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# LIVER TRANSPLANTATION IN MAN *

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Until quite recently it was possible to give only highly tentative opinions on the role of liver transplantation in the treatment of patients dying of incurable liver disease. Now, a much more authoritative position concerning clinical liver transplantation can be taken, since there have been six patients who have lived for more than a year after removal of their own diseased livers and replacement with cadaveric organs.

The mortality has been high, just as it was in the first trials with renal transplantation. Nevertheless, we believe that the future role of liver transplantation in hepatic disease will not be fundamentally different than cadaveric kidney transplantation in the field of renal disease. In this paper we will give the justification for this optimistic view, mention the indications for such operations as they have become clear in the last year and, above all, focus attention upon the errors in technique or judgment we have made which have accounted for most of the early deaths in our experience.

## INDICATIONS

### *Nonneoplastic Disease*

Liver transplantation at the present time is indicated only for patients with severe and otherwise untreatable liver disease. A common indication is congenital biliary atresia, when the abnormality cannot be corrected by conventional surgical techniques. End-stage cirrhosis of the liver also provides a large pool of potential candidates for transplantation.

It is almost certain that a variety of inborn errors of metabolism could be cured by liver transplantation, since it has already been established that a number of proteins with identifiable phenotypes are changed after orthotopic liver transplantation to types previously present in the donor.

The role of liver transplantation for the treatment of acute hepatic disease caused by viruses or drugs has not been adequately evaluated. In such cases, two major handicaps are the fulminating nature of the hepatic failure and the possibility that the agents responsible for the original hepatic injury could also adversely affect the homograft.

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### *Neoplastic Disease*

It was once thought that a prime indication for liver replacement would be malignant hepatoma. As will be mentioned later, this expectation has not been fulfilled since we have invariably encountered recurrent neoplasm in our experience despite what was thought to be complete excision of the primary tumors at the time of total hepatectomy and liver replacement.

## Auxiliary Liver Transplantation

In this kind of liver transplantation, the host's diseased organ is not removed but a second liver is placed in some ectopic location such as the right paravertebral gutter, pelvis, or splenic fossa. At first thought this kind of operation has a special appeal, since it does not involve sacrificing whatever residual function may be left in the host's own liver. However, no patient so treated has been rehabilitated, and the maximum survival in any such operation has been only 35 days.

There are serious disadvantages to auxiliary liver transplantation. First, such homografts ideally should receive a double blood supply, the venous component coming from the splanchnic bed, a condition that from a technical point of view may be extremely difficult to realize in humans. Secondly, a kind of physiologic competition may exist between the homograft and the host's own liver even though the autologous organ is diseased. In dogs, this competion can easily be shown to cause atrophy of the transplant. In clinical cases the role of interliver competition is not known, although there is some evidence that it may be a factor.[1]

There is another disadvantage of auxiliary transplantation. Victims of terminal liver disease are unusually prone to all kinds of infectious complications, especially those involving the lungs. The placement of an extra organ in the abdominal cavity of such recipients has not been well tolerated in respect to respiratory physiology. Throughout the world reports have come in, with deadly consistency, of these patients developing lethal pneumonitis.

## Orthotopic Liver Transplantation

Those clinical successes mentioned in the introduction have all been with orthotopic transplantation. In this operation a place is made for the new organ by removal of the diseased liver. In principle the procedure could hardly be more simple, since it involves the restoration of normal vascular channels plus provision for biliary drainage, usually with a cholecystoduodenostomy. In practice, however, the operation may be difficult because of the extremely poor condition of most prospective recipients, because severe portal hypertension must usually be dealt with, and perhaps most importantly because of a high incidence of anatomic anomalies which are encountered.

## *Anatomic Anomalies*

### *Vascular*

The most common vascular anomaly is that found when the arterial supply comes both from the celiac axis and the superior mesenteric artery. Some variation from normal can be expected in about 20% of livers. Since the anomaly may occur in either the donor or the recipient, it is necessary to perform a modified procedure in almost 40% of human cases.

When double arteries are encountered in the donor liver, they can either be anastomosed directly to the right and left hepatic arteries of the recipient, or a segment of the donor aorta in continuity with the origins of hepatic arteries can be sewn to the host aorta. When the double arteries are encountered in the recipient, they are often of small size and it may be preferable to ligate them. In that case, a Carrel patch of the donor aorta bearing the celiac axis and its hepatic branch can be sewn into the anterior wall of the recipient aorta.

In one of the two cases in which this was done a large caudate lobe of the liver caused compression of the arterial supply, leading to prompt death of the patient. In the second case this also occurred, but the problem was recognized on the operating table and the donor celiac axis was then anastomosed to the host's right hepatic artery. However, the patient died 12 hours later of portal vein thrombosis. This was probably caused by a gross disparity in size between the donor and recipient veins, the vessel in the host being hypoplastic.

### *Biliary Tract*

Anomalies of the bile ducts may also contribute to the hazards of the operation. In three patients, the cystic duct ran parallel to or behind the common bile duct for some distance before finally entering it. In one patient the problem was not recognized during donor hepatectomy, and a ligature was inadvertently placed around both structures causing obstruction proximal to the cholecystoduodenostomy. The patient developed progressive jaundice and died. In the other two patients the anomaly was recognized, the gallbladder was removed, and choledocho-choledochostomy was performed. However, the recipients died of upper abdominal sepsis.

## *Ischemic Injury of the Liver*

We have described only a partial list of the technical problems that have been directly responsible for failure. Another kind of combined technical and judgment error is the use of an organ that has been irreparably damaged by ischemia in the donor. After operation, evidence of very serious ischemic injury is manifested by an early rise in the transaminase values, deepening jaundice, and deterioration of other liver functions. The use of such badly damaged organs has essentially been eliminated in most centers by clarification of the criteria of brain death that have made it possible to remove organs at an earlier time.

### *Preservation of Donor Liver*

There have been other innovations which have made it possible to assure good quality liver homografts. After death, circulation to the liver can be maintained while it is being dissected free by simply using a standard cardiopulmonary bypass. In addition, a heat exchanger is used in the circuit to provide hypothermia of the perfused liver. After excision of the liver, it can be transplanted immediately or placed in a conservation chamber employing low-flow perfusion, hyperbaric oxygenation, and hypothermia. Using the latter method, the organ can be kept in good condition for as long as eight hours.

### *Rejection*

Apart from technical risks, the main threat to the liver is rejection by the host. This may take one of several forms. One variety is subclinical rejection, in which there is only biochemical evidence of deterioration of function of the transplanted liver after an initial period of satisfactory performance. The bilirubin level does not rise, but there are definite increases in the serum transaminases and the alkaline phosphatase. In most cases, these eventually return to normal. A very common finding at the time of hepatic homograft rejection is swelling of the homograft, as can be demonstrated by serial liver scans.

A second form of rejection is of a rather indolent nature. Jaundice develops slowly and insidiously over a period of many weeks. The elevated bilirubin level is accompanied by elevation of the alkaline phosphatase. With prolonged steroid therapy, the immunologic process can eventually be reversed.

On several occasions, a third variety of rejection has presented as a crisis. In these cases the patients have often become violently ill, since jaundice has developed with amazing rapidity. In one patient, the bilirubin rose from almost normal levels to 15 mg% in little more than one day. At the peak of the rejection crisis a gram-negative septicemia may develop, indicating that the injured liver is unable to clear microorganisms reaching it from the bowel.

In experimental animals, it has been shown that liver rejection is invariably accompanied by a sharp decline in the total hepatic blood flow. Serial liver scans in patients may reveal changes which are probably due to similar immunologically mediated falls in blood flow. As the rejection crisis develops, large areas of the liver cease to take up the technetium isotope. However, with relief of the rejection, the poorly opacified portion of the liver regains its reticuloendothelial function and the scan appearance improves.

It is probable that the chain of events just described occurred in five of the first patients who achieved extended survival after liver transplantation to such a severe degree that frank necrosis of the liver resulted. Associated with the appearance of large filling defects in the liver scans, the patients became prostrated, developed a gram-negative septicemia, and at reoperation had regional necrosis of their homografts which tended to be localized to the right lobe. The septicemia apparently resulted from the devitalized hepatic tissue being invaded by bacteria that are normally present in the intestine. The microorganisms were then disseminated from the focus of gangrene.

A mechanical factor probably contributed to the localization of the hepatic

infarctions to the right lobe in these early cases. This was shown by performing simulated liver transplants in recently deceased cadavers. The suspensory ligaments of the liver were incised and a choledochoduodenostomy was constructed. The liver was then able to rotate slightly and cause minor kinking of the right hepatic artery. However, the primary factor in causing the hepatic infarctions even in these patients probably was low-grade rejection which, in turn, was due to inadequate immunosuppression. Thus, paradoxically, the way to avoid this complication of hepatic sepsis is to give heavy immunosuppression in the early postoperative period.

A fourth variety of rejection is a chronic form which starts late after transplantation and usually proves to be nonreversible. It is manifested by a clinical picture resembling obstructive jaundice, with elevation of the bilirubin and alkaline phosphatase levels. Despite this, the patients may remain surprisingly well with retention of good synthetic function in the liver for many months or even years. Alternatively, there may be a slow progressive decline in liver function that may necessitate retransplantation as was done in one of our patients 12½ months after an initial transplantation for a hepatoma.

### *Long-Term Results*

It has become clear to us that efforts to treat hepatic malignancy with liver replacement are not going to be very fruitful. To date, we have had five patients with hepatoma who have lived long enough following operation to permit meaningful observations about the natural history of this disease after what was thought to be complete excision of the neoplasm. Recurrent tumor developed in all five cases. One of the patients died of other causes after 2½ months although there were already pulmonary metastases. The other four were killed by their malignancies after 5, 12, 13, and 14½ months. The homograft itself became the seat of metastases in four of the cases, and was largely replaced by tumor in two of these.

There is a great deal of evidence that immunosuppressive agents may actually increase the growth rate of malignant cells. Consequently, if hepatomas are to be treated with transplantation, stringent precautions must be taken to be sure that no tumor is left behind.

To date we have treated three patients for benign disease (biliary atresia), with survival for more than a year. One of these recipients died of hepatic insufficiency after 14 months. A second is in good condition after 20½ months, although he has imperfect liver function. The third patient was treated 15 months ago, and has completely normal hepatic function today.

There is now enough information to permit the construction of life survival curves in recipients of orthotopic liver homografts. FIGURE 1 summarizes our total experience from March 1963 until February 1969. There were 25 consecutive cases. The first seven attempts resulted in death of the recipient within 23 days or less. The first patient who achieved extended survival was operated upon in July 1967. Of the remaining patients treated, those still living now have a minimum follow-up of 15 months so that the life survival curve is complete beyond one year. Six of these last eighteen patients lived for at least one year. This survival rate of 33% is almost identical to that achieved in cadaveric renal transplantation when the first successful trials with that opera-

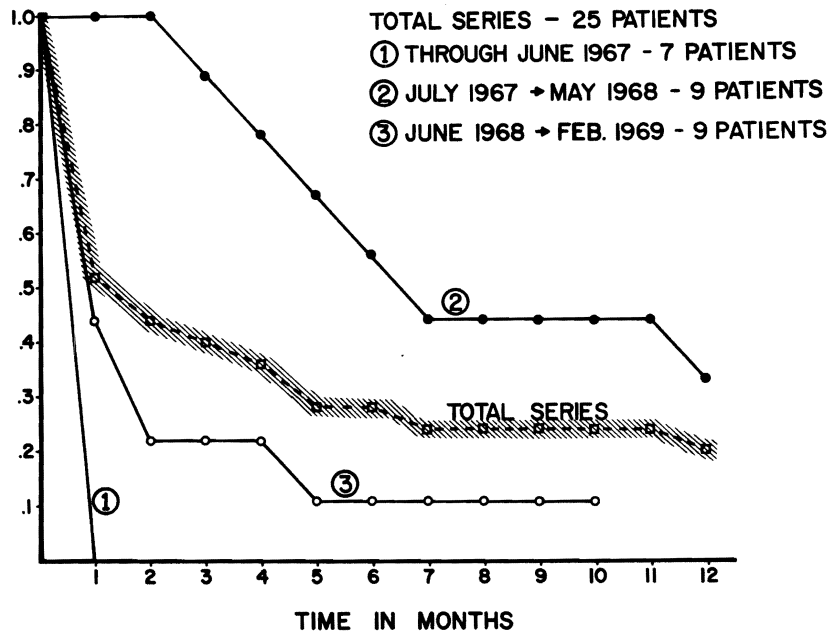


FIGURE 1. Survival curve of 25 patients treated at our institutions with orthotopic liver transplantation between March 1963 and February 1969. The shortest follow-up for recipients who were still alive in June 1969 is 15 months. Thus the curves may be considered complete to one year. The results have also been divided according to the first, second, and third intervals of our total experience.

tion were made from 1962–1964. The uncorrected one-year survival, including the first seven failures, was 24%. Thus, the results of liver transplantation are hardly discouraging, since all these patients would otherwise have been doomed to an early death. Moreover, we can be certain that by avoiding the pitfalls already mentioned, these statistics will be steadily improved, as has occurred with renal transplantation.

## SUMMARY

Orthotopic liver transplantation, which proved to be a feasible undertaking in dogs more than five years ago, has become possible in humans. Six patients with liver replacement have now lived for more than a year; the maximum survival time so far has been 20 months in a patient who is still alive. The prime indication for liver transplantation is benign hepatic disease. Liver replacement for hepatoma has, in our experience, not prevented the development of metastases. It now seems certain that liver transplantation will achieve a legitimate and important place in the armamentarium available for the treatment of severe liver disease.

REFERENCE

1. STARZL, T. E. (with the assistance of C. W. Putnam). 1969. Experience in Hepatic Transplantation. W. B. Saunders Co. Philadelphia, Pa.

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## DISCUSSION OF THE PAPER

UNIDENTIFIED SPEAKER: Assuming we can find a way to get better tissue matches, I wonder if the liver may do better than some other organs in transplantation.

DR. PENN: We will not attempt to do a transplant of any organ without prior histocompatibility matching. In the case of transplants of organs between related living donors, as in kidney transplantation, we believe that histocompatibility matching is a very useful guide. A good match in general means little rejection, whereas a bad match would indicate problems with rejection. However when we come to transplant organs from unrelated cadaver donors, we do not know what the significance of histocompatibility matching is. We have seen numerous cases where bad matches have given good results and good matches have led to poor results. In fact, many of our best results with liver transplantation have been in patients with bad matches, the so-called Terasaki C or D match. The one child I showed you, is a 15 months survivor with a D match involving a mismatch of three of the HLA antigens. So I'm afraid I don't know what the significance of histocompatibility matching is as regards cadaver organs.

DR. LEE (*Richmond, Va.*): I would like to comment on the correlation with histocompatibilities. The difficulty here is, as he says, in understanding its significance. In cadaver transplant of kidneys, the correlation isn't as good as it is with living related siblings. The second point I would make is illustrated by one experience we had in a recent liver transplant attempt. We had a donor which matched very well, then cross-matched it to make sure that the recipient didn't have a serum antibody against the donor cells, using the peripheral lymphocyte, as we always do. Again this was negative. So we transplanted the liver and it worked well, the liver pinked up immediately and everyone was pleased. Within a few hours, however, the patient was doing poorly, and at reoperation, the liver was pale and blotchy. This is somewhat analogous with so-called hyperacute rejection in the kidney. We suspected thrombosis as a result of a mechanical problem, but actually at postmortem examination there was no thrombosis in the major arteries. We rechecked the matches and found that the donor's kidney cells and liver cells did indeed react with recipient's serum, which we couldn't do before transplant was completed. So it is not as simple as assuming that if tissue matching is good, the result will be good.

DR. PENN: So far, we've avoided the problem that Dr. Lee mentions.

DR. ZUIDEMA (*Johns Hopkins University, Baltimore, Md.*): Dr. Penn, would you care to comment on the pig liver transplants? I believe that several of these have been carried out without immunosuppression; would you comment on that point.

DR. PENN: I think this is one of the most interesting aspects of transplantation of the liver. This is work that's been done mainly by Dr. Roy Calne in Cambridge, England, who has done transplants between unrelated pigs, and has demonstrated prolonged survival in some of the animals, even though there were histocompatibility barriers. Now what the exact explanation for this is, is not known, but he believes that it is possible that the liver may produce some substance which may affect the immune apparatus.

We have had some similar results in dogs who were kept on immunosuppression for a period. The immunosuppression was then stopped; some of the animals died of rejection, but there were a few of the animals that have survived. We have two dogs that are now alive five years following liver transplantation, who only had immunosuppression for the first four months following the transplant.

DR. DEUTSCH (*Philadelphia, Pa.*): Is there any relation in your animal work between the mass of liver tissue transplanted and the rejection?

DR. PENN: Studies have been done about so-called antigenic overload. It appears that this is not of importance in liver transplantation. We've seen some frightful rejections with liver transplantation in man.