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CLINICAL LIVER TRANSPLANTATION

Thomas E. Starzl, M.D., Ph.D.

Shunzaburo Iwatsuki, M.D.

Byers W. Shaw, Jr., M.D.

Roger L. Jenkins, M.D.

Authors affiliations are:

Thomas E. Starzl, Professor of Surgery, Shunzaburo Iwatsuki, Assistant Professor of Surgery, Byers W. Shaw, Jr., Assistant Professor of Surgery, University of Pittsburgh, School of Medicine, Department of Surgery, Roger L. Jenkins, Clinical Instructor of Surgery, Harvard Medical School, Department of Surgery.

There are two general approaches to transplantation of the liver. With the first, the diseased native liver is removed and replaced with a homograft (orthotopic transplantation). The alternative technique is the insertion of an extra liver at an ectopic site (auxiliary homotransplantation). The latter procedure has had only sporadic and for the most part unsuccessful trials. In contrast, more than 500 orthotopic transplantations have been carried out throughout the world, and with increasing numbers of successes, particularly in recent years.

The experimental work justifying clinical trials of liver transplantation was performed about two decades ago and has been thoroughly summarized in a number of reviews (1, 2). In this chapter we will discuss only human transplantation and with the main emphasis on the orthotopic procedure.

INDICATIONS FOR LIVER TRANSPLANTATION

Between our own experience (2) and that of the English team working at Cambridge and King's College Hospital in London (3), about 400 liver transplantations had been performed by the summer of 1982. At least one hundred additional cases had been compiled in a dozen or more other centers (2). Most of the publications describing this experience have not placed much emphasis on the criteria for candidacy, and for this reason the following assessment is based largely on our own experience with 237 consecutive recipients treated from 1 March 1963 through April 1982. One hundred and twelve were classified as pediatric recipients (Table 1), with ages ranging from 5 months to 18 years. The 125 adults (Table 2) were 19 to 68 years old.

Experience has taught us the importance of systematically reviewing the features shown in Table 3 for any potential liver recipients. An important consideration is the so called "propriety factor" which is judged in part by how much meaningful life is thought to be left to the patient without transplantation. Other considerations include the possibility of recurrence in a

transplant of the disease which destroyed the native liver, and by the presence of other factors such as prior abdominal operations and the state of metabolic deterioration that can jeopardize the prognosis. From our experience, a fairly complete understanding has evolved with many specific diseases about what advice to give 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 (Table 3).

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. Our general guideline has been that transplantation for non-neoplastic liver disease becomes justifiable with the advent of social and vocational invalidism (4). This condition usually is reflected in repeated hospitalizations for encephalopathy, variceal hemorrhage, hepato-renal syndrome, uncontrolled coagulation disorders, intractible ascites, and other complications of hepatic disease.

PRINCIPLES OF EVALUATION

The workup includes confirmation of the prior diagnosis, analysis of residual liver function, measurement of the recipients' intellectual and psychiatric state, assessment of abnormalities of extrahepatic organ systems, and determination, insofar as possible, if liver replacement will be anatomically possible. The last detail has been particularly important. In about 10% of the recipients treated early in our experience portal vein thrombosis or congenital anomalies were found at operation, making the usual procedure of orthotopic transplantation impossible. All of these recipients died. In recent years the systematic use of ultrasonography and computerized axial tomography (CAT) has made tentative identification possible of many such

situations. If there are questions about the portal vein after the non-invasive diagnostic studies, angiography should be performed.

For each of the diseases which may lead to hepatic transplantation, it is important for the health care team to know if recurrence of the original disease can be expected in the homograft. This factor can be a relative, although not an absolute, contraindication to liver transplantation with at least 2 diagnoses. Patients whose indication for transplantation is a primary hepatic malignancy have had an exceptionally high incidence of tumor recurrence. Thus, candidates for total hepatectomy and transplantation for the indication of hepatic malignancy must be screened with exceptional care. It is probable that certain kinds of hepatic neoplasms including fibrolamellar hepatomas, malignancies complicating other hepatic disorders such as tyrosenimia, alpha-1-antitrypsin deficiency and chronic aggressive hepatitis may be bona fide candidates in the future.

Except for patients with hepatic cancer, the most serious problems with disease recurrence have been in patients with chronic active hepatitis caused by the B virus. The documentation of disease recurrence, leading to graft destruction and death has been unequivocal (2, 5). In the last six patients treated by us under these circumstances, five have developed recurrent disease, and in two the complication has already led to death.

Recurrent disease also has been described or is a distinct possibility with primary biliary cirrhosis, Budd-Chiari syndrome, and sclerosing cholangitis (2). However, there is now enough experience to permit the tentative conclusion that recurrence will not be common in these diseases.

Patients with inborn errors of metabolism have provided an interesting opportunity for "metabolic engineering" (Table 1). When these disorders have been liver based, the metabolic specificity of the liver has remained permanently that of the donor. Thus patients with alpha-1-antitrypsin disease, PiZZ

phenotype, have permanently assumed the Pi (protease inhibitor) type of the donor at the same time as the alpha-1-antitrypsin levels have increased to normal in the blood (6). The longest follow up of a patient with an inborn error has been more than twelve years after liver replacement for Wilson's disease.

In assessing the feasibility of liver transplantation, the presence or absence of previous surgical operations is an important factor. Patients who have had portacaval shunts, or prior attempts at biliary tract reconstruction may present such severe technical problems as to preclude liver replacement. In spite of the handicap imposed by prior surgery, attempts are still being made to treat this kind of patient, but the perioperative mortality is increased (2).

TISSUE TYPING

Tissue matching at the A B and D loci for selection of cadaveric kidney donors has had an extensive evaluation with disappointing results. Such efforts have been feasible in a population of uremic patients since the alternative therapies of hemodialysis or peritoneal dialysis are available. Prospective recipients of livers for whom the prospect of artificial organ support does not exist do not have this luxury and immunologic screening in attempts to find compatible donors is a luxury that almost never can be afforded. In many patients it has even been necessary to transplant livers to recipients who present the kinds of cytotoxins which cause hyperacute rejection of renal grafts. Fortunately the liver has been inexplicably resistant to this kind of humoral rejection and the results have not been substantially different than in patients with negative cross matches (2, 4). It has even been possible in the event of dire emergencies to violate the ABO blood group guidelines that were designed to avoid subjecting an organ to preformed anti-graft isoagglutinins (4).

THE DONOR OPERATION

It may be that the most important factor in obtaining a satisfactory liver for transplantation is the wise screening of donors with the elimination of those whose physiologic situation could jeopardize vital organ function in advance of the procurement operation. Hepatic function tests of the donor are important, but in addition it may be dangerous for the recipient to procede with donor hepatectomy in the face of cardiovascular instability, a need for excessive vasopressor support, or an excessive period (several days) between injury and pronouncement of brain death. If renal function of the donor deteriorates, this suggests poor perfusion of other organs. The details of liver harvest have been well standardized (1, 7), and consist of skeletonizing the structures entering and leaving the liver.

The donor operation is best done through a midline sternotomy and celiotomy extending from the sternal notch to the pubic symphysis. It is important to assess the possibility of anomalies of the hepatic arterial supply (Figure 1). Some of the anomalies are not serious. For example an artery to the left lateral segment commonly arises from the left gastric artery, but the vessel can be preserved in continuity with its left gastric origin and coeliac axis allowing a single anatomosis in the recipient. If part of the blood supply of the liver comes from the superior mesenteric artery, the anomalous vessel almost always lies directly posterior to the portal vein (Figure 1) and can be easily identified there with a finger placed through the foramen of Winslow. If the hepatic blood supply is derived from both the superior mesenteric artery and coeliac axis, the two vessels of origin can be joined into a common trunk permitting a single anastomosis to the hepatic artery (Figure 2) or alternatively an aortic segment can be removed in continuity with both the superior mesenteric artery and coeliac axis and anastomosed to the recipient aorta.

Once the skeletonization has been carried out the final steps are planned which usually take into account the protection of other organs such as the kidneys or even the heart. The donor is anti-coagulated with heparin, and large cannulas are inserted into the distal aorta and terminal inferior vena cava to allow in situ infusion of cold solution and bleeding off of central blood volume, respectively (Figure 3).

The portal vein perfusion with cold lactated Ringer's solution is begun while there is still an effective donor circulation. This has the effect of reducing the temperature of the liver tissue while an adquate flow of oxygenated arterial blood is still present. It also adds protection to the kidney and other organs since donor core temperatures during the pre-cooling phase drift quickly down to 32°C at the same time as the liver temperature drops several degrees below this. When the pre-cooling is terminated, in situ aortic flushing of the liver, kidneys or other organs can be done (Figure 3).

By following this sequence all of the abdominal organs are cooled and can be quickly removed. If heart donation is also desired, the heart is removed at about this time. The early function of cadaveric kidneys obtained during heart and liver procurement (7) or both has been far better than that achieved in our center and elsewhere with renal procurement alone. This advantage for renal recipients is probably due to the more discriminating donor selection and the greater intensity of surgical technical care that are features of the multiple organ harvesting operation.

The chilled liver is placed in a plastic bag that contains Collins solution. The bag is sealed and packed in ice in a picnic refrigerator. A liver 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 six or eight hours (2). Using a preservation solution the Cambridge workers described similar time limitations.

After the organs are out the distal aorta and vena cava, and the iliac veins, and the iliac arteries are removed and stored separately in balanced electrolyte solution. These vascular segments often have been needed for the subsequent performance of transplantation.

THE RECIPIENT OPERATION

Good exposure is usually provided with a bilateral subcostal incision with an upper midline extension through which the xiphoid process is excised (Figure 4). A thoracic extension is occasionally needed. The recipient operation is much the same as already described for the donor with skeletonization of the structures entering and leaving the liver. The usual first step is to find the hilum, encircle it, and to dissect the proper and common hepatic artery, the common duct, and the portal vein. The inferior vena cava above and below the liver are encircled.

The performance of these seemingly straightforward tasks can lead to one of the most difficult operations in surgery since almost all prospective liver recipients have portal hypertension and the majority have serious clotting abnormalities. Patient with alcoholic or non-alcoholic cirrhosis have presented the most serious technical problems because of the scarring and antomic distortion which is present above and below the liver and in the retrohepatic area. In such patients it may be impossible to enter the bare area without causing a lethal hemorrhage and should this be the case, variations of the straight forward operation must be considered (2). Once the diseased native liver has been removed, the revascularization of the new liver is a straight forward exercise in vascular surgery. The vena caval anastomoses are carried out first (Figure 5) taking care to wash out air and potassium entrapped in the organ. The portal blood flow is usually restored first, and the hepatic arterial anastomosis is ordinarily performed as a final step (Figure 6).

Many kinds of biliary tract reconstruction have been tried throughout the years, (Figure 7) but we now perform either duct to duct anastomis with a T-tube or internal stent, or a choledochojejunostomy to a Roux limb. With the use of these straightforward biliary anastomoses, the frequent problems with biliary tract obstruction or biliary fistula encountered early in our experience have virtually disappeared. In cases in which there is inadequate length of the homograft common duct the procedure preferred by Calne et al (3) can be used whereby the homograft common duct is anastomosed to the homograft gallbladder and the latter structure is used for the distal anastomosis to recipient duct or bowel (Figure 7 c, d).

During the time when the new liver is being sewn in, it is necessary to occlude the splanchnic and systemic venous beds normally drained through the portal vein and inferior vena cava. These occlusions can usually be 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 upon the collaterals that develop with human liver disease.

However some patients can be gravely jeopardized by the venous cross-clamping and even in those who survive the cross-clamping, the practice may not be completely safe. Usually there is gross swelling of the intestine during the period of portal occlusion and subsequently many such patients suffer from third space fluid sequestration and 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 all recent adult patients to the practice of veno-venous bypass which we abandoned long ago. Cannulas are introduced into the inferior vena cava 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 is returned to a reservoir and pumped to one of the large veins in the neck or arm. With the use of the atraumatic pumps and heparin coated tubing which are now available, it has been possible to use the veno-venous bypasses without giving systemic heparin. The maintenance of patient physiology has been strikingly improved during liver transplantation with this technique and we now believe that it will become a standard part of the operation.

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, exclusive of the earlier trials with total body irradiation (12) which were never used for liver transplantation. Most liver recipients treated by us until early 1980 were given "triple drug therapy" with azathioprine (or cyclophosphamide), prednisone and antilymphocyte globulin (ALG) (Table 4). Most of Calne's experience from 1968 to 1980 was with the double drug therapy of azathioprine and prednisone (3). Neither the double or triple drug immunosuppressive regimens provided the margin of safety which might have made liver transplantation a practical undertaking in the 1960's and 1970's. There were problems with the control of rejection on one hand, and on the other with infectious complications that resulted from the high doses of drugs required to prevent or reverse rejection.

In early 1980 a systematic trial was begun with the new double drug immunosuppressive program of cyclosporine and prednisone. This combination of agents was first worked out in cadaveric renal graft recipients (24, 25) and extrapolated almost unchanged to the care of hepatic recipients (2). Cyclosporine is started a few hours preoperatively with an oral dose of 17.5 mg/Kg or with an intravenous dose of about one third this quantity. Cyclosporine is

continued daily, usually intravenously until diet is resumed and orally thereafter. The oral doses are reduced subsequently if nephrotoxicity develops. Steroids are also started on the day of operation, using a 5 day burst of prednisolone or solumedrol, and ending with a maintenance dose for adults of 20 mg/per day after 5 days. Further reductions in cyclosporine and steroid doses are made on an individualized basis in the ensuing months. Initial mainentance therapy with steroids is scaled down in infants and children.

REJECTION UNDER IMMUNOSUPPRESSION

It is only a slight over simplification to say that there are two clinical patterns of rejection which have much in common with acute and chronic hepatitis. With acute rejection the patient becomes abruptly jaundiced at the same time that there are variable increases in the transaminases indicating hepatic necrosis. If the steroid doses are increased, it is usually possible to reverse this kind of rejection, particularly if the base therapy is being provided by cyclosporine. The timing of rejection is usually a week to 10 days after transplantation, but acute rejection has been observed months or even years postoperatively, especially if the patient has been guilty of noncompliance. The histopathologic criteria of acute rejection were carefully worked out by Professor K. A. Porter of St. Mary's Hospital and Medical School, London, many years ago and consist of mononuclear cell invasion, secondary reticulum collapse of the lobular patterns, and less frequently the involvement of the arterial supply by humoral antibodies that has been described in renal homografts.

Chronic rejection under immunosuppression is characterized by slowly developing jaundice, deterioration of hepatic synthetic functions and minimal disturbances of tests that connote hepatic necrosis. Histopathologically chronically rejected livers may have arterial occlusive disease, fibrosis

which can progress to frank cirrhosis and the disappearance of hepatic ducts and ductules.

SURVIVAL 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 the conventional double drug or triple drug therapy summarized in Table 4. 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 8.

Of the 170 patients entered into this series, 56 lived out the first postoperative year. Twenty-three subsequently died (2). 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 4 to 13 1/3 years. Between 1963 and 1979, there was an almost equal division between adult and pediatric recipients. From the sixth month onward the younger patients had about a 10% survival advantage.

The siren call 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 (3). In the English series, 22 (23.7%) of the first 93 recipients lived for at least one year (Figure 8), 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 (2, 3), 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. By the first of May, 1982, 40 recipients had been treated with this new immunosuppression with the survival projections shown in Figure 8. Since then the survival of pediatric recipients has been maintained at about the same level, although less favorable results in adults have brought the 1 year survival curve down. In addition, 3 of the patients treated with cyclosporine and steroids who reached or passed the 1 year mark died in their 13th, 16th, and 20th postoperative months. The causes of the late deaths were recurrent carcinoma, recurrent Budd-Chiari syndrome, and chronic rejection (with unsuccessful retransplantation).

The influence of cyclosporine upon survival in the Cambridge-King's College trials has not yet been clearly defined (3), 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 et al to the better immunosuppression which they can now provide (3).

CAUSES OF MORTALITY

In both the early trials of liver transplantation under conventional immunosuppression and those with cyclosporine-steroid therapy, the principal mortality after liver transplantation has been early. Detailed analyses of the causes for this mortality have been published (1, 2). Throughout the years, the causes for failure have included the use of grafts damaged by ischemia, massive operative hemorrhage, thrombosis of the reconstituted homograft blood supply, intraoperative cerebral air embolism, unsuspected recipient abnormalities (particularly of the portal triad structures), hopeless

anatomical situations created by multiple previous operations, irreversible pre-existing debilitation, and defective biliary tract reconstruction.

In addition, acute or subacute homograft rejection was an undoubted factor, but one whose dimensions could not be clearly delineated. At autopsy, histopathologic findings of acute rejection have been found in the minority of cases. This prompted speculation in the earlier days when biopsy was not often performed that over immunosuppression, especially with prednisone, may have been responsible for unnecessary deaths. However when serial biopsies were obtained in later cases (2) this simplistic view had to be revised. Many of the biopsies contained unmistakable findings of rejection for which the appropriate response had been more steroids. Yet after death, which was most commonly caused by terminal infection, findings of rejection were absent. This same chain of deadly events is still seen up to the present time, but less frequently than before. Under such circumstances, it may be difficult to find a single explanation for failure.

In contrast, assessment of the reasons for late deaths has been less ambiguous. Recurrent liver failure was responsible for the deaths of 3/4 of the 26 patients who died after 1 year if the 5 who died after attempted re-transplantation are included (2). The dominant pathological diagnoses in late failing grafts have been chronic rejection in the majority of cases, with biliary obstruction, recurrent carcinoma, chronic hepatitis, portal vein thrombosis, and recurrent Budd-Chiari syndrome being progressively more distant contenders (2).

These findings in chronically surviving patients were remarkedly different from those reported by Calne et al (3) in 11 patients who died after 1 year. Recurrent carcinoma was the main homograft abnormality in 5 of their patients. In the other 6 grafts, there was biliary sludge and cholangitis. Chronic rejection was not mentioned. Thus, our findings have suggested that

ongoing problems with immunologic control will continue to take a gradual toll long after transplantation, whereas the interpretation of the pathologic findings in the English recipients have minimized the importance of chronic rejection.

STEPS TO REDUCE MORTALITY

A glance at the life survival curves from the earlier days of our experience, or even in recent times (Figure 8) 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.

The way in which the original disease dictates the technical difficulty of transplantation (see Table 3) was not clearly perceived until relatively recently. The consequent hidden risk factor could be improved by trying to treat patients with "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, liver transplantation may not be a reasonable option especially if the patient's physical and metabolic decay is extreme.

Veno-venous bypasses during removal of the recipient liver and implantation of the new organ were discussed in an earlier section. The use of bypasses may be mandatory in patients who have undergone a previous portacaval shunt, since the venous collaterals which usually make it safe to occlude the inferior vena cava and portal vein are apt to have undergone involution. As noted earlier, other patients are probably candidates for veno-venous bypasses as well, and we are now doing bypasses on all adults.

For B-virus carriers who have postnecrotic cirrhosis and for patients with hepatic malignancies, there is not yet enough evidence to foreclose liver

transplantation as an avenue of treatment. However, it will be important for workers in the field to pool data in order to arrive at a concensus. Too many late deaths from recurrence of these disease have occurred, a problem that has not been so overwhelming with any of the other disorders that have recurrence potential.

It has become uncommon to have defective vascular or biliary tract anastomoses. The single most common problem has become the marginally functioning donor liver. When this has occurred, it usually has been found that the orderly stages of donor liver removal including the "pre-cooling" step with an intact hepatic artery have been abridged or otherwise changed from the standard procedure. The second most common explanation has been acceptance of a physiologically unstable donor who frequently has required large amounts of vasopressor medications for maintenance of blood pressure. Abandonment of the donor effort under the questionable circumstances will be increasingly necessary.

When a transplanted liver fails either early or late from rejection or other causes, aggressive attempts at retransplantation 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 30 patients have undergone retransplantation since 1968 (2). Only recently have these efforts been encouraging. More than a dozen patients treated in 1980-1982 had retransplantation a few days to 20 months after primary grafting and the majority are surviving with subsequent followups of up to 1½ years.

The performance of retransplantation has usually been surprisingly 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.

THE OPTION OF AUXILIARY LIVER TRANSPLANTATION

Clinical efforts to transplant an extra liver (auxiliary transplantation) without removal of the diseased native organ have been discouraging as has been noted by Fortner et al (26). Of more than 50 well documented auxiliary transplantations only two could be pronounced an unequivocal success, one in New York City (26) and the other in Paris (27).

Auxiliary liver transplantation may be useful in patients with potentially reversible hepatic disease. The extra liver could be used as a temporary support organ and later removed. In addition, we have seen increasing numbers of patients with chronic disease whose portal vein has clotted in the hepatic hilum making it technically impossible to consider liver replacement. Auxiliary liver transplantation might be an option under such circumstances or in patients with extensive previous surgery in the right upper quadrant for whom orthotopic transplantation would be excessively difficult or impossible. The physiologic requirements for auxiliary liver transplantation have been discussed elsewhere (28, 29).

Figure 1. Anomalies of hepatic arterial blood supply. From Shaw, et al, 7.

Figure 2. 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. From Shaw et al, 8.

Figure 3. 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. From Shaw et al, 7.

Figure 4. Incisions for orthotopic liver transplantations. 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. From Starzl et al, 9.

Figure 5. Initial steps in the implantation of a new liver. (A), Infusion with lactated Ringer's solution in order to wash out the potassium rich Collins 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. From Starzl et al, 10.

Figure 6. Completion of vascular reconstructions at hilum, and duct to duct biliary anastomosis over a T-tube stent. From Starzl et al, 11.

Figure 7. 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 (see text for discussion).

Figure 8. The actuarial survival of patients treated with cyclosporine and low dose steroids compared to the actual one-year survival obtained under conventional immunosuppression by us (azathioprine) and by the workers at Cambridge. The data for the Cambridge curve was obtained from published reports (3). From Starzl et al, 2.

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TABLE 1 INDICATIONS FOR TRANSPLANTATION IN PEDIATRIC PATIENTS (<18 YEARS) FROM 1 MARCH 1963 THROUGH APRIL 1982

Biliary Atresia	62*
Inborn Metabolic Errors	21**
Non-alcoholic Cirrhosis	15
Hepatoma	3***
Neonatal Hepatitis	3
Secondary Biliary Cirrhosis	3****
Byler's Disease	2
Congenital Hepatic Fibrosis	2
Budd-Chiari Syndrome	1
	112

* 2 had Alagilles 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
	21

*** 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 2 INDICATIONS FOR TRANSPLANTATION IN ADULT PATIENTS (>18 YEARS) FROM 1 MARCH 1963 THROUGH APRIL 1982

Non-alcoholic Cirrhosis	47	
Primary Malignancy	24	*, **
Alcoholic Cirrhosis	15	
Primary Biliary Cirrhosis	12	
Sclerosing Cholangitis	10	
Secondary Biliary Cirrhosis	6	***
Alpha-1-antitrypsin Deficiency	4	
Budd-Chiari Syndrome	3	
Acute Hepatitis B	1	
Adenomatosis	1	*
Hemochromatosis	1	
Protoporphyria	1	
	125	

* One patient in each group had previous (one and 4½ 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 3 METABOLIC, OPERATIVE, AND OTHER FEATURES OF SPECIFIC DISEASES IN 237 LIVER TRANSPLANTATION RECIPIENTS

DISEASE	NO CASES	DECISION ABOUT PROPRIETY OF TRANSPLANTATION	INCIDENCE OF PRIOR ABDOMINAL SURGERY	AVERAGE TECHNICAL DIFFICULTY	USUAL METABOLIC ABNORMALITIES	DISEASE RECURRENCE
Non-alcoholic Cirrhosis	62	Previously difficult until moribund, easier now	52%	Extreme	Severe	Usual with HBs Ag
Biliary Atresia	62	Easy	100%	Easy to extreme	Moderate	None
Hepatic Malignancy	27	Easy at first, difficult now	96%	Easy to moderate	Minimal to moderate	Common
Inborn Errors	25	Easy until now	24%	Easy to moderate	Moderate to severe	None
Alcoholic Cirrhosis	15	Difficult	13%	Extreme	Severe	Unknown
Primary Biliary Cirrhosis	12	Relatively easy	58%	Easy	Moderate to severe	Has been described
Sclerosing Cholangitis	10	Relatively difficult	90%	Moderate to extreme	Moderate to severe	None, but unknown
Secondary Biliary Cirrhosis	9	Easy	100%	Extreme	Moderate to severe	None
Budd-Chiari Syndrome	4	Relatively difficult	75%	Moderate	Moderate to severe	Has been described
Neonatal Hepatitis	3	Easy	33%	Easy to moderate	Severe	None
Congenital Hepatic Fibrosis	2	Easy	50%	Moderate	Severe	None
Byler's Syndrome	2	Easy	50%	Easy	Moderate to severe	None
Hemochromatosis	1	Easy	100%			
Protoporphyria	1	Easy	100%			
Adenomatosis	1	Easy	100%			
Acute Hepatitis B	1	Difficult	0%			

TABLE 4 CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION.

AGENTS	YEAR DESCRIBED AND REPORTED	PLACE	DEFICIENCIES	USED FOR LIVER TRANSPLANTATION
Azathioprine	1962 (12)	Boston	Ineffective, dangerous	No
Azathioprine-Steroids	1963 (13-16)	Denver, Richmond, Boston, Edinborough	Suboptimal	Yes
Thoracic Duct Drainage as Adjunct	1963 (17)	Stockholm pretreatment	Nuisance;requires 20-30 days	Yes
ALG as Adjunct	1966 (18)	Denver	Still suboptimal	Yes
Cyclophosphamide Substitute for Azathioprine	1970 (19)	Denver	No advantage except for patients with azathioprine toxicity	Yes
Total Lymphoid Irradiation	1979 (20, 21)	Palo Alto, Minneapolis	Dangerous; extensive preparation; not quickly reversible	No
Cyclosporine Alone	1978-1979 (22, 23)	Cambridge	Suboptimal	Yes
Cyclosporine-Steroids	1980 (24, 25)	Denver	Under evaluation	Yes

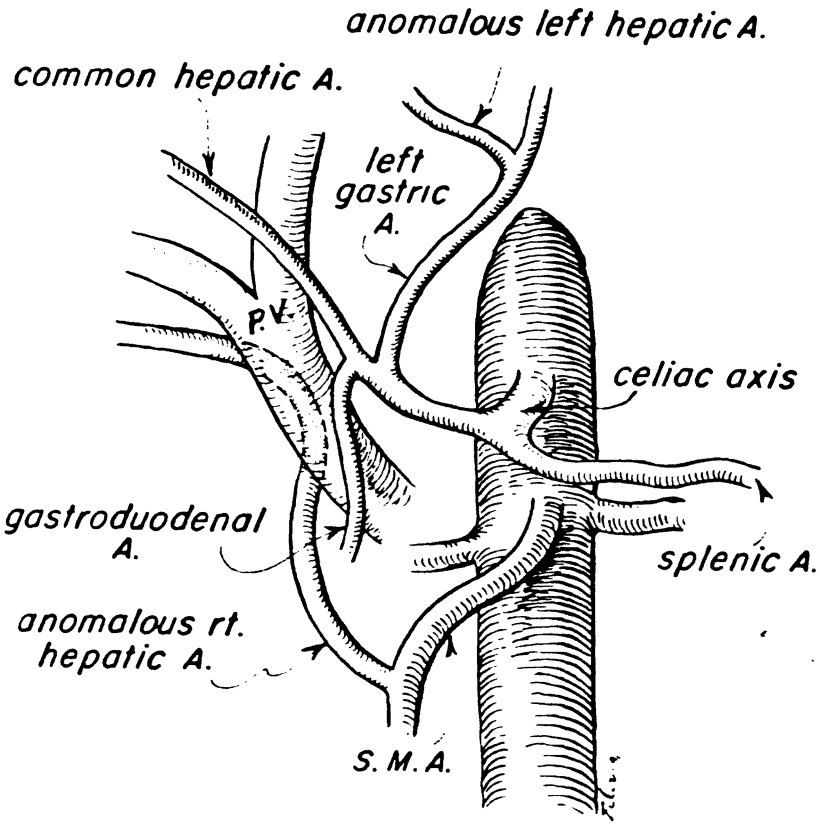
anomalous left hepatic A.
common hepatic A.
left gastric A.
P.V.
celiac axis
gastroduodenal A.
splenic A.
anomalous rt. hepatic A.
S. M. A.

Figure 1

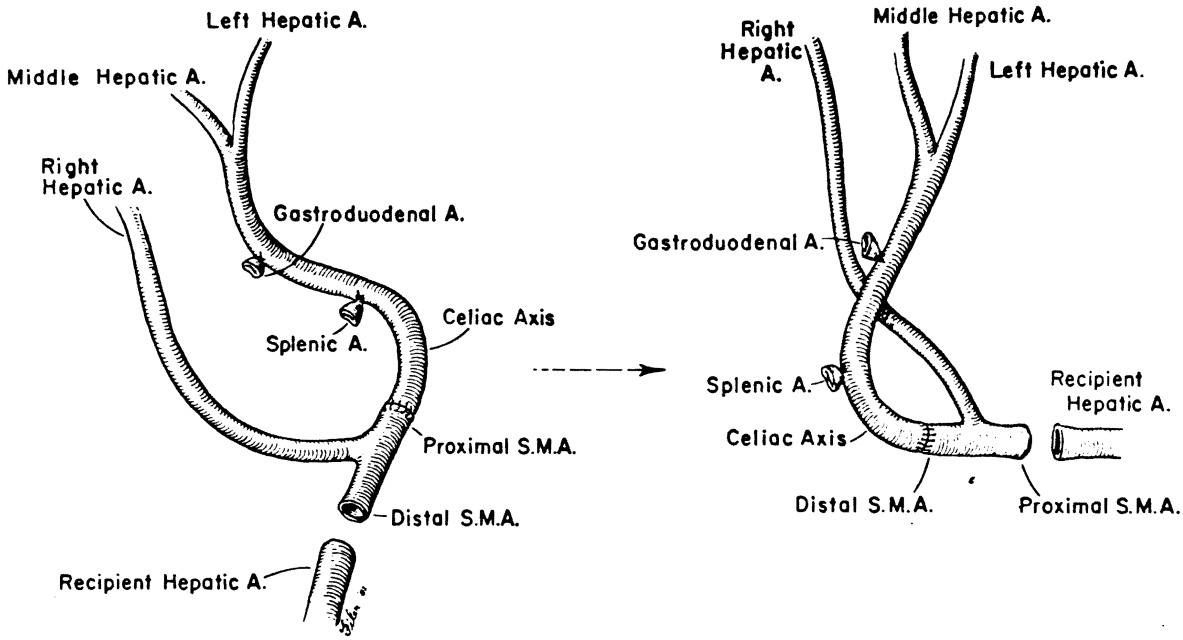
Left Hepatic A.
Middle Hepatic A.
Right Hepatic A.
Gastroduodenal A.
Celiac Axis
Splenic A.
Proximal S.M.A.
Distal S.M.A.
Recipient Hepatic A.
Middle Hepatic A.
Right Hepatic A.
Left Hepatic A.
Gastroduodenal A.
Splenic A.
Recipient Hepatic A.
Celiac Axis
Distal S.M.A.
Proximal S.M.A.

Figure 2

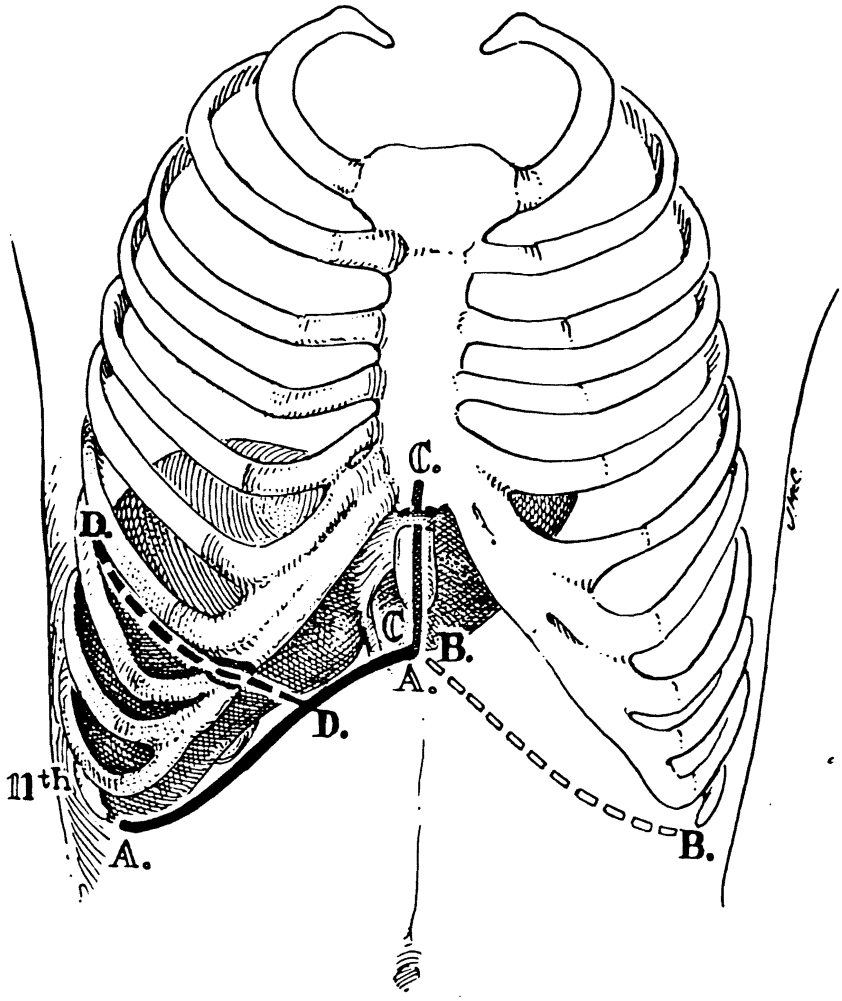

Figure 4

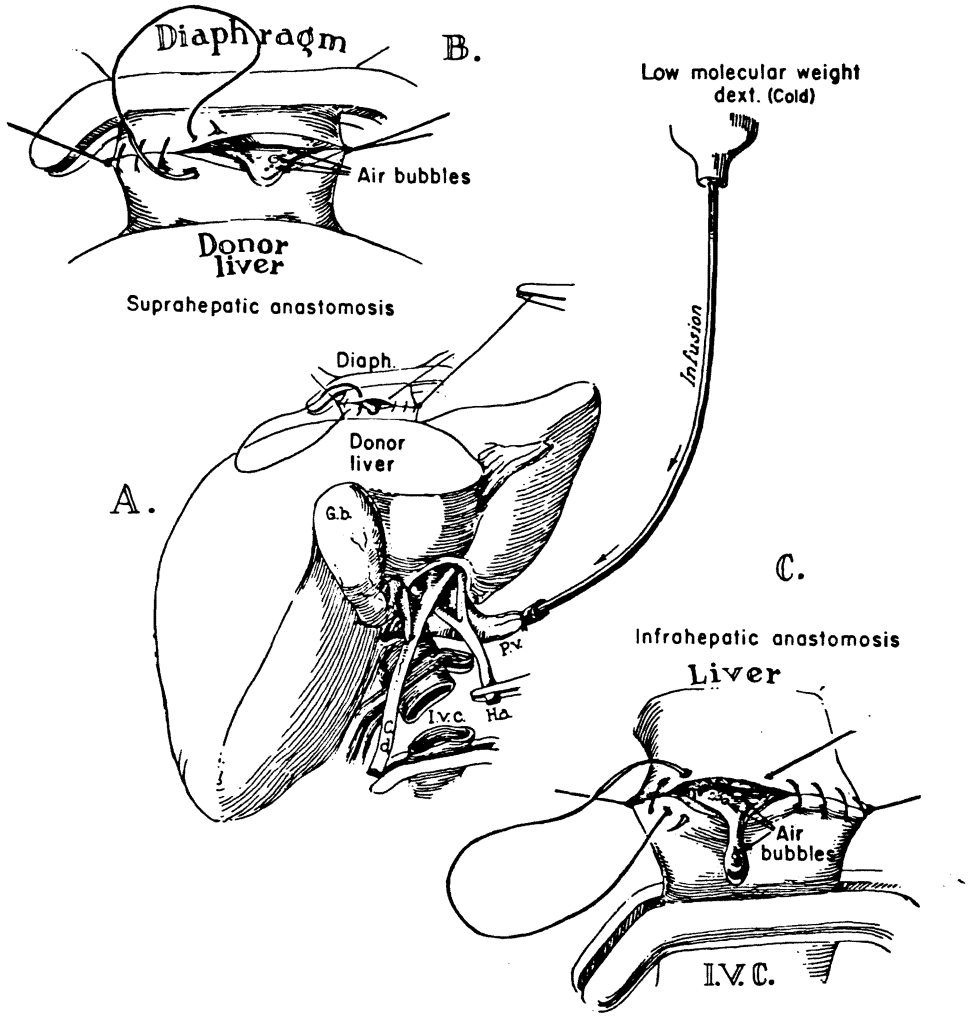
Diaphragm
B.
Air bubbles
Donor liver
Suprahepatic anastomosis
Low molecular weight dext. (Cold)
Infusion
Diaph.
Donor liver
A.
G.b.
P.v.
I.v.c.
Ha
C
d
C.
Infrahepatic anastomosis
Liver
Air bubbles
I.V.C.

Figure 5

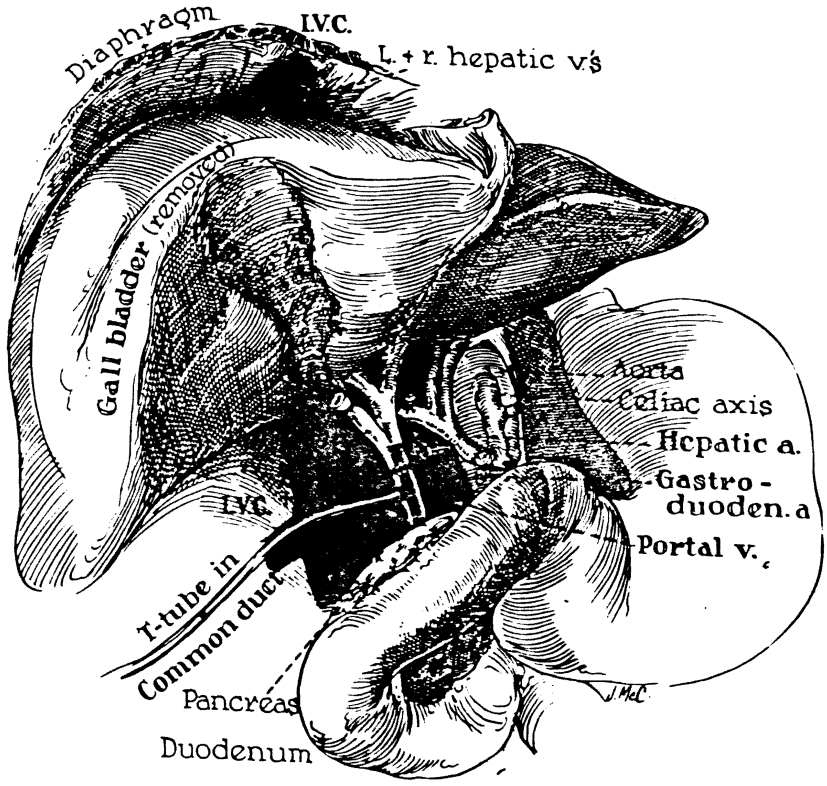
Diaphragm
I.V.C.
L. + r. hepatic v's
Gall bladder (removed)
Aorta
Coeliac axis
Hepatic a.
Gastro-duoden. a
Portal v.
I.V.C.
T-tube in Common duct
Pancreas
Duodenum

Figure 6

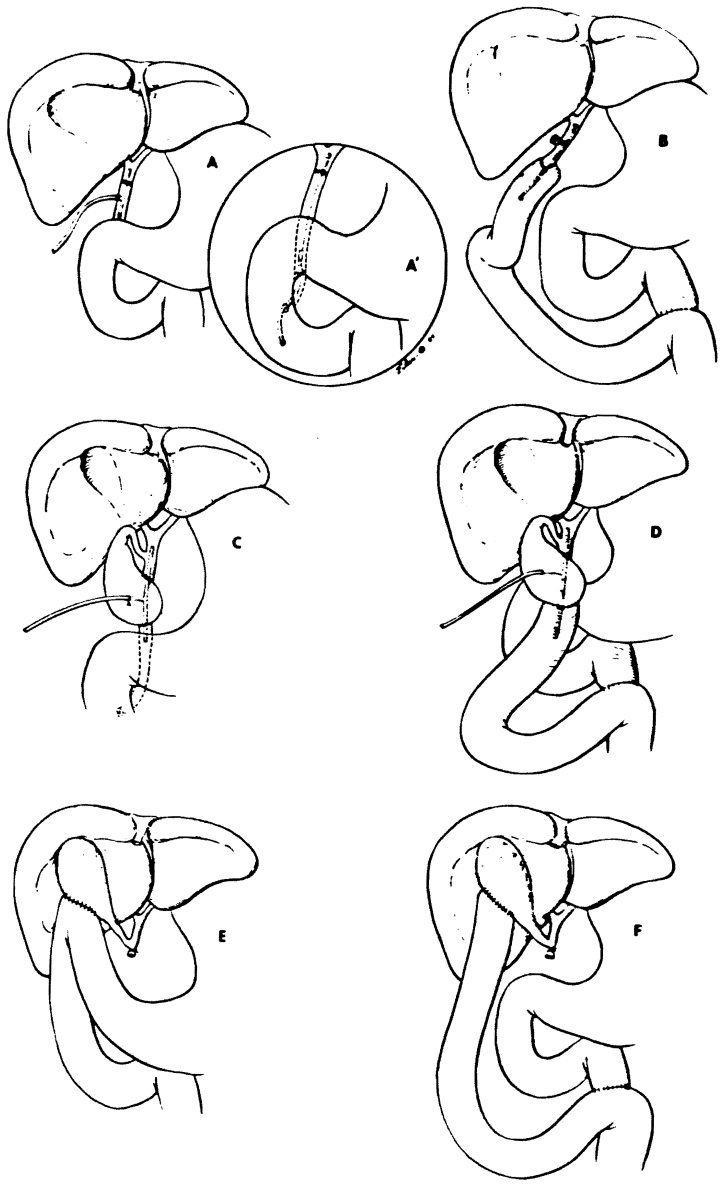

Figure 7

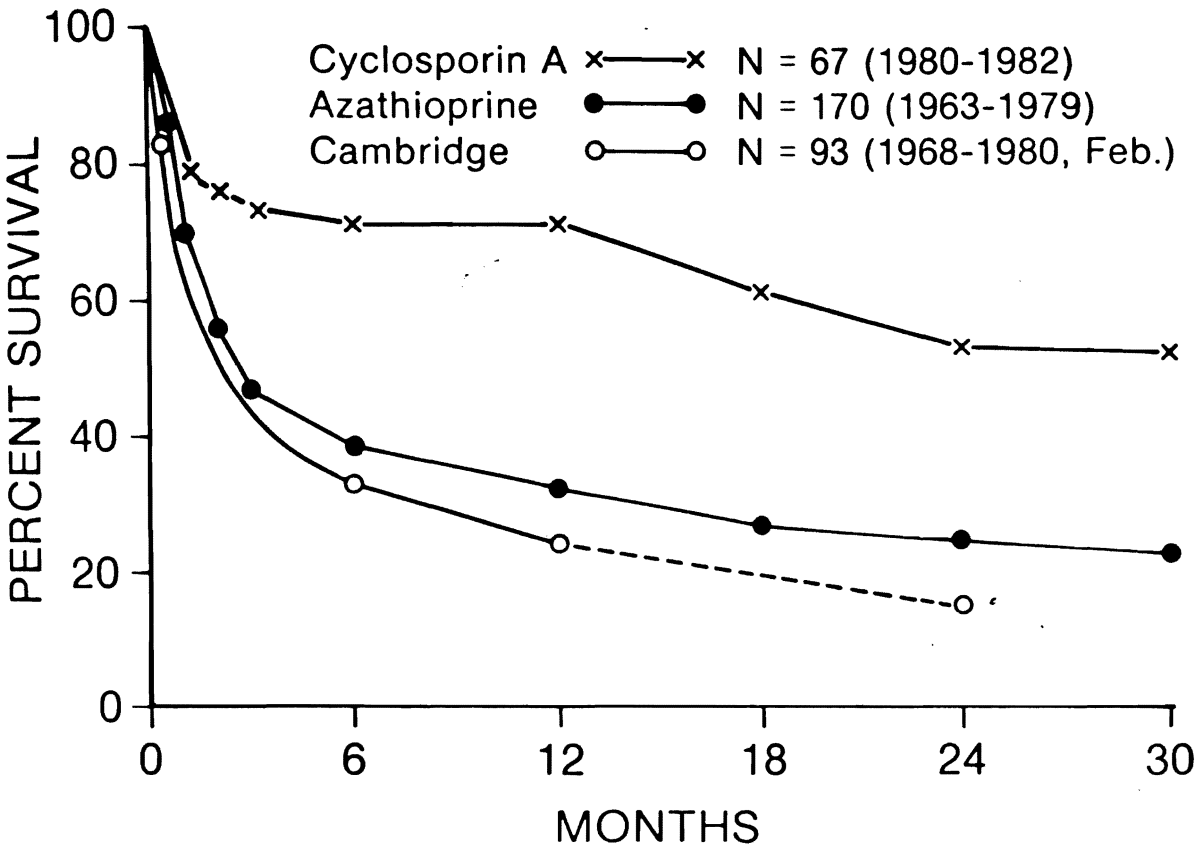
100
80
60
40
20
0
PERCENT SURVIVAL
Cyclosporin A
Azathioprine
Cambridge
N = 67 (1980-1982)
N = 170 (1963-1979)
N = 93 (1968-1980, Feb.)
0
6
12
18
24
30
MONTHS

Figure 8