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T. E. STARZL, M.D.
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J. H. HOLMES, M.D.
G. HERMANN, M.D.
R. S. BRITTAIN, M.D.
O. H. STONINGTON, M.D.
D. W. TALMAGE, M.D.
W. R. WADDELL, M.D.
Denver, Colo.

From the Department of Surgery, University of Colorado Medical Center, and the Denver Veterans Administration Hospital

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Renal homografts in patients with major donor-recipient blood group incompatibilities

T. E. STARZL, M.D.*
T. L. MARCHIORO, M.D.
J. H. HOLMES, M.D.
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DENVER, COLO.
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It has often been stated that renal homografts should be used only when the major blood types of the donor and recipient patients are identical.[1, 5, 6, 8, 11, 15] Although blood groups are not generally thought to be involved in the immunologic process of rejection, it has been feared that hemagglutination would occur within the grafts. In previous attempts at renal homotransplantation under these circumstances, graft function has not occurred,[8, 15] except in two cases recently reported by Hume and his associates.[9]

The purpose of this report is to document experience with 3 cases of renal homotransplantation in which the major blood groups of the donor and recipient patients were different (Table I). Two of the renal homografts were obtained from living donors and the third, from a cadaver. No immediate or delayed problems were encountered which were thought to be due to blood group incompatibilities.

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*Markle Scholar.

CASE REPORTS

Case 1. A 38-year-old male was admitted with terminal chronic glomerulonephritis. He was prepared for renal transplantation with a thymectomy on Jan. 18, 1963. Renal transplantation was carried out on Jan. 30, 1963. The renal homograft was obtained from the patient's 32-year-old sister. Her blood type was B-positive and that of the recipient was A-positive.

The donor was cooled to 32° C. and the left kidney was removed through a flank incision. Immediately upon removal, the plastic tip of an intravenous infusion set was wedged in the renal artery and gravity perfusion was begun with lactated Ringer's solution which had been cooled to 15° C.

Table I

Donor		*Age of recipient (yr.)*	*Donor blood group*	*Recipient blood group*	*Period of ischemia (min.)*	*Outcome*
Relationship	*Age (yr.)*					
Sister	32	38	B+	A+	28	Normal BUN, 74 days
Wife	30	34	A+	AB+	36	Normal BUN, 49 days
Cadaver	32	21	A+	O+	105	Died, 24 days

Perfusion pressure was controlled at 120 cm. H_2O (90 mm. Hg) by adjustment of the height of the intravenous stand (Fig. 1). The perfusion solution contained 50 mg. of heparin and 50 c.c. of 2 percent procaine chloride per liter. After approximately 250 c.c. of solution had been perfused, the effluent from the renal vein was clear and the kidney was white in color. The time spent for the perfusion was 3 minutes.

At this time the kidney was removed to the recipient's room and transplanted into the right iliac fossa. During revascularization, 200 c.c. of 20 percent mannitol was given. The total period of ischemia was 28 minutes. Eight minutes after restoration of circulation, vigorous urine flow was detected. A ureterovesical anastomosis was performed with the Paquin-Marshall technique.[12] After the wound was closed, the upper abdomen was prepared and splenectomy and left nephrectomy were performed.

Prior to operation, the patient had anasarca which was not controlled despite 3 hemodialyses. After operation, a massive diuresis occurred which lasted for 3 days. The daily urinary output during this time was 8,300 c.c. There was a prompt restoration of the blood urea nitrogen level to normal (Fig. 2). Creatinine clearance measured within 3 days after operation was 106 c.c. per minute. Normal renal function continued until the twenty-seventh postoperative day, at which time a severe rejection reaction occurred with a sudden rise in the BUN level. Despite the development of profound oliguria, the rejection was reversed (Fig. 2) with the use of an increased steroid dose and actinomycin C, added to the pre-existing therapy with Imuran. Urinary function has subsequently been clinically satisfactory. The BUN level has returned to high normal values (Fig. 2).

Case 2. A 34-year-old man with AB-positive blood received a renal homotransplant from his A-positive 30-year-old wife, 2 weeks after thymectomy, splenectomy, and bilateral nephrectomy had been performed in one stage as preparation for the transplant. The right kidney was removed from the donor on Feb. 25, 1963, and placed in the left iliac fossa of the recipient. Perfusion of the renal homograft was carried out as in Case 1, although the flow of perfusate was sluggish and difficult to maintain with a hydrostatic pressure of 135 cm. of water (100 mm. Hg). It was subsequently discovered that only 0.2 Gm. procaine had been added to the perfusate. Eleven minutes was the time required before the fluid returning from the renal vein was clear. Total time of ischemia was 36 minutes. Two hundred cubic centimeters of 20 percent mannitol solution was given intravenously during completion of the vascular anastomoses.

Following transplantation of the kidney, a brisk diuresis occurred, first seen 8 minutes after revascularization. Blood urea nitrogen returned to normal by the ninth postoperative day. On the twenty-second day after operation, early evidence of rejection was manifested by a slight rise in the blood urea nitrogen level to 29 mg. percent. This was treated with actinomycin C added to the pre-existing treatment with Imuran and 50 mg. per day of prednisone. Blood urea nitrogen returned to normal within 3 days and renal function has subsequently been normal. On March 29, 1963, abdominal exploration and lysis of adhesions were performed for intestinal obstruction. Recovery from this operation was uneventful.

On April 3, the patient, while straining on the toilet, had a massive pulmonary embolus with cardiac arrest. He was resuscitated with closed chest massage and pulmonary embolectomy performed with the assistance of total cardiopulmonary bypass (T.L.M.). Two days later, a vena caval plication was performed. Recovery from these operations was prompt.

Case 3. An emergency renal transplantation was performed on March 21, 1963, to a 21-year-old Caucasian man with terminal glomerulonephritis. His blood type was O-positive. An A-positive donor kidney was obtained from a 32-year-old Negro man who had died from a central nervous system disorder. The cadaver kidney was prepared by a technique described in detail previously.[10] Essentially, this consisted of the institution of extracorporeal circulation and rapid cooling to 15° C. with a heat exchanger. While the cadaver was being perfused, the recipient patient was taken to the operating room and prepared. Upon the signal that the recipient site was ready, the left kidney was removed from the cadaver and perfused in the same manner described in Cases 1 and 2, with the smaller dose of procaine in the perfusate. It was then taken from the Denver Veterans Hospital

to Colorado General Hospital and transplanted to the right iliac fossa of the recipient. The time from death to revascularization in the recipient site was 105 minutes.

For the first 8 hours after the operation, the recipient patient's oliguria, which had existed prior to transplantation, persisted, despite the fact that 200 c.c. of 20 percent mannitol had been administered in the operating room. After 8 hours, a brisk diuresis occurred, ranging from 1,500 to 2,000 c.c. per day. The anasarca which had been present before operation was relieved almost immediately, but the elevated blood urea nitrogen level, which was 160 at the time of operation, declined rather slowly to a low of 119 mg. percent 10 days after operation, rising thereafter to 285 mg. percent just before death. An infected lymph collection in the retroperitoneal space was widely drained on the ninth postoperative day, necessitating exposure of the transplanted organ. The patient died of septicemia 24 days after operation. At autopsy, the kidney was found to have been rejected.

DISCUSSION

It is of considerable importance to discover whether renal homografts must be obtained from donors of the same major blood groups as those of the recipient patients. Adherence to the widely accepted view that transplants are possible only among individuals of the same blood group severely restricts the donor pool and has undoubtedly resulted in the denial of therapy to otherwise acceptable candidates. The potential disadvantages of transplantation between patients with different blood types is based upon consideration of the red cell antigens which are not thought to be directly involved in the rejection reaction. Anxiety has been expressed over the possibility that the mixing of blood groups would result in acute hemagglutination reactions shortly after revascularization. In addition, the red cell antigens are found in various organs[2, 4, 7, 14] including the kidney,[7] a fact which could conceivably lead to hemagglutination in the late stages.

In addition, the most discouraging indictment of transplantation under these circumstances has been the general failure of renal function. In the past, the invariable result has been graft anuria from the outset, with the exception of the 2 cases recently reported

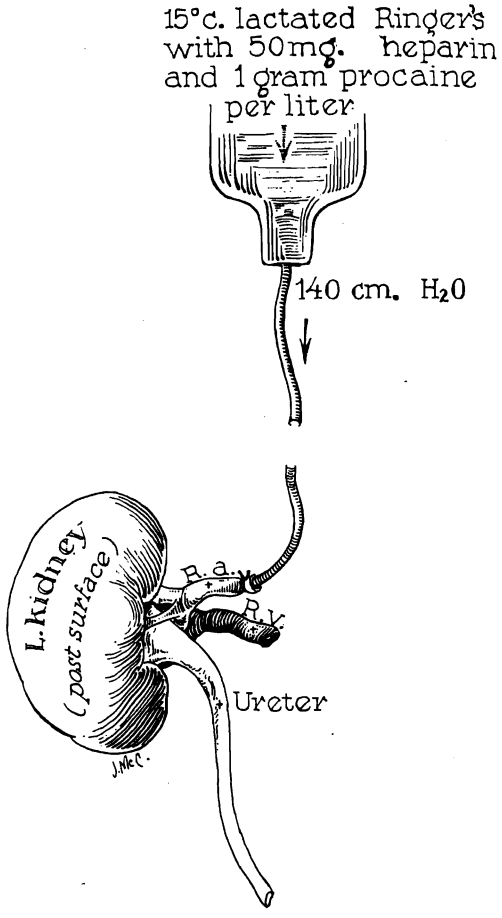

Fig. 1. Technique of perfusion of kidney with cold Ringer's lactate. The primary objective is to remove as many red cells as possible before restoration of blood flow.

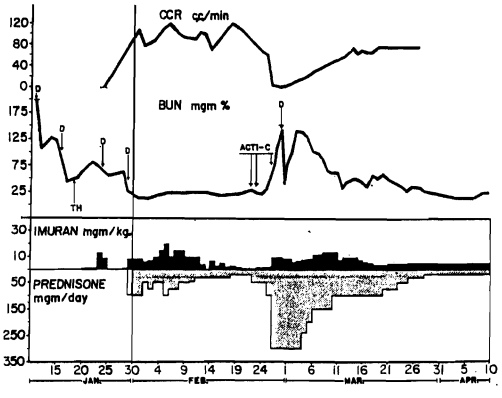

Fig. 2. Graphic record of Case 1. A B-positive kidney was donated by a sister to her A-positive brother. Note reversal of rejection by addition of actinomycin C and increased dose of prednisone.

by Hume and associates.[9] From review of the previous cases of renal transplantation performed in the presence of mismatched major blood groups,[8, 15] it appears likely that the importance of this factor could not be adequately assessed. Virtually all of the cases were from before 1955, at a time when effective antirejection therapy was not available. Generally, the kidney was obtained from a cadaver, with periods of ischemia ranging from 150 to 500 minutes. Some of these organs did not have the benefit of cooling, and in all cases, the duration of ischemia was excessive.

The present study makes it clear that the immediate results with transplantation in the presence of major blood group incompatibilities are in no way inferior to those reported by others, in which the major blood groups are the same. There are several features which we think may be of importance when transplantations are performed in the presence of blood group incompatibilities. If the residual blood from the donor kidney is thoroughly washed before it is placed in the bloodstream of the recipient, the probability of an immediate hemagglutination reaction is reduced. It has been found in the laboratory that in order to carry out such perfusion successfully, the addition of procaine to the solution is necessary. When cold solutions are infused into the kidney of the dog, there is an almost immediate cessation of flow, presumably due to afferent arteriolar constriction. This phenomenon was encountered by Couch, Cassie, and Murray,[3] and has been noted subsequently by others. In addition, the provision of heparin in the perfusing solution may be of importance in preventing sludging and clot formation.

The use of perfusion to wash out the donor kidney has the disadvantage of using time which might otherwise be expended for the insertion of the kidney. The time loss has ranged from 3 to 11 minutes in these 3 cases. This loss of time is compensated for to some extent by the fact that the solution cools the kidney almost immediately, thereby reducing its metabolic needs.

Another adjunct of unknown benefit has been the use of mannitol to promote immediate diuresis. In the 3 cases reported here, a test dose of mannitol (12.5 Gm. of 50 percent solution) was given during the completion of the vascular anastomoses. Thereafter, an additional dose of mannitol was given (200 ml. of 20 percent solution at 4 ml. per minute). The benefit of mannitol in the protection of renal grafts cannot be proved on the basis of these experiences, but there is some experimental evidence that mannitol can prevent tubular damage under a variety of experimental situations, including those involving the deliberate introduction of blood pigments and by-products into the bloodstream.[13] The mechanism of protection under these circumstances is thought to be a rapid washing of tubular debris.

SUMMARY

Three documented cases of clinical renal transplantation in which the donor and recipient patients had different major blood types have been presented. The relationship of the donor-recipient pairs ranged from that of sister-to-brother to that of totally unrelated patients of different races. The renal homografts were obtained from living donors in 2 cases and from a recently dead cadaver in the third. Renal function was prompt and excellent when living donors were used, and more indolent when a cadaver kidney subjected to a long period of ischemia was employed. Two of the patients have normal renal function after 74 and 49 days. The third patient died with rejection and sepsis 24 days after transplantation.

This study demonstrates the feasibility of obtaining both immediate and prolonged renal function despite the presence of major blood group incompatibilities between donor and recipient patients. This knowledge should expand the donor pool, making it possible to transfer renal homografts under much less stringent requirements than has been the case in the past.

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ADDENDUM

Since the submission of this report, additional experience has accumulated which permits more discriminating recommendations concerning the violation of blood group barriers. Including the 3 cases described here, there have now been 13 instances in which homografts were taken from donors who had major blood types that were different from those of the recipients (Addendum Table I). The donor-recipient transfers were O to A in 4 patients, A to O in 3 patients, B to A in 1 patient, A to AB in 1 patient, and B to O in 1 patient. In 3 of these ABO mismatches, there were coexistent Rh differences, and in 3 more, the sole incompatibility was in the Rh system, either Rh+ to Rh− or the converse. Although good function was obtained with various combinations of these mismatches, 2 accidents have occurred with the use of A and B donors, respectively, to O recipients.

Addendum Table I. *Blood group mismatches*

Blood group	*No. of mismatches*	*Good early function*	*Alive*
O to A	4	4	3
A to O	3	1	2*
B to A	1	1	1
A to AB	1	1	0
B to O	1	0	1*
Rh+ to Rh−	2	2	2
Rh− to Rh+	4	4	4

*Second homograft placed in one patient from each group.

Immediately upon revascularization in these 2 cases, the kidneys became cyanotic and it was obvious that blood flow to the cortex was inadequate. After being observed for several hours, the homografts were removed. Angiograms of the surgical specimens showed absent vascularization of the cortex, and subsequent histologic sections showed intravascular hemagglutination involving the small vessels and the glomeruli. Second transplants to these 2 patients were provided 14 and 10 days later with satisfactory results.

These experiences have led to two conclusions. First, homotransplantation in the presence of donor-recipient blood group incompatibility may be successful with almost any combination. However, certain mismatches appear to carry a higher risk (Addendum Table II). The situations in

Addendum Table II. *Direction of acceptable mismatched tissue transfer**

O to non-O	Safe
Rh− to Rh+	Safe
Rh+ to Rh−	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB	Dangerous

*O is universal donor; AB is universal recipient.

which this would be the case are A to non-A, B to non-B, and AB to non-AB. The donor to recipient incompatibilities which would be relatively safe are O to non-O and Rh incompatibilities, except in the unusual and predictable circumstance in which recipient pre-sensitization has occurred in an Rh negative patient. Thus the pattern of acceptable tissue transfer in the ABO system appears to be comparable to that already defined for blood transfusions, in that O patients are probably universal donors and AB patients are universal recipients.

Of the patients originally described, one is still alive with normal renal function 9 months after operation (Case 1). In view of the more recent information, this particular combination of donor-recipient blood group incompatibility, B to A, would not now be accepted for use. Patient 2, in whose case an A donor provided a kidney to an AB recipient, died of sepsis 118 days after operation. Renal function remained essentially normal until the time of death. In the presently defined scheme of tissue transfer as influenced by blood types, this would still be accepted as a safe breach of incompatibility.