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PROGRESS ARTICLE

Fifteen Years of Clinical Liver Transplantation

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Few undertakings have passed through more identifiable steps from laboratory inception to clinical application than has liver transplantation. The placement of auxiliary whole livers in dogs was described in 1955 by Welch,[1] and within 5 yr, attempts at total host hepatectomy and orthotopic canine liver transplantation (liver replacement in the normal location) were successful at both Harvard[2,3] and Northwestern University[4,5]; technical problems and the features of rejection in untreated animals were delineated.[2-7] Under immunosuppression with azathioprine[8] or antilymphocyte serum (ALS) and its globulin derivative (ALG),[9] chronic survival was achieved after liver replacement in a number of mongrel dogs,[7-9] of which one lived for 11.66 yr.[10]

In pigs, it was soon found that rejection of hepatic homografts was relatively mild in comparison with that in dogs and that many orthotopic porcine grafts supported life for long times, even though immunosuppressive treatment was not provided.[7,11-13] Hundreds of experimental studies in various species have since been published, clarifying various questions, filling in innumerable details, and evaluating alternative means to prevent rejection.

The purpose of this article, however, is not to review experimental work. Attention is directed instead to the clinical trials that have been made with increasing frequency and success since the first human transplantation in 1963.[14] Orthotopic liver transplantation has seemed to be the most promising procedure, but mention is also made in the following remarks of provision of an extra liver in an ectopic location (auxiliary hepatic transplantation). Auxiliary liver transplantation was first performed clinically by Absolon et al.[15]

Orthotopic Transplantation

Liver replacement on a large scale has been carried out in the United States only at the University of Colorado. From March 1963, to December 1977, we treated 141 patients with liver replacement. Follow-ups are available to January 1979. In the meanwhile, a major English program was established by Calne and Williams, working between the University Hospital at Cambridge and King's College Hospital in London.[16,17] Between May 1968, and December 1977, they treated 74 patients with orthotopic liver transplantations and have generously supplied to us an unpublished report of these cases brought up to May 1978.[18]

The following remarks are based largely on the 215 cases of the two foregoing series. Other trials have been made, of which only a minority have appeared in the literature[19-31] as case reports or small series. The number of unreported cases can be appreciated by the fact that 250 orthotopic liver transplantations had already been recorded 1.5 yr ago in the July 1977 issue of the now obsolete Newsletter of the Organ Transplantation Registry of the American College of Surgeons. Although important, the isolated and sporadic experiences have been hard to compile and to follow up accurately for the purposes of this review, which are several: (a) to recount the early experience with liver replacement; (b) to assess the causes of the overwhelming acute mortality in these early cases; (c) to describe the impact of

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management adjustments upon the subsequent results; (d) to catalogue the fate of chronic survivors; (e) to describe changing or controversial views about indications for this operation; (f) to assess the quality of life in long-term survivors; and (g) to look at the prospects for future improvements.

In reviewing the evolution of the field, results are given at the outset, because our opinions about management, indications for operation, and the need for alternative treatment programs have changed throughout the years as increasing experience was acquired. In England, viewpoints also have shifted about several aspects of this complex undertaking.

The Early Experience

In Colorado, 111 consecutive patients were treated with orthotopic liver transplantation between March 1963 and July 1976. Of these, only 31 (28%) survived for as long as 1 yr (Table 1). The rate of chronic survival improved only slightly during this time. The first 25 recipients, who formed the basis of a monograph on liver transplantation,[7] included only five 1-yr survivors (20%). The next group of 25 contained six (24%), and the group after that had eight (32%). There were 12 (33%) 1-yr survivors among the 36 patients, beginning with OT (orthotopic transplant) 76 and ending at OT 111. The subsequent fate of the 31 1-yr survivors from our first 111 cases is considered below.

The Cambridge-King's College team headed by Calne and Williams also had initially discouraging early results. Among their first 35 recipients, there were only three 1-yr survivors, of whom one lived for more than 5 yr.[18]

Reasons for Acute Mortality

In late 1975 and early 1976, an exhaustive review was undertaken to determine the reasons for the high acute mortality at our center. The reasons for failure or success in every case were retrospectively examined. The central findings[32] changed our attitudes about the management of subsequent cases.

One expected cause of failure was uncontrolled acute rejection. However, acute rejection was the primary reason for death in less than 20% of the cases. Similarly, chronic rejection, which is typified by occlusive arterial disease and parenchymal fibrosis of the homograft, accounted for only a few failures within the 1st yr.

The main causes of the exorbitant acute mortality up to that time were technical or mechanical.[32] These included thrombosis of the homograft blood supply, the use of grafts damaged by ischemia, operative hemorrhage, intraoperative cerebral air embolization originating in the homograft (see below), and most importantly, complications from biliary duct reconstruction. In the English series, as in our own, the role of technical and mechanical problems was also recognized.[17,18] At the beginning of both the Colorado and English series, grafts damaged by warm ischemia were used. With acceptance of brain death, first in the United States and later in England, the specter of transplanting dead organs was almost eliminated, because organs could be removed from heart-beating cadavers and cooled immediately. However, even recently, we have transplanted hopelessly damaged organs taken from apparently good donors. There is at present no reliable way to prevent such tragedies by any practical test for homograft viability.

The special problem of biliary reconstruction. Realization that the biliary tract was the Achilles' heel of liver transplantation prompted major reforms both at our center and in England. Until 1976, we commonly performed cholecystoduodenostomy (Figure 1*A*). Although the operation was simple, obstruction (Figure 2) or bile fistula formation occurred in 30% of the first 93 patients, almost always leading to death.[33,34] Furthermore, homografts seemingly were subjected to repeated bacterial contamination with resulting cholangitis and consequent systemic infection.[7,35,36] If cholecystoduodenostomy was the first reconstruction and if a secondary operation became necessary, there was a high incidence of subsequent duodenal fistula.[34] Even worse, many of the biliary tract problems were not diagnosed until autopsy.

Table 1. Survival in the Early and Late Phases of the Colorado Experience (Follow-up to January 1979)

	Total	Lived > 1 yr	Alive now
Series I (March 1963–July 1976)	111[a]	31 (28%)	14 (after 3–9 yr)[b]
Series II (August 1976–December 1977)	30[c]	15 (50%)	13 (after 1–2.5 yr)[d]

[a] For patients < 18 yr old, the 1-yr survival was 21/61 (34%). For adults, survival was 10/50 (20%).
[b] The 17 late deaths were after 1–6 yr.
[c] For patients < 18 yr old, the 1-yr survival was 8/13 (62%). For adults, 1-yr survival was 7/17 (41%).
[d] One late death was at 23 mo, and the other at 16.5 mo.

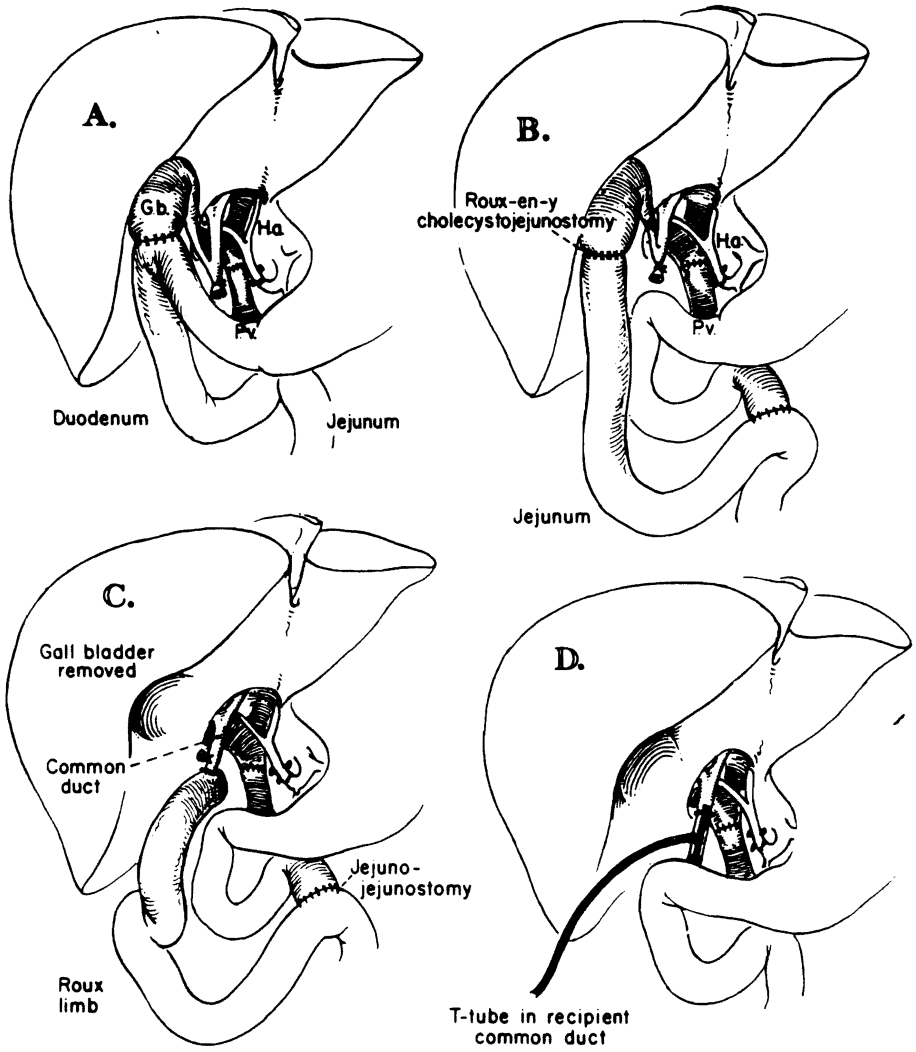

Figure 1. Techniques of biliary duct reconstruction used for most of the transplantation recipients in the Colorado series. *A.* Cholecystoduodenostomy. This operation is no longer performed. *B.* Cholecystojejunostomy. *C.* Choledochojejunostomy after removal of gallbladder. *D.* Choledochocholedochostomy. Note that the T-tube is placed, if possible, in recipient common duct. (By permission of SURGERY, GYNECOLOGY & OBSTETRICS 142:487, 1976.)

We now believe that the ideal biliary reconstruction is choledochocholedochostomy using a T-tube stent (Figure 1*D*). After operation, the T-tube has been left in place as briefly as 1 mo to as long as 2 yr. The ability to obtain T-tube cholangiograms postoperatively as part of the work-up if jaundice reappears has been a great advantage in designing management. After the T-tube is removed, periodic retrograde cholangiography via the duodenum (Figure 3) is planned for such recipients.

Choledochocholedochostomy often is not feasible, as, for example, in children with biliary atresia. As an alternative we perform cholecystojejunostomy (Figure 1*B*) or choledochojejunostomy (Figure 1*C*) to a Roux limb of jejunum. The advantage of cholecystojejunostomy is that a large caliber anastomosis is possible, even using pediatric livers. No stenting or drainage is necessary. The disadvantage is that obstruction of the cystic duct (Figure 2) has necessitated reoperation and conversion to choledochojejunostomy (Figure 1*B* to *C*) in almost one-third of the cases. In Figure 4 is shown a transhepatic cholangiogram of a patient who had undergone conversion from cholecystojejunostomy to choledochojejunostomy. In immunosuppressed patients, the initial construction of the Roux limb has carried an intrinsic risk in that perforations of the Roux limb itself or the jejunojejunostomy below it occurred in 8 patients among the first 141.[37] Seven of the 8 patients died from this complication.

Calne and his associates have advocated a different surgical approach.[38] With Calne's technique, the common duct and gallbladder are connected together into a common chamber, and a second anastomosis of the gallbladder fundus is made to the recipient common duct (or sometimes to a Roux

Figure 2. Transhepatic cholangiogram 4 yr after liver transplantation for alcoholic cirrhosis (OT 82). Cholecystoduodenostomy was used for biliary drainage. The obstruction was at the cystic duct, which cannot be seen well. The intrahepatic ducts are almost normal, but there is a definite dilatation of the common duct including the blind sac distal to the cystic duct entrance (*arrow*). The patient presented with fever, jaundice, and gram negative bacteremia. The diagnosis was cholangitis. Cholecystoduodenostomy was converted to Roux-Y choledochojejunostomy.

limb).[38] The cholecystocholedochostomy is stented with a T-tube, enabling the biliary system to be frequently studied or irrigated. The English workers have been satisfied with this procedure and with it biliary tract complications have been reduced.[18] Because the same thing has been accomplished in our later series using more conventional procedures, experience alone will tell if Calne's somewhat more complicated reconstruction is necessary or desirable.

Other technical improvements. By 1976, other refinements besides standardization of biliary tract reconstruction had been instituted. Frequent use was made of microsurgical techniques for vascular and sometimes for biliary duct anastomoses. This was particularly important in children. Methods that permitted longer storage were developed in the laboratory and clinical trials were started. The Cambridge-King's College team has used a plasma solution for cold infusion of the homografts,[39,40] and we have employed an electrolyte (Collins) solution with a composition similar to that found in cells.[41] In dogs, the two approaches yield comparable results[41] and permit safe preservation for up to 12 hr. The same applies in humans and has permitted the shipment of livers from city to city. McMaster et al.[40] have cautioned that ischemia and/or bile left within the ducts may cause autolysis and set the stage for delayed mucosal sloughing and cast formation. It has been clear for a long time that thorough washing

Figure 3. Transduodenal cholangiogram in an alcoholic patient (OT 102) who received a liver 2 yr ago with choledochocholedochostomy. The T-tube was left in for 1 yr, and the cholangiogram was obtained 6 mo after its removal.

of the biliary tree is necessary at the time of organ removal from the donor.[4]

In patients with cirrhosis and end-stage liver disease, the combination of portal venous hypertension plus coagulation deficiencies can create a surgical nightmare. Techniques to reduce the blood loss have been described.[32] At times, devascularization of the native liver and its emergency removal offer the only chance of survival. Once a well-functioning graft is in place, portal hypertension is immediately alleviated and normal clotting slowly develops. In spite of extensive experience, however, the loss of as much as 50 units of blood still occasionally occurs.

Air embolus. Neurologic invalidism was seen in 9 of the first 48 adult patients who underwent liver replacement. The complications occurred during or shortly after operation. Several of these patients awakened from anesthesia but then had a secondary decrease in consciousness, seizures, and other crippling abnormalities. At autopsy, from a few days to 2 mo later,[42] neuropathologic abnormalities consisted of multifocal areas of infarction in cerebral cortex and basal ganglia in 5 patients, central pontine myelinolysis in 5 (often more extensive than usually reported with liver disease), Wernicke's encephalopathy in 3, glial nodules in 2, and fungal abscesses in 1. Alzheimer II astrocytosis was found in all brains available for retrospective study. Most of the foregoing abnormalities were clearly associated with preexisting liver disease. It ultimately was realized, however, that air emboli from the homografts were responsible for some if not all of the focal infarctions. The ease with which air passed to the systemic circulation was explicable by the right to left venous-arterial shunts that are common in chronic liver disease. Air released into the pulmonary circulation apparently passed through these collaterals to the systemic circulation, including the arterial supply to the brain.

With the delineation of this cause for the neurologic complications, preventive measures were instituted.[42] During revascularization of the liver, electrolyte solution was slowly infused through a portal vein cannula. While the vena caval anastomoses

were carried out, air bubbles could escape from the graft vessels before blood supply was restored. Since instituting this simple preventive measure, no further such difficulty has been encountered.

Diagnostic pitfalls. Until the past 2 or 3 yr, postoperative hepatic dysfunction was too readily ascribed to rejection when, in fact, biliary obstruction and/or cholangitis were frequently responsible. Even in the absence of biliary tract problems, rejection may not be responsible. Hepatitis caused by HBsAg, CMV, and other viruses have been observed, as well as drug toxicity. At the present time, the development of jaundice after transplantation is a signal for cholangiography and usually for liver biopsy. The histopathologic findings in the biopsy tissue may not provide an unequivocal answer. Thus, the diagnosis of rejection must be made by exclusion.

Subsequent Experience

In July 1976, a new series was begun, which was completed in December 1977. The operative, diagnostic, and management improvements described above were used. Of the 30 consecutive recipients, 13 are alive after 1–2.5 yr (Table 1). A fourteenth recipient, a child, died at 23 mo of systemic chicken pox and bacterial infection. A fifteenth patient died after 16.5 mo, with chronic rejection and portal vein thrombosis. Thus, the 1-yr survival in this most recent experience was 50% (Table 1). Compared with the first series, the 1-yr survival of children has essentially doubled (34% to 62%), as has the survival of the adults (20% to 41%).

Early Deaths in Second Series

It is pertinent to examine the reasons for the 15 failures within the 1st yr in the latest Colorado series (Table 2). Technical and mechanical problems were still common in spite of efforts to prevent these. Some were due to preexisting pathology. Thrombosed portal veins were found in two recipients at the time of transplantation, making complete revascularization impossible; the patients died within a few days of liver failure.

There were five enteric fistulas (two small bowel, one colonic, one biliary, and one from the hepatic artery into the jejunum). Three of the 5 patients, including 1 who required emergency colectomy, had sclerosing cholangitis and a history of ulcerative colitis. An additional patient received a liver homograft so large that the abdominal incision could not be closed; he was never able to breathe. A child with congenital heart disease who had a satisfactory liver transplantation died 9 days later of heart failure and pulmonary edema. Thus, the acceptance of high-risk or even hopeless candidates contributed to some of the failures.

The policy of liberal use of liver biopsy has permitted a better assessment of the role of rejection in the complex postoperative events. In our early cases, only the autopsy livers were available for study, and these organs usually had few signs of rejection. On this basis, we speculated that systemic overtreatment with immunosuppressive agents, especially prednisone, might have been responsible for unnecessary deaths.[17,18,32,43]

This view undoubtedly requires some revision, in light of our recent experience. As before, irreversible rejection in the recent series was not common, but definite rejection was frequently seen in the biopsies and was highly variable in degree according to the timing of the biopsy (see case OT 134, Table 2). Yet, many of the homografts at autopsy were free of rejection. Intensification of immunosuppression was a justified action to save these livers, but a lethal one if there were any other kind of problem, including a technical or mechanical one. Thus, the tendency to ascribe most of the high mortality after liver transplantation to factors other than rejection[17,18,32,43] is probably not completely correct. The possibilities for more effective immunosuppression are discussed below, and it is upon such advances that the next major jump in survival will undoubtedly depend.

The gradual increase in survival with increased experience has not been unique in Colorado. A similar improvement has occurred in the Cambridge-King's College units. Among the 39 patients treated there in 1976 and 1977, 9 had lived more than 1 yr as of May 1978, and 6 more were alive with shorter follow-ups of 1 wk to 10 mo.[18]

Deaths After One Year

As mentioned above, 46 liver recipients have lived for at least 1 yr after having received orthotopic liver grafts in Colorado. Nineteen of these 46 patients subsequently died (Table 3). Their total survival averaged more than 3 yr, with the range of 12.5 mo to 6 yr.

Seven patients each received two liver transplants (Table 3). When retransplantation was attempted because of liver failure 1 yr or more after the original grafting, 4 of 5 patients died within the 2 ensuing months from infections and from technical complications such as enteric fistulas. However, 1 patient, whose first graft failed after 23 mo, lived for another 13 mo on a second liver. The record was only slightly more encouraging with early retransplantation. Two children whose primary grafts failed after 5 and 9 wk, respectively, lived for 11 and 15 mo after

Figure 4. Transhepatic cholangiogram 14 mo postoperative in a 12-yr-old patient (OT 126) who received an orthotopic liver transplant 15 mo previously. Biliary reconstruction initially was with cholecystojejunostomy (see Figure 1*B*). Twelve months postoperatively, this was converted to choledochojejunostomy (see Figure 1C). The cholecochojejunal anastomosis is marked with an *arrow*. *J* = jejunum.

retransplantation (OT 16 and 98, Table 3). Chronic rejection, with its characteristic occlusive arterial lesions and parenchymal fibrosis, was diagnosed in five of the seven primary grafts that were replaced with second grafts (Table 3).

With or without retransplantation, the causes of death were invariably multiple, and in almost all cases infection supervened terminally. However, one or two most important underlying factors were usually identifiable (Table 3). Liver failure was the most common (11 examples), usually caused by chronic rejection (Table 3). Four patients, however, died from complications of treated or untreated biliary obstruction, and in 2 more, hepatitis was responsible (Table 3).

Overwhelming systemic infections as an isolated complication (two examples) and recurrent cancer (two examples) were responsible for other deaths after 1 yr.

Generally speaking, the patients who died after 12 mo were already in trouble at the 1-yr mark. Only 7 were thought to be satisfactory or excellent at that time. The other 12 were receiving too much prednisone to have a good long-term outlook. Doses in individual cases are given in Table 3. In the entire group of 19, the prednisone doses at 1 yr averaged 0.74 mg/kg/day. Eleven of the 19 patients were jaundiced at 1 yr; their bilirubin values ranged from 2 to 40 mg% (Table 3). The average bilirubin in all 19 patients was 9.1 mg%.

Late mortality has also been encountered in the Cambridge-King's College experience.[18] By May 1978, Calne and Williams had followed 12 patients for at least 1 yr, of whom 6 subsequently died. The latest of the deaths was at 5.3 yr and was caused by biliary obstruction and cholangitis.

The Quality of Life

Patients who died after one year. The generally poor course of the 19 patients who died after 1 yr was reflected in the length of their hospital-

Table 2. Main Cause of Death Within First Year of 15 Patients in the Recent Colorado Series of 30

OT number and Age (yr)	Days survival	Original disease	Pathology of homografts	Main cause of death
118 (24)	12 (10 + 2)[a]	Alpha$_1$-antitrypsin deficiency	1. Central and midzonal necrosis 2. Massive necrosis	Recipient portal vein thrombosed, grafts could not be vascularized; liver failure; variceal bleeding
119 (23)	33	Sclerosing cholangitis; ulcerative colitis	Biliary obstruction, intrahepatic sludge formation, and cholangitis; no rejection	Obstructed cholecystojejunostomy converted to choledochojejunostomy; subsequent rupture of mycotic hepatic artery aneurysm into jejunum
121 (32)	163	Hepatoma	HBsAg hepatitis and diffuse interstitial fibrosis; chronic rejection with arterial narrowing and bile ductule loss	Brain injury after falling from bed; inanition and pneumonitis thereafter
122 (28)	131	Chronic aggressive hepatitis	Chronic rejection	Pneumococcal meningitis; liver failure; liver abscesses
123 (40)	22	Chronic aggressive hepatitis	Nonspecific centrilobular necrosis; no rejection	Liver too large to permit abdominal wound closure; pneumonitis; bone marrow depression
124 (41)	203	Chronic aggressive hepatitis	Centrilobular and midzonal necrosis; early chronic rejection	Liver failure; portal vein thrombosis; bleeding peptic ulcer; bleeding varices
127 (5.5)	9	? Alpha$_1$-antitrypsin deficiency (PIMZ)	Centrilobular necrosis; no rejection	Intractable heart failure and pulmonary edema; congenital heart disease; hepatic artery thrombosis
128 (3.5)	174	Biliary atresia	Cellular rejection	Hypertension, heart failure, pneumonitis, steroid toxicity was price of graft function
129 (14)	175	Chronic aggressive hepatitis of hepatic remnant after resection	Chronic rejection	Small intestinal injury led to uncontrolled fistula; eventual liver failure
130 (35)	40	Alcoholic cirrhosis	Centrilobular cholestasis; ? rejection	Leak choledochocholedochostomy; disseminated candidiasis
131 (46)	2	Alcoholic cirrhosis	Widespread necrosis	Recipient portal vein thrombosed and recannulized; clotted postop; liver failure and variceal hemorrhage
132 (1)	166	Biliary atresia	Centrilobular cholestasis; hepatocyte atrophy and fatty infiltration; no rejection	Steroid toxicity was price of graft function; pneumonitis
134 (1.5)	110 (69 + 41)[a]	Type IV glycogen storage	1. Chronic rejection 2. Necrotic graft (acute rejection in biopsy 25 days earlier)	Liver failure after both grafts; infection
136 (43)	33	Sclerosing cholangitis; ulcerative colitis	Centrilobular necrosis; no rejection	Leak Roux-Y anastomosis; infection
138 (42)	108	Sclerosing cholangitis; ulcerative colitis	Chronic cholangitis; no rejection	Leak of colonic anastomosis after emergency colectomy; infection; liver failure; pulmonary failure (massive CMV infection)

[a] Time residence of successive grafts.

Table 3. Prednisone Doses and Serum Bilirubin Concentrations at 1 Yr and Causes of Eventual Death in 19 Patients Who Died More Than 1 Yr After Liver Transplantation

OT No.	Days survival	Age at operation (yr)	Original disease	Pathology of graft	Main cause of death	Bilirubin at 1 yr (mg%)	Prednisone dose at 1 yr (mg/kg/day)
8	400	1.5	Hepatoma	Biliary obstruction; metastatic tumor	Recurrent cancer	12.5	0.33
13	901 (881 + 20)[a]	2	Biliary atresia	1. Chronic rejection 2. Aspergillus infection	Infection after retransplantation	16.4	0.39
14	436 (379 + 57)	16	Hepatoma	1. Chronic rejection 2. Normal	Technical and infectious complications after second grafting	37.5	0.26
16	404 (65 + 339)[a]	2	Biliary atresia	1. Chronic rejection 2. Chronic rejection	Liver failure	10.0	1.25
19	1238	4	Biliary atresia	Chronic rejection	Liver failure; lung infection	0.7	1.5
27	2190	11	Wilson's disease	Partial biliary obstruction; chronic rejection	Liver failure	0.5	0.33
29	377	5	Biliary atresia	Chronic hepatitis	Liver failure	7.0	0.6
36	623	28	Chronic aggressive hepatitis	Chronic aggressive hepatitis	Liver failure; nocardial infection	1.0	0.38
54	586 (566 + 22)[a]	22	Chronic aggressive hepatitis	1. Biliary obstruction 2. Normal	Hemorrhagic pancreatitis; infection after retransplantation	0.6	0.5
55	780	6	Chronic aggressive hepatitis	Biliary obstruction	Liver failure	28.0	0.7
58	407	34	Chronic aggressive hepatitis	Biliary obstruction	Liver failure	40.8	0.36
74	855 (820 + 35)[a]	16	Alpha$_1$-antitrypsin deficiency	1. Chronic rejection 2. Normal	Injection after retransplantation	0.8	0.7
78	747	48	Duct cell carcinoma	Tumor recurrence	Recurrent cancer	0.5	0.29
89	590	3.5	Biliary atresia	Chronic rejection; thrombosis of intrahepatic portal branches	Infection	0.4	0.71
98	511 (37 + 474)[a]	1	Biliary atresia	1. Acute rejection 2. Chronic rejection	Liver failure	2.3	2.5
103	1085 (682 + 403)[a]	21	Primary biliary cirrhosis	1. Chronic rejection 2. Chronic rejection; massive liver necrosis	Infection after conversion of cholecystojejunostomy to choledochojejunostomy; liver failure	4.0	0.55
106	469	19	Chronic aggressive hepatitis	Healed acute rejection	Infection; liver failure	2.0	0.33
113	695	3	Biliary atresia	Massive liver necrosis	Systemic chicken pox; bacterial infection	0.6	1.7
126	497	11	Biliary atresia	Chronic rejection; portal vein thrombosis	Liver failure; gastrointestinal hemorrhage	4.0	0.8

[a] Underwent retransplantation. Figures in parentheses are survival of first and second grafts.

ization.[44] As a group, they were institutionalized an average of 55% of the time during the 1st yr, and during their subsequent survival they spent 58% of their time in the hospital.

Thus, it was not surprising that good rehabilitation was not obtained. Almost all of the eight infants in this failed group created severe domiciliary problems for their parents. Of 11 preadolescents, teenagers, and adults, only six returned to school or work for significant periods.

The best rehabilitation was in 4 patients who had an excellent clinical result at 1 yr (OT 19, 27, 36, and 78; Table 3). One adult died after 25 mo of recurrence of the duct cell carcinoma for which he was treated originally (OT 78). A 4-yr-old child was well for 3 yr but sustained crippling liver and renal damage after a hemophilus infection and died several weeks later (OT 19); the homograft had chronic rejection. Another patient died from biliary tract complications and chronic rejection 6 yr after transplantation (OT 27). The fourth recipient (OT 28) eventually had recurrence of chronic aggressive hepatitis, HBsAg positive, which had destroyed the native liver.[44]

Patients still alive. In contrast to those who died after 1 yr, the 27 patients who are still alive were doing well at 12 mo. At the 1-yr mark, only 2 were jaundiced, and the average bilirubin in the entire group was 1.4 ± 2.3 (S.D.) mg%. The prednisone dose averaged 0.59 ± 0.4 mg/kg/day.

Most of these patients returned to society. Although they spent an average of 37% of the 1st yr after transplantation in the hospital, thereafter they have been hospitalized an average of only 4% of the time. Thus, they became free to pursue normal interests and achieved a high degree of rehabilitation. All the adults returned to work. The adolescents, teenagers, and children have been in public or special schools. Many of the children who were infants at the time of transplantation eventually became students, reflecting the fact that in this group of 27 presently alive, there have been more than a dozen 4-yr survivors and seven who have been living for more than 5 yr.

Children with good clinical results have tended to remain small as a result of long-term steroid therapy, but they have achieved steady growth. One of our adult female recipients who is 4 yr post transplantation had a normal baby more than a 1.5 yr ago.

Changing Views About Recipient Selection

The indications and appropriate conditions for liver transplantation have evolved empirically at our center and in England, and have undergone major changes in the last 15 yr according to expanding experience. The diseases for which liver replacement has been carried out in Colorado are listed in Table 4, along with the survivals at 1 yr and beyond.

Hepatic malignancy. When the operation was first performed on a human in 1963, it was thought that otherwise unresectable primary hepatic malignancy would be a prime indication. Consequently, 12 of the first 26 recipients had primary hepatic malignancies. In subsequent cases (OT 27–141), only 7 more patients of this kind were represented, for a total of 19. Ten of the 19 recipients died within the first 3 mo but not because of tumor; 2 of the 10 had metastases at autopsy. Of the 9 who lived longer than 3 mo, all but 1 eventually developed metastases, including 4 with hepatomas, 2 with duct cell carcinomas, and 1 each with heman-

Table 4. Indications for Orthotopic Liver Transplantation at the University of Colorado

Diagnosis	Number of cases	Lived > 1 yr	Presently alive (1–9 yr)
Biliary atresia	48	16	8
Chronic aggressive hepatitis	36[a]	12	7
Primary liver malignancy	19	5	2
Alcoholic cirrhosis	15	4	4
Alpha$_1$-antitrypsin deficiency	5	3	2
Primary biliary cirrhosis	5	1	
Sclerosing cholangitis	4	0	
Secondary biliary cirrhosis	2	1	1
Wilson's disease	2	2	1
Massive hepatic necrosis (B virus)	1	0	
Congenital biliary cirrhosis[b]	1	1	1
Budd-Chiari syndrome	1	1	1
Congenital tyrosinemia	1	0	
Type IV glycogen storage disease	1	0	
Total	141	46	27

[a] Two had neonatal hepatitis and were treated at ages 7.5 and 30 yr.
[b] With congenital deafness.

gioendothelial sarcoma and sclerosing cholangiocarcinoma. The only exception was a woman who died of neurologic complications 5 mo after liver transplantation for hepatoma. Thus, the recurrence rate was 89% in patients living beyond 3 mo.

Five of the patients who survived 3 mo lived for more than 1 yr, and some of them achieved worthwhile palliation. Two patients with hepatomas lived for 13 and 14 mo; metastases were present in both but were primarily responsible for the death of only one. One patient with duct cell carcinoma died of metastases after 25 mo, and another one is alive 4.25 yr postoperatively, but with known recurrence. A 5th patient is still alive more than 2 yr postoperatively but she has metastases from a sclerosing cholangiocarcinoma.

The only patient cured of a hepatic malignancy by us was a child, not included in the aforementioned 19 cases, who had a small incidental hepatoma in her liver at the time of transplantation for biliary atresia. This girl is now 9 yr postoperative. Another child whose alpha$_1$-antitrypsin deficient liver contained an incidental small hepatoblastoma seems tumor free at 1 yr.

A high incidence of recurrence has also been reported from Cambridge-King's College (70% in patients with extended survival). The English workers' view of liver replacement for hepatic malignancy is, however, more optimistic than ours, particularly with respect to hepatomas.[16-18] Like us, they have uniformly had recurrence of duct cell carcinomas. However, the yield from liver replacement for primary hepatic malignancy is apt to be limited. The argument has even been advanced that residual tumor growth may actually be accelerated by the immunosuppression necessary to control rejection.[7]

Non-neoplastic disease. We have come to the general position that anyone with chronic non-neoplastic liver disease, who is less than 45 or 50 yr old (exceptional older patients may be acceptable), and who has a hopeless prognosis is a potential candidate for liver transplantation. Our experience with infants and children has actually been better than that with adults (Table 1). Thus, we consider the pediatric recipient to be favored. This attitude is reflected in the high numbers of patients treated for biliary atresia (Table 3). Biliary atresia was the single most common indication for liver replacement at Colorado. The Cambridge-King's College team does not perform the procedure on pediatric recipients, partly because of the concern with the growth retardation with long-term high-dose steroid therapy and partly because of their difficulty in finding pediatric donors.[18]

There has been a high proportion of cirrhotics in our experience. Among the 68 adults treated by us from 1963 through 1977, 51 had Laennec's cirrhosis or chronic aggressive hepatitis (Table 3). It is in such patients that the technical challenges mentioned earlier are encountered. Nevertheless, we continue to treat such patients, believing that this is where the most important future application of liver transplantation lies in adults.

For patients with chronic aggressive hepatitis, it would be ideal to have the patient virus free, but some of the patients have preexisting positive HBsAg tests. The Cambridge-King's College physicians have succeeded in clearing the HBsAg marker postoperatively with the use of hyperimmune serum.[17,18] We have not been successful in permanently eliminating the HBsAg marker. Several of our longest survivors have remained or become HBsAg carriers. Two have developed chronic aggressive hepatitis in a modified form (OT 121, Table 2; OT 36, Table 3). One of these cases has been reported in detail.[45] Even so, the presence of the HBsAg is not necessarily a contraindication to transplantation, although the public health hazards of such carrier patients are obvious.

In our series, a small group with inborn errors of metabolism have been unusually interesting because of the biochemical abnormalities that could be studied.[46-49] These have included Wilson's disease, alpha$_1$-antitrypsin deficiency, congenital tyrosinemia, and Type IV glycogen storage disease. The metabolic derangements of all these disorders are corrected for as long as the new liver functions.

The role of tissue typing in patient selection. It is unlikely that shopping for well-matched livers will be possible in the near future. The need for transplantation is so pressing in appropriate candidates that it too often is obligatory to proceed with the first available organ. Thus, almost all the matches in our series have been bad ones. In 100 consecutive Colorado cases, only 2 patients received livers with three or four antigen matches. One of the recipients of a well-matched organ died of technical complications 62 days after operation. The other is well after 11 mo.

Because of urgent needs, a number of liver transplantations have been performed despite the presence of the recipients of cytotoxic antibodies that were anti-donor specific. We have carried out ten liver transplantations under these circumstances. There were no examples of hyperacute rejection, which almost invariably destroys renal homografts under these circumstances, and in fact, no unequivocal harmful effects have been seen later (Table 5) compared with patients without cytotoxic antibodies. Seven of the patients lived for more than 2 mo and 5 for more than 6 mo. We[32,43] and Calne and Williams[17,18] have concluded that the liver is highly

Table 5. Liver Transplantation into Recipients with Anti-donor Antibodies

	Number of cases	Hyperacute rejection	Survival > 2 mo	Survival > 6 mo
Positive cytotoxic cross-match	10	0	7	5
Blood group incompatibility	11	None definite	8	6

privileged in confrontations with preformed cytotoxic antibodies.

Renal homografts are also hyperacutely rejected if there is a breach of blood group barriers. We have proceeded in spite of this adverse factor in 11 liver recipients who could not wait for blood group compatible organs (Table 5). The livers did not function well in two of the recipients, leading to attempted retransplantation and eventual death. The blood violations in these cases were B to O and B to A. The excised primary livers had superficial infarcts and focal necrosis, but histopathologically there was nothing to suggest damage by anti-blood group isoagglutinins. Thus, we will still perform transplantation despite blood group incompatibility, although we avoid the condition, if possible. Except in the two exceptional cases, the other patients did not behave differently than those given blood group compatible livers (Table 5).

A Need for Better Immunosuppression

The complexity of liver transplantation has been made clear in preceding sections, with emphasis on the technical and management difficulties that may be encountered. As solutions to such problems are evolved, further improvements in results will depend upon better means to control rejection. In the past, immunosuppression has been with double (azathioprine and prednisone) or triple drug (azathioprine, prednisone, and heterologous ALG) treatment. Cyclophosphamide can be substituted for azathioprine. The complications of these agents have already been mentioned.

One possibility for improvement could be better drug treatment. A promising new agent, the fungus extract, Cyclosporin A,[50,51] has permitted spectacular success after skin and/or whole organ transplantation in rats, rabbits, dogs, and pigs[50-54] and has been used in a limited clinical trial of renal homotransplantation at Cambridge, England. Calne says that several human recipients of cadaveric kidneys have been treated with this drug and discharged from the hospital in good condition even though no corticosteroids were given.

An alternative that we have been examining in our liver recipients is thoracic duct drainage.[55] Between February and early July 1978, patients had thoracic duct drainage instituted at the time of liver transplantation (seven examples), or 2 or 3 wk later (two examples). Triple drug immunosuppression was used. It has seemed possible with this approach to use much less than the conventional doses of prednisone with adequate control of rejection. Five of the 9 patients have been discharged from the hospital and have been followed for 6–11 mo. Four died, but the causes of death were unrelated to the success of the thoracic duct fistula. Two of the patients died from gastrointestinal perforations and fistulas which resulted in overwhelming infections. In a third case, a 5-yr-old child with a seemingly perfect result died of systemic chicken pox (including pneumonitis and hepatitis) 72 days postoperatively. A 4th patient, who received a liver in violation of red blood cell match and whose new liver never functioned well, is described above. Thoracic duct drainage in combination with the conventional triple drug therapy described above is planned for all cases in the immediate future. Our present policy is to establish the thoracic duct fistulas preoperatively, if circumstances permit, and to continue them for about 2 mo.

Auxiliary Liver Transplantation

The alternative to hepatic replacement is to leave the native liver in place and to transplant an extra liver to an ectopic site such as splenic bed, right or left paravertebral gutter, or pelvis. This approach was originally conceived by Welch[1] and first tried clinically by Absolon et al.[15] The main theoretical advantage of auxiliary transplantation is that the recipient is not at the outset placed totally at the mercy of homograft function. A second possible advantage would be avoidance of the technical hazards of recipient hepatectomy.

By May 1969, nine auxiliary liver transplants had been performed, four at the University of Colorado and one each at five other institutions. These early cases were summarized in a book.[7] The longest survival was 36 days. Of the many problems encountered, not the least was difficulty in finding room for an extra organ in an already overcrowded abdomen. In addition, it had been learned from animal studies[7,56,57] that optimum condition for the transplanted liver was portal venous inflow of splanchnic venous blood. Subsequent work[58] has shown that specific substances in portal blood (especially insulin) can influence hepatic structure, function, and the capacity for regeneration.

Since 1969, we have performed only one auxiliary transplantation, for the treatment of a child with Crigler-Najjar syndrome. The recipient died after the homograft vessels thrombosed. Fortner and his associates have maintained, however, an interest in auxiliary transplantation, and in September 1978, they summarized their results and those obtained elsewhere.[59]

By that time, they had information on 43 cases, including seven of their own. There was one unqualified success, of a patient with biliary atresia who was alive 5.5 yr postoperatively. During the period after transplantation, the native liver had undergone striking atrophy and the original proturberance of the overdistended abdomen had receded. Another of Fortner's patients with biliary obstruction from an intrahepatic cancer had temporary clearing of jaundice but died 8 mo later. The other 41 patients died in less than 2 mo from a variety of complications.[59]

Fortner has concluded that patients with nonneoplastic liver disease who have small livers are candidates for auxiliary hepatic transplantation. The possible attractiveness of such an option has been diminished by the improved results with liver replacement. Our view is that auxiliary transplantation should be reserved for patients with acute hepatic disease in which the objective is temporary life support during which recovery of the native liver can be obtained. The feasibility of this approach has been proved in several animal studies, but not yet in humans.

Summary

Liver transplantation in humans was first attempted more than 15 yr ago. The 1-yr survival has slowly improved until it has now reached about 50%. In our experience, 46 patients have lived for at least 1 yr, with the longest survival being 9 yr. The high acute mortality in early trials was due in many cases to technical and management errors and to the use of damaged organs. With elimination of such factors, survival increased. Further improvements will depend upon better immunosuppression. Orthotopic liver transplantation (liver replacement) is the preferred operation in most cases, but placement of an extra liver (auxiliary transplantation) may have a role under special circumstances.

References

1. Welch CS: A note on transplantation of the whole liver in dogs. Transplantation Bull 2:54–55, 1955
2. Moore FD, Smith LL, Burnap TK, Dallenbach, FD, Dammin GJ, Gruber UF, Shoemaker WC, Steenburg RW, Ball MR, Belko JS: One-stage homotransplantation of the liver following total hepatectomy in dogs. Transplantation Bull 6:103–107, 1959
3. Moore FD, Wheeler HB, Demissianos HV, Smith LL, Balankura O, Abel K, Greenberg JB, Dammin GJ: Experimental whole-organ transplantation of the liver and of the spleen. Ann Surg 152:374–387, 1960
4. Starzl TE, Kaupp HA, Brock DR, Lazarus RE, Johnson RV: Reconstructive problems in canine liver homotransplantation with special reference to the postoperative role of hepatic venous flow. Surg Gynecol Obstet 111:733–743, 1960
5. Starzl TE, Kaupp HA, Brock DR, Linman JR: Studies on the rejection of the transplanted homologous dog liver. Surg Gynecol Obstet 112:135–144, 1961
6. Groth CG, Porter KA, Otte JB, Daloze PM, Marchioro TL, Brettschneider L, Starzl TE: Studies of blood flow and ultrastructural changes in rejecting and nonrejecting canine orthotopic liver homografts. Surgery 63:658–668, 1968
7. Starzl TE (with the assistance of Putnam CW): Experience in Hepatic Transplantation. Philadelphia, W. B. Saunders Co., 1969, 1–553
8. Starzl TE, Marchioro TL, Porter KA, Taylor PD, Faris TD, Herrmann TJ, Hlad CJ, and Waddell WR: Factors determining short- and long-term survival after orthotopic liver homotransplantation in the dog. Surgery 58:131–155, 1965
9. Starzl TE, Marchioro TL, Porter KA, Iwasaki Y, Cerilli GJ: The use of heterologous antilymphoid agents in canine renal and liver homo-transplantation and in human renal homotransplantation. Surg Gynecol Obstet 124:301–318, 1967
10. Starzl TE, Porter KA, Putnam CW: Eleven and two-thirds years survival after canine orthotopic liver transplantation. Transplantation 23:168–171, 1977
11. Garnier H, Clot JP, Bertrand M, Complez P, Kunlin A, Gorin JP, LeGoaziou F, Levy R, Cordier G: Biologie Experimentale: Greffe de foie chez le Porc: Approche chirurgicale. CR Acad Sci (Paris) 260:5621–5623, 1965
12. Peacock JH, Terblanche J: Orthotopic homotransplantation of the liver in the pig. *In* The Liver. Edited by AE Read. London, Buttonworth and Co. Ltd., 1967, p 333–336
13. Calne RY, White HJO, Yoffa DR, Binns RM, Maginn RR, Herbertson RM, Millard PR, Molina VP, Davis DR: Prolonged survival of liver transplants in the pig. Br Med J 4:645–648, 1967
14. Starzl TE, Marchioro TL, von Kaulla KN, Hermann G, Brittain RS, Waddell WR: Homotransplantation of the liver in humans. Surg Gynecol Obstet 117:659–676, 1963
15. Absolon KB, Hagihara PF, Griffen WO, Jr, Lillehei RC: Experimental and clinical heterotopic liver homotransplantation. Rev Int Hepat 15:1481–1490, 1965
16. Williams R, Smith M, Shilkin KB, Herbertson B, Jaysey B, Calne RY: Liver transplantation in man; the frequency of rejection, biliary tract complications, and recurrence of malignancy based on an analysis of 26 cases. Gastroenterology 64:1026–1048, 1973
17. Calne RY, McMaster P, Portmann B, Wall WJ, Williams R: Observations on preservation, bile drainage and rejection. Ann Surg 186:282–290, 1977
18. Calne RY, Williams R: Liver transplantation. *In* Current Problems in Surgery. Edited by MM Ravitch Chicago, Year Book Medical Publishers, Inc. 16:3–44, 1979
19. Moore FD, Birtch AG, Dagher F, Veith F, Krisher JA, Order SE, Shucart WA, Dammin GJ, Couch NP: Immunosuppression and vascular insufficiency in liver transplantation. Ann NY Acad Sci 120:729–738, 1964
20. Alper CA, Johnson AM, Birth AG, Moore FD: Human C'3: Evidence for the liver as the primary site of synthesis. Science 163:286–288, 1969
21. Demirleau, Noureddine, Vignes, Prawerman, Reziciner, Larraud, Louvier: Tentative d'homogreffe hepatique (Attempted

hepatic homograft). Mem Acad Chir (Paris) 90:177-179, 1964
22. Fonkalsrud EW, Stevens GH, Joseph WL, Rangel D, Yakeishi Y, Longmire WP, Jr: Orthotopic liver allotransplantation using an internal vascular shunt. Surg Gynecol Obstet 127:1051-1057, 1968
23. Daloze P, Delvin EE, Glorieux FH, Corman JL, Bettez P, Toussi T: Replacement therapy for inherited enzyme deficiency: Liver orthotopic transplantation in Nieman-Pick disease Type A. Am J Med Genet 1:221-239, 1977
24. Lie TS, Kauffer C, Siedek M, Prange CH, Rommelsheim K, Fillman B, Gutgemann A: Prolonged ischemic tolerance time of the human liver with successful grafting. Munch Med Wochenschr 116:1013-1020, 1974
25. Bechtelsheimer H, Gedigk P, Muller R, Lie TS: Pathologic anatomic observations after three orthotopic allogenic transplantations of the liver in adults. Virchows Arch (Pathol Anat) 360:287-304, 1973
26. Machado MD, Monteiro da Cunha JE, Margarido NF, Bacchella J, Goncalves EL, Raia AA: Hyperosmolar coma-associated with clinical liver transplantation. Int Surg 61:368-369, 1976
27. Abouna GM, Preshaw RM, Silva JLU, Hollingsworth WJ, Hershfield NB, Novak W, Shaw DT, Vetters JM: Liver transplantation in a patient with cholangiocarcinoma and ulcerative colitis. Can Med Assoc J 115:615-619, 1976
28. Birtch AG, Moore FD: Experiences in liver transplantation. Transplant Rev 2:90-128, 1969
29. Fortner JG, Beattie EJ, Jr, Shiu, MH, Kawano N, Howland WS: Orthotopic and heterotopic liver homografts in man. Ann Surg 172:23-32, 1970
30. Hume DM, Wolf JS, Lee HM, Abouna G: Liver transplantation. Transplant Proc 4:781-784, 1972
31. Lampe EW, II, Simmons RL, Najarian JS: Hyperglycemic nonketotic coma after liver transplantation. Arch Surg 105:774-776, 1972
32. Starzl TE, Porter KA, Putnam CW, Schroter GPJ, Halgrimson CG, Weil R, III, Hoelscher M, Reid HAS: Orthotopic liver transplantation in ninety-three patients. Surg Gynecol Obstet 142:487-505, 1976
33. Martineau G, Porter KA, Corman J, Launois B, Schroter G, Palmer W, Putnam CW, Groth CG, Halgrimson CG, Penn I, Starzl TE: Delayed biliary duct obstruction after orthotopic liver transplantation. Surgery 72:604-610, 1972
34. Starzl TE, Porter KA, Putnam CW, Hansburgh JF, Reid HAS: Biliary complications after liver transplantation: With special reference to the biliary cast syndrome and techniques of secondary duct repair. Surgery 81:213-221, 1976
35. Schroter GPJ, Hoelscher M, Putnam CW, Porter KA, Hansbrough JF, Starzl TE: Infections complicating orthotopic liver transplantation: With emphasis on graft related septicemia. Arch Surg 111:1337-1347, 1976
36. Schroter GPJ, Hoelscher M, Putnam CW, Porter KA, Starzl TE: Fungus infections after liver transplantation. Ann Surg 186:115-122, 1977
37. Koep LJ, Starzl TE, Weil R, III: Gastrointestinal complications of hepatic transplantation. Transplant Proc 11:257-261, 1979
38. Calne RY: A new technique for biliary drainage in orthotopic liver transplantation utilizing the gallbladder as a pedicle graft conduit between the donor and recipient common bile ducts. Ann Surg 184:605-609, 1976
39. Wall WJ, Calne RY, Herbertson BM, Smith, DP, Underwood J, Kostakis A, Williams R: Simple hypothermic preservation for transporting human livers long distances for transplantation. Transplantation 23:210-216, 1977
40. McMaster P, Herbertson B, Cusick C, Calne RY, Williams R: Biliary sludging following liver transplantation in man. Transplantation 25:56-62, 1978
41. Benichou J, Halgrimson CG, Weil R, III, Koep LJ, Starzl TE: Canine and human liver preservation for 6-18 hours by cold infusion. Transplantation 24:407-411, 1977
42. Starzl TE, Schneck SA, Mazzoni G, Aldrete JA, Porter KA, Schroter GPJ, Koep LJ, Putnam CW: Acute neurological complications after liver transplantation: With particular reference to intraoperative cerebral air embolus. Ann Surg 187:236-240, 1978
43. Starzl TE, Koep LJ, Halgrimson CG, Hood J, Schroter GPJ, Porter KA, Weil R, III: Liver transplantation, 1978. Transplant Proc 11:240-246, 1979
44. Starzl TE, Koep LJ, Schroter GPJ, Hood J, Halgrimson CG, Porter KA, Weil R: The quality of life after liver transplantation. Transplant Proc 11:252-256, 1979
45. Corman JL, Putnam CW, Iwatsuki S, Redeker AG, Porter KA, Peters RL, Schroter G, Starzl TE: Liver homotransplantation for chronic active hepatitis with macronodular cirrhosis, HB_s AG positive. Arch Surg 114:75-78, 1979
46. Groth CG, Dubois RS, Corman J, Gustafsson A, Iwatsuki S, Rodgerson DO, Halgrimson CG, Starzl TE: Metabolic effects of hepatic replacement in Wilson's disease. Transplant Proc 5:829-833, 1973
47. Starzl TE, Putnam CW, Koep L: Liver transplantation for inborn errors of metabolism. *In* Liver and Bile (Proceedings of the IV International Congress of Liver Diseases, Basel, Switzerland). Edited by L Bianchi, W Gerok, K Sickinger. Lancaster, England, MTP Press Limited, 1977, p 343-348
48. Putnam CW, Porter KA, Peters RL, Ashcavi M, Redeker AG, Starzl TE: Liver replacement for $alpha_1$-antitrypsin deficiency. Surgery 81:258-261, 1977
49. Fisch RO, McCabe ERB, Doeden D, Koep LJ, Kohlhoff BA, Silverman A, Starzl TE: Homotransplantation of the liver in a patient with hepatoma in hereditary tyrosinemia. J Pediatr 93:592-596, 1978
50. Borel JF, Feurer C, Gubler HA, Stahelin H: Biological effects of cyclosporin A: a new antilymphocytic agent. Agents Actions 6:468-475, 1976
51. Borel JF, Feurer C, Magnee C, Stahelin H: Effects of the new antilymphocytic peptide cyclosporin A in animals. Immunology 32:1017-1025, 1977
52. Calne RY, White DJG: Cyclosporin A—A powerful immunosuppressant in dogs with renal allografts. IRCS Med Sci 5:595, 1977
53. Green CJ, Allison AC: Extensive prolongation of rabbit kidney allograft survival after short term cyclosporin A treatment. Lancet 1:1182-1183, 1978
54. Calne RY, White DJG, Rolles K, Smith BP, Herbertson BM: Prolonged survival of pig orthotopic heart grafts treated with cyclosporin A. Lancet 1:1183-1185, 1978
55. Starzl TE, Koep LJ, Weil R, III, Halgrimson CG, Franks JJ: Thoracic duct drainage in organ transplantation; will it permit better immunosuppression? Transplant Proc 11:276-284, 1979
56. Starzl TE, Marchioro TL, Rowlands DT, Jr, Kirkpatrick CH, Wilson WEC, Rifkind D, Waddel WR: Immunosuppression after experimental and clinical homotransplantation of the liver. Ann Surg 160:411-439, 1964
57. Marchioro TL, Porter KA, Dickinson TC, Faris TD, Starzl TE: Physiologic requirements for auxiliary liver homotransplantation. Surg Gynecol Obstet 121:17-31, 1965
58. Starzl TE, Terblanche J: Hepatotrophic substances. *In* Progress in Liver Diseases, Volume Six (Eds. Popper, H. and Schaffner, F.). New York, Grune and Stratton, 1979, p 135-152
59. Fortner JG, Yeh SDJ, Kim DK, Shui MH, Kinne DW: The case for and technique of heterotopic liver grafting. Transplant Proc 11:269-275, 1979