History

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Evolution of Liver Transplantation

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Two general kinds of liver transplantation have been attempted clinically. With one approach, the host liver is removed and replaced with a homograft (orthotopic liver transplantation); alternatively, an extra liver is inserted at an ectopic site (auxiliary homotransplantation). This review concerns only orthotopic liver transplantation.

The first effort to replace a human liver was made at the University of Colorado on March 1, 1963. That patient died as did four others during the next 7 months (1, 2) (Table 1). In September, 1963 and January, 1964, other unsuccessful attempts at liver replacement were made in Boston (3) and Paris (4) (Table 1). The first clinical trials were not frivolously undertaken. Members of the Boston and Denver teams had developed techniques for liver replacement in dogs in the late 1950s and, in both laboratories, research on liver transplantation had been continuously performed for more than 4 years.

Nevertheless, the consecutive failures in three institutions halted all clinical trials until our sixth and seventh equally unsuccessful attempts in October, 1966 and May, 1967. Finally, on July 23, 1967, the first extended survival of a human recipient was achieved (5). The patient, a 1½-year-old girl, lived for more than 13 months before dying of metastases from the hepatocellular carcinoma for which she had been treated. From then until the first week of May, 1982, we have treated 230 more patients, 163 at the University of Colorado and 67 at the University Health Center of Pittsburgh for a total of 237. The yearly frequency of transplantation throughout our experience is shown in Figure 1. The highest number of 30 was reached in 1981; the number of new cases in 1982 is projected at between 60 and 80.

A signal event in the development of orthotopic liver transplantation occurred on May 2, 1968 when Calne and Williams of the University Hospital at Cambridge and the King's College in London, respectively, treated the first patient in their program (6, 7) which had since generated more than 125 well-studied cases. Calne's contributions in experimental renal transplantation has been a major factor in the early development (8) of chemical immunosuppression, without which transplantation of any organ was not realistic until 2 decades ago. The fact that both men had the personal qualities to be able to accept defeat or victory with equal grace was fortunate since failure was the dominant theme with all such efforts until recent times.

In this review, emphasis will be placed on the more than 350 cases in these two series. However, between 1968 and 1978, other single attempts or small series were reported from Boston (9, 10), Los Angeles (11), Montreal (12), Bonn (13, 14), Sao Paulo (15), Calgary (16), New York City (17), Richmond (18), Minneapolis (19), Manchester (20), and Oslo (21). It is probable that these documented cases were a minority of those attempted in that decade, exclusive of the English and Colorado series. Since 1978, programs have been reopened or started new from which important information can be expected. In the United States, clinical liver transplantation programs are active at the University of Minnesota (J. S. Najarian, unpublished observations) and the University of Tennessee (J. W. Williams, unpublished observations). Series of six or more cases each have been reported or are in preparation from Holland (22), East Germany (23), West Germany (24, 25), France (26), and the Republic of China (H. Q. Hong, unpublished observations). The number of cases in the West German series (25) has passed 50, but the results have not yet been published in detail.

EARLY EXPERIMENTAL BACKGROUND

The first known efforts at experimental orthotopic transplantation of the liver were made by Dr. Jack Cannon of Los Angeles (27). This report was so brief that it lacked a title, description of methods, and notation of the animal species. The animals did not survive operation.

TABLE 1. THE FIRST TRIALS OF ORTHOTOPIC LIVER TRANSPLANTATIONS

| No.	Location (ref.)	Age (yr)	Disease	Survival (days)	Main cause of death
1	Denver (1)	3	Extrahepatic biliary atresia	0	Hemorrhage
2	Denver (1)	48	Hepatocellular cancer, cirrhosis	22	Pulmonary emboli, sepsis
3	Denver (1)	68	Duct cell carcinoma	7½	Sepsis, pulmonary emboli, gastrointestinal bleeding
4	Denver (2)	52	Hepatocellular cancer, cirrhosis	6½	Pulmonary emboli, ? hepatic failure, pulmonary edema
5	Boston (3)	58	Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
6	Denver (2)	29	Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
7	Paris (4)	75	Metastatic colon carcinoma	0	Hemorrhage
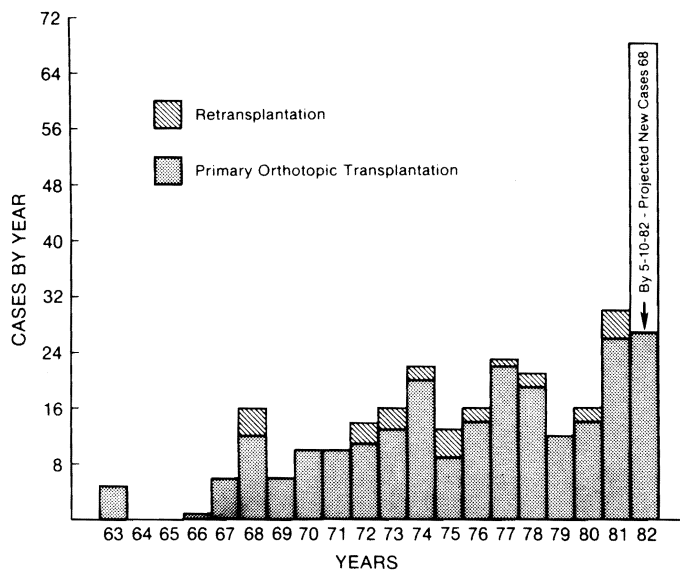
FIG. 1. Yearly number of liver transplantations at the University of Colorado (1963 to 1980) and the University of Pittsburgh (1981 to 1982). Note that retransplantation has been attempted frequently.

In June, 1958, a program of orthotopic transplantation of the canine liver was initiated at the Peter Bent Brigham Hospital under the direction of Dr. Frances D. Moore (28), and in August, our first experiments in the same species were begun at Northwestern University in Chicago (29, 30).

The technical problems of liver replacement and the features of rejection in untreated canine recipients were delineated (28–31). Eventually, using immunosuppression with azathioprine (32–34) and antilymphocyte serum or its antilymphocyte globulin (ALG) derivative (32, 35–38), chronic survival was achieved in mongrel dogs of which one lived for almost 12 years (39).

In 1965, Garnier of Paris (40) made the important observation that rejection of pig liver homografts was mild in comparison to that in dogs. Several porcine recipients lived for long times without immunosuppression. Workers in Bristol (41), Cambridge (42), and Denver (32) promptly confirmed Garnier's work. The value of the pig for transplantation research has been demonstrated frequently in the investigations of Calne and his associates.

Hundreds of significant experimental studies in various species have since been published. Review of this work

will not be attempted although some of it has influenced the clinical trials as will be noted later.

NOTATIONS ABOUT SURGICAL TECHNIQUES IN HUMANS

A training period in the animal laboratories is an important preparatory step for teams planning clinical programs; however, not all of the experimental techniques are identical in humans. Our methods of orthotopic liver transplantation (1, 5, 32, 43–52) and the modifications introduced by Calne et al. (6, 47, 53) have been described.

The operation is simple in principle (Figure 2), but its execution has been exceptionally difficult because of the almost invariable debilitation of the recipients and the profoundly abnormal vascularization patterns caused by portal hypertension in endstage liver disease. Defects in clotting have been present in most cases (1, 32, 54, 55), and adhesions or other alterations secondary to previous operations are often complicating factors. With such a background, it is not surprising that the postoperative care of many patients has been an exercise in resuscitation (32). The most common difficulties have been pulmonary insufficiency (requiring mechanical ventilation for several months in some cases), renal failure with massive fluid shifts, and persistent clotting abnormalities. These problems are managed with conventional methods of intensive care with emphasis on biochemical and hemodynamic monitoring. Recovery can be expected from encephalopathy and the hepatorenal syndrome (56).

The ability to survive this critical period depends upon what has transpired in the operating room. Thus, in the following remarks, we will touch upon details of surgical technique which require reemphasis or points of view which have changed from those expressed in the past.

ORGAN PROCUREMENT AND PRESERVATION

Until 1976, techniques for preserving the liver either severely limited the acceptable time of cold ischemia or were too complicated for use in outlying hospitals (32). In 1976, simple methods that permitted reasonably long storage were developed, and clinical trials were started. We have employed an electrolyte (Collins) solution with a composition similar to that found intracellularly (57). The Cambridge-King's College team uses a plasma solution for similar cold infusion of the homograft (58). In dogs, the two methods yielded similar results (57) and allowed safe preservation for up to 12 hr. These tech-
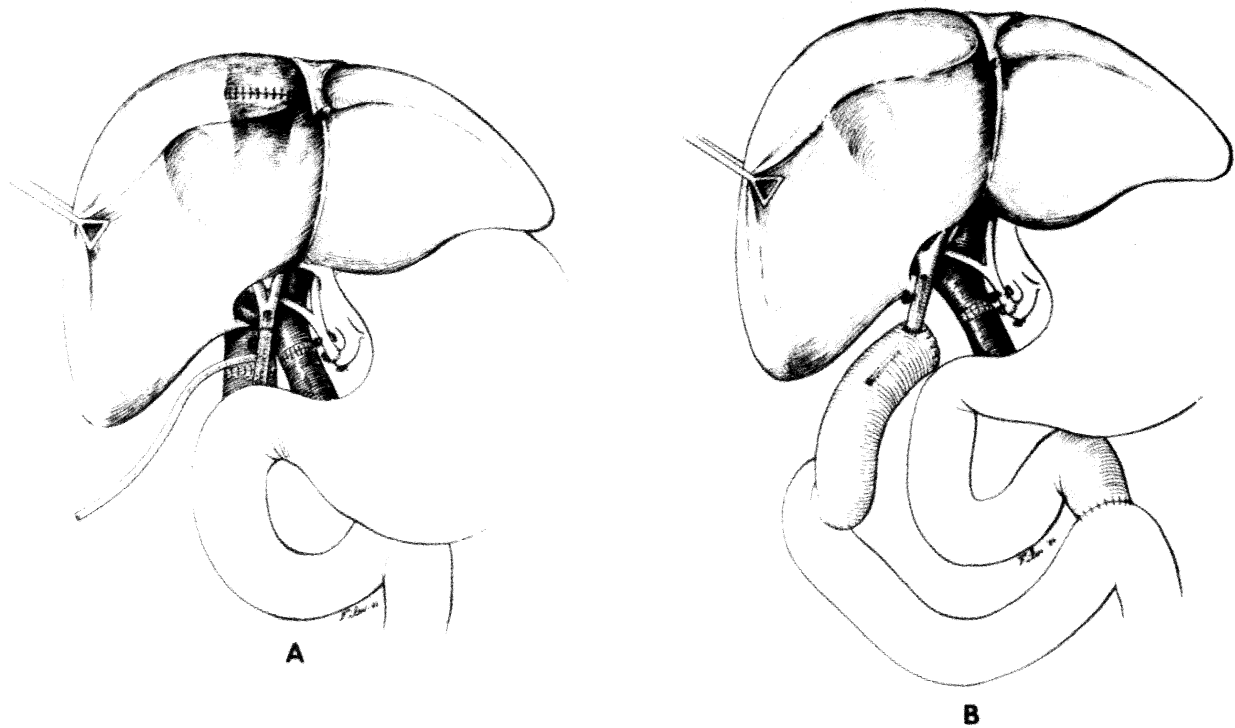
Fig. 2. Completed orthotopic liver transplantation. (A) Biliary tract reconstruction with choledochocholedochostomy. (B) Biliary tract reconstruction with choledochojejunostomy, using a Roux limb.

niques permit shipment of livers from city to city. More than two-thirds of the livers used in the Pittsburgh program have been obtained outside of the normal procurement area for this region; the longest transit being from Phoenix, Ariz. Efficient air travel arrangements are necessary; to meet this objective, several Pittsburgh corporations have donated their private jet airplanes.

Liver procurement outside of the local area has depended on cooperation with other procurement centers whose main function was previously to provide cadaveric kidneys. Fear that kidney grafts would be jeopardized by giving too high a priority to the liver has been allayed by standardization of techniques which protect all organs equally and which can be adapted to the local surgeons' wishes (59).

A midline incision is made from the pubis to the neck, and the sternum is split. The structures entering and leaving the liver are skeletonized, and the necessary preliminary steps for kidney removal are taken in the presence of an intact circulation. Then a cannula is placed through the splenic vein into the superior mesenteric vein. Rapid infusion of cold lactated Ringers' solution is used to start cooling of the liver. After 1 or 2 liters have been infused, cold Collins solution is infused through the terminal aorta at the same time as the distal thoracic aorta is cross-clamped and the cadaveric donor is exsanguinated from a cannula previously placed in the distal inferior vena cava. After removal, the cold liver is

flushed with Collins solution and protected by a plastic bag which is placed in slushed ice. The performance of kidneys removed from liver donors with this technique was as good or better than has been achieved in most centers with kidney removal alone (59). With minor modifications, it has also been possible to remove the heart in addition to kidneys and liver from seven donors.

During 1981 when 30 liver homografts were used, there were 176 offers of organs. The inability to use the other 146 livers was usually because there was a disparity in size between the donor and recipient, the donor blood group was incompatible with the recipient, or Pittsburgh facilities for liver recipient care were saturated. An actual shortage of pediatric donors has existed in the 1- to 5-year age group.

RECIPIENT HEPATECTOMY

The most demanding aspect of liver transplantation is removal of the diseased native organ. The technical difficulties are usually determined by the underlying disease. The easiest situations are in patients with primary hepatic malignancies or primary biliary cirrhosis. The most difficult are in recipients with the shrunken livers of macronodular cirrhosis or in patients with multiple previous operations. On the average, hepatectomy is easier in infants and children than in adolescents and adults.

The preexisting pathologic changes often necessitate

deviations from a standard plan; however, the first step is to find the hilum and dearterialize the liver which expedites hilar dissection and slows hemorrhage from the liver surface. During hilar dissection, the bile duct 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 minimal dissection. The left triangular and falciform ligaments are incised until the suprahepatic vena cava is identified. The suprahepatic vena cava is encircled to allow placement of a cross-clamp.

If all of these maneuvers are successfully executed, the liver can be isolated from the circulation by cross-clamping vessels which have been encircled but are intact. Cuffs of the suprahepatic and infrahepatic vena cava are fashioned from these vessels as the liver is removed. Sufficient infrahepatic vena cava is not difficult to obtain, but development of an adequate suprahepatic cuff may require tailoring of the vena cava which is mobilized from within the liver (46). The technique of isolating the liver and peeling it out in a bloodless state permits all residual tissue connections of the right triangular ligament and the bare areas (including the right adrenal vein) to be ligated under direct vision. The penalty with this approach is an increase (usually about 30 min) in the time of portal and vena caval cross-clamping, compared to cross-clamp time with previously described techniques (1, 32, 43).

Such cross-clamping is usually tolerated in patients with chronic disease in spite of major declines in cardiac output and variable hypotension (60): the same thing has been demonstrated in dogs subjected to chronic bile duct obstruction (61). Because of this, venous bypasses which were used in our first cases were discontinued (1, 2).

Some patients are jeopardized by the venous cross-clamping. If severe hypotension occurs after cross-clamping, Calne et al. (52, 53) recommend femoral vein-to-femoral artery bypass with an intervening oxygenator. About 10% of the English patients are so treated. One death in our last 67 patients (OT 233, Table 14), as well as a cardiac arrest which was successfully treated, may have been avoided by this precaution.

The fact that most patients 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 occlusion. Subsequently, many patients suffer from third-space fluid sequestration and postoperative renal failure. The extent to which these complex physiologic events contribute to the high perioperative mortality has not yet been delineated. For this reason, we returned in recent cases (not reported in this communication) to the practice of venous bypass which had been abandoned. Cannulas are placed 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 a large vein in the neck or arm. Although this kind of bypass requires total body heparinization, bleeding has not been excessive since the "heparin effect" can be effectively reversed even in patients with severe liver disease.

BILIARY TRACT RECONSTRUCTION

Difficulties with biliary tract reconstruction were frequently lethal in our experience (43, 62, 63) and in that of the English workers (7, 49–51) until the mid-1970s. Anatomic studies by Terblanche et al. (64) suggest that deficient blood supply of the homograft duct system may be a contributory factor; however, our principal problems were due to the frequent (and inappropriate) use of cholecystoduodenostomy and to failure to diagnose the complications. The latter deficiency was resolved with the frequent use of postoperative cholangiography (Figure 3) and reoperation, if necessary. The incidence of complications has been reduced with better primary reconstruction.

We now consider duct-to-duct anastomosis to be the procedure of choice (Figure 2A). When this is not feasible, the duct is anastomosed to a Roux limb of jejunum (Figure 2B). With either technique, the homograft gallbladder is removed. The results of biliary tract reconstruction in the last 67 cases are shown in Table 2. Using choledochocholedochostomy or choledochojejunostomy, an eventually satisfactory result was obtained in more than 95% of cases, although the use of an internal stent (instead of a T-tube stent) for duct-to-duct anastomoses led to a high rate of reoperation. Only two deaths resulted directly from biliary tract reconstruction.

Since 1976, Calne et al. (48) have used a technique in which the homograft common duct and gallbladder are fashioned into a common channel and anastomosed to recipient common duct or a Roux limb. Waddell and Grover (65) had described such a common channel procedure for difficult biliary tract problems.

THE QUESTION OF SPLENECTOMY

The spleen was removed in most of our early patients, in part to achieve immunodepression, but mainly to relieve hypersplenism and leukopenia which prevented the effective use of azathioprine or cyclophosphamide (32). With the advent of cyclosporin A, splenectomy was discontinued.

UNTREATABLE COMPLICATIONS

Technical complications that have occurred after liver transplantation are legion. All have been potentially treatable except for irreversible ischemic injury of the graft or early loss of its blood supply. Retransplantation is the only hope for a patient who has been given an irreversibly damaged or devascularized organ. In one of our patients, portal vein stenosis at the anastomosis was diagnosed 8 months after transplantation, and, at reoperation, the stenosis was successfully resected in spite of the fact that thrombosis had occurred requiring thrombectomy (Figure 4).

TISSUE MATCHING

The time constraints of liver preservation and urgent recipient need usually preclude systematic efforts at tis-

FIG. 3. Biliary obstruction 8 months after liver transplantation and a duct-to-duct reconstruction in a 10-year-old child. Note the ectasia of the recipient common duct (*arrow*). At reoperation, the graft common duct was anastomosed to a Roux limb of jejunum with a good result.

sue matching. With the random donor-recipient pairing, good matches at the A, B, and DR loci have never been obtained.

Hepatic transplantation has been performed (45, 50, 51, 66) against the recipient anti-donor T-warm antibodies which cause hyperacute rejection of kidney homografts. To our knowledge, hyperacute rejection of the liver has never been seen.

However, much more experience will be required before concluding that acceptance of "positive cross-matches" against T-warm recipient antibodies is without jeopardy. Data from the first 53 Pittsburgh cases is summarized in Table 3. Patients for whom cross-matches could not be performed or whose sera cross-matched negative with recipient cells had better results than those with cross-match positive donors. Although hyperacute rejection was not observed in the latter recipients, the

postoperative courses were stormy. At least two of the livers developed delayed massive necrosis.

From experimental studies, it is known that the liver is resistant to hyperacute rejection. However, in animal xenograft models in which the recipient has performed heterospecific cytotoxins, humoral antibody rejection of the liver is merely slower than that of the kidney; the mechanisms of destruction are the same. The extent (if any) to which the outlook after clinical liver transplantation is depreciated by preformed antibodies is unknown; many liver candidates have widely reacting T-warm cytotoxic antibodies which reflect sensitization by previous blood transfusions. For the time being, we continue to treat such highly sensitized patients.

If donor-recipient ABO blood group incompatibility exists, renal grafts can be destroyed by isoagglutinins (67). Liver grafts are resistant to this kind of hyperacute

TABLE 2. PRIMARY BILE DUCT PROCEDURES AND COMPLICATIONS IN 75 LIVER TRANSPLANTATIONS ON 67 CONSECUTIVE PATIENTS IN THE CYCLOSPORIN ERA

	Choledochochole-dochostomy with T-tube	Choledochochole-dochostomy with internal stent	Choledochojejunos-tomy in Roux-en-Y with stent	Cholecystojejunos-tomy in Roux-en-Y	External tube drainage	Biliary reconstruc-tion not completed (intraoperative death)
No.	25	19	20	6	3[a]	2
Success	20	11	18	1	—	—
	(80%)	(58%)	(90%)	(17%)		
Failure	5	8	2	5	—	—
Reoperation required	4[b]	7[b]	2	5	—	—
Cause of death	0	1	1	0	—	—
Nature of failure						
Obstruction	1	3	0	4[c]	—	—
Bile leakage	4	4	2	1	—	—
Arterioductal fistula	0	1	0	0	—	—

[a] Reconstruction was never completed in 2 of the 3 patients.

[b] One patient was treated with transhepatic dilation under X-ray control.

[c] One patient developed a large fungal liver abscess, which led to retransplantation. He is doing well with the second liver graft 1 year later.
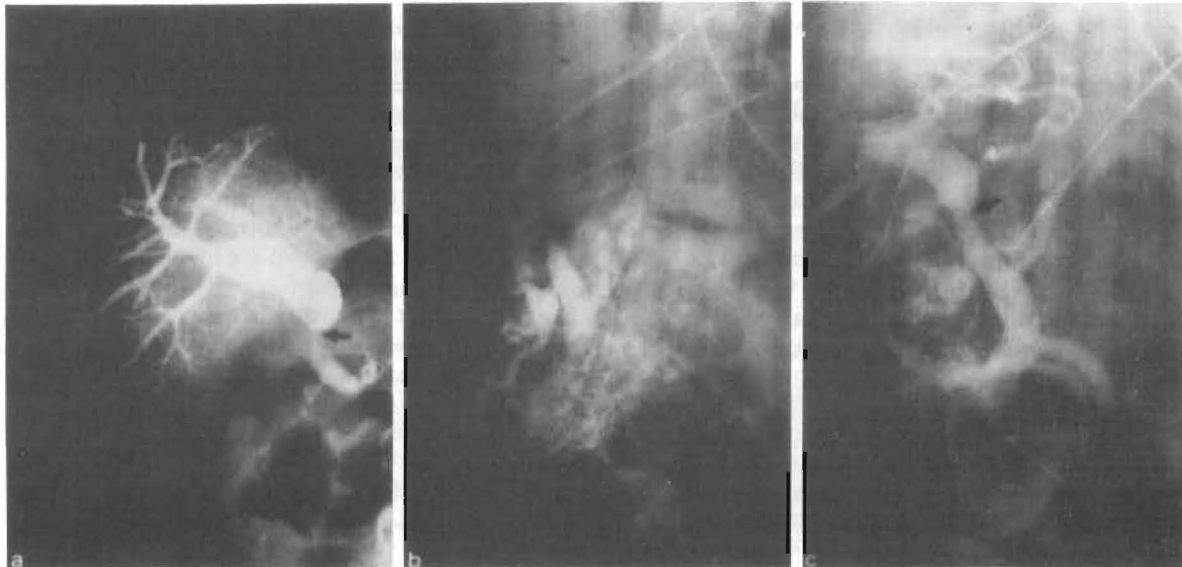

FIG. 4. (a) Stenosis of the portal vein anastomosis (*arrow*) diagnosed by transhepatic portography in the same patient whose biliary system is shown in Fig. 3. (b) Operative venogram obtained through a mesenteric vein a few days later. The obstruction was complete, and the homograft portal vein was full of thrombus. (c) Patent system after resection of the stenosis, thrombectomy, and reanastomosis.

TABLE 3. INFLUENCE OF TRANSPLANTATION AGAINST DONOR-SPECIFIC CYTOTOXIC T-WARM ANTIBODIES (CYCLOSPORIN ERA)[a]

	No.	Survival (months)				
		>1	>2	>6	>12	Now
Negative cross-match	31	24 (77%)	22	14	3	21 (68%)
Positive cross-match	8	5 (63%)	5 (63%)	2	1	4 (50%)
Cross-match not done	14	13 (93%)	10	2		12 (86%)

[a] Data from 53 consecutive primary transplants at the University of Pittsburgh.

TABLE 4. CASES OF DONOR-RECIPIENT BLOOD GROUP INCOMPATIBILITY IN 53 CONSECUTIVE PRIMARY LIVER TRANSPLANTATIONS AT THE UNIVERSITY OF PITTSBURGH

OT	Incompatibil-ity	Early graft function	Outcome
193	A → B	Good	Well, 12 months
196	A → B	Good	Died, systemic aspergil-losis, 8 days

rejection (45). In two of our Pittsburgh cases, two incompatible donors were used (Table 4). The course of one of these patients is shown in Figure 6. We have tried to avoid this practice since blood group compatible donors can usually be found.

IMMUNOSUPPRESSION FOR HUMANS (THE KIDNEY TRANSPLANT PROTOTYPE)

It was important to demonstrate in animals that chronic survival is possible after liver transplantation under immunosuppression. However, such laboratory investigations contributed relatively little to the immunosuppressive regimens which have been used clinically. Liver transplantation, either in animals or man, was too complex to be used as a model to evaluate drugs or drug

combinations. Instead, all methods to prevent or reverse rejection of whole organs have depended upon observations after renal transplantation.

The immunosuppressive protocols that have been developed for human renal transplantation are summarized in Table 5, exclusive of the historically important trials with total body irradiation (68). Because the first genuinely promising drug, azathioprine (8), proved to be effective only rarely when given alone (69), the "modern" era was not entered until it was realized that azathioprine and prednisone have an additive (or possibly synergistic) effect (67, 70–73). At the outset, our policy was to begin therapy after renal transplantation with azathioprine and to add high doses of prednisone with the first signs of rejection (70). Because it was rare to escape rejection even after transplantation from closely related donors, our recommendation (67) was to begin treatment with both drugs immediately after transplantation with a gradual reduction in prednisone. Such "double-drug therapy" has been the most commonly used immunosuppression for almost 20 years.

With transplantation from consanguineous donors under double-drug treatment, chronic renal graft function was achieved almost immediately in more than two-thirds of cases. However, during the first year after cadaveric renal transplantation, the graft loss rate in multicenter compilations remains at about 50% (74, 75). Liver recipients for whom cadaveric donors were obligatory, and who did not have the option of fall-back maintenance on an artificial organ therapy analogous to renal dialysis in the event of rejection, were confronted with a bleak outlook.

Between 1963 and 1979, several alternative therapeutic programs were introduced for renal transplantation (Table 5); all were modifications of or additions to the original double-drug therapy. A promising approach involved lymphoid depletion with ALG (36) which was given i.m. or i.v. as an adjunct to azathioprine and prednisone during the first few weeks or months when the risk of rejection is the greatest. "Triple-drug therapy" has been the second most commonly used technique of immunosuppression. A conceptually important but pragmatically inconsequential detail was that cyclophosphamide could be freely substituted for azathioprine (76). The results of 1-year graft survival after cadaveric renal transplantation under triple-drug therapy were improved in most centers. After the discontinuance of ALG, there was an unacceptable rate of delayed rejection which, not surprisingly, also occurred after liver transplantation (32). The alternative of temporary lymphoid depletion with thoracic duct drainage (TDD) (77) in preparation of patients for cadaveric renal transplantation (78) had the same disadvantage (79). Efforts to use preoperative TDD in liver recipients usually created insurmountable problems because of the prodigious quantities (as much as 2 liters per hr) of thoracic duct lymph which patients with hepatic insufficiency produced (80). Lymphoid depletion by total lymphoid irradiation for conditioning before grafting (81, 82) has not been tried in liver recipients.

There was widespread discontent with all techniques of immunosuppression from 1963 to 1978. Many kidney transplant surgeons attempted to escape the consequences of this therapeutic cul de sac by exploiting developments in tissue typing and matching, or by systematically conditioning prospective renal recipients with preoperative blood transfusions. The former efforts yielded disappointing results after cadaveric kidney transplantation; the latter practice of conditioning by transfusion allowed an increased success rate in patients not accidentally sensitized during their preparation. In any event, liver transplantation candidates usually were too ill to wait for a well-matched liver or to undergo stages of preoperative preparation. For future trials of liver transplantation, it was necessary to hope for better immunosuppressive drugs. This did not seem realistic until the advent of cyclosporin A.

Cyclosporin A is an extract from the fungi *Cylindrocarpon lucidum* and *Trichoderma polysporum*. It was discovered and characterized biochemically by scientists at the Sandoz Corp., Basel, Switzerland. Cyclosporin A was shown to be immunosuppressive by Borel et al. (83, 84) in mice, rats, and guinea pigs. The drug depressed humoral and cellular immunity with a preferential and quickly reversible action against T-lymphocytes. These effects were not accompanied by bone marrow depression which frequently limits the doses of azathioprine and cyclophosphamide. The unusual effectiveness of cyclosporin A in preventing or delaying rejection of mouse skin homografts was demonstrated by Borel et al. (83,

TABLE 5. CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION

Agents	Year described and reported	Place	Deficiencies	Used for liver transplantation
Azathioprine	1962 (69)	Boston	Ineffective, dangerous	No
Azathioprine—Steroids	1963 (70–73)	Denver, Boston, Richmond, Edinborough	Suboptimal	Yes
Thoracic duct drainage as adjunct	1963 (77)ᵃ	Stockholm	Nuisance; requires 20–30 days pretreatment	Yes
ALG as adjunct	1966 (36)	Denver	Still suboptimal	Yes
Cyclophosphamide substitute for azathioprine	1970 (76)	Denver	No advantage except for patients with azathioprine toxicity	Yes
Total lymphoid irradiation	1979 (81, 82)	Palo Alto, Minneapolis	Dangerous; extensive preparation; not quickly reversible	No
Cyclosporin A alone	1978–1979 (90, 91)	Cambridge	Suboptimal	Yes
Cyclosporin A—Steroids	1980 (92, 93)	Denver	Under evaluation	Yes

ᵃ It was not realized until much later that pretreatment for 3 to 4 weeks before transplantation was a necessary condition (78).

84). Analogous observations in which heart, kidney, liver, and pancreatic grafts were protected in rats, rabbits, dogs, and pigs were reported by Kostakis (85), Calne (86–88), and Green (89) and their associates.

When cyclosporin A was first used in patients by Calne and coworkers (90, 91), it was hoped that no other drug would be routinely required. Our dissenting opinion is that cyclosporin A should be combined with steroid therapy from the outset (92, 93). The extent to which steroids are required with cyclosporin A remains to be clarified, but it is clear that kidney survival of greater than 80% can be expected 1 year after primary cadaveric transplantation (93, 94). Long-term follow-up of our original recipients and those of Calne has not shown a tendency for patients under cyclosporin A to have "catch-up" graft losses or unexpected delayed morbidity from other causes. We and Calne have not had the disillusionment reported by Carpenter et al. (95) and Sweny et al. (96) in their first trials with cyclosporin A for cadaveric renal transplantation.

As new teams begin using cyclosporin A, it will be important to avoid unrealistic expectations about early convalescence that could be engendered by the high success rates achieved after cadaveric renal transplantations. In a recent analysis of 42 consecutive cadaveric renal recipients (97), only one-third had a completely uneventful recovery. Of the remainder, most developed rejection which was usually reversed with augmented steroid therapy. In every case, the major differential diagnosis was rejection vs. nephrotoxicity from cyclosporin A.

Nephrotoxicity of cyclosporin A was first noted by Calne (90, 91) and Powles (98), and has been confirmed elsewhere (92, 99). To sharpen the interrelationship between therapeutic effect and toxicity, pharmacologic (cyclosporin A blood and/or plasma levels) and immunologic monitoring were advocated by Keown (100), Rynasiewicz (101), and Kahan (102). Our techniques of management have not depended upon these monitoring techniques. Fortunately, nephrotoxicity usually has promptly reversed with reduction of cyclosporin A doses. As a last resort, a change from cyclosporin A to azathioprine has been made but at an increased risk of rejection (99).

Most other side effects of cyclosporin A (90–94) are not serious and include gingival hyperplasia, tremor, regional flushing or vague abdominal discomfort just after drug ingestion, and development of breast fibroadenomas in women. Although hepatotoxicity occurs in about one-fifth of cases (103), it is rarely serious enough to necessitate a change to azathioprine.

The most publicized question about cyclosporin A concerns its potential oncogenicity. It has been known for 15 years that conventional immunosuppression results in an increased incidence of de novo tumors, of which approximately one-third are lymphomas (104). Early reports by Calne (91) of lymphoma development in patients treated with cyclosporin A were not surprising, although the incidence of three lymphomas in 34 recipients was sobering. Calne attributed this high incidence to the concomitant use of other cytotoxic drugs and possibly steroids. In our own experience with cyclosporin A and steroid therapy in almost 200 cadaveric renal

recipients, there have been two lymphomas. One was an incidental finding at autopsy following a fatal infection (93). The other was successfully treated by intestinal resection after it had caused a perforation (97). To our knowledge, no de novo epithelial tumors have been seen in renal recipients. As experience with cyclosporin A accumulated worldwide, the spectre of this drug being a spectacular tumor producer has receded. None of the liver recipients treated with cyclosporin A and steroids has developed new malignancies.

IMMUNOSUPPRESSION AND LIVER TRANSPLANTATION

Two patients are known to have been given orthotopic liver grafts without immunosuppression or with steroid therapy only. The first patient was in the Cambridge series (7); the other was treated in Oslo (21). One factor in these decisions may have been the demonstration in dogs (32, 33) and pigs (32, 40–42) that rejection of liver grafts was less severe than that after renal transplantation. In addition, the English recipient had hepatitis which it was feared would be reactivated by immunosuppression. Both organs promptly failed with early death of the patients.

All other patients were given some variant of the double- or triple-drug treatment summarized in Table 5. Our first five recipients and occasional ones later were treated with azathioprine and prednisone. The same treatment was used for almost all patients in the Cambridge series from 1968 through 1979.

Triple-drug treatment was used in the majority of recipients from 1966 through 1979. The most common regimen was azathioprine, prednisone, and a variable course of i.m. ALG which was begun on the day of operation. The duration of ALG was usually limited to a few weeks because of sensitization of the recipients to horse, rabbit, or goat globulin; however, treatment with ALG was continued in some cases for 6 to 12 months.

In a modification of triple-drug therapy (Table 5), cyclophosphamide instead of azathioprine was given to 16 patients (OT 42–57) from March, 1971 to August, 1972 (105). Six (37.5%) recipients lived for at least 1 year, and four (OT 42, 46, 53, 56) are still alive more than 10 years later. From a few months to several years after transplantation, all surviving patients were switched to azathioprine. Because the results during this period were not markedly different than with the original triple-drug management, cyclophosphamide was not further used as a first line drug.

In 1978 and 1979, TDD was used as an adjunct to therapy with azathioprine and prednisone in 21 patients (80). TDD was started 10 to 18 days before transplantation in 2 patients, on the day of operation in 17 patients, and 2 and 4 weeks after transplantation in the other two. Six (31.6%) of 19 recipients who had TDD started prior to or on the day of transplantation lived for at least 1 year and five are alive after 3⅔ to 4⅓ years. The management dilemma was that in the kidney transplantation model, TDD was ineffective unless applied at least 3 weeks in advance of transplantation (78), but potential liver recipients could not tolerate the chronic, high-volume thoracic lymph drainage associated with hepatic

disease. If TDD is to be tried again in liver transplanta-
tion, a closed system will be required in which lympho-
cytes can be removed in transit without the necessity for
lymph removal and later reinfusion.

Calne et al. (91) were the first to use cyclosporin A for
liver transplantation. In their first two cases, cyclosporin
was used alone. However, most of their experience has
been with delayed administration of the drug (53, 106).
Azathioprine (1.5 mg per kg per day) and prednisolone
(0.4 mg per kg per day) were used until renal and hepatic
functions were adequate. Then, cyclosporin A (10 mg per
kg per day) was begun, and the steroid dose was slowly
reduced to zero. The supervention of acute rejection
during treatment with azathioprine and prednisone was
troublesome and, in the last review by Calne et al. (53),
they recommend shortening this period.

Our practice (107-109) has been to start cyclosporin A
a few hours preoperatively with an p.o. dose of 17.5 mg
per kg (Figures 5 to 7). Cyclosporin A is continued daily,
but with reduced i.m. or i.v. quantities (Figure 7) until
p.o. diet is resumed. Subsequently an p.o. dose of 17.5
mg per kg per day is given, usually with half the daily
dose every 12 hr. The quantities are reduced subse-
quently if toxic manifestations develop, of which neph-
rotoxicity has been the most important (Figures 5 and
6). Usually, steroids are also started on the day of oper-
ation. 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 mainte-
nance dose of 20 mg per day (Figure 5). Further reduc-
tions of cyclosporin A and steroid doses are made on an
individualized basis. Initial and maintenance therapy
with steroids are reduced in infants and children (Fig-
ure 6).

If the patient was in poor postoperative condition, the
initial burst of high-dose steroid therapy was omitted for

a few days or greatly reduced (Figure 7). A few patients
suspected of having nephrotoxicity from cyclosporin A
were switched temporarily to azathioprine with resump-
tion of cyclosporin A treatment as renal function im-
proved (Figure 6). With less severe renal impairment
(Figures 5 and 7), the dose of cyclosporin A was reduced.
No patient has been changed to azathioprine perma-
nently. If rejection occurred in spite of this therapy, the
principal responses have been to administer intermit-
tently large i.v. doses of hydrocortisone (or prednisolone)
(Figures 5 and 7), repeat the original 5-day burst of
steroids (Figure 7), and settle at a higher maintenance
level of steroids. Although cyclosporin A does not permit
much dose maneuverability, it has sometimes been pos-
sible to increase the amounts given despite the risk of
nephrotoxicity.

REJECTION AND ITS MODIFICATION

To interpret much of the statistical information to be
presented later in this review, it will be necessary to
describe the features of homograft rejection as these have
been perceived by the pathologist and surgeon.

THE MORPHOLOGIC EVENTS OF REJECTION

Despite treatment with any of the immunosuppressive
regimens so far used, rejection of human hepatic homo-
grafts has been observed. A clear picture can be pieced
together from studies of orthotopic liver transplantation
in rats, dogs, pigs, baboons, and humans of the sequence
of pathologic events which occur when a modified or
unmodified recipient rejects a liver graft (110-113).

In untreated members of all species (the principal
observations have been in dogs), there is a quiescent
phase of at least 2 or 3 days during which only rare small
lymphocytes are found in the tissue spaces of the liver
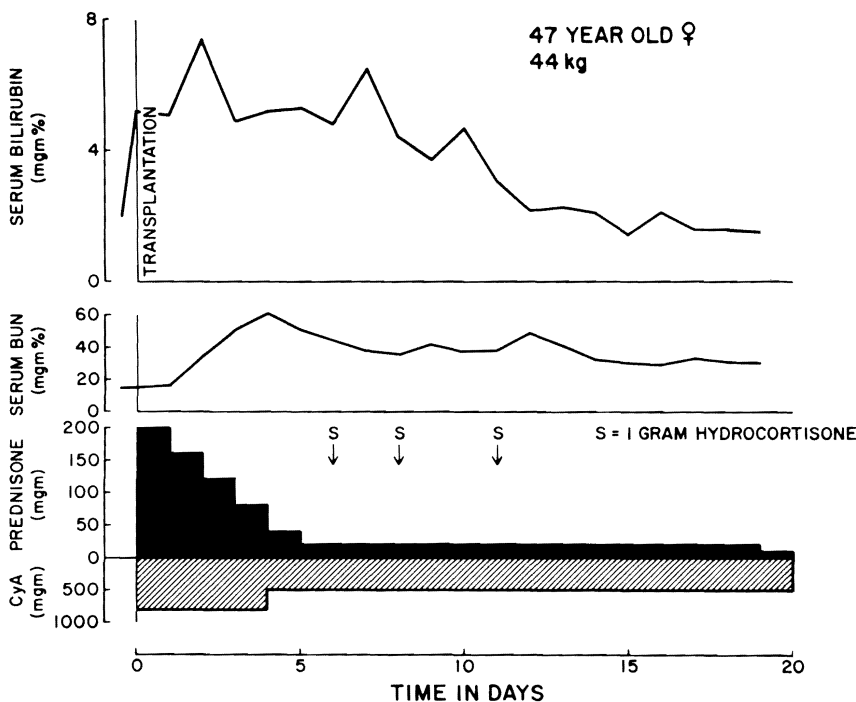

FIG. 5. Double-drug immunosuppres-
sion with cyclosporin A and steroids. The
patient (OT 198) had a hepatoma, α-1-
antitrypsin deficiency, and chronic ac-
tive hepatitis. The reduction of the cy-
closporin A dosage after 4 days was be-
cause of the increasing azotemia. The
boluses of hydrocortisone were given be-
cause of a possibly unwarranted suspi-
cion of early rejection.

FIG. 6. Immunosuppression with cyclosporin A 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 cyclosporin A and replacement with azathioprine between postoperative Days 10 and 15 was because of probable cyclosporin nephrotoxicity. The patient who was of B blood type was given the liver of an A donor.
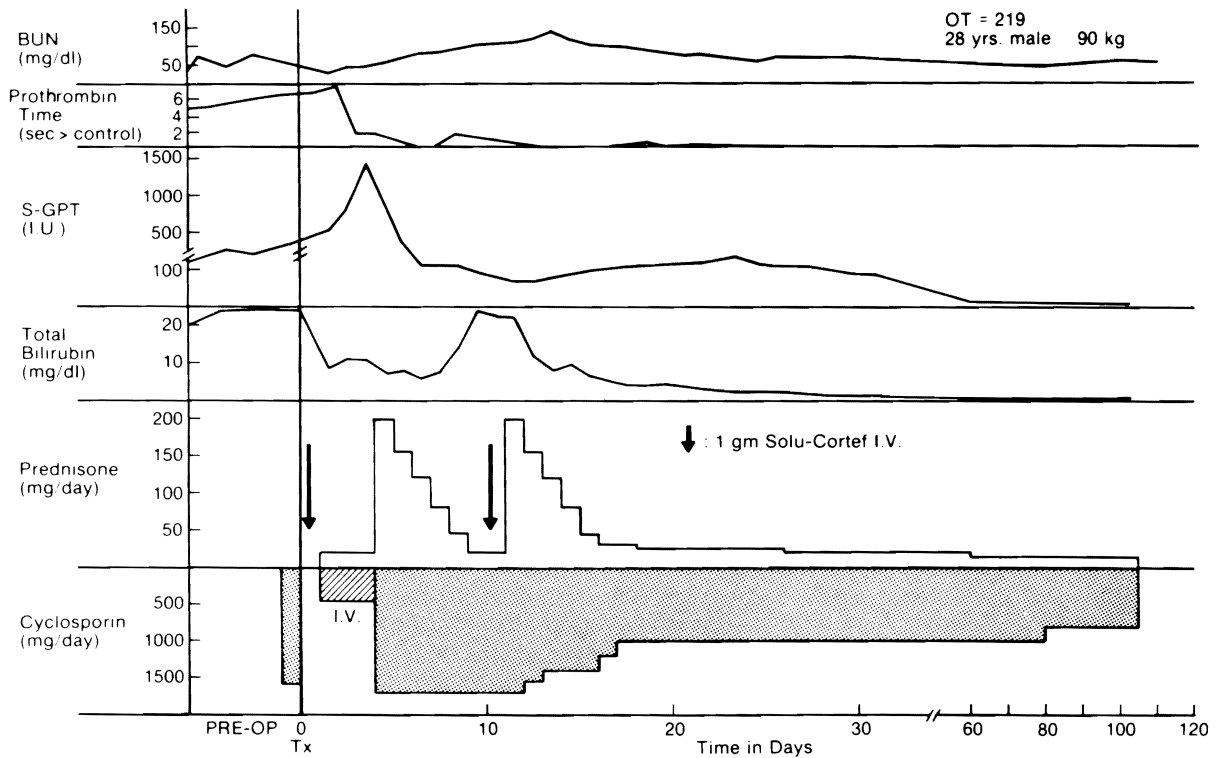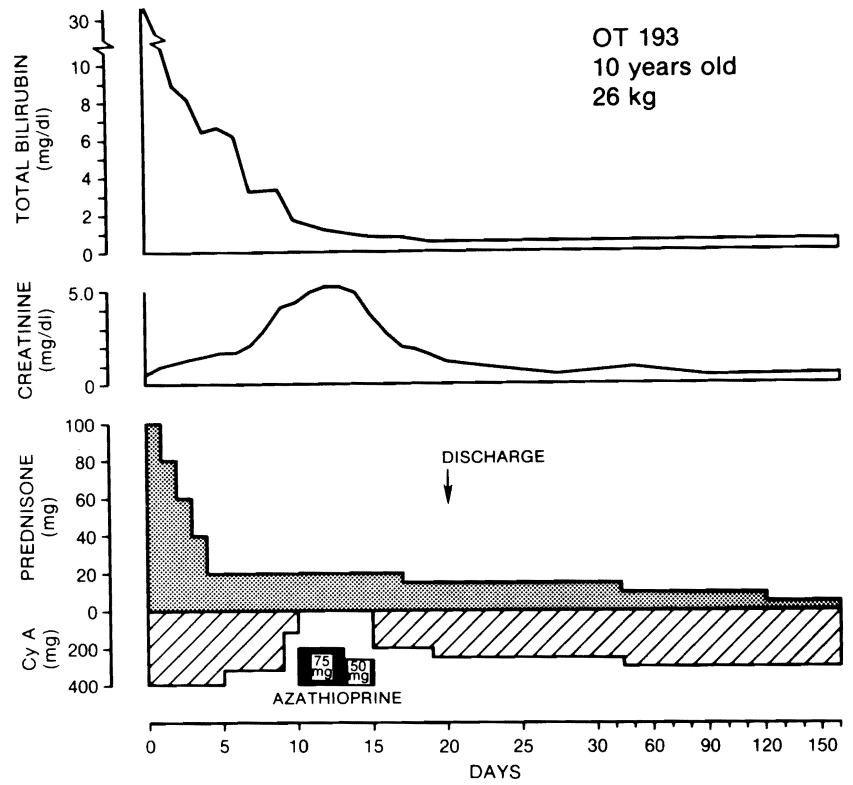
FIG. 7. Deviation from standard steroid therapy in a patient (OT 219) whose perioperative condition was frail. The 5-day burst of postoperative steroids was begun several days postoperatively but had to be repeated when rejection supervened. Before operation, the patient had hepatorenal syndrome and 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 innominant 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. He is at home 5 months after transplantation.

which remain normal except for nonspecific changes. However, during this period, large pyroninophilic cells start proliferating in the paracortical zones of the host lymph nodes. About 3 days after transplantation, lymphoid cells begin to leave portal vein tributaries randomly throughout the graft. The venous endothelium is separated from the basement membrane, and fibrin collects in the subendothelial space. After passing through the vessel wall, lymphocytes accumulate in the portal tracts. Smaller numbers of lymphoid cells migrate through the walls of the central vein and the endothelial lining of sinusoids. These cells invade the space of Disse and some enter between hepatocytes. Immunoglobulins are rare in the cytoplasm of the infiltrating cells at this time.

Associated with cellular infiltration, the cells of many sinusoids disintegrate, blood flow through the liver begins to decrease, and some centrilobular cells die. As the centrilobular necrosis progresses to midzonal necrosis, liver function becomes affected. Inspissated bile appears in surviving bile canaliculi and lipid droplets accumulate in the hepatocytes around the portal tract. Shortly before the death of the untreated recipient, foci of fibrinoid necrosis sometimes occur in the walls of small branches of the hepatic artery associated with deposition of immunoglobulin and complement in the intima and media.

When rejection is mild, as in pigs (115), or is modified by immunosuppressive agents, as in dogs and humans (110, 112–114, 116), destruction of hepatocytes ceases, cellular infiltration diminishes and may disappear, but the central part of the lobular reticulin framework often collapses. Accumulation of bile in surviving centrilobular hepatocytes and in bile canaliculi occurs; the cause of this severe cholestasis is not known and may be secondary to widespread loss or distortion of canalicular microvilli. An alternative possibility has been put forward by Myburgh et al. (111) who drew attention to the progressive hypertrophy and dilatation of smooth endoplasmic reticulum in the centrilobular hepatocytes and suggested that these intracellular changes might be caused by humoral antibody and result in disrupted cholesterol and bile salt metabolism with production of excess lithocholate. In some patients, the larger interlobular bile ducts disappear as modified rejection continues. This phenomenon is characterized by rapid and relentless rise in serum bilirubin (49–51, 116).

As rejection progresses, connecting bands of reticulin are often laid down between the central areas, subdividing the lobules. What triggers progression to hepatic fibrosis in some grafts is unknown; excess lithocholate has been implicated (111). In some patients, cirrhosis is produced. Another characteristic feature of chronic rejection is progressive thickening of the intima of the branches of the hepatic artery in the homograft. The intima contains fat-laden smooth muscle cells and macrophages, and the lumen is narrowed or occluded. These arterial changes occur in many long-surviving liver homografts. The accumulation of immunoglobulins and complement in the altered vessel wall has raised the possibility that this damage is a late manifestation of rejection brought about by circulating antibody. Deposition of immunoglobulins is less striking in hepatic grafts than in transplant kidneys (117), prompting speculation that hepatic rejection was more a phenomenon of cell-mediated immunity (as opposed to damage by circulating antibodies) than has been thought to be the case with rejecting kidney grafts.

Some histopathologic changes in liver homografts may be caused by hepatotoxic drugs, viral hepatitis, or other factors. However, a comparison of changes in human specimens with those in animal homografts emphasizes that the major alterations are immunologic in etiology.

The Clinical Manifestations of Acute Rejection

Rejection as defined by us (32) and Williams and Calne (7) in patients treated with conventional immunosuppression also occurs during treatment with cyclosporin A and steroids. Many patients lose their appetites and become depressed. Fever, vague upper abdominal pain, and ascites are variable. By palpation, grafts are frequently swollen, hard, and mildly tender. Radioisotopes used for liver scanning are poorly concentrated, whether these depend upon parenchymal or reticuloendothelial function. Elevations may occur in serum bilirubin, alkaline phosphatase, and transaminases. Failure of synthetic function is most readily detected by measurements of prothrombin time.

The various manifestations of rejection occur in different combinations, to variable degrees, and at unpredictable times. The resulting patterns have been categorized as "anicteric," "indolent," and "crisis" (32). With a rejection crisis, jaundice can develop with astonishing rapidity, usually just after or accompanied by major rises in transaminases. The insidious indolent rejections have been the most difficult to reverse.

All patterns of graft deterioration are nonspecific. Proven alternative etiologies include ischemic injury, biliary obstruction, cholangitis, hepatitis (B virus, cytomegalovirus, adenovirus, herpes), and drug toxicity. Consequently, diagnostic procedures, often including cholangiography and needle biopsy, must be considered if the postoperative evolution is not satisfactory. In the interim, steroid dosage is temporarily increased and returned to baseline if a diagnosis other than rejection is established. Clinical management is particularly difficult and fraught with error if good initial graft function was not achieved.

A devastating complication of rejection, termed "septic hepatic gangrene," occurred in patients who were treated with azathioprine, ALG, and relatively low doses of prednisone. After days or weeks of slightly abnormal hepatic function, these patients developed massive hepatic necrosis with extremely elevated serum transaminase activities and deterioration of other measures of hepatic function. Raging fevers, bacteremia, and disappearance on liver scans of large portions of hepatic parenchyma signaled regional infarctions within the transplants. Kinking of lobar or segmental hepatic arteries was originally postulated to be responsible for this complication (5), but the most important factor is poorly controlled rejection (32). With diminution in total hepatic blood flow, as was documented in canine experiments by Groth et al. (31), invasion of the ischemic homograft by microorganisms from the adjacent intestinal tract is not surprising.

Study of patients with septic hepatic gangrene and confirmatory observations by Brettschneider et al. (118) after canine and porcine liver transplantations clarified

the interaction between rejection and homograft bacterial colonization. In animal studies, the normally low incidence of positive cultures from liver tissue of dogs and pigs increased after sham operations. When an hepatic ischemic injury was added by performance of simulated autotransplantation, all livers became contaminated, primarily with the same organisms concomitantly present in the upper intestine. Bacterial counts were somewhat lower if the common bile duct was left intact than when the duct was ligated and bile drainage restored by cholecystoenterostomy. The bacterial changes were more pronounced in liver homografts transplanted to unmodified or immunosuppressed animal recipients.

Presumably, any ischemic or necrotic area can become a septic focus, particularly if the host is given immunosuppressive therapy and cannot respond normally to invading microorganisms. The spectrum of resulting infections under conventional immunosuppression has been well studied (32, 119-121). Paradoxically, one of the most important ways to prevent nontreatable liver infection is to protect the graft with potent immunosuppression, especially during the early postoperative period. The second obvious step is to provide systematically designed antibiotic therapy intraoperatively and for several days thereafter.

Acute cellular rejection in grafts sampled by biopsy or at autopsy has been encountered many months or years after transplantation. Some patients were known to have discontinued their medications but others had been given unwise advice about lowering maintenance medications. Increased steroid therapy was given under such circumstances.

CHRONIC REJECTION

The diagnosis of chronic rejection was restricted to patients whose grafts had arterial intimal thickening, hepatic fibrosis, and other findings described previously. These findings are not necessarily time-related since they often develop within the first few months. Clinical manifestations of chronic rejection were not much different from those of chronic liver failure from endstage disease of differing etiologies. Treatment with increased immunosuppression was ineffective.

SURVIVAL AFTER TRANSPLANTATION

The introduction of cyclosporin A and steroids has had such a major influence upon results that patients have been divided into those treated before and after this event. By so doing, it is possible to reexamine several factors whose significance was previously unclear.

PRECYCLOSPORIN ERA (1963 TO 1979)

Between 1963 and the end of 1979, 170 patients had liver replacement. In previous publications, the identifi-

cation of individual recipients by orthotopic transplantation (OT) numbers made it possible for the interested reader to follow their progress from report to report. The same code numbers will be used throughout this review.

In past reports (45, 80, 107), the first 170 recipients were divided into the three successive series summarized in Table 6 and Figure 8. In the first, second, and third of these consecutive groups, 1-year survival was 28.8, 50, and 34.5%.

Of the 56 recipients who survived the first postoperative year, 23 died at the times shown in Table 6. Although 13 of 23 late deaths were in the second postoperative year, deaths occurred as late as 6 years. Of the original 170 patients, 33 (19.4%) are alive after follow-ups of 2½ to 12½ years. Twenty have survived for more than 5 years and four are into the second postoperative decade.

There was an almost equal division in the total period of 1963 to 1979 between adult (≥19 years) and pediatric (≤18 years) recipients. From the sixth month onward, the younger patients had about a 10% survival advantage (Figure 9).
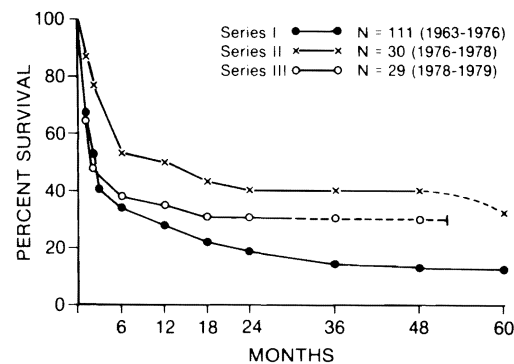
FIG. 8. Survival of three consecutive series of patients treated with orthotopic liver transplantation under conventional immunosuppression. The *dashed lines* in Series 2 and 3 are actuarial projections.
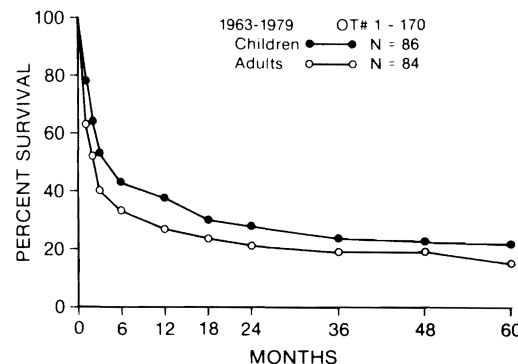
FIG. 9. The life survival of adults vs. children in patients treated with conventional immunosuppression.

TABLE 6. LATE DEATHS IN 170 PATIENTS DURING PRECYCLOSPORIN A ERA (1963-1979)

	No.	Alive after 1 year	Died after 1 year	Time of late death to nearest postop month	Alive now	Years follow-up of survivors
Series 1	111	31 (28.8%)	18	12, 13, 13, 13, 14, 16, 17, 20, 20, 21 25, 26, 28, 30, 36, 41, 54, 72	13	6½-12½
Series 2	30	15 (50%)	4	17, 23, 49, 56	11	4½-5¾
Series 3	29	10 (34.5%)	1	13	9	2½-4¼

Table 7 summarizes the results in the Cambridge-King's College trials from 1968 through early 1980 (53, 122). In this series, 22 (23.7%) of the first 93 recipients lived for at least 1 year, with 11 subsequent deaths during the second to sixth years; the 11 survivors had been followed for 1 to 6 years. The better 1-year survival in the American compared to the English trial (33 vs. 24%) was partly illusory since Calne and Williams accepted for surgery few pediatric patients with whom (Figure 9) our best results were obtained in those years.

Our results in the pediatric age group after transplantation for different indications are given in Table 8. Similar information for adult recipients is provided in Table 9.

CYCLOSPORIN ERA (1980 TO 1982)

The longest follow-ups for our patients treated with cyclosporin A and steroids are only 2⅓ years. During the

TABLE 7. ACTUAL 1-YEAR SURVIVAL[a] IN CAMBRIDGE/KING'S COLLEGE SERIES OF 93 CASES (1968 TO FEBRUARY, 1980)

No.	1 week	6 months	1 year
93	77 (82.8%)	31 (33.3%)	22 (23.7%)

[a] Information from (122). Of the 22 one-year survivors, 11 had subsequently died from 1 to more than 5 years postoperatively. The other 11 were living in their second to sixth postoperative year. An actuarial projection of this data beyond 1 year is depicted in Figure 10.

TABLE 8. INDICATIONS FOR TRANSPLANTATION AND SURVIVAL IN PEDIATRIC PATIENTS (≤18 YEARS) FROM 1963 THROUGH 1979 (PRECYCLOSPORIN A)

	No.	Survival (months)				
		>1	>2	>6	>12	Now[a]
Biliary atresia	51	37 (73%)	27 (53%)	16 (31%)	14 (27%)	7 (14%)
Inborn metabolic errors	13[b]	12 (92%)	11 (85%)	8 (62%)	8 (62%)	6 (46%)
Chronic aggressive hepatitis	13	11 (85%)	10 (77%)	7 (54%)	5 (38%)	3 (23%)
Hepatoma	3[c]	3	3	2	2	0
Neonatal hepatitis	2	1	1	1	1	0
Congenital hepatic fibrosis	2	1	1	1	1	1
Secondary biliary cirrhosis	2[d]	2	2	2	2	1
	86	67 (78%)	55 (64%)	37 (43%)	33 (38%)	18 (21%)

[a] Follow-ups for living patients are 2½ to 12½ years.

[b] Inborn errors

α-1-antitrypsin deficiency	9
Wilson's disease	2
Tyrosinemia	1
Type IV glycogen storage disease	1
	13

[c] Five other patients had incidental malignancies (4 hepatomas and 1 hepatoblastoma) in their excised livers. The principal diagnoses in these five cases were biliary atresia (3 examples), α-1-antitrypsin deficiency (1 example), and congenital tyrosinemia (1 example). The diagnosis of the neoplastic change was known in advance only in 2 of the 5 cases.

[d] Secondary to trauma or choledochal cyst (one each).

TABLE 9. INDICATIONS FOR TRANSPLANTATION AND SURVIVAL IN ADULT PATIENTS (≥19 YEARS) FROM 1963 THROUGH 1979 (PRECYCLOSPORIN A)

	No.	Survival (months)				
		>1	>2	>6	>12	Now[a]
Chronic aggressive hepatitis	33	21 (64%)	17 (52%)	14 (42%)	11 (33%)	7 (21%)
Alcoholic cirrhosis	15	8 (53%)	5 (33%)	4 (27%)	4 (27%)	3 (20%)
Primary malignancy	15[b]	9 (60%)	7 (47%)	4 (27%)	3 (20%)	1 (7%)
Sclerosing cholangitis	7	7	4	2	2	0
Primary biliary cirrhosis	6	3	3	2	1	1
α-1-antitrypsin deficiency	2	1	1	0	0	0
Secondary biliary cirrhosis	2[c]	1	1	1	1	1
Hemochromatosis	1	1	0	0	0	0
Protoporphyria	1	0	0	0	0	0
Budd-Chiari syndrome	1	1	1	1	1	1
Acute hepatitis B	1	1	1	0	0	0
	84	53 (63%)	40 (48%)	28 (33%)	23 (27%)	14 (17%)

[a] Follow-ups for living patients are 2½ to 8½ years.

[b] Seven hepatomas, 5 duct cell carcinomas (Klatskin), 1 cholangiocarcinoma, 1 hemangioendothelialsarcoma, and 1 unclassified sarcoma.

[c] One example each of possible duct hypoplasia and choledochal cyst; both patients had had multiple operations.

first 9 months of 1980, 14 patients entered into this trial at the University of Colorado (108); 2 died during the operation, and 1 died after 19 days. The other 11 patients survived for more than 1 year. Eight are alive after 21 to 28 months. The 1-year survival of 78.6% could have represented a sampling accident. However, at the University Health Center of Pittsburgh, 26 patients were treated in 1981. Five died in the first postoperative month, and additional deaths occurred in the second, third, and fourth months. With follow-ups of 6 months to more than 1 year, the remaining 18 (69.2%) recipients are alive and at home; none has poor hepatic function.

The pattern of predominantly early mortality seen in 1980 and 1981 has continued into 1982. Of the first 27 recipients treated in 1982, 8 died. Six, one, and one of these deaths were in the first, second, and third postoperative months, respectively.

It is too early to assess the rate at which late deaths will occur, since only 18 patients treated with cyclosporin A have reached or passed the 1-year mark. Of these, three died in their thirteenth, sixteenth, and twentieth postoperative months for reasons that will be considered in the next section.

The actuarial survival calculated from the cases in the cyclosporin era studied to date is shown in Figure 10. In comparison to our previous experience in the precyclosporin era and in comparison to the Cambridge-King's College compilation, survival has more than doubled.
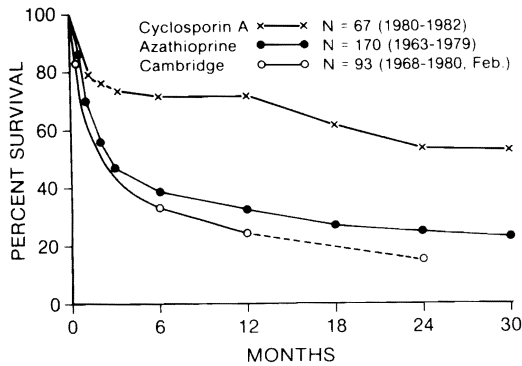
FIG. 10. The actuarial survival of patients treated with cyclosporin A and low-dose steroids compared to the actual 1-year survival obtained under conventional immunosuppression by us (azathioprine) and the workers at Cambridge. The data for the Cambridge curve were obtained from published reports (53, 122).

The results calculated for the first 12 postoperative months have not been different in adults and children (Figure 11). A breakdown of results according to original disease in the pediatric and adult cases is provided in Tables 10 and 11.

The influence of cyclosporin A upon survival in the Cambridge-King's College trials has not been clearly defined, because the drug has not been regularly used and because it was started late in most cases after an initial course of azathioprine and steroids. Nevertheless, improved results have been attributed by Calne et al. (53) to better immunosuppression.

CAUSES OF MORTALITY

PRECYCLOSPORIN ERA

Early Death. The appalling early mortality after liver transplantation has prompted exhaustive clinical-pathologic analyses of our failed cases. Using the OT code numbers of the patients, the results have been reported in such a way that individual assessment of almost every early death in the first 170 cases can be made by the interested reader (43, 45, 80). Mortality figures included the use of grafts damaged by ischemia, massive operative hemorrhage, thrombosis of the reconstituted homograft blood supply, intraoperative cerebral air embolism (44), unsuspected recipient abnormalities (such as prior thrombosis of the portal vein), hopeless anatomical situations created by multiple previous operations, irreversible preexisting debilitation, and (above all) defective biliary tract reconstruction.

With or without such factors, overwhelming infection was frequently a terminal event. At autopsy, histopathologic findings of acute rejection were found in 10 to 15% of cases, prompting speculation that over immunosuppression, especially with prednisone, may have been responsible for unnecessary deaths (43).

When serial biopsies were obtained in later cases (45, 80), this simplistic view had to be revised. Many biopsies contained unmistakable findings of rejection for which the appropriate response had been more steroids. After death caused by infection, the findings of rejection were absent. The conclusion was reached that even after a perfect operation, the unacceptable acute mortality would remain until improved immunosuppression be-
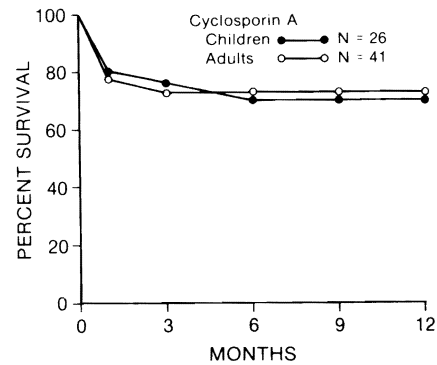

FIG. 11. The 1-year actuarial survival of adults vs. children after liver transplantation under immunosuppression with cyclosporin A and steroids.

TABLE 10. INDICATIONS FOR TRANSPLANTATION IN PEDIATRIC PATIENTS (≤18 YEARS) FROM MID-1980 TO MAY, 1982 (CYCLOSPORIN ERA). FOLLOW-UPS FOR SURVIVORS ARE 1–21 MONTHS

	No.	Living
Biliary atresia[a]	11	8
α-1-antitrypsin deficiency[b]	4	2
Chronic aggressive hepatitis	2	2
Byler's disease[c]	2	1
Secondary biliary cirrhosis[d]	1	0
Budd-Chiari syndrome	1	0
Neonatal hepatitis	1	1
Subacute Wilson's disease[b]	1	1
Tyrosinemia[b]	1	1
Type I glycogen storage disease[b]	1	1
Sea-blue histiocyte syndrome[b]	1	1
	26	18 (70%)

[a] Two had Alagille's syndrome.

[b] Inborn errors of metabolism. The children with tyrosinemia and sea-blue histiocyte syndrome had incidental hepatomas in their cirrhotic livers.

[c] Diagnosis equivocal in one case.

[d] Choledochal cyst with multiple operations.

TABLE 11. INDICATIONS FOR TRANSPLANTATION IN ADULT PATIENTS (≥19 YEARS) FROM MARCH 1, 1980 TO MAY 1, 1982 (CYCLOSPORIN ERA). FOLLOW-UP FOR SURVIVORS WAS 1–27 MONTHS

	No.	Living
Chronic aggressive hepatitis	14	9
Malignancy[a]	9	7
Primary biliary cirrhosis	6	5
Secondary biliary cirrhosis	4	2
2 trauma		
1 Caroli		
1 choledochal cyst		
Sclerosing cholangitis	3	2
α-1-antitrypsin deficiency	2	1
Budd-Chiari syndrome	2	1
Adenomatosis[a]	1	1
	41	28 (68%)

[a] One patient in each group had previous (1 and 4½ years earlier) right hepatic trisegmentectomy. At transplantation, the regenerated left-lateral segment was replaced with a whole liver.

came available. Both nonimmunologic and immunologic complications have continued to cause early deaths in the cyclosporin era albeit at a reduced rate.

Deaths After 1 Year. Assessment of the reasons for late death in older cases may help to predict the spectrum of problems which can be expected in future patients. The causes of mortality after 1 year in patients treated with conventional immunosuppression are listed in Table 12. Recurrent liver failure was responsible for death in ¾ of 23 patients, if the four who died after attempted retransplantation are included. In three patients, the main mortality factor was recurrence of malignancy. One of the late deaths was caused by chicken pox hepatitis during an epidemic on the transplantation ward. The patient (OT 112) whose death was classified under self-abuse was an alcoholic, drug abuser, and derelict who resumed the same life style after transplantation. Fifty-six months after transplantation, he was found unconscious in a ditch in Florida and died of pneumonitis.

The dominant pathologic diagnoses of the 24 first or second grafts which functioned chronically in these 23 patients are listed in Table 13. Chronic rejection was the

most common final diagnosis, followed by biliary obstruction and recurrent cancer. There were two examples each of chronic hepatitis and portal vein thrombosis.

These findings differ from those reported by Calne et al. (53) in 11 patients who died after 1 year; recurrent carcinoma was the main homograft abnormality in five patients. In the other six grafts, there was biliary sludge and cholangitis. Chronic rejection was not mentioned. Our findings suggest that ongoing problems with immunologic control will continue to take a gradual toll long after successful transplantation, whereas interpretation of the pathologic findings in the English recipients is different. Clarification of this divergence of observations will be important.

CYCLOSPORIN ERA

Twenty-two of the 67 patients treated in 1980 to 1982 died. Three deaths were after 1 year, and the other 19 were early.

Early Death. Fourteen of 19 early deaths, including two on the operating table, occurred in the first postoperative month. In the second, third, and fourth postoperative months, there were 1, 1, and 2 more death(s), respectively (Table 14).

Eight deaths were directly attributable to preexisting anatomic conditions including multiple previous operations (OT 178), earlier portacaval shunt (OT 180), and right-to-left pulmonary shunts secondary to the liver disease (systemic arterial pO_2 was 30 mm Hg) which did not subsequently close (OT 203). However, the most important abnormalities were in liver blood supply or the vena cava (OT 217, 220, 228, 232, 233) which had not been diagnosed preoperatively. At operation, it was not possible to vascularize adequately homografts in 4 of these latter 5 recipients. In the fourth (OT 233), the superior vena cava was discovered at autopsy to have been replaced by two innominate veins which descended into the abdomen and emptied into the inferior vena cava below the renal veins. During the vena caval cross-clamping of the anhepatic phase of transplantation, the child developed an acute superior vena caval syndrome with irreversible brain injury.

Eight early deaths were technical and thus avoidable, including the use of inadequately preserved grafts (OT 185 to 188), hepatic artery thrombosis (OT 183, 225), and complications of biliary tract reconstruction (OT 201, 208). Problems in preservation were encountered in the first four cases at a new institution.

Deaths After 1 Year. Patients died late (Table 14) of recurrent Budd-Chiari syndrome (OT 174), recurrent duct cell carcinoma (OT 176), and after retransplantation after a primary graft was chronically rejected (OT 181).

THE POSSIBILITY OF RETRANSPLANTATION

In assessing ways of reducing patient mortality, it was obvious almost from the beginning that aggressive attempts at retransplantation offered the only chance of survival for many patients whose first grafts failed either early or late. Such efforts, which have been made in 27 patients (2 of the 27 also were given third grafts) since 1968 (Figure 1), usually have born bitter fruit. The few successes that have been achieved have served as an important stimulus for further trials.

TABLE 12. CAUSES OF 23 DEATHS[a] AFTER 1 YEAR OF PATIENTS TREATED WITH AZATHIOPRINE (OR CYCLOPHOSPHAMIDE), PREDNISONE, AND ALG

Cause of death	No.
Predominant liver failure	8
Liver failure plus sepsis	5
Early after retransplantation	4[b]
Recurrent cancer	3
Predominant sepsis	2
Self-abuse	1
Total	23

[a] Deaths were usually caused by multiple problems, but only the single most important factors are listed.

[b] Infection invariably contributed to death after retransplantation. In addition, two patients had lethal technical complications and two more had rejection.

TABLE 13. PRINCIPAL PATHOLOGIC CHANGES IN 24 LIVER GRAFTS THAT HAD FUNCTIONED UNDER CONVENTIONAL IMMUNOSUPPRESSION FOR 339 TO 2,190 DAYS BEFORE THE DEATH OF THE PATIENT.[a] IN 5 OF THE 24 GRAFTS, TWO DIAGNOSES WERE GIVEN

Pathologic changes	No.
Chronic rejection	11
Biliary obstruction	6
Recurrent cancer	4
Chronic hepatitis	2
Portal vein thrombosis	2
Chronic cholangitis	1
Chicken pox, hepatitis with necrosis	1
Early alcoholic hepatitis	1
Diffuse fatty changes with centrilobular necrosis	1
Total	29

[a] These 24 grafts were from the 23 patients who died after 1 year (Table 12). Seven of the 23 patients were given two livers, but chronic function (682 plus 403 days) was obtained from both organs in only one case (OT 103); in the other six, the pathologic changes are tabulated only for the long-surviving grafts. Most of the specimens were obtained at autopsy, but a few were from surgical or closed biopsies.

TABLE 14. MAJOR CAUSES OF 22 DEATHS IN CYCLOSPORIN ERA

OT	Age	Sex	Pathology before transplant	Major causes of death	Postoperative month of death
174	20	F	Budd-Chiari syndrome, portacaval shunt	Recurrent Budd-Chiari syndrome, liver failure, sepsis	16
176	33	F	Sclerosing cholangitis, duct cell carcinoma	Recurrent duct cell cancer	13
178	37	M	Secondary biliary cirrhosis, gunshot wound to liver	Operative	1
180	40	M	Sclerosing cholangitis, portacaval shunt	Operative	1
181	16	F	Budd-Chiari syndrome	1st graft: chronic rejection 2nd graft: acute rejection 3rd graft: liver failure, renal failure	20
183	8	F	Byler's disease	Hepatic artery thrombosis	1
185	56	M	Klatskin's tumor	Graft necrosis, sepsis	1
186	17	F	Secondary biliary cirrhosis, Caroli's disease	Graft necrosis, sepsis, bile leakage	1
187	37	F	Chronic aggressive hepatitis, portacaval shunt	Graft necrosis	1
188	46	M	Chronic aggressive hepatitis	Graft necrosis, sepsis	1
196	36	F	Chronic aggressive hepatitis	Systemic aspergillosis	1
201	4	M	α-1-antitrypsin deficiency disease	Hemorrhage during exploration of intrahepatic abscess and mycotic aneurysm	2
203	18	M	α-1-antitrypsin deficiency disease, extensive pulmonary A-V shunt	1st graft: graft hypoxia due to pulmonary A-V shunt 2nd graft: graft hypoxia; rejection 3rd graft: graft hypoxia; cerebral hemorrhage	4
208	42	M	Chronic aggressive hepatitis, α-1-antitrypsin deficiency disease, primary biliary cirrhosis	Hemorrhage from hepatic artery, bile duct fistula	3
215	39	F	Primary biliary cirrhosis	Rejection; sepsis due to duodenal stump leakage after total gastrectomy for stress ulcer hemorrhage	3
216	2	F	Biliary atresia, Kasai operation	Chronic rejection, liver failure, sepsis	4
217	44	M	Chronic aggressive hepatitis, splenectomy, portal vein hypoplasia[a]	Operative	1
220	8	F	Secondary biliary cirrhosis, choledochal cyst, portal vein thrombosis[a]	1st graft: graft necrosis 2nd graft: cerebral hemorrhage	1
225	44	M	α-1-antitrypsin deficiency disease	1st graft: rejection, hepatic artery thrombosis 2nd graft: rejection, sepsis	1
228	3	M	Alagille's syndrome, absent hepatic artery[a], hypoplastic portal vein[a]	Graft necrosis	1
232	6	F	Biliary atresia, Kasai operation, absent inferior vena cava[a], malrotation[a]	Diffuse clotting in graft	1
233	2½	F	Biliary atresia, Kasai operation, absent superior vena cava with innominate drainage into inferior vena cava[a]	Perioperative brain death	1

[a] Anomalies or abnormalities not known before operation.

The attempts at retransplantation in 27 patients are summarized in Table 15. Eighteen of 27 second transplantations were within the first 3 months, 3 were between 3 and 12 months, and 6 were after 12½ to 29 months.

Extended subsequent survival occasionally was achieved with early and later retransplantation. The fate of six patients whose lives were significantly prolonged is summarized in Table 16. Much of life for the first four recipients was a nightmare of morbidity because of the combination of high steroid needs and slowly failing graft function. However, the two patients who had successful retransplantation in the cyclosporin A era, 1 and 3 weeks after primary grafting, have had perfect results and are at home 6 and 12 months later on daily prednisone doses of 5 and 15 mg per day, respectively. In the first patient, the primary graft had developed a huge fungus abscess; in the second patient, the first graft had been rejected.

The performance of retransplantation has sometimes 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.

THE INFLUENCE OF ORIGINAL DISEASE UPON RESULTS

Evaluation of the influence on survival of preexisting hepatic disease is complicated by the fact that many patients have more than one diagnosis (Table 17). Ten (14.9%) of our last 67 patients had two coexisting hepatic

TABLE 15. ATTEMPT AT RETRANSPLANTATION IN 27 PATIENTS[a, b]

	No.	Months between first and second transplantation	Months survival after second transplantation
Conventional immuno-suppression	21	<1 × 9 patients, 1¼, 2, 2¼, 3, 3½, 5¼, 6, 12½, 16½, 22½, 27, 29	<1 × 11 patients, 1, 1, 1⅓, 1½, 1¾, 2, 6, 12, 13, 16
Cyclosporin—Steroids	6	<1 × 5 patients, 19	<1 × 3 patients, 3½, 6[c], 12[c]

[a] Two of the 27 had third transplantations, 1 and 7½ weeks after second transplantation had failed.

[b] One patient had a chimpanzee heterograft on the second occasion.

[c] Alive.

TABLE 16. TIME OF RETRANSPLANTATION IN SIX PATIENTS WHO SUBSEQUENTLY LIVED FOR >6 MONTHS

OT No.	Duration of first graft	Survival in months after second graft
16	2 months	11
98	5¼ weeks	16
103	22½ months	13
156	2 weeks	6
191	3 weeks	12[a]
209	1 week	6[a]

[a] In cyclosporin series, both alive.

TABLE 17. PATIENTS IN CYCLOSPORIN A SERIES (67 CASES) WITH MULTIPLE DIAGNOSES

OT No.	Main diagnosis	Other diagnosis
176	Cholangiocarcinoma	Sclerosing cholangitis
188	Chronic aggressive hepatitis	Heterozygous α-1-antitrypsin disease
198	Hepatoma	α-1-antitrypsin disease, chronic aggressive hepatitis
206	Tyrosinemia	Hepatoma, diagnosed at previous operation
208	Chronic aggressive hepatitis	α-1-antitrypsin disease
218	Type I glycogen storage disease	Multiple hepatic adenomas
222	Sea-blue histiocyte syndrome	Hepatoma, diagnosed at previous operation
225	α-1-antitrypsin disease (Pi ZZ)	Hemachromatosis
227	Hepatoma	Chronic aggressive hepatitis
234	Hepatoma	Chronic aggressive hepatitis

diseases; however, in most of our analyses (Table 8 to 11), only the most important diagnosis was tabulated.

No disease for which transplantation has been used can be categorically excluded for further trials. This can be appreciated by examination of results with different kinds of disease in pediatric and adult patients before and after the introduction of cyclosporin A (Tables 8 to 11).

Nevertheless, special problems can be expected in treating some hepatic diseases. In the past, some patients with biliary atresia died because of unexpected anomalies which jeopardized performance of a technically satisfactory transplantation (32); specific examples are listed in Table 14.

Noncompliance may be a problem in patients treated for Laennec's cirrhosis. Of our first nine patients with alcoholic cirrhosis, eight died too soon to evaluate this potential problem (123). There were several subsequent successes (Table 9); only one recipient returned to toxic drinking.

THE SPECIAL PROBLEM OF HEPATIC MALIGNANCY

The possibility that immunosuppression may accelerate metastatic tumor growth has been recognized (32). Evaluations of transplantation in treating hepatic malignancies were made in 1981 by Iwatsuki et al. (124) and by Calne (122). Although recurrent disease exceeded 50% in both series, the results did not allow definitive recommendations about continuation of these efforts.

Our case material has been divided into three groups. In the first category were three children whose livers contained malignant tumors (2 hepatocellular cancers, 1 hepatoblastoma) that had not been suspected preoperatively (Table 18). The two recipients who survived operation have no evidence of recurrence after 4¼ to 12½ years. These observations suggest that malignancies can be cured by liver replacement.

In the second category were eight patients, all treated early in our experience, who died less than 1 month after liver replacement for hepatic or duct cell cancer (Table 19). From this case collection, it was possible to determine by autopsy studies the frequency with which extrahepatic tumor spread had been missed in preoperative evaluation. Only 1 of the 8 recipients had metastases.

Twenty-two additional patients, including one (OT 176) whose neoplastic lesion was missed at the initial pathologic examination, lived long enough to evaluate the influence of transplantation upon the malignancy (Table 20). The first 12 were treated in the precyclosporin era; nine recipients developed metastases. A tenth patient with an unclassified sarcoma had extrahepatic metastases at transplantation, and she is well 5½ years later with no clinical evidence of advancing disease. Five patients survived for longer than 1 year; even for those who eventually died of metastases, the extension of useful life seemed to be worthwhile.

Ten more patients have been treated in the cyclosporin era (Table 20). Three had duct cell carcinomas (one with sclerosing cholangitis); one of whom (OT 185) died early without evidence of residual cancer. The second patient (OT 176) died of metastatic cholangiocarcinoma after 1 year. The third (OT 200) is alive in the ninth postoperative month and has metastases. All patients with hepatocellular carcinoma are alive. The tumors were enormous in three cases. In the other four, the lesions were smaller but could not be resected with conventional techniques because of coexisting cirrhosis. It seems likely that selected patients with hepatic or possibly biliary duct malignancies can be effectively treated with transplantation; however, no patient with duct cell carcinoma has ever been cured (53, 122, 124). The prospects may be more favorable for young patients whose hepatocellular cancers could be treated with conventional partial hepatectomy were it not for coexisting cirrhosis.

Heroic efforts may be justifiable for patients with the recently described "fibrolamellar hepatoma" which is

TABLE 18. PATIENTS TREATED FOR ENDSTAGE BENIGN LIVER DISEASE WHOSE REMOVED LIVERS CONTAINED AN UNSUSPECTED PRIMARY LIVER MALIGNANCY AS WELL. ALL WERE TREATED WITH AZATHIOPRINE, PREDNISONE, AND ALG

Patient	Age (yr)	Sex	Primary indication for transplant	Incidentally found liver malignancy	Survival	Tumor recurrence
OT 33	3	F	Biliary atresia	Hepatoma	Alive 12½ years	No
OT 80	7	F	Biliary atresia	Hepatoma	Operative death	—
OT 142	5	F	α-1-antitrypsin deficiency	Hepatoblastoma	Alive at 4½ years	No

TABLE 19. PATIENTS WITH KNOWN PRIMARY LIVER MALIGNANCY WHOSE EARLY DEATH AFTER TRANSPLANTATION PRECLUDED OBSERVATIONS OF THE COURSE OF THE MALIGNANCY. ALL WERE TREATED WITH CONVENTIONAL IMMUNOSUPPRESSION BEFORE 1975

Patient	Age (yr)	Sex	Diagnosis	Survival (days)	Metastases at autopsy and locations	Main cause of death
OT 2	48	M	Hepatoma, cirrhosis	21	No	Pulmonary emboli, sepsis
OT 3	68	M	Bile duct carcinoma (Klatskin's tumor)	8	No	Sepsis, pulmonary emboli, gastrointestinal bleeding
OT 4	52	M	Cholangiocarcinoma cirrhosis	5	Bone, lung, kidney, lymph nodes	Pulmonary emboli, hepatic failure, pulmonary edema
OT 5	29	F	Hepatoma	24	No	Sepsis, bile peritonitis, hepatic failure
OT 6	29	M	Hepatoma	7	No	Hepatic failure, sepsis
OT 7	24	F	Hepatoma	17	No	Pneumonitis
OT 25	45	M	Hepatoma	29	No	Bile peritonitis, sepsis, hepatic failure
OT 79	60	M	Bile duct carcinoma (Klatskin's tumor)	19	No	Hepatic failure due to biliary obstruction

characterized by indolent primary growth and late metastases (125, 126). Three of our last 10 patients with hepatic malignancy have had this diagnosis. In all three, the tumors were massive. In one patient who was treated more than 2 years ago (OT 172), a large tumor thrombus originating in a hepatic vein was extracted at operation from the vena cava and right atrium. He is tumor-free. A second patient, who also is tumor-free after almost 1 year (OT 194), had complete obstruction of the portal vein by tumor. A third patient treated 2 months ago (OT 231) developed recurrence in the residual lateral segment after a right trisegmentectomy 4½ years earlier. The tumor-laden residual segment was replaced with a new liver with a satisfactory result thus far.

At the moment, the prospects for cure seem bleak for patients with duct cell carcinomas, and scarcely better for those with unresectable conventional hepatocellular carcinomas. Patients with smaller malignancies in livers with other diseases, or those with fibrolamellar hepatomas may be more susceptible to treatment.

RECURRENCE OF OTHER HEPATIC DISEASES

In pediatric recipients (Tables 8 and 10), recurrence of nonneoplastic hepatic disease has not been observed. A special feature of transplantation in the younger age group has been the metabolic "cure" of at least five and possibly six so-called inborn errors (Tables 8 and 10) (126–131). With cyclosporin A, the prospects of using transplantation to treat children with a variety of diseases has been heightened because chronic high-dose steroid therapy can be avoided (132).

That the original disease can be recapitulated in homografts was demonstrated in adult recipients. Two patients with Australia antigenemia and chronic aggressive hepatitis redeveloped their original disease and died (133). Other patients with recurrent or newly developing

Australian antigenemia have lived for as long as 8 years with the carrier state. It has been our policy to treat HBsAG positive transplant recipients with hyperimmune globulin postoperatively. Antigenemia has returned in every case, sometimes after becoming undetectable for months. With such treatment, Johnson et al. reported permanent antigen clearing in a patient (134).

Recurrent primary biliary cirrhosis (135) as described in the English series was not seen in five grafts studied at autopsy after a few days to more than 6 months, and five patients still living have had no evidence of recurrence in spite of the reappearance of antimiochondrial antibodies in the longest survivors (2¼ and almost 4 years).

We have treated three patients for the Budd-Chiari syndrome. One (OT 174) developed the same disease in the graft and died after 15 months. The terminal course of this patient was triggered by unwise discontinuance of anticoagulant therapy in preparation for a closed liver biopsy. Calne et al. (53) reported a similar occurrence.

THE INFLUENCE OF PREVIOUS OPERATIONS

The technical problems engendered by prior surgery have been so great that the Cambridge-King's College Team consider multiple earlier operations as a relative contraindication to transplantation. However, the majority of candidates evaluated by us and the English workers have had previous operations. The influence of this factor was evaluated in the first 40 patients treated with cyclosporin A and prednisone (Table 21) in whom the results were more analyzable than in our earlier cases.

Fourteen of 40 recipients had major procedures on portal triad structures (Table 21) including six portal-systemic shunts and five biliary duct reconstructions. The risk of death in the first postoperative month was double that in patients with lesser or no earlier operations. There were two operative deaths (OT 176 and 180) (Table 21) including one that occurred while trying to

TABLE 20. PATIENTS WITH PRIMARY HEPATIC MALIGNANCY. THE DIAGNOSIS OF NEOPLASIA WAS KNOWN IN ADVANCE OF TRANSPLANTATION EXCEPT IN OT 176. POSTOPERATIVE SURVIVAL WAS AT LEAST 2 MONTHS FOR ALL BUT ONE PATIENT

Patient	Age (yr)	Sex	Diagnosis	Survival (months)	Metastases	Malignancy factor in death
			Precyclosporin Era			
OT 8	1⁷⁄₁₂	F	Hepatocellular cancer	>13	Brains, lungs, liver other abdominal organs	Main
OT 14	16	F	Hepatocellular cancer	>14	Diaphragm, retroperitoneal space, liver, pancreas	Major
OT 15	43	M	Hepatocellular cancer, cirrhosis	>11	Lungs, liver, diaphragm	Main
OT 23	15	M	Hepatocellular cancer	>4	Brain, lungs, liver, retroperitoneal space	Main
OT 26	11	F	Biliary atresia, hepatocellular cancer	>2	Lung	None
OT 45	53	M	Hemangioendothelial sarcoma	>2	Brain, lungs, liver, spleen, pericardium, peritoneum, stomach, pancreas, kidney	Main
OT 78	48	M	Bile duct carcinoma (Klatskin's tumor)	>24	Liver, bile duct at reoperation. No autopsy	Main
OT 90	41	M	Bile duct carcinoma (Klatskin's tumor)	>54	Bile duct, liver, duodenum at reoperation No autopsy	Main
OT 102	51	F	Bile duct carcinoma (Klatskin's tumor)	>2	None	None
OT 111	9	F	Tyrosinemia, hepatocellular cancer	>3	Microscopic metastasis in the lung and paraaortic lymph nodes at autopsy	Minor
OT 114	27	F	Sarcoma (undetermined cell type) of liver invading diaphragm, metastasis to right lung and peritoneum	>68 (Alive)	Grossly fine intraabdominal and pulmonary metastases at time of transplantation which have been quiescent for 5½ years	Alive
OT 121	32	F	Hepatocellular cancer	>5	None	None
			Cyclosporin Era			
OT 172	24	M	Hepatocellular cancer[a]	>27	None	Alive
OT 176	33	F	Sclerosing cholangitis, duct cell carcinoma[b]	>12	Liver, duct, peritoneum	Main
OT 185	56	M	Duct cell carcinoma (Klatskin's tumor)	>½	None	None
OT 194	26	M	Hepatocellular cancer[a]	>11	None	Alive
OT 198	47	F	α-1-antitrypsin disease, cirrhosis, hepatocellular cancer	>9	None	Alive
OT 200	27	M	Duct cell carcinoma (Klatskin's tumor)	>8	Liver, operative wound	Alive
OT 206	2	F	Tyrosinemia, hepatocellular cancer	>7	None	Alive
OT 227	53	M	Cirrhosis, hepatocellular cancer	>3	None	Alive
OT 231	23	F	Hepatocellular cancer[a], previous right trisegmentectomy	>2	None	Alive
OT 234	24	F	Hepatocellular cancer, cirrhosis	>1	None	Alive

[a] Fibrolamellar.

[b] Diagnosis of cancer missed in surgical specimen, but diagnosed at surgical margin and within the native liver by reexamination 9 months later.

TABLE 21. INFLUENCE OF PREVIOUS MAJOR HEPATOBILIARY SURGERY[a] UPON RESULTS IN 40 CONSECUTIVE CASES (CYCLOSPORIN ERA)

	No.	Survival (months)		
		>1	>2	>6
Previous major operation(s)[a]	14	10	10	10
No major operation[b]	26	22	21	19

[a] Six portal-systemic shunts (5 portacaval, 1 distal splenorenal), 5 bile duct reconstructions, and 3 portoenterostomies (Kasai).

[b] Previous exploration, open liver biopsy, cholecystectomy, T-tube insertion, and splenectomy were not counted as major prior procedures although the resulting vascular adhesions were usually troublesome. Twelve of the 26 patients had one or more of these "minor" previous operations including 4 cholecystectomies, 3 T-tube insertions, and 1 splenectomy.

take down a portacaval shunt. The portal vein after portacaval shunt (especially side to side) may have suboptimal length and can be so sclerotic that suturing is difficult or impossible. For patients who survive the first postoperative month, the background of previous major operations was no longer a factor (Table 21). These results suggest that a prudent decision may be against transplantation in patients with a complex surgical history, but that a "clean abdomen" is not a criterion of selection.

THE OPTION OF AUXILIARY LIVER TRANSPLANTATION

The alternative to orthotopic liver transplantation is transplantation of an extra liver (auxiliary transplanta-

tion) without removal of the diseased native organ. Clinical trials have been discouraging, as summarized by Fortner et al. (136) from the compiled world experience. Of nearly 50 well-documented auxiliary transplantations, only one was an unequivocal success. Subsequently a report from Paris described a second success (137).

Our opinion has been that auxiliary liver transplantation should be restricted to patients with potentially reversible liver disease. In such a situation, the extra liver could be construed as a temporary support organ which can be removed later. However, we have encountered increasing numbers of patients whose portal vein has clotted in the hepatic hilum, making it technically impossible to consider liver replacement. Other candidates are those with extensive previous surgery in the right upper quadrant. Such patients can theoretically be helped by an auxiliary liver transplantation, particularly when the superior mesenteric vein or other distal tributories to the main portal circulation are still open. The optimal conditions for vascularization of an auxiliary liver graft require input from the portal circulation (2, 32, 138, 139), largely because of its high concentrations of endogenous hormones.

DETERMINANTS OF THE FUTURE

THE QUESTION OF FINANCING

Through 1980 in the United States, almost all liver transplantations were performed in the Clinical Research Centers (CRC) supported by the National Institutes of Health. The fraction of the per case cost born by this government agency shrank from year to year because of the increasing willingness of many third party insurance carriers to pay for part or all of the service. Third party payments were collected by the institution and remanded back to the National CRC headquarters which included such collections as part of the total grant funding. In the last years of the program at the University of Colorado, approximately 85% of CRC expenditures for liver transplantation were paid for in this way. By having CRC support for the other 15%, it was not necessary to screen candidates for their ability to pay. This creative practice of federal and private cost sharing was conceived and made practical by Dr. William DeCaesare, Director of the Clinical Research Center Division, Bethesda, Md. Thanks to the administrative leadership that flowed from DeCaesare's office for more than 2 decades, almost all modern-day techniques of immunosuppression and transplantation of all organs, beginning with the kidney, were developed on CRC units.

However, it is not reasonable to look indefinitely to the CRC for support. So far, none of the liver recipients at the University Health Center of Pittsburgh has been treated on the pediatric or adult CRC. The principal financing for their care has been from health insurance programs or, less commonly, from private sources including community fund raising. The collection rate for bills has been greater than in the Colorado experience. With the exception of Blue Cross/Blue Shield and some health maintenance organization programs, the major health insurance companies have willingly accepted their re-

sponsibility for liver transplant candidates providing they were forewarned. The patterns of support from Blue Cross/Blue Shield have been irregular, probably because of their close association with MediCare.

It is ironic that government decisions or opinions have impeded the movement of liver transplantation to the private sector of medicine. A pronouncement by a state or federal official of MediCare to the effect that liver transplantation is "experimental" and not fundable has often been the basis for a similar decision by regional officials of Blue Cross and/or Blue Shield or by a cost-conscious health maintenance organization. Even so, a rapidly growing number of state (or Blue Cross) agencies (including those in Pennsylvania, New York, and New Jersey) have classified liver transplantation as a service.

In spite of the advantage of a preexisting federally funded organ procurement network in the United States as part of the End Stage Renal Disease Program, the financing of liver procurement is not on a solid base. There are no formal guidelines about how to proportion the extra costs of removing extrarenal organs from a multiple organ donor, or how to ensure against the potential malpractice and other liability that could be incurred. Etna Life Insurance Company, the carrier for the National Kidney Procurement Program, recently drew attention to these policy gaps in a document that had a chilling effect on some transplant coordinators.

The approximate average cost of a liver transplantation in Pittsburgh has been $55,000 (range $23,000 to $150,000). The procedure offers hope of genuine rehabilitation. Dying of endstage liver disease with no hope of real recovery may be even more expensive. O'Donnell et al. (140) reported from Boston that the average cost of nonsurgical treatment of patient for variceal hemorrhage was $35,000. The use of any operative procedure increased the total to $53,000. In many of our patients, the expenses incurred during repeated hospitalizations before transplantation dwarfed those incurred by transplantation itself.

THE POTENTIAL INFLUENCE OF TRANSPLANTATION UPON THE PRACTICE OF HEPATOLOGY

Five to 10 years from now, we believe that every major center for the treatment of liver disease will have either transplantation capabilities or direct access to this kind of service. The surgical techniques are within the grasp of many practicing surgeons. The frequency with which liver transplantation can be used will be great although this has not been properly assessed. Our estimate is that at least 20 centers will be required in the United States.

Knowledge that the provision of new liver tissue is a realistic objective at the end of the line will influence decisions about treatment. It will be increasingly important to avoid major and often futile surgical operations that jeopardize ultimate candidacy for transplantation. Fortunately, there are alternative approaches. Sclerosing therapy for the control of variceal hemorrhage instead of portal diversion has become increasingly accepted. "Interventional radiologists" often have been able to ameliorate duct strictures in sclerosing cholangitis and

other diseases as effectively as can surgeons at open operation. When procedures such as porticoenterostomy (Kasai) are performed in infants with biliary atresia, it will be worthwhile to avoid deviations from the standard Roux-Y technique and multiple reoperations which make transplantation difficult or impossible.

The presence of regional units undoubtedly will move the timing of transplantation forward in the course of the disease. The fact that there has been a very high preoperative mortality of patients accepted as candidates for new livers is an indication of the lateness of referrals. Throughout the years, many others have reached the operating room in such appalling condition that there was little hope of survival.

An avalanche of new scientific information should become available to hepatologists and surgeons as the result of progress in transplantation. Much has already been learned about the synthesis of proteins whose origin was not previously clear (2, 9, 141–143). Further improvements in surgical techniques and immunosuppression will increase the harvest. The history of medicine is that what was inconceivable yesterday and barely achievable today often becomes routine tomorrow.

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