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Continuing our Classic Paper series, T E Starzl looks back at his pioneering baboon-to-human transplants of the 1960s.

The first baboon-to-human transplants

T E Starzl

University of Pittsburg, 5C Falk Clinic, Pittsburg, PA 15213, USA.

A crisis followed the demonstration in 1962–1963 at the University of Colorado that azathioprine and prednisone, two immunosuppressants which were relatively ineffective individually, could in combination permit prolonged renal allograft and patient survival in the majority of human cases. This unexpected development came before other ingredients of an effective end-stage renal disease program were in place. Only a handful of dialysis facilities existed in the USA. Brain death pronouncement of cadaveric donors was 5 years away, and most kidney transplant candidates who did not have live volunteer donors died while waiting.

Xenotransplantation appeared to offer a way out of the dilemma. Consequently, the enthusiasm ignited by Keith Reemtsma's kidney xenotransplant trials of 1963 at Tulane University in New Orleans was both immediate and sustained. Although fierce rejection had destroyed a rhesus graft in a few days after its transplantation by Reemtsma, it was obvious that some of the chimpanzee grafts might function for long periods.

In ploughing new ground, Reemtsma already had proved that kidneys from at least two non-human primate donor species would not be abruptly rejected. This observation was critical. By 1963, Roy Calne had observed immediate kidney rejection following transplantation between discordant species. It also had been learned in Colorado that hyperacute rejection similar to that observed by Calne was often triggered by isoagglutinins in human recipients of ABO-mismatched kidney allografts. As a result of Reemtsma's pioneer efforts, it could be concluded that rhesus and chimpanzee kidneys would be spared this fate.

A few weeks after Reemtsma's cases became public, Claude Hitchcock, Chief of Surgical Services, Hennapin County Hospital, Minneapolis, telephoned me with the information that a kidney from a third Old World primate species, the baboon, had also escaped hyperacute rejection. On 16 February 1963, Hitchcock had secretly engrafted a baboon kidney into a 65-year-old woman with an immediate diuresis. The graft suddenly stopped functioning after 4 days due to a hepatic arterial thrombosis, which he attributed to a flawed vascular anastomosis.

Hitchcock was a baboon expert, having acquired a unique experience with this species during several preceding years in pioneer studies of auto- and allotransplantation of the lung, in collaboration with scientists attached to the large baboon colony at the Southwest Foundation for Research and Education, San Antonio, Texas. Fearful of public and professional criticism of his clinical kidney case (later reported in the *Journal of the American Medical Association*), Hitchcock had concealed its existence until Reemtsma's initiatives were widely known.

Regretting this decision, Hitchcock proposed a collaboration. It was appreciated that the threatened extinction as well as the anthropomorphic qualities of the chimpanzee would curtail the use of this animal as a donor. In contrast, the baboon had flourished in southern and central Africa and did not have such striking humanoid behavior. Because there was not yet a kidney transplant program in Minneapolis, the patients were to be treated at the University of Colorado, which had experience of nearly 50 renal allotransplantations under azathioprine/prednisone immune suppression.

Preparation required several months and included on-site collaborations with experts in zoonoses (Dr S S Kalter [NIH] and his San Antonio associates) and primate specialists (e.g. J J Moor-Jankowski [NIH]), many of whom also had worked with Reemtsma. Reemtsma, himself, was an invaluable source of advice. His generosity eventually made possible Kendrick A Porter's classical histopathologic comparison of rhesus, baboon, and chimpanzee kidney xenograft rejection by human recipients. ▶

Renal heterotransplantation from baboon to man: experience with 6 cases*

T E Starzl, T L Marchioro, G N Peters, C H Kirkpatrick, W E C Wilson, K A Porter, D Rifkind, D A Ogden, C R Hitchcock, W R Waddell

Departments of Surgery and Medicine, University of Colorado School of Medicine and Denver Veterans Administration Hospital, Denver; Department of Pathology, St. Mary's Hospital Medical School, London; and Department of Surgery, Hennepin County General Hospital, Minneapolis

SUMMARY

Six patients with terminal uremia due to glomerulonephritis or pyelonephritis were treated with heterografts from East African baboons. Immunosuppressive therapy was provided both before and after operation with azathioprine and prednisone and postoperatively local transplant irradiation and actinomycin C were administered intermittently. The individual rejection episodes in the post-transplant period could be reversed relatively easily but these recurred vigorously and repetitively, making it impossible to relax the stringent requirements of antirejection therapy. The continued need for high-dose immunosuppressive therapy precipitated lethal infections in the majority of cases.

The patients lived for 19 to 98 days after heterotransplantation. Four died with the baboon kidneys still in place after 19, 23, 35, and 49 days. In the other two cases the heterografts were removed after 60 and 49 days respectively, at a time when urine excretion was still present, and homografts from volunteer convict donors were placed on the opposite side. Both the latter recipients died of septic complications following the second operation, after 39, and 44 days. Complete cessation of heterograft urine excretion appeared only in two cases, although renal function was failing in the remainder prior to death or before removal of the heterografts. The relation of the renal function to changes in the heteroagglutinin and hemagglutinin titers is described.

After residence in the host for 19 to 60 days, all the heterotransplants were heavily infiltrated with plasma cells and large lymphoid cells with pyroninophilic cytoplasm. There was also disruption of peritubular capillaries, interstitial edema, widespread tubular damage, swelling of endothelial cells lining arterioles, fibrinoid necrosis of the walls of arterioles and interlobular arteries by fibrin and platelet deposits on the

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▶ Although we predicted from the Reemtsma/Hitchcock experience that the baboon kidneys would not be hyperacutely rejected, the specter of more subtle antibody rejection hung heavily over the trials, prospectively and afterwards. It would be another year before hyperacute rejection associated with lymphocytotoxic antibodies was recognized in ABO-compatible allograft recipients[1]. Consequently, a study of such antigraft antibodies was not done. Instead, attention was focused by David Talmage's immunology fellows (Charles Kirkpatrick and W E C Wilson) on the effect of hetero(xeno)specific hemagglutinins.

The baboon xenografts functioned for a mean of 41 days when there was ABO compatibility (n = 3) versus 21 days when there was not (n = 3). Although this suggested an important ABO effect, there was serologic evidence that xenospecific hemagglutinins also bound to the transplanted kidneys in every case. It appeared from the clinical observations, and especially from Porter's histopathologic analyses, that humoral xenograft rejection was uncontrollable with cell-directed immune suppression, even in the phylogenetically close baboon-to-human combination.

Therefore, we concluded that, "until improved methods of management become available, further trials do not seem justified, and none are contemplated by us until that time". The moratorium lasted more than 28 years until our two laboratory-based attempts at baboon-to-human liver transplantation of 1992–93. These also failed because of a less obvious humoral rejection, but with unmistakable complement activation despite complete freedom from cellular rejection out to 70 days. As in 1964, the rejection of 'concordant' xenografts was a 'slow motion' version of that seen with 'discordant' xenografts[2]. It was time for a new moratorium.

The humoral component of ▶

intima. The pre-glomerular vascular lesions were accompanied by focal infarcts and extensive interstitial hemorrhages. All the pathologic changes were more severe then those seen by Reemtsma in comparable series of chimpanzee-to-man heterotransplants, where cellular infiltration was slight and vascular lesions uncommon in the presence of major blood group incompatibility between donor and recipient.

During the developmental era of vascular surgery, five clinical renal heterotransplantations are known to have been tried, each with a different type of animal donor (4,7,16,19). Significant renal function was not obtained in any instance, and the longest survival was 9 days. No additional attempts at heterotransplantation were made in the ensuing 40 years, and the tacit assumption became firmly entrenched that such avenues of investigation presented insurmountable biologic difficulties.

In 1963, Reemtsma (12,14) and Hitchcock (2) and their associates re-examined the possibility that heterograft function could be obtained and sustained with the aid of various immunosuppressive agents. It was established that immediate urine excretion of chimpanzee (12–14), rhesus monkey (12), and baboon kidneys (2) followed after transplantation to the human, and that maintenance of relatively protracted chimpanzee heterograft function could be expected at least in the occasional case.

The present study is an account of a clinical study of renal heterotransplantation carried out at the University of Colorado Medical Center in December, 1963, and January, 1964, using baboons for donors. By comparison of the results with those previously obtained with homotransplantation (17) it was hoped to define the differences and similarities of homograft and heterograft behavior in the human host. In addition, it became possible as the result of an exchange of functional and pathologic data with Reemtsma to arrive at tentative conclusions concerning the biologic suitability for human heterograft donation of different subhuman primates.

Results

Clinical course. Four patients died with baboon kidneys still in place [?]. In Cases 3 and 4, the heterografts were removed after 60 and 49 days respectively, and homografts from volunteer convict donors were placed on opposite side. Survival after the second operation was 39 days in Patient 3 and 44 days in Patient 4. Complete cessation of heterograft excretion occurred only in Cases 2 and 5 (Table 3 [not shown]), although renal function was failing in the remainder prior to death (Patients 1 and 6) or before removal of the transplant (Patients 3 and 4). All patients exhibited a marked early clinical improvement at the time of initial diuresis and for varying periods thereafter. Recovery was, however, interrupted in each instance except Patient 1 by early rejection crises, which were characterized by transplant site tenderness, and by multifaceted evidence of acute renal failure. The timing of the rejection episodes is indicated in Table 4 [not shown] and the influence upon renal function is graphically portrayed in Figures 2–4 [not shown].

Ultimately, each of the last five cases became unmanageable because of the repetitive and closely-spaced rejections. Although the individual crises could be at least partially controlled in most instances, with local transplant irradiation, actinomycin C or increases in steroid dosage, the adverse consequences could not be completely reversed before the onset of the next assault. The cumulative effect was progressive deterioration, interrupted by incomplete remissions. In Patients 3 and 4, removal of the heterografts was precipitated by the sudden formation of masses in the transplant areas, of such magnitude in Case 3 as to produce massive edema of the right leg which was apparently due to local compression of

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▶ xenograft rejection was discussed in our 1964 article as an Arthus reaction, the same term (or alternatively 'Shwartzman reaction') used to described hyperacute allograft rejection in patients who had preformed antigraft cytotoxic antibodies (classical pathway of complement activation) but also in exceptional patients who were antibody free (alternative pathway)[3]. Thus, it was recognized almost from the beginning that humoral rejection of allografts under specific circumstances and that of xenografts involved an acute inflammatory reaction that would not yield to conventional immune suppression.

John Najarian, in commenting 30 years later on his own classical studies[4], has pointed out how little progress has resulted from the cyclic 'rediscovery' of the pathogenesis of xenograft rejection, and of treatment strategies, using increasingly sophisticated technologies to delineate what was already quite obvious by the late 1960s. An exception to the futility was the recognition by Gus Dalmasso and Fritz Bach that the seminal problem of complement activation could be resolved by providing the target donor tissues with complement regulatory peptides of the recipient species. This objective was achieved when 'humanized' transgenic animals were produced by David White in England and by John Logan in the USA with the collaboration of Jeffrey Platt and other colleagues. With this progress in cracking the shell of the xenotransplant problem, what remains to be done is the induction of organ acceptance by the same chimerism-dependent mechanisms that have spawned successful allotransplantation[5].

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