Liver Transplantation

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This presentation assesses the role of liver transplantation in treating end-stage liver disease today. Most of the unresolved issues in human liver transplantation have been developed in two major series, the one from Denver and the other from the combined Cambridge/Kings College Hospital effort in England. The findings of these groups are highlighted, as are the changes in technique that have led to considerably improved survival in the past 2 years.

THE CURRENT STATUS OF HUMAN LIVER TRANSPLANTATION

Human liver transplantation has developed frustratingly slowly since the first liver graft in man was performed in Denver in March 1963. However, the success rate has improved remarkably in the last 2 years and the procedure has at last moved out of the developmental and experimental phase and become a truly therapeutic procedure in Denver.

The Denver experience can be divided into a First Series of 111 patients operated on between March 1963 and July 1976 and a Second Series of 30 patients from August 1976 through December 1977. The reasons for the improved results in the Second Series will be discussed later.

In the First Series only 28 per cent of the 111 patients survived for 1 year. The fact that the number of long-term survivors increased only slightly during the course of the First Series (11 of the first 50 recipients — 22 per cent; 20 of the next 61 patients —33 per cent) was cause for concern. On the other hand, 45 per cent of the 1 year survivors from the First Series are currently alive at between 2⅜ and 8⅝ years.[14, 27] The 17 patients who died late at between 1 and 6 years were usually already in trouble at the 1 year mark.[25] Thus, the 1 year assessment should be a useful guide in predicting long-term survival. The details of the patients who died after 1 year, and the causes of death, have been presented elsewhere.[22, 23]

As a result of these findings and conclusions, surgical management policy was changed in mid 1976 and the Second Series was commenced. Of the 30 patients in the Second Series, 1 year survival was 50 per cent with 2 late deaths at 16½ and 23 months. The majority of the patients in the Second Series, who are currently alive, were well when assessed at the 1 year mark. This, together with a better understanding of the biliary tract anastomosis which had been responsible for some of the late deaths, should markedly improve the long term prognosis in the 1 year survivors.

There has also been an improved survival in the other large series of Calne and Williams. There were only 3 one year survivors in their first 35 recipients. Of the next 39 patients, 9 have lived for more than a year and 6 additional patients are alive with shorter follow up.[4]

The above data have referred only to total replacement or orthotopic liver transplants. Although an accessory or additional (heterotopic) liver transplant should have some theoretical advantages, only 1 really long-term survivor has been achieved by Fortner.[8] This technique is further discussed below.

The quality of life after liver transplantation has been assessed in the Denver patients and ranged from poor to superior. The details are presented elsewhere but it is worth re-emphasizing the finding that a good long term prognosis was usually evident by 1 year after operation.[25]

WHY HAVE THE RESULTS IMPROVED RECENTLY?

Rejection, Immunosuppression, and Infection

Rejection is much more difficult to diagnose after liver grafting than after kidney transplantation. In addition it is difficult to separate rejection (requiring increased immunosuppression) from sepsis, especially ascending cholangitis (where increased immunosuppression would be harmful). The problem was well demonstrated in a series of un-immunosuppressed pig liver transplants in a group of animals with a low incidence of rejection.[7] Both the Denver and the Cambridge groups have emphasized this problem in man. Postoperative hepatic dysfunction is no longer so easily ascribed to rejection and frequent liver biopsies and cholangiography (transhepatic, T-tube, or retrograde

endoscopic) have now become routine in Denver if the explanation of postoperative jaundice is not obvious.[24, 27] In addition to the Denver group,[22] Calne has also emphasized the "tendency to over-immunosuppressed patients" in the past.[4] All the evidence points to the liver being less liable to severe rejection than the kidney, with few patients dying primarily of rejection.

Biliary Anastomosis

The realization that the biliary tract was the Achilles heel of human liver transplantation has led to major changes in technique.

The Denver group have emphasized that the ideal form of biliary reconstruction is a choledochocholedochostomy (direct bile duct to bile duct anastomosis) using a T-tube stent (Fig. 1A).[24] The advantage of retaining the sphincter of Oddi in preventing ascending cholangitis has been clearly demonstrated in animal experiments.[7] However, approximately 50 per cent of patients in the early experience with a choledochocholedochostomy developed leakage at the site of anastomosis with an almost universal mortality. The Denver group recognized the need to cut the donor bile duct high enough to insure adequate blood supply, as visualized by bleeding from the cut end of the donor duct after the vascular anastomoses had been completed, and the importance of meticulous technique. With these provisos, a direct bile duct to bile duct anastomosis is currently the favored technique and, when technically feasible, has led to few problems in the Second Series of patients.

When a choledochocholedochostomy is not feasible, the Denver group currently prefer either a cholecystojejunostomy or a choledocho-jejunostomy using a Roux loop (Fig. 1 B and C). Although the chole-cystojejunostomy has the advantages of a large caliber anastomosis, especially in pediatric recipients, and of not requiring a stent, the major disadvantage has been obstruction to the cystic duct which has

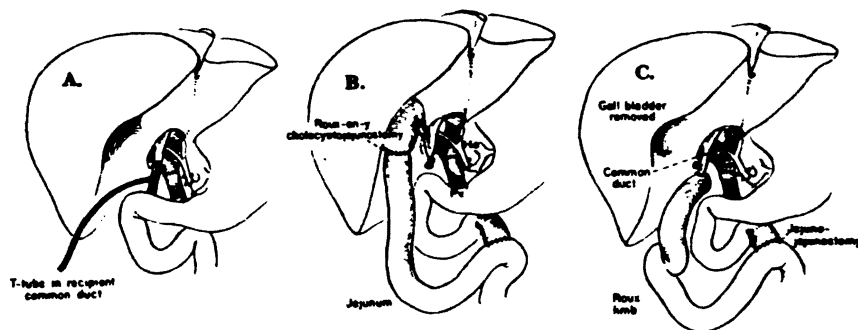Figure 1. Techniques of biliary duct reconstruction acceptable to us for most transplantation recipients. A. Choledochocholedochostomy. Note that the T-tube is placed, if possible, in recipient common duct. B, Cholecystojejunostomy. C, Choledochojejunostomy after removal of gallbladder. (From Starzl, T. E., Koep, L. J., Halgrimson, C. G., et al.: Liver transplantation, 1978. Transplant. Proc., 1978, in press. By permission.)

necessitated reoperation and conversion to a choledochojejunostomy in 20 to 35 per cent of cases (Fig. 1 B to C). The possible vascular explanations for this are described below. Furthermore, the Roux limb or the jejunostomy below it have developed perforation in 8 cases and this was the major cause of death in 7 patients.[11, 27]

Calne and Williams have also emphasized the problems of the biliary anastomosis.[4] They have advocated a choledochocholedochostomy (Fig. 1A) in the past because this provided good anatomical biliary drainage as it preserved the sphincter of Oddi. However, leakage at this anastomosis site with high mortality has led Calne to develop a new technique of biliary anastomosis, which also retains the sphincter of Oddi, namely gallbladder interposition with the gallbladder acting as a conduit (Fig. 2). The anastomosis is stented with a T-tube which is used for irrigation and allows the biliary system to be studied radiologically in the postoperative period.[3] In designing the new operation, Calne recognized and emphasized the precarious blood supply of the donor common bile duct (vide infra).

However, the implications of the bile duct blood supply in biliary

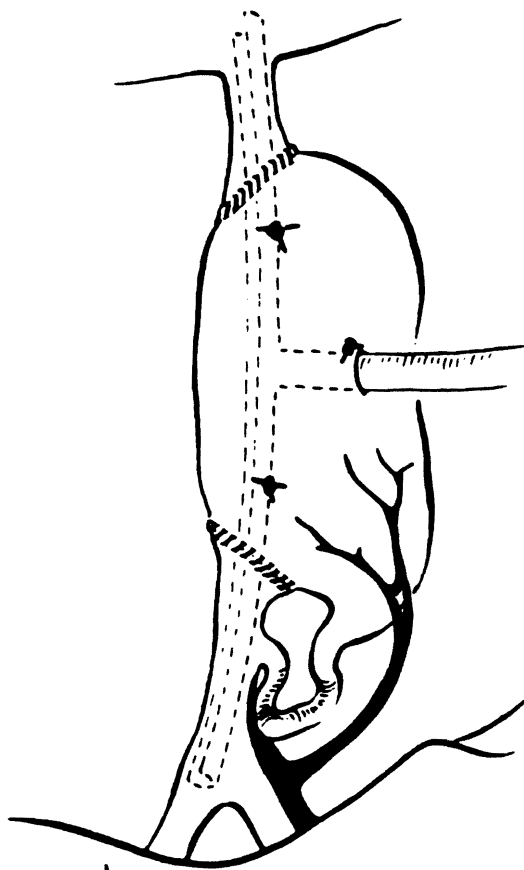Figure 2. Diagram showing the completed anastomoses between Hartmann's pouch and the donor common duct and the fundus and the recipient's common duct. The T-tube is splinting both anastomoses. (From Calne, R. Y.: A new technique for biliary drainage in orthotopic liver transplantation utilizing the gallbladder as a pedicle graft conduit between the donor and recipient common bile ducts. Ann. Surg., 184:605–609. 1976. By permission.)

tract problems were not fully appreciated until the blood supply of the human bile duct was clearly defined. This is emphasized by the fairly long donor duct depicted in Figure 2. Calne and Williams have also recently emphasized that in using the gallbladder interposition technique the donor common bile duct must be trimmed back until it bleeds, even if the cystic duct has to be ligated and the common hepatic duct cut back until adequate bleeding is noted.[4]

Northover (who had been involved in the Calne/Williams Series as a young trainee at Kings College Hospital, London) investigated the problem of the biliary anastomosis in Cape Town. The Cape Town group were intrigued by the fact that a direct bile duct to bile duct anastomosis seldom gave problems in animals. In assessing the possible reasons for this fundamental difference between man and animals, two factors that would only affect man became evident. They were the advanced debility of many of the human transplant recipients when compared with the fit experimental animals (which would be difficult to quantitate), and the possibility of an anatomic difference in the bile duct blood supply between man and the animals used for liver transplant experiments.[13]

The anatomic theory was investigated by developing a refined polyester resin casting-tissue maceration technique and using this to define the blood supply of the bile duct in the pig and baboon. In addition, this technique clearly defined the blood supply of the human bile duct for the first time. The pig and baboon ducts were shown to be well vascularized. The baboon bile duct was supplied axially, as in man, but with more profuse vessels of a relatively large caliber supplying the duct, while the pig bile duct had a very adequate blood supply which came in laterally in a pattern similar to the small bowel blood supply. This anatomic finding probably accounts for the trouble-free bile duct to bile duct anastomoses noted in these species.[13] In man the intrahepatic and retropancreatic portions of the bile ducts were shown to have an excellent blood supply from adjacent vessels, but the supraduodenal bile duct had a tenuous blood supply and was supplied axially by small vessels from below and above. In most cases 3 and 9 o'clock arteries were present on each side of the bile duct but were of small caliber (±0.3 mm average diameter). Two-thirds of the arterial input to these vessels came from below and only one-third from above from the right hepatic and cystic arteries.[14] In addition, a previously undescribed major artery, which has been named the retroportal artery, was found. In 20 per cent of the initial series (one-third of the completed series) this vessel ascended on the back of the bile duct to join the right hepatic artery, but in the remainder, the retroportal artery only contributed very small branches to supply the supraduodenal bile duct from below (Figs. 3 and 4). The retroportal artery supplying the duct, when present, was of larger caliber than the 3 and 9 o'clock arteries (±0.53 mm average diameter).[13, 14] On the basis of these findings, it has been suggested that the human donor bile duct is more liable to develop ischemia because of the tenuous blood supply from above, than the recipient duct which should be well supplied from below. In
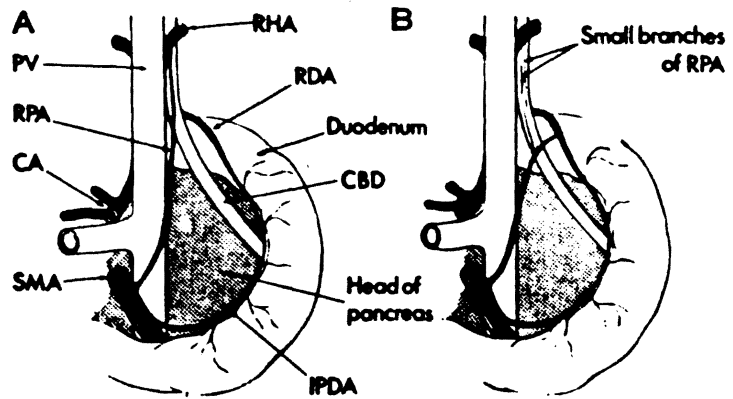
Figure 3. Retroportal artery. Posterior views of upper abdominal organs to show the usual configurations of this artery. A, Retroportal artery ascending to join the right hepatic artery supplying the common bile duct en route (20 per cent of specimens). B, Retroportal artery joining the retroduodenal artery, and sending small branches to the supraduodenal common bile duct (60 per cent of specimens). CA, celiac axis; CBD, common bile duct; IPDA, inferior pancreatico-duodenal artery; PV, portal vein; RDA, retroduodenal artery; RHA, right hepatic artery; RPA, retroportal artery; SMA, superior mesenteric artery. (*From* Northover, J., and Terblanche, J.: Bile duct blood supply. Its importance in human liver transplantation. Transplantation, 26:67–69, 1978. By permission.)

Figure 4. Retroportal artery. Photograph and drawing of a cast to demonstrate this vessel; in the drawing it is emphasized in black. It arises from the dorsal pancreatic branch of the celiac axis, and in this case conforms to both patterns shown in Figure 3. (*From* Northover, J. and Terblanche, J.: Bile duct blood supply. Its importance in human liver transplantation. Transplantation, 26:67–69, 1978. By permission.)

the third of patients in whom the retroportal artery was of the type I configuration (running up the back of the bile duct to join the right hepatic artery), the donor bile duct would be much better supplied from above. This study provided an anatomic basis for the bile duct problems noted in many human liver transplant patients.

These findings also supported the recent recommendations on the biliary anastomosis, made by both the Denver and Cambridge groups, which have led to considerably fewer bile duct anastomosis problems than before. Whether the more complicated approach of an interposed gallbladder, as advocated by Calne, is necessary or desirable will only become evident with time.

McMaster has documented after transplantation a type of sludge obstruction in the biliary tree. The obstruction, which consisted of amorphous collagen,[12] was localized to the donor duct system. This obstruction has been attributed to ischemia associated with the donor operation, but could well be due to ischemia related to a donor duct with poor blood supply, especially if the retroportal artery did not provide a major supply to the duct from above as would occur in the Type II retroportal artery configuration.[13, 14] The 20 to 35 per cent incidence of reoperation for obstruction after cholecystojejunostomy (Fig. 1 B) might also be related to relative ischemia of the donor duct at and below the entry of the cystic duct or of the cystic duct itself.

Other Technical Modifications

These have been described in recent publications from Denver[24, 27] and Cambridge.[4] They include the increasing use of microsurgical techniques for both vascular and biliary tract anastomoses especially in pediatric recipients, the avoidance of air embolism during the recipient operation,[27] and meticulous attention to detail during the recipient operation and anesthesia.

INDICATIONS FOR LIVER TRANSPLANTATION

Anyone with chronic end-stage liver disease who is less than 45 or 50 years old, who is not infected, who has a hopeless prognosis, and who does not have widespread malignant disease is a *potential* candidate for liver transplantation. The improved results currently being achieved after liver transplantation should make the selection of patients for transplant somewhat easier.

It is, however, important to emphasize that major differences of opinion still exist between the two groups with extensive experience of this operation. The main differences are summarized below:

INDICATION	DENVER	CAMBRIDGE
Malignant diseases	Not favored	Favored
Pediatric patient	Favored	Not favored
Cirrhosis	Favored	Reservations

Age of Recipients

Calne and Williams do not accept the upper age limit of 45 to 50 mentioned by the Denver group and have indicated that they have performed liver transplants in patients in their 50's with good results. They emphasize individual considerations and in particular the biological age of the patient.[4] There is, in fact, no real difference of opinion about the age question as the Denver group is not bound by the arbitrary upper age limit.

Secondary Hepatic Malignancy

Neither group currently considers patients with secondary malignant disease of the liver for transplantation, as all patients receiving transplants for this indication in the past have developed recurrent malignant disease shortly after transplantation. A nonresectable secondary malignant growth in the liver is invariably a manifestation of a generalized disease process, which rapidly manifests itself in the immunosuppressed patient after transplantation.

Primary Hepatic Malignant Disease

The Denver group have become increasingly disenchanted with transplantation for primary hepatic malignant disease. In all, 19 patients with primary hepatic carcinoma (including hepatocellular carcinoma, duct cell carcinoma, cholangiocarcinoma, and angiosarcoma) have received transplants in Denver. Recurrences have eventually developed in 8 of the 9 patients who survived for 3 months or more after transplantation. The exception died at 5 months as a result of neurologic complications, but with no evidence of a malignant process at post-mortem examination. Five of the 9 survivors lived for over a year, and received moderate palliation.[27] The only patient cured of hepatic carcinoma in Denver was a child who had a small incidental hepatoma in the liver which was removed for biliary atresia. She is currently the longest survivor after liver grafting and is alive at 8⅚ years after transplantation.

Carcinoma of the main hepatic duct junction has been a major area of controversy.[21, 33, 34] One of the Denver patients died of metastases more than 2 years post transplant and another is alive more than 4 years after operation, with proven recurrences. The authors currently agree that this lesion is not usually an indication for liver transplantation today,[33] although a young patient with a favorable lesion may be an exception in the future. This view is shared by Calne and Williams.[4] The Cape Town group have advocated the use of a replaceable U-tube stent, after dilating the lesion, combined with high dose radiotherapy to the localized area of the tumor.[30, 31] The results of dilatation and some form of intubation with or without radiotherapy in 15 consecutive patients, treated in Cape Town between 1968 and January 1973, and followed prospectively to the present, have been most encouraging. Two of the four patients who had the U-tube procedure combined with radiotherapy are currently alive and well at over 7 years. Two-thirds survived more than 1 year, most of them for pro-

longed periods, while the average age of the one-third who died early
was 79 years.[37] The Denver group currently favor a more aggressive
approach with resection if possible. With nonresectable lesions one of
the authors (LJK) has confirmed the Cape Town experience in 6 patients.

Patients with primary hepatocellular carcinoma are not receiving
transplants in Denver at present because of the unfavorable past expe-
rience already discussed. Calne's group, however, feel that most of
their patients with this lesion have received palliation. Their longest
survivor died of cholangitis more than 5 years after transplant with no
evidence of recurrence.[4] Although the authors do not share Calne and
Williams' optimism, they would be prepared to consider a well moti-
vated patient who understood the implications and still requested a
transplant as a palliative procedure.

Pediatric Patients

Pediatric patients constitute an area of major controversy. Calne
and Williams do not recommend the procedure in children. In addition
to their difficulty in obtaining donors, they are concerned about growth
retardation which is predictable if long term, high dose steroid thera-
py is required.[4] The Denver group do not agree and recommend liver
transplantation in children. The majority of children receiving trans-
plants in Denver have had biliary atresia. The results have been better
in pediatric patients in both the First and Second Denver Series (34
per cent 1 year survival in children versus 20 per cent in adults in the
First Series, and 58 per cent in children versus 44 per cent in adults in
the Second Series).[37] Pediatric recipients are therefore considered to be
favored and likely to have a better prognosis. The Cape Town group
still have reservations, although they concede that a number of chil-
dren have done extremely well in the Denver experience.

Cirrhosis

The authors believe that the most important future application of
liver transplantation lies in treating cirrhosis of the liver, particularly
non-alcoholic cirrhosis. Cirrhosis is the major indication for liver
transplantation in adults in Denver.[22, 24, 27] On the other hand, Calne
and Williams have some reservations in regard to this indication.[4] No-
body will deny that there are problems in treating cirrhotics by liver
transplantation. The difficulty of the operation in cirrhotic patients is
hard to describe. The procedure may take 12 to 18 hours and require
the use of literally dozens of liters of blood. The timing of the operation
in the course of the individual patient's disease is also difficult. One
must be certain that the patient has reached the end stage of the dis-
ease, but the operation must not be delayed until the patient is mori-
bund, otherwise the outcome will inevitably be fatal. Patients with al-
coholic cirrhosis should probably not undergo transplantation unless
they have clearly given up the abuse of alcohol.

From a technical point of view, adult patients with primary biliary
cirrhosis are ideal candidates. They do not have severe portal hyper-
tension and their livers are so soft and compliant that the technique is

almost comparable in simplicity to that in normal animals.[34] The Budd-Chiari syndrome may also constitute a rare but important indication in some patients, especially if they are deteriorating rapidly and not responding to conservative treatment.[17] However, the authors would currently first consider the use of portocaval shunting procedures in patients without inferior vena caval occlusion.[15, 16]

The ability to stop acute exsanguinating variceal bleeding by the combined use of a Sengstaken-Blakemore tube and peresophageal injection sclerotherapy[35] might well result in more cirrhotic patients surviving long enough to be candidates for liver transplantation. Furthermore, the eradication of esophageal varices and prevention of rebleeding using the simple technique of repeated peresophageal injection sclerotherapy[36] should also increase the potential pool of cirrhotic recipients.

Inborn Errors of Metabolism

Perhaps the most exciting chapter in liver transplantation has been the ability to cure inborn errors of metabolism by liver replacement. At present this applies particularly to alpha$_1$-antitrypsin deficiency and Wilson's disease with severe hepatic dysfunction.[32] Patients with congenital tyrosinemia and type IV glycogen storage disease have also undergone transplantation in Denver. The metabolic derangements in all these conditions have been corrected as long as the liver functioned.[27]

TISSUE TYPING, LIVER PRESERVATION, AND IMMUNOSUPPRESSION

Tissue Typing

Almost all the matches in the Denver Series have been bad. It has never been possible to give tissue typing a fair trial in liver grafting, because the need for transplantation in appropriate candidates has been so pressing that shopping for well matched livers has not been, and is unlikely to become, possible. Nevertheless, rejection has not been a major problem in liver transplantation. Acute rejection has been the primary cause of death in less than 20 per cent of patients in the Denver series, and chronic rejection has occurred in very few of the patients who died in the first year.[27]

Furthermore, hyperacute rejection has surprisingly not been seen in the 10 transplants performed in Denver in recipients with anti-donor specific cytotoxic antibodies. Both the Denver and the Cambridge groups have concluded that the liver is a highly privileged organ in confrontations with preformed cytotoxic antibodies.[24, 27]

Because of the urgency for transplantation in some patients, blood group barriers have been breached on 11 occasions. Although this should be avoided if possible, hyperacute rejection, which would occur commonly in kidneys transplanted under the same circumstances, has not been seen except in two exceptional cases.[24]

Liver Preservation

Simple hypothermic immersion storage of the liver for up to 8 hours was first reported using the pig by three groups, including the Cape Town group in 1971,[18] and by two groups using the baboon in 1970 and 1971. The details of these various simple techniques are summarized elsewhere.[2, 4, 18, 19] Short interval simple hypothermic preservation techniques have had extensive trials in man in both Denver and England with the shipment of livers from city to city. The Cambridge-Kings College group have used a plasma solution for cold infusion of homografts,[28] while the Denver group have used Collins solution.[2] The two techniques have been shown to yield comparable results and permit safe preservation of up to 12 hours in dogs. The same has been achieved in human beings.[2, 4, 24, 27] Complicated equipment is avoided, contamination by microorganisms is less likely, and transportation of the small box containing the chilled liver is simple.

Immunosuppression

The immunosuppressive regimens of the two major groups have become fairly standardized and include azathioprine (or alternatively cyclophosphamide) as well as steroids. The Denver group differ in that they often administer anti-lymphoid globulin in addition.

The major emphasis on non-immunologic factors as the cause of failure of liver grafts, as already described, and the apparent lesser rejection seen after liver transplantation than with other organ grafts, should not lead to the erroneous conclusion that the above immunosuppressive regimen is satisfactory. Although overimmunosuppression has been a major factor leading to infective problems, some patients have had rejection (vide supra). Furthermore, the side-effects of steroids, especially in children, constitute another major problem.

In an effort to reduce steroid requirements and to facilitate "graft acceptance," the Denver group have reported on 9 liver recipients treated by a thoracic duct fistula.[36] The fistula was inserted concomitantly with the liver graft in 7 patients and as a later procedure in 2. Five patients are currently alive (for periods ranging up to 9 months) including 3 of the 7 patients receiving concomitant transplant and thoracic duct fistula. Five of the patients with concomitant thoracic duct fistula have had either no demonstrable rejection, or easily controlled episodes of rejection, but unfortunately 2 patients with perfect liver function died of infections. The experience to date does not permit definite conclusions. However, thoracic duct fistulas are being routinely used at present in recipients of liver transplants.[37]

An interesting observation that may have an important bearing on the understanding of the immunologic problems of all organ transplants, but especially the lesser degree of rejection noted in liver grafts, has been made in liver transplantation in the pig. Independently, Cordier and Garnier and their colleagues in France and Terblanche and Peacock of Bristol, England, noted prolonged survival in un-immunosuppressed unrelated pigs after liver transplantation.[5, 26, 29] The first really long term survival of an un-immunosuppressed pig with a

liver graft from an unrelated donor was presented to the British Surgical Research Society in November 1966.[28] This young pig received a transplant on the 15th of June 1966 and weighed 64 pounds at the time of transplant. It survived for more than 2 years before dying of an unrelated intercurrent viral infection. In the meantime it had grown normally and ultimately weighed over 700 pounds. This pig confirmed the feasibility of performing transplants in children, without growth retardation, if the harmful side-effects of immunosuppression, especially steroids, could be avoided. After visiting Bristol to observe the technique in the pig, Calne's group in Cambridge changed from the dog to the pig model. They subsequently expanded the study of the immunologic manifestations of transplantation in the pig initiated in Bristol[10] and undertook a number of elegant and ingenious studies which have been summarized in a recent paper.[4] The work begun in Bristol has been continued and expanded in Cape Town[32] and elsewhere. Although no definitive answers have been forthcoming to date, the Cape Town group believe that the pig might yet hold important clues to a better understanding of the immunologic manifestations of organ transplantation in general.

HETEROTOPIC LIVER TRANSPLANTATION

Only 43 human heterotopic liver transplants have been reported to date.[8] The disappointing results have already been alluded to, as well as the one unique survival of over 5½ years achieved by Fortner.[8] A successful technique of heterotopic liver transplantation would have particular application to cirrhotic patients with severe portal hypertension and extensive vascular collateral vessels which make total removal and replacement of the liver (orthotopic transplantation) extraordinarily difficult. One reservation would be the possible late development of carcinoma in the diseased cirrhotic liver which would still be in situ.

A number of techniques of placing the graft have been described. None has met the ideal criteria for a heterotopic graft, namely direct venous drainage of the graft via its superior vena cava, the presence of an arterial as well as a venous supply, deviation of the total portal venous flow to the donor liver to prevent graft atrophy, and physiologic biliary drainage with retention of the sphincter of Oddi.[9,20] A modification of the original Gonzalez technique[1] has been developed in Cape Town and shown to be successful in the pig model.[6,9] This technique has also been shown to be technically feasible in man in a cadaver study.[6] The Cape Town group believe that this new modified technique merits a human trial in a limited number of cirrhotic patients in whom liver removal is judged to be particularly hazardous. On the other hand, the Denver group believe that some kind of auxiliary transplant could be used to tide over patients with fulminant hepatic failure until their diseased native livers recovered.[27]

CONCLUSIONS

Human liver transplantation, which was first performed in man in Denver 15 years ago, has finally come of age in the past 2 years. The 1 year survival has improved from 28 per cent to 50 per cent in the recent Denver Second Series.

Past experience has shown that long-term prognosis can usually be determined based on the 1 year assessment. Patients who are fit with a well functioning liver are likely to remain well. This applied to the 45 per cent of the 1 year survivors in the First Denver Series, who are still alive today at between 2⅚ and 8⅚ years. It has, however, been a much more frequent finding in the Second Series, which suggests that a significant number of patients should be long-term survivors in the future.

Improved survival has been attributed to a number of factors including a better understanding of the rejection and infection problems in immunosuppressed liver recipients. Postoperative hepatic dysfunction is no longer as easily ascribed to rejection, and an aggressive diagnostic approach has helped to prevent over-immunosuppression. Furthermore, new approaches to the biliary anastomosis, and a better understanding of the blood supply of the human bile duct, is currently preventing many of the earlier catastrophes related to this, the Achilles heel of liver transplantation.

The indications for liver grafting remain controversial. The best survival has been achieved in pediatric recipients in the Denver experience, although the issue of liver transplantation in children is not yet resolved. The authors believe that the most important future application of liver grafting will be in non-alcoholic cirrhosis.

The liver appears to be a relatively privileged organ in the human organ transplant setting. Although, immunosuppressive techniques have become standardized, they are not yet ideal. Recent experience in Denver with the addition of thoracic duct drainage has been encouraging. The pig liver transplant model may yet provide answers to some unresolved questions in organ transplantation.

Short-term liver preservation has improved, with simple hypothermic techniques providing satisfactory storage for up to 12 hours and allowing inter-city shipment of donor livers.

Finally, heterotopic liver transplantation, which has been almost uniformly unsuccessful in the past, may still be worthy of consideration under specific conditions if a successful technique can be developed for use in man.

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