T.E. Starzl, A. Tzakis, L. Makowka, J. Fung, G. Klintmalm, S. Todo, R. Gordon, and M. Griffin

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# Combined Liver and Kidney Transplantation with Particular Reference to Positive Cytotoxic Crossmatches


## SUMMARY

Nine patients were provided with 10 livers and 10 kidneys. Nine of the paired allografts were from the same donors. Seven of the 9 recipients are alive after 6 to 26 months. At least 3 and possibly as many as 5 of the paired transplantations were to patients whose sera possessed preformed antigraft cytotoxic antibodies. Only one of the livers seemed harmed by the antibodies, and the kidneys that were transplanted after the livers were in place were thereby seemingly protected from antibody injury in 2 of the 3 unequivocal cases. These observations may provide a clue for the development of new methods to prevent hyperacute renal rejection.


## INTRODUCTION

In a recent inquiry by an Italian journalist, the question was posed, "Do you think that in the next decade a 'puzzle man' with heart, liver, and pancreas taken from other human beings might be feasible?" The answer is that there are already examples of puzzle men who have received a heart and kidney, a pancreas and kidney, a heart and lungs, and even a heart and liver taken from other human beings. The increasing boldness with which transplantation is being developed makes it certain that other and more complicated combinations will be forthcoming in the near future.

The extent to which multiple organ transplantation has entered our clinical consciousness could be illustrated by any of the foregoing multiple organ procedures, particularly by hundreds of cases of combined renal and pancreas transplantation. However, in this communication we will describe the less well known combination of hepatic and renal transplantation from common or different donors. The subject holds a special fascination, since the liver apparently can protect a subsequently transplanted kidney from the hyperacute rejection that is caused by recipient anti-donor cytotoxic antibodies.

## METHODS

Nine patients aged 12 to 65 years with a variety of hepatic and renal diseases were studied. One patient had a liver plus kidney transplant on two occasions. In each case but one, the primary reason for proceeding was end-stage liver disease in which the expectation of survival was limited to a few weeks or months (Table 1). In the exceptional patient, the diagnosis was polycystic liver and renal disease. Hepatic function in this patient was normal, but she was dying of respiratory insufficiency caused by expansion of her enormously enlarged liver, which at the time of its removal weighed 13 kg (28.6 pounds) (Fig.1). The serum creatinine level in this exceptional patient was 2.1 mg%, but her creatinine clearance was estimated at 20 to 25 mL/minute.

From the Department of Surgery, University of Pittsburgh, Pittsburgh, Pennsylvania

**Table 1.** Clinical Factors in 9 Patients who had Liver and Kidney Transplants

| *OT Number* | *Age/Sex* | *Date of Liver Transplant* | *Date Kidney Transplant* | *Liver Disease* | *Kidney Disease* | *Preop Cr (mg%)* | *Preop CCr (ml/min)* | *Outcome* | *Cause of Death* |
|---|---|---|---|---|---|---|---|---|---|
| 419 | 44/F | 7/22/84 | Same | Polycystic | Polycystic | 2 | 20–25 | Alive | |
| 464 | 15/F | 11/18/84 | Same | Polycystic with cirrhosis | Polycystic and glomerulo-nephritis | On Dialysis | 0 | Alive | |
| 495 | 43/F | 2/12/85 | Same | Primary biliary cirrhosis | Glomerulo-nephritis | 4 | 20 | Alive | |
| 164 | 39/F | 6/16/85 | Same | Rejection of previous graft after 6 years | Indeterminate | 6 | 10 | Died 7/7/85 | Fungal infection |
| | | 6/28/85 | Same | Dearterialized graft | | | | | |
| 584 | 38/M | 8/15/85 | Same | Postnecrotic cirrhosis | Glomerulo-nephritis | 4 | 10 | Alive | |
| 680 | 50/M | 12/19/85 | 3/25/86 | Postnecrotic cirrhosis | Did not recover from hepatorenal syndrome | On Dialysis | 0 | Alive | |
| 708 | 34/M | 1/28/86 | Same | Micronodular cirrhosis | Glomerulo-nephritis | 2.1 | 30 | Alive | |
| 725 | 65/M | 2/22/86 | Same | Alcoholic cirrhosis | Glomerulo-nephritis | 2.5 | Not done | Died 6/28/86 | Pneumocystis pneumonia |
| 736 | 12/M | 3/4/86 | Same | Cysteamine toxicity | Cystinosis | 6 | 5 | Alive but on dialysis | |

Abbreviations: OT = orthotopic transplant; Cr = Creatinine; CCr = CCr = creatinine clearance.

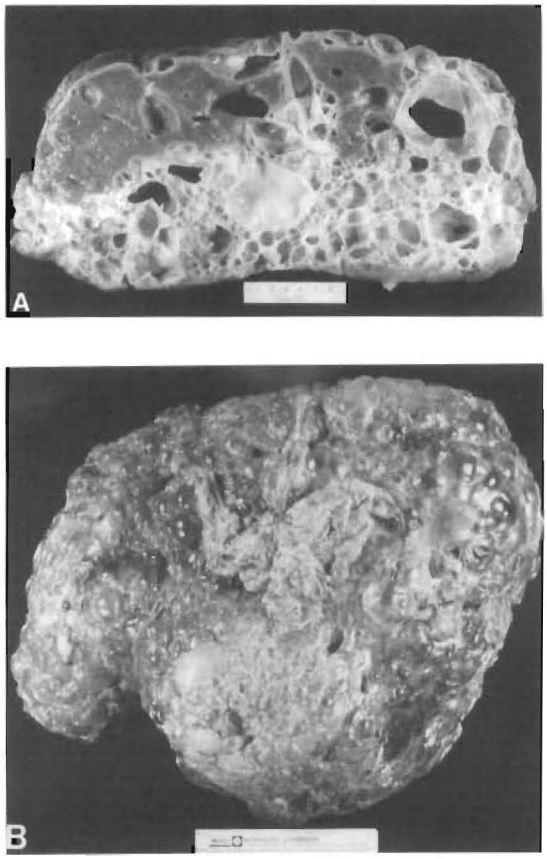


**Fig. 1.** Thirteen Kg polycystic liver replaced in patient OT 464.

The other 8 patients had various degrees of renal insufficiency, ranging from total renal failure (cases OT 464 and OT 680) to early renal failure, which under ordinary circumstances would not have called for immediate treatment by either renal transplantation or dialysis (Table 1). Eight of the 9 patients had transplantations of both organs from a common donor. The ninth patient (OT 680) had a liver replacement on December 19, 1985. When the preexisting renal failure showed no sign of recovery 3 months later, an immediately functioning renal transplant was placed from another donor.

Tissue matching was random in all cases, and the tissue matches at the A, B, and Dr loci were poor (Table 2). In 3 of the 10 transplants that were performed in 9 patients, there were unequivocally positive cytotoxic crossmatches of the kind which, under ordinary circumstances, would have precluded renal transplantation (Table 2). In these 3 instances and in 2 other patients with doubtfully positive crossmatches, the liver grafts were placed first, and after a few hours, the kidneys from the same donors were inserted.

Immunosuppressive therapy consisted of cyclosporine (CsA) and prednisone, to which monoclonal antibody therapy (OKT3) was added early in the postoperative period in 2 patients. The lymphocytotoxic crossmatches were performed with conventional techniques as described in detail elsewhere.[1] In the patients who possessed preformed cytotoxic antibodies against their donors, the reactivity and specificity of the antibodies were assessed with absorption techniques.[1]

The amount of blood lost in the various cases is listed in Table 2. The blood loss data was considered important because of the possibility of dilution of the recipient antibodies by transfusion.

## RESULTS

### Mortality

One of the 9 recipients died 25 days after an initial double organ transplantation and 10 days after a second similar attempt. This recipient had been treated with liver transplantation in 1979 (6 years previously) using azathioprine-steroid maintenance therapy. The liver had slowly failed over a period of many months during which efforts at salvage were made by the late institution of CsA. Renal failure which was already present was made worse. The first attempt at retransplantation on June 16, 1985 failed because of thrombosis of the hepatic artery with secondary failure of the concomitantly placed kidney. The defective liver was removed at another operation on June 28, 1985, leaving in place the kidney graft which had not functioned. Although both the liver and kidney placed on June 28 functioned, the patient died of fungemia 10 days later.

Patient OT 725, a 65 year old man, died of *Pneumocystis carinii* pneumonitis 4 months after hepatic and renal transplantation. He had been treated with heavy immunosuppression because of persistent and recurrent rejection of both organs.

### Graft Function

The other 7 patients are well from 6 to 26 months postoperatively. All 7 have essentially normal hepatic function and 6 have well-functioning renal grafts. In those patients whose pre-existing renal failure was not yet poor enough to justify transplantation on such grounds alone, radionuclide scans have shown that the renal allograft has become the dominant organ (Fig. 2).

**Table 2.** Typing and Serologic Data.

| *OT Number* | *Donor-Recipient ABO* | *HLA Antigens Matched* | *Panel Reactive Antibody* | *Preop Cytotoxic Crossmatch* | *Blood Loss (ml)* | *Crossmatch After LTX* | *Crossmatch Later* |
|---|---|---|---|---|---|---|---|
| 419 | B-B | A29 | 0% | Negative | 2400 | — | — |
| 464 | B-B | — | 0% | Doubtful positive | 8000 | — | — |
| 495 | A-A | 0 | 94% | Strongly positive | 3000 | Negative | Negative |
| 164a | O-O | 0 | 0% | Negative | 2400 | Negative | — |
| 164b | | A1, B8 | 0% | Negative | 1600 | Negative | — |
| 584 | B-B | A2 | 0% | Negative | 2400 | Negative | — |
| 680 | O-O | Liver A1, DR3 Kidney 0 | 0% | Negative | — | Negative | — |
| 708 | A-A | A2 | 0% | Doubtful positive | 6000 | — | — |
| 725 | O-O | 0 | 21% | Strongly positive | 8000 | Doubtful positive | — |
| 736 | O-O | A2 | 91% | Strongly positive | 20,000 | Strongly positive | — |

One patient with cystinosis, whose liver had been destroyed by an idiosyncratic reaction to experimental therapy with cysteamine, went through a very stormy and protracted postoperative course but eventually attained completely normal hepatic function. Although the renal graft from the same donor has blood flow, it has not yet functioned satisfactorily after 6 months.

### The Influence of Preformed Antigraft Antibodies

Hyperacute rejection of the 3 hepatic grafts that were confronted with cytotoxic antidonor antibodies did not occur. However, one of the recipients experienced massive fibrinolysis, which necessitated intensive pharmacologic and surgical care in an operation that lasted nearly 24 hours. It was suspected that the liver had undergone an abortive attack by antibodies. Although 50 units of blood were required in this small 12-year-old child, the crossmatch with the donor remained positive.

Two of the renal grafts that were put in place after the liver had been revascularized functioned promptly and permanently. The cytotoxic antibodies in these 2 recipients were reduced or had disappeared after the liver was in place (Table 2). However, the kidney placed in patient OT 736 against a persistent cytotoxic crossmatch did not function at the time and has not functioned properly in the subsequent 6 months. Although the renal allograft had fair blood flow on a radionuclide scan, it undoubtedly sustained a severe and possibly irreversible insult from the antibody attack.

## DISCUSSION

Patients being considered for liver transplantation have presented to us with a high incidence of secondary renal failure from the hepatorenal syndrome, drug toxicity, shock, and other causes.[2,3] Renal transplantation in conjunction with hepatic replacement under such circumstances is not usually a serious consideration, since provision of good liver function usually corrects the renal pathophysiology; complete recovery of the kidneys is expected. Imaging techniques such as ultrasound or CT scan are invaluable in assessing potential reversibility. If the kidneys are small and shrunken, the diagnosis of significant chronic renal disease can be considered established.

If chronic renal disease is documented, concomitant renal transplantation may be indicated. Combined hepatic and renal transplantation is apt to become more common in the years ahead. Chronic renal disease is often seen in patients with end-stage liver disease, especially in those in whom the diagnosis is chronic active hepatitis, a disease that is frequently associated with glomerulonephritis. Other examples

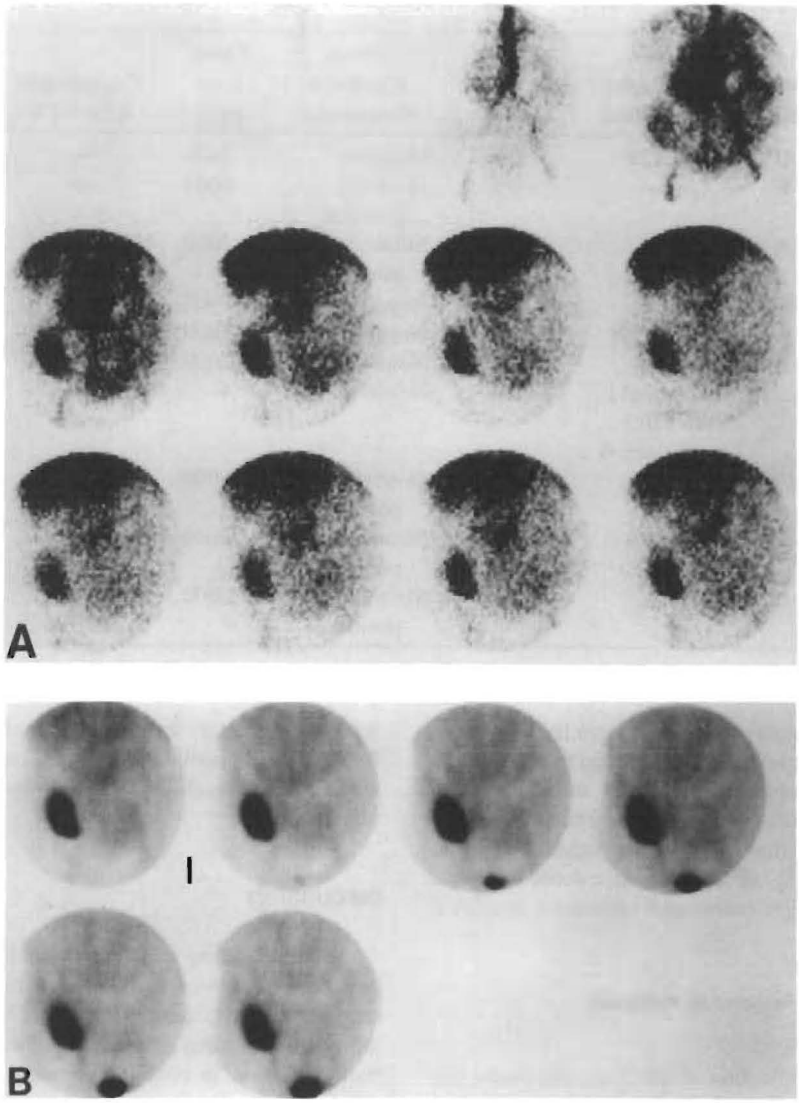


**Fig. 2.** Radionuclide scan in patient OT 495. Note the dominance of the transplant compared with the diseased native kidneys. The upper scan demonstrates flow to the transplant kidney, the lower, secretion. The transplant was in the right iliac fossa.

in our series were patients with polycystic disease of both liver and kidney. In such liver recipients, it would be futile to attempt hepatic transplantation without providing a kidney as well.

In 7 of our 9 patients, renal transplantation was carried out at a stage of chronic renal disease that ordinarily would not have been considered appropriate for renal transplantation. There were two reasons for proceeding early. First, it was impossible to envision going forward with liver transplantation using the nephrotoxic immunosuppressive drug CsA, without ensuring good renal function. Otherwise, the optimal immunosuppression for the liver would have been jeopardized. Second, the sera of a significant number of patients contained T-warm cytotoxic antibodies of the kind which preclude renal transplantation in the event of anti-donor specificity. In the event of a positive crossmatch, it was expected that the liver would provide protection for the kidney from the same donor, thus providing a unique and one time

only opportunity for patients whose cytotoxic antibodies were widely reactive. The basis for the speculation was the well known resistance of the liver to hyperacute rejection caused by such antibodies.[4–6]

This hypothesis was supported not only by the clinical observations reported here but also by special serologic tests. In patients OT 495 and 725, strongly positive crossmatches before the liver was revascularized became negative or doubtfully positive in the subsequent hours, allowing the kidneys to be transplanted in an antibody depleted milieu. The specificity with which the antibodies were deleted was well demonstrated in patient OT 495, whose sera retained widely reactive antibodies at the same time as the antibodies against the donor lymphocytes were lost. This case and others have been reported in detail elsewhere.[1] It is noteworthy that good kidney function was not obtained in a third patient whose antibodies did not disappear after transplantation of the liver.

Although there was good evidence of immunologic advantage endowed by the liver upon the kidney in the foregoing examples, the long-term effect of multiple organ transplantation on the outcome of individual organs is not known. Although evidence can be cited from numerous publications that multiple organs protect each other,[7] an almost equal number of citations to the contrary could be found by the reader with the converse bias. For the moment, we have concluded that neither a clear advantage nor disadvantage is demonstrable with multiple organs.

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