Liver transplantation in a patient with cholangiocarcinoma and ulcerative colitis

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A 39-year-old patient with cholangiocarcinoma and pre-existing ulcerative colitis was successfully treated by orthotopic liver transplantation. He was given low doses of prednisone and azathioprine and survived for more than 9 months, dying with tumour metastases, thrombosis of the inferior vena cava and an intra-abdominal abscess. At autopsy the homograft showed little evidence of rejection.

Preoperatively the patient had septicemia. Removal of his liver was difficult. The discrepancy between donor and recipient in size of blood vessels and the presence of two hepatic arteries in the donor caused problems during the vascular anastomoses. During the operation cardiac arrest occurred. Postoperatively there were several medical and surgical problems, including intraperitoneal and gastrointestinal hemorrhage, paralysis of the right dome of the diaphragm, sinus bradycardia, massive diuresis, peroneal nerve palsy, and one major and three minor episodes of rejection, which were reversed by giving pulse doses of methylprednisolone intravenously.

Un patient âgé de 39 ans souffrant d'un cholangiocarcinome et porteur d'une colite ulcérative pré-existante a été traité avec succès par une greffe orthotopique du foie. Il a reçu de faibles doses de prednisone et d'azathioprine et a survécu pendant plus de 9 mois; il est décédé de métastases de la tumeur accompagnée d'une thrombose de la veine cave inférieure et d'un abcès intra-abdominal. A l'autopsie l'homogreffe n'a présenté que peu de signes de rejet.

Avant l'opération le patient souffrait de septicémie. La résection du foie a été difficile. La différence de calibre entre les vaisseaux sanguins du donneur et ceux du receveur et la présence de deux artères hépatiques chez le donneur ont causé des problèmes au moment des anatomoses vasculaires. Un arrêt cardiaque est survenu durant l'opération. Plusieurs problèmes médicaux et chirurgicaux ont été rencontrés dans la période postopératoire, dont une hémorragie gastrointestinale et intrapéritonéale, une paralysie du plafond droit du diaphragme, une bradycardie sinusale, une diurèse massive, une paralysie du nerf péronier ainsi qu'un épisode majeur et trois épisodes mineurs de rejet qui ont pu être contrôlés par des injections répétées de méthylprednisolone intraveineux.

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Since the first attempts at liver transplantation in man in 1963 by Starzl and Moore and their colleagues,[1,2] some 250 transplants have been performed throughout the world for both benign and malignant conditions of the liver. The indications have included biliary atresia, cirrhosis, hepatic necrosis and liver failure, Wilson's disease and other inborn errors of metabolism, cholangiocarcinoma, hemangioendothelial sarcoma and metastatic liver cancer.[3-10]

Liver transplantation has not been reported in a patient with cholangiocarcinoma and pre-existing ulcerative colitis. We report here details of such a case, in which there were also unusual medical and technical problems, in a 39-year-old man who lived for more than 9 months after successful orthotopic liver transplantation.

Case report

Clinical history

A 39-year-old male rancher was admitted to Foothills Provincial General Hospital, Calgary, because of increasing pruritus and jaundice.

Ulcerative colitis affecting the colon and rectum had been diagnosed 16 years previously. After several years of medical treatment a panproctocolectomy with ileostomy had been carried out in August 1967 at the Cardston (Alta.) Municipal Hospital. His immediate postoperative course was complicated by deepening jaundice (highest serum bilirubin value, 29 mg/dl) and clinical and biochemical features of hepatic failure, and necrosis of the ileostomy stoma. At laparotomy the liver was found to be enlarged and nodular. The ileostomy was revised. Histologic examination of a liver biopsy showed bile duct proliferation with pericanalicular and portal round-cell infiltration and other features of intrahepatic pericholangitis with early biliary cirrhosis. Liver failure and jaundice gradually and completely subsided and he was discharged from hospital 1 month after laparotomy. He was readmitted later in 1967 for revision of the ileostomy and in June 1971 because of episodes of bowel obstruction. In April 1975 increasing pruritus and jaundice developed and he was referred to Foothills Hospital and University of Calgary for investigation and treatment.

He was deeply jaundiced and the liver was enlarged. Results of gastrointestinal

radiography and duodenal and bile duct endoscopy were normal. Blood analysis showed the following values: total protein, 7 g/dl; albumin, 2.1 g/dl; blood urea nitrogen (BUN), 27 mg/dl; total bilirubin, 26 mg/dl; alkaline phosphatase, 550 IU/*l*; and aspartic transaminase, 120 IU/*l*. Liver scan showed a large space-occupying lesion in the region of the porta hepatis involving both lobes of the liver (Fig. 1), and a selective hepatic angiogram showed a large vascular tumour occupying the central portion of the liver with extension to both hepatic lobes.

At laparotomy a large, nonresectable tumour was found to occupy the area of the porta hepatis, obstructing both hepatic ducts. There was no evidence of extrahepatic spread. Biopsy of the tumour showed a well differentiated cholangiocarcinoma. In an attempt to relieve the jaundice the empty common bile duct was opened. A U-shaped Silastic tube was worked through the tumour and out through the substance of the liver to provide external biliary drainage, as described by Terblanche and Lauw.[11] This resulted in temporary amelioration of the jaundice.

During the next few weeks persistent fever and other features of cholangitis developed. Bile culture grew *Streptococcus faecalis* and later *Pseudomonas aeruginosa*. Episodic encephalopathy developed and he was treated with the standard medical regimen for hepatic failure, including administration of chloramphenicol and later gentamicin. The biliary drainage tube was removed and a Scribner arteriovenous shunt was placed in the right arm for intravenous hyperalimentation and possible extracorporeal hepatic support while the patient was awaiting liver transplantation.

Intermittent pyrexia (41°C) continued and failed to respond to chemotherapy. In addition, ascites and large pleural effusions that had to be drained developed; the aspirate contained neither microorganisms nor malignant cells. The serum bilirubin value increased to 41 mg/dl and the serum alkaline phosphatase value to 1700 IU/*l*. Oliguria developed. The serum creatinine value increased to 2.1 mg/dl and the BUN to 43 mg/dl. The patient was treated by hemoperfusion for 3 hours with an activated charcoal column[12] and one subsequent exchange transfusion of fresh blood, but this had only a transient effect on the progressing hepatic failure.

The patient became increasingly confused and his body weight decreased to 52 kg. The liver enlarged and became tender; the serum bilirubin value increased to 60 mg/dl. Extensive radiologic examination of the chest, including whole-lung tomography and total-body bone scans, showed no evidence of metastatic tumour spread. It was clear that the patient's condition was critical and that the only hope for survival was through successful orthotopic liver transplantation. This was readily accepted by the patient and his relatives.

Orthotopic liver transplantation

On July 30, 1975 a suitable cadaver donor became available — the 16-year-old victim of a traffic accident. HLA type of the donor was A2,3;B13,w15 and that of the recipient, A1,w29;B8,14. Direct lymphocytotoxic crossmatch yielded negative results. Cholangiography showed in the donor a normal biliary tree, but arteriography demonstrated two hepatic arteries, one arising from the celiac axis and the other from the superior mesenteric artery.

A bilateral subcostal incision just clearing the ileostomy was made in the recipient. The liver was enormous and full of tumour, which had now extended to the gallbladder and the common bile duct. Owing to the previous operations and the liver's size and adherence to the diaphragm, dissection and mobilization of the organ were extremely difficult. Examination of frozen sections of tissues surrounding the liver, including the lymph nodes at the porta hepatis, showed no tumour.

The donor's liver and entire celiac and superior mesenteric arteries were then removed. The liver was cooled by perfusion through the portal vein and the two hepatic arteries with an electrolyte solution, as previously described.[13] The recipient's liver was then excised.

Orthotopic liver transplantation was carried out by a modified technique of Starzl.[3] The vascular anastomoses were carried out in the following order: suprahepatic inferior vena cava, portal vein, two hepatic arteries and infrahepatic inferior vena cava (Fig. 2). Biliary drainage was carried out by cholecystoduodenostomy.

In addition to the technical problems of a difficult hepatectomy, the ileostomy, and the two hepatic arteries in the donor, there were other serious problems during the transplantation. The donor liver was small and a discrepancy between donor and recipient in the size of the blood vessels caused problems during the vascular anastomoses. While the patient was in the anhepatic phase and the vessels were being anastomosed cardiac arrest occurred. Resuscitation was started immediately and cardiac massage was continued while the anastomoses were being completed. After 50 minutes of cardiac massage spontaneous and regular cardiac rhythm was established.

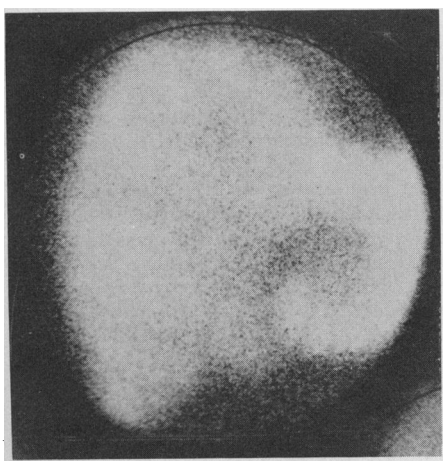

FIG. 1—Hepatomegaly and centrally placed large primary tumour of liver demonstrated on preoperative technetium-99m (^{99m}Tc) liver scan.

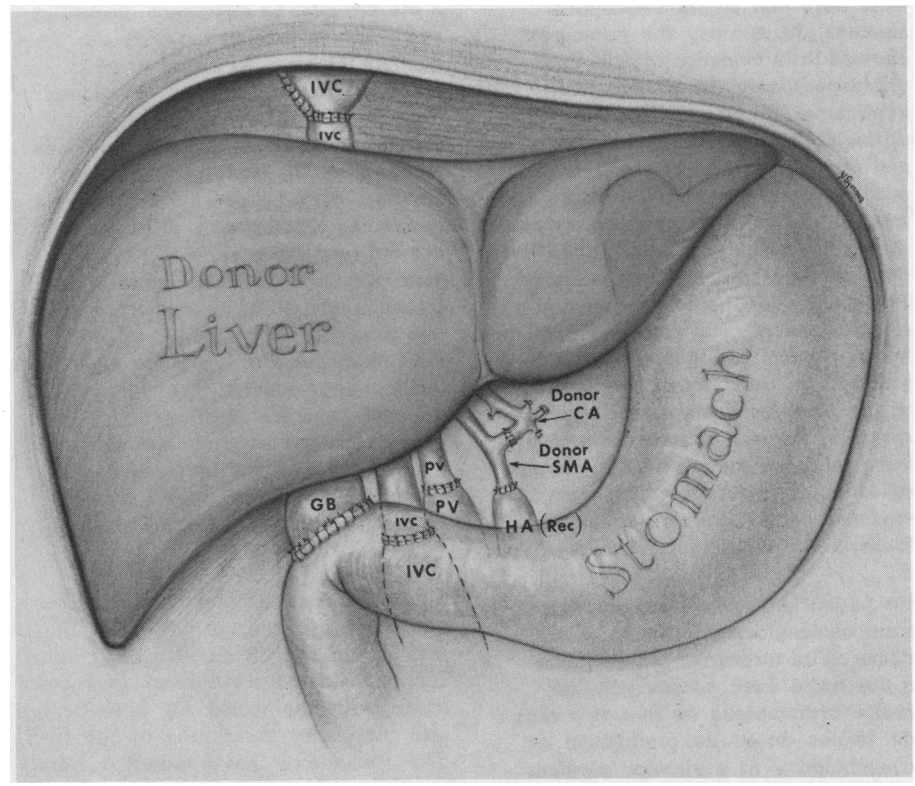

FIG. 2—Technique of orthotopic liver transplantation. Note discrepancy in vessel size between donor and recipient and technique for anastomosing two hepatic arteries: donor celiac and superior mesenteric arteries were sutured together, then distal end of superior mesenteric artery was joined to recipient's single hepatic artery. IVC = inferior vena cava; PV = portal vein; CA = celiac axis; SMA = superior mesenteric artery; HA (Rec) = hepatic artery of recipient; GB = gallbladder.

When adequate circulation was established in the recipient the vascular clamps were removed. The liver homograft assumed an excellent colour and within a short time bile flow was established. At the conclusion of the operation the patient appeared to be in good condition with normal circulation; he awoke quickly from anesthesia. The total blood requirement was about 40 units.

The recipient's liver weighed 3.8 kg and contained a centrally placed tumour, 8 cm in diameter, which had spread throughout the liver along the biliary ducts; these contained many abscesses, from which *Pseudomonas* was cultured.

An immunosuppressive regimen of prednisone, 3 mg/kg, and azathioprine, 5 mg/kg, was begun the day before operation (Fig. 3), together with prophylactic antibiotics — gentamicin, cloxacillin and clindamycin.

Postoperative course

On the 1st postoperative day the patient was alert and communicating with attendants, but signs of intraperitoneal hemorrhage developed and worsened. A large intraperitoneal hematoma was evacuated 36 hours after transplantation. Numerous bleeding points on the raw surface of the diaphragm were secured by suture and coagulation. The liver homograft appeared in excellent condition. The patient's condition improved immediately and the transplanted liver continued to function. The serum bilirubin value decreased to 7.5 mg/dl and the serum alkaline phosphatase value to 50 IU/*l* within the first 48 hours (Fig. 3).

During the next 4 weeks several serious complications, some of which have not previously been described, were successfully managed.

Sinus bradycardia (pulse rate, 40 beats/min) developed 4 days after transplantation and persisted for 2 weeks. This was treated with intermittent administration of atropine sulfate.

Elevation of the right dome of the diaphragm was noted in the immediate postoperative period, but this did not appear to cause the patient any respiratory difficulty and it gradually and completely cleared over the next 10 weeks.

Although all cultures of blood drawn preoperatively were negative, one culture of blood taken immediately before transplantation was positive for *P. aeruginosa*. Consequently, the patient was treated with carbenicillin for 2 weeks, then with tobramycin for another 2 weeks. Cultures of blood and urine collected 15 days after transplantation grew *Candida albicans*. The patient was therefore given amphotericin B intravenously (IV) for 2 weeks (total dose, 220 mg).

By the 7th postoperative day the serum bilirubin value was 20 mg/dl. Extensive investigation, including endoscopy and gastrointestinal radiography, failed to demonstrate biliary obstruction. A diagnosis of liver allograft rejection was therefore made and this was treated with intermittent large doses of methylprednisolone. The immunosuppressive regimen was supplemented with antilymphocyte globulin, 4 ml/d intramuscularly. Rejection was completely controlled by the 14th postoperative day (Fig. 3).

On the 12th postoperative day sudden and massive gastrointestinal hemorrhage developed through the ileostomy, requiring transfusions of 5 to 6 units of blood daily. Endoscopy, gastrointestinal barium radiography and arteriography failed to disclose the source of the hemorrhage. Treatment was continued with transfusion of fresh blood, intermittent gastric cooling and antacid therapy until all signs of bleeding stopped on the 18th postoperative day. During the period of hemorrhage the BUN value increased to 95 mg/dl. During this period and while blood transfusions were being given to maintain adequate circulation, massive diuresis (5 to 9 *l*/d) occurred but the urinary concentrations of sodium and potassium and the creatinine clearance remained normal. When the bleeding subsided the BUN decreased to 30 mg/dl and the diuresis ceased.

Bilateral footdrop and sensory deficit in the distribution of the lateral peroneal nerves were observed early in the postoperative period. This responded slowly to physiotherapy and use of supportive footwear.

From the 20th postoperative day the patient's course was relatively smooth except for one minor episode of rejection on the 28th day, which was successfully treated with methylprednisolone, 1 g IV daily for 3 days. Administration of antilymphocyte globulin was discontinued on the 36th day, following a serious anaphylactic reaction. Liver function, including synthesis of liver-dependent coagulation factors (Fig. 4), continued to improve and became normal. Renal function improved greatly after transplantation: creatinine clearance increased from a preoperative value of 53 ml/min to 115 ml/min, urinary sodium excretion increased from 57 to 109 mmol/d and urinary potassium excretion decreased from 47 to 29 mmol/d. The patient's clinical condition continued to improve and his weight increased gradually. He was discharged from hospital 40 days after transplantation.

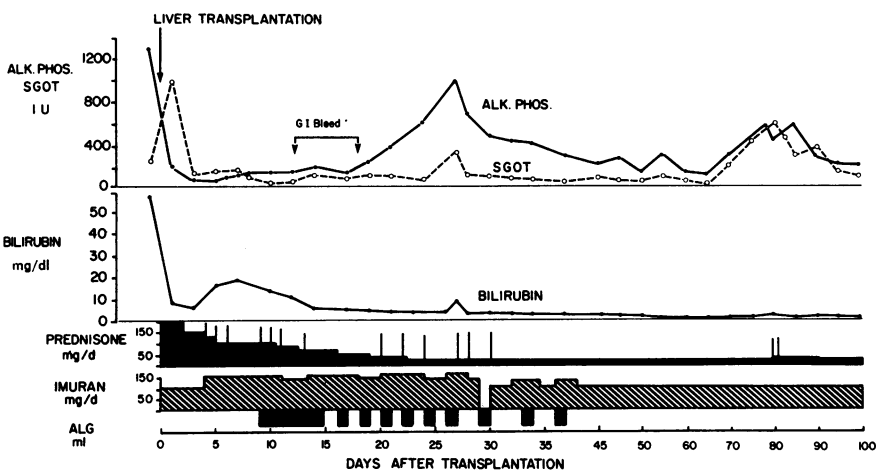

FIG. 3—Postoperative course during first 100 days after liver transplantation. Note sharp decrease in serum bilirubin and alkaline phosphatase values immediately after transplantation. One major and two minor rejection episodes were successfully reversed. Apart from some increase in serum alkaline phosphatase concentration the patient had normal liver function 6 months after transplantation.

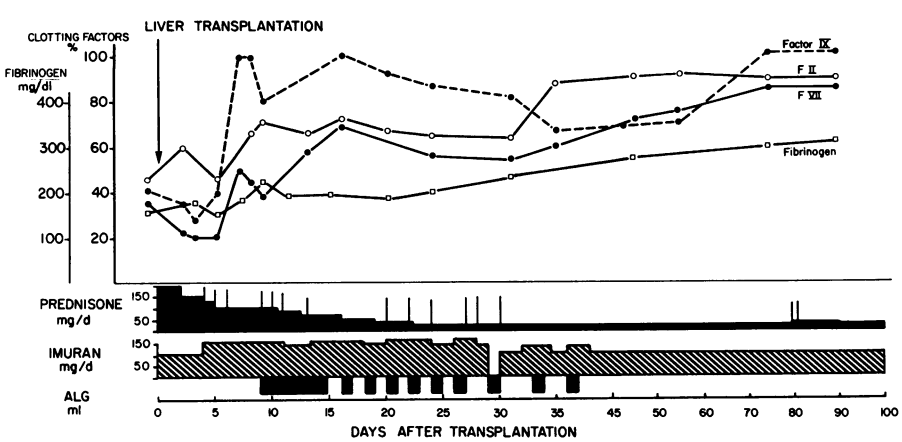

FIG. 4—Synthesis of coagulation factors after liver transplantation. Note rapid increase in the concentrations of fibrinogen and other liver-dependent clotting factors.

Follow-up

The patient was followed up at frequent intervals as an outpatient and, apart from two minor rejection episodes at 80 and 163 days, which were reversed with two 1-g pulse doses of methylprednisolone IV, he remained well. Maintenance immuno-

suppressive therapy consisted of azathioprine, 100 mg/d, and prednisone, 15 mg/d.

Liver homograft function remained good and at 6 months after transplantation his weight was 69 kg, chest radiograph and liver (Fig. 5) and bone scans were normal, prothrombin time was 100% of normal and platelet count was 309 x10^9/*l*. Serum values were as follows: total bilirubin, 0.8 mg/dl; albumin, 3.7 g/dl; cholesterol, 210 mg/dl; and creatinine, 1.2 mg/dl.

The concentration of α_1-fetoprotein (AFP) in the patient's serum was measured regularly by radioimmunoassay in an attempt to detect tumour recurrence before it became manifest clinically.[14] Just before transplantation the concentration was nearly 2000 ng/ml (normal, less than 500 ng/ml). There was a transient increase to 2200 ng/ml immediately after transplantation, but thereafter the values decreased; AFP became undetectable 2 months after transplantation and remained so.

Abdominal and back pain appeared 7½ months after transplantation and became progressively more severe. Investigations, including bone scan, showed evidence of bone metastases. Cancer chemotherapy, which included a course of 5-fluorouracil given IV, had no effect and he died more than 9 months after transplantation.

Autopsy revealed tumour metastases, particularly in bone, thrombosis of the inferior vena cava below the renal veins and an intra-abdominal abscess. Histologic examination of the liver homograft showed little evidence of rejection.

Discussion

Since 1963 some 70 patients have received liver transplantation for the treatment of various types of malignant hepatic tumours. Of the 37 patients who received their transplant because of primary hepatoma, 13 survived for more than 3 months (Organ Transplant Registry, Chicago: personal communication, January 1976). Two of these were alive 7 months and nearly 2 years, respectively, after transplantation (R.Y. Calne: personal communication, January 1976). A third patient, a child who had had biliary atresia and a small hepatoma, was alive 6½ years after transplantation (T.E. Starzl: personal communication, November 1975). Seven of the remaining 10 patients died of recurrence of tumour at 4 to 14 months.[3,5,15,16] However, one woman, also a patient of Calne, survived for 5 years after transplantation and at autopsy there was no evidence of tumour recurrence.[17,18]

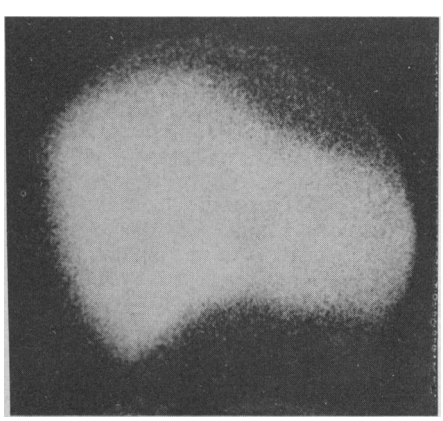

FIG. 5—Liver homograft of normal size, with uniform uptake of ^{99m}Tc 6 months after transplantation.

Twenty-three patients received liver transplantation because of primary cholangiocarcinoma of the liver. Five of these, including our patient, were alive 3 to 23 months after transplantation. Four other patients survived for more than 3 months and, of these, two died at 8 months with recurrence of tumour[19] (Organ Transplant Registry, Chicago: personal communication, 1976).

Although our patient was the 22nd to have received orthotopic liver transplantation for cholangiocarcinoma, he was the only transplant patient in whom the hepatic tumour might have developed secondary to ulcerative colitis.[20] Pericholangitis, sclerosing cholangitis and carcinoma of the hepatic ducts have all been reported as complications of ulcerative colitis.[20-22] It is plausible, therefore, that in this patient the early pericholangitis and the subsequent development of cholangiocarcinoma were the consequences of his ulcerative colitis, even though the tumour developed several years after total colectomy and ileostomy.

The cause of cardic arrest during the anhepatic phase in this patient remains obscure. Sudden and dangerous changes in blood pH and concentrations of serum electrolytes have been reported in patients undergoing liver transplantation.[23] However, the values of these variables, which were monitored regularly during the intraoperative period, remained stable.

Some of the observations made and problems encountered during the postoperative period were unusual. *Pseudomonas* septicemia was present, though undetected, before transplantation, and yet this did not appear to have any adverse effect, as had been feared; this could have been because the patient was given adequate prophylactic chemotherapy before the operation. Paralysis of the right dome of the diaphragm, which is generally thought to be due to crushing of the right phrenic nerve during clamping of the inferior vena cava,[3] caused no respiratory problem and it cleared completely 10 weeks after transplantation. Bradycardia of the degree seen in this patient has not been reported after liver transplantation, but has been seen by one of us (G.M.A.) in patients recovering from hepatic coma following extracorporeal liver perfusion.[24] In both situations sinus bradycardia responded readily to subcutaneous administration of atropine.

The great improvement in renal function that was noted in this patient has been reported in other patients with severe liver disease following liver transplantation[14] as well as following ex vivo human liver perfusion.[25] However, the massive diuresis that accompanied the gastrointestinal hemorrhage has not been reported. Such diuresis was probably due to the osmotic effect of the high BUN concentration in the presence of normal renal function, since the diuresis ceased when the BUN value decreased from 95 to 30 mg/dl. It is somewhat surprising that such a massive diuresis should have taken place while several units of blood were required daily to maintain normal circulatory homeostasis.

Peroneal nerve palsy has been reported in patients undergoing lengthy renal and hepatic transplant operations. This can be prevented by protective measures such as those described by Aldrete.[26]

Despite the fact that the donor and recipient had no HLA antigens in common, there was only one major rejection episode, which was controlled by administration of pulse doses of methylprednisolone and the addition of antilymphocyte globulin to the immunosuppressive regimen of prednisone and azathioprine. The remarkable resistance of the liver homograft to rejection, even in the face of complete HLA incompatibility, has been well documented in man[5,10] and in certain animals, such as the pig.[27]

The advisability of carrying out liver transplantation in patients with malignant liver tumours is still controversial, largely because of the high incidence of tumour recurrence after transplantation while the patient is receiving immunosuppressive therapy.[3,5,28] Such a high recurrence rate was first described by Starzl,[3] who still holds the view that hepatic replacement for primary malignant disease of the liver is a questionable, although possibly still defensible, procedure (personal communication, 1975). However, other investigators, particularly Fortner and colleagues[16] and Williams and Calne and their associates,[5] hold a much less pessimistic view and they rightly argue that tumour recurrence occurs after all types of operations for malignant disease, including liver transplantation; for the individual patient the chance of cure or of worthwhile palliation is sufficient justification for liver transplantation.

We do not believe that the financial cost of this procedure is out of line

if measured against other new forms of treatment. Kidney transplantations, for example, may be followed by numerous complications that are expensive and time-consuming to treat, yet ultimately the patient dies. In the treatment of patients with terminal disseminated cancer, high-dose methotrexate and citrovorum-rescue therapy may result in an annual cost in excess of $50 000 for the medication.

In view of the poor prognosis in patients with unresectable hepatic malignant tumours[29] and the relatively long survival after liver transplantation in a few patients with hepatoma, we are inclined to support the opinions expressed by Williams and his colleagues.[5] There is no doubt that the incidence of recurrence and the prognosis in liver transplantation depend on the type of liver tumour and the extent of spread at the time of the operation, and it is likely that the results of liver transplantation in patients with hepatic tumours will be improved greatly if transplantation is carried out early, before local and metastatic spread have taken place.

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References

1. STARZL TE, MARCHIORO TL, VON KAULLA K, et al: Homotransplantation of the liver in humans. *Surg Gynecol Obstet* 117: 659, 1963
2. MOORE FD, BIRTCH AG, DAGHER F, et al: Immunosuppression and vascular insufficiency in liver transplantation. *Ann NY Acad Sci* 120: 729, 1964
3. STARZL TE, PUTNAM CW: *Experience in Hepatic Transplantation*, Philadelphia, Saunders, 1969
4. STARZL TE, GILLES G, LILLY GR, et al: Indications for orthotopic liver transplantation. *Transplant Proc* 3: 308, 1971
5. WILLIAMS R, SMITH M, SKILLKIN KB, et al: Liver transplantation in man. *Gastroenterology* 64: 1026, 1973
6. GROTH CG, DUBOIS RS, CORMAN J, et al: Metabolic effects of hepatic replacement in Wilson's disease. *Transplant Proc* 5: 829, 1973
7. DALOZE P, CORMAN J, BLOCK P, et al: Enzyme replacement in Niemann-Pick disease. *Transplant Proc* 7: 607, 1975
8. CALNE RY, WILLIAMS R: Liver transplantation in man. I. Observation on technique and organization in five cases. *Br Med J* 4: 535, 1968
9. FORTNER JG, BEATTIE EJ JR, SHIU MH, et al: Orthotopic and heterotopic liver transplantation in man. *Ann Surg* 172: 23, 1970
10. STARZL TE, ISHIKAW M, PUTNAM CW, et al: Progress in and deterrent to orthotopic liver transplantation with special reference to survival resistance, to hyperacute rejection, and biliary duct reconstruction. *Transplant Proc* 6: 129, 1974
11. TERBLANCHE J, LAUW JH: U-tube drainage in the palliative therapy of carcinoma of the main hepatic duct junction. *Surg Clin North Am* 53: 1245, 1973
12. ABOUNA GM, GILCHRIST T, PETTIT JE, et al: Hemoperfusion with activated charcoal in treatment of acute hepatic failure, in *Artificial Liver Support*, WILLIAMS R, MURRAY-LYONS I (eds), London, Pitman, 1975, p 180
13. ABOUNA GM: Liver preservation, in *Organ Preservation for Transplantation*, KAROW A, ABOUNA GM, HUMPHRIES AL (eds), Boston, Little, 1974, p 349
14. ALPERT E, STARZL TE, SCHUR PH, et al: Serum α-feto protein in hepatoma after liver transplantation. *Gastroenterology* 61: 144, 1971
15. HUME DM, WOLF JS, LEE HM, et al: Liver transplantation. *Transplant Proc* 4: 781, 1972
16. FORTNER JG, KINNE DW, SHIU MH, et al: Clinical heterologic liver transplantation. *Surgery* 74: 739, 1973
17. CALNE RY, WILLIAMS R: Survival after orthotopic liver transplantation. *Br Med J* 3: 436, 1970
18. Liver transplantation (E). *Lancet* 2: 29, 1974
19. BERGAN JJ: A review of human solid organ transplantation. *Bull Am Coll Surg* 60: 24, 1975
20. SHERLOCK S: *Diseases of the Liver and Biliary System*, 4th ed, Oxford, Blackwell, 1968, p 648
21. BODEN RW, RANKIN JG, GOULSTON SJM, et al: The liver in ulcerative colitis. *Lancet* 2: 245, 1959
22. BODEN RW, SKYRING AP, GOULSTON SJM: Obstructive jaundice due to bile duct carcinoma. *Gut* 7: 433, 1966
23. ABOUNA GM, ALDRETE JA, STARZL TE: Changes in serum potassium and blood pH during clinical and experimental liver transplantation. *Surgery* 69: 419, 1971
24. ABOUNA GM, SERROU B, BOEHMIG HJ, et al: Long term hepatic support by intermittent multispecies liver perfusions. *Lancet* 2: 239, 1970
25. ABOUNA GM, FISHER LM, PORTER KA, et al: Experience in the treatment of hepatic failure by intermittent ex vivo liver perfusions. *Surg Gynecol Obstet* 137: 741, 1973
26. ALDRETE JA: Anesthesia and intraoperative care, in *Experience in Hepatic Transplantation*, STARZL TE, PUTNAM CW (eds), Philadelphia, Saunders, 1969, p 83
27. CALNE RY, WHITE HJO, YOFFA DE, et al: Observations on orthotopic liver transplantation in the pig. *Br Med J* 2: 478, 1967
28. STARZL TE, CORMAN J, GROTH C, et al: Personal experience with orthotopic liver transplantation. *Transplant Proc* 4: 759, 1972
29. BENGMARK S, HAFSTROM L: The natural history of primary and secondary malignant tumours of the liver. *Cancer* 23: 198, 1969

Immunologic response in vitro after thymectomy in patients with myasthenia gravis

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Thymectomy in adult animals impairs immune functions such as lymphocyte response to phytohemagglutinin (PHA) and to allogeneic cells. The responses of lymphocytes from 18 myasthenia gravis patients, 12 of whom had undergone thymectomy, were studied; the interval between thymectomy and investigation ranged from 1 month to 26 years (mean, 9.5 years). Peripheral blood lymphocytes were cultured in autochthonous plasma or homologous AB serum. In vitro responses to stimulation with PHA, concanavalin A and allogeneic mononuclear cells were within the 95% range of normal responses in all patients. Because our findings contrast with the definite immune defects resulting from thymectomy found in adult animals, longer follow-up is needed.

La thymectomie chez l'animal adulte altère les fonctions immunologiques telles que la réponse lymphocytaire à la phytohémagglutinine (PHA) et aux cellules allogéniques. On a étudié la réponse lymphocytaire de 18 patients atteints de myasthénie grave, dont 12 avaient subit une thymectomie; l'intervalle écoulé entre la thymectomie et le moment de l'étude a varié entre 1 mois et 26 ans (moyenne, 9.5 années). Les lymphocytes du sang périphérique ont été cultivés dans un plasma autochtone ou dans un sérum AB homologue. Les réponses in vitro à la stimulation par la PHA, la concanavaline A et par les cellules mononucléaires allogéniques sont demeurées à l'intérieur de 95% des variations normales. Comme nos résultats contrastent avec le net déficit immunologique résultant de la thymectomie chez l'animal adulte, une période d'observation plus prolongée est requise.

Thymectomy is frequently performed as a part of therapy in myasthenia gravis (MG).[1] As in all ablative interventions, side effects must be expected and should be looked for carefully. Thymectomy has been performed experimentally at birth in a variety of animals to establish a well known wasting syndrome with severe immunodeficiency and drastic shortening of life.[2] However, the importance of the thymus in supporting immunologic function in

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