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344

Hepatic Sepsis: Generally Applicable Lessons Learned from Liver Transplantation

Thomas E. Starzl, M.D., Ph.D. and Charles W. Putnam, M.D.

This paper should not be entitled "liver abscesses." There is no way I could possibly discuss liver abscesses briefly and I very much doubt if you would want me to try.

Instead, I will be talking about liver sepsis, using mainly our experience with liver transplantation as a model with which we think we have learned a lot about infections of the liver that can and should be applied to the understanding and treatment of abscesses, cholangitis and other conditions. In addition, the problems I will relate will have to be solved before the procedure of liver transplantation can become widely practical.

The most widely used method of bile duct reconstruction is the cholecystoduodenostomy that is shown in Figure 1A. With this operation, the distal common duct is ligated or sewn shut so that the bile passes through the cystic duct and gallbladder, to be delivered into the duodenum. The other biliary reconstruction we used early in our experience was a standard choledochocholedochostomy placing the T-tube through a stab wound in the recipient common duct (Fig. 2).

With liver transplantation and cholecystoduodenostomy, a series of terrible complications were encountered in several of our early cases in which prolonged survival was obtained. We called this complication "septic hepatic infarction" and its consequences were characteristic and resulted in three distinctive clinical and laboratory findings, of which two are shown in Figure 3. The components of the triad were gram negative septicemia and evidence from transaminase determinations of massive liver necrosis. The bacteremia and transaminasemia were relatively isolated

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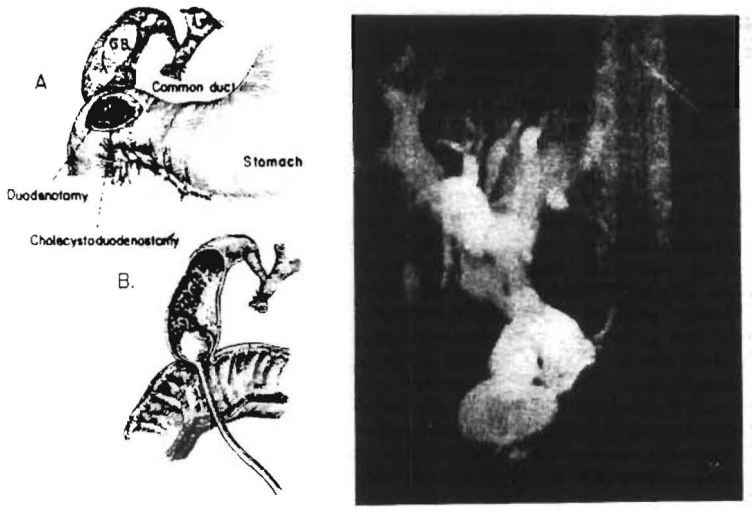

FIG. 1. The intra-operative diagnosis of a complication of cholecystoduodenostomy. On the left, cholecystoduodenostomy anastomosis was visualized through an anterior duodenotomy. Through an inflated Foley catheter, dye was introduced. Dilatation of the intrahepatic ducts was apparently due to partial obstruction of cystic duct. (By permission of *Surgery*, 72:604-610, 1972.)

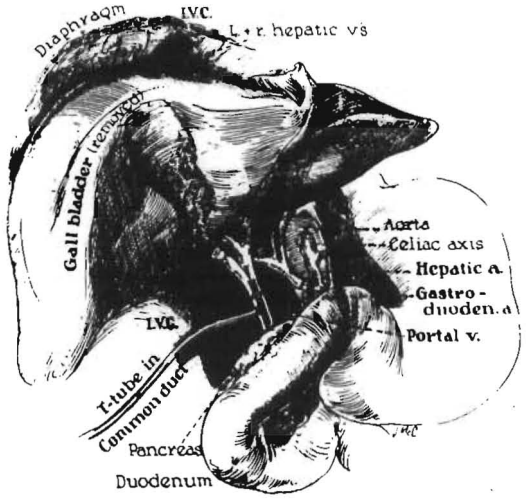

FIG. 2. Choledochocholedochostomy with T-tube drainage. This procedure has had a high incidence of biliary fistula. (By permission of W. B. Saunders Company, 1969.)

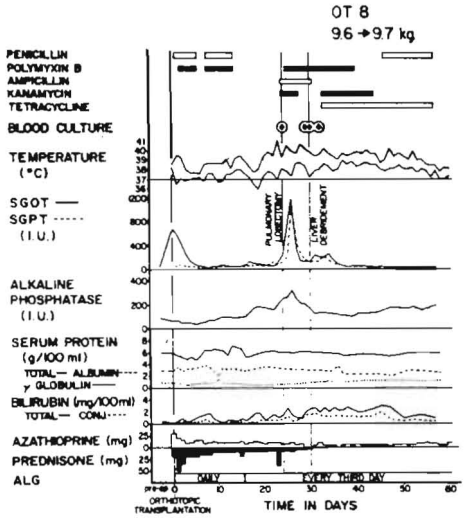

FIG. 3. The first 60 posttransplantation days in a patient after liver replacement. During third postoperative week there was evidence of an "anicteric" rejection, but significance of function changes was not appreciated at the time. Lung resection was carried out because right upper lobe was collapsed and it was suspected that this was the source of the unexplained fever. In retrospect, pulmonary lobectomy was probably not indicated. One day later, definitive evidence of septic hepatic infarction and abscess formation had appeared. All the positive blood cultures were of *Aerobacter-Klebsiella*. This patient was the first to survive for a prolonged period after human liver transplantation. Indication for operation was hepatoma. (By permission of W. B. Saunders Company, 1969.)

findings in the orthotopic liver recipient, shown in Figure 3. Protein synthesis, level of bilirubin and other liver functions were not particularly suggestive of a rejection.

The third component of the triad is seen in Figure 4, namely, the development on serial liver scans of persistently absent isotope concentration in the homograft. When these areas were explored, they were found to consist of gangrene with or without pus. In caring for these patients, who were usually children, we learned a lot about how to drain liver abscesses or to debride necrotic or infected hepatic tissue. Our approaches were subcostal, posterior extraperitoneal below the 12th rib and most commonly (Fig. 5) by the lateral route, sometimes using the two-stage procedure which was designed by Adams of the Leahy Clinic to avoid entering the pleural cavity.

Eventually, however, it was concluded that the combination of too little immunosuppression and inadequate antibiotic coverage made this

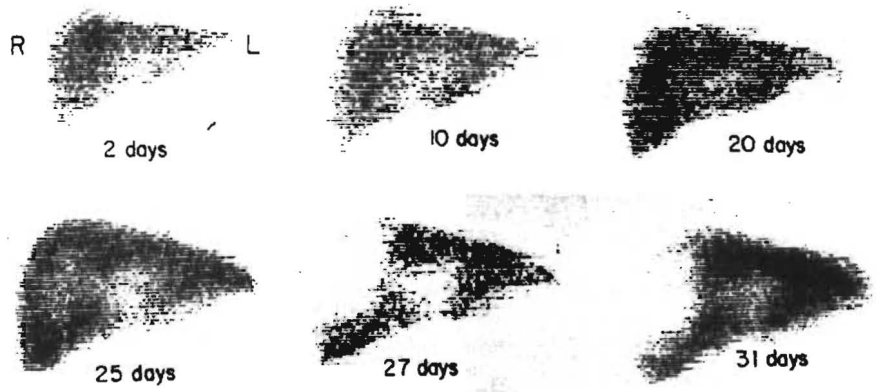

FIG. 4. Postoperative technetium scans of an orthotopic liver transplant – 2 days: small homograft is normal; 10 days: an increase in size is evident although the general configuration of the organ is still normal; 20 days: no further change is noted; 25 days: examination conducted as an emergency when child developed gram negative septicemia and very high increases in the transaminases. Areas of decreased isotope uptake are obvious in right lobe and central part of liver; 27 days: a striking extension of the process can be seen less than 48 hours later. A debridement procedure was carried out the same evening; 31 days: four days after debridement the radiographic appearance was improved. (By permission of W. B. Saunders Company, 1969.)

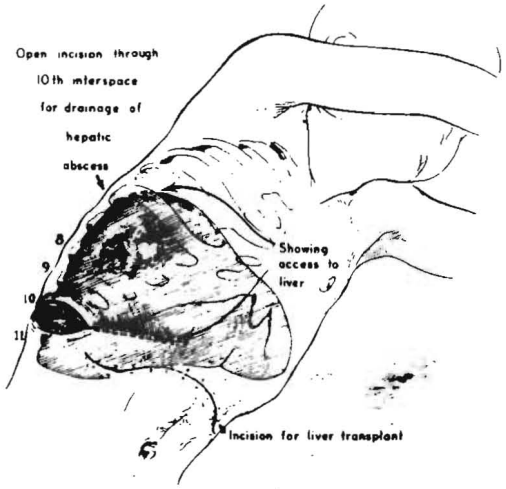

FIG. 5. Lateral operative approach to septic liver infarctions or abscesses of the right lobe through the tenth intercostal space. Neither pleural nor peritoneal cavities were entered. (By permission of *Annals of Surgery*, 168:392, 1968.)

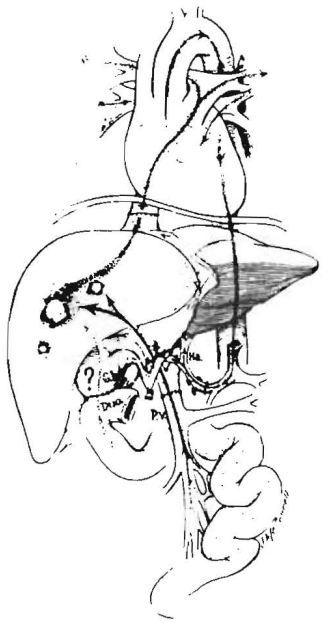

FIG. 6. An explanation of the predisposition of the liver to bacterial sepsis. Presumably, invading microorganisms enter via portal vein or through reconstructed biliary tract. (By permission of *Annals of Surgery*, 168:392, 1968.)

peculiar kind of septic infarction or abscess formation possible. The pathogenesis was envisioned as shown in Figure 6. An initiating event would be injury to the liver parenchyma whether caused by ischemic damage during the preservation, rejection (most commonly), vascular accidents or other factors. In any event, the liver, interposed as it is between the intestines and the heart, would be sure to become infected in its devitalized parts. Bacteremia, spreading infection within the liver itself, and toxicity followed. In those days which were in 1967 and 1968, our belief was that the portal of bacterial entry into the liver was almost surely hematogenous from the portal vein and that entry through the duct reconstruction was uncommon. We now believe that this was a foolish conclusion, as I will emphasize again later.

In time, it was learned how to more effectively prevent this lethal sequence of events leading to septic hepatic infarction. More intensive immunosuppression was given to avoid the necrosis of graft rejection. With the slightest impression of sepsis, intensive antibiotics were instituted.

Although septic hepatic infarction was thereby avoided, the liver transplant recipient has been at a very real risk from what we now

recognize as liver sepsis long after operation. Periodic blood cultures at a time when these recipients have no symptoms may grow out *Proteus, Clostridium perfringens, E. coli* and other microorganisms at different times. Then, sudden death from overwhelming sepsis may follow. We now believe that these bacteremias are from this duct portal of entry (Fig. 7A).

The exposed relation of the duct system of the orthotopic liver to gastrointestinal flora is probably the first step in bacterial "leak" through a homograft which may well be bacteriologically porous *without* the presence of biliary duct obstruction or of histopathologically significant cholangitis. This special porosity would derive from the fact that all such patients are receiving immunosuppression and would not require a duct complication of the usual mechanical variety. This is not to say that the mechanical aspects of duct reconstruction have been satisfactorily handled. Indeed, the Achilles' heel of liver transplantation has been consistent flaws in biliary duct reconstruction. The different techniques we have tried to restore bile drainage include choledochocholedochostomy with or without a T-tube (Fig. 2), cholecystoduodenostomy after ligation of the graft common duct (Fig. 1) 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 (Fig. 7B). The obvious biliary duct problems have been obstruction (Fig. 1) and biliary fistula from anastomotic leaks. In our 82 cases of orthotopic liver transplantation, the initial biliary reconstruction was eventually shown to be unsatisfactory and either led to death or early reoperation in these 25 cases for the staggering incidence of 30%; the true frequency was undoubtedly even higher, since many patients died so early postoperatively that an incipient duct problem would not yet be manifest.

Because of our profound conviction that the biliary duct reconstruction is the main reason, either for mechanical or the bacteriologic reasons I mentioned earlier, why liver transplantation has failed to become a practical clinical pursuit, we are now attempting to evolve a workable strategy based on five guiding principles. The principles are: (1) avoidance of stents or drains; (2) preservation of maximum extrahepatic biliary duct tissue; (3) intensification of diagnostic efforts to differentiate between duct obstruction and rejection, including performance of cholangiography in all homografts prior to transplantation; (4) early reoperation for suspicion of obstruction; and (5) placement of the liver in a relatively bacteria-free relation to the mainstream gastrointestinal continuity. None of the presently available operations completely meet all of these objectives, so that considerable individualization of care is necessary.

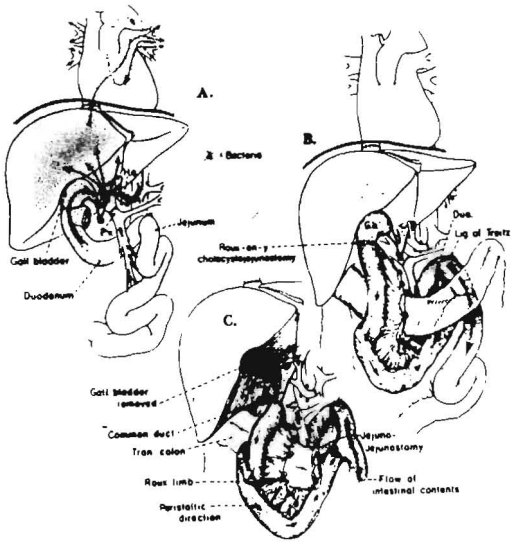

FIG. 7. Schematic representation of the bacterial contamination or lack thereof in three different kinds of biliary reconstruction. (*A*) Cholecystoduodenostomy. This extremely simple operation probably carries the greatest risk of graft infection. (*B*) Roux-en-Y cholecystojejunostomy. This operation protects from hepatic sepsis by placing the new liver outside the main gastrointestinal stream. Isoperistaltic limb is made 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 as would be the case if a conversion became necessary from (*B*) to (*C*).

A Roux-en-Y cholecystojejunostomy (Fig. 7B), our present procedure of choice, permits all the above listed objectives to be partly met. If postoperative biliary obstruction later develops, the Roux limb can be detached, the gallbladder removed and an anastomosis performed to the now dilated common duct (Fig. 7C).

No matter what the initial procedure, an intense suspicion about the cause for postoperative jaundice is a necessary condition of postoperative management. The simplest precaution is to perform routine intravenous cholangiography in the early postoperative period. The intravenous cholangiogram of a cholecystojejunostomy, shown in Figure 8, was considered suspicious with slight dilatation of the ducts which contained air. However, the function was so perfect that reoperation has not been performed.

In almost all of our patients who develop jaundice, transhepatic cholangiography and percutaneous needle biopsy are now performed (Fig. 9). Cholangiography has been greatly expedited by our use of the Chiba needle introduced in Japan and now being used in several American

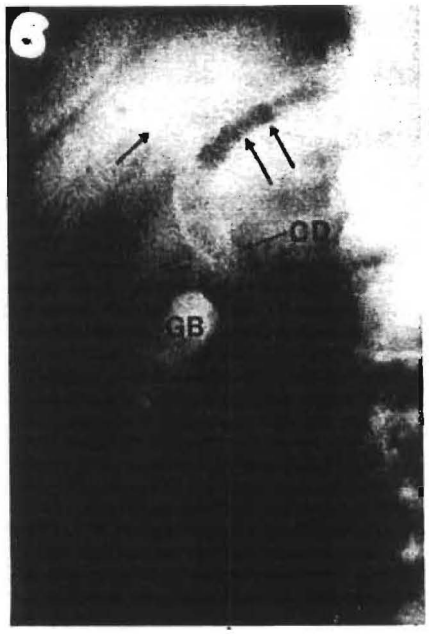

FIG. 8. Posttransplantation cholangiographic studies. Intravenous cholangiogram in a 47-year-old recipient of a hepatic homograft, the biliary drainage for which was with Roux-en-Y cholecystojejunostomy. Patient's liver function studies were normal at time of examination. However, findings of a very slightly dilated common duct and air in the biliary system (*arrows*) are suspicious for low grade obstruction.

centers. These thin-walled small caliber needles have great flexibility that permits the diagnostic studies to be done with an improvement in safety. The obstruction in Figure 9 after Roux-en-Y cholecystojejunostomy was relieved by conversion to a choledochojejunostomy using the same jejunal limb. The bilirubin, which had been about 10 mg%, fell immediately to normal.

In summary, I have used our experience in liver transplantation for two purposes. First, I wanted to show you how the pathogenesis of intrahepatic sepsis, including abscess formation, is probably almost always due to some combination of contamination from the intestines through either the portal vein or duct system, and that injury to the liver itself could very easily make the infectious foothold possible. These lessons so well learned in liver recipients surely have wide applicability. Second, I wanted to indicate to you that I believe contamination through the ducts is the main portal of bacterial entry, at least in the liver recipient. This probability has led to the evolution of a strategy for bile duct

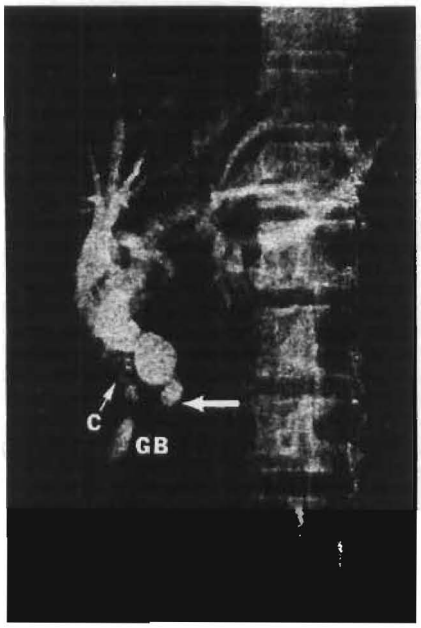

FIG. 9. A percutaneous transhepatic cholangiogram performed four weeks posttransplantation because of persistent elevations of the serum bilirubin (8-10 mg%). At time of transplantation, biliary drainage had been established with a Roux-en-Y cholecystojejunostomy (Fig. 7). After obtaining this study, patient was re-explored, gallbladder removed and Roux limb anastomosed to the dilated common duct (*large arrow*), as shown in Figure 7C. Patient's jaundice rapidly cleared and he now has normal liver function four months posttransplantation. GB – gallbladder; → – common bile duct; C – cystic duct.

reconstruction of liver homografts that puts the new liver as far away from the mainstream gastrointestinal tract as possible and which encourages reoperation for the slightest indication of duct obstruction or of cholangitis.

Bibliography

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