IN VIVO KIDNEY STORAGE

A PRELIMINARY COMMUNICATION

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In more and more centres cadaver grafts are used for renal homotransplantation, for many reasons, and this necessitates some method of storage. However, even when such a procedure is successful, pre-mortem renal damage may vitiate satisfactory renal function after transplantation.

No method exists for the assessment of renal function during storage, partly because organs cannot safely be stored for any length of time, and also because such investigations are not possible when the *in vitro* storage techniques are employed. We have attempted experimentally to prolong storage time and also to devise a method to assess renal function during the storage period.

Renal heterotransplants have been used clinically but, although immediate function was encouraging, prolonged survival was not achieved.[1,2] Antigenic dissimilarity between baboon or chimpanzee and man produces florid and repeated episodes of rejection, necessitating the administration of dangerous and often fatal dosages of immunosuppressive drugs. We do, however, envisage the development of heterotransplantation as a method of organ storage. In the preliminary investigation of this idea we have only used dogs.

MATERIAL AND METHODS

There were 3 groups of experimental animals:

Group I. 24 hours of live storage with subsequent return of the kidney to the original donor (Fig. 1).

Group II. 24 hours of live storage in an intermediate host with subsequent transplantation of the kidney into an unrelated third animal (Fig. 2).

Group III. 5 days of live storage in an intermediate host followed by transplantation into a third, unrelated animal (Fig. 3).

From previous experience[3,4] it was decided to withhold cytotoxics from the storage (intermediate) animals when 24 hours of storage was used (Groups I and II). In Group III, however, massive doses were administered during the 5 days storage period.

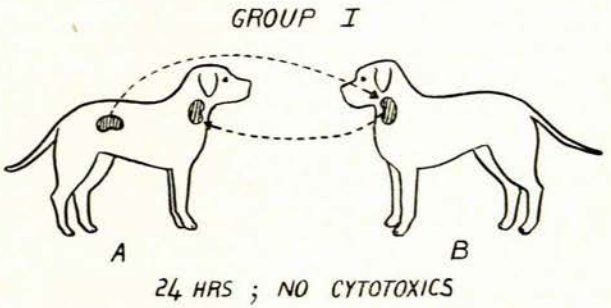

Fig. 1. Diagram showing live storage of kidney from dog A in dog B for 24 hours, and autotransplantation to dog A. No cytotoxic agents were employed.

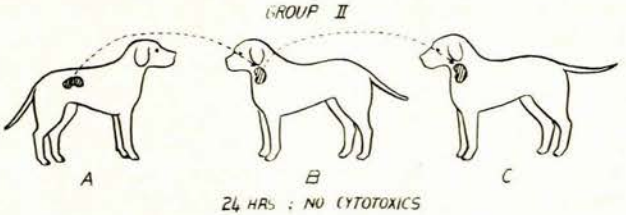

Fig. 2. Diagram showing 24 hours' storage of kidney from dog A in dog B with homotransplantation into dog C after storage. Cytotoxic agents were administered to dog C only.

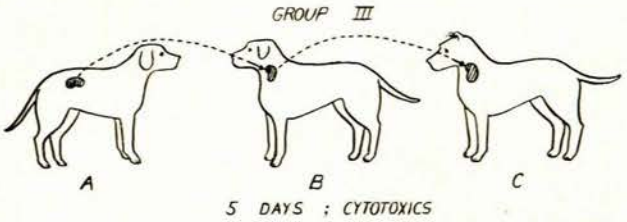

Fig. 3. Diagram illustrating 5 days' live storage of kidney from dog A in dog B and homotransplantation into dog C. Immuno-suppression was necessary in both storage animal and in final recipient.

In Groups II and III, where the kidney was transplanted after storage to an unrelated third animal, the final recipient received a standard, conventional regime of immuno-suppression.[5] In Group I, post-storage function was not complicated by rejection and immuno-suppression was not necessary, the kidney being returned to the original donor (autotransplant).

Investigation was directed at the diagnosis of rejection and the assessment of renal function, both during and after storage. The stored kidney was transplanted after storage into a bilaterally nephrectomized animal. Survival, which was taken as 14 days, was therefore wholly dependent upon the stored and transplanted kidney.

RESULTS AND CONCLUSIONS

Disadvantages

At the outset of investigation, 4 possible disadvantages of this method of *in vivo* storage were envisaged.

1. The technical hazards of transplanting a kidney twice. With meticulous attention to the initial nephrectomy,[6] and the careful primary transplantation into the storage animal, this did not constitute a source of failure. In Group I, where rejection did not interfere to any extent, renal function after storage was good and no technical failure was encountered (Fig. 4).

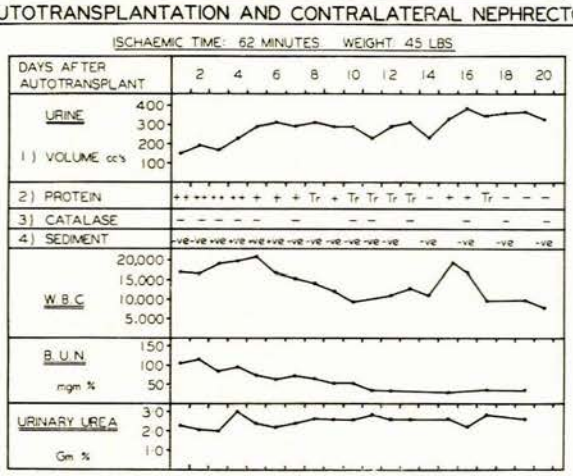

Fig. 4. Composite chart showing the changes in various parameters investigated in Group I. Some diagnostic criteria for rejection appeared on the 3rd day after transplant, but regressed spontaneously. Normal function had returned within 7 days.

2. It was anticipated that signs of rejection would manifest themselves earlier than usual. Generally, in canine renal homotransplants, diagnostic criteria of graft rejection appear at between 5 and 7 days after transplantation. In all 3 groups in this series repudiation was diagnosed 2 - 3 days earlier. In Group I these signs disappeared spontaneously, whereas in the other two groups (whether 24 hours or 5 days of storage was involved) cytotoxic treatment was instituted (Figs. 5 and 6). Positive criteria of rejection appeared at approximately the same time, irrespective of the length of storage time.

3. The possibility that threatened rejection would be more difficult to reverse. Groups II and III constituted

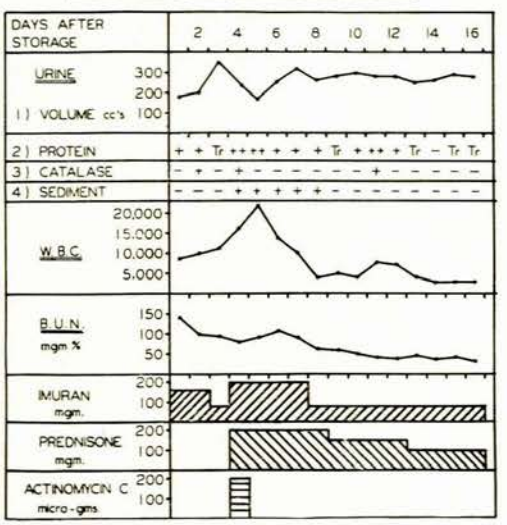

Fig. 5. Composite chart showing the changes in various parameters investigated in Group II. There was evidence of rejection on the 5th day after homotransplant, readily reversed with immuno-suppressive drugs. By the 8th day after storage, function had returned to within normal limits.

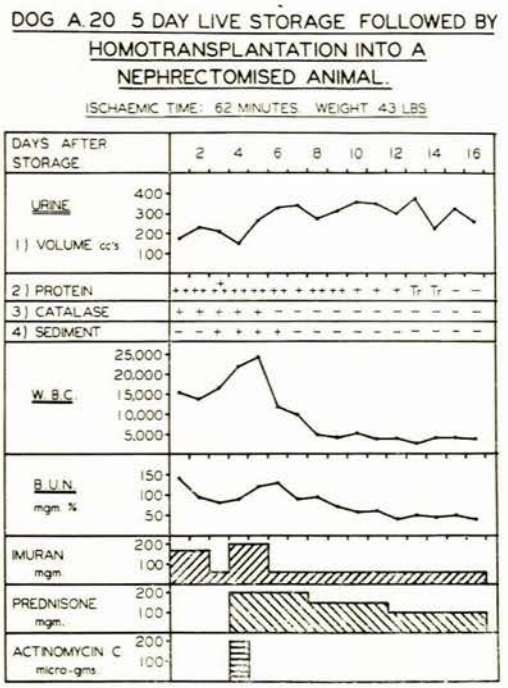

Fig. 6. Composite chart showing various parameters investigated in Group III. After 5 days' storage, there was evidence of rejection on the 3rd day following transplantation. This was quite easily reversed with cytotoxic agents and normal function returned within 7 days.

double homotransplants, and it was feared that such an immunological assault on the kidney would result either in a more prolonged rejection episode or in a more accentuated response. However, in no experiment was there any more difficulty than usual in reversing threatened rejection in single homotransplants without any intervening storage (Figs. 5 and 6).

4. It was felt that the attendant complications of cytotoxics would cause major problems during storage. Local sepsis did account for all 3 kidneys being discarded as unsuitable in the Group III series, and similar sepsis caused 1 death in this group 5 days after final transplantation (Fig. 7). In this latter case infection was almost

GROUP	NUMBER OF DOGS	STORAGE TIME	CYTOTOXICS		NUMBER OF STORED KIDNEYS UNFIT FOR TRANSPLANT	AUTO- OR HOMO-TRANSPLANT POST-STORAGE	NEPHRECTOMISED	SURVIVORS
			STORAGE ANIMAL	FINAL RECIPIENT				
1	6	24 HRS	NO	NO	–	AUTO-TRANSPLANT	YES	6
2	7	24 HRS	NO	YES	–	HOMO-TRANSPLANT	YES	5 (2 DIED)
3	12	5 DAYS	YES	YES	3	HOMO-TRANSPLANT	7 YES 2 NO	5 2 (2 DIED)

Fig. 7. Table showing the results in the 3 groups. (In Group III 3 kidneys were discarded during the storage period; the remaining 9 kidneys were transplanted after 5 days' storage into a third, unrelated animal and, of these, 2 later died of infection within 14 days.)

certainly present during storage. For canine experiments, however, this is not a high rate of sepsis incidence.

Advantages

There are several advantages to live storage:

1. The length of storage possible (Fig. 7). In Groups I and II 24 hours of storage was achieved with a 100% success rate. In these animals post-storage renal function was only slightly impaired initially and invariably returned to within normal limits.

In Group III, after 5 days of storage, initial function was relatively more disordered—perhaps the result of prolonged ischaemia at the time of final transplantation. Rejection phenomena complicated the picture, but eventual normal function was the rule. Two animals in this group did not survive 14 days. The cause of death in one has already been discussed (local sepsis), and the other resulted from pneumonia, which is hardly surprising with the use of immuno-suppressive drugs.

2. The feasibility of the assessment of function during storage (Fig. 8). This, we feel, constitutes the greatest single advantage of *in vivo* storage. There are many instances in clinical human cadaver transplants of non-function after transplantation as a result of previous irreversible ischaemic damage.[7] In our series of experiments function could be gauged during the storage period and non- or malfunctioning kidneys detected and discarded.

3. Dispensability of both the storage animal and the stored kidney. This advantage applies particularly to clinical practice. The cadaver organ and the storage animal both may be discarded if there is any doubt as to the functional capacity of the kidney. The importance of this lies in the fact that the prospective recipient will receive a transplant that is known to function satisfactorily.

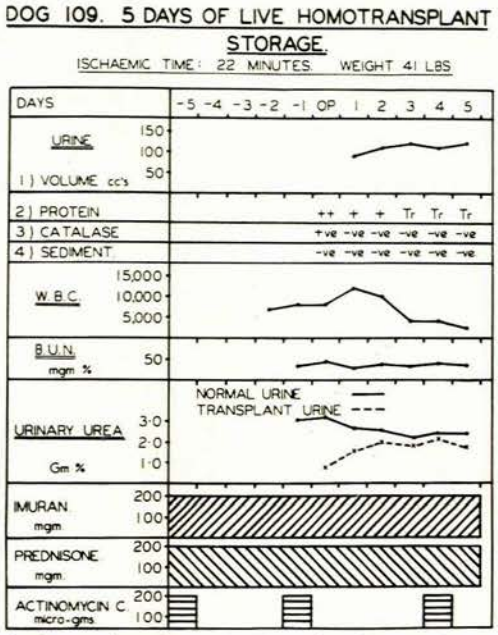

Fig. 8. Composite chart showing the changes in various parameters investigated in the storage animals of Group III to assess renal function of the stored organ. Massive doses of cytotoxic agents were necessary. There was no evidence of rejection.

4. The possibility of the institution of an 'Organ Bank'—an exciting prospect which is directly dependent upon the availability of both suitable cadaver grafts and of appropriate primate storage animals.

In conclusion, the concept of 'live storage' of kidneys is a new one and is still in the experimental stage. It is known that primate kidneys will function in human beings and it is tentatively assumed that human kidneys likewise will function in other primates. The intention is to store human cadaver kidneys in baboons, as the next step, knowing that no immunological deficit results in dogs from a double homotransplant. This may well be a practical method of organ storage.

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