TRANSPLANTATION OF THE HUMAN LIVER

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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 C. S. Welch of whole-organ hepatic transplantation in dogs was only 28 years ago. Furthermore, the first clinical attempts at liver transplantation were not described until 1963. Consequently, these as well as most of the other early articles on liver transplantation are still of current interest.

Until recently liver transplantation was considered an experimental operation. At a Consensus Development Conference held in Bethesda, Maryland on June 20-23, 1983, under the sponsorship of several federal agencies, the adjudication was made that the operation had become therapeutic. With this change in classification, it is certain that a number of new liver transplantation centers will spring up in the United States in the next year or two. Thus, for the first time liver transplantation will become an acknowledged part of the surgical armamentarium available for the treatment of end stage hepatic disease.

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 a procedure that Welch envisioned 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 artery. Venous inflow is reconstituted by anastomosing the host superior mesenteric vein to the homograft portal vein. Outflow is into the inferior vena cava.

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 ailing 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 assumed initially 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 in-
flow, 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 (often referred to as hepatotrophic physiology) can be found in other texts.

Here, it will only be noted that most patients 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 resulted in the significant prolongation of life for only two patients. One was a child with biliary atresia who is still well as of August 1983, more than 10 1/2 years after auxiliary transplantation by Fortner, of New York, using a technique similar to that shown in Figure 1. The second patient, an adult, treated in Paris had lived for more than 2 years at the time of his reporting in May, 1980.

The reasons for failure in the vast majority of patients have been several. In many cases good initial homograft function was not obtained due to an ischemic injury during and/or 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 anatomic reconstruction as possible. Survival in dogs and human subjects has been achieved exceeding 12 and 13 2/3 years, respectively. The remarks in succeeding sections will pertain to orthotopic transplantation.

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. Nevertheless, 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.
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

Of the 237 patients treated from 1 March 1963 through April 1982, 112 were classed as pediatric recipients (Table 1); their ages ranged from 5 months to 18 years. The 125 adults (Table 2) were 19 to 68 years old.

It is now clear that none of the disorders for which transplantation has been attempted can be excluded categorically from future trials. At the same time, a fairly complete understanding has evolved with many specific diseases about what advice to give to prospective recipients and their families, when and if the operation should be decided upon, how much risk there is of deterioration and death during the search for a donor organ, and what are the technical difficulties to be anticipated during the transplantation.

At present, candidacy is restricted to patients who are less than 55 years old, who are free of extrahepatic infection, and who do not have an extrahepatic malignancy. Within this group,
the 2 main principles in case selection concern, first the propriety of a decision to proceed and, second, the feasibility of an attempt. In the early days of transplantation, the propriety issue was the dominant theme because of anxiety that meaningful life might be foreshortened by a dangerous and unpredictable surgical undertaking. Our general guideline was that transplantation for non-neoplastic liver disease became justifiable with the advent of social and vocational invalidism. This condition usually was reflected in repeated hospitalizations for encephalopathy, variceal hemorrhage, hepatorenal syndrome, uncontrolled coagulation disorders, intractible ascites and other complications of hepatic disease.

According to Underlying Diseases

**Hepatic Malignancy** — — When orthotopic liver transplantation was first attempted in humans, primary liver malignancy was considered to be an outstanding indication for proceeding. Liver replacement was conceived of as a means of extending the limits of resectability in patients who did not have extrahepatic spread of their tumors.

In actual experience our results in our early cases were discouraging. About 80 percent of our patients who had liver replacement for hepatomas, intrahepatic duct cell carcinomas, cholangiocarcinomas, and sarcomas and who lived through the early postoperative interval developed tumor recurrence. Most commonly, the posttransplantation metastases involved the new liver (Figure 2). Deaths from recurrence have occurred as early as 143 days (Figure 2) and longer than 4 years after transplantation.
It is 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 dl of alpha fetoprotein. After operation in January 1970, the fetoprotein disappeared from the serum (Figure 3) and has not recurred in the 13 2/3 years of posttransplantation life. Apparently, this child has achieved a cure from her hepatoma. Another of our patients, a 28-year-old woman, is well 6 3/4 years after transplantation for sclerosing cholangiocarcinoma. Palliation or even cure of primary hepatic malignancies has also been reported by Calne.

Since immunosuppression with cyclosporine and steroids has been used, the incidence of recurrence has been much less. This may only reflect better case selection. However, it cannot be assumed out of hand that cyclosporine does not have some anticancer qualities.

Biliary Atresia — Nevertheless, 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, since 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 if alcoholism is a significant etiologic factor that could be eliminated by abstinence. Other common disease in our series (Tables 1 and 2) have been chronic aggressive hepatitis, inborn errors of metabolism (Wilson's disease, alpha-1-antitrypsin deficiency, Types 1 and 4 glycogen storage disease, tyrosinemia, sea blue histiocyte syndrome), sclerosing cholangitis, and primary biliary cirrhosis. Patients with acute liver disease usually are not considered since they may have the capacity to recover spontaneously. Contraindications would include advanced age, 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, coexisting severe heart disease.

According to Immunologic Criteria

ABO Matching and Cytotoxic Antibodies - - - When possible, the rules of tissue transfer are followed (Table 3). These are designed to avoid the transplantation of an organ into a recipient who possesses preformed antidonor isoagglutinins. Violation of these guidelines in kidney transplantation can lead to immediate graft destruction by hyperacute rejection. The liver has proved resistant to this complication, meaning that blood group barriers can be breached in the case of desperate need. Even more surprisingly, the presence of preformed cytotoxic antibodies against donor tissues does not usually cause hyperacute liver rejection.
HL-A Matching — The poor correlation in renal, cardiac, and liver transplantation between matching at the A, B, and Dr histocompatibility loci and clinical outcome has led us to ignore the question of tissue 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, our major criterion concerns who has the most pressing need.

DONOR PROCUREMENT

The most common explanation for transplantation of an inadequately preserved liver is pre-existing hepatic injury, rather than poor harvesting or preservation technique. Thus, removal of a satisfactory liver for transplantation begins with wise screening of donors and elimination of those whose physiologic situation could jeopardize vital organ function in advance of procurement. Aside from abnormalities in the hepatic function profile, signals that it may be dangerous to the recipient to proceed with the donor hepatectomy are donor cardiovascular instability, a need for excessive vasopressor support, an excessive period (several days) between injury and the pronouncement of brain death, or the deterioration of renal function which may suggest poor perfusion of other organs.

OPERATIVE PROCEDURES

The Donor Operation

Initial dissection — A midline sternotomy and celiotomy extending from the sternal notch to the pubic symphysis provides excellent exposure not only of the liver but of the kidneys and
other organs which might be needed. After assessing the liver and other organs for gross suitability, anomalies of the hepatic arterial supply are looked for (Figure 4). A common variant is an artery to the left lateral segment arising from the left gastric artery. It can be found coursing from left to right in the gastro-hepatic ligament accompanied by fibers from the vagus nerve. This vessel can be preserved in continuity with its left gastric origin and the celiac axis.

The right lobe of the liver (and sometimes the entire liver) may be supplied by a branch from the superior mesenteric artery (Figure 4). Almost invariably this branch lies posterior to the portal vein and can be felt there with a finger placed through the foramen of Winslow (Figure 5A). On rare occasions, in which the left gastric or superior mesenteric artery branches supply the entire liver, a true common hepatic artery arising from the celiac axis may not be found.

After the anomalies have been identified, the structures of the portal triad are dissected, staying as far from the liver as possible. Usually, the hepatic artery is dissected retrograde, starting with ligation and division of the gastro-duodenal and right gastric arteries (Figure 5). The splenic and left gastric (and sometimes phrenic) branches of the celiac axis are ligated and divided. The proximal dissection is facilitated by cutting the diaphragmatic crura, exposing the origin of the celiac axis and a short segment of the subdiaphragmatic aorta. If a good view of the common hepatic artery, the celiac axis and the aorta cannot be obtained easily with this anterior approach, the spleen
and stomach can be mobilized and reflected to the right, and the aorta is approached from the left side (Figure 6). At some time during the dissection, the origin of the superior mesenteric artery is also exposed so that it can be ligated later.

An anomalous superior mesenteric artery branch to the right hepatic lobe (occasionally it is the sole arterial supply of the liver) is best approached by performing a Kocher maneuver and reflecting the duodenum and head of the pancreas to the left. The hepatic artery (Figure 4) can be seen posterior to the portal vein, duodenum and pancreas and traced back to its take off which is at a right angle from the superior mesenteric artery. Small branches to the pancreas are ligated and divided. The superior mesenteric artery distal to its hepatic branch is dissected so that later ligation is possible. The superior mesenteric artery proximal to this point is cleaned back to its origin from the aorta. This may be most easily done from the left side (Figure 6) or from an inferior approach.

Having completed the dissection of the arterial supply, the portal vein is isolated at the superior border of the pancreas. The pancreas can be divided at this level between two mass ligatures and exposure of adequate lengths of splenic and superior mesenteric veins obtained. All other branches to the portal vein are ligated or divided, the most constant being coronary veins (Figure 5).

The common bile duct is encircled as close to the superior margin of the duodenum as possible. A transverse incision is made high on the fundus of the gallbladder and the extrahepatic
biliary tract flushed out with saline to prevent later autolysis of the mucosa by bile.

It remains to dissect the inferior vena cava. The falciform, left and right triangular, and coronary ligaments are divided and the suprahepatic vena cava is encircled (Figures 7-9). Care is taken to identify, ligate and divide the right, left and posterior phrenic veins. The right lobe is retracted anteromedially and the retrohepatic vena cava is dissected free to the level of the renal vein inferiorly (Figure 9). This step requires ligation and division of a large right adrenal vein and occasionally smaller tributaries.

In some cases, retraction of the liver from the liver fossa causes color changes in the organ reflecting either inflow or outflow obstruction. If the donor mean arterial pressure falls, the cause usually is outflow obstruction with compromised cardiac filling from loss of venous return. In such an event, retrohepatic vena caval dissection is deferred until the final steps.

Our present policy is to carry out in situ infusion of the kidneys and liver, although many surgeons with whom we collaborate prefer to excise the kidneys at this time and to flush them ex-vivo. With either method for the kidney removal, the principles of the hepatectomy are the same. The donor is anti-coagulated with heparin (300 USP units per kg.) and a large cannula is inserted into the distal aorta near the bifurcation to provide for in situ infusion of cold (4°C) preservation solution (Figure 10). A second cannula is placed into the distal vena cava to allow bleeding off of central venous volume during the subsequent infusion of cold solutions (Figure 10).
Precooling of the Liver

A critical principle in the procurement of satisfactory livers is to bring the infusion of cold solution into the portal vein while there is still an effective donor circulation. This step of hepatic precooling eliminates warm ischemia by reducing the temperature of the liver tissue while an adequate flow of oxygenated arterial blood is still present. At the same time, added protection to the kidney and other organs is provided since donor core temperatures during this precooling phase drift quickly to 28-32°C at the same time as the liver temperature drops several degrees below this.

The precooling solution is introduced into the portal vein via a cannula inserted into the previously dissected splenic vein (Figure 10). Cold (4°C) lactated Ringer's solution is rapidly infused and during the infusion the superior mesenteric artery and vein are ligated in that order. Perfusion pressures of 80-100 cm of water are maintained by elevation of the infusion reservoir. Central venous hypertension is avoided by intermittently bleeding off blood volume via the previously placed inferior vena cava cannula. After approximately a liter of lactated Ringer's solution has been infused, the liver becomes noticeably cool to palpation. Any increased firmness of the organ suggests hepatic venous hypertension and demands immediate lowering of central venous pressures by bleeding off from the caval cannula and slowing of the portal infusion. The infusion is continued until a total of approximately 2000 ml of lactated Ringer's have been given, until donor core temperature reaches 28-30°C, or until
there is difficulty maintaining the donor blood pressure. During the precooling, a vasolytic agent (e.g. chlorpromazine, phentolamine, tolazoline) is given as an intravenous bolus injection.

**Final Stages**

As portal precooling is terminated, *in situ* aortic flushing of the liver, kidneys, or other organs is begun (Figure 10). The abdominal aorta is clamped at the diaphragm and rapid infusion of cold (4°C) modified Collin's solution (Travenol®) is begun via the distal aortic cannula at the same time as the vena cava cannula is opened to allow free drainage of blood to a collection bag placed on the floor. The portal vein infusion of lactated Ringer's solution is changed to a modified Collin's solution (Travenol®) for a final flush in adult donors of about 500 ml or of a proportionately smaller amount in pediatric donors.

All of the abdominal organs are now cold. The liver is removed first. The suprahepatic vena cava is transected as high as possible (Figure 11). A piece of the right atrium sometimes is included. The liver is peeled out from the retroperitoneum from a superior to inferior direction by gentle anterior traction on the liver, care being taken to ligate all posterior tributaries to the retrohepatic vena cava. The vena cava is transected just superior to the entrance of the renal veins. The aorta is re-clamped just distal to the celiac axis so that further infusion of the kidneys may be continued if desired. The liver is removed.
The nephrectomy team proceeds with removal of the kidneys. The most common practice is to remove the organs en bloc with a long segment of aorta and vena cava. The early function of cadaveric kidneys obtained during heart and liver procurement, or both heart and liver, has been better than that achieved in our center and elsewhere with renal procurement alone. This advantage for the eventual renal recipients probably is due to the more discriminating donor selection and the greater intensity of surgical technical care that are features of the multiple organ harvesting operations. It should be specifically noted that heart and liver grafts can be obtained from the same donor with minor modifications of the described technique.

The chilled liver is placed in a plastic bag that contains Collin's solution. The bag is sealed and packed in ice in a standard picnic refrigerator. Canine livers so processed can support the life of a recipient after storage for 12 to 24 hours but in humans, an effort is made to keep the cold preservation time to less than 6 or 8 hours. Using a different infusion solution, the Cambridge workers have described similar time limitations.

Contingency Vascular Grafts

After the organs are out, the distal aorta and vena cava, the iliac veins, and the iliac arteries are removed and stored separately in balanced electrolyte solution. It is surprising how often these vascular segments have been desperately needed for the subsequent performance of a renal or hepatic transplantation (Figure 12).
The Recipient Operation

A bilateral subcostal incision is used with an upper midline extension through which the xiphoid process is excised (Figure 13). The midline extension with xiphoid removal provides badly needed exposure for dissection of the hepatic ligaments and the suprahepatic inferior vena cava. If it is obvious that there will be a struggle to remove the liver, another extension should be made immediately into the right seventh intercostal space (Figure 13). This is most commonly needed if the liver is unusually shrunken.

Uncomplicated Transplantation

The pre-existing pathologic changes often necessitate deviations from a standard plan. However, the usual first step is to find the hilum to encircle it (Figure 14), and to dissect the proper and common hepatic artery in the same way as described for the donor (Figure 5). If the artery is of inadequate size, it should be mobilized proximal to the gastroduodenal and right gastric artery. In difficult cases, the proper hepatic artery can be ligated at this time. This can expedite dissection of the other hilar structures and slow hemorrhage from the liver surface later in the procedure. During the hilar dissection, the bile duct (if one is present) is transected as high as possible so that the option of duct to duct anastomosis is retained. The portal vein is left intact until later in order not to aggravate the portal hypertension.
The inferior vena cava below the liver is encircled with as little dissection as possible. The left triangular and falciform ligaments are incised until the suprahepatic vena cava can be identified. The suprahepatic vena cava is encircled, usually from the left side with enough dissection to allow the placement of a cross clamp. In some cases, the encirclement may be easier from the right side. If these maneuvers can be successfully executed, the safety of subsequent steps is increased since, in the event of an accident, such as a laceration of the vena cava, the liver can be removed from the circulation by emergency cross-clamping of the encircled but intact vessels.

In straightforward cases, the right triangular and coronary ligaments are incised and the bare area is entered. With retraction of the liver toward the left, it becomes safer to dissect lengths of the inferior vena cava above and below the liver (Figure 9). If the native disease is an "easy" one (primary biliary cirrhosis for example), adequate cuffs may be obtained with the liver in place and the mobilization of the entire specimen including ligation of the right adrenal vein can be completed now in the same way as with donor hepatectomy (Figures 7-9). If this is feasible the time of later portal and vena caval cross-clamping is only that necessary to transect the vessels and suture in the new liver. The upper vena caval cuff can be fashioned at the entry of the main hepatic veins (Figure 15). If the clamp is placed too superior, it is possible to crush the right phrenic nerve (Figure 16).
This phase of the operation often is not easy because of scarring and anatomic distortion above and below the liver and in the retrohepatic area. In patients with cirrhosis, it may be impossible to enter the bare area without causing a lethal hemorrhage. Then the step of liver isolation described earlier may be necessary, with the clamping of the residual hilar structures and the previous encircled vena cava above and below the liver. When this has been done, the liver including the retrohepatic vena cava can be peeled out of the hepatic fossa from below (Figure 17) or from above (Figure 18). Cuffs of the suprahepatic and infrahepatic vena cava can be fashioned as the liver is removed. Sufficient infrahepatic vena cava is not difficult to obtain, but the development of an adequate suprahepatic cuff may require considerable tailoring of the vena cava which is mobilized from within the liver (Figure 18). The technique of isolating the liver in this way and peeling it out in the bloodless state permits all residual tissue connections of the right triangular ligament and the bare area, including the right adrenal vein, to be ligated under perfect vision. The penalty is an increased time of portal and vena caval occlusion, which if excessive can set into motion an irreversible spiral of physiologic deterioration (see later).

With the liver out, the wound is checked for major sites of bleeding, realizing that total hemostasis of the bare area and elsewhere is not possible at this time. The suprahepatic and infrahepatic vena caval anastomoses are performed first, followed
usually by reconstruction of the portal vein. At a convenient
time, air and the potassium rich preservation fluid in the graft
should be washed out (Figure 19) to prevent air embolism or hy-
perkalemia with revascularization. An alternative to the infu-
sion technique shown in Figure 19 is to flush the liver with the
first surge of restored portal blood, allowing the outflow to
escape through a vent in the lower caval anastomosis before re-
leasing the upper caval clamp.

Portal blood flow is usually restored first. After checking
for major anastomotic leaks, the hepatic arterial anastomosis is
performed (Figure 20). Frequently, the new liver is at first
swollen and hard, and there is diffuse hemorrhage from all raw
areas. With time and the administration of platelets and fresh
frozen plasma, the problems are usually reversible providing a
major bleeder has not been missed. Efforts at mechanical hemo-
stasis are continued until it is thought safe to perform the
biliary tract reconstruction.

Notations About Vascular Anastomoses

The back wall of both vena caval anastomoses and that of the
portal vein must be sutured from the inside. Attempts to develop
long enough cuffs for external suturing may be fruitless on one
hand, or if successful, the reconstructed vessels may kink from
the excessive length. We have used a continuous intraluminal
suturing technique.

The principle of the method, as demonstrated in Figure 21,
is the immediate formation of intraluminal shoulders in both
vessels to be joined. First, sutures are placed in the extremiti-
ties of the anastomosis. The swaged needle is passed into the posterior part of the lumen of one of the vessels one mm from the line of incision (Figure 21, A2). A firm bite of the other vessel is then taken, making sure that the entry and exit sites of the needle pass through the intima at some distance from the cut edge (Figure 21, A3). The full thickness of the wall is included. The same kind of bite is taken in the back wall of the other vessel. A mound of protruding tissue presents which makes easy the similar placement of subsequent sutures (Figure 21, A4). The back wall is automatically everted. When the opposite end of the posterior anastomotic line is reached, the needle is passed outside (Figure 21, A4) and the anterior row is completed with an everting over and over suture (Figure 21, A5). The steps are almost exactly the same for an end-to-end (Figure 21, B) or end-to-side anastomosis (Figure 21, C).

The degree of eversion obtained in the back wall is the same as if the sewing were done from the outside (Figure 21, A6). Consequently, the amount of intraluminal suture material is not increased. There are other advantages. A perfect intimal coaptation can be assured. If the orifices of tributaries to the anastomosed vessels are identified near the suture line, they can be incorporated into the shoulder, thereby circumventing potential para-anastomotic leaks. Gentle traction on the suture facilitates placement of the next bite, making it unnecessary to grasp or manipulate the vessel wall with forceps.

In the early years of our experience, silk was used for the vascular suturing. More recently we have preferred prolene, a
material which causes little advential pull, but which can purse string an anastomosis because of its easy movement through sutured tissues. A minor purse string effect at the large vena caval anastomosis has not been a concern but special precautions in addition to avoidance of excessive tension on the suture are taken to protect the portal vein and hepatic artery. Half of the continuous anastomosis is performed with one suture (Figure 22-2), and its mate is used for the other half of the circumference (Figure 22-3). The 2 are tied where they meet, but the knots are set at a distance from the vessel of about a third of the circumference (Figure 22-3). When blood flow is restored, the slippery prolene pulls back into the suture line and the slack gradually is distributed back toward the opposite end (Figure 22-4). The process can be encouraged by gentle circular kneading of the anastomosis. Any bleeding from resulting gaps in the anastomosis is controlled with additional simple sutures.

The extra suture material has been referred to as a "growth factor". Some observers have been aghast at this seemingly heretical technique until they see the astounding way that small anastomoses expand (Figure 22-4), and with little bleeding. Postoperative anastomotic hemorrhage has not been seen. The growth factor technique is used for the hepatic arteries and portal-venous anastomoses in all patients. In pediatric recipients, we believe it to be at least as important as the use of loupe magnification in the routine ability to reconstruct these tiny structures at the hepatic hilum.
The Question of Venous Bypasses

Portal and vena caval occlusion during the anhepatic phase often is reasonably well tolerated during a 45 to 90 minute anhepatic phase in spite of major declines in cardiac output and variable hypotension. The relative safety of the occlusions depends on the collaterals that develop with human liver disease. The same thing has been demonstrated in dogs subjected to chronic bile duct obstruction. Because of this we abandoned the venous bypasses which we had used in all of our first cases.

However, some patients can be gravely jeopardized by the venous cross clamping. If severe hypotension occurs after cross clamping, Calne has recommended femoral vein to femoral artery bypass with an intervening oxygenator. About 10% of the English patients are so treated. One death during the last year in our series could have been avoided by this precaution as well as a cardiac arrest which was successfully treated.

The fact that most patients can recover from portal and vena inferior caval cross clamping may have created a false impression about the safety of this practice. Usually there is gross swelling of the intestine during the period of portal occlusion. Subsequently, many such patients suffer from third space fluid sequestration, and from postoperative renal failure. The extent to which these complex physiologic events have contributed to the high perioperative mortality of liver transplantation has not yet been delineated. For this reason we have returned in 1982 to the practice of venous bypass which we abandoned long ago. Cannulae were placed into the inferior vena caval (through an iliac or
femoral vein) and into the portal system through the open end of
the transected portal vein. During the anhepatic phase the blood
was returned to a reservoir, and pumped to one of the large veins
in the neck or arm. This kind of bypass required total body
heparinization and the amount of bleeding was so excessive and
nonresponsive to later protamine reversal that 2 of the patients
died on the operating table.

Eventually, the feasibility of using pump driven venous by-
passes with no heparin was proved in dogs, using heparin coated
tubing and non-traumatic closed-system pumps without a reser-
voir. Clinical application was promptly undertaken and now this
technique is used for all adult recipients. With this change,
liver transplantation has become possible with maintenance of
better patient physiology and without so much stress on the anes-
thesiologists and surgeons. Removal of the devascularized liver
in a meticulous and deliberate way as well as more leisurely per-
formance of the vascular anastomoses for the first time has made
transplantation a pleasant operation instead of a desperate race
against the clock.

Variant Technical Problems and Solutions

The "Frozen" liver hilum -- Patients with previous opera-
tions may have such severe right upper quadrant adhesions that it
is virtually impossible to enter the abdomen. In such recip-
ients, it is essential with sharp dissection to develop an exact
plane on the undersurface of the liver, and eventually to en-
circle the portal triad (Figure 14). If the lesser omental sac
can be found and entered, through the avascular gastrohepatic ligament, the encirclement usually is easiest from the left side. If it is then impossible to dissect the individual structures of the portal triad, the triad mass can be transected after placement of a vascular clamp (Figure 23). The individual structures can be identified at the cut surface and traced back for the development of cuffs.

**Arterialization of graft anomalies**—-Problems posed by homograft arterial anomalies (Figure 4) have been described with various technical solutions. A double arterial supply originating from the celiac axis and superior mesenteric artery once was thought to be too troublesome to warrant an effort at reconstruction. In several recent cases, the celiac axis and superior mesenteric artery have been connected (Figure 24), and one or the other end of the superior mesenteric artery has been anastomosed to the recipient hepatic artery.

**Inadequate recipient artery**—-Contingency plans should be made in the event that a recipient hepatic artery is too small or too inconveniently located to permit an effective anastomosis. The most common cause for this circumstance is an anomalous recipient arterial supply such as that described in previous sections.

In our earliest experience in such recipients, attempts were made to perform an anastomosis of the graft aorta or celiac axis to the aorta of the recipient above the recipient celiac axis. The dissection required to clean off the recipient aorta in this inaccessible area was difficult, and aortic cross-clamping which
was usually required during the anastomosis had devastating physio
ologic effects. Consequently this approach has been abandoned.

The easiest solution is to attach the homograft blood supply to the recipient abdominal aorta, inferior to the origin of the renal arteries (Figure 25). The exposure of the distal aorta is relatively easy, even in patients with severe portal hypertension. The ascending colon is retracted to the left. The most convenient site for anastomosis is near the origin of the inferior mesenteric artery. The extra length of graft vessel necessary to reach this location can be provided by retaining the thoracic aorta of the donor in continuity with the celiac axis and by turning the aorta 180 degrees (Figure 25). The occasional need for this technical deviation has prompted the donor team to retain the thoracic aorta with the specimen whenever possible.

Another option to obtain the needed length is to anastomose the free common iliac artery graft to the same location in the recipient aorta with ligation of the hypogastric artery. The external iliac artery is almost a perfect match for anastomosis to the graft celiac axis.

**Thrombosed or Hypoplastic portal vein** -- One of the great tragedies of liver transplantation has been the discovery at operation of an unsuspected thrombosis or hypoplasia of the portal vein. If effective revascularization of the homograft portal vein has not been accomplished, survival has never been obtained. In two patients, the suprarenal inferior vena cava has been anastomosed to the graft portal vein, providing the liver with systemic venous inflow as with a portacaval transposition.
This anastomosis thrombosed in one patient who died of massive hemorrhage from esophageal varices a month later, and the other patient died of massive graft necrosis.

If the thrombosis (or hypoplasia) has not involved the splenic and superior mesenteric veins, the confluence of these portal tributaries can be dissected free from beneath the pancreas. We have then developed a cloaca at this junction to which an iliac vein graft has been anastomosed to provide added length. The use of an interposition host graft under these circumstances (Figure 12) has been life saving.

If thrombosis of the portal vein has been recent, thrombophlebectomy has been accomplished on several occasions. Although a rough intimal surface has been left, the portal venous system has remained open.

**Biliary Tract Reconstruction**

In the early days of liver transplantation, the now abandoned procedure of cholecystoduodenostomy was frequently used (Figure 26, E). Obstruction at the homograft cystic duct occurred in almost half of the cases. Even without obstruction the biliary tract became the site of entry of bacteria (Figure 27). Organisms which could be cultured from the blood stream were those indigenous to the gastro-intestinal tract. It was envisioned that the liver was being frequently contaminated with enteric contents, followed by systemic dissemination of the bacteria (Figure 27).

The systematic use of a defunctionalized jejunal limb (Roux-en-Y) to which the gallbladder was anastomosed (Figure 26, F) was
an improvement. However the problem of cystic duct obstruction in more than 1/3 of the recipients remained (Figure 28), necessitating frequent secondary revisions with conversion to choledochojejunostomy (Figure 26, B).

If biliary enteric anastomosis is necessary, we now perform a choledochojejunostomy (Roux-en-Y) at the first operation (Figure 26, B). This is done with a single layer of continuous absorbable suture (Figure 29). A few tacking sutures can be used for reinforcement (Figure 29). An internal stent is used (Figure 26, B). When choledochojejunostomy is performed, the gallbladder is removed.

Biliary tract reconstruction by duct to duct anastomosis was the first one used by us and then temporarily abandoned because of a high incidence of biliary leaks which were lethal in the patients treated 15 to 20 years ago. The duct to duct anastomosis (Figure 26, A) is performed with interrupted absorbable sutures. A T-tube stent is used whenever possible (Figure 26, A), and the T limb is brought out through a choledochotomy in the recipient portion of the composite duct. In small children, and occasionally adults, the available T-tubes are too large and an internal stent is used with the distal tip passed into the duodenum (Figure 26, A').

In 1973, Waddell and Grover recommended that the homograft duct be anastomosed to the graft gallbladder as part of the biliary reconstruction in liver transplantation. Calne has used this technique extensively in the Cambridge program and for him it is the method of choice. The distal anastomosis with the
fundus of the homograft gallbladder is made either to the recipient common duct (Figure 26, C) or to a Roux limb of jejunum (Figure 26, D). In either case, both of the anastomoses are stented with a T-tube which can be used for irrigation. We have used the Waddell-Calne procedure only when the extra length provided by the gallbladder was necessary to bridge a gap between the graft and the distal anastomosis.

In our hands, choledochocholedochostomy and choledochojejunostomy have both provided excellent results. Our experience with the Waddell-Calne procedure has been too limited to warrant comment, but the Cambridge team has been pleased with the results.

Control of Hemorrhage

The most important factor in hemorrhage is portal hypertension with extensive venous collaterals. In addition, coagulation defects must be anticipated routinely with depletion of clotting factors produced by the liver. In addition, fibrinolysis may begin shortly before the revascularization of the homograft and assume crisis proportions shortly afterwards.

Control of bleeding must start with the mechanical means of ligation, suture ligation and cautery. With the new liver in place, there is decompression of the portal system through the new organ with elimination of the adverse mechanical factor of portal hypertension. If the liver functions well, the perturbations in clotting can be expected to self correct but this may require hours. In the meanwhile platelets, fresh frozen plasma and blood constituents may be used as a temporary expedients.
POSTOPERATIVE CARE

The commonest early difficulties have been with pulmonary insufficiency requiring prolonged mechanical ventilation, renal failure at the same time that massive fluid shifts are occurring, and persistent clotting abnormalities. These problems are managed with conventional methods of intensive care with great emphasis on biochemical and hemodynamic monitoring. Recovery can be expected from preexisting encephalopathy and the hepatorenal syndrome. Patients who have received well functioning livers can have an almost miraculous recovery, but defective performance by the graft at the outset may preclude recovery unless another organ can be quickly found for retransplantation.

IMMUNOSUPPRESSION

All of the methods to prevent or reverse rejection of whole organs have been developed with the simpler procedure of renal transplantation. These are summarized in Table 4, with a notation about their use in liver recipients.

Although there was widespread discontent with all techniques of immunosuppression available from 1963 to 1978, improved drug therapy was not possible until the advent of cyclosporine. Cyclosporine is an extract from the fungus Cylindrocarpon lucidum and Trichoderma polysporum. It was discovered and characterized biochemically by scientists at the Sandoz Corporation, Basel, Switzerland, who showed it to be immunosuppressive in mice, rats and guinea pigs. The drug depressed humoral and cellular immunity with a quickly reversible action. These effects were not accompanied by the bone marrow depression which had frequently limited the doses of azathioprine and cyclophosphamide.
When cyclosporin A was first used in patients by Calne of Cambridge it was hoped that no other drug would be routinely required. Our experience has been that cyclosporine should be combined with steroid therapy from the outset although the steroid component with this version of double drug therapy has been smaller than in the past.

Nephrotoxicity is the most serious side effect of cyclosporine (Figure 30). Fortunately the renal complications are promptly reversed with the reduction of the cyclosporine doses. Most of the other side effects of cyclosporine have not been serious, including hirsutism, gum hyperplasia, tremor, regional flushing or vague abdominal discomfort just after drug ingestion, and the development of breast fibroadenomas in women. Although hepatotoxicity has been seen in about one fifth of cases, this has rarely been serious and it can be controlled by dose reduction.

For liver transplantation, cyclosporine is started a few hours preoperatively with an oral dose of 17.5 mg/Kg (Figure 30). Cyclosporine is continued daily, but with reduced intramuscular or intravenous (Figure 31) quantities until diet is resumed. Subsequently an oral dose of 17.5 mg/Kg/day is given, usually with half every 12 hours. The doses are reduced subsequently if nephrotoxicity develops. Steroids also are started on the day of operation. For adult patients who leave the operating room in relatively good condition a 5 day burst of prednisolone is given, starting at 200 mg and stopping with a maintenance dose of 20 mg per day. Further reductions of cyclosporine and steroid doses are made on an individualized basis in the ensuing
months. Initial maintenance therapy with steroids is scaled down in infants and children (Figure 30).

If rejection occurs in spite of this beginning therapy, the principal responses have been to administer intermittent large doses of hydrocortisone (or prednisolone) intravenously (Figure 31), to repeat the original 5 day burst of steroids (Figure 31), and to settle at a higher maintenance level of steroids. Although cyclosporine is not a drug which permits much dose maneuverability, it has sometimes been possible to increase the amounts given, the limiting factor being nephrotoxicity. Dose adjustments of cyclosporine can be aided by pharmacologic monitoring of plasma or blood levels.

RESULTS AFTER LIVER REPLACEMENT

The introduction of cyclosporine-steroid therapy has had a major influence upon the results after orthotopic liver transplantation.

Before Cyclosporine (1963-1979)

During this time, from 1963-1979, 170 patients underwent orthotopic liver transplantation under conventional double drug or triple drug therapy. The one year survival ranged between 28.8 and 50% throughout this time, but without an identifiable trend of improvement. The results during this 16 year period are summarized in Figure 32.

Of the 170 patients entered into this series, 56 lived out the first postoperative year. Twenty-three subsequently died. Although 13 of the 23 late deaths were in the second postoperative year losses occurred as late as 6 years. Of the original
170 patients, 33 (19.4%) are still alive after followups of 3 1/2 to 13 1/3 years. Between 1963 and 1979, there was an almost equal division between adult and pediatric recipients (Tables 1 and 2). From the sixth month onward the younger patients had about a 10% survival advantage.

A similar experience of occasional spectacular successes interspersed with a larger number of failures was also heard in the Cambridge-King's College trials from the beginning of that program in 1968 through early 1980. In the English series, 22 (23.7%) of the first 93 recipients lived for at least one year, with 11 subsequent deaths during the second to sixth years; at the time of last reporting the 11 survivors had been followed for 1 to 6 years.

The Cyclosporine Era (1980-1982)

The predictability and reliability with which liver transplantation could be carried out improved abruptly with the first trials of cyclosporine-steroid therapy, and this promise has been sustained with subsequent experience. Since 1980, the majority of liver recipients have been brought through the early postoperative convalescence and have been able to leave the hospital for out-patient care (Figure 32).

The survival in the first 67 consecutive recipients in the cyclosporine era is summarized in Figure 32 and contrasted with the pooled previous experience. All of the cyclosporine patients in Figure 32 had their operations before 1 May 1982, and thus have minimum one year followups. The one year and subsequent survival was doubled overnight compared to past expectations.
Of the first 67 recipients in the cyclosporine series treated over a period of more than two years, 42 passed the one-year mark. This was almost as many survivors as had been acquired in the nearly 17 preceding years. Six of the 42 one-year survivors subsequently died. In four the cause of the late failure was recurrence of the original disease (2 hepatic malignancies, 1 example each of Budd-Chiari syndrome and B-virus chronic hepatitis). The other late deaths were caused by an airway obstruction secondary to an upper respiratory infection in one patient, and by complications after retransplantation in a patient whose first graft was chronically rejected. In spite of these 6 deaths after one year, the late decline of the life survival curve has been slower than in past patients who entered the second postoperative year under azathioprine and prednisone (Figure 32).

A natural question would be if these results could be explained by a sudden change in candidacy criteria or by a difference in the diseases for which transplantation was performed. Analysis according to the recipient diseases showed that this was not the case. Instead, the results with almost all of the diseases were improved (Table 5). This was obvious with all of the diagnoses that contributed heavily to the case material before and after the introduction of cyclosporine — such as biliary atresia, non-alcoholic cirrhosis, primary hepatic malignancy, primary biliary cirrhosis, and the heterogenous group of inborn errors of metabolism.

With these improved results the pace of liver transplantation has quickened. Between 1963 and the end of 1979, the av-
average yearly case load was not much over a dozen. The number of transplantations rose to 30 in 1981 and to 80 in 1982. In the first four months of 1983, 34 liver replacements were done, a rate that extrapolates to 100 for this year.

To be a service, a new surgical procedure must be within the capability of more than the occasional surgeon. Until 1982, virtually all of our liver transplantation procedures over a span of 19 years were performed by a single surgeon. During 1982, 40% of the procedures were performed by another young faculty member or by the fellows and this year this figure has been 70%.

The influence of cyclosporine upon survival in the Cambridge-King's College trials has not yet been clearly defined, in part because the drug has not been used regularly and in part because it has been started late in most cases after an initial course of azathioprine and steroid. Nevertheless, improved results have been attributed by Calne to the better immunosuppression which they can now provide.

Steps to Reduce Mortality

A glance at the life survival curves from the earlier days of our experience, or even in recent times (Figure 32) shows that the highest priority for improved management is reduction of the perioperative mortality. However the fact that the survival curves continue to decline even after 3 or 4 months means that strategies to circumvent late mortality will also be important. Policy adjustments may have an impact in both periods.

The way in which the original disease dictates the technical difficulty of transplantation and thus the early mortality was
not clearly perceived until relatively recently. The consequent hidden risk factor could be improved by trying to treat patients with technically "dangerous" diseases like postnecrotic cirrhosis, alcoholic cirrhosis, and secondary biliary cirrhosis at an earlier time. When such patients have had previous operations at or near the hepatic hilum (such as repeated biliary tract reconstructions or especially portacaval shunts) it may be reasonable to conclude in some cases that liver transplantation is no longer a reasonable option especially if the patient's physical and metabolic decay is extreme. Almost all of our deaths on the operating table and many not long afterwards have been of such patients. We now believe that all adult patients are candidates for veno-venous bypasses. None of the candidates need this advantage more than the patients with previous portacaval shunt.

Incomplete knowledge of the recipient anatomy cannot be accepted in future cases. Of all the adverse possibilities, an inadequate recipient portal vein is the worst and the only one for which there usually is not a technical remedy. Means to detect a defective portal vein with ultrasound are now available.

Liver transplantation for postnecrotic cirrhosis in B-virus carriers and for patients with hepatic malignancies has resulted in disease recurrence in the grafts. There is not yet enough evidence to foreclose this avenue of treatment but it will be important for workers in the field to pool data in order to arrive at a consensus. Too many late deaths from recurrence of
these disease have occurred, a problem that has not been so over­
whelming with any of the other disorders that have recurrence
potential.

When a transplanted liver fails either early or late from
rejection or other causes, aggressive attempts at retransplanta­
tion usually offer the only chance for survival. One of the
commonest judgement errors we have made is to hope vainly for
improvement in hepatic function until the hope of reintervention
was lost. Despite this, more than 40 patients have undergone
retransplantation since 1968. Only recently have these efforts
been encouraging. More than 30 patients treated in 1980-1983 had
retransplantation a few days to 20 months after primary grafting
and the majority are surviving with subsequent followups of up to
$1\frac{1}{2}$ years.

The performance of retransplantation has usually been sur­
prisingly easy. The procedure has been greatly simplified by
retaining cuffs from the suprahepatic and infrahepatic vena cava
and from the portal vein of the first graft. Usually it has been
necessary to perform the arterial anastomosis proximal to the
previous site of anastomosis. Failure to do this in a recent
case resulted in thrombosis of the arterial segment retained from
the failed first graft for anastomosis to the celiac axis of the
second liver.

SUMMARY

During the 20 years since transplantation was first attemp­
ted in humans, the procedure has gone from an experimental to a
difficult but therapeutic procedure. As the manifold problems
associated with this complex form of care have been resolved, the survival after liver replacement has improved to the point where two thirds of recipients can now be expected to live through the first postoperative year. Within the next 2 or 3 years a national network of cooperating centers providing this form of advanced service can be expected to be in place in the United States.
<table>
<thead>
<tr>
<th>Indication</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary Atresia</td>
<td>62*</td>
</tr>
<tr>
<td>Inborn Metabolic Errors</td>
<td>21**</td>
</tr>
<tr>
<td>Non-alcoholic Cirrhosis</td>
<td>15</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>3***</td>
</tr>
<tr>
<td>Neonatal Hepatitis</td>
<td>3</td>
</tr>
<tr>
<td>Secondary Biliary Cirrhosis</td>
<td>3****</td>
</tr>
<tr>
<td>Byler's Disease</td>
<td>2</td>
</tr>
<tr>
<td>Congenital Hepatic Fibrosis</td>
<td>2</td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>1</td>
</tr>
</tbody>
</table>

* 2 had Allagilles syndrome
** Inborn errors
  - Alpha-1-antitrypsin Deficiency: 13
  - Wilson's Disease: 3
  - Tyrosinemia: 2
  - Type I Glycogen Storage Disease: 1
  - Type IV Glycogen Storage Disease: 1
  - Sea Blue Histiocyte Syndrome: 1

*** Seven other patients had incidental malignancies (6 hepatomas and 1 hepatoblastoma) in their excised livers. The principal diagnoses in these 7 cases were biliary atresia (3 examples), congenital tyrosinemia (2 examples), alpha-1-antitrypsin deficiency (1 example), and sea blue histiocyte syndrome (1 example). The diagnosis of the neoplastic change was known in advance in 4 of the 7 cases.

**** Secondary to choledochal cyst (two) or trauma (one).
<table>
<thead>
<tr>
<th>Indication</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-alcoholic Cirrhosis</td>
<td>47</td>
</tr>
<tr>
<td>Primary Malignancy</td>
<td>24</td>
</tr>
<tr>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Alcohol Cirrhosis</td>
<td>15</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>12</td>
</tr>
<tr>
<td>Sclerosing Cholangitis</td>
<td>10</td>
</tr>
<tr>
<td>Secondary Biliary Cirrhosis</td>
<td>6</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin Deficiency</td>
<td>4</td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>3</td>
</tr>
<tr>
<td>Acute Hepatitis B</td>
<td>1</td>
</tr>
<tr>
<td>Adenomatosis</td>
<td>1</td>
</tr>
<tr>
<td>Hemochromatosis</td>
<td>1</td>
</tr>
<tr>
<td>Protoporphyrria</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>125</td>
</tr>
</tbody>
</table>

* One patient in each group had previous (one and 1/2 years earlier) right hepatic trisegmentectomy. At transplantation, the regenerated left lateral segment was replaced with a whole liver.

** Thirteen hepatomas, 7 duct cell carcinomas (Klatskin), two cholangiocarcinomas one hemangioendothelial sarcoma, one unclassified sarcoma.

*** Two examples each of choledochal cyst and trauma; one example each of duct hypoplasia and Caroli syndrome. All 6 patients had had multiple previous operations.
<table>
<thead>
<tr>
<th>Direction</th>
<th>Acceptable Mismatched Tissue Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>O to non-O*</td>
<td>Safe</td>
</tr>
<tr>
<td>Rh- to Rh+</td>
<td>Safe</td>
</tr>
<tr>
<td>Rh+ to Rh-</td>
<td>Relatively safe</td>
</tr>
<tr>
<td>A to non-A</td>
<td>Dangerous</td>
</tr>
<tr>
<td>B to non-B</td>
<td>Dangerous</td>
</tr>
<tr>
<td>AB to non-AB**</td>
<td>Dangerous</td>
</tr>
</tbody>
</table>

* is universal donor  
** AB is universal recipient
<table>
<thead>
<tr>
<th>AGENTS</th>
<th>YEAR DESCRIBED AND REPORTED</th>
<th>PLACE</th>
<th>DEFICIENCIES</th>
<th>USED FOR LIVER TRANSPLANTATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine</td>
<td>1962</td>
<td>Boston</td>
<td>Ineffective, dangerous</td>
<td>No</td>
</tr>
<tr>
<td>Azathioprine-Steroids</td>
<td>1963</td>
<td>Denver, Richmond, Boston, Edinborough</td>
<td>Suboptimal</td>
<td>Yes</td>
</tr>
<tr>
<td>Thoracic Duct Drainage as Adjunct</td>
<td>1963*</td>
<td>Stockholm</td>
<td>Nuisance; requires 20-30 days pretreatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Thymectomy as adjunct</td>
<td>1963</td>
<td>Denver</td>
<td>Unproven value</td>
<td>No</td>
</tr>
<tr>
<td>Splenectomy as adjunct</td>
<td>1963</td>
<td>Denver</td>
<td>No longer necessary</td>
<td>Yes</td>
</tr>
<tr>
<td>ALG as Adjunct</td>
<td>1966</td>
<td>Denver</td>
<td>Still suboptimal</td>
<td>Yes</td>
</tr>
<tr>
<td>Cyclophosphamide Substitute for Azathioprine</td>
<td>1970</td>
<td>Denver</td>
<td>No advantage except for patients with azathioprine toxicity</td>
<td>Yes</td>
</tr>
<tr>
<td>Total Lymphoid Irradiation</td>
<td>1979</td>
<td>Palo Alto, Minneapolis</td>
<td>Dangerous; extensive preparation; not quickly reversible</td>
<td>No</td>
</tr>
<tr>
<td>Cyclosporine Alone</td>
<td>1978-1979</td>
<td>Cambridge</td>
<td>Suboptimal</td>
<td>Yes</td>
</tr>
<tr>
<td>Cyclosporine-Steroids</td>
<td>1980</td>
<td>Denver</td>
<td>Under evaluation</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* It was not realized until much later that pretreatment for 3 to 4 weeks before transplantation was a necessary condition.
## TABLE 5: INFLUENCE OF DISEASE UPON ONE YEAR SURVIVAL IN 237 PATIENTS *

<table>
<thead>
<tr>
<th>CONDITION</th>
<th>CONVENTIONAL THERAPY</th>
<th>CYCLOSPORINE-STEROIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO.</td>
<td>1 YEAR**</td>
</tr>
<tr>
<td>Biliary Atresia</td>
<td>51</td>
<td>14 (27%)</td>
</tr>
<tr>
<td>Non Alcoholic Cirrhosis</td>
<td>46</td>
<td>16 (34.8%)</td>
</tr>
<tr>
<td>Primary Liver Malignancy</td>
<td>18</td>
<td>5 (27.8%)</td>
</tr>
<tr>
<td>Inborn Errors ****</td>
<td>15</td>
<td>8 (53.3%)</td>
</tr>
<tr>
<td>Alcoholic Cirrhosis</td>
<td>15</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>6</td>
<td>1 (16.7%)</td>
</tr>
<tr>
<td>Sclerosing Cholangitis</td>
<td>7</td>
<td>2 (28.6%)</td>
</tr>
<tr>
<td>Secondary Biliary Cirrhosis</td>
<td>4</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Budd-Chiari Syndrome</td>
<td>1</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Miscellaneous *****</td>
<td>7</td>
<td>2 (28.6%)</td>
</tr>
</tbody>
</table>

* The same case material was analyzed in detail elsewhere but with shorter followups.

** Thirty-two of these 52 patients are still alive with followups 3 1/2 to 13 1/2 years.

*** Thirty-six of these 42 patients are still alive with followups 1 to 3 1/4 years.

**** Alpha-1-Antitrypsin Deficiency (17 examples), Wilson's Disease (3 examples), Tyrosinemia (2 examples), Glycogen Storage Disease (2 examples), Sea Blue Histiocyte Syndrome (1 example).

***** Neonatal Hepatitis (3 examples), Congenital Hepatic Fibrosis (2 examples), Byler's Disease (2 examples), Adenomatosis, Hemachromatosis, Protoporphyria, Acute Hepatitis B (1 example each).
Recipient
Cirrhotic liver

G.b.

Recipient vessels left intact

S.m.v.
Portal v.
Superior aspect of donor I.v.c.
Recipient I.v.c.
Aorta
Celiac axis

Jejunum (limb of Roux-en-Y)

Figure 1
Figure 3

FETOPROTEIN (mg%) vs TIME IN MONTHS

TRANSPLANTATION

OT 33

(NEGATIVE)
Figure 5

- Common hepatic a.
- R gastric a.
- Gastrroduodenal a.
- Stomach
- Pancreas
- Common bile duct
- Duodenum
- Proper hepatic a.
- Portal v.
- Coronary v.
- Celiac axis
- Aorta
- Coronary v.

Figure 5
Figure 8
Index finger behind I.V.C.

R.H.V.

Right lobe of liver

Figure 9
Diaphragm
LV C
RH V
L H V
Left triangular
lig.
Left lobe
Liver
Figure 11
Figure 12
Figure 14
Figure 16
Suprahepatic anastomosis.

A.

Figure 19

Infrahepatic anastomosis

Low molecular weight dext. (Cold)
Figure 24
A. Interrupted stitches through serosa
B. Common duct
C. Jejunum
D. Submucosa
E. Omentum

Disc of mucosa and submucosa removed

Figure 29
OT 193
10 years old
26 kg

Figure 30
Figure 31
Figure 32

SURVIVAL AFTER LIVER TRANSPLANTATION

- △ CYCLOSPORINE (N=67)
- ○ AZATHIOPRINE (N=170)
Bibliography


FIGURES

Figure 1. Technique of auxiliary liver transplantation that provides splanchnic venous flow for the homograft. Because of portal hypertension caused by the diseased native liver, splanchnic flow will pass preferentially through the homograft. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 2. 99mTc 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 posttransplantation. At autopsy, the homograft was almost completely replaced with carcinoma. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 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 13 2/3 years after transplantation. Alpha-fetoprotein determinations continue to be negative and she remains free of tumor.


Figure 5. Dissection of the portal triad during donor hepatectomy. A, The common duct and the gastroduodenal and right gastric arteries are tied and divided. B, The hepatic artery has been mobilized far enough so that the anterior surface of the portal vein is
uncovered. The coronary vein entering the left side of the portal trunk, or into the splenic vein as shown, is almost always found; this tributary is ligated and divided. C, The portal vein has been freed and the celiac axis mobilized. The splenic artery has not yet been ligated and divided. When the liver is removed, all of the celiac axis is usually retained with the specimen, and it may be advisable to include a segment of aorta as well. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 6. Alternative approach to arterial supply of liver. During the initial dissection, all the aortic branches except the celiac axis and superior mesenteric artery are ligated and divided; the latter vessel is cut only after it has been shown not to give rise to an anomalous hepatic arterial branch. A segment of aorta is usually removed in continuity with the celiac axis. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 7. Exposure and initial dissection of the suprahepatic vena cava and its tributaries. This is done by 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. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 8. Retraction of the liver to the left. The bare area of the right hepatic lobe has been opened, 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 of the dissection the right hepatic vein (R. H. V.) can be identified. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 9. Sweeping behind the retrohepatic vena cava with a dissecting finger. This should be possible 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. R. a. v. - ligated right adrenal vein. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 10. En bloc infusion of liver and kidneys. Note the infusion cannulas in the aorta and splenic veins, and the bleed-off cannula in the inferior vena cava. (Shaw BW Jr, Hakala T, Rosenthal JT, Iwatsuki S, Broznick B, Starzl TE. Combination donor hepatectomy and nephrectomy and early functional results of allografts. Surg Gynecol Obstet 1982;155:321-325.)

Figure 11. Dissection above the liver. A, Development of suprahepatic vena caval cuff. At this stage it is desirable to ligate and divide one or more phrenic veins on each side. Extra length can also be obtained by dissecting off the diaphragmatic reflection, as is being shown. B, Cross sectional appearance of the venous confluence above the liver as it is seen from above. The cloaca is formed by the junction of the right and left hepatic veins with the inferior vena cava. (Starzl TE, (With the assistance of CW

Figure 12. The uses to which aortic, vena caval, and iliac vascular grafts have been put in renal (A) and hepatic (B) transplantation. (Starzl TE, Halgrimson OG, Koep LJ, Weil R III, Taylor PD. Vascular homografts from cadaveric organ donors. (The Surgeon At Work) Surg Gynecol Obstet 1979;149:737.)

Figure 13. Incisions for orthotopic liver transplantations and for hepatic resections, right or left. Note that several extensions may be made from the basic right subcostal incision, A to A, that is almost always used. More than one of the depicted extensions may be required in a given patient. (Starzl TE, Bell RH, Beart RW, Putnam CW. Hepatic trisegmentectomy and other liver resections. Surg Gynecol Obstet 1975;141:429-37.)

Figure 14. A, Encirclement of the portal structures preparatory to their individual dissection. This can be done either from the right side as indicated or from the left through the lesser omental sac. B, Spatial relationships of the components of the portal triad. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 15. Transection of the suprahepatic inferior vena cava. Note that the line of incision is kept as close to the liver as possible in order to retain the maximum vessel length for subsequent anastomosis. R. h. v. = right hepatic vein; L. h. v. = left hepatic vein; I. V. C. = inferior vena cava. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)
Figure 16. Probable mechanism of operative injury of the right phrenic nerve in several pediatric patients. Note the inclusion of the nerve in the bite of the vascular clamp, which has been placed across the suprahepatic vena cava and which has also included a piece of diaphragm. (Starzl TE, (With the assistance of CW Putnam). Experience in Hepatic Transplantation. Philadelphia: WB Saunders, 1969.)

Figure 17. C, Operative field after retrograde liver mobilization. The last remaining structure, the suprahepatic inferior vena cava, has been clamped above the liver. D, Technique for mobilizing a suitable length of suprahepatic vena cava after placement of clamp. In adults, this usually involves cutting away cirrhotic liver tissue over the frequently distorted and foreshortened right and left hepatic veins. (Starzl TE, Porter KA, Putnam CW, Schroter GPJ, Halgrimson CG, Weil R III, Hoelscher M, Reid HAS. Orthotopic liver transplantation in 93 patients. Surg Gynecol Obstet 1976;142:487-505.)

Figure 18. Development of a suprahepatic cuff of inferior vena cava. This technique is required most commonly if the native disease is non-alcoholic or alcoholic cirrhosis. Note that the suprahepatic vena cava is encircled and clamped (A) and that length is developed by cutting and peeling away the diseased liver tissue and scar (B). The eventual cuff usually has a lateral closure of either the left (C, D) or right hepatic vein. (Starzl TE, Koep LJ, Weil R III, Halgrimson CG. Development of a suprahepatic recipient vena cava cuff for liver transplantation. Surg Gynecol Obstet 1979;149:76-77.)
Figure 19. Initial steps in the implantation of a new liver. (A), Infusion with lactated Ringer's solution in order to wash out the potassium rich Collin's solution. (B), Completion of suprahepatic anastomosis. (C), Completion of infrahepatic vena cava anastomosis. Note in B and C the escape of air bubbles which if not expelled could lead to air embolism. (Starzl TE, Schneck SA, Mazzoni G, Aldrete JA, Porter KA, Schroter GPJ, Koep LJ, Putnam CW. Acute neurological complications after liver transplantation with particular reference to intraoperative cerebral air embolus. Ann Surg 1978;187:236-240.)

Figure 20. Completion of vascular reconstructions at hilum, and duct to duct biliary anastomosis over a T-tube stent. (Starzl TE, Marchioro TL, Huntley RT, Rifking D, Rowlands DT Jr, Dickinson TC, Waddell WR. Experimental and clinical homotransplantation of the liver. Ann N Y Acad Sci 1964;120:739-65.)

Figure 21. Technique of intraluminal everting vascular suture. A, Side-to-side; B, end-to-end; and C, end-to-side. (Starzl TE, Groth CG, Brettschneider L. An everting technique for intraluminal vascular suturing. Surg Gynecol Obstet 1968;127:125-26.)

Figure 22. Method of avoiding strictures of small vascular anastomoses. (Starzl TE, Iwatsuki S, Shaw BW Jr. A "Growth Factor" in fine vascular anastomoses. Surg Gynecol Obstet (in press).

Figure 23. Incision en masse of the portal triad. This maneuver has been necessary on several occasions when the individual structures could not be dissected free. After the transection, the portal vein and hepatic artery can be liberated enough to permit the vascular anastomoses to be performed. (Starzl TE, (With the

Figure 24. The management of a common graft anomaly in which part of the liver blood supply is derived from the superior mesenteric artery. Note that the celiac axis is anastomosed to one end of the main superior mesenteric artery and the other end is used for anastomosis to a recipient vessel. (Shaw BW Jr, Iwatsuki, S, Starzl TE. Alternative methods of hepatic graft arterialization. Surg Gynecol Obstet (in press).

Figure 25. Technical solution if an adequate recipient artery cannot be found in the area of the portal triad. A piece of graft aorta in continuity with the graft celiac axis can be anastomosed to the abdominal aorta of the recipient. Alternatively an iliac artery graft can be attached to the recipient aorta with a distal anastomosis to the celiac axis. The latter technique depends upon the availability of contingency grafts procured at the time of the liver harvest (Figure 12). (Shaw BW Jr, Iwatsuki, S, Starzl TE. Alternative methods of hepatic graft arterialization. Surg Gynecol Obstet (in press).

Figure 26. Methods of biliary tract reconstruction that have been used with liver transplantation. The techniques shown in E and F are so defective that they have been abandoned. Depending upon the anatomic and clinical circumstances, each of the other methods may be useful in individual cases.

Figure 27. Development of regional and systemic infectious complications secondary to contamination and/or partial obstruction of the biliary tract. (Starzl TE, Groth CG, Brettschneider L, Penn I,

Figure 28. Transhepatic cholangiograms in four patients whose original biliary reconstructions were with Roux-en-Y cholecystojejunostomy. (A), minimal obstruction; (B), moderate obstruction; (C), severe obstruction with leak and abscess formation; (D), very severe obstruction; at reoperation the common duct was necrotic. (Key to abbreviations: A = leak and abscess formation; C = common duct; CD = cystic duct; GB = gallbladder; J = jejunum; large arrow = site of common duct ligation). (Starzl TE, Putnam CW, Hansbrough JF, Porter KA, Reid HAS. Biliary complications after liver transplantation; with special reference to the biliary cast syndrome and techniques of secondary duct repair. Surgery 1977;81:212-21.)

Figure 29. Technique of choledochojjunostomy. (Starzl TE, Putnam CW, Hansbrough JF, Porter KA and Reid HAS. Biliary complications after liver transplantation: with special reference to the biliary cast syndrome and techniques of secondary duct repair. Surgery 1977;81:212-21.)

Figure 30. Immunosuppression with cyclosporine and steroids (plus temporary azathioprine) in a 10-year-old girl (OT 193). Note that the 5-day opening burst of prednisone therapy was scaled down because of her small size. The temporary discontinuance of cyclosporine and replacement with azathioprine between postoperative Days 10 and 15 was because of probable cyclosporine nephrotoxicity. The patient who was of B blood type was given the liver of an A donor.
Figure 31. Deviation from standard steroid therapy in a patient (OT 219) whose perioperative condition was frail. The 5-day burst of postoperative steroids was begun several days postoperatively but had to be repeated when rejection supervened. Before operation, the patient had hepatorenal syndrome and encephalopathy and he had been on a ventilator for more than 1 week. Because of defective clotting, efforts to place central venous lines before starting transplantation resulted in uncontrolled hemorrhage with the loss of 20 liters of blood. The subclavian and innominate vessels were explored through cervical and thoracotomy incisions, and the bleeding was mechanically controlled before transplantation was started. The blood loss from placement of the vascular lines exceeded that incurred during transplantation. The patient survived because of prompt correction of the coagulation abnormalities. (Starzl TE, Iwatsuki S, Van Thiel DH, Gartner JC, Zitelli BJ, Malatack JJ, Schade RR, Shaw BW Jr, Hakala TR, Rosenthal JT, Porter KA. Evolution of liver transplantation. Hepatology 1982;2:614-36.)

Figure 32. The survival of 67 patients treated with cyclosporine and low dose steroids (minimum follow 16 months) compared to the survival obtained under conventional immunosuppression (azathioprine). (Starzl TE, Iwatsuki S, Van Thiel DH, Gartner JC, Zitelli BJ, Malatack JJ, Schade RR, Shaw BW Jr, Hakala TR, Rosenthal JT.
Report of Colorado-Pittsburgh liver transplantation studies.

Transplant Proceedings In press.)