CURRENT POLICIES IN HEPATIC TRANSPLANTATION: CANDIDACY OF PATIENTS WITH ALCOHOLIC LIVER DISEASE OR PREFORMED ANTIDONOR ANTIBODIES AND A REAPPRAISAL OF BILIARY DUCT RECONSTRUCTION*

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INTRODUCTION

During the 10 years since the first orthotopic hepatic transplantation was performed in Denver, over 200 patients have had liver replacement throughout the world, according to the American College of Surgeons Registry.[6] We have contributed 82 cases to this total, at a rate of about 10 per year since 1967, when the first long-term survivor was treated.[14]

In this communication, the survivals for these 82 recipients will be recorded. In addition, current policy will be reexamined in 3 areas on the basis of recently acquired or summarized data. Two of the questions pertain to candidacy for liver transplantation with particular reference to patients with alcoholic liver disease and to recipients who possess performed antidonor antibodies. Finally, a reappraisal of our experience with biliary reconstruction has led to modifications in the approach to this major area of technical failure.

SURVIVAL STATISTICS

The 1- and 2-year survivors from our 82 consecutive cases have been 18 and 9, respectively (TABLE 1). Our longest survivor of the 13 still alive is now nearly 5 years posttransplantation, another is $4\frac{1}{2}$ years, and 2 others have passed the 3-year mark.

The 10 late deaths, the causes for which are given in TABLE 2, have occurred from 12 to 41 months postoperatively. The latest mortality (OT 19), at $3\frac{1}{2}$ years,

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TABLE 1
Cases of Orthotopic Liver Transplantation Treated in Denver

	Number	Lived 1 Year	Lived 2 Years	Alive Now
1963–1966	6	0	0	0
1967	6	1	0	0
1968	12	5	2	0
1969	6	2	1	1
1970	10	2	1	1
1971	11	2	2	2
1972	11	5	3	3
1973	13	1	0	3
1974 (to April 1)	7	0	0	3
Total	82	18	9	13

followed a bout of *Hemophilus* septicemia. At autopsy, the homograft arteries had occlusive lesions similar to those seen in renal transplants.[13]

The most important causes of the high acute failure rate have been technical, of which complications of biliary duct reconstruction are the most common. The important contribution of faulty biliary drainage to mortality and morbidity, including cholangitis, will be discussed in a later section. After technical failures, rejection and systemic infection lead the list.

Transplantation for Alcoholic Liver Disease

Early in our experience it was suggested that patients with alcoholic liver disease presented an especially poor candidacy for hepatic transplantation.[14] The reasons for this opinion were twofold. First, cirrhotic patients have a predictably

TABLE 2
The Present Status of 18 1-Year Survivors After Orthotopic Liver Transplantation. Eight Are Still Alive from 14 to 58 Months. The Other 10 Eventually Died from the Causes Listed Below.

OT NO.	Time of Death (Months)	Cause of Death
15	12	Recurrent cancer
29	12	Serum hepatitis and liver failure
8	13	Recurrent cancer
58	13½	? Chronic rejection ? Recurrent hepatitis
16	13½	Rejection and liver failure
14	14	Recurrent cancer
54	19	Multiple liver abscesses necessitating retransplantation
36	20	Systemic *Nocardia* infection and chronic aggressive hepatitis
13	30	Rejection and liver failure following retransplantation
19	41	*Hemophilus* septicemia and secondary liver and renal failure

TABLE 3

Alcoholic vs Nonalcoholic Liver Disease Treated by Orthotopic Hepatic Transplantation

	Alcoholic	Nonalcoholic	Total
No. of Patients	10	72	82
Alive	1*	12	13
Dead	9	60	69
Mean Survival of those who died	29 days	136 days	122 days

*3 weeks posttransplantation.

higher operative risk, in part due to the frequency of pulmonary and other infectious complications. Secondly, for all but those patients with clearly terminal esophageal variceal hemorrhage, hepatic coma or advanced secondary renal failure, uncertainty about the natural course of the disease usually leads to a decision against transplantation until such time as the patient's condition becomes patently hopeless. Many then die before a suitable liver becomes available; the few who are given transplants enter the operating room in a moribund state.

Of the 82 consecutive recipients of hepatic homografts, 1 was treated for alcoholic hepatitis and 9 carried the diagnosis of Laennec's cirrhosis without concurrent hepatoma (TABLE 3). Nine of the 10 patients have died, from 3 to 121 (mean 29) days posttransplantation; the only surviving recipient is in good condition 4 weeks postoperatively. In contrast, 12 of the 72 patients with transplants for nonalcoholic liver disease are still alive from a few weeks to nearly 5 years later. The mean survival of the patients in the nonalcoholic group who have died is more than 4 times that of the alcoholic recipients (TABLE 3).

The causes of death for the alcoholic patients are given in TABLE 4. Two deaths were the result of complications of biliary reconstruction (see later), and 3 were related to homograft rejection. Of the remaining 4 patients, 2 died in

TABLE 4

Duration of Survival and Cause of Death in 10 Alcoholic Recipients of Hepatic Homografts

OT No.	Age (Years)	Survival (Days)	Cause of Death
22	33	10	Biliary obstruction
28	39	13	Disruption of choledochoduodenostomy, bile peritonitis
32	46	3	Unexplained coma
39	47	26	Unrelieved preexisting coma
40	44	32	Rejection, pneumonitis, petechial hemorrhages of CNS
62	44	121	Rejection and liver failure, pulmonary emboli
70	40	34	Pneumonitis
75	48	8	Rejection and liver failure
81	47	15	*Aspergillus* pneumonitis with dissemination
82	37	Alive (4 weeks)	—

coma, which was unrelieved by transplantation or which evolved immediately postoperatively, and 2 succumbed to pulmonary infectious complications.

CURRENT POLICY

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, and other complications, and given transplants before their condition has markedly deteriorated. The latest patient (OT 82) in the alcoholic group met these criteria, and his early postoperative convalescence has been untroubled. Despite the otherwise poor results to date, we will continue to consider the occasional patient with alcoholic liver disease with a hopeless prognosis, but who is not moribund and does not have potentially lethal infectious or other complications, as an acceptable candidate for liver transplantation.

CANDIDACY OF RECIPIENTS WITH PREFORMED ANTIDONOR ANTIBODIES

Hyperacute Rejection of Hepatic Homografts

The pathophysiology of hyperacute rejection has been well worked out in recent years. The initiating event is apparently fixation of preformed antidonor antibody to the transplant. This was first noted in kidneys (which contain blood-group antigens) transplanted to ABO-incompatible recipients.[11] In more recent years, the predominant cause of hyperacute rejection has been the presence in the serum of the recipient of antigraft cytotoxic antibodies, as was first described by Terasaki[15] and confirmed by Kissmeyer-Nielsen[7] and others.[12,17]

In the laboratory, a form of hyperacute rejection can be produced by transplanting organs between widely disparate species, as for example from pigs to dogs.[4] Canine serum contains heterospecific antiporcine cytotoxic antibodies that rapidly affix to the graft, setting into motion a chain of events that destroys it in minutes.

With either heterografts or homografts transplanted to recipients that possess preformed antigraft antibodies, the actual destruction of the organ is a complex process in which formed blood elements and clotting factors are entrapped by the graft.[5,10,12] The resulting occlusion of the major vessels causes ischemic necrosis, which gives a characteristic purple or mottled appearance to the tissue.

Because of the special filtering properties of the renal microvasculature, the kidney is unusually prone to the irreversible consequences of hyperacute rejection. In contrast, there is evidence that the liver may be unusually resistant to this process. For example, pig livers continue to perform rudimentary functions for a number of hours while being perfused with human blood.[3] Even in the difficult pig-to-dog heterograft model, in which kidneys are grossly rejected in a few seconds, the liver often does not suffer this fate until more than an hour has elapsed after revascularization.[5]

If the resistance of the liver to hyperacute rejection proves to be sufficiently great to permit its transplantation under conditions that would be categorically unacceptable for kidneys, an important limitation to the practicality of the procedure may be eased. Patients dying of liver disease, particularly those with alcoholic liver disease, as discussed above, usually cannot wait long for their homografts. If liver transplantation can be carried out despite preformed antibody states, some patients who would otherwise be deprived of treatment might no longer be arbitrarily excluded. In this connection, our experience with 6 patients given transplants despite preformed antibodies—of the antiblood group or the lymphocytotoxic varieties—will be discussed.

TABLE 5

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TABLE 5
Three Cases of Orthotopic Transplantation of ABO-Incompatible Livers

OT Number	Age (Years)	Diagnosis	Donor Recipient ABO Types	Preoperative Isoagglutinin Titer	Survival	Cause of Death	Pathologic Changes in Liver
59	11/12	Biliary atresia	AB ⟶ A	1:4 (anti-B)	173 days	Septicemia (from liver?)	Arterial and arteriolar narrowing (past rejection)
60	46	Primary biliary cirrhosis	AB ⟶ A	1:32 (anti-B)	61 days	Septicemia (from liver?) Pulmonary emboli	Mild cytomegaloviral infection No rejection
61	42	Postnecrotic cirrhosis	A ⟶ O	1:512 (anti-A)	41 days	Disseminated Herpes and cytomegalovirus Pulmonary emboli Brain infarction	Cytomegalovirus infection No rejection

ABO Incompatibility

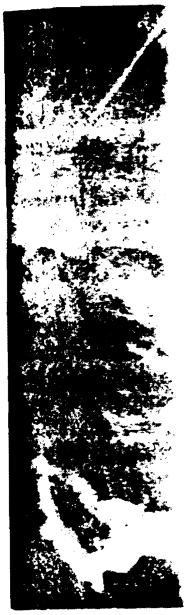
In 1972, 3 patients with ABO-mismatched livers were donors to recipients whose condition was considered sufficiently grave that they could not wait for a compatible organ (TABLE 5). Hyperacute rejection did not occur, and no other obvious adverse consequences were seen. The titers of antigraft isoagglutinins were variable, but at least in 1 case (OT 61) reached prodigious levels (TABLE 6). The 3 patients all eventually died but the pathologic findings in the homografts were remarkably minor. The homograft biliary system of one of the patients (OT 60) became partially obstructed by the mechanism of cystic duct stenosis shown in FIGURE 1B; following biliary reconstruction, the recipient died of pulmonary and septic complications. The other 2 patients had almost no abnormalities in their liver when they died of infectious complications.

TABLE 6
Serial Antigraft Isoagglutinin Titers in the 3 Recipients of ABO-Incompatible Livers Described in TABLE 4

Posttransplantation Day	OT 59	OT 60	OT 61
	(ANTI-B)	(ANTI-B)	(ANTI-A)
0	1:4	1:32	1:512
1	1:4	1:16	
3	1:1	1:4	1:64
5	1:1	1:2	1:64
7	1:1	1:8	1:2048
9	1:4	1:64	1:8192
11	1:4	1:64	1:8192
13	1:4	1:32	1:4096
15	1:4	1:16	1:2048
17	–	1:8	1:1024
19	1:2	1:4	1:1024
21	1:1	1:4	1:512
28	1:1	1:2	1:256
35	1:2	1:2	1:128
42	1:2	1:2	
49	1:2	1:1	
56	1:2	1:8	
63	1:2		
70	1:2		
77	1:8		
84	1:4		

Cytotoxic Antibodies

The ability of the ABO-incompatible liver to remain healthy under conditions that would be predictably harmful to most kidneys is a feature we have also seen in another kind of preformed-antibody situation. During the last 2 years, 3 potential liver recipients were found to have in their serum cytotoxins against most of the lymphocyte donors of an indifferent screening panel. Thus, the prospect of finding a liver donor without a positive cytotoxic antibody crossmatch was considered nil. Consequently, the decision was made to proceed with the transplantations, in the face of positive crossmatches, despite the potentially adverse prognostic implications.



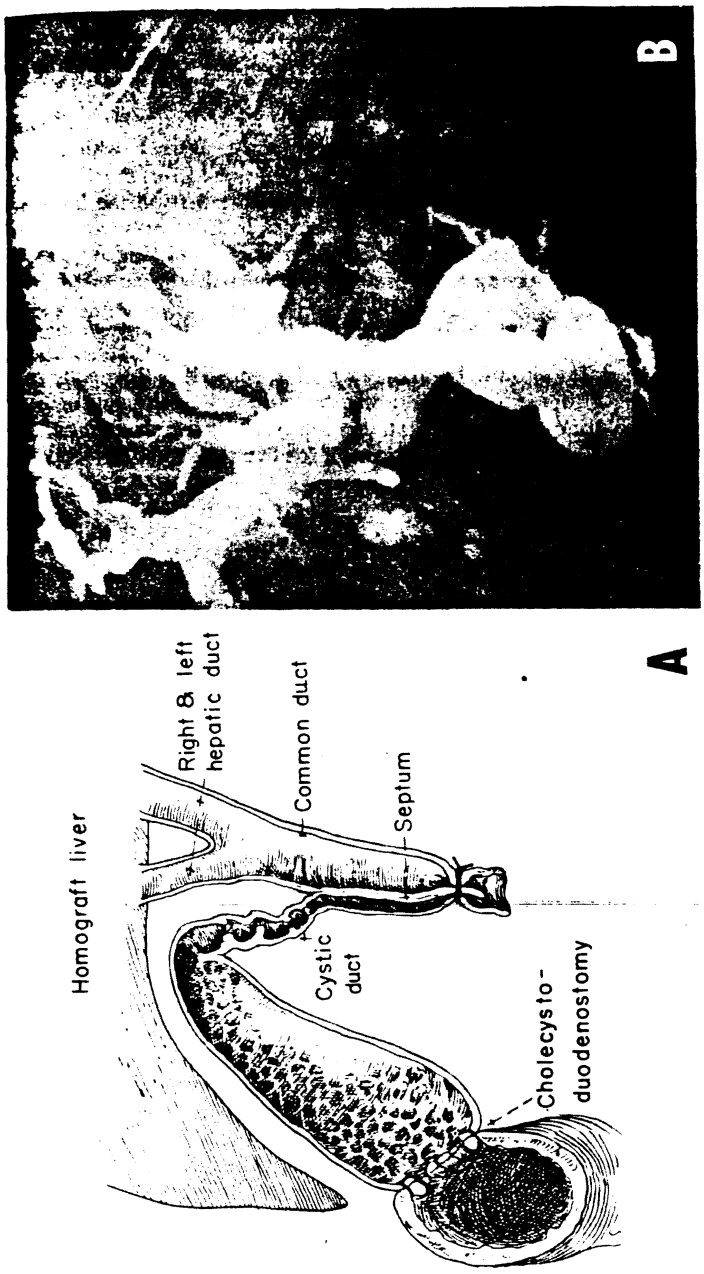


FIGURE 1. Two kinds of biliary duct obstruction after cholecystoduodenostomy. (A) The anatomic basis for a technical error that cost the life of 3 patients. Distal ligation of the double-barreled extrahepatic duct system resulted in total biliary obstruction. This recurrent accident has caused us to perform cholangiography on all liver homografts before transplantation. (B) The kind of biliary obstruction caused by stenosis of the cystic duct. Martineau reported that cytomegalovirus infection of the duct could be responsible for this development,[8] but frequently no obvious etiologic factor can be found.

None of the 3 patients developed hyperacute rejection. They all eventually died, however, from $3\frac{1}{2}$ weeks to $13\frac{1}{2}$ months later (TABLE 7). In 2 cases (OT 58 and 63), the homograft livers had only minor histopathologic changes at late biopsy or autopsy. In the third (OT 71), the homograft functioned poorly from the start. Although this could have been a manifestation of acute antibody-mediated rejection, the organ appeared to be severely damaged by ischemia, as well as cellular rejection, when removed 10 days after its transplantation. The homograft was replaced with a chimpanzee heterograft, against which the recipient also had cytotoxins. The chimpanzee liver functioned for most of the 14 subsequent days of the patient's life. Upon pathologic examination the heterograft was well preserved, with little evidence of rejection. Centrilobular cholestasis was a prominent feature. This was our third trial of chimpanzee-to-man transplantation, the other two having been previously reported.[4,14]

Current Policy

Preformed antibody states should be avoided if at all possible. However, the experience cited above with recipients having either anti-red cells or cytotoxic antibodies against their donors suggests that this kind of positive crossmatch is not an absolute but only a *relative contraindication* for liver transplantation.

A Reappraisal of Biliary Reconstruction

As mentioned earlier, complications of biliary reconstruction have claimed many of the early posttransplantation casualties. Biliary drainage has been reconstituted with several techniques, including cholecystoduodenostomy after ligation of the graft common duct, choledochocholedochostomy with or without a T-tube, choledochoduodenostomy, and most recently Roux-en-Y cholecystojejunostomy. The lethal complications with these procedures have been of two kinds, one mechanical, obvious, and provable, and the other bacteriologic, subtle, and as yet speculative.

Problems of Faulty Biliary Drainage

Mechanical Problems

The mechanical biliary duct problems have been obstruction and biliary fistulae. In the 82 cases of orthotopic transplantation, 25 (30%) of the initial biliary reconstructions were eventually found to be mechanically unsatisfactory, leading to death or early reoperation (TABLE 8). The true incidence of this problem is probably even higher, since incipient duct problems may not have been recognized in those patients dying soon after transplantation. Thirteen of the 25 patients with established biliary complications were reoperated on and efforts made to reconstruct the duct. Only 4 patients recovered from the reinterventions and only two are alive today, 3 months and 2 years respectively after transplantation.

There were failures with each kind of reconstruction (TABLE 8). With cholecystoduodenostomy (FIGURE 2A), the most frequently employed technique, fistulae were uncommon but 25% of the patients had proved obstruction (TABLE 8). In a few, acute obstruction was caused by the accidental ligation of the cystic duct at the time of donor hepatectomy (FIGURE 1A). *Delayed* obstruction (FIGURE 1B) of the cystic duct portion of the bile conduit was diagnosed weeks to months postoperatively. In some cases, cytomegalovirus (CMV) infection of the duct was implicated,[8] but in most instances no obvious etiologic factor ac-

TABLE 7

Three Cases of Orthotopic Hepatic Transplantation in Which the Recipients Had Antidonor Cytotoxic Antibodies

OT Number	Age (Years)	Diagnosis	Preoperative Cytotoxicity Titer	Survival	Cause of Death	Pathologic Changes in Liver
58	34	Chronic aggressive hepatitis	1:2	407 days	Stopped immunosuppression Hepatic insufficiency	Resolution of previous obstructive changes at $8\frac{1}{2}$-month biopsy. (No autopsy)

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58	34	Chronic aggressive hepatitis	1:2	407 days	Stopped immunosuppression Hepatic insufficiency	Resolution of previous obstructive changes at 8½-month biopsy. (No autopsy)
63	49	Primary biliary cirrhosis	1:64	26 days	Gastrointestinal hemorrhage	Normal liver
71	1 11/12	Biliary atresia	1:16 (Homograft)	(Removal of the graft at 10 days)		Acute rejection, cellular and humoral
			1:16 (Heterograft)	14 days after retransplantation	Pulmonary edema, bronchial hemorrhage	No evidence of cellular rejection. Centrilobular cholestasis.

TABLE 8

Kind of Primary Bile Duct Reconstruction used in 82 Consecutive Cases of Orthotopic Liver Transplantation

	Cholecysto-duodenostomy	Choledocho-choledochostomy	Roux-en-Y Cholecysto-jejunostomy	Choledocho-duodenostomy	Cholecysto-Loop Jejunostomy	Total
Number	59	9	8	4	2	82
Obstruction	15	0	2	0	0	17*
Fistula	2	5	0	1	0	8*

*In these 25 cases, reoperation(s) was performed in 13 patients with attempt at duct reconstruction. A satisfactory recovery followed in only 4 of the recipients. Two later died after 6 and 13½ months posttransplantation survival. The other 2 are alive after 3 months and 2 years, respectively. Both survivors now have the final biliary duct reconstruction shown in FIGURE 2C.

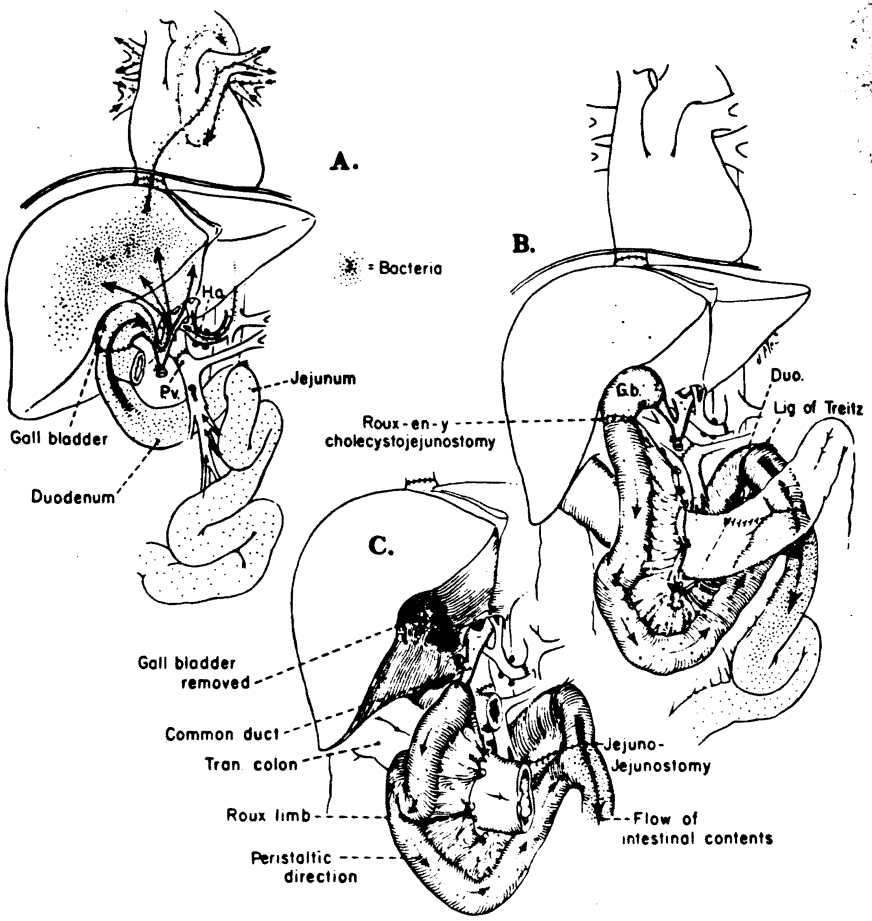


FIGURE 2. Schematic representation of the bacterial contamination or lack thereof in 3 different kinds of biliary reconstruction. (A) Cholecystoduodenostomy. This extremely simple operation probably carries the greatest risk of graft infection. (B) Roux-en-Y cholecystojejunostomy. This operation protects from hepatic sepsis by placing the new liver at a distance from the main gastrointestinal stream by virtue of an isoperistaltic limb of jejunum at least 18 inches long. (C) Roux-en-Y choledochojejunostomy. The end-to-end duct-to-bowel anastomosis is simple if the duct is dilated (FIGURE 3B), as would be the case if a conversion became necessary from B to C.

counted for the partial obstruction. With anastomosis of the graft common duct to the host duct or duodenum, biliary fistulae developed in about half the recipients. Obstruction has not been documented after these kinds of reconstruction.

Eight primary reconstructions with Roux-en-Y cholecystojejunostomy (FIGURE 2B) have been performed. One acute obstruction was caused by the technical accident shown in FIGURE 1A. A second patient had a delayed partial obstruction

of the cystic duct diagnosed by transhepatic cholangiography (FIGURE 3B). He was reexplored and the drainage converted to Roux-en-Y choledochojejunostomy (FIGURE 2C).

Bacteriologic Complications

With the technical problems discussed above, clinical (and usually histopathologic) evidence of cholangitis was frequently documented.

Another kind of infectious complication, as yet hypothetical, may occur despite a technically satisfactory biliary reconstruction and no morphologic evidence of cholangitis. It has been documented that systemic infections and even asymptomatic bacteremia are common after hepatic transplantation.[14] For years, it has been suspected that the transplanted liver itself was the portal by which the microorganisms gained access to the blood stream, since no other foci of infection could be identified and because the kinds of bacteria detected by blood cultures in these patients were strikingly similar to those found in dogs and pigs subjected to liver injury or hepatic transplantation.[1] Theoretically, at least, the bacteria could have entered the homograft by either of 2 routes, the portal vein or the biliary duct system. The latter now seems to be the far more important source.

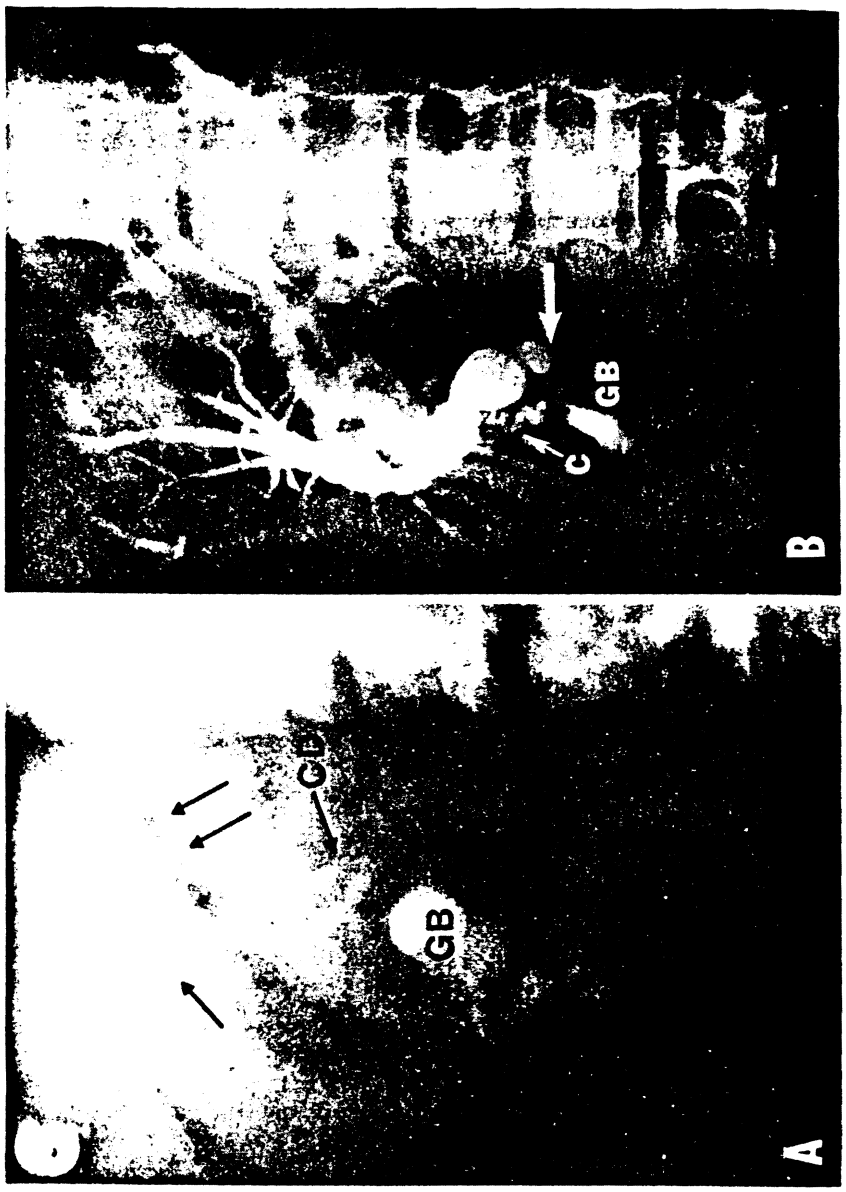
The reason for this view lies in the exposed position of the biliary duct system in relation to the gastrointestinal flora, as depicted schematically for a cholecystoduodenostomy in FIGURE 2A. Once bacteria gain access to the liver by this route, they may then escape through a bacteriologically porous liver without producing any histopathologically significant cholangitis on the way. If bacteria do indeed gain access to the liver and then the circulation via the biliary system, then a logical approach would be to place the homograft ducts as far removed from the mainstream of the gastrointestinal tract as possible, as in FIGURES 2B and 2C.

Current Policy

With these technical and bacteriologic considerations in mind, we have evolved and are attempting to follow 6 principles in establishing and assessing biliary drainage: (1) preservation of maximum homograft extrahepatic biliary duct tissue; (2) performance of cholangiography in all homografts prior to transplantation; (3) placement of the liver in a relatively bacteria-free relation to the mainstream gastrointestinal continuity; (4) avoidance of stents and drains; (5) intensification of diagnostic efforts to differentiate between obstruction and rejection in the recipient with abnormal liver function; and (6) early reoperation for suspicion of obstruction. None of the currently available methods of reconstruction completely meets all of these objectives, so that considerable individualization of care is necessary.

A Roux-en-Y cholecystojejunostomy (FIGURE 2B), our present procedure of choice, does at least partially meet all of the above objectives. If biliary obstruction later develops, the Roux limb can be detached, the gallbladder removed, and an anastomosis performed to the now dilated common duct (FIGURE 2C).

The most important objection to this approach is that creation of the Roux-en-Y jejunal limb can be extremely difficult in liver recipients, adding 3–6 hours of operating time and considerable additional blood loss to the already lengthy and bloody procedure. The reason for this is that in the adult recipient dying of hepatic failure, the small-bowel mesentery usually is quite edematous and laced with massive collaterals. Under these adverse conditions, it may be the better part of valor to perform a simple cholecystoduodenostomy with the objective of



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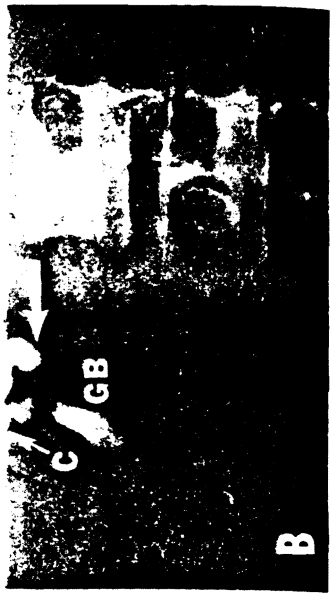

reexploring at a later time if the biliary drainage is suspected of being inadequate. If at the time of transplantation the gallbladder is found to be defective, we would now make a choice between choledochocholedochostomy with T-tube stenting and a Roux-en-Y choledochojejunostomy.

No matter what the initial procedure, an intense suspicion about and investigation of the cause for postoperative jaundice is the basic principle of postoperative management. A simple precaution is to routinely perform intravenous cholangiography early in the postoperative period (FIGURE 3A) in order to establish baseline delineation of the biliary anatomy. In almost all of our patients who do develop jaundice, transhepatic cholangiography (FIGURE 3B) and percutaneous needle biopsy are part of the work-up. Percutaneous transhepatic cholangiography has been greatly expedited by using the Chiba needle, introduced in Japan[9,16] and now being employed in several American centers. These thin-walled, small-caliber, flexible needles permit the diagnostic studies to be done with greater safety.

It is not yet established that these changes in policy will improve the results of liver transplantation. Our approach is fundamentally different from that proposed by Calne, who believes that duct-to-duct reconstruction over a T-tube and preservation of the Sphincter of Oddi when possible, will be the better solution to the technical and infectious complications of biliary drainage.[2] The fact that different methods are being tried to solve a generally recognized set of problems should be an advantage in evolving solutions that can be eventually agreed upon and applied by all.

SUMMARY

Eighty-two patients have been treated by orthotopic hepatic transplantation in Denver since 1963. Eighteen and nine patients have lived for 1 year and 2 years posttransplantation, respectively. Thirteen recipients are still alive from 3 weeks to almost 5 years postoperatively.

Current policy has been reexamined in 3 areas in light of this experience. First, only the occasional potential recipient with alcoholic liver disease, free of infectious or other complications, is an acceptable candidate for this procedure. Second, the presence in the recipient's serum of preformed anti-red cell or lymphocytotoxic antibodies to his donor is a *relative*, but not an absolute, contraindication to hepatic transplantation, since the liver appears to be more resistant to hyperacute rejection than the kidney. Finally, a 6-point program has been outlined for establishing and evaluating bile drainage, in order to prevent or

FIGURE 3. Posttransplantation cholangiographic studies. (A) Intravenous cholangiogram in a 47-year-old recipient of a hepatic homograft, the biliary drainage for which was with Roux-en-Y cholecystojejunostomy (FIGURE 2B). The patient's liver function studies were normal at the time of the examination. However, the findings of a very slightly dilated common duct and air in the biliary system (*arrows*) are suspicious for low-grade obstruction. (B) A percutaneous transhepatic cholangiogram performed 4 weeks posttransplantation because of persistent elevations of the serum bilirubin (8–10 mg%). At the time of transplantation, biliary drainage had been established with a Roux-en-Y cholecystojejunostomy (FIGURE 2B). After obtaining this study, the patient was reexplored, the gallbladder removed, and the Roux limb anastomosed to the dilated common duct (*large arrow*), as shown in FIGURE 2C. The patient's jaundice rapidly cleared, and he now has normal liver function, 3 months posttransplantation. GB–gallbladder; CD–common bile duct; C–cystic duct.

remedy both the technical and bacteriologic complications associated with faulty biliary reconstruction.

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