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TRANSPLANTATION OF THE LIVER IN HUMAN SUBJECTS

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In this chapter, the usual practice has been omitted of devoting a section to historical background. The reason is that the first report by Welch [1] of whole-organ hepatic transplantation in animals was only 17 years ago. Furthermore, the first clinical attempts at liver transplantation were not made until 1963.[2] Consequently, these as well as most of the other early articles on liver transplantation are still of current interest. A complete bibliography of this subject through early 1969 is available in a recently published text.[3]

KINDS OF OPERATIONS

Auxiliary Transplantation

There are two general approaches to transplantation of the liver. With one method, an extra liver is inserted at an ectopic site without removal of the diseased native organ. This was the procedure that Welch [1] developed in dogs with the ultimate objective of treating patients who were dying of cirrhosis or other non-neoplastic hepatic diseases.

One technique used for auxiliary hepatic transplantation as adapted to human subjects is depicted in Figure 1. Here, the extra liver is placed in the right paravertebral gutter or right pelvis. Its hepatic arterial supply is derived from the aorta or an iliac branch. Venous inflow is reconstituted by anastomosing the distal inferior vena cava or a distal iliac vein to the homograft portal vein. Outflow is into the inferior vena cava. In the patient whose operation is shown, portacaval shunt (stage I) for the control of variceal hemorrhage was carried out 3 days prior to the transplantation.

At first thought, the use of auxiliary homografts for the treatment of benign hepatic disease has a special appeal. First, sacrifice of the remaining, albeit limited, function of the failing recipient liver can be avoided. Thus, in the event of poor initial performance by the homograft due to ischemia or to a severe but reversible rejection, it might be hoped that some assistance would be provided by the diseased host liver during a transition recovery period. This would be predicted to be a particularly significant advantage in patients with biliary atresia, since the synthesizing functions of the liver are often retained until the terminal stages of this disease. Second, it was initially assumed that the placement of an extra liver would be safer and technically less demanding than the orthotopic procedure.

In actual practice, auxiliary transplantation has lost much favor. The results in animals have been inferior to those with liver replacement, partly because coexisting livers have the capacity to damage each other to a variable degree, according to which organ is the "dominant" one. Factors favoring dominance include a splanchnic source of the blood for portal venous inflow, perfect biliary drainage, optimal total hepatic blood flow, and unimpeded venous outflow. An auxiliary canine liver graft, which does not enjoy these advantages relative to the host liver, undergoes rapid atrophy by mechanisms that have been ascribed to "interliver competition." A detailed discussion of this fascinating topic has been published.[3]

Here, it will only be noted that most pa-

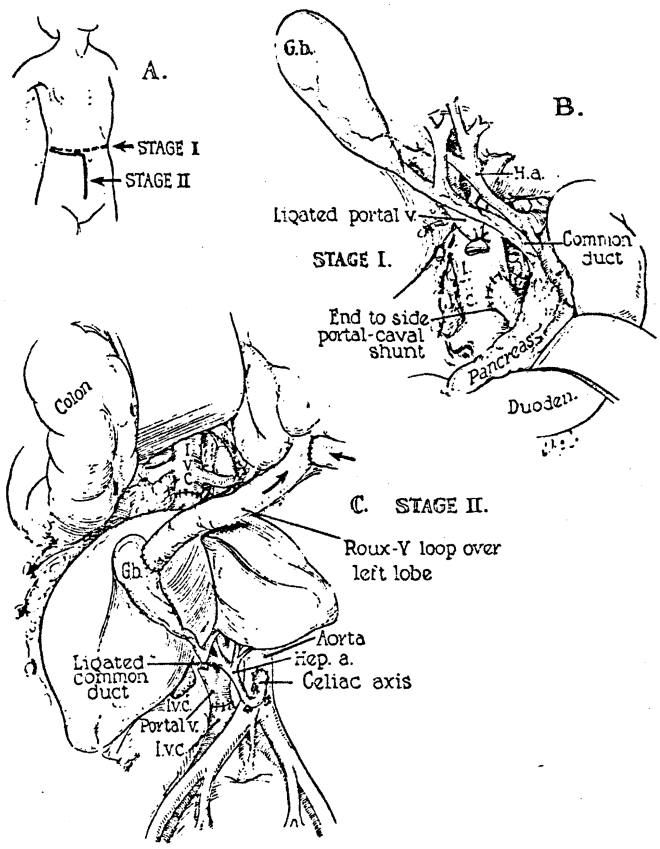

FIG. 1. One technique of clinical auxiliary liver transplantation. (A) Incisions used for two closely spaced operations. (B) Stage 1, an emergency portacaval shunt was performed prior to transplantation for the control of massive hemorrhage from esophageal varices. (C) A completed auxiliary transplantation. The portal venous inflow is derived from the distal inferior vena cava. The hepatic arterial source is from the aorta. (From Halgrimson. *AMA Arch. Surg.* 93:107, 1966.)

tients who would be candidates for liver transplantation do not have adequately functioning livers, so that the concept of competition may not be a critical one in clinical practice. Nevertheless, auxiliary liver transplantation for the indication of hepatic failure has not yet resulted in the significant prolongation of life for any patient. The reasons for failure have been several. In many cases good initial homograft function was not obtained due to ischemic injury during and after donor death. In others, the presence of an extra organ within the abdomen was not well tolerated with restriction of diaphragmatic movement and consequent lethal pulmonary complications. Finally, the expectation that the placement of an extra organ would be technically simpler than with liver replacement has not been borne out by actual experience, as evidenced by an extremely high incidence of mechanical complications. Because of the poor clinical results, the number of attempts at human auxiliary transplantation has declined to the point that this kind of operation will not be considered further in the rest of the chapter.

Orthotopic Transplantation

In contrast, there is mounting evidence that the operation of orthotopic hepatic transplantation (liver replacement) will play an increasing role in the future treatment of liver disorders. With this procedure,

the diseased host liver is removed, creating a space into which a graft is transplanted with as normal an anatomical reconstruction as possible. Survival in dogs and human subjects has been achieved exceeding 8½ and 3¼ years, respectively. The remarks in succeeding sections will pertain to orthotopic transplantation as opposed to the auxiliary operation just discussed.

PREOPERATIVE PREPARATION

Virtually all prospective liver recipients are poor risks for a major operation, and many of those with hepatic failure from non-neoplastic diseases appear at first evaluation to be hopeless. Symptomatic relief may be obtained by the performance of procedures such as paracentesis or thoracocentesis. But, unfortunately, there is probably little of real value that can be done to reduce the consequent operative hazards short of providing liver tissue.

It has been suggested that one way of transiently increasing liver function before the definitive procedure would be with ex vivo hepatic support, using an extracorporeal heterologous liver in the way described by Eiseman.[4] To our knowledge, such an approach to preoperative resuscitation has not yet been tried prior to transplantation. One reason is that even patients near death from complications of hepatic disease can be brought through the transplantation procedure with almost immediate improvement providing the homograft functions properly and promptly.

The paradoxical ability of these moribund recipients to survive such major surgery may be related partly to the troublesome operative bleeding which is almost invariably encountered. The consequent necessity for major blood replacement frequently results in intraoperative exchange transfusions of at least the magnitude that have been reported by Trey, Burns, and Saunders of Cape Town to be of benefit in acute liver insufficiency.[5] The coincidental therapeutic effect of massive transfusion, as well as the immediate benefits of good hepatic function by the transplant, have usually resulted in patients returning to the ward in better condition than at the time of their departure.

This does not mean that efforts should be discontinued to find a better means of ex vivo hepatic support. At the present time, only a small fraction of patients who might be candidates for liver transplantation can actually be treated, since there are no means of providing therapy analogous to that with the artificial kidney which can tide over prospective recipients while an organ is being found. Until an artificial liver is developed that will provide some of the more crucial hepatic functions, liver transplantation will not be able to achieve anything like its true potential.

Although little can be done for the preexisting liver failure, secondary abnormalities of other organs can sometimes be effectively ameliorated. For example, the effects of renal failure secondary to the hepatorenal syndrome can be treated with the artificial kidney. Pulmonary manifestations may be improved by simple tracheobronchial toilet, particularly if aspiration has occurred. Transfusions of blood or albumin may be useful for the correction of blood volume or other fluid space abnormalities. If fresh whole blood, fresh frozen plasma, or platelets are judiciously given, some improvement in coagulation may be possible.

CASE SELECTION

According to Underlying Disease

Hepatic malignancy. When orthotopic liver transplantation was first attempted in humans, hepatoma was considered to be an outstanding indication for proceeding. There were some minor reasons for this attitude, including the fact that the state of liver failure and the development of venous collaterals would on the average be less than in patients with end-stage non-neoplastic hepatic disorders. The major rationale was, however, that complete removal of the recipient liver was an obligatory component of the undertaking if cure was to be achieved. Thus, liver replacement was conceived of as a means of extending the limits of resectability in patients who did not have extrahepatic

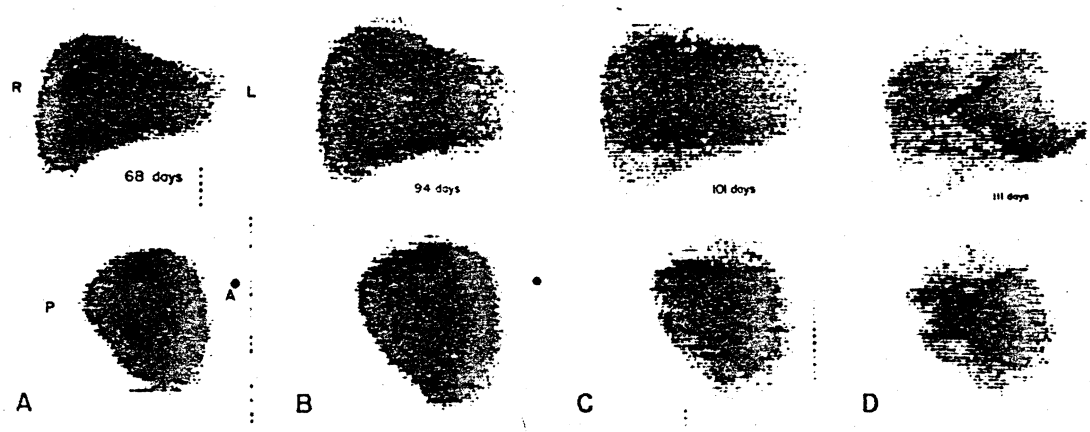

FIG. 2. 99M technetium liver scans in a patient whose indication for transplantation was hepatoma. Note progressive invasion of liver homograft by tumor beginning at 94 days. The patient died of carcinomatosis 143 days post-transplantation. At autopsy, the homograft was almost completely replaced with carcinoma. (From Starzl. *Experience in Hepatic Transplantation*. Courtesy of W. B. Saunders, Philadelphia, 1969.)

spread of their tumors.

Actual experience with liver replacement for the indication of an hepatic malignant lesion has not supported this reasoning and, in fact, has led us to declare a moratorium on such cases. At the University of Colorado, a total of 14 patients have undergone liver replacement for primary hepatic malignancy. In seven cases, the attempt was "successful" in a technical sense, and with survival for at least 2½ postoperative months. Six of the seven recipients developed a recurrence of the malignant lesion from 2 to 13 months later. Eventually, these six patients died, and in most instances the tumor recurrence either caused death or contributed to it in an important way (Fig. 2). Lethal and widespread metastases were responsible for death as early as 143 days after operation and as late as 14 months.

Hepatoma was the histopathological diagnosis in all but one of the foregoing seven cases with extended postoperative follow-up. The exceptional patient had a hemangioendotheliosarcoma. Although he made a satisfactory recovery from operation, he also developed widespread metastases and died in less than 4 months.

We have suggested [3] that the immunosuppressive therapy necessary to prevent rejection may itself have contributed to the aggressiveness of the metastatic growth. Such speculations are based in one way or another on the surveillance hypothesis of cancer proposed by Thomas [6] and Burnet,[7] which holds that the immune system is an important factor in the limitation of growth of mutant neoplastic cells. Whether immunosuppression contributed to the unsuccessful outcome under the specific conditions of liver transplantation cannot be proved, since the results may only have been a reflection of the highly malignant natural history of these particular neoplasms.

It is conceivable that other kinds of hepatic malignant lesions with a more indolent natural course may be less prone to post-transplantation reccurrence and spread. One example might be relatively slow-growing intrahepatic duct cell carcinomas. To our knowledge, no patient has yet been treated by transplantation for this kind of tumor.

It is a bit too early to conclude once and for all that liver replacement in the face of hepatic malignancy is a futile undertaking. One of our patients, whose primary reason for liver transplantation was biliary atresia, had an incidental hepatoma in the total hepatectomy specimen. Her preoperative serum contained almost 4 mg per 100 ml of alpha fetoprotein. After operation in January 1970, the fetoprotein disappeared from the serum

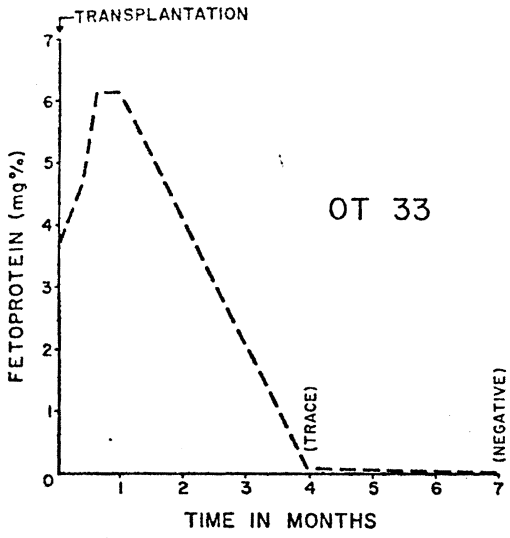

FIG. 3. Alpha-fetoprotein determinations in a 3-year-old child who underwent transplantation for biliary atresia. A small hepatoma was discovered within the operative specimen. The child is now 3½ years after transplantation. Alpha-fetoprotein determinations continue to be negative and she remains free of tumor.

(Fig. 3) and has not recurred in the 3½ years of post-transplantation life. Apparently, this child has achieved a cure from her hepatoma. Isolated cures of hepatic malignancy after liver replacement have also been reported by Roy Calne[8]* of Cambridge and by Pierre Daloze* of Montreal. Nevertheless, the high rate of recurrence of tumor in our hands has made us reluctant, for the time being, to accumulate more such cases.

Biliary atresia. Instead, the prime indications for orthotopic liver transplantation have come to be terminal liver diseases of non-neoplastic origin. Of these, extrahepatic biliary atresia is perhaps the least questionable, since death is inevitable after a relatively predictable interval and without any hope in the remaining life for rehabilitation. With intrahepatic biliary atresia, more conservatism is exercised, as some of these children can survive for many years.

Other benign diseases. The problem of the proper time for liver transplantation may be a difficult one for almost all other kinds of non-neoplastic liver disease. This is particularly so if alcoholism is a significant etiological factor that could be eliminated by abstinence. All gastroenterologists of experience have seen occasional patients with Laennec's cirrhosis who were apparently dying of profound hepatic failure but who recovered and subsequently left the hospital. Appreciation of this fact has probably been responsible for the rather small numbers of liver transplantations where the diagnosis is alcoholic cirrhosis.

The outcome is somewhat more predictable in patients with postnecrotic cirrhosis and less common disorders such as primary biliary cirrhosis, medically refractory Wilson's hepatolenticular degeneration, irreparable biliary duct injury, and some of the more lethal inborn errors of metabolism. But even with these diseases, there initially was reluctance for proceeding until incontrovertible evidence was obtained that extended survival was possible in human subjects after liver transplantation. Now that the feasibility of long-term survival has been proved, it will be possible to relax the restrictions on intervention so that treatment may be instituted before the terminal stages of the disease. Otherwise, it is unlikely that the results in future cases will be significantly improved.

At the present time, it is our belief that all patients who are dying from an otherwise untreatable non-neoplastic hepatic disease are potential candidates for liver transplantation, providing there are not other medical contraindications. Such contraindications would include advanced age (probably above 50 years), a history of sociopathic behavior that would prevent postoperative management, preexisting and untreatable systemic or local infections, or serious disease of organs other than the liver, as, for example, with coexisting severe heart disease.

According to Immunological Criteria

ABO matching. When a seriously ill person is identified as a possible organ donor, the ABO blood type is determined. When patients are considered for receipt of the liver, it is considered desirable to have the same ABO group as the donor. Failing this,

* *Follow-up by personal communication in June 1972.*

Table 1. DIRECTION OF ACCEPTABLE MISMATCHED TISSUE TRANSFER

0 to non-0[a]	Safe
Rh− to Rh+	Safe
Rh+ to Rh−	Relatively safe
A to non-A	Dangerous
B to non-B	Dangerous
AB to non-AB[b]	Dangerous

[a] *0 is universal donor.*
[b] *AB is universal recipient.*

the rules of tissue transfer are followed which are summarized in Table 1. The guide lines are designed to avoid the transplantation of an organ into a recipient who possesses preformed antidonor isoagglutinins. Erythrocyte antigens against which these isoagglutinins react are found not only in erythrocytes but also in most nucleated cells including hepatocytes. Thus, violation of the rules of tissue transfer in Table 1 can result in an acute immunological insult to a graft and even to immediate rejection.[9]

HL-A matching. Several years ago, it was hoped that clinical results after liver transplantation might be improved by effective donor-recipient matching of histocompatibility (HL-A) antigens. Unfortunately, the results obtained so far with hepatic, cardiac, and renal transplantation have not correlated well with the quality of the matches. These findings in our own experience and in that of others have led us, for the moment, to ignore the question of HL-A matching for liver transplantation. Nor do we even use the most favorable matching as an instrument of selection amongst a given group of candidates for transplantation. At the present time, our major criterion concerns who has the most pressing need.

DONOR PROCUREMENT

One of the important advances in transplantation has been social in nature, consisting of acceptance by the public of the concept of cadaveric organ removal. In the United States and many other countries, this acceptance has led to a sharpening and liberalization of the criteria of death in accordance with the concept of irreversible brain injury. If brain death is accepted, one of the most serious problems in organ transplantation is virtually eliminated, since the interval of normothermic ischemic injury subsequent to cardiac arrest is reduced essentially to zero inasmuch as the dissection prior to the removal of the liver or other organs can be carried out or even completed in the presence of an effective circulation.

With or without the advantages conferred by the acceptance of brain death, it is possible to maintain a well perfused liver in situ up to the moment of its excision. One way of achieving this, even in a patient who has suffered an irreversible cardiac arrest, is by the rapid insertion of cannulas through a femoral artery and vein into the great abdominal vessels. A patient may then be connected to a cardiopulmonary bypass. With a heat exchanger interposed in the circuit, the cadaver may be simultaneously perfused and cooled (Fig. 4). Finally, refinements in technology have made possible the successful preservation of canine and human livers for many hours after their excision and insertion into perfusion chambers.[3] With these various advances, all achieved within the last decade, it is hardly excusable today to carry out a liver transplantation with an organ that has been significantly injured either before or after death.

OPERATIVE PROCEDURES

Donor Hepatectomy

The essential feature of liver removal is extremely straightforward and consists of skeletonization of the structures entering and leaving the liver. Frequently, the first step upon entering the abdomen and after examining the liver is incision of the restraining ligaments of the liver. The falciform ligament is divided down to or near the entry of the hepatic veins (Fig. 5). The left triangular ligament is incised (Fig. 6), as well as the right triangular and coronary ligaments (Fig. 7).

It is particularly important in freeing the right lobe of the liver from the bare area

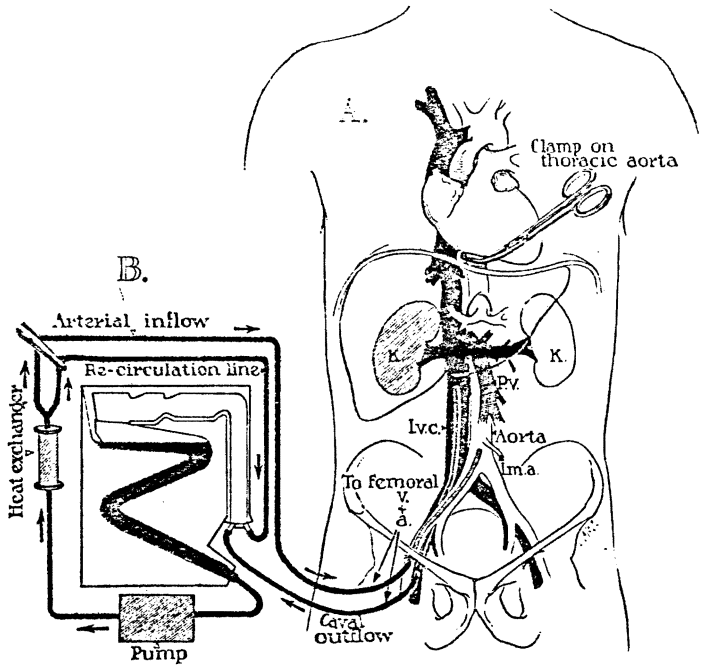

FIG. 4. Technique for postmortem extracorporeal perfusion of organ donors with a heart-lung machine. Catheters are inserted via the femoral vessels into the aorta and vena cava as soon as possible after death. Temperature control is provided by the heat exchanger. Cross-clamping of the thoracic aorta partially limits perfusion to the lower part of the body. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

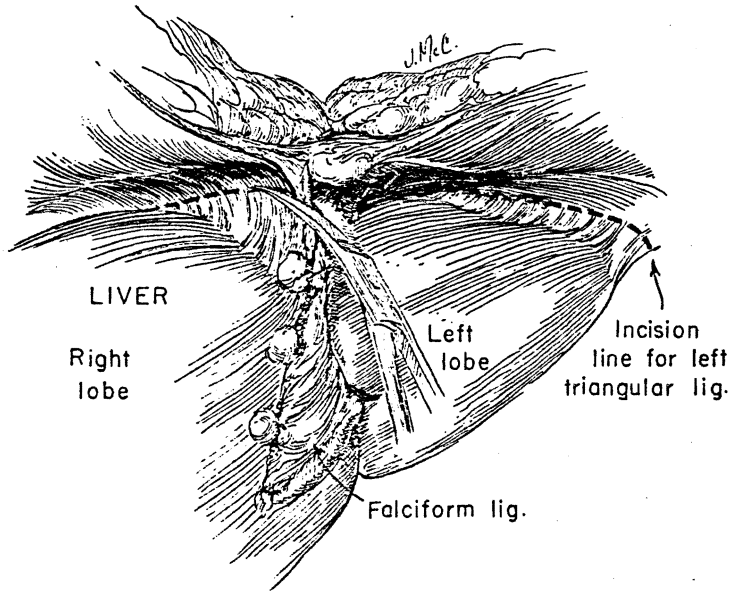

FIG. 5. Initial steps in donor hepatectomy. Note that the ligaments are incised as far away from the liver as possible so that they can be later resutured to the companion structures in the recipient if desired. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

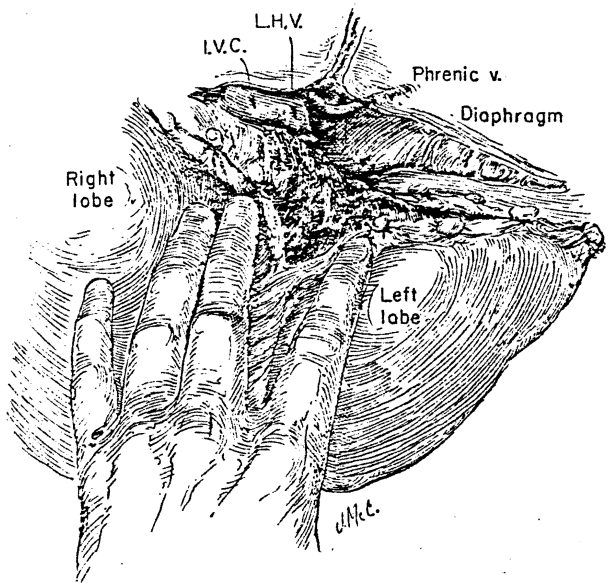

FIG. 6. Donor hepatectomy (continued). Exposure and the initial dissection of the suprahepatic vena cava and its tributaries. After entering the raw area formed by divergence of the leaves of the falciform and triangular ligaments, a short segment of the left hepatic vein (L.H.V.) is usually seen first. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

that the dissection be carried out sharply. Otherwise, subcapsular hematomas or capsular tears may inadvertently be caused. As the right lobe of the liver is rotated into the wound with exposure of the bare area, the right adrenal vein is readily identified entering the vena cava behind the liver (Fig. 8); this vessel is ligated and divided. After clearing loose areolar tissue away, it is usually possible to sweep behind the vena cava from the diaphragm to the entry of the renal veins without encountering resistance (Fig. 9).

The rest of the dissection of the donor liver consists in isolating the structures below the liver as depicted in Figure 10. Usually the hepatic artery is dissected back to its origin from the celiac axis, ligating its gastroduodenal and right gastric branches (Fig. 10 A and B). A long segment of the portal vein is similarly freed inferiorly to at least the entrance of the splenic vein (Fig. 10 C). In most cases, the biliary drainage procedure of cholecystoduodenostomy is planned. If this is contemplated, the common duct is ligated below the entrance of the cystic duct and an incision into the gallbladder is made so that the bile may be washed out. In experimental animals, failure to observe this precaution may lead to autolysis of the extrahepatic biliary duct system during the time when the organ is without a circulation.

The final step in the removal of the liver is further development of the cuff of vena cava above the liver into which empty the main hepatic veins (Fig. 11). This segment of vena cava is extremely short and is actually a confluence of vessels to form a venous cloaca. When the vena cava is finally transected and one peers into the liver side of this cloaca, the view is as shown in Figure 11 *(inset).*

With removal of the liver, infusion with a chilled solution is carried out via the portal vein (Fig. 12). In addition to cooling the organ, blood is washed out, thereby facilitating the anastomoses which can be performed in a clean field. There have been a number of infusion fluids recommended ranging from simple electrolyte solutions to very elaborate concoctions.

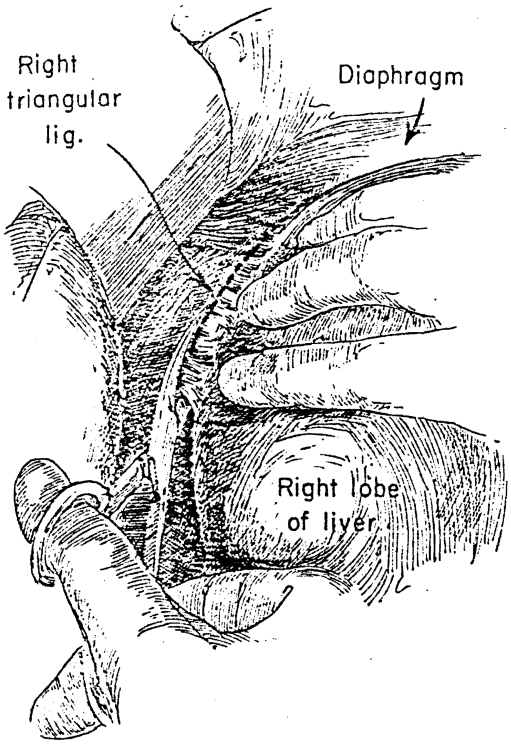

FIG. 7. Donor hepatectomy (continued). Incision of the right triangular ligament and the anterior leaf of the right coronary ligament. (From Starzl. *Experience in Hepatic Transplanation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

The Recipient Operation

Most of the steps in the recipient are identical or similar to those described above under the donor except that the long cuffs are left with the patient rather than with the homograft. After removal of the liver, the residual anatomy consists of cuffs of four vessels, the common duct stump (except in biliary atresia), and the raw areas left by incision of the various hepatic ligaments (Fig. 13). The reconstruction consists of anastomosing the individual vessels to the companion vessels of the homograft as quickly as feasible. The "standard" operations are shown in Figure 14.

One feature of the vascular reconstruction that is a special one in liver transplantation is the necessity to perform some of the vascular anastomoses in cramped quarters and with short vessel lengths. To permit this kind of anastomosis, intraluminal suturing techniques have been developed (Fig. 15), in which the principle is the formation of shoulders of venous wall posteriorly with systematic eversion.[3] This has sometimes been done with a double posterior layer (Fig. 15) or more recently a single everting layer has been employed.

The most commonly employed biliary reconstruction has been with cholecystoduodenostomy (Fig. 14), connecting the gallbladder to the duodenum with an external layer of interrupted silk and a continuous internal layer of catgut. More will be said later about alternative techniques.

Technical Difficulties and Dangers

Hemorrhage. Acute bleeding can be particularly troublesome during the actual liver transplantation because of the portal hypertension that is present in nearly every patient. During the operation, the usual sequence is mechanical bleeding that can rapidly assume nightmare proportions if a severe coagulation disorder supervenes. Many of the normal coagulation factors that might help control hemorrhage are dependent on the liver and are, therefore, defective to begin with in the diseased recipient. These coagulation deficiencies may become rapidly worse, after revascularization of an organ which has suffered ischemic damage, apparently because of consumption of clotting factors by the injured graft.[10]

When hemorrhage occurs, all mechanical hemostatic tactics including ligature, suture, and cautery are used until the revascularized homograft can participate in what is hoped will be appropriate coagulation function. In our early patients, an attempt was made to treat such bleeding problems by administering thrombogenic agents such as epsilon amino caproic acid (EACA). Lately, we have studiously avoided such practices for reasons to be discussed later. Instead, complete dependence is placed on natural processes for correction of the abnormalities.

Anesthesia problems. The complexity of anesthetic management during liver transplantation is increased by the fact that

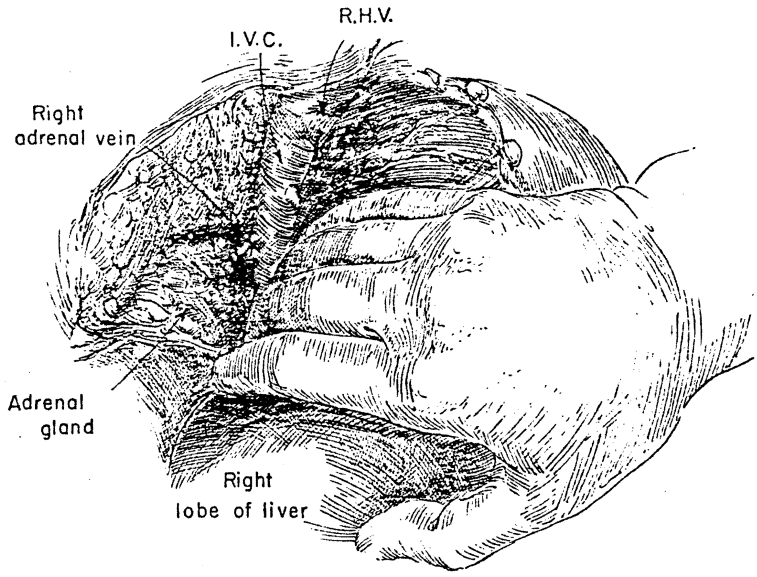

FIG. 8. Donor hepatectomy (continued). The liver is retracted to the left, opening the bare area of the right hepatic lobe and exposing the adrenal gland. The right adrenal vein is ligated and divided. This is usually the only posterior tributary to the retrohepatic vena cava. At this stage, the right hepatic vein (R.H.V.) can be identified. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

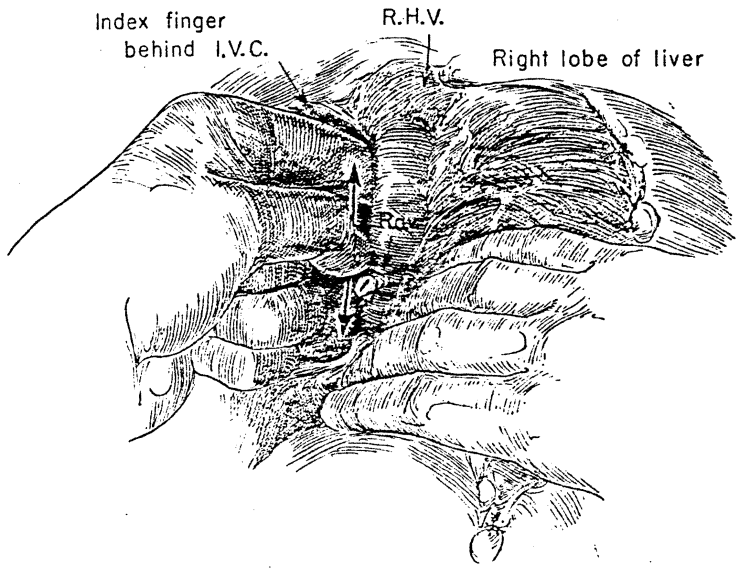

FIG. 9. Donor hepatectomy (continued). After ligating the right adrenal vein (R.a.v.), it should be possible to sweep the finger behind the retrohepatic vena cava from the diaphragm to the renal veins. If resistance is encountered, it usually indicates the presence of extra branches which must be ligated and divided. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

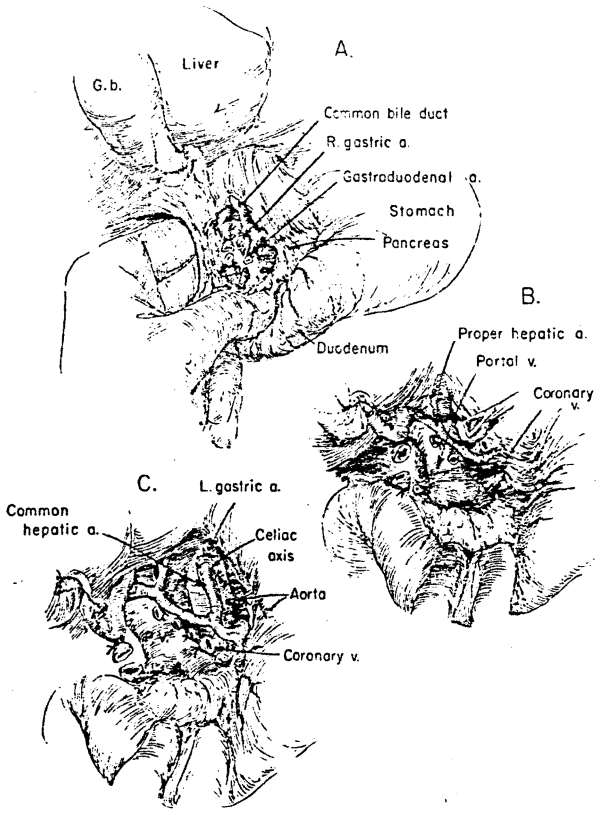

FIG. 10. Donor hepatectomy (continued). Dissection of the portal triad. (A) The gastroduodenal and right gastric arteries are tied off and divided. Before ligating the common duct, it should be determined that it communicates freely with the gallbladder via the cystic duct (see Fig. 8). (B) The hepatic artery is mobilized, uncovering the anterior surface of the portal vein. The coronary vein entering the left side of the portal trunk is almost always found; this tributary is ligated and divided. (C) Mobilization of the celiac axis. The splenic artery has not yet been ligated and divided. The entire celiac axis is usually retained with the homograft and in children it may be advisable to include a segment of aorta as well. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

the procedure is long, difficult, and often bloody. Even more importantly, it is an operation on the primary organ involved in the metabolism and detoxification of most common anesthetics. The task of the anesthesiologist is to adminster correctly drugs that, first, are not hepatotoxic and, second, do not depend primarily on the liver for their degradation. In our cases, reliance has been placed mainly on combinations of volatile agents such as fluoroxene and nitrous oxide-oxygen in nonexplosive concentrations. Such management permits use of the electrocautery, gives flexibility in lightening or deepening anesthesia, and allows anesthesia to be abruptly stopped if required by changing physiological circumstances.

A number of swiftly changing metabolic conditions have to be carefully scrutinized during the anhepatic phase and immediately afterward. Since the patient is at risk from acute hypoglycemia, a constant infusion of glucose is required, and for proper control of the situation frequent blood sugar determinations must be obtained. At the same time, the majority of recipients develop some element of acute metabolic acidosis, also requiring monitoring and correction. A third life-

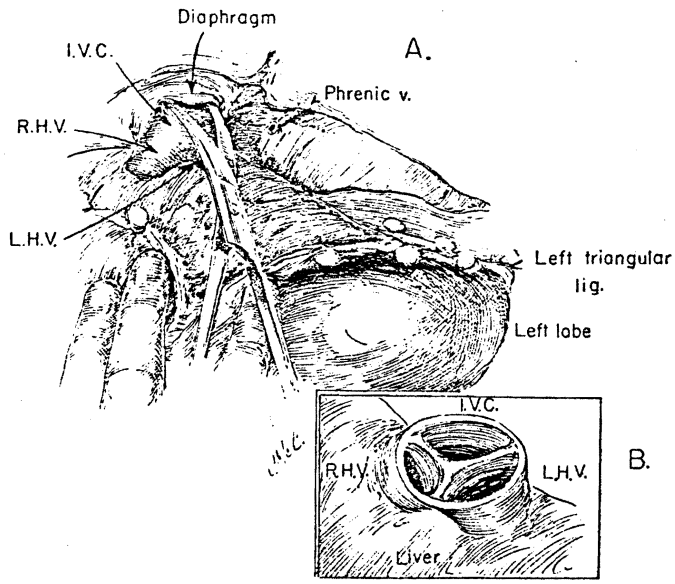

FIG. 11. Donor hepatectomy (continued). Dissection above the liver. (A) Development of suprahepatic vena caval cuff. A longer caval segment for subsequent anastomosis may be obtained by ligating and dividing one or more phrenic veins on each side and by dissecting off the diaphragmatic reflection, as shown. (B) (*Inset*) The cross-sectional appearance of the venous confluence above the liver, as seen from above. The venous cloaca is formed by the junction of the right and left hepatic veins with the inferior vena cava. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

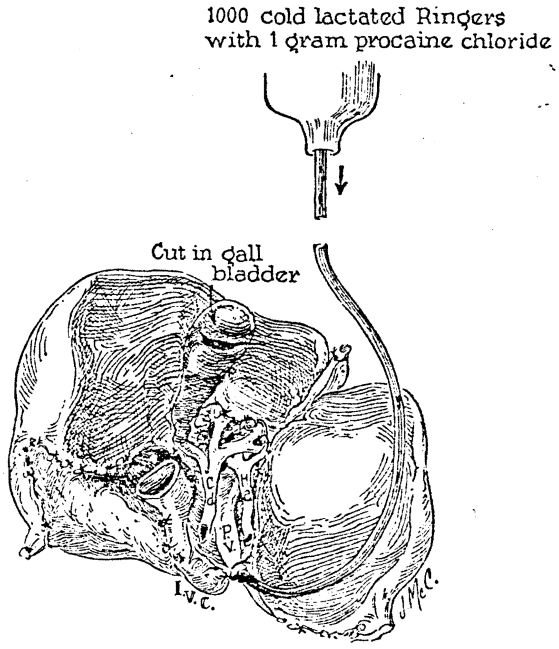

FIG. 12. Perfusion of the excised homograft with a chilled electrolyte solution infused through a catheter inserted into the portal vein. (From Starzl. *Surg. Gynecol. Obstet.* 117:659, 1963.)

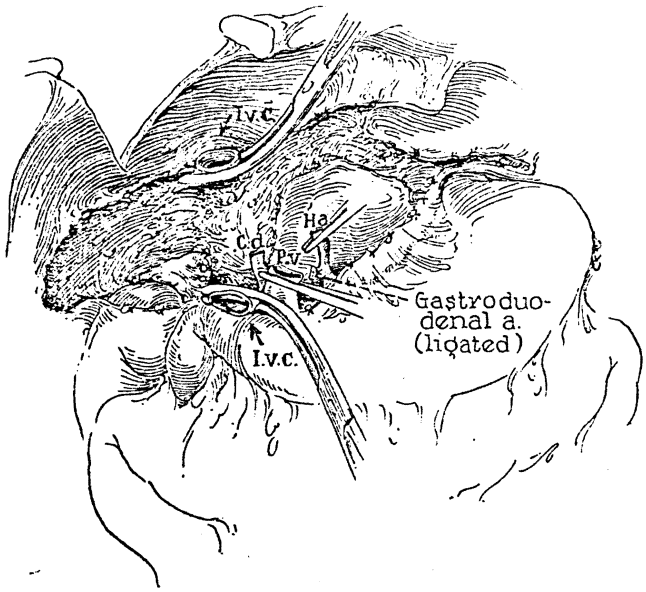

FIG. 13. Recipient operation. The operative field after removal of the diseased host liver. The thoraco-abdominal exposure shown is no longer employed. C.d.-common duct; H.a.-hepatic artery; I.v.c.-inferior vena cava; P.v.-portal vein. (From Starzl. *Surg. Gynecol. Obstet.* 117:659, 1963.)

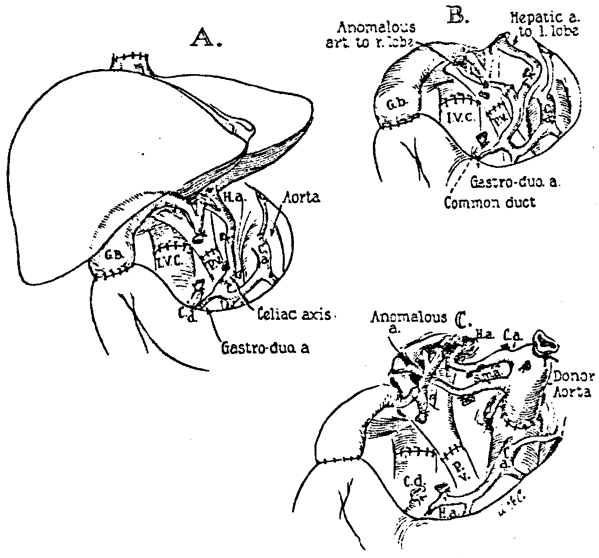

FIG 14 Recipient operations. (A) Usually the homograft celiac axis or common hepatic artery is attached to the proper or common hepatic artery of the recipient. (B) When two homograft arteries are present, the vessels may be individually anastomosed to branches of the recipient proper hepatic artery. (C) Anastomosis of the homograft aorta to the recipient aorta, in a pediatric recipient of a liver having a double arterial supply. In most recent cases, cholecystoduodenostomy has been performed for biliary drainage as shown. C.a.-celiac axis; C.d.-common duct; G.B.-gallbladder; H.a.-hepatic artery; I.V.C.-inferior vena cava; P.v.-portal vein; S.m.a.-superior mesenteric artery. (From Starzl. *Ann. Surg.* 168:392, 1968.)

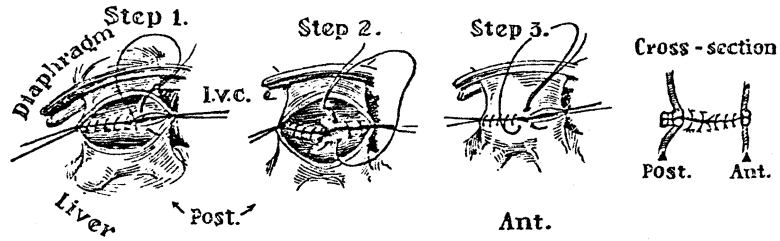

FIG. 15. Intraluminal suturing technique for the performance of the suprahepatic vena caval anastomosis. The posterior row may be fashioned in two layers from within the lumen, but recently a single layer everting technique has been employed. (From Starzl. *Surg. Gynecol. Obstet.* 117:659, 1963.)

threatening complication that has been frequently seen just after revascularization and lasting for several hours is hypokalemia. Apparently, the potassium is sequestered in the grafts to the extent that serum potassium concentrations as low as 1.5 mEq per liter have been observed.

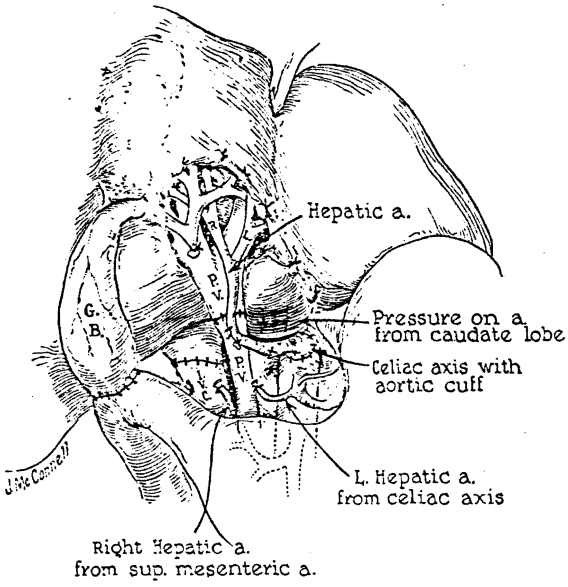

FIG. 16. Fatal compression of the homograft arterial supply by an oversized homograft. In this patient, the recipient right hepatic artery originated from the superior mesenteric artery. The homograft celiac axis was therefore anastomosed directly to the recipient aorta. (From Starzl. *Experience in Hepatic Transplantation*, Courtesy of W. B. Saunders, Philadelphia, 1969.)

Spatial problems. Not surprisingly, a homograft of exactly the right size may be difficult to find for any given recipient. Consequently, major size disparities often have had to be accepted. There have been few difficulties in using undersized organs. For example, it has been possible to carry out orthotopic transplantation of a 5-year-old liver to a full-sized adult. Other size mismatches nearly as extreme have been safe.

On the other hand, serious risks are borne when the donor organ is disproportionately large. Size disparities in this direction may lead to compression of the blood supply (Fig. 16). This kind of complication tends to occur just as the abdomen is being closed, in which case an adverse chain of events leading to death may be set in motion, but not appreciated, until it is too late for correction.

Vascular anomalies. Anatomical variations of either the graft or host arteries have been encountered in almost 40 percent of our cases. Multiple arteries have been the most frequent anomalies (Fig. 14 B and C). When these have been found in the recipient, most commonly the graft celiac axis has been connected to the host aorta. When the multiplicity has been of the transplant vessels, multiple arterial anastomoses (Fig. 14 B) or other variant procedures (Fig. 14 C and 17) have been used. Unquestionably, the need to improvise in these situations imposes an extra risk, particularly in the very young recipients whose arteries are quite small and thin-walled. In patients with biliary atresia, anomalies may be encountered of which the complexity may be so great as to make it vir-

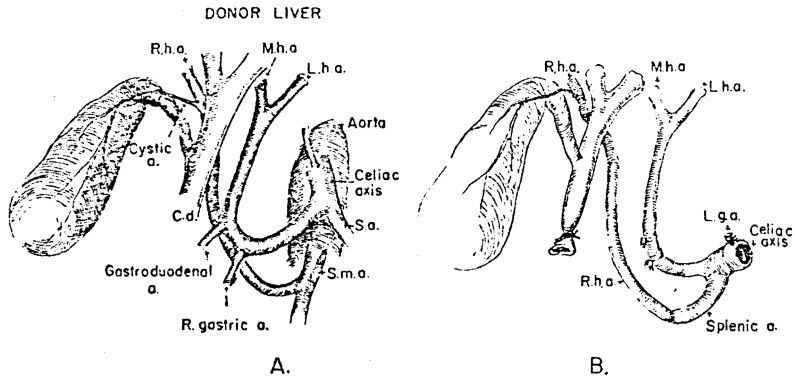

FIG. 17. Method of arterial reconstruction employed because of the presence of two homograft arteries. (A) The anomalous arterial supply in the donor. (B) The homograft celiac axis was anastomosed to the common hepatic artery of the recipient. After blood flow was restored through the larger left branch, the homograft splenic artery was attached to the small right hepatic branch. C.d.-common duct; L.g.a.-left gastric artery; L.h.a.-left hepatic artery; M.h.a.-middle hepatic artery; R.h.a.-right hepatic artery; S.a.-splenic artery; S.m.a.-superior mesenteric artery. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

tually impossible to succeed. Two of our infants with biliary atresia had a curious type of malrotation in which the portal vein passed in front of the pancreas and duodenum, the arterial blood supply issuing from the superior mesenteric artery rather than from the celiac axis, which was absent. In addition, the retrohepatic inferior vena cava was missing. In both cases,[3] corrective maneuvers to overcome the structural deficits

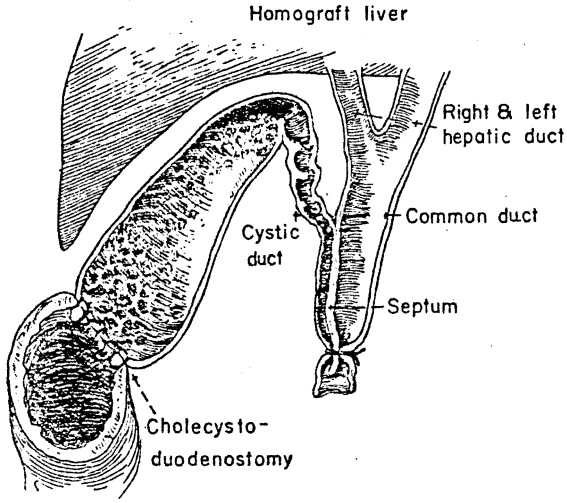

FIG. 18. The anatomical basis for a technical error which cost the lives of two patients. Distal ligation of the double-barreled extrahepatic duct system resulted in total biliary obstruction. (From Starzl. *Experience in Hepatic Transplantation,* Courtesy of W. B. Saunders, Philadelphia, 1969.)

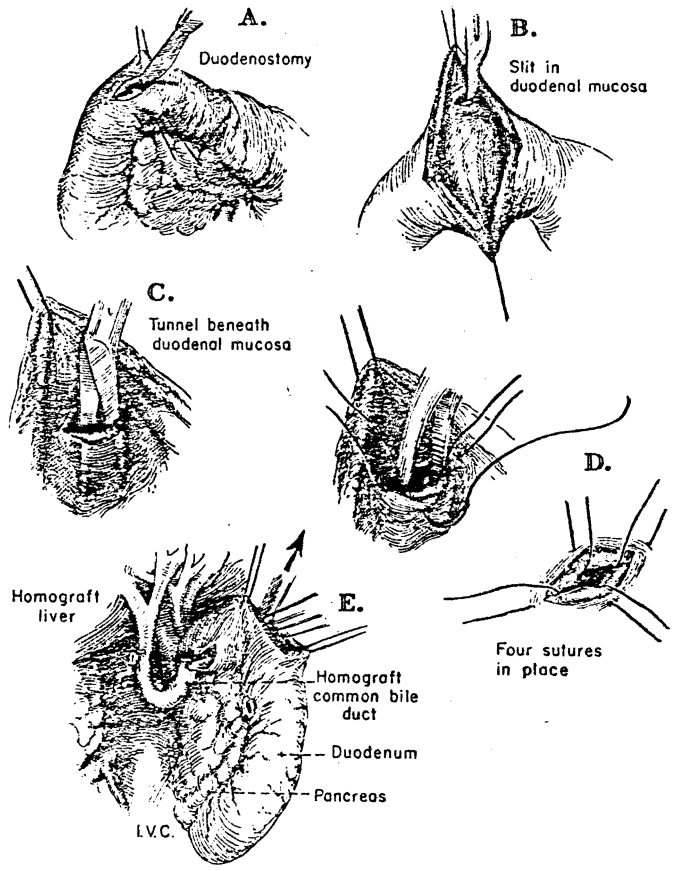

FIG. 19. Method of choledochoduodenostomy employed in several recipients of liver homografts. After opening the duodenum, a short submucosal tunnel is formed, through which the homograft common bile duct is drawn.

was unsuccessful and the patients died within a few days.

Bile duct problems. An end-to-end anastomosis of the common duct, if it were normal, would have the advantage of preserving the sphincter of Oddi, thus reducing the chances of reflux of food or bacteria. Of course, such an option is not available in recipients with biliary atresia. In other kinds of cases, we believe that because of the factor of immunosuppression this anastomosis involves too high a risk of leakage and infection in the face of T tube stents and drains. Consequently, the safer if somewhat less elegant technique is used of anastomosing the gallbladder directly to the duodenum and ligating the common duct (Fig. 14). By so doing, all stents and drains can be avoided.

Ligation of the transplant common duct in conjunction with cholecystoduodenostomy may be dangerous if there are unrecognized anomalies such as a septum between the cystic and common ducts. In two cases in our experience, biliary drainage was inadvertently obstructed when the common duct ligature closed both parallel passages (Fig. 18), a technical error that subsequent surgery failed to correct and that proved fatal.

While cholecystoduodenostomy remains the preferred primary operation, the slightest suspicion that it will not provide effective drainage for anatomical or other reasons should lead to a decision for an alternative technique. With biliary atresia, choledocho-

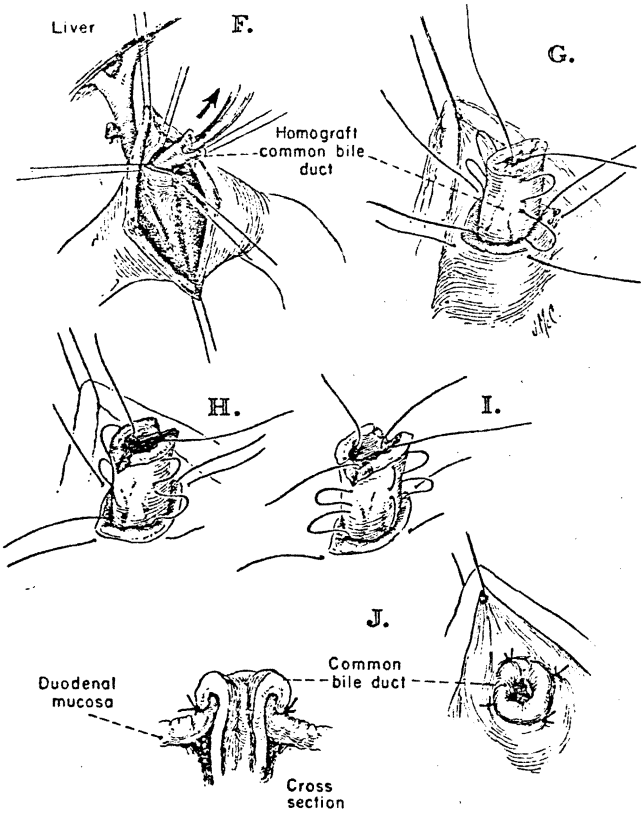

FIG. 20. Choledochoduodenostomy (continued). The common bile duct is then everted to form a nipple and its mucosa approximated to that of the duodenum with fine silk sutures.

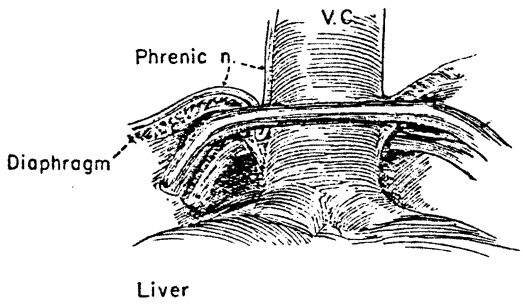

FIG. 21. Mechanism of operative injury of the right phrenic nerve. Note the inclusion of the nerve with a portion of the diaphragm in the bite of the vascular clamp placed across the suprahepatic vena cava. (From Starzl. *Experience in Hepatic Transplantation*, Courtesy of W. B. Saunders, Philadelphia, 1969.)

duodenostomy has been performed with the method depicted in Figures 19 and 20. In cases where a normal distal common duct is present, end-to-end choledochocholedochostomy has been performed both with and without stenting by a T tube.

Other operative problems. A long list of other technical pitfalls includes venous infarction of the right adrenal gland secondary to sacrifice of the adrenal vein (see earlier), air embolism during recipient hepatectomy, and crushing of the right phrenic nerve by clamps placed too superiorly on the upper vena caval cuff (Fig. 21) to mention only three examples. A more detailed discussion of these and other surgical problems has recently been published.[3]

NONIMMUNOLOGICAL POSTOPERATIVE COMPLICATIONS

Aberrations of Coagulation

Earlier, the problems were discussed of an intraoperative bleeding diathesis secondary to hepatic insufficiency. The consequent hemorrhage may continue unchecked into the postoperative period if the transplanted organ is of poor quality. On the other hand, the provision of a well-functioning hepatic homograft will promptly correct the coagulation defect and there has been some evidence that a rebound hypercoaguability may actually occur.[10] In every significant series of liver transplantations, at least one example of a lethal thrombotic complication has been noted. These have included venous thrombosis of the legs with or without pulmonary embolism. In addition, delayed thrombosis of the homograft hepatic artery or portal vein has occurred on several occasions.

In a few early trials of liver transplantation, heparin was tried as a means of preventing postoperative thrombotic complications, but the hemorrhagic complications of anticoagulation were devastating in some of these recipients. Consequently, we now avoid iatrogenic manipulation of the clotting process after liver transplantation and use neither thrombogenic nor anticoagulant agents.

Delayed Biliary Obstruction

For reasons already described, the most commonly used method of biliary duct reconstruction has been with cholecystoduodenostomy (Fig 22). In at least four patients who had satisfactory initial bile drainage with this reconstruction, delayed obstructive jaundice appeared which was diagnosed by the technique of cholangiography, illustrated in Figure 23. The point of obstruction was at or near the junction of the cystic and common ducts (Fig. 23). All four patients died in spite of the fact that two of them had secondary conversion of the cholecystoduodenostomy to choledochoduodenostomy.

The pathological findings in the gallbladder and biliary ducts of these homografts

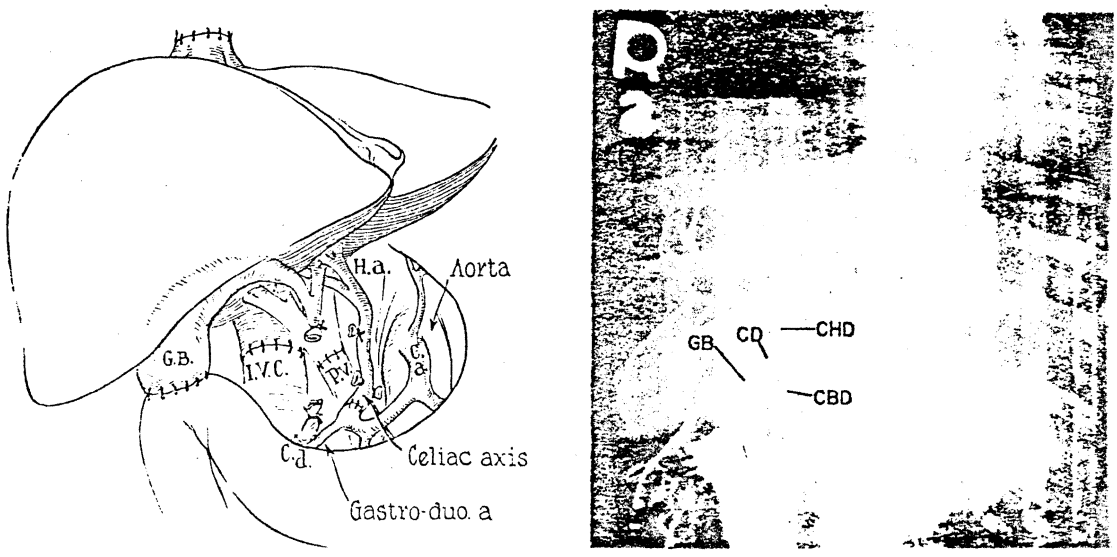

FIG. 22. Cholecystoduodenostomy. (Left) The gallbladder has been anastomosed to the duodenum. (Right) Normal operative cholangiogram obtained by the technique shown in Figure 23. There is free passage of the contrast medium through the cystic duct. C.d.-cystic duct; C.H.D.-Common hepatic duct; C.B.D.-common bile duct; GB-gallbladder. (From Martineau et al. *Surgery* 72:604, 1972. Courtesy of The C. V. Mosby Company, St. Louis.)

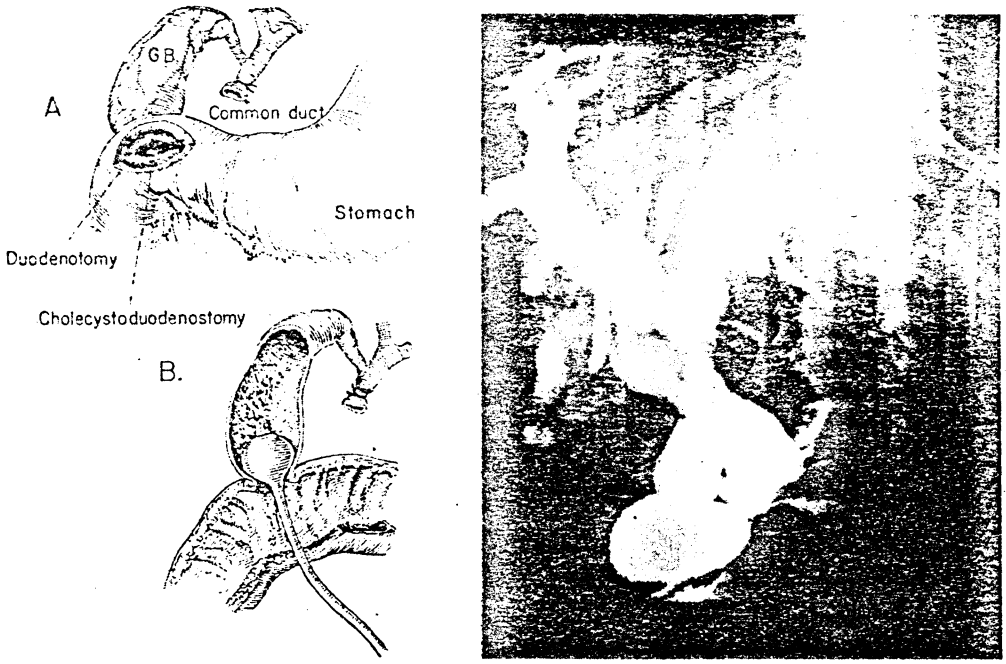

FIG. 23. Cholangiography of hepatic homografts. (Left) Technique of dye injection through a duodenotomy and the anastomosis. (Right) Obstructed duct system in a liver recipient whose primary biliary reconstruction was with cholecystoduodenostomy. (From Martineau et al. *Surgery* 72:604, 1972. Courtesy of The C. V. Mosby Company, St. Louis.)

were of great interest.[11] The walls were infested with cytomegalovirus (CMV), which had caused swelling and shedding of the epithelial cells. Consequently, the etiology of this complication was at least partly infectious and presumably secondary to the immunosuppression which is required in all such cases.

Because of the background of immunosuppression, the development of cholangitis secondary to mechanical duct obstruction has extremely serious implications in liver recipients. In both experimental animals and man, homograft cholangitis may lead to multiple intrahepatic abscesses which cannot be effectively treated. Bacteremia results, usually with microorganisms that are indigenous to the intestinal tract (Fig. 24). All the manifestations of gram-negative septicemia, including cardiovascular collapse, may follow. In following patients with liver transplantation through the postoperative period, blood cultures are frequently obtained. If these become positive, biliary duct obstruction or some other complication of the homograft such as devascularization should be suspected.

Miscellaneous Complications

Full recovery from anesthesia may be delayed in liver recipients, requiring ventilatory support for as long as 1 or 2 days after return to the intensive care center. Even after extubation, meticulous tracheobronchial toilet must be provided, including systematic nasotracheal suction. In spite of these precautions, early pneumonitis or atelectasis have been relatively common and a number of our patients have required bronchoscopy. Control of secretions has been a particularly difficult task in those patients who suffered unilateral phrenic nerve injury intraoperatively (see Fig. 21).

Gastrointestinal hemorrhage is a rather common complication of the steroid component of the immunosuppressive regimen that all such organ recipients require. This has been particularly well documented in the renal transplant population,[9] but the same

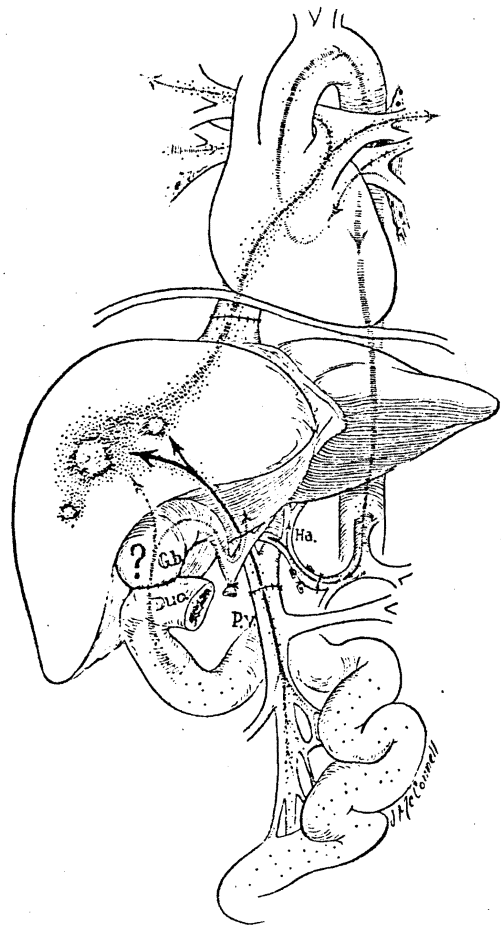

FIG. 24. An explanation for the predisposition of the liver to bacterial sepsis. Presumably the invading microorganisms enter via the portal vein or through the reconstructed biliary tract. (From Starzl. *Ann. Surg.* 168:392, 1968.)

thing has been reported in liver recipients.[3] The most common etiology of the hemorrhage is peptic disease of the duodenum or stomach, but fatal gastrointestinal bleeding has resulted from enteritis caused by *Candida albicans* infestation of the bowel wall.

The same kind of fungal infection has also been responsible for at least one example of post-transplantation pancreatitis. In addition, a number of liver recipients dying from a few days to more than a year after transplantation have had histopathological findings of idiopathic acute, subacute, or chronic pancreatis. Pancreatitis is undoubtedly related at least in part to the need for chronic immunosuppression.

In children, arterial hypertension has been seen quite frequently. This has been attributed partly to the effects of steroid therapy but, in addition, the inability of the new liver to deal with pressor substrates may have contributed. For example, evidence has been reported [3] of defective tyramine degradation. Tyramine is an aromatic amine which is normally formed in the gastrointestinal tract by the decarboxylation of tyrosine and which is then detoxified by hepatic monoamine oxidase. The sympathomimetic properties of tyramine are thought to be by its induction of norepinephrine release from adrenergic nerve endings.

IMMUNOSUPPRESSION

With the transplantation of any whole organ from other than an identical twin donor, a special problem must be dealt with, namely the prevention of rejection. Since the process of rejection is a manifestation of the immunological defense of the host against antigens identified as "nonself," its control depends upon the systematic weakening of the host defenses which ordinarily provide resistance against invasion by a wide spectrum of microorganisms.

Techniques of Immunosuppression

The therapeutic regimens that are used for hepatic recipients were evolved and tested in patients treated by renal homotransplantation. These treatment programs have been used essentially without modification for the liver recipients.

Double drug therapy. The first protocol which was used for all organ recipients in most transplantation centers throughout the world consisted of "double drug' treatment [3, 9] with azathioprine and the synthetic adrenal corticosteroid, prednisone. Evolution of the use of these two agents together, appreciation of their marked synergism, and demonstration that rejection could be easily reversed by increasing the steroid doses were among the advances which made clinical

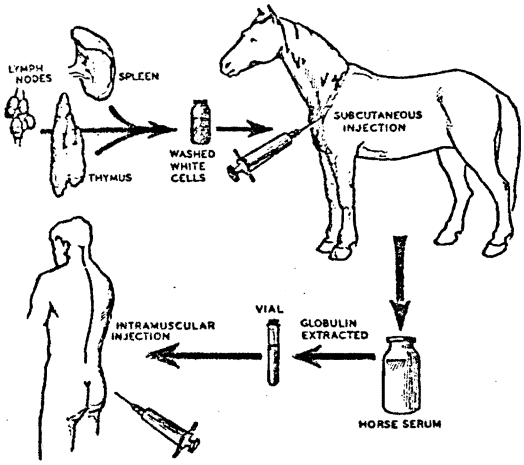

FIG. 25. The preparation of horse heterologous antilymphocyte globulin for use in patients. (From Starzl. *Christopher's Textbook of Surgery*, Courtesy of W. B. Saunders, Philadelphia, 1968.)

transplantation practical and which introduced what is known as the modern era of this clinical field. But in spite of fair results with renal transplantation, the double drug therapy either did not prevent rejection of hepatic homografts in the early trials or else it proved too toxic to permit host survival. All patients treated with liver transplantation from 1963 to 1966 under this kind of treatment died in a month or less.[3]

Triple drug therapy including ALG. In 1966, heterologous antilymphocyte globulin (ALG) was introduced clinically at our center as a third immunosuppressive agent added to the drugs mentioned above.[9] Since then, this "triple drug" therapy has been given to essentially all our renal, hepatic, and cardiac recipients. ALG is the globulin removed from the serum of an animal immunized against lymphoid tissue obtained from the species to be treated. Our greatest experience has been with ALG obtained from horses immunized against human lymphocytes (Fig. 25). It has seemed to us that rejection has been more easily and regularly controlled and the risks and morbidity imposed by the necessity for high-dose steroid therapy have been reduced with the use of the triple drug program (Fig. 26).

More recently, cyclophosphamide, a well-known cancer chemotherapeutic agent with potent cytotoxic properties, has been used

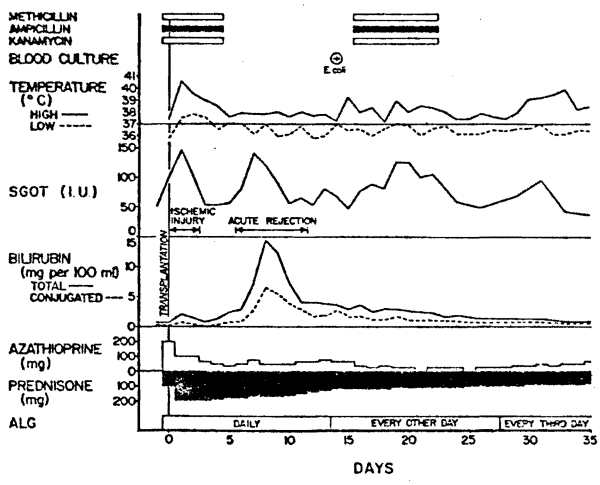

FIG. 26. The course of a patient who underwent a rejection crisis while under treatment with a triple drug program that included azathioprine, prednisone, and ALG. The rejection began on the sixth day, reached a peak within 2 days, and receded promptly. Gram-negative bacteremia was diagnosed from a blood specimen obtained on post-transplantation day 14. Note that the immunosuppressive therapy was actually lightened with the development and evolution of the rejection crisis.

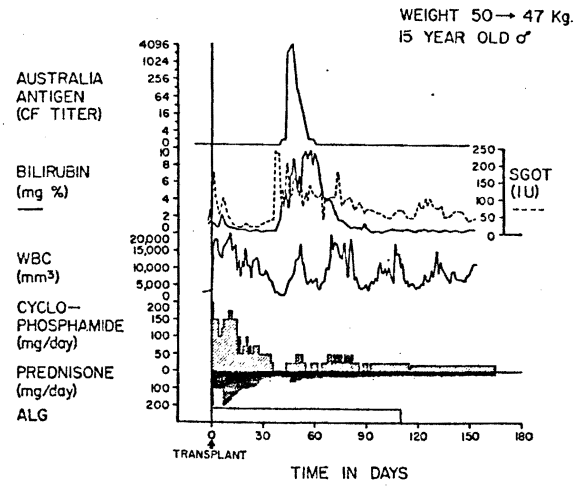

FIG. 27. The course of a patient who had triple drug therapy with cyclophosphamide (instead of azathioprine), prednisone, and horse ALG. Note that there was excellent liver function except during the second and third postoperative months, when the patient developed jaundice and rises in the levels of the serum transaminases. These abnormalities were coincidental with the appearance of the Australia antigen in the serum and consequently were probably reflections of serum hepatitis rather than rejection. The recipient's original diagnosis was Wilson's disease. He is well 1½ years after transplantation.

during the early postoperative period instead of azathioprine in the triple drug regimen. There are potential advantages to the use of cyclophosphamide, including the fact that it apparently has somewhat less hepatotoxicity than azathioprine. After 1 or 2 months, azathioprine has been substituted for cyclophosphamide for maintenance treatment (Fig. 27).

Manifestations of Rejection

In spite of immunosuppressive therapy, most patients develop some signs of hepatic homograft rejection and usually these appear within the first few postoperative weeks. Jaundice appears, with increases in both the total and conjugated bilirubin, as might be expected with biliary duct obstruction. It has come to be recognized, however, that these biochemical manifestations are a reflection of intrahepatic cholestasis. Consequently, it is not surprising that sharp rises in the alkaline phosphatase also occur.

Additional abnormalities in the liver function tests may indicate variable hepatic necrosis. There are increases in the SGOT, SGPT, and the liver-specific enzyme, isocitric dehydrogenase. The synthetic functions of the liver are surprisingly well maintained even with advanced degrees of rejection.

The findings of rejection occupy a wide spectrum of manifestations. The process may be very indolent, with jaundice being the main finding, or it can even be so mild that clinically obvious icterus never appears. At the other extreme, rejection may occur as an acute crisis (Fig. 26), with evidence of massive tissue necrosis. Then, bacteremia may complicate matters, apparently as the result of seeding by bacteria of necrotic foci within the liver by a mechanism to be discussed later.

Fortunately, rejection is a highly reversible process with increased doses of steroids or sometimes without any adjustment in therapy at all (Fig. 26). After rejection is controlled, it is often possible ultimately to reduce the amount of day-to-day immunosuppression that is required to prevent a recurrence.

Penalties of Immunosuppression

Risks with all organs. Heightened susceptibility to infection is the most obvious penalty of a depressed immune system. In the early compilations of results in kidney transplant recipients, a repeated and often fatal chain of events was infection by bacteria, fungi, viruses, or even protozoa. When these infections were caused by common pathogenic bacteria against which effective antibiotics were available, treatment was usually not difficult. Infection with opportunistic fungi or other microorganisms for which antibiotics are not available emerged as the most serious late problem after transplantation, however.

It has also become obvious [3, 12] that chronically immunosuppressed patients have an increased vulnerability to de novo malignant conditions. In our own series of chronic survivors after renal transplantation, more than 5 percent have developed either mesenchymal or epithelial malignant tumors. Almost all other major transplantation centers have recorded this same complication, which is presumably due to failure of the depressed immunological surveillance mechanism to identify mutant neoplastic cells as alien and to eliminate them or to restrict their growth. Fortunately, these tumors can usually be treated by conventional means, including surgical excision and radiotherapy.

To date, there have not yet been any examples of de novo malignancy in chronically surviving recipients of hepatic homografts. As has already been noted in an earlier section, however, there has been an almost universal recurrence of tumors in patients whose indication for hepatic replacement was the presence of an otherwise nonresectable hepatoma. The regular and often rapidly growing recurrences in these cases may conceivably have been contributed to by the loss of full immunological defense.

Extra risks for liver recipients. In addition to the foregoing general liabilities of immunosuppression, there are some special risks for the liver recipient. Of the chronic survivors after hepatic transplantation in our center, about one-third have developed some serological evidence of serum hepatitis by tests for the Australia antigen (Fig. 27). In other liver recipients, hepatotoxicity of the immunosuppressive drugs rather than uncontrolled rejection may have been responsible for deterioration of graft function, although this possibility has been difficult to prove. With liver malfunction, whatever its cause, dose control of some of the immunosuppressive agents may become difficult, since the liver participates in their pathways of action and/or degradation.

In the liver recipient, postoperative sepsis of the graft itself has proved to be a special problem, without doubt partly because of the anatomical location of the orthotopically placed organ, interposed between the intestinal tract and the heart. Bacteria from the bowel, particularly of the gram-negative variety, can thus be brought into contact with the transplanted liver via the intestinal veins draining into the portal vein or alternatively by retrograde spread up the duct system after passage through the biliary anastomosis. In either event, the presence of nonviable hepatic tissue provides a perfect medium for bacteriological growth and then systemic dissemination (Fig. 24). Almost paradoxically, one of the most important ways by which hepatic sepsis can be avoided is to administer heavy doses of steroids in the early postoperative period, thereby circumventing rejection episodes and consequent tissue ischemia. In addition, heavy antibiotic treatment is indicated for the first postoperative week, including agents effective against gram-negative bacteria.

CLINICAL RESULTS

Our own experience, including all patients treated with orthotopic liver transplantation from March 1963 until July 1971, 12 months ago, has consisted of 46 cases. Survival of at least 1 year has been obtained in 12 of the 46 recipients.

After 1 year, eight patients were lost for the reasons and the times shown in Table 2. The causes of late failure were carcinomatosis (three examples), late or chronic homograft rejection (three examples), and serum hepatitis (two examples). Deaths have oc-

Table 2. TWELVE 1-YEAR SURVIVORS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Alive	4/12	1 to 3 years
Died	8/12	1 to 3½ years

12 Months – Cancer[a]
12 Months – Serum hepatitis, liver failure
14 Months – Cancer
15 Months – Cancer
15 Months – Rejection, liver failure
20 Months – Chronic aggressive hepatitis and disseminated nocardia infection[b]
30 Months – Rejection, liver failure
42 Months – ? Rejection, liver failure

[a] *This patient actually died a few days short of 1 year*

[b] *The homograft showed severe chronic aggressive hepatitis, just as in her previously removed native liver*

curred as long as 3½ years after operation.

In view of the serious implications of serum hepatitis in liver transplant recipients, it could be questioned if liver transplantation would offer any hope in the treatment of lethal serum hepatitis. In one extraordinary patient whose reason for transplantation was chronic aggressive hepatitis, Australia antigen positive, life was definitely prolonged by the provision of a new liver.

Transplantation was carried out in the summer of 1970. The Australia antigen became negative for almost 2 months and then returned to positive at the same time as a clinically obvious bout of acute serum hepatitis. She recovered from this but her Australia antigen remained positive until she died of recurrent chronic aggressive hepatitis 20 months later. Nevertheless, her health was satisfactory for all but the last month or so of her survival.

The experience in treating both hepatoma and serum hepatitis has demonstrated how adversely the original disease can affect the ultimate outcome. Such should not be the case with inborn errors of metabolism, providing the new liver can compensate for preexisting metabolic defects. Two of our patients have had liver replacement for Wilson's disease, a disorder characterized by widespread tissue copper accumulation. Both are alive with excellent liver function after 3 and 1½ years. Copper storage in their homografts has not occurred.

Similarly, the course after liver transplantation should not be affected by the previous diagnosis of congenital biliary atresia. Six (32 percent) of our 19 patients with biliary atresia lived for more than 1 year after transplantation. The high mortality rate in these cases had a heavy contribution from technical factors of which many were related to the small size of the structures being anastomosed.

So far, the most discouraging results of all have been with Laennec's cirrhosis, primarily because of the debilitated condition of the patients. To date, extended survival has not been obtained after transplantation for this disease, while at the same time patients with cirrhosis from other causes have lived for long times.

FUTURE PROSPECTS

Earlier in this chapter, the contribution of structural anomalies to technical failure was mentioned. The accurate identification of such variations in advance of operation, both in the donor and recipient, is useful. Recently, a very much wider use of angiography and cholangiography preoperatively and intraoperatively has reduced the number of technical surgical accidents.

So far the least satisfactory surgical detail of liver transplantation has been the provision of bile drainage, at least six early deaths in our series having been due to acute or delayed biliary obstruction. In the future, prompt reexploration of the homograft duct system should be carried out if there is any suspicion of obstruction. Procrastination in past cases has permitted the development of fatal intrahepatic sepsis.

In addition to improving the technical performance of liver transplantation, the use of immunosuppressive drugs with low hepatotoxicity may prove to be helpful, and it was with this objective that the substitution of cyclophosphamide for azathioprine was undertaken. This major change in therapy will require much more evaluation before it can be generally recommended. Even now it

seems clear, however, that cyclophosphamide is equivalent in its immunosuppressive action to azathioprine. With this new therapeutic regimen, five patients have been treated with liver transplantation in 1972. With follow-ups of 4 to 8 months, four of these recipients are well. The fifth died of a technical complication.

The history of hepatic transplantation viewed 10 years hence is apt to be very similar to that of renal transplantation viewed now from a 10-year retrospective vantage. The feasibility stage of hepatic transplantation has long since been passed, since there have now been two patients who have survived for as long as 3½ years after this operation, one in our series and the other reported by Professor Roy Calne of Cambridge. The inconsistent results so far obtained will undoubtedly improve, particularly if patients are accepted before the terminal stages of their disease, as has been the practice until recently. It seems certain that liver transplantation will become as much a part of the therapeutic armamentarium for the treatment of hepatic disease as the analogous operation kidney transplantation has become in the treatment of kidney disorders.

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A. HYDATID DISEASE OF THE LIVER AND OTHER VISCERA

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This chapter is dedicated to the memory of two eminent investigators of hydatid disease: to Sir Harold Dew, who, for over 20 years, was the author of this chapter in its various editions, and to the great pioneer, the grand maitre *of hydatid disease, Professor Felix Devè*

Today, hydatid disease interests not only surgeons of the countries where the disease is endemic but also medical men throughout the world. The alienation of vast numbers of people from country to country during the past 30 years, either during war or peace, has made infestation become more prevalent than at any previous time. Thus, such patients are being operated upon in many countries.