THE INCIDENCE, CAUSE, AND SIGNIFICANCE OF IMMEDIATE AND DELAYED OLIGURIA OR ANURIA AFTER HUMAN RENAL TRANSPLANTATION

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IN HUMAN renal homotransplantation, one of the most important factors in obtaining ultimate success is the attainment of good immediate homograft function. When this is achieved, we have found that there is massive postoperative diuresis with consequent improvement in the patient's general condition (10). In most patients, a subsequent "rejection crisis" occurs with hyperpyrexia, secondary oliguria or anuria, and return of azotemia. The rejection crisis can regularly be reversed, with the addition of appropriate drugs to the pre-existing regimen, providing its onset can be accurately identified by the deterioration of initially satisfactory function.

Because of the great importance of obtaining prompt and adequate homotransplant function, special attention has been focused in the present study upon several aspects of the early postoperative behavior of homografts. First, the incidence of success in obtaining good early renal function has been tabulated, and the factors have been analyzed which predispose to instant organ failure. Second, the times of onset and the variations in vigor of the subsequently occurring rejection crisis have been documented. Finally, certain patterns of urine composition are described which were observed during the postoperative diuresis and which have a practical bearing on the fluid and electrolyte therapy provided during this period.

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METHODS

Twenty-eight patients received a total of 30 homografts in the interval from 24 November 1962 to 29 August 1963. In 2 cases, previously documented by Marchioro and his associates, the kidneys were obtained from recently deceased cadavers by a technique of hypothermic extracorporeal cadaver perfusion. In both instances, the moribund state of the eventual donor was protracted with prolonged premortem hypotension. Transplantation was carried out approximately 2 hours after death.

In the other 26 patients, 28 living donors were used. These included 6 mother and 1 father to offspring transfers, 13 sibling donations including 2 pairs of fraternal twins, and 8 from genetically nonrelated donors (Table I). In 7 patients female kidneys were transplanted to male recipients, and in 2 others an intersex change was made in the reverse direction. Homograft cooling was provided, either by total body donor hypothermia or intra-arterial perfusion of the excised kidney with cold lactated Ringer's solution where a major donor-recipient blood type incompatibility existed. The periods of total ischemia ranged from 17 to 71 minutes, with a mean of 33.5 minutes. The technique of Murray and Harrison (6) was used for the transplantation. In 2 instances to be described, immediate failure occurred at the operating table necessitating removal of the

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grafts. Second homografts were placed 14 days and 10 days later with satisfactory function.

The management employed at this center has been previously described (10, 11). In all but 1 patient, splenectomy was carried out before or at the time of transplantation. Eight patients had preliminary thymectomy, a procedure no longer employed. All but 3 recipients (Patients 1, 4, and 7) had both kidneys removed, usually at the time of transplantation. In general, antirejection therapy was provided with a single agent, azathioprine, until the diagnosis of a rejection crisis had been made. At this time, 150 to 300 milligrams of prednisone per day were added, as well as intermittent courses of 200 to 400 micrograms of intravenously administered actinomycin C per day. In half the patients (Table I), 12.5 to 40 milligrams per kilogram of mannitol were given intravenously during and after revascularization of the kidney.

After restoration of vascular continuity, the time of onset of urine flow was recorded, as well as the volume output. Later in the postoperative period the time of onset of the rejection crisis, which appeared in 22 of the 28 patients, was fixed by the development of fever and secondary deterioration of renal function.

Thirteen of the homografts were taken from donors who had a different major blood type than the recipient (Table I). The donor-recipient transfers were: O to A, 4 patients; A to O, 3 patients; B to A, 1 patient; A to AB, 1 patient; and B to O, 1 patient. In 3 of the pairs, there was a coexistent Rh incompatibility, and in 3 more the Rh difference was the sole incompatibility (Table I).

RESULTS

Early function of cadaveric kidneys. Neither cadaveric kidney ever functioned well. In Patient 1, urine production was delayed for 10 hours, and the maximum output obtained was 2,100 milliliters on the sixth postoperative day. The peak creatinine clearance, on the third and fourth postoperative days, was 8 milliliters per minute. Blood urea nitrogen fell from 150 to 118 milligrams per cent by the tenth postoperative day, and then rose to 300 milligrams per cent just before death 25 days after operation. In retrospect, the rejection crisis probably started on the tenth postoperative day, but this was neither recognized nor effectively treated. There was extensive hemorrhage and arteriolitis in the autopsy specimen with minimal evidence of cellular rejection.

The second cadaveric kidney was anuric from the outset until its removal 12 days later, after traumatic rupture. The diagnosis of a rejection crisis was not made nor was effective secondary antirejection therapy started. Histologic evidence of extensive cellular rejection was present in the surgical specimen.

Promptness of diuresis with homografts from living donors. In 25 of the 28 kidneys obtained from living donors diuresis began while the patient was still on the operating table. The mean interval between revascularization and the detection of first urine flow in these 25 patients was 23.5 ± 4.9 (SE) minutes, ranging from 5 to 90 minutes.

Cardiac arrest developed in 1 patient during anastomosis of the renal artery, necessitating discontinuance of the procedure while open cardiac massage was performed. He was hypotensive for several hours after the transplantation had been completed. Urine flow began 10 hours postoperatively, reaching a maximum daily volume of 3,900 milliliters 8 days later. Blood urea nitrogen remained elevated at 110 to 150 milligrams per cent. Maximum creatinine clearance was 28 milliliters per minute on the ninth day. He died of sepsis after 10 days. The kidney obtained at autopsy was histologically normal, except for minimal proliferative changes in the tubules which were compatible with acute tubular necrosis.

Two other homografts taken from living volunteers were judged to be failures at the time of transplantation and were immediately removed. Because of the possible relation

TABLE I.—URINE VOLUME IN FIRST 12 HOURS AFTER RENAL HOMOTRANSPLANTATION, AND TIME OF ONSET OF SUBSEQUENT REJECTION CRISIS

Patient No.	*Donor*	*Donor to recipient blood group*	*Urine volume 1st 12 hours*	*Time rejection crisis*
* 1	Cadaver	A+.....O+	546	? 10 days
2	Cadaver	A+.....A+	0	Unknown
3	Mother	B+.....B+	2800	14 days
* 4	Sister	B+.....A+	10,000	25 days
* 5	Frat. twin	A+.....A+	5850	None
* 6	Wife	A+.....AB+	6070	17, 42 days
* 7	Unrelated	A+.....A+	760	Died 10 days
* 8	Brother	O+.....O+	7700	18 days
* 9	Wife	O+.....A+	4605	19 days
*10	Brother	O+.....O+	2430	4 days
*11	Frat. twin	O+.....A+	11,400	5, 34, 71 days
*12	Unrelated	O+.....O−	9050	3 days
13	Brother	O+.....O+	5800	1 day
*14	Brother	A+.....A+	4645	7 days
15	Mother	A+.....A+	6100	13 days
16	Brother	A−.....A−	3240	23 days
*17	Brother	O+.....A−	5685	1½ days
*18	Brother	A−.....A+	7280	5, 29 days
*19	Mother	O−.....O+	8940	42 days
20	Sister	O+.....O+	5900	6 days
21	Mother	A+.....O+	0	—
	Unrelated	O+.....O+	2830	9 days
22	Mother	A−.....O+	5500	1 day
23	Wife	O−.....A+	3215	4 days
24	Mother	O+.....O+	4525	23 days
25	Brother	B+.....O+	0	—
*	Unrelated	O+.....O+	5700	Recent
26	Unrelated	A+.....A+	1340	2 days
27	Brother	O+.....O+	2800	Recent
28	Father	A+.....A+	15,690	Died 12 hours

*Received mannitol.
All recipients were males except patients 18, 19, 24 and 28.

of the unfavorable outcome to the use of donors with different blood groups than the recipient patients, these 2 particular instances will be discussed in detail in a separate section.

Magnitude of early diuresis. As previously mentioned, the cadaveric kidneys were oliguric or anuric at the outset. With the use of homografts from living donors, a diuretic phase was seen from 25 of the 28 kidneys (Table I), being absent only in the patient who had a cardiac arrest and in the 2 who had immediate transplant failures. The hourly urine output from these 25 homografts averaged 497±52.6 (SE) milliliters for the first 12 hours, being somewhat greater when mannitol was used. In most instances, blood urea nitrogen and creatinine clearance returned to normal within 24 to 48 hours. During the next 1 to 3 days, urine volumes diminished to 1,000 to 3,000 milliliters per day except in those patients who underwent a premature rejection crisis.

Urine composition during diuresis. Urinary sodium and chloride content were most predictable, the mean concentrations being 95.8±3.7 (SE) milliequivalents per liter and 74.8±3.4 (SE) milliequivalents per liter, respectively. Potassium content was 18.5± 2.9 (SE) milliequivalents per liter. Specific gravity was 1.012±.0008 (SE). Urine urea concentration was 271±27.2 (SE) milligrams per cent, and creatinine was 52.5± 8.0 (SE) milligrams per cent. It is noteworthy that significant proteinuria was common initially with 3.7±.87 (SE) grams per 24 hours but that this finding disappeared within a few days in those patients not having an early rejection crisis.

Because the general range of electrolyte loss was known, it was possible to evolve a simple empiric regimen of intravenous replacement. The patients were given 75 per cent of each preceding hour's urine output as 5 per cent glucose in .45 per cent saline or lactated Ringer's solution. When diuresis

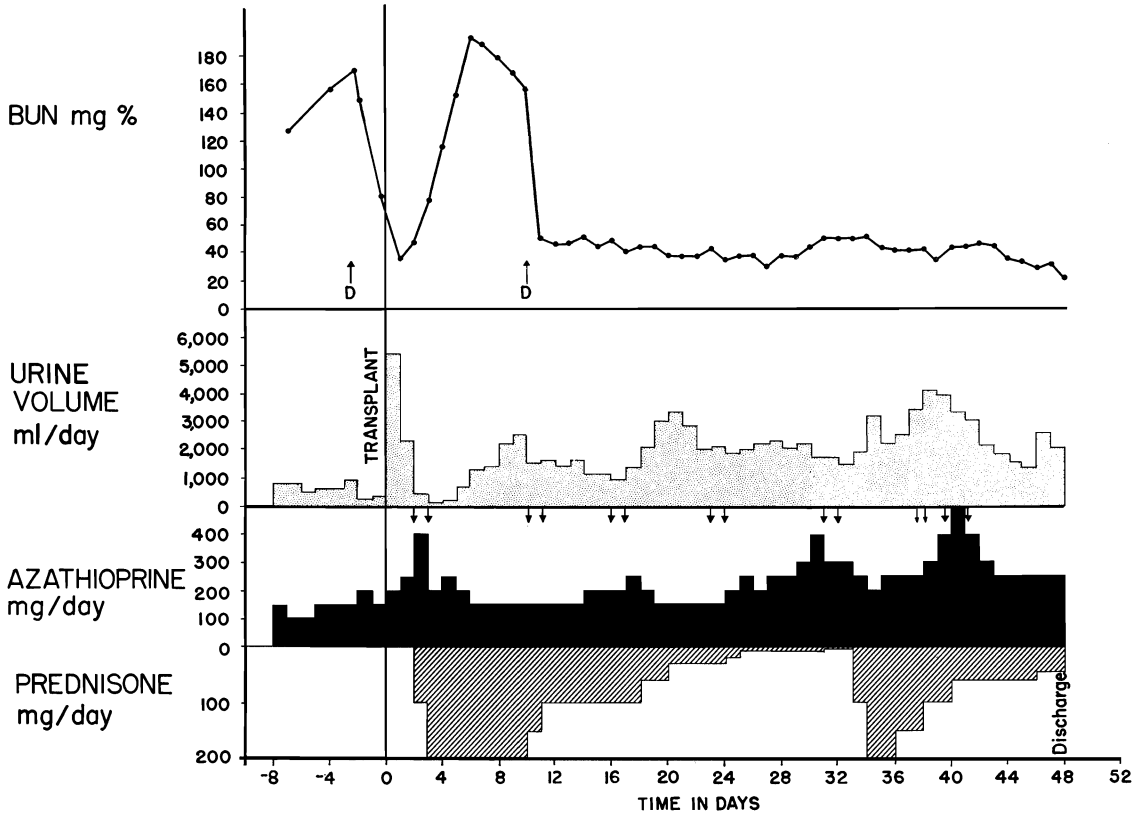


FIG. 1. Development of early rejection crisis after 36 hours in Patient 17, following initial brisk diuresis. Although temporary anuria resulted, the crisis was reversed. A similar course has been observed in 3 other patients. Splenectomy and bilateral nephrectomy were performed on the same day as transplantation. *D*, dialysis. Each of the lower arrows indicates intravenous administration of 200 to 400 micrograms of actinomycin C.

was massive, 20 milliequivalents per liter of potassium chloride were added to this fluid. Notable serum electrolyte abnormalities did not develop in any of the patients treated in this way except Patient 28, a 16 year old girl, who died 12 hours after operation with hyponatremia and hyperkalemia. Her urine excretion had averaged 1,310 milliliters per hour. During this critical period, sodium losses were not fully replaced, and she was accidentally administered excessive quantities of potassium chloride. Cardiac arrest was the cause of death.

Timing of rejection crisis. In 4 patients, the early diuresis was succeeded within 1 to 1½ days by an early and violent rejection crisis (Table I), with fever, azotemia, decline in creatinine clearance, hypertension, and proteinuria. Within a few hours, profound oliguria or anuria had developed (Fig. 1). In 18 others, the same adverse events occurred more gradually, starting after 3 to 42 days of good initial renal function. It was possible to reverse the process in all patients who had either early or later rejection crises with the addition of prednisone and actinomycin C to the previous regimen of azathioprine, provided that an initial diuresis was first obtained. The difficulty of reversal was greater in those patients who had early crises.

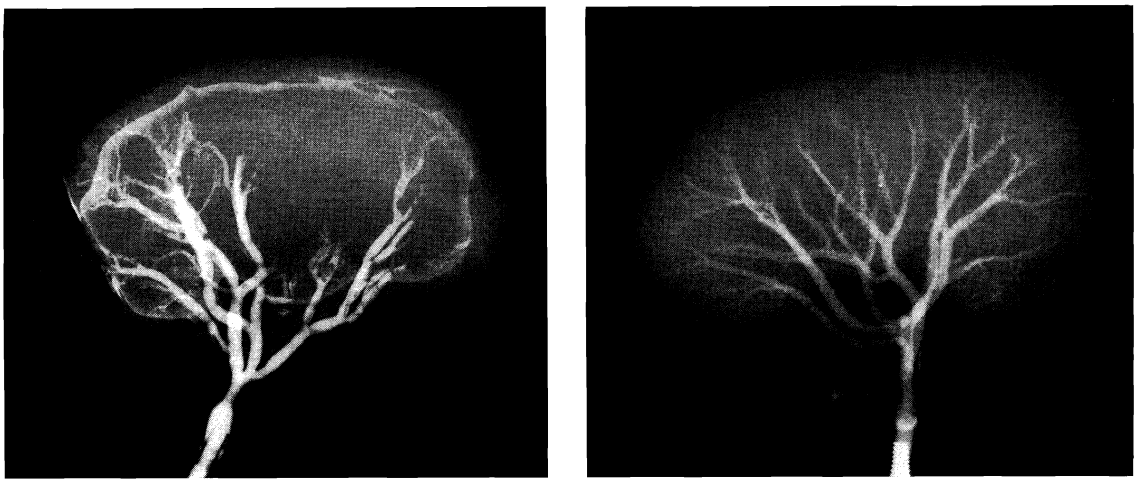
Relation of blood group incompatibility to early failure. The 2 immediate organ failures in the 28 transplants provided by living donors were probably due to differences in the blood types of the donors and recipients. A

Rh positive and B Rh positive kidneys, respectively, were given to recipients of O Rh positive blood group. Within a few minutes after revascularization, the homografts became cyanotic. Incision into the parenchyma resulted in venous hemorrhage but little or no arterial bleeding in the cortex. More deeply, within the medulla, sluggish arterial bleeding was present. The kidneys remained soft, without restoration of the firmness and turgor normally seen. After removal and transection, from 2 to 3 hours later, areas of hemorrhagic discoloration were observed at the corticomedullary junction (Fig. 2). Arteriograms of the surgical specimens showed filling of the major arterial ramifications with absent (Fig. 3a) or poor (Fig. 3b) vascularization of the cortex. Histologic sections of the 2 kidneys were interpreted as normal except for areas of congestion and aggregation of red cells, particularly in the glomeruli and small arteries (Fig. 4). No thromboses were present. In the patient who received the A Rh positive kidney, the titer of anti-A hemagglutinins rose from 1/16 preoperatively to 1/512 at 3 days after operation, followed by a subsequent decline.

Late results. Although in this report we do not purport to document the long term clinical results of homotransplantation, it is appropriate briefly to relate the ultimate fate of the 28 patients to the quality of early renal function. The 3 patients who received seriously damaged kidneys all died within 5 weeks with a combination of sepsis and continuing uremia, 2 of them having received cadaveric kidneys and the third being the patient who had cardiac arrest during transplantation. Twenty of the 25 patients who received an immediately functioning graft are alive, in satisfactory condition from 9½ months to 7 days postoperatively, including the 2 patients who received second homografts. Fourteen of this group have been discharged from the hospital and have returned to school or vocations. All of the outpatients except 1 have essentially normal renal function, and in the exception (Patient 11) the blood urea nitrogen is 39 and creatinine clearance is 50 milliliters per minute.

FIG. 2. Kidney removed from Patient 21, 3 hours after revascularization. Note dark color of organ and hemorrhagic zone at corticomedullary junction. Kidney was provided by an A Rh+ donor to an O Rh+ recipient. A second transplant, 14 days later, functioned satisfactorily.

The 5 deaths within the group of 25 who had good initial renal function occurred 113, 79, 62, 24, and .5 days after transplantation (Patients 4, 9, 10, 13, and 28). Four of the 5 recipients had good renal function prior to death, and the fifth (Patient 13) was just emerging from a rejection crisis. Septicemia secondary to deep wound infections was the cause of death in Patients 4, 9, and 13. Another patient returned to the hospital a few days after his discharge, convulsions developed a few hours later, and he died in 24 hours despite normal renal function (Patient 10). No cause for death was found at autopsy. He had been under psychiatric care because of self-destructive attitudes, and toxicologic tissue studies are in process to prove the most likely diagnosis of suicide. Histologic studies in these 4 kidneys showed either completely normal architecture or minimal mononuclear cell infiltration. The other death, which occurred 12 hours after operation as a result of an acute electrolyte



a b

FIG. 3. Arteriograms in homografts after removal from Patients 21, a, and 25, b, a few hours after revascularization. The transplants to O Rh+ recipients from A Rh+ and B Rh+ donors, respectively, have open major vessels, but the cortex appears not to be well vascularized. Note dye staining at corticomedullary junction in "a," at site of gross hemorrhagic area seen in Figure 2. Ureteric blood supply is present in "b," but not in "a."

imbalance, was described in the section on urinary composition during diuresis.

DISCUSSION

Oliguria or anuria after human renal transplantation has been noted by several authorities. Although Egdahl and Hume believe that immediate anuria is a rarity in dogs, Dempster's collected data (2) indicate that a substantial number of human renal homografts never excrete urine in adequate quantities, and he has suggested that the factors responsible for some of these sudden failures are immunologic rather than technical.

Knowledge concerning the true incidence of immediate postoperative homograft anuria is of the utmost importance for 2 reasons. First, the demonstration of a significant incidence of instant organ failure due to an immunologic mechanism would require the use of prophylactic measures designed to prevent this eventuality. Second, the behavior of the initially successful homograft usually follows a characteristic pattern. At a variable time after transplantation, in most patients a "rejection crisis" develops which consists of hyperpyrexia and multifaceted evidence of deterioration of renal function. With appropriate treatment, it is possible to halt and reverse the events of the homograft repudiation. The most significant factor in providing effective treatment at this time is the accurate diagnosis and proper therapy of the crisis. If the graft functions well from the beginning, the diagnosis of a rejection episode is easy. With poor or absent initial function, the diagnosis may be virtually impossible inasmuch as the principal clinical features of rejection cannot be observed.

The data herein presented indicate that immediate postoperative anuria is an uncommon occurrence and define as well the circumstances which appear to have been responsible for the acute homograft failures in this series. The infliction of excessive ischemia upon the transplanted tissue probably accounts for the absent or sluggish early kidney function in 3 patients. In 2 others, the presence of highly unfavorable donor and recipient blood group incompatibilities seems to have provided the mechanism of acute renal injury.

The degree to which excessive ischemic injury of the homograft impairs its early function is not known with any degree of cer-

tainty. It has been assumed by many authorities that the large margin of safety, which has allowed success in human isografts despite prolonged normothermic ischemia, is equivalent with the use of homotransplants. The fallacy of such reasoning in terms of long term homograft function has previously been pointed out (10). It is equally possible that the initial function of the homograft is more dependent than genetically identical tissue upon minimization of ischemia, particularly in view of the classical studies of Dempster (1) which showed an acute edematous reaction in renal homografts but not in comparable autografts. It has been our growing conviction that improvement in the technical aspects of tissue transfer, including homograft cooling and heparinization, are important elements in the attainment of prompt function.

Special attention must also be directed to the role of blood group incompatibility in producing acute anuria. Recently, Hume and Starzl (8, 9) and their colleagues reported the successful use of renal homografts provided by donors of different major blood groups than the recipient patients. While this information is of value in expanding the donor pool, it has become apparent that discrimination will be necessary in crossing blood types. In the present series, 13 blood type mismatches were used with 2 instant failures in which A Rh positive and B Rh positive kidneys were transplanted to O Rh positive recipients. Although these events did not occur in 2 other O Rh positive patients who received A Rh positive kidneys, a similar reaction has been observed by Murray and his associates (7), in which cortical necrosis developed in a B Rh positive kidney which was transplanted to an O Rh positive recipient.

Consequently, it would seem advisable to restrict the use of mismatched blood group combinations to those situations in which preformed agglutinating humoral antibodies are not present in the host. The donor to recipient incompatibilities which would be

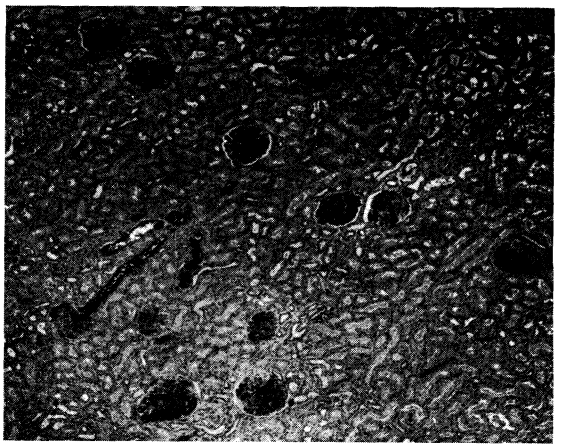


FIG. 4. Histologic appearance of unsuccessful homograft in Patient 21. Note aggregation of red cells, particularly in glomeruli and around periphery of small arteries. Hematoxylin and eosin, ×15.

relatively safe are: O to non-O, Rh negative to Rh positive, Rh positive to Rh negative except in the unusual and predictable circumstance in which recipient presensitization has occurred. The combinations which involve a heightened risk are: A to non-A, B to non-B, and AB to non-AB. Thus, the pattern of acceptable tissue transfer within the ABO system is comparable to that already defined for blood transfusions, in that O patients are probably universal donors whereas AB patients are universal recipients.

The importance of obtaining an early homograft diuresis in determining the onset of the subsequent rejection crisis has already been stressed. It is also of interest to collect as much information as possible concerning the time of beginning of the crisis, in order eventually to evolve empiric regimens of treatment which would allow the successful use of damaged organs such as those obtained from cadavers in which initial function often is absent. Unfortunately, one of the most characteristic features of the rejection crisis has been unpredictability of its onset. In 22 patients, in whom it has been observed, the interval after surgery ranged from 1 to 42 days.

In a discussion of the timing of the rejection crisis, particular attention should be

focused upon those patients in whom the stigmas of fever and acute renal failure appear early, within 24 to 48 hours after operation. In his penetrating analysis of post-homotransplantation anuria, Dempster (2) clearly delineated the features of the syndrome of oliguria and anuria which occasionally follows 1 or 2 days of good function. He suggested that various causes might be responsible including mechanical compression of the renal circulation, blood type incompatibilities of the subgroups, or preexisting host antibodies of the type that might be found in a genuine accelerated rejection.

Whatever its cause, this syndrome, as observed in 4 of the patients in the present series, resembles the crisis observed in most patients at a later time except that the development of fever, hypertension, oliguria, proteinuria, and azotemia is much more rapid and persistent. Under these circumstances, the need for secondary antirejection therapy constitutes a true emergency in which a delay of even a few hours may result in irreversible damage to the homograft. It is encouraging to note that this early "crisis" was successfully reversed in all 4 patients, despite the fact that 2 of the patients became temporarily anuric. The fact that recovery of function was achieved with the pharmacotherapy used generally for the reversal of later less violent rejection crises suggests that the mechanism of renal damage may be similar in all, differing only in degree.

SUMMARY

After renal homotransplantation, diuresis from the homograft has been observed within 90 minutes in 83 per cent of all patients, and in 89.3 per cent of kidneys provided by living donors. Poor initial renal function has been seen only under 2 circumstances. The first of these was when there was a prolonged period of devascularization of the organ. The second was when kidneys from A Rh positive and B Rh positive donors, respectively, were transplanted to O Rh positive recipients.

The use of kidneys which are anuric from the beginning appears to be preventable. Excessive ischemic damage can be avoided by proper selection of donor sources with particularly critical scrutiny when cadavers are to be used, by reduction of the time necessary to perform the vascular anastomoses, and by cooling of the homografts. When the donors and recipients are of different major blood types, difficulties can be circumvented by avoiding certain combinations. The donor to recipient pairs which probably carry an increased risk of instant failure are A to non-A, B to non-B, and AB to non-AB. The mismatched combinations which are probably safe are O to non-O, and Rh incompatibilities since preformed host hemagglutinins should not usually be present. The pattern of acceptable tissue transfer within the ABO system is thus probably comparable to that already defined for blood transfusions in that O patients are universal donors and AB patients are universal recipients.

Further data are provided concerning the onset of the rejection crisis which occurs during the postoperative period in the majority of patients. Such an episode has been observed in 22 patients, occurring 1 to 42 days after transplantation. The intensity of the crisis has been accentuated when it has occurred early, requiring immediate and prolonged emergency therapy.

The ultimate fate of the 28 patients in this series is closely related to the quality of immediate renal function. All 3 patients who received damaged kidneys died within 5 weeks. Twenty of 25 patients who received a promptly functioning homograft are alive from 9½ months to 1 week postoperatively, including 2 who received second homografts. Fourteen of these 20 patients have been discharged and are being managed as outpatients.

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