time, the tools of cellular immunology and molecular biology are sophisticated beyond the comprehension of most practising physicians and surgeons. Yet, serious gaps at a less esoteric level still exist. It is conceded that the antibody barrier is the presently insurmountable obstacle, but what to do about it, or even if the critical antibodies are of the IgM or IgG class, are debated constantly. Strategies are focused on the prevention of endothelial cell activation of the vasculature of solid organs, possibly with gene transfection or by inhibiting complement components[12], or by creation of xenogeneic chimeras with contemporaneous or prior bone marrow transplantation[7].

In spite of optimistic speculation, the related but easier problem has eluded solution of surmounting the lymphocytotoxic allospecific antibodies which prevent the transplantation of a growing population of potential renal recipients. If humoral rejection of allografts, and then of xenografts, could be prevented there is much speculation, and some evidence, that subsequent cellular immunity will be less formidable with xenografts than with allografts[12].

However, support for this idea has come only from *in vitro* experiments and has engendered instinctive scepticism. Nature is not usually this careless.

If heterotransplantation can be accomplished, it is almost certain that the difficulty will vary with different organs. Because it is resistant to antibody-mediated rejection[19], the liver is expected to be at the easy end of the spectrum. However, success could carry its own new set of penalties. Many genetic disorders are caused and defined by specific defects of the body's chemical machinery. If these are liver based, they are corrected by liver transplantation because the hepatocytes retain the metabolic specificity of the donor even though the lymphoreticular cells are repopulated by cells of the recipient[16]. It is conceivable that iatrogenic inborn errors of metabolism could be caused by the proteins and other synthetic products of the heterograft liver in proportion to the species disparity between the animal donor and the human recipient.

No matter what the organ, those who have worked with heterografts in the laboratory or clinic have the kind of respect for the species barrier that has been nourished by the frustration of repeated failures. The techniques of immunosuppression which already have brought organ allotransplantation to a high level of success will be part of the therapy required, but something else which is not yet apparent will be needed. The artful manipulation of the immune system to achieve tolerance has not been practical even for allotransplantation, and it is difficult to imagine that this approach will allow the widespread use of animal organs. I believe that the answer will be in drugs which inhibit other targets than those of classical immunosuppression. The most successful agents for antibody rejection are apt to be those which modify effectors of the inflammatory response[9–11,20].

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