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Current status of transplantation surgery

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I am going to endeavour to cover 3 questions that arise with regard to orthotopic liver transplantation, that is to say regarding liver *replacement*: (1) What are the indications for hepatic transplantation? (2) What have been the results? (3) What are the prospects for their future improvement?

As a reminder of what exactly *is* implied by orthotopic liver transplantation, with this operation the diseased native liver is removed, thus creating a space which is to accommodate the cadaveric graft. Orthotopic liver transplantation is often very difficult, mostly because of the existing liver pathology that essentially always engenders a severe portal hypertension and produces extensive venous collaterals; thus the removal of the native liver may indeed well be an extremely formidable undertaking. Revascularization of the graft is performed in as anatomically normal a way as is possible – anastomosing the portal vein and hepatic artery end-to-end and reconstructing the vena cava above and below the liver.

By far the most unsatisfactory aspect of this operation so far has been adequate biliary duct reconstruction; for most of our cases we have anastomosed the gallbladder to the duodenum after ligating the distal common bile duct. This hook-up has many real advantages under conditions of immunosuppression because it can be performed without stents and drains; nevertheless, there have been a number of fatal complications connected with these cholecystoduodenostomies, an important point to which I will return later.

With these preliminary remarks I shall now turn to the first question – what are the indications for this operation? In the beginning we thought that the ideal reason for liver replacement should be primary hepatic malignancies, including hepatomas, typically exemplified by the kind of extensive hepatoma we treated in this way in the early trials. Our enthusiasm was quickly dampened by a repetitive experience such as we encountered in the following typical individual case.

The chest X-ray of a 15-year-old boy a few weeks after a successful orthotopic liver transplantation for a gigantic hepatoma already showed evidence of a small pulmonary metastasis. He died 143 days after the operation with his lungs almost replaced by metastases. During this same interval his new liver was similarly invaded as could be followed with serial scans. There was evidence of metastases at all times from 3 months onwards after the operation.

With the destruction of his liver the patient became secondarily jaundiced and he finally died of combined hepatic and pulmonary insufficiency. At autopsy his lungs were one mass of tumour. The same was true of the transplanted liver to such an extent that

only a tiny remnant of normal hepatic tissue remained. We have had a half dozen other so-called successful liver transplantations with subsequent widespread metastases and in actual fact 3 of our patients died over one year post transplantation from this complication.

Nevertheless, it is a bit early to conclude once and for all that liver transplantation cannot be used to treat a hepatoma, which is also clearly illustrated by another case. In the liver of a child with biliary atresia a small 2 cm hepatoma was found purely as an incidental pathological feature. The child was referred from the Illinois Research Hospital of Chicago. She has a perfect result without any evidence of tumour recurrence 2.5 years later. Long survival after liver replacement for a hepatoma has also been reported by Calne of Cambridge, Deloze of Montreal and Fortner of New York. Nevertheless, I personally would prefer *not* to do more liver replacements for hepatomas at this time since the high incidence of metastases (80% in our hands) has beclouded the kind of conclusions that must be reached properly to evaluate any new procedure.

It has seemed possible that the outlook might be rather less gloomy if the malignant tumour were of some kind other than a hepatoma. I would not be surprised if non-resectable cholangiocarcinomas proved to be good candidates. Then there are the rare neoplasms: a gross specimen with widespread multifocal primaries was seen in a 52-year-old man who had a haemangioendothelial sarcoma. The neoplasm kills with incredible swiftness, usually within a few weeks and by intra-abdominal haemorrhage or by the development of hepatic insufficiency *rather than by tumoral spread*. We treated this patient in 1971. Postoperatively, the bilirubin fell from 40 to nearly normal, along with an improvement in other liver functions. Then the patient survived a severe rejection which was eventually completely reversed. After achieving nearly normal liver function for more than 3 months, this patient also unfortunately developed widespread pulmonary metastases, as well as an extensive tumour recurrence in his liver graft. Thus we have here one more characteristic example of the usual futility of treating hepatic malignancy with a hepatic transplantation.

I should like to draw your attention to the fact that one of the immunosuppressive agents used for this patient was cyclophosphamide rather than Imuran. Cyclophosphamide itself is one of the most widely used of the anti-cancer chemotherapeutic drugs. It is also one of the best immunosuppressants. In addition, ALG and prednisone were also used.

Although I sincerely apologize for starting in such a seemingly negative way about the indications for liver replacement, this is one way of indicating that really the important future for hepatic transplantation is in the treatment of *benign* hepatic disease. I will not even bother to list the diseases for you since the end-stage is always the same. In fact, the general position we adopt now is that anyone under 40, who is not a sociopath and who is dying of hepatic insufficiency should theoretically be a suitable candidate for a liver transplantation. The most common diagnoses would of course be cirrhosis, chronic aggressive hepatitis, and biliary atresia.

The longest survivor in the world to date after a liver transplantation was a boy whose operation was in July 1968. There was a very minimal rejection crisis in the second postoperative month. His liver was biopsied 3 years later and was found to be almost normal, then suddenly just before Christmas 1971 he developed massive hepatic necrosis for which the aetiological explanation has not so far been clarified although late rejection may well have been the responsible factor. He died of acute hepatic insufficiency a few days later after a total survival time of 3.5 years, happily all of which was in good health.

Another patient with benign disease was a child suffering from Wilson's disease which led to cirrhosis and finally to profound liver failure. After the operation he had a grave rejection crisis which eventually reversed and with an ultimately good result he is still alive to date after more than 2.5 years. He has returned to his home in Ohio where he now goes to school.

As many of you know, Wilson's disease is an inborn error of metabolism of which the precise pathophysiology has never been completely worked out. The essential biochemi-

cal finding is a deposition of copper in all tissues, including the liver and the brain. The characteristic Kayser-Kleischer rings by which the ophthalmologist can make the diagnosis are in fact nothing more than copper accumulations in the cornea. The information we have about this case leads us to believe that this copper accumulation does not occur post transplantation; on the contrary, the tissue copper probably remains normal. After the operation there was a massive cupruresis which lasted for almost 6 months and which was augmented in the end by a course of penicillamine. At this time the liver was biopsied and then biopsy was repeated after 1.5 years and after 2.5 years; on all 3 occasions the liver copper content was entirely normal.

We also treated another patient with Wilson's disease, this time more than one year ago. In the case of this second patient the main indication for proceeding was his extremely severe neurological involvement that was not able to be controlled by penicillamine therapy; in fact, the recipient was so neurologically crippled that he even had some respiratory distress. The first important point to note is that immunosuppressive treatment was again with cyclophosphamide (or Cytoxan) instead of with Imuran and in addition to the cyclophosphamide, horse ALG and prednisone were administered. The second important point is that rejection probably never occurred in this patient. There was a marked deterioration of hepatic function in the second postoperative month at which time the boy became jaundiced and had rises in his transaminases. This was probably not rejection as at the same time he developed Australia antigenaemia, with prodigious increase in his complement fixation titres. Immunosuppression was not intensified and he spontaneously recovered. The reason for mentioning this second point is that we now realize how many factors *other* than rejection can cause a deterioration of the hepatic homograft function. The most important of these non-immunological complications are serum hepatitis, such as evidenced here, biliary duct obstruction, which I shall come back to later since it is a much dreaded complication, and drug-induced hepatotoxicity.

This concludes my remarks about the indications for hepatic transplantation. If perchance I have not made my position entirely clear, I can aptly summarize it with one sentence. We believe the situation is completely analogous to that applying to renal transplantation in which field *benign* disease is also the primary indication for treatment. I now pass to the second question, namely what are the results obtained? Between the spring of 1963 and July 1967, 7 attempts at an orthotopic liver transplantation were made in Denver, all of which failed with death in 21 days or even less. Our own experience, including these cases and all subsequent ones undertaken until one year ago, comprises 42 cases. A survival time of at least one year was obtained for all of these 42 recipients (26%). This record cannot be described as disgraceful as all these patients were doomed to certain and early death, but it can certainly stand improvement.

As I already mentioned, the most common causes for late failures were carcinomatosis and late rejection, accounting for 3 of the deaths each after one year, while serum hepatitis caused 2 late deaths. The whole question of serum hepatitis in transplant patients is just beginning to unfold but there is plenty of reason to know that potentially it is a most serious matter. Liver disease and specifically hepatitis in renal transplant patients is a very common complication, occurring in 10–20% of all kidney recipients in our centre. The incidence of serum hepatitis in our liver patients is even higher and I have already mentioned one example of this. In view of these observations, is there any hope of treating fatal serum hepatitis by a liver transplantation? I must confess that I do not know the answer to this question. However, I would like to tell you about one extraordinary patient whose reason for liver transplantation was chronic aggressive hepatitis, Australia antigen positive. She was in profound hepatic failure. Transplantation was done in August 1970. The Australia antigen became negative for almost 2 months and then returned to positive at the same time as she had a clinical bout of acute serum hepatitis. She recovered from this but her Australia antigen remained positive. A repeat biopsy 14 and 18 months after transplantation revealed that there was a recurrence of the chronic aggressive hepatitis in her transplanted liver and she died from a nocardial infection 20

months postoperatively. The aggressive hepatitis had progressed; nevertheless, her health had been reasonably satisfactory for most of her time of survival and for this patient meaningful life was prolonged. In view of this the issue as to whether more similar patients to this one should be so treated is perhaps more of a philosophical nature than it is a medical one.

I will now turn to the third question I posed at the outset, namely what are the prospects of improving the outlook after liver replacement, at the same time making the assumption that only reasonable candidates with non-malignant disease are accepted. First of all, we are absolutely convinced that one of the real Achilles heels of this procedure is ineffective reconstruction of the biliary duct.

Using cholecystoduodenostomy we have experienced obstruction at or near the junction of the common and cystic ducts. The true nature of the lesion can be appreciated by an operative cholangiogram performed with the Foley catheter inserted into the gallbladder; the obstructed duct system is quite obvious. This was corrected in 2 cases at reoperation but too late, all 4 of the patients with this lesion died. Dr. K.A. Porter of London has examined tissues from these homograft biliary ducts and gallbladders. He found widespread evidence of cytomegalovirus (CMV) and ulceration apparently caused by this agent; thus this kind of obstruction may at least stem from a partially infectious aetiology.

In 4 recent cases of liver transplantation we have performed choledochoduodenostomy by the method of passing the common duct through a short duodenal tunnel and then everting it with a few sutures. Unfortunately the choledochoduodenostomy disrupted in one of these patients leading eventually to death from a biliary peritonitis; consequently we have now changed back to cholecystoduodenostomy as a routine. However, we now wish to follow a policy of early re-exploration, cholangiography, and the consideration of a secondary repair *if* postoperative jaundice develops and is persistent.

In addition to proving the correct management and judgment regarding possible homograft biliary obstruction, we believe it is important to try to use immunosuppressive agents that have low hepatotoxicity and with this objective we have switched since early last year to cyclophosphamide instead of Imuran for all our new cases. It must be emphasized that the usefulness of this major change will require much more evaluation before it can be generally recommended.

Liver transplantation can be a very discouraging field. Because of our apparent inability to improve our results, we declared a moratorium for almost the entire latter half of 1971, but then we began again in January 1972. We have treated 5 patients, all with triple drug immunosuppression, including cyclophosphamide. One died of hepatic artery thrombosis, the other 4 are still alive, all with excellent liver function from 1 to 4 months postoperatively. They represent the best group of liver transplant recipients that we have ever seen. We hope that they are providing some useful insight into the next great phase in the development of this difficult surgical field, but of course it is too soon to assert this as a definitive opinion.

I will summarize now by giving a brief answer to each of the 3 questions I posed at the beginning. First, the prime indication for liver replacement is non-neoplastic hepatic disease. Secondly, the 1-year survival rate in our clinic for all patients treated *up to* one year ago was between 25% and 30%. Thirdly, there is good reason for considerable optimism that this survival rate can be much improved by better technical performance and more especially by improved biliary duct drainage. Some recent developments in immunosuppression when cyclophosphamide has been used to replace or supplement Imuran may also be beneficial.