Clinical Orthotopic and Auxiliary Liver Transplantation

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The concept of replacing diseased tissue by a graft from another individual was recorded some 800 years ago. The organ in that instance was a nose. In the intervening 2700 years, many legends about the replacement of tissues have evolved. In Florence, Italy, for example, you can see a painting which illustrates the legend of the black leg. Two Christian saints, Cosmos and Damian, transplanted a leg from a Negro to a saint of the church. According to legend, the patient’s leg was amputated because of a tumor, and on that particular day, the Negro donor just happened to die. The legend tells us that the transplantation was a success, but the length of the follow-up period is not given.

It was not until the 20th century that organ transplantation was recorded in medical history. In 1902, Alman described in detail the transplantation of a dog’s kidney from its normal position to the neck of the animal. In the same year, Alexis Carrel published an article in the Lyon Medicale on kidney transplantation. Alman and Carrel showed that vascular anastomoses was possible. Carrel, under the influence of von Guthrie, perfected his technique and received the Nobel Prize in 1912 for this work.

Transplantation was still far from a clinical realization at this time because of the then insurmountable rejection barrier. In 1912, Schone concluded that all allografts were rejected, but less strongly when the animals were of the same species. This introduced the genetic basis for transplantation. The mechanism of rejection remained unanswered until 1944 when Gibson and Medawar published their studies on the fate of skin allografts used in the treatment of burns. They observed the hastened rejection of grafts put on a second time from the same donor. This suggested an actively acquired immune rejection and was analyzed in basic studies by Burnett, Medawar,Billingham, Brent and Mitchison.

After the second World War, geneticists and immunologists began to work intensively on the subject. French workers removed the kidneys from recently guillotined criminals and placed the kidneys in patients chronically ill with uremia. Hamburger, Merrill and Hume,
studying cadaveric kidney transplantation around 1950, concluded that the allograft barrier
was insurmountable. However, identical twin transplantations performed in Boston and
Paris by these workers demonstrated that the operation could be performed surgically and that
such a transplanted organ could work.

The first attack on the rejection barrier was made in 1959 using whole body irradiation.
Despite a few successes, generally the graft lived but the patients died. In 1958, Schwartz
et al. discussed immune suppression with 6 mercaptopurine. Only a few months after this
publication, Calne and Zukoski found that this drug could delay the rejection of renal allo-
grafts in dogs. Two years later the first publication of successful clinical transplantation under
drug protection was published. In 1964, Starzl published the first large series of successful
renal transplants using drugs. More than 12,000 kidney grafts have now been done and
the success rate is most impressive.

The development of liver transplantation is now about where kidney transplantation was
ten years ago. I will review our present position with the liver. There are two main types
of liver transplants: an orthotopic graft in which the patient's liver is removed and the new
liver put in its place; the second type is a heterotopic or auxiliary graft in which the patient's
own diseased liver is untouched and the second liver is placed in a convenient site within the
abdomen. Historically, numerous attempts were made to perform both orthotopic and
heterotopic grafts in man in the spring of 1963. Success was not achieved for the orthotopic
graft until 1967 when Starzl performed the first successful orthotopic liver transplant. It was
not until 1969 when Fortner performed the first successful heterotopic graft. The latter was

Orthotopic Graft This procedure is particularly useful for patients with primary
cancer of the liver or extra hepatic bile ducts. It is also useful for patients with end stage
liver disease as seen for example, with cirrhosis, biliary atresia, yellow atrophy, Wilson's disease
or end stage viral hepatitis.

Briefly, the operative technique consists of mobilization of the liver including the vena
cava above and below the liver, and dissecting out the portal vein, hepatic artery and common
bile duct. The donor liver is similarly mobilized from the cadaver. A catheter is then
placed in the superior mesenteric vein so that the donor liver is perfused with a chilled low
molecular weight dextran solution. Once this is done, the liver is rapidly removed by cutting
the aorta above and below the origin of the celiac axis; cutting the portal vein; transecting the
vena cava above and below the liver; and transecting the common bile duct near the duo-
denum.

Attention is turned then to the recipient liver which is then removed by clamping and
transecting the hepatic artery, portal vein, bile duct and vena cava above and below the liver.
Following this, the donor liver is placed in the liver bed and vascular recontinuity re-established by end-to-end anastomosis. Reconstitution of the biliary tract has been a difficult problem. A variety of techniques have been used but we believe that a Roux-en-Y choledochojejunostomy is preferable. A T-tube is placed in the common bile duct.

During 1972, 22 orthotopic hepatic transplantations were carried out, bringing the world total to 145. Divergent opinion is present among liver transplanters as to the advisability of liver transplantation in cancer patients. Starzl believes that the high incidence of tumor recurrence precludes considering patients with hepatic malignancy as candidates for liver replacement. This view is not shared by Professor Roy Calne at the University of Cambridge, for he has one survivor more than 4 1/2 years after orthotopic replacement and another after 5 months for total resection of the liver for hepatoma. I consider patients with hepatic and extra hepatic bile duct cancer to be prime candidates for total hepatectomy and orthotopic liver transplantation. In the world series of orthotopic hepatic transplantation, one patient is alive more than 4 years after transplantation, and two patients survived more than 3 years. The original disease in these long term survivors were primary hepatoma, biliary atresia and Wilson's disease, respectively. In the liver of the child with biliary atresia, there was an incidental finding of a small hepatoma. In addition, 14 patients are alive more than one year after transplantation; six are alive more than two years after transplantation; four are alive three years after transplantation.

More recently, there appears to be some improvement in results due to several changes in management. The operation is performed in an earlier stage than in the past; careful preoperative evaluation of the recipients helps prevent technical complications; agressive re-exploration and reconstruction is practiced if complications do occur. Furthermore, it appears that the addition of cyclophosphamide to the immune suppressive regime is preferable to that of azathioprine in Starzl's experience as well as our own.

Heterotopic (Auxiliary) Graft An auxiliary liver transplant would appear to be an excellent way of treating end stage, non-cancerous liver disease for it obviates the need to remove the patient's own liver as with an orthotopic graft. The procedure is particularly attractive for individuals with cirrhosis, biliary atresia, or liver enzyme deficiencies, and could provide support for individuals in hepatic coma. In effect, an auxiliary graft adds functioning liver tissue and give portal decompression without depriving the patient of any of his own liver tissue. An additional feature is the support which the patient's own, partially functioning, liver might give during any life threatening rejection of the transplant. Despite these attractive theoretical considerations, clinical auxiliary liver transplantation heretofore has been singularly unsuccessful. The first clinical attempt by Absolon in 1964 was in a one year old child with biliary atresia who survived 13 days after the transplant. A total of 34 patients,
other than those reported here, have received an auxiliary graft with survival times ranging from a few hours to 34 days. The first relatively long term survival was reported briefly by Fortner et al. in 1969. The patient lived 240 days after the auxiliary liver transplant with continued good function of the graft throughout this period. Now, I can report on four patients who have received auxiliary liver transplants. Patient survival times were 37 days; 8 months; one is living and well nearly one year after transplantation; and the fourth was transplanted three weeks ago and is doing quite well.

Case Reports

Case 1: 72 year old woman with non-resectable, but localized cancer of the extra hepatic bile ducts. The portal vein was partially compressed by circumferential constriction of the cancer. A heterotopic auxiliary liver transplant was carried out on April 26, 1969 as a palliative measure to relieve intense icterus and pruritis. The patient lived 240 days with an allograft which appeared to function normally. She succumbed from multiple abscesses in her own obstructed liver, a subphrenic abscess, and a bleeding gastric ulcer.

Case 2: 42 year old woman with end stage chronic active hepatitis received an auxiliary liver allograft on October 28, 1972. An end-to-side anastomosis of donor superior mesenteric vein to the larger of two primary branches of the recipient's superior mesenteric vein was done. In the absence of portal hypertension, the recipient's vein was ligated distally so that a portion of splanchnic blood flow was preferentially through the graft. A cholecystojejunostomy was performed. Graft function was excellent, but a biliary intestinal fistula developed on the 9th postoperative day. She succumbed on the 37th post transplant day from sepsis.

Case 3: 4 1/2 year old male with biliary atresia received an auxiliary liver transplant on December 13, 1973. Donor superior mesenteric vein was anastomosed end-to-side to the recipient's superior mesenteric vein. The latter was not ligated since portal hypertension was present. A Roux-en-Y choledochojejunostomy over a T-tube was performed. The patient's postoperative course was uneventful. He is now almost one year after transplantation with a serum bilirubin of less than 1.0 mg%.

Case 4: 3 year old girl with biliary atresia. An auxiliary or heterotopic liver transplant was carried out on November 9, 1973. Her serum bilirubin is now within normal limits and she has had an uneventful postoperative course.

There are several problems encountered with auxiliary or heterotopic liver transplantation which are unique. One concerns site and space for the second liver. The right paravertebral gutter has proven to be a most satisfactory site for all of our grafts. However, closure of the abdominal wall is always of concern. In the first patient it was achieved by using a prosthetic film composed of polyethylene and Marlex to close a large defect in the musculature of the abdominal wall. In subsequent cases, ascites has been allowed to accumulate before
transplantation so as to stretch the abdominal wall. In its absence, a pneumoperitoneum has been used to gradually distend the abdominal cavity. A pneumoperitoneum is used for preparation of all of our candidates for auxiliary liver transplantation where the abdominal cavity does not seem large enough to permit placement of a second liver.

Vascular circuitry for heterotopic allografts has been the subject of much experimental study. Findings both of our own laboratory and that of others, indicate the need for each allograft to receive splanchnic blood flow preferentially to the recipient's own liver. Clinically, pathophysiological conditions related to splanchnic blood flow differed for each of our patients. Localized constriction of the recipient portal vein by cancer in the first auxiliary liver graft appeared to provide resistance so that splanchnic blood flow was directed preferentially to the graft. Significant portal flow persisted to the patient's liver and a balanced state seems to have been reached between the two livers for their weights were essentially the same at necropsy eight months after transplantation.

In the absence of overt portal hypertension in the second auxiliary liver transplant, ligation of a primary branch of the superior mesenteric vein distal to the anastomosis, was carried out. Splanchnic blood of intestinal origin was thereby directed preferentially through the graft. The patient's own liver received splanchnic blood through a second primary branch of the superior mesenteric vein as well as through the splenic vein. The presence of sepsis and a survival time of only 37 days complicate the findings, but graft atrophy was not present at necropsy.

Portal hypertension secondary to end stage biliary atresia was present in patients receiving auxiliary grafts Case 3 and Case 4. This provided a pathologic state whereby portal blood flow was preferentially through the graft. Serial technetium 99 sulfur colloid scans showed a shrinkage of the patient's liver to about 70% by the fifth post transplant day. This progressed so that by the 80th day the recipient's liver was barely visualized on scanning. Uptake by the transplant was normal and revealed a normal size liver. Radioisotope uptake in the patient's spleen showed a decrease similar to that of the liver. These findings suggest excellent reticuloendothelial function of the grafted liver and are consistent with a shunting of blood through the grafted liver.

Moderately severe allograft rejection was evident in the third auxiliary liver transplant on the 131st post transplant day. At this time, the recipient's liver and spleen showed an increased uptake. Clinical splenomegaly and thrombocytopenia corroborated these findings. Rejection was generally reversed and a slowly progressive decrease in recipient liver and spleen uptake and size again developed. There has been a corresponding decrease in spleen size on physical examination and a gradual return of normal platelet counts. These findings are consistent with the development of increased vascular resistance in the graft at the time of
rejection which approximated or exceeded that in the patient's own diseased liver. Splanchnic blood flow then be directed preferentially through the host liver. With control of rejection, vascular resistance in the graft decreased in relation to the patient's liver, resulting in reversal of dominant flow in this parallel flow system. Graft size has since remained constant.

Further clinical use of the auxiliary or heterotopic liver allograft is clearly indicated. Compared to orthotopic grafts, operative stress, risks and time are minimized since the recipient's liver is left in situ. Inter-liver competition between the patient's liver and the transplanted liver is not evident in our patients. Rather, both the patient's liver and the graft appear to behave as though they were a single unit.

Immune suppression for both the orthotopic and heterotopic liver grafts utilizes equine antilymphocyte globulin, steroids and either azathioprine or cyclophosphamide. Methylprednisolone (20 mg/kilo) is given intravenously daily for the first few days after transplantation, and with any sign of rejection. The latter being evident by clinical failures and changes in serum biochemical tests, liver scans and in vitro reactivity of cultured peripheral blood leukocytes.

Clearly, liver transplantation is making rapid progress toward achieving an important place in the treatment of liver disease. Improved tissue matching; improved methods of immune suppression; and further delineation of the various physiological factors involved will permit liver transplantation to achieve the same excellent results that kidney transplantation does today.

References
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