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Hepatic transplantation, 1975

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Summary

This report reviews experience with 97 patients given liver transplants. We regard our survival statistics as unsatisfactory, but feel they should encourage further work since 22 patients have survived at least one year with a maximum survival of 5⅔ years. The Achilles' heel of liver transplantation is bile duct reconstruction. We presently rely upon Roux-en-Y reconstruction, or alternatively, duct-to-duct anastomosis with a T-tube stent. The prime indication for liver replacement is non-neoplastic liver disease, but a favourable malignancy for treatment may prove to be small intrahepatic duct cell carcinomas.

DURING the last ten years over 200 patients have had liver replacement throughout the world. The University of Colorado Group has contributed 97 cases to this total, at a rate of 10 to 20 per year, since 1967, when the first long term survival was achieved (Starzl and Putnam, 1969). On the basis of this experience, we would like to provide a progress report regarding survival statistics, indications for operation, our present views about bile duct reconstruction, and our current programme of immunosuppression.

Survival

Table 1 depicts our 97 cases. Twenty-two patients have lived for one year after operation, ten for two years and six have survived for three years. Two have passed the five years mark and both are alive now. Eighteen recipients are still alive, from three weeks to 5⅔ years postoperatively. An 18-year-old boy who is alive 5⅔ years after transplantation represents the longest survival after liver transplantation in the world.

There have been 11 late deaths, from 12 to 41 months postoperatively, for the reasons listed in Table 2. Two late deaths were the direct consequence of failure of biliary drainage. The latest mortality was at three years, five months, and was related to an episode of haemophilus septicaemia. Recurrent cancer in patients treated for hepatoma caused three deaths after one year. This disease has also killed some of our patients earlier than this, and we therefore consider hepatoma to be a relatively poor indication for liver transplantation. However, it is not an absolute contraindication since one of our five year survivors had a hepatoma in addition to biliary atresia. Calne, and Daloze of Montreal, have also apparently cured hepatomas with liver transplantation.

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TABLE 1. Cases of orthotopic liver transplantation treated in Denver

		Lived				
	Number	1 year	2 years	3 years	5 years	Alive now*
1963–1966	6	0	0	0	0	0
1967	6	1	0	0	0	0
1968	12	5	2	1	0	0
1969	6	2	1	1	1	1
1970	10	2	1	1	1	1
1971	11	2	2	2	0	2
1972	11	5	3	1	0	2
1973	13	3	1	0	0	3
1974	20	2	0	0	0	8
1975	2	0	0	0	0	1
	97	22	10	6	2	18

* Longest survivors: 5⅔ years; 5 years.

TABLE 2. Present status of 22 one-year survivors

Alive 11/22—12 months to 68 months
Dead 11/22—12 months to 3½ years
Recurrent cancer—3
Chronic rejection—2
Chronic hepatitis—2
Bile duct obstruction—2
Other infections—2

Biliary recons

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Biliary reconstruction

With only 22 one-year survivors, it is obvious that the operation is at present unsafe. The single most important factor in the high acute failure rate has been a multiplicity of technical misadventures, of which complications of biliary duct reconstruction lead the list. Indeed, this is now the main technical problem that we face. The different techniques we have used to restore bile drainage include choledochocholedochostomy with or without a T-tube, cholecystoduodenostomy after ligation of the graft common duct and choledochoduodenostomy. Because of continuing dissatisfaction with all of the aforementioned techniques of duct reconstruction, we have recently embarked on a trial of Roux-en-Y cholecystojejunostomy (Starzl *et al.*, 1974).

None of the commonly used methods of biliary duct reconstruction has been trouble-free. With cholecystoenterostomy, fistulae are uncommon, but obstruction occurs in 25% of the cases. These obstructions at the cystic duct (Fig. 1) are sometimes due to cytomegalovirus (CMV) infection. Most commonly, however, no obvious aetiologic cause accounting for the partial cystic duct obstruction is evident.

Our main objection to choledochocholedochostomy is the high incidence, about 50%, of bile fistula with subsequent subhepatic sepsis. We are sure that bile leak is always going to be a problem in the immunosuppressed recipient, so that if one does perform a duct-to-duct reconstruction, broad drainage, such as by leaving part of the wound wide open, must be carried out. Under these conditions, we have recently employed end-to-end duct reconstruction in two adult recipients. One patient is only three weeks post-transplantation, but the other is well six months after operation.

With such well-defined technical complications, clinical evidence of cholangitis is easily understandable and is often accompanied by histopathologic

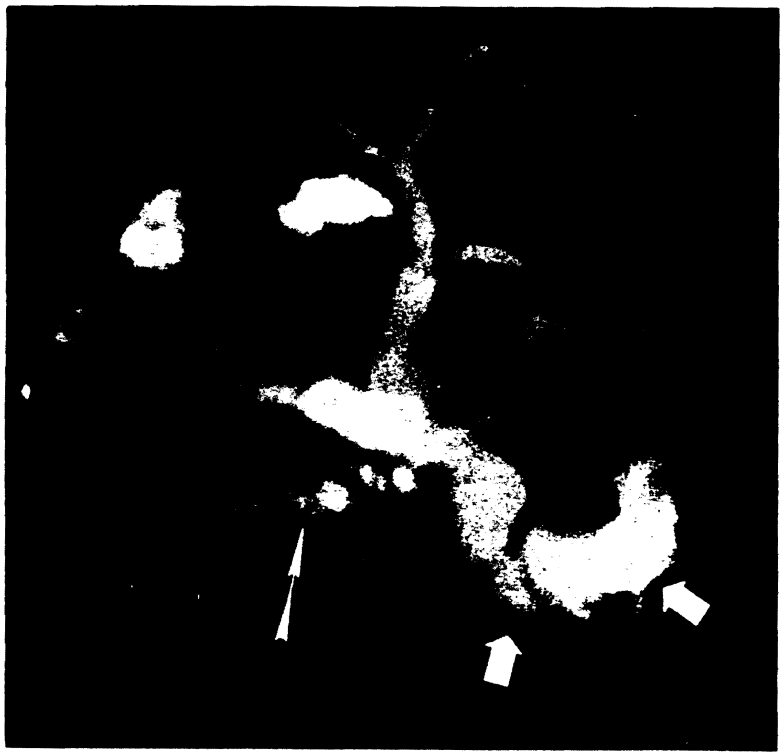

FIG. 1. Partial cystic duct obstruction following orthotopic liver transplantation. Biliary drainage was provided by a Roux-en-Y cholecystojejunostomy. Two months after operation the patient suddenly became jaundiced. A transhepatic cholangiogram showed a partial obstruction of the cystic duct (small arrow). There was also a leak of the ligated common bile duct (large arrows). The patient died of sepsis before a secondary reconstruction could be accomplished.

findings of cholangitis. In addition, a subtle and as yet hypothetical complication may occur in spite of an apparently satisfactory biliary duct reconstruction. We have reported that systemic infection and even asymptomatic bacteraemia are common problems in liver patients (Starzl and Putnam, 1969). In the liver recipients with bacteraemia, the failure to find any other focus of infection necessitates indictment of the homograft, as the site of entry, by the process of exclusion. The two possible routes of entry could be the portal vein or the duct system, but the latter seems the more likely to us.

The exposed relation of the duct system of the orthotopic liver to gastrointestinal flora is probably the first step in bacterial 'leak' through the homograft which may well be bacteriologically porous without the presence of histopathologically significant cholangitis. If bacteria enter the circulation through the duct system of hepatic homografts, the logical solution would be to carry out liver transplantation as far removed from the mainstream of the gastrointestinal tract as is possible (Fig. 2). The alternative would be to retain the sphincter of Oddi by using a choledochocholedochostomy with the important secondary defence provided by massive drainage.

Obviously, we are recommending individualization of biliary duct reconstruction depending upon the circumstances of the case. But whatever the original technique, the development of either jaundice or systemic sepsis should cause intensification of diagnostic efforts to differentiate between duct obstruction and rejection. We always perform

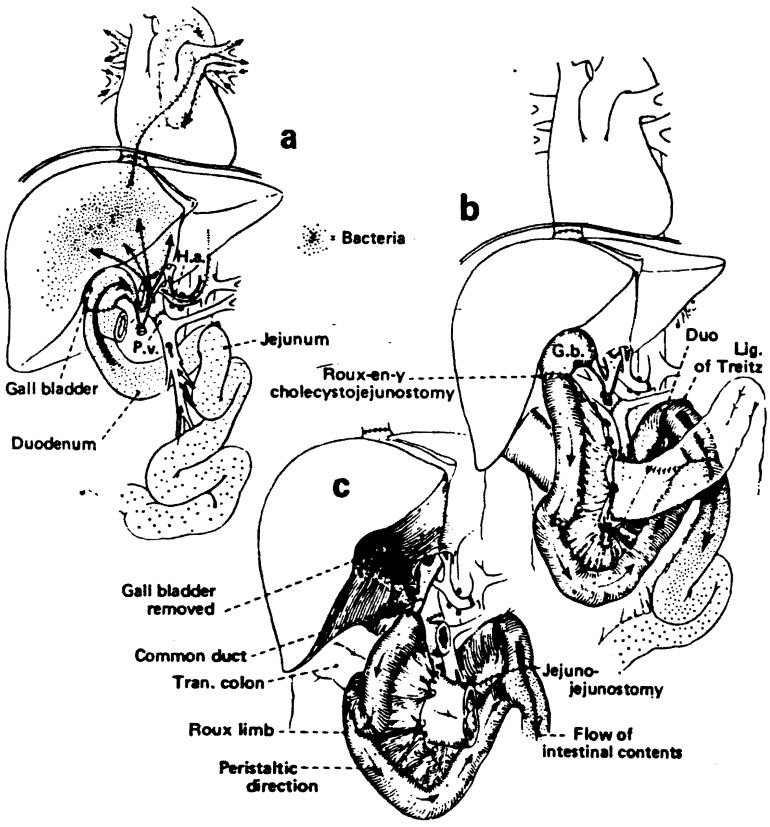

FIG. 2. Relative bacterial contamination with three kinds of biliary reconstruction. (A) Cholecystoduodenostomy. This procedure is the simplest, but probably carries the greatest risk of infection of the graft. (B) Roux-en-Y cholecystojejunostomy. The liver is protected from bacterial contamination by creating an isoperistaltic limb of jejunum, 18 inches in length, isolating the biliary tree from the gastrointestinal tract. (C) Roux-en-Y choledochojejunostomy. A duct-to-bowel anastomosis is simple if the duct has become dilated, as would be the case if a conversion from B to C became necessary because of a cystic duct obstruction. (By permission of *Transplantation Proceedings*, 6, 129, 1974.)

intravenous cholangiography in the early post-operative period. In almost all of our patients who develop jaundice, transhepatic cholangiography (Fig. 1) and, frequently, percutaneous needle biopsy are performed. Cholangiography has been greatly expedited by the use of a thin-walled, small calibre needle which has great flexibility, permitting the diagnostic studies to be done with increased safety.

Indications

Indications for liver transplantation are becoming increasingly clear. Although we do not consider hepatomas to be a good indication, we have done three cases of small, unresectable duct cell carcinomas which were located at the bifurcation of the intrahepatic ducts (Fig. 3). Two of these patients are still alive, one at six months and the other one year after transplantation. Neither has evidence of recurrence.

The best candidates for liver replacement are those with non-neoplastic liver disease. Biliary atresia, chronic aggressive hepatitis and Wilson's disease are disorders with which we have had multiple successes. Our worst results have been with alcoholics. Ten of 11 patients with end-stage Laennec's cirrhosis have died from three to 121 days post-transplantation.

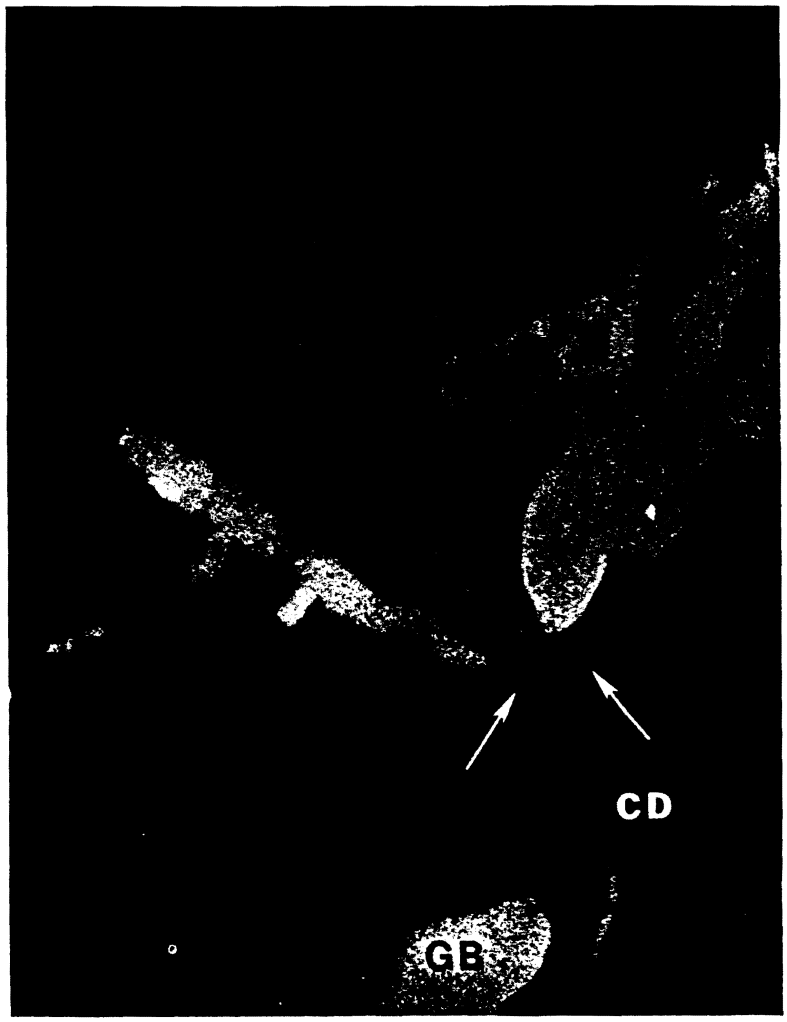

FIG. 3. Cholangiocarcinoma, diagnosed by transhepatic cholangiography, and treated by orthotopic hepatic transplantation. The patient is well one year later. GB = gall bladder; CD = common duct.

The only surviving recipient is in good condition ten months postoperative. If liver transplantation is to succeed in patients with alcoholic cirrhosis, potential recipients must be selected earlier, treated aggressively to prevent or correct infectious, pulmonary or other complications, and transplanted before their condition has markedly deteriorated.

Immunosuppression

Finally, a few words about immunosuppression, particularly antilymphocyte globulin. Our regimen of immunosuppression for liver transplantation has not changed appreciably in seven years. We use azathioprine and prednisone from the start. If we suspect hepatotoxicity from the azathioprine, we change to cyclophosphamide. Superimposed on these two drugs is a one-month course of antilymphocyte globulin. We are now using horse antilymphoblast globulin raised according to the schedules developed by Groth *et al.* (1972). In the average adult we give 4 ml per day for two weeks, then alternate days for another two weeks. We have not tried any kind of controlled study in our liver recipients—there are far too many variables and too few cases—but we are sure that our thinking about antilymphocyte globulin in these patients will be influenced by the information shared at this conference and by what we see in controlled trials in renal recipients.

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Discussion

HOBBS: As all your patients had ALG we cannot draw any conclusions about its role in liver transplantation, but I would like to know if any of your patients developed a cholestatic jaundice unrelated to technical surgical problems. My reason for asking is that two other cases who had ALG for bone marrow transplantation, as well as the one I reported, developed a cholestatic jaundice. I think that this is almost certainly a form of chronic graft-versus-host reaction but it could be an unknown side effect of ALG.

PUTNAM: We have had some cases of cholestatic jaundice but then this is a very prominent finding in rejection of liver grafts. It is difficult to separate drug related cholestasis from rejection. On biopsy using immunofluorescent techniques we have not found any evidence that ALG could be a causative factor.

CALNE (*Cambridge, United Kingdom*): It is quite possible to perform liver grafts without ALG. We have done 40 cases to date and our rejection rate would appear to be slightly less than yours. We have had many problems with bile drainage.

The concept of maximum immunosuppression may well be wrong in all kinds of organ grafting, but especially in liver grafting. We have been able to have patients with liver transplants off steroids entirely which is something we have never been able to do in kidney graft patients.

I feel the idea of the liver being less likely to reject is true for man as well as other species.

I was also particularly pleased to hear that you had gone back to using azathioprine as a primary immunosuppressant drug. Our early experimental work with cyclophosphamide suggested that it was a much less satisfactory immunosuppressant in kidney grafts in dogs, although it destroyed lymphocytes more efficiently than azathioprine. Naturally it is useful to have cyclophosphamide as an alternative if the azathioprine causes hepatotoxicity but all in all I feel azathioprine is a better immunosuppressant.

PUTNAM: I agree entirely with your comments regarding the liver graft and the need for immunosuppression. One thing we have come to realize is the tremendous flexibility required in the immunosuppressive regime if one is to achieve success in a liver graft. Some patients require absolute minimal suppression. Although we usually start with fairly large doses of prednisone, we attempt to reduce them rapidly. In some cases, with potential septic problems, we commence with a very small dose, and maintain this until obvious signs of rejection occur. In some of these latter cases this never happens. Thus all in all the liver may well be less susceptible to rejection.