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The First 100 Liver Transplants at UCLA

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A clinical program in liver transplantation was begun at UCLA in 1984 after a period of laboratory investigation. The first 100 orthotopic liver transplants (OLT) were performed in 83 patients (43 adults and 40 children) between February 1, 1984 and November 1, 1986. Donors and recipients were matched only for size and ABO blood group compatibility, with OLT performed across blood groups in 28 patients. Standard operative techniques were used, including venous–venous bypass in adults. Arterial reconstruction was performed using an aortic Carrel patch or "branch patch" in 65% of cases and by end-to-end or aortic conduit techniques in the remainder. The hepatic artery thrombosis rate was 5%. Biliary reconstruction was choledochocholedochostomy in 67 OLT and Roux-en-Y chole-

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dochojejunostomy in 33 (complication rate of 24% and 24%, respectively). Average lengths and ranges of donor liver ischemia, operating time, and blood replacement were 4 hours (range: 1–10 hours), 7.6 hours (range: 4–15 hours), and 17 units packed cells (range: 2–220 units). Immunosuppressive regimen was cyclosporine–steroid combination, with monoclonal anti–T-cell antibody (OKT3) used for refractory rejection. All patients had one or more complications: pulmonary (78%), infectious (51%), renal dialysis (25%), neurologic (22%). All patients had at least one episode of acute rejection, and 3.6% had chronic rejection. Retransplantation was needed in nine patients once and in four patients twice. The overall retransplant survival rate was 54%, and two of four patients who received a second retransplant are alive. Sixty-three of the 83 patients (76%) are alive (adults 72%, children 80%). The 1- and 2-year actuarial survival rate is 73% (adults 68%, children 78%). Thirty-eight of 43 patients (88%) who had transplantation in the past year are alive. Of 14 perioperative variables assessed as predictors of early mortality, only postoperative dialysis (p < 0.0005) and presence of severe rejection (p < 0.01) had statistical significance. Seventy per cent of adults returned to work, and 84% of children had normal or accelerated growth. A new program in liver transplantation provides a dramatic option in patient care and an academic stimulus to the entire medical center.

TABLE 1. *Pediatric Patients Evaluated and Transplanted February 1, 1984–November 1, 1986*

Diseases	Patients Evaluated	Patients Transplanted*	Survival (%)
Biliary atresia			
Biliary atresia	40	18 (4)†	14/18 (78)
Biliary hypoplasia	1	1	1/1 (100)
Alagille's syndrome	1	0	—
Cirrhosis			
Idiopathic cholestasis/ cirrhosis	9	2	2/2 (100)
Familial cirrhosis	4	2 (1)	2/2 (100)
Chronic active hepatitis	2	1	1/1 (100)
Congenital hepatic fibrosis	1	0	—
Metabolic disorders			
Hemophilia	1	0	—
Alpha-1-antitrypsin deficiency	10	6	5/6 (83)
Wollmans syndrome	1	0	—
Tyrosinemia	2	2	0/2 (0)
San Fillipo syndrome	1	1 (1)	1/1 (100)
Wilson's disease	1	0	—
Inflammatory diseases			
Acute hepatic necrosis	5	2	1/2 (50)
Subacute hepatic necrosis	1	1	1/1 (100)
Reye's syndrome	1	0	—
Tumors			
Hepatoblastoma	4	1	1/1 (100)
Hemangioendothelioma	1	1	1/1 (100)
Metastatic Leiomyosarcoma	1	1	1/1 (100)
Miscellaneous			
Budd-Chiari syndrome	1	1 (1)	1/1 (100)
Total	**88**	**40 (7)**	**32/40 (80)**

* Retransplants in parentheses.
† One patient retransplanted twice.

THE FIRST HUMAN ORTHOTOPIC LIVER TRANSPLANT (OLT) was performed in 1963.[1] Although this achievement marked a dramatic surgical milestone, two decades would pass before clinical liver transplantation was recognized by a national medical consensus as a therapeutic option for patients with end-stage liver disease. During those 20 years, intensive laboratory and clinical investigation was conducted primarily by Starzl and colleagues[2,3] and later by Calne et al.[4] on immunology, technique, and applications of the procedure.

At the time of the National Institutes of Health Consensus Conference on Liver Transplantation in 1983,[5] there was only one major center in the United States (Denver/Pittsburgh) with a sizeable experience in OLT. Several other centers had reactivated or initiated new programs. By 1987, over 50 centers in the U.S. have programs in OLT, emphasizing the rapid acceptance of this therapy. At the University of California at Los Angeles (UCLA), a liver transplant program was organized in 1983, and the first clinical transplant was performed on February 1, 1984. Between that date and November 1, 1986, 100 transplants were performed in 83 patients. Forty-seven transplants that have been performed in 40 children (less than 18 years of age) and 53 transplants in 43 adults form the basis of this report.

Materials and Methods

The organization, development, and structure of the UCLA Program have been described.[6–8] The Liver Transplant Team includes the following individuals involved with the day-to-day care of both adults and children: surgeons (4), anesthesiologists (2), surgical residents (2), and a surgical fellow, anesthesia fellow, hepatologist, nephrologist, infectious disease specialist, psychiatrist, social worker, clinical nurse coordinator, donor nurse coordinator, administrative coordinator, and perfusionist. Personnel involved in the care of pediatric patients specifically include hepatologists (3) and specialists in critical care, nephrology, infectious diseases, and psychiatry. Prospective transplant recipients are evaluated in the hospital on the pediatric or adult liver transplant services and presented to the multidisciplinary Patient Selection Committee, which considers both adult and pediatric candidates. All patients are managed before and after operation by the surgical team in close collaboration with either the adult or pediatric specialists.

Patients Evaluated and Transplanted

Two hundred thirty-six patients were evaluated for transplantation. The diagnoses of these patients evaluated and transplanted and the individual survivals are shown in Tables 1 and 2. Mean age for children was 5 years with a range of five months to 16 years. Biliary atresia and its variants were the diseases seen and transplanted most frequently among children (Table 1). End-stage cirrhosis from various causes and metabolic disorders, particularly alpha-1-antitrypsin deficiency, were also common. Inflammatory diseases were seen less often, and only a few pediatric patients were evaluated for hepatic tumors. Mean age for adults was 41 years with a range of 18–60 years. Among adults, chronic active hepatitis, primary biliary cirrhosis, sclerosing cholangitis, and cryptogenic cirrhosis were the most common diseases seen and transplanted (Table 2).

Follow-up for all patients transplanted has been 100%. Range of follow-up is 1–33 months with a mean of 11.8 months. Each patient is numbered by transplant. Donors and recipients were matched for size (weight

and height) and ABO blood groups. No prospective tissue matching was performed. Transplants were performed across blood groups in 28 patients. In 24 of these patients, a Type O liver was placed in an A or B recipient. In four patients, a Type A or B liver was placed in an O recipient because of an urgent need for transplantation (two retransplants and two first transplants).

Twenty patients (12 pediatric and 8 adult) who had been accepted for transplantation died before a suitable donor could be found. Average age of the pediatric patients was 9.5 months (range 6–16 months). Diagnoses were biliary atresia in nine patients (previous portoenterostomy procedure in 7) and fulminant liver failure, Wilson's disease, and end-stage cholestatic cirrhosis in one patient each. All had severely depressed hepatic synthetic function. Adults who died while waiting for transplantation included three patients with chronic active hepatitis, two with cryptogenic cirrhosis, and one each with primary biliary cirrhosis, protoporphyria, and fulminant hepatic necrosis. Overall, for every three pediatric patients transplanted, one died waiting; for every five adults, one died waiting.

TABLE 2. *Adult Patients Evaluated and Transplanted, February 1, 1984–November 1, 1986*

Diseases	Patients Evaluated	Patients Transplanted*	Survival (%)
Inflammatory			
Acute/subacute hepatic necrosis	5	2 (1)	2/2 (100)
Sclerosing cholangitis	24	7 (2)†	5/7 (71)
Cirrhosis			
Chronic active hepatitis	45	12 (1)	9/12 (75)
Primary biliary cirrhosis	35	10	8/10 (80)
Cryptogenic cirrhosis	15	4 (3)†	3/4 (75)
Alcoholic cirrhosis	5	1	0/1 (0)
Metabolic			
Alpha-1-antitrypsin deficiency	2	1	1/1 (100)
Hemophilia	1	0	—
Protoporphyria	1	0	—
Tumors			
Hepatocellular carcinoma	4	2 (1)	1/2 (50)
Schwannoma	1	1	0/1 (0)
Hemangioendothelioma	1	1	1/1 (100)
Leiomyosarcoma (metastatic)	1	0	—
Embryonal sarcoma	1	0	—
Miscellaneous			
Budd-Chiari syndrome	5	2 (2)†	1/2 (50)
Polycystic kidney and liver disease	2	0	—
Total	148	43 (10)	31/43 (72)

* Retransplants in parentheses.
† One patient retransplanted twice.

- Stable donor
- Dissection porta hepatis & supraceliac aorta
- Precooling via portal v.
- *In situ* aortic flush
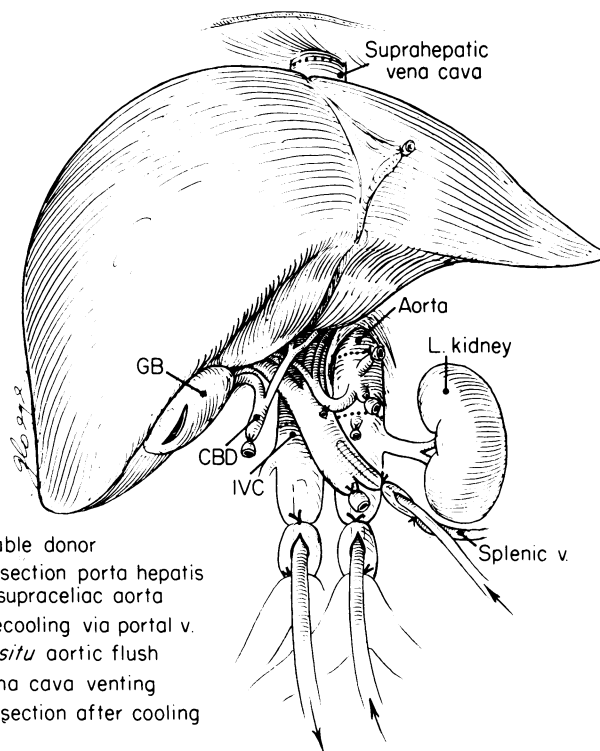- Vena cava venting
- Dissection after cooling

FIG. 1. Preparation for harvesting of the donor liver.

Operative Approach and Complications

Donor and recipient operations were performed using techniques described by Starzl et al.[9] Ninety-eight of 100 liver harvests were performed by members of our team who traveled to the donor hospital. In two cases, another team, Pittsburgh and Dallas, performed the donor hepatectomy and sent the organ to UCLA. The donor procedure allows for harvesting of heart, liver, and kidneys[10,11] (Fig. 1).

For the recipient, large-bore intravenous catheters and Silastic (Hickman® or Broviac®) catheters were placed before operation. Pulmonary artery monitoring, always used in adults, was rarely used in children except in teenagers. The abdomen was entered *via* a bilateral subcostal incision with midline extensions to the xiphoid in adults. A thoracotomy extension was used only once (OLT #64), and one patient (OLT #23) required transdiaphragmatic intrapericardial control of the inferior vena cava because of extensive previous surgery. No irreversible surgical maneuvers were performed during recipient hepatectomy before return of the donor liver to UCLA, although a satisfactory liver was harvested in every instance. In one case, recipient hepatectomy was not begun when the donor liver was found to be cirrhotic. Transplantation was also aborted in one patient with a hepatoblastoma and in one patient with hepatocellular carcinoma who were found to have tumor ex-
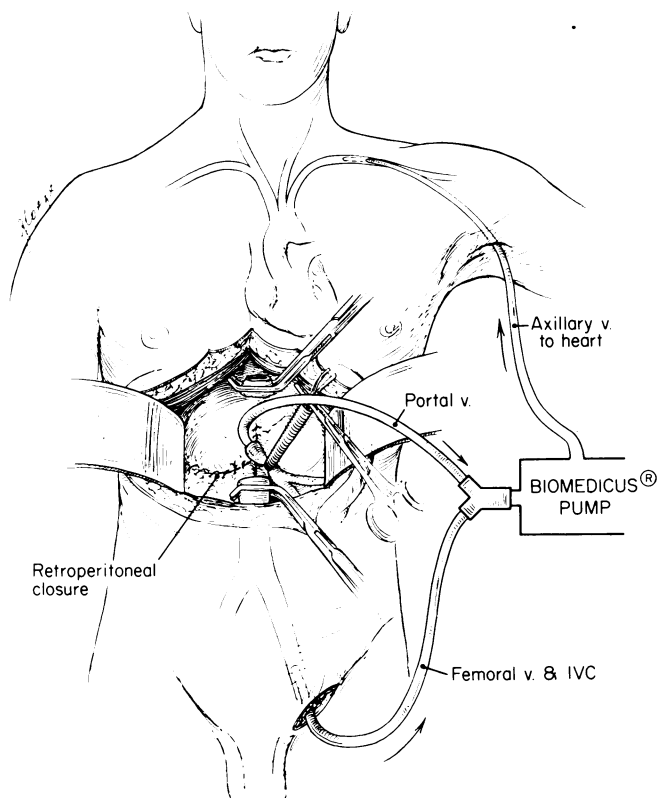
FIG. 2. Venous–venous bypass for circulatory support during the anhepatic phase.
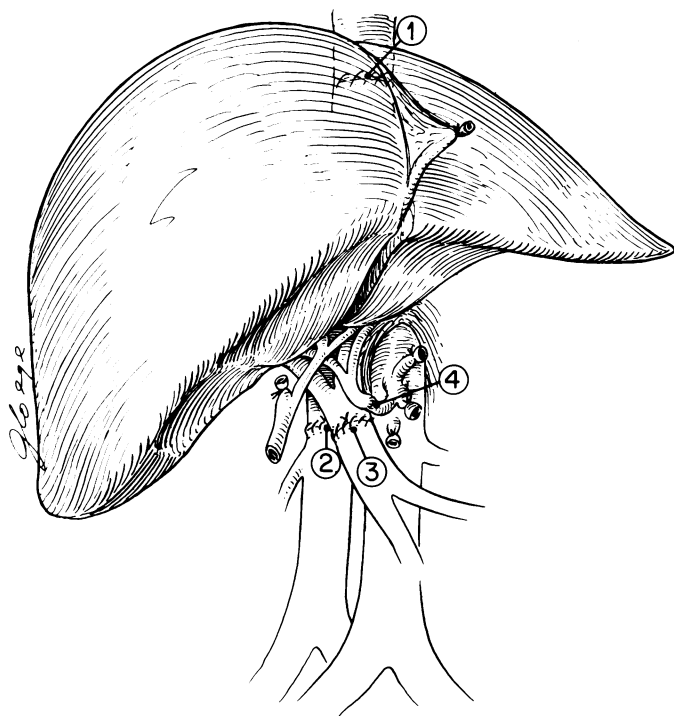

FIG. 3. Order of vascular anastomoses (see text).

tension beyond the liver thus precluding a curative resection.

Before removal of the native liver, trial clamping of the vena cava was performed. This was tolerated well in 44 of 100 transplants. Venous–venous bypass using femoral and portal venous return and axillary venous inflow, a routine in adults, was used in only three children, two (ages 14 and 15 years) who exhibited hypotension on trial clamping and one (OLT #23) with massive bleeding from multiple adhesions and portal hypertension who was placed on bypass for circulatory support (Fig. 2).

Vascular Anastomoses

Anastomoses were performed in the following order: suprahepatic inferior vena cava (IVC), infrahepatic IVC, portal vein, and hepatic artery (Fig. 3). While the infrahepatic IVC was being completed, the liver was flushed with cold normal saline solution via an indwelling portal vein cannula that had been placed for precooling during the donor hepatectomy. In the latter part of the series, 25 g of mannitol were added to the flushing solution. After the portal vein anastomosis was completed, the vena caval clamps were removed and the liver was reperfused with portal blood while the arterial anastomosis was performed.

Venous. The supra- and infrahepatic inferior vena caval and portal venous anastomoses were performed using a running polypropylene suture (3-0 or 4-0 for vena cava and 6-0 or 7-0 for portal vein). The posterior wall was sewn from within, with care taken to achieve an everting intima-to-intima approximation. An interrupted anterior row was used in small children to allow for growth of the vessel. "Growth factors" were used occasionally in adults.[12]

Arterial. Arterial reconstruction (Table 3) was variable and depended on donor and recipient anatomy.[13] Although most donor livers had normal (Type 1) arterial anatomy, variants were seen in 19 cases: 10 Type 2 (replaced left hepatic artery arising from left gastric artery), two Type 4 (right hepatic replaced from superior mesenteric and left hepatic replaced from left gastric arteries), and seven Type 3 (right hepatic replaced from superior mesenteric artery [SMA]). Recipient arterial anatomy was Type 2 in two cases, Type 3 in one case, and Type 1 in all others.

Running or interrupted sutures of 6-0 or 7-0 polypropylene were used for arterial anastomoses. A "branch patch" technique described by our group was often used to facilitate anastomosis of small vessels.[14]

An aortic Carrel patch of the entire donor celiac artery used in 21 transplants was sewn to a branch patch of the proper hepatic-gastroduodenal bifurcation (9 trans-

plants), to a branch patch of the common hepatic bifurcation (7), to a branch patch of the celiac-splenic bifurcation (3), to the aorta (2), and to the common hepatic, and SMA (1 each). Although use of the celiac-hepatic trunk with a Carrel patch generally produced a redundant lie that would seem to be prone to kinking, no instances of arterial thrombosis occurred with this reconstruction.

A simple end-to-end technique was used in 21 transplants: hepatic-to-hepatic (13), hepatic-to-celiac (1), and celiac-to-hepatic (5), hepatic-to-recipient aorta with iliac graft (1), and donor SMA trunk-to-recipient celiac axis (1). There was one episode of thrombosis treated with retransplantation and arterial reconstruction using an aortic conduit (OLT #26).

A primary branch patch technique was used in 42 transplants. In 28 transplants, the hepatic artery or celiac-splenic bifurcation was sewn to a branch patch of the hepaticogastroduodenal bifurcation. In one transplant, the hepatic artery was sewn to a branch patch of the common hepatic bifurcation. In the donor with a double replaced arterial supply, the proximal SMA was joined to the celiac and the distal SMA to a branch patch of the hepaticogastroduodenal bifurcation. There were three thromboses, one of the celiac axis branch patch-to-recipient aorta and two of the hepatic-to-hepatic gastroduodenal branch patch type. One (OLT #27) thrombosis of the left hepatic artery occurred and produced left lobar necrosis and a biliary fistula. The lobar necrosis manifested as Citrobacter sepsis and was treated with operative lobar debridement; the later biliary fistula was treated with Roux-en-Y jejunal onlay on the fistulous orifice. The other thromboses (OLT #36 and OLT #79) involved the entire artery and were treated successfully with two subsequent retransplants in one patient and with a single retransplant in the other.

An aortic conduit from donor-to-recipient aorta was used in eight transplants, principally in our early experience. The initial episode of thrombosis in OLT #36 was managed with retransplantation and arterial reconstruction using an aortic conduit and an iliac artery interposition graft. This in turn thrombosed, and arterial anastomosis in the successful third transplant was performed using an aortic Carrel patch to a branch patch of the celiac-splenic bifurcation.

All thromboses occurred in the pediatric patients, and it is our impression that the majority occurred because of the small caliber of the donor arteries. Arterial inflow was tested carefully, and if it did not appear to be adequate, an alternative inflow was chosen. This experience with arterial reconstruction has indicated that each anastomosis must be individualized to accommodate the variable anatomy of donor and recipient.

TABLE 3. Arterial Reconstruction

	Donor Anatomy Type					
	N	1	2	3	4	Thrombosis
Aortic Carrel patch	19	13	4	2		
End-to-end	24	18	4	2		1
"Branch patch"	46	41	1	2	2	3*
Aortic conduit	8	7	1			1
End-to-side	3	2		1		
Total	100	81	10	7	2	5

* 1 left lobar infarction.

Biliary Reconstruction

The biliary anastomosis was a choledochocholedochostomy with a t-tube stent in 67 transplants and Roux-en-Y choledochojejunostomy with a straight tube or internal stent in 33 transplants (Fig. 4). Technetium-HIDA hepatobiliary scintigraphy was found useful for postoperative evaluation of the biliary anastomoses as well as of graft function.[15]

The overall biliary complication rate was 24%. There were 16 complications of choledochocholedochostomy (24%): bile peritonitis in nine after t-tube removal (reoperation required in 2), t-tube malposition or migration in four (reoperation in 2), biliary fistula in two, and bile duct tumor recurrence in one (anastomotic and distant recurrence). There were eight complications of choledochojejunostomy (24%). Five complications were related to duct-jejunal anastomosis: fistulas in three (one due to hepatic artery thrombosis), obstruction in one, and a tube problem in one. Three complications were related to the jejunojejunal anastomosis: perforation in two and bleeding in one. There were no deaths attributable to biliary complications, although one patient died of recurrent cholangiocarcinoma.

Other Operative Considerations

Average length of liver ischemia was 4 hours (range: 1–10 hours); of operation, 7.6 hours (range: 4–15 hours); and of anesthesia, 8.4 hours (range: 5.5–16 hours). Average requirements for blood and products were: packed red cells, 17.0 units (range: 2–220 units); fresh frozen plasma, 18.2 units (range: 2–190 units); platelets, 14.7 units (range: 0–100 units). Re-exploration for bleeding was necessary in 17 of 100 transplants; only two of these were done in the past year.

Splenectomy was performed in five patients, one at the time of the transplant to permit abdominal closure (OLT #33) and four later. One late splenectomy was done for thrombocytopenia from hypersplenism (OLT
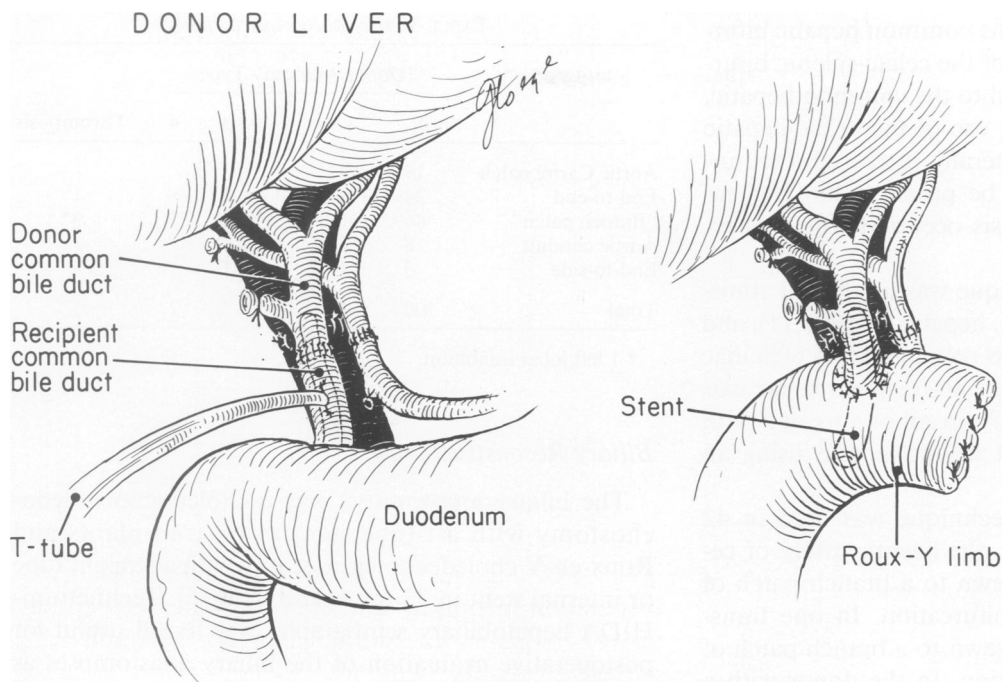
DONOR LIVER

Donor
common
bile duct

Recipient
common
bile duct

T-tube

Duodenum

Stent

Roux-Y limb

FIG. 4. Biliary reconstruction by choledochocholedochostomy with T-tube stent (left) or Roux-en-Y choledochojejunostomy with indwelling straight stent.

#30), one as part of a gastric devascularization for bleeding (OLT #15), and the other to facilitate ventilator weaning made difficult by diaphragmatic pressure from the large spleen (OLT #26). One adult had splenectomy for a lacerated spleen (OLT #52). The first patient had an episode of *Hemophilus influenzae* sepsis 5 months after transplantation that was treated successfully, the second patient has done well for 15 post-transplant months, and the other three patients (OLT #26, OLT #15, OLT #52) died of sepsis and liver failure in the postoperative period.

Immunosuppression and Rejection

Cyclosporine and prednisone were used as the principal regimen. Before operation, the patients received cyclosporine, 17.5 mg/kg orally (5 mg/kg intravenously if oral intake was not possible), and methylprednisolone, 20 mg/kg intravenously. After transplantation, they received cyclosporine, 5 mg/kg/day intravenously, in divided doses until oral intake was adequate, then 17 mg/kg/day orally in divided doses. There was usually a 5–7 day crossover period during which both intravenous and oral cyclosporine were given to ensure adequate blood levels. Cyclosporine levels (plasma radioimmunoassay) were followed daily and dosages adjusted to maintain a trough level of 200–300 ng/mL and for renal dysfunction. Intravenous methylprednisolone dose after operation was 10 mg/kg/day initially, tapered to 0.3

mg/kg/day by the end of the first week. Prednisone was given by mouth when oral intake resumed.

When acute rejection was suspected based on clinical findings or on abnormalities in tests of liver function or liver biopsy, an algorithmic approach was used. Intravenous methylprednisolone, 20 mg/kg, was given for 2 days. If a response was seen, the patient was returned to maintenance cyclosporine and methylprednisolone. If there was no response, a 5-day methylprednisolone recycle was begun, 30 mg/kg on the first day, then 10 mg/kg tapered to 0.3 mg/kg. If this did not reverse rejection, the patient was enrolled in a protocol to evaluate OKT3 monoclonal T-cell antibody.[16] Retransplantation was considered for failure to respond to OKT3. Responders received azathioprine, 1–2 mg/kg/day.

Virtually all patients had at least one mild rejection episode treated with a steroid pulse. Twenty-one patients refractory to these measures were treated on the OKT3 monoclonal antibody protocol, 17 with acute rejection during their initial hospitalization and four with chronic rejection who were readmitted to the hospital. Thirteen patients had a complete response with normalization of liver function, eight had a partial response, and two patients died of ongoing sepsis. Two patients eventually required retransplantation, one for hepatic artery thrombosis and one for chronic rejection. The remaining 17 grafts (76%) are currently functioning satisfactorily. Measurements of total bilirubin, SGOT, and SGPT were found to be reduced significantly after

OKT3 therapy. Survival of patients receiving OKT3 was 86%.

Percutaneous liver biopsies were performed on 114 occasions in 57 patients. Half of the biopsies showed rejection and half showed other phenomena such as ischemic injury, viral hepatitis, or cholangitis. Liver biopsy was a safe procedure: one bleeding episode requiring transfusion was the only complication. The results of biopsy data have been reported previously.[17]

Results

Postoperative Course

Average length of hospitalization for the 63 patients who survived after transplantation was 50 days (range: 18–155 days). Certain complications were seen on a recurring basis.

Seizures. Eighteen of 83 patients (22%) had grand mal seizures. In only one of these patients was a focal neurologic deficit found. This was a 2-year-old child in stage IV hepatic coma in whom postoperative sepsis developed before brain herniation and death. In the other patients, seizures were multifactorial. However, in six of 10 adults and in five of eight children, magnesium levels were below 1.6 mg/mL. Mean trough cyclosporine level of patients who had seizures was 405 ng/mL. No other significant abnormalities in electrolyte, glucose, or osmolar balance were found. Thirteen of the 18 patients survived to leave the hospital, and none had neurologic sequelae.

Pulmonary complications. Twenty-one patients (25%) required mechanical ventilation for more than 5 days after operation. Causes included limited nutritional reserve, diaphragmatic compression by abdominal viscera (both before and after transplant), and diaphragmatic paralysis. Paralysis of the right diaphragm occurred in 12 patients. This was a chest x-ray finding that was confirmed with real-time ultrasonography and is probably the result of a clamp injury to the phrenic nerve when obtaining control of the suprahepatic vena cava cuff. Transient right-sided pleural effusions occurred in 45 patients and right upper lobe atelectasis occurred in 36 patients.

Renal failure. Virtually all patients exhibited oliguria in the first 24–48 hours after transplant, and 50 (60%) had elevations of serum creatinine levels to twice the preoperative value. Of four children (OLT #19, 23, 26, 75) requiring hemodialysis because of severe oliguria with resultant fluid overload, hyperkalemia, and acidosis, all ultimately died of sepsis and organ failure (one of these children, OLT #75, had fibrinolysis as the cause

TABLE 4. *Infectious Complications in 42 of 83 Patients (51%)*

	No. of Episodes
Early	
Bacterial	34
Viral	22
Fungal (Candida)	15
Late	
Viral	7
Bacterial	10

Early = less than 2 months.
Late = greater than 2 months.

of her organ failure). Seventeen adults required hemodialysis in the perioperative period, and six died.

Infection. Patients were scrutinized closely for infectious complications. All received oral antibiotic bowel preparation (neomycin and erythromycin base), nystatin and chlortrimazole antifungal prophylaxis, and perioperative parenteral antibiotic therapy with ampicillin and cefotaxime for 72 hours. Antiviral prophylaxis (Acyclovir®) was not used. Postoperative infections occurred in 42 patients, or 51% (Table 4). Half of the patients who died had at least one infection identified. A detailed analysis of our infectious complications was the subject of another report.[18]

Hypertension. Systolic and diastolic hypertension was a frequent finding in the children. This is perhaps an effect of cyclosporine and steroids. Thirty-three children (87%) required intravenous antihypertensive therapy, and discharge medications included antihypertensives in 16 of 31 patients who left the hospital. Only eight of 33 adults were discharged requiring antihypertensives.

Survival

Of the 83 patients, 63 are alive (76%; adults 72%, children 80%). The 1- and 2-year actuarial survival rate is 73% and 73% respectively (68% and 68% in adults, 78% and 78% in children) (Fig. 5). Of 43 patients transplanted in the past year, 38 are alive (adults 88%, children 89%). Causes of the 20 deaths are shown in Table 5.

There were no operative deaths. Three late deaths were due to recurrent tumors. Three patients died in the early postoperative period; one of a ruptured splenic artery aneurysm, one of pulmonary hemorrhage and resultant respiratory failure due to an episode of primary fibrinolysis that occurred shortly after liver reperfusion, and one of ongoing bleeding after transplantation for alcoholic cirrhosis. The remaining 15 deaths occurred within 4 months of transplantation and were due to varying combinations of sepsis, organ failure, rejection, and bleeding.
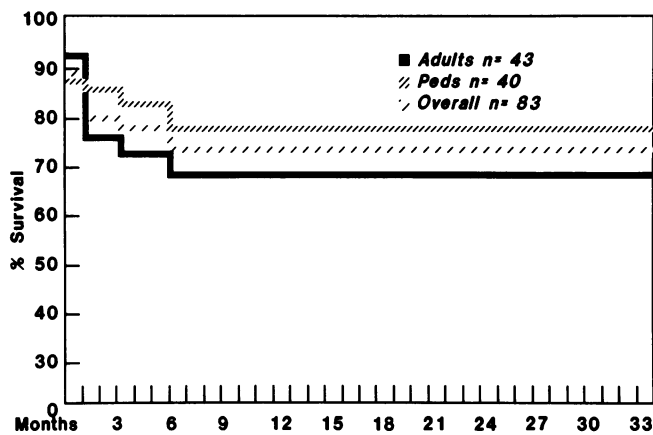
FIG. 5. Acturial survival curve of all patients undergoing liver transplantation. Computed by Kaplan-Meier method.

Of four patients who received an ABO incompatible liver, three are alive and one died. This patient (OLT #26), with blood type O, was retransplanted with a type A liver and died of sepsis and liver failure. One patient (OLT #41) with blood type A was retransplanted with a type B liver due to emergent circumstances. She had a second retransplantation with a type A liver 7 months later because of chronic rejection and is now well. The

other two patients (OLT #56 and #82), both blood type O, received type B livers and have normal liver function at 8 months and 2 months, respectively. Of 21 patients with a compatible, yet not identical, ABO match, eight patients died. The overall graft survival is significantly lower at both 1 and 2 years in ABO nonidentical matches versus ABO identical matches (Fig. 6).

Routine cytotoxic antibody testing against donor lymphocytes was performed but did not play a role in donor selection. Graft survival versus reactivity to B-cell warm, B-cell cold, and T-cell warm antibodies was evaluated. No statistical difference in survival was seen, although there was a suggestion of lower 1-year graft survival in those patients with greater than 10% T-cell warm antibodies compared with patients with less than 10%; graft survival was 50% versus 65.4%, respectively.

Retransplantation

A total of 17 retransplants were performed in 83 patients (20%). Four patients had retransplantation twice. Overall retransplant survival was seven of 13 patients (54%). Survival of retransplantation for hepatic artery thrombosis, rejection, and primary nongraft function were 100%, 57%, and 33%, respectively (Table 6).

TABLE 5. Mortality in 20 of 83 Patients

OLT #	Disease	Cause of Death	Time Post-transplant	Comment
1	Hepatic schwannoma	Recurrent tumor	4 months	
4	Hepatocellular carcinoma	Anoxic brain death	32 days	Retransplant
5	Budd-Chiari	Disseminated herpes	28 days	1st Retransplant primary nonfunction 2nd Retransplant for suspected rejection
8	Idiopathic cirrhosis	Chronic rejection/sepsis	3 months	
11	Tyrosinemia with hepatoma	Recurrent tumor	10 months	Tumor involved hepatic veins
13	Primary biliary cirrhosis	Liver failure/sepsis	12 days	
15	Primary biliary cirrhosis	Sepsis	49 days	
16	Biliary atresia	Disseminated adenovirus	17 days	Retransplanted for suspected rejection
19	Biliary atresia	Fungal sepsis/liver failure	7 weeks	
23	Biliary atresia	Fungal sepsis	25 days	Extensive previous biliary surgery (12 operations)
24	Chronic active hepatitis	Chronic rejection	2 months	Refused retransplant
26	Biliary atresia	Sepsis/liver failure	4.5 months	Retransplant/hepatic artery thrombosis
28	Chronic active hepatitis with hepatocellular carcinoma	Recurrent tumor	9.5 months	
29	Chronic active hepatitis	Fungal sepsis	27 days	Retransplant
31	Acute hepatitis A	Brain dead	10 days	Did not regain consciousness
46	Sclerosing cholangitis	Sepsis, liver failure	2.5 months	Retransplant twice for nonfunction
51	Alpha-1-antitrypsin	Ruptured splenic artery aneurysm	5 days	Normal liver function
52	Alcoholic cirrhosis	Coagulopathy/ARDS	3 days	
61	Sclerosing cholangitis	Pseudomonas pneumonia	37 days	Normal liver function
75	Tyrosinemia	Intrapulmonary hemorrhage	2 days	Primary fibrinolysis

Risk Factors

A number of pre-, intra-, and postoperative factors were assessed to determine if variables predictive of early (2 months) postoperative survival could be identified. In addition, a group of pre- and intraoperative factors were analyzed to seek a correlation with blood loss. Factors assessed included age, diagnosis of liver disease, previous operations, liver chemistries, encephalopathy, donor liver ischemia, rejection, and need for dialysis. The unpaired Student's t-test was used to compare means and chi-square analysis to compare proportions. Overall 2-month survival was 67 of 83 patients (81%). None of these factors showed statistical correlation with survival except the need for dialysis and severe rejection (requiring retransplantation). Only 11 of 21 patients (43%) of those requiring dialysis survived versus 56 of 62 patients (90%) who did not (p < 0.0005). In patients who have severe rejection, five of 11 (45%) survived versus 42 of 52 (81%) with mild rejection and 20 of 20 (100%) with moderate rejection (p < 0.01).

Age over 50 years and presence of a portacaval shunt significantly affected intraoperative blood loss (p < 0.02 and p < 0.005, respectively). Blood loss could not be correlated with diagnosis, previous abdominal surgery (including nonportacaval portasystemic shunts), or liver chemistries. Actuarial survival curves of 100 allografts are shown in Figure 7. The three curves illustrate three groups of patients according to intraoperative blood loss; group I, 1–10 units PRBC; group II, 11–30 units; group III, greater than 30 units. One-year graft survival was superior in group I versus group II (p = 0.04). Although a trend toward improved long-term survival with lower blood loss is evident, this did not reach statistical significance.

Growth and Development

The effects of liver transplantation on growth of 29 pediatric patients was assessed. Mean follow-up was 13.9 months (range: 4–33 months). Average age at the time of transplant was 5.8 years (range: 7 months to 16 years). Percentiles for weight, height, and weight-for-height were calculated before and after transplantation. Results are shown in Table 7.

Most patients exhibited normal or accelerated growth after transplant. The three patients who showed growth failure had been receiving higher than usual steroid dosages for repeated bouts of rejection. The growth velocity index (GVI), or increment of height per year, was also assessed. These results are compared with velocity standards for height based on chronologic age. Twenty-seven (93%) of patients demonstrated a GVI greater than 100 (normal value is greater than 80). GVI before
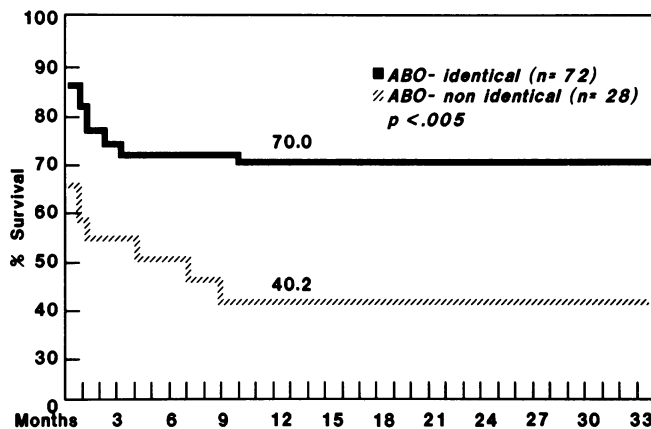

FIG. 6. Actuarial graft survival of ABO identical and ABO nonidentical donor/recipient matches. All grafts included.

transplant was 79.6 ± 20.78 versus 147.4 ± 16.36 after transplant (p < 0.01).

The effects of liver transplantation on cognitive and intellectual development are anecdotal at present. Currently we are evaluating our patients with psychomotor tests.

Through December 1, 1986, 29 adults who had transplantation have been discharged from the hospital for a minimum of 4 months follow-up. Twenty of 29 patients (70%) have returned to normal activity or returned to work. Nine patients have improved activity compared with pretransplant status. No discharged patients have demonstrated a regression in functional capability.

Fiscal considerations

The financial burden of the procedure falls to commercial insurance carriers, state-funded medical pro-

TABLE 6. Retransplantation

OLT #	Indication	Outcome
4	Rejection	Dead
5	#1—Primary nongraft function	Dead
	#2—Presumed rejection*	
16	Presumed rejection*	Dead
21	Rejection	Alive
26	Rejection	Dead
29	Primary nongraft function	Dead
36	#1—Arterial thrombosis	Alive
	#2—Arterial thrombosis	
41	#1—Rejection (acute)	Alive
	#2—Rejection (chronic)	
46	#1—Rejection	Dead
	#2—Rejection	
54	Primary nongraft function	Alive
78	Rejection	Alive
79	Hepatic artery thrombosis	Alive
80	Rejection	Alive

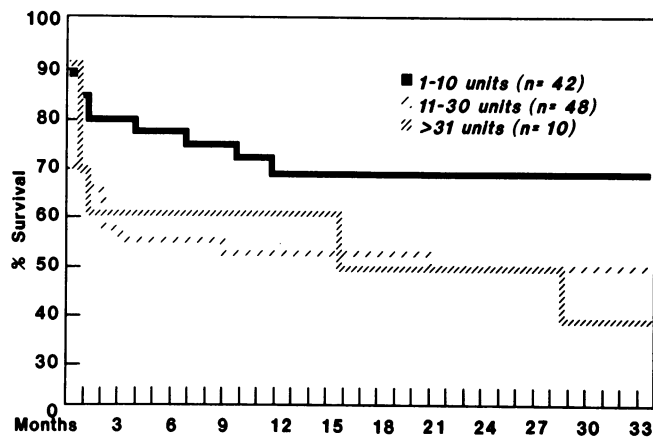* Pathologic findings revealed overwhelming viral infection and not rejection.

FIG. 7. Acturial graft survival comparing differences in operative blood loss.

grams, or self-payment. At the UCLA Medical Center, guarantee of payment is required before a patient is placed on the active list. Adherence to this hospital policy is mandatory to maintain solvency. Hospital charge for pediatric patients has ranged from $46,000 to $637,000, with a median of $109,000; hospital charge for adult patients has ranged from $66,000 to $609,000, with a median of $138,000. Mean charges for children and adults have been $164,000 and $175,000, respectively.

Discussion

After the National Institutes of Health Consensus Conference on liver transplantation concluded that the procedure should be considered a therapeutic modality in selected patients with end-stage liver disease, a number of centers either expressed intent or initiated programs in OLT. UCLA began its preparation for such a program 6 months before the Consensus Conference. This program was built on a foundation of basic laboratory preparation and cautious early clinical efforts. Expansion was gradual but steady, with 20 OLTs performed in 1984, 38 in 1985, and 53 in 1986. The 100th transplant occurred in the 33rd month of the program.

The protocols for both pediatric and adult patient

TABLE 7. Growth Data in 29 Pediatric Patients

	Percentile Curves After OLT					
	Weight		Height		Weight for Height	
	N	(%)	N	(%)	N	(%)
Accelerated	25	86	17	59	23	80
No change	4	14	11	38	3	10
Loss	0		1	3	2	10

evaluation and selection have been detailed.[6,7] As our program has evolved, an increasing number of patients are being referred for consideration. The primary reason for this phenomenon is that OLT is now recognized more frequently by both the gastroenterologist and primary care physician as the definitive treatment for patients with chronic liver disease. Rarely is a patient categorically rejected from consideration until a full evaluation is performed. In many cases, patients who might be judged as noncandidates at first presentation have been accepted and transplanted. With improving results, absolute contraindications are decreasing. Although age greater than 55 years was considered a relative contraindication, we and other groups have transplanted patients in the seventh and eighth decades who have returned to productive lifestyles. A recent report[19] suggests no difference in survival of patients over 50 years of age. Although the numbers are small, our results indicate a poorer survival in patients over 50 years of age because of greater blood loss in this group. Our current policy is not to refuse candidacy on the basis of age alone if a thorough cardiopulmonary and renal assessment does not disclose a specific physiologic contraindication.

"Unresectable hepatic malignancy" is one of the most problematic indications for transplantation. Reports from other centers[20] and ours[21] have indicated a 50–70% recurrence rate within 2 years. Moreover, even the most thorough preoperative assessment may not discern the presence of extrahepatic spread, which would preclude a curative operation with total liver replacement. Despite these pitfalls, we have offered transplantation to carefully selected patients with malignancy. Of seven patients transplanted for this indication, five are alive and free of disease from 5 months to 3 years after transplant. In all patients, the quality of life after transplant has offset the uncertainty of tumor recurrence. Adjuvant chemotherapy has been given before and after operation in some patients. Protocols based on increasing experience will be needed to define specific indications for liver transplantation in patients with malignancy.

Liver transplantation in the adult population for chronic active hepatitis, primary biliary cirrhosis, and sclerosing cholangitis is becoming well accepted with patients with end-stage disease. However, as has been pointed out by Neuberger et al.,[22] the timing of OLT is perhaps one of the most crucial issues in the evolution of this treatment.

In our series, we have seen no significant differences in survival after OLT among adults with chronic active hepatitis, sclerosing cholangitis, or primary biliary cirrhosis. This is in contrast to the experience of Starzl et al.,[23] in which patients with cirrhosis secondary to chronic active hepatitis fared worse. The longer followup in the Pittsburgh series, with recurrence of chronic

active hepatitis in some patients, may contribute to this difference. In a recent report, Demetris et al.[24] found a 100% recurrence of antigen positivity after 2 months in patients transplanted for hepatitis B. In our series, recurrent B antigen positivity developed in 50% of patients despite the administration of hyperimmune anti–B-gamma globulin during the anhepatic phase. However, no patients thus far have had histologic evidence of recurrence of chronic active hepatitis up to a 2-year follow-up.

The results of liver transplantation in children have been generally superior to those for adults.[23] Not only is the pediatric patient more resilient to the rigors of transplantation, but there appears to be a lack of influence of the primary disease on the eventual outcome after OLT. This is evident both in children with biliary atresia and with inborn errors of metabolism. Actuarial survival in each group at 2 years is close to 80%. Because of the favorable statistics, it is rare to reject a child for transplantation despite substantial preoperative risk factors. In many cases, the transplant procedure will be technically much more demanding after multiple attempts at portoenterostomy revision, yet this has not proved to be a significant deterrent to success.

It is accepted that for OLT to be successful, the operation must be technically perfect. This assumes a well-preserved and immediately functional graft, an expeditious and blood-sparing recipient hepatectomy, and a precise anastomotic reconstruction of vascular and biliary components. Our techniques in these phases of the operation have been based on those described by Starzl et al.,[9] modified and adapted to our own team.[11] Flexibility in response to changing demands of the operative circumstances is essential to the conduct of the procedure. This is illustrated by our approach to arterial reconstruction, in which five different methods have been used. Using this adaptable strategy, we have achieved a 95% patency rate, which is comparable to the Pittsburgh series (93%).[25] There have been no arterial thromboses in our adult series. Our methods of biliary reconstruction have been choledochocholedochostomy or Roux-en-Y choledochojejunostomy. The complication rate has been 24%, but no complications have resulted in death of any patient. This figure, although higher, is similar to the 13.2% complication rate reported by Lerut and colleagues[26] in 393 grafts.

The use of cyclosporine has been the single most important factor in the improved survival for OLT. In the early series (1963–1979) reported by Starzl et al.,[3] less than one third of patients lived 1 year. Now, it is routine for 1-year survival to be twice that figure. An important adjuvant to the cyclosporine/steroid immunosuppression regimen has been the introduction of OKT3 monoclonal antibody to treat acute allograft rejection.[27] Our

experience has mirrored the multi-institutional trial[28] in that all of our patients have had either a partial or complete reversal of rejection. The results of OKT3 have been so favorable and its lack of nephrotoxicity is so appealing that a trial for prophylactic use has been initiated.

An actuarial survival rate of 73% at 1 and 2 years after OLT in our series has been comparable with outcomes reported by others.[23,29,30] Also, the pediatric population has fared better than the adults, with a 2-year actuarial survival rate of 78% versus 68% for adults. It appears that the 9-month survival is most important, since late attrition after this time is significantly decreased. Factors that influence late mortality include recurrence of primary disease, chronic rejection, and late infectious complications. In our patients, recurrent tumor and infection were the predominant causes of late death.

The causes and predictors of early mortality after OLT have been studied extensively by Shaw et al.[31] In a similar analysis of our patients, only need for dialysis or severe rejection predicted early mortality. However, intraoperative blood loss that exceeded 10 units resulted in a statistically lower 1-year survival than a blood loss of less than 10 units. No difference was found in blood loss from 10–30 units or greater than 30 units. This is in contrast to the report of Shaw et al.[31] that demonstrated superior survival in the group requiring 0–35 units versus 36–100 units versus greater than 100 units, respectively. Our data support the observation that of all factors studied, low intraoperative blood loss correlates most strongly with early survival.

Although recent experimental data by Knechtle and co-workers[32] demonstrate the occurrence of hyperacute hepatic allograft rejection in sensitized recipients, we have not observed graft survival to be decreased significantly in patients with preformed cytotoxic antibodies. However, in our analysis of graft survival, nonidentical ABO-matched organs faired worse than identically matched ones. A much larger analysis of this has been presented by Gordon et al.[33] with similar results.

Despite the major role that cyclosporine has played in the improvement of patient survival after OLT, there is the continued threat, particularly in the first 3 months, of irreparable allograft dysfunction. Retransplantation is the only hope for these patients. We have maintained an aggressive posture in this regard, with 17 of our first 100 cases being retransplants (20%). Best results are obtained if the indication for retransplantation is arterial thrombosis or early acute refractory rejection. Primary graft nonfunction generally has a poorer prognosis both in our series and that of others.[34]

Extrahepatic postoperative complications after OLT are expected and must be anticipated. An operative endeavor of such magnitude performed on a compromised

host who is then immunosuppressed cannot be expected to be free of problems. Infection, renal failure, pulmonary, gastrointestinal, and neurologic complications occurred singly or in combination in approximately 60% of patients in this series. Notably absent, except in terminal patients, were cardiac complications such as arrhythmias, congestive heart failure, or myocardial infarction. Neurologic complications were unexpectedly frequent with grand mal seizures occurring in 22% of patients. In most patients, seizures were associated with low magnesium and elevated cyclosporine levels. The relationship between hypomagnesemia and cyclosporine-induced neurotoxicity has been previously reported by Thompson and co-workers.[35] None of our patients exhibiting seizures had permanent neurologic deficits.

Return of functional status in adults and growth and development in children are important parameters in the ultimate assessment of the benefits of OLT. Seventy per cent of our discharged adults have returned to gainful employment and virtually complete rehabilitation to their premorbid condition. The remainder have shown significant improvement, without a single patient demonstrating regression. More objective criteria are available for evaluation of the success of OLT in pediatric patients. When growth and development were monitored, 59–86% of our children demonstrated acceleration of weight, height, or weight-for-height ratio.[36] Gartner et al.[37] analyzed a similar series of 22 patients and found accelerated growth in 11, normal growth in 10, and growth failure in only one.

Liver transplantation is a procedure in evolution. Through the principal pioneering efforts of Starzl et al.,[1] this therapy may now be offered to patients in a logistical scope that was barely thinkable less than one decade ago. The cost of this procedure is high. However, the operation has now provided successful treatment and cure of diseases heretofore considered dismal or hopeless. As a consequence of transplant-related research, our basic understanding of hepatobiliary physiology, pathology, and surgery have expanded dramatically. Fertile areas for future study include preservation and protection of the ischemic liver, the molecular basis of acute and chronic rejection, multiple organ transplantation, and new immunosuppressive agents.

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DISCUSSION

DR. JOHN S. NAJARIAN (Minneapolis, Minnesota): I would like to congratulate Ron Busuttil on an excellent paper, which is both beauti-fully illustrated and presented. In addition, this paper chronicles the establishment of a new liver transplant unit, and I believe that similar results are now being achieved at other units.

I had the privilege of reading this manuscript before, and I have a few comments and a few questions.

Dr. Busuttil has noted a high incidence of rejection. He is quoted as stating that 100% of the patients had at least one rejection episode and several had more.

(Slide) At this point in our own program, we have carefully followed a program that was started in Minnesota using triple therapy, as we reported 3 years ago in our kidney transplantation program. You can see that with triple therapy, which is azathioprine, prednisone, and cyclosporine, we had results with our HLA-matched relatives of 100% over 1 year, 95% with mismatched-related donors, and approximately 85% using cadaver kidneys.

(Slide) If we then turned our attention to cardiac transplantation, again using triple therapy, we have achieved about 95% graft survival in 73 cardiac transplants over the past 2 years.

(Slide) Finally, with liver transplantation we now are looking at approximately 76% patient survival, which is similar to what Dr. Bu-suttil showed. However, our retransplant rate is only 3%, not 20%, as presented, so that basically our survival statistics here not only repre-sent patients but they represent graft survival as well. Therefore, we believe that triple therapy can save some of the high retransplantation rates, and as was pointed out by Dr. Busuttil, those patients fare less well, about 54%, when they require retransplantation.

If we look at our statistics in liver transplantation, we see that in the very young, under the age of 10, we do well (85%), and between 10 and 18 years of age, we also have excellent survival statistics. However, our adults over the age of 19 have a graft survival of around 70%, results that are not too dissimilar from those shown by Dr. Busuttil.

The second point concerns arterial problems. We found that the only arterial problems we observed are primarily seen in our pediatric population, in which we noted five thromboses. All occurred when we used an aortic-to-aortic anastomosis for a total rate of about 8%; there-fore, we believe that this type of arterial revascularization should be avoided if possible. Currently, we no longer do aortic-to-aortic anasto-moses.

I would like to ask a few questions. There was one case that came up in the manuscript in which a splenectomy was done and gastric devas-cularization was performed for esophageal bleeding. Was this done because of an occlusion of the portal vein, and if so, how was the diagnosis made?

Secondly, Dr. Busuttil reported an infection rate of 51%. This is about right, but the concern that I had is if this rate is any higher in the group of steroid-resistant rejections that required OKT3 or was it simi-lar in both groups? In other words, was it possible that OKT3 added to the higher infection rate compared with those patients who just re-ceived steroids alone?

The third question concerns blood loss. Dr. Busuttil reported that there was no good correlation of blood loss and mortality noted. Under 10 units there was a good correlation with survival; from 19 to 30 units, Dr. Busuttil did not have a good correlation; above 30 units there was no correlation. My question is since we found a very close correlation with blood loss and survival statistics, are your results affected primar-ily by pediatric cases? Certainly, a 10-unit blood loss in a small infant is quite different than a 10-unit blood loss in an adult.

My final two questions are: virtually all of the patients had oliguria, and from that group, 60% had a doubling of their serum creatinine level. Dialysis was required in 25% and of 21 patients, 10 died who required dialysis. Six of 17 adults died requiring dialysis. We do not use a veno-veno shunt. We have not found it necessary in any of our patients, and we wondered if with the lower renal dysfunction rate, which is supposed to be one of the advantages of the veno-veno shunt, why do you think you had this high rate of oliguria and eventually renal failure? Is there some problem here that we do not recognize, because certainly, without the use of the veno-veno shunt, we have had only 6% of our patients require dialysis.

We believe that it is important to keep the operation short. Our mean operative time is 6 hours or less, and we believe that elimination of the use of the veno-veno shunt is helpful in that regard. I would be interested in Ron's comments.

Finally, Dr. Busuttil reported that 22% of his patients had grand mal seizures. This occurred in 18 patients. Five of these patients died. We saw this complication in only 5% of our patients.

We started using Decadron before operation, during operation, and for the next 72 hours. Since that time we have not had a single episode of seizures. Have you tried using Decadron, or what have you done to try to decrease the number of seizures in your patients?

DR. G. KLINTMALM (Dallas, Texas): I truly enjoyed this paper very much. The results that have been achieved at UCLA are absolutely staggering.

At Baylor in Dallas we have our own program since 2 years back, and we have performed about 95 transplants with a survival rate of 85%. I have one comment and one question.

We have routinely measured the hepatic and arterial blood flows in all our patients, and as a consequence of the findings, during the transplant surgery we have revascularized three arteries and one portal vein. I believe that this technique may help to prevent some of the unexpected problems such as vascular thrombosis we may find after operation.

Despite this, we have found three arterial thromboses, and they have been caused twice by acute angulation of the artery and once by a recipient artery intimal dissection.

The three patients were rushed to surgery where revascularization including thrombectomy and arterial reconstruction was carried out. The outcome of these patients was satisfactory. I propose that the concept that we have had up to this time that we should go to retrans-plantation in hepatoarterial thrombosis is not valid any more.

My question is the same as Dr. Najarian's. You have an extremely