

# HOMOLOGOUS HUMAN KIDNEY TRANSPLANTATION

## Experience with Six Patients

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EXCELLENT results with renal transplantation between identical twins by Murray, Merrill and Harrison (1958) proved that a transplanted kidney can maintain permanent normal function. In 1959 successful transplantations between non-identical twins by Merrill and by Hamburger and their respective teams with good, long-term results opened a new era in the field of human kidney transplantation and we know of more than 30 such operations since 1959.

This paper will not cover the basic problem of the homograft reaction but deal with data from six kidney transplantations performed at the *Centre Médico-Chirurgical Foch* at Suresnes. None were twins and four were done between non-related persons. In five cases total body irradiation was used to prevent rejection. It was given at the Gustave Roussy Institute at Villejuif (Seine) under the supervision of Drs. Tubiana and

Lalanne. The treatment of such patients requires the help of a skilled medical and nursing staff. We are most grateful to all who helped us. Some results have already been published (Kuss, 1960 and 1961).

A summary of all cases is presented in the following table.

### Selection of the Donor

We consider that at the present time this is the major problem. Most of the recent attempts involved the removal of a normal kidney from a healthy volunteer. In our series this was done four times. The risk, immediate and secondary, of a nephrectomy to the donor compared with the still small probability of a long-term success of the transplantation faces the physician in charge of the decision with very difficult moral, religious and legal problems.

TABLE I  
HUMAN RENAL HOMOTRANSPLANTATION

No. of Case	Date of Transplantation	Prevention of Rejection	Relationship	Evolution
1	17/1/1960	Total body irradiation 400r + 200r/spleen	Sister to brother	Death 26/5/60 (5th month). Metastatic carcinoma of the liver. Good renal function.
2	22/6/1960	Total body irradiation 400r + 200r/spleen 7th week: total body irradiation 100r + 6-MP + cortisone + local irradiation	None Donor: brother-in-law	Death 25/11/61 (17th month). Slow homograft rejection.
3	6/11/1960	Total body irradiation 600r	Brother to brother	Death 17th day from irradiation
4	7/1/1961	Total body irradiation 400r + 200r/spleen	None Wife to husband	Immediate anuria. Thrombosis of arterial anastomosis.
5	26/4/1961	Drugs before transplantation	None Cadaver kidney	Immediate anuria. Necrosis of kidney
6	3/12/1961	Total body irradiation 250r + 6-MP + cortisone + local irradiation	None Matson kidney	August 1962 (9th month). Good clinical condition. Blood urea 50 mg./100 ml.

The long-term survival (17 months) of case 2 and the present good progress of case 6 after nine months, both transplantations being performed between unrelated persons, provide strong evidence that close familial relationship between donor and recipient is not a necessary condition for the long survival of the transplant. The use of a cadaver kidney should be the answer to the very disturbing 'donor problem'. Of course, transplantation from a dead human donor means a lengthened period of ischemia prior to death and delay before transplantation. Severe damage could be partly avoided by refrigeration of the kidney. Such a technique was used in case 5 but unfortunately we were unable to prevent necrosis from total ischemia lasting four hours. Of course, the unique opportunity to transplant a kidney that has to be removed for a subarachnoid-ureteral anastomosis should be taken as frequently as possible. This was done with success in case 6.

We do not know of any good practical test for the selection of a possible donor. Determinations of different erythrocyte and leucocyte antigens (Dausset, 1956) were performed in all cases. Total identity is desirable but has not been considered a necessary condition for transplantation. The major blood groups were identical in five cases and compatible in case 3 (donor O, recipient A). Small differences between erythrocyte and leucocyte antigens of recipient and donor were present in cases 2 and 6.

### Selection of the Recipient

Terminal chronic uræmia is at the present time the only condition for transplantation. Death should be expected in the following few weeks. Attention should be paid to the original disease. Chronic pyelonephritis may be associated with chronic urinary infection that could damage the transplanted kidney, as we feared in case 2. From work by Murray and others on transplants between identical twins it seems better to avoid cases with subacute glomerulonephritis to exclude the risk of deterioration of the transplant by reason of the original disease.

Hypertension is not a contraindication. Our cases and data from other groups have shown that severe hypertension could be cured by transplantation alone of a normal kidney or in association with bilateral nephrectomy.

As we feel that removal of the diseased kidneys should be performed if possible before or at the time of the transplantation, patients with only one kidney are considered particularly suitable candidates.

### Surgical Procedure

Since 1951 one of us (Kuss) has used a tech-

nique now widely accepted. Through an extra-peritoneal approach the renal artery is anastomosed end-to-end to the hypogastric artery and the renal vein end-to-side to the common iliac vein. After investigation by arteriography the left kidney is removed and put in the right iliac fossa. Except for the cadaver kidney, the duration of ischæmia is between 40 and 65 minutes. According to circumstances the ureter is implanted into the bladder or sutured to the ureter of the recipient.

Since our experience in case 1, in which anuria on the third day ceased immediately after decapsulation, this procedure is routinely performed at the end of the transplantation.

### Prevention of Rejection

Since work by Schwartz and Dameshek in 1960 with 6-mercaptopurine (6-MP) and encouraging results obtained on dogs by Calne (1961) and Pierce, Varco and Good (1961) have offered a good experimental basis for trying to prevent rejection in humans by *antimetabolites*, these have been used by Merrill, Hopewell, Calne and Mowbray (personal communications). We used 6-mercaptopurine in cases 2, 5 and 6, and we feel that patients with a transplanted kidney should be maintained on long-term treatment by drugs, e.g. 6-MP.

On dogs, extensive experimentation by Dempster, Mannick and Zukoski using *total body irradiation* either in the sublethal or supralethal range has been discouraging. On humans, more data are required to allow a proper evaluation of the real benefit of total body irradiation. Five of our six patients have received total body irradiation from a cobalt bomb at the Gustave Roussy Institute under the supervision of Drs. Lalanne and Tubiana. In cases 1, 2 and 4 the dose was 400 r at one time plus 200 r to the spleen. From our cases and data from Hamburger and Merrill this dose can be considered as insufficient to give a prolonged, complete tolerance even between closely related persons, with the exception of non-identical twins. In case 3 we tried to increase the dose up to 600 r. The patient died on the 18th day after irradiation, from the primary irradiation syndrome. The transplanted kidney at the time of death was normal. In case 6 the dose of irradiation was only 250 r.

All patients were placed after transplantation in a 'sterile unit' and submitted to conservative treatment, including blood and platelet transfusion, and the very cautious use of antibiotics.

From experimental and clinical work now available, we think that the best non-specific treatment is a combination of total body irradiation in the sublethal range and chemotherapy with antimetabolites. Given before transplantation,

total body irradiation should have the beneficial effect of decreasing the ratio:

$$\frac{\text{antigen mass}}{\text{immunological competent cells}}$$

as recently demonstrated by Michie and Woodruff (1962). Antimetabolites, which have been proved efficient after transplantation, should decrease the proliferation of the so-called immunologically competent cells stimulated by the antigen.

Local irradiation of the kidney as suggested and done by Dempster (1961) was used in cases 1, 2 and 6 at different periods of evolution. It is impossible to give in our cases a proper evaluation of the clinical results.

As Merrill and Dammin have proved that chronic uraemia enhances tolerance we think that efficient treatment of renal insufficiency before transplantation by repeated dialysis should be avoided if possible.

### Accidents after Transplantation

In dogs Dempster (1955) has very well described the different types of anuria that can follow transplantation. In patients, different types of accidents can occur and must be diagnosed as soon as possible to enable special treatment to be carried out, of which the efficiency is demonstrated in cases 1 and 2.

*Initial anuria* from large-vessel thrombosis as in case 4 should easily be differentiated from reversible tubulo-interstitial nephropathy, which requires very careful conservative management together with dialysis if a secondary recovery of kidney function is to occur, as was first proved by Hume, Merrill, Miller and Thorn (1955).

*Early secondary anuria* has been reported by different groups. It is our opinion that apparently similar clinical facts cover different intra-renal processes. Few observations, if any, give evidence of an early classical accelerated homograft reaction. In some cases a mechanical process could be involved and in case 1 decapsulation has coincided with the return of a good urine output. More investigations are urgently needed to explain these accidents, perhaps due to previous sensitization or to intrarenal vascular disturbances.

*Late accidents.* Except for possible secondary

mechanical complications, with or without infection and involvement of the transplanted kidney by the original disease, these should be considered as an immunological rejection.

Rejection can be acute with irreversible oliguria or anuria developing within a few hours. After treatment by antimetabolites or total body irradiation homograft rejection can be very slow, clinically latent, and only diagnosed by histological and biochemical studies. A critical febrile episode, simulating acute pyelonephritis, but reversible as was demonstrated by case 2 (Kuss, 1960), can occur and calls for effective treatment. In that case, six weeks after transplantation, deterioration of renal function and information from a kidney biopsy showing pyronin-positive cell infiltration justified treatment including cortisone, 6-MP and 100 r total body irradiation and local irradiation. This treatment allowed the patient to recover from severe renal insufficiency and a 'compromise' between host and transplant was reached for many months.

### Prospects

Some data in the literature and our own results are encouraging. Observations 2 and 6 definitely proved that *a human being can live a long time with a transplanted kidney from an unrelated donor (17 months in case 2)*. The success achieved in case 6 without any harm to the donor is very encouraging. Relationship should not be considered a condition necessary for transplantation and this is a new argument for using a cadaver kidney.

Differences between experimental and clinical results justify new attempts at human transplantation on selected cases.

Apart from basic immunological research into the specific prevention of the homograft reaction, for example by transplantation of haematopoietic cells, present research in the clinical field of kidney transplantation should deal with the following problems: devising tests to select a possible donor, improvement of the technical conditions of the transplantation of a cadaver kidney, comprehension and prevention of the mechanisms involved in the early secondary anuria, and determination of the best non-specific treatment of the immunological rejection.

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