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Prog. Allergy, vol. 38, pp. 366–394 (Karger, Basel 1986)

Liver Transplantation in the Ciclosporin Era¹

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The concept of liver transplantation is a relatively recent one. The first descriptions of liver replacement in experimental animals were published less than 25 years ago [1, 2] and the first attempt at clinical liver transplantation was not made until March 1, 1963 [3]. However, the great avalanche of human liver transplantations worldwide did not begin until 1980, just about 5 years ago. A number of factors contributed to the growing interest in and success with orthotopic liver transplantation, but, of these, the most important by far was the introduction of the new immunosuppressive agent, ciclosporin. In the following sections, the influence of this drug as well as other factors which conspired to make liver transplantation practical will be described. The principal topics to be considered will be immunosuppression, tissue matching, improvements in surgical techniques, and advances in organ procurement and preservation.

Immunosuppression

The possibility of obtaining truly long survival after liver transplantation between outbred mongrel dogs was demonstrated more than 20 years ago [4]. From a series of more than 100 canine experiments, 10 dogs under treatment

¹Supported by Research Grants from the Veterans Administration and Project Grant No. AM-29961 from the National Institutes of Health, Bethesda, Md.

with azathioprine lived for 4 postoperative months, after which their drug therapy was discontinued. A number of these animals lived on for long periods [5], and one did not die until more than 10 years later. Within 2 years, similar results were obtained with heterologous antilymphocyte serum (ALS) and its globulin derivative (ALG) [6].

Proof of the feasibility of liver replacement under these difficult laboratory conditions was the great stimulus for the first clinical trials and for persistence in these trials in spite of repeated early failures. The first extended survival of a human liver recipient was accomplished in the summer of 1967 [7], and the longest survival of any patient in the world today is now more than 15 years. This recipient whose original disease was biliary atresia with an incidental hepatoma was treated with azathioprine, prednisone, and ALG.

Clinical Immunosuppressive Regimens before Ciclosporin

With Renal Transplantation

The various drug regimens that have made whole liver transplantation feasible were worked out with the simpler model of renal transplantation (table I). The first step was the use of azathioprine as the sole or principal immunosuppressive agent in the Boston trials of 1962 [8]. There were no long survivors and since that time, it has been recognized that cadaver organ transplantation could rarely, if ever, be successful using azathioprine alone.

The so-called modern era of whole organ transplantation began in 1962 and 1963 when it was realized that azathioprine and steroids had at least additive, if not synergistic, actions [9]. With the introduction of this so-called double-drug therapy which was quickly adopted in at least three other centers [10–12], significant numbers of patients began to emerge from renal transplantation clinics with chronically functioning grafts [13]. However, satisfactory results then and for more than a decade were obtained only with living related donors. The morbidity and mortality from the transplantation of cadaveric kidneys were excessive and the rate of graft function at one year hovered at the 50% range for many years [14].

The addition of antilymphocyte globulin (ALG) as a third and short-term immunosuppressive adjunct [6, 15] improved the results in most centers in which this expedient was tried. However, the usefulness of ALG was limited by the facts that the drug could not be standardized, that it had a number of undesirable side effects, and that its discontinuance often was followed by rejection [5, 15]. Nevertheless, the role of ALG therapy probably

Table I. Immunosuppressive drug regimens and adjuncts for kidney transplantation and applied later for extrarenal organs

Agents	Year described and reported	Place	Deficiencies	Used for livers
Azathioprine	1962 [8]	Boston	ineffective, dangerous	no
Azathioprine-steroids	1963 [9]	Denver	suboptimal	yes
Thoracic duct drainage as adjunct	1963 [21] ¹	Stockholm	nuisance: requires 20–30 days pretreatment	yes
ALG as adjunct	1966 [6]	Denver	suboptimal	yes
Cyclophosphamide substitute for azathioprine	1970 [20]	Denver	no advantage except for patients with azathioprine toxicity	yes
Total lymphoid irradiation	1979 [23, 24]	Palo Alto, Minn.	dangerous; extensive preparation; not quickly reversible	yes
Ciclosporin alone	1978–1979 [27]	Cambridge	suboptimal	yes
Ciclosporin-steroids	1980 [29]	Denver	under evaluation	yes
Monoclonal ALG as adjunct	1981 [17]	Boston	under evaluation	yes

¹It was not realized until much later that pretreatment for 3–4 weeks before transplantation was a necessary condition [22].

will become increasingly important since it is now possible to raise potent and highly standardized antilymphoid antibodies with the monoclonal antibody techniques of *Kohler and Milstein* [16]. The first trials were carried out by *Cosimi et al.* [17] using monoclonal antibodies raised against mature T lymphocytes (T₃). These studies and others which have followed have shown that otherwise intractable rejections often can be reversed with good monoclonal preparations [18, 19]. However, if maintenance therapy is being provided with azathioprine and prednisone, there is a very high probability of recurrence of rejection when the course of monoclonal therapy is completed [17–19].

Other variations in immunosuppression between 1962 and 1979 are summarized in table I including the substitution of cyclophosphamide for azathioprine [20], and the use of thoracic duct drainage [21, 22] or total lymphoid irradiation [23, 24] as an alternative to ALG for lymphoid depletion. None of these techniques has had a major impact on clinical transplantation.

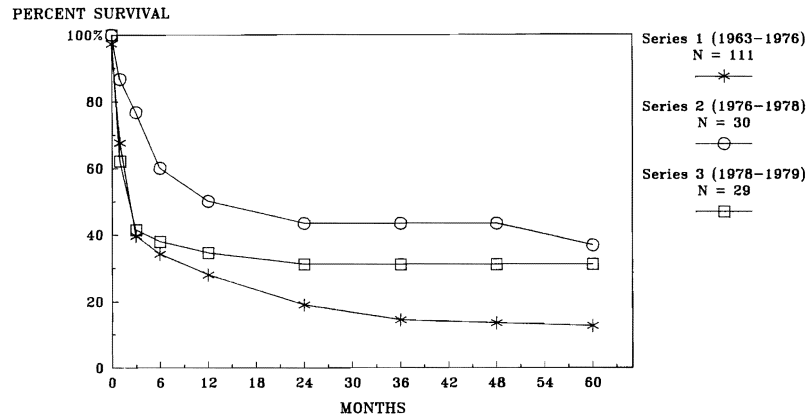


Fig. 1. Results obtained over a 16-year period using the conventional immunosuppression shown in table I. Note the failure to improve the results despite the acquisition of considerable experience.

With Liver Transplantation

Most of our liver recipients from 1963 through 1979 had triple-drug immunosuppression with azathioprine, prednisone and ALG. In some, cyclophosphamide was substituted for azathioprine and in a few others, lymphoid depletion was achieved with thoracic duct drainage instead of ALG. Details of these variations are summarized elsewhere [25]. The failure of any of the variations to influence the survival after liver transplantation is evident from figure 1. In the first trials from 1963 to 1976, only about one-third of the patients lived for as long as 1 year. In a smaller second series of 30 patients treated from 1976 to 1978, the 1-year survival rose to 50% but this improvement could not be sustained in the next 29 cases (fig. 1).

The Ciclosporin Era

In 1976, *Borel* et al. [26] reported studies in rodents of a new immunosuppressive agent called cyclosporin A and in late 1979, *Calne* et al. [27] reported the first major clinical experience with this drug.

With Renal Transplantation

The supremely encouraging observation in *Calne's* experience was that cyclosporin allowed prolonged graft survival in almost half of his recipients of 32 kidneys, 2 livers, and 2 pancreases with no other immunosuppressive

drug [27]. This kind of systematic reliance upon a single agent to control rejection had never been feasible before. Although *Calne's* publication became one of the most important in the history of clinical transplantation, it contained three pieces of information so troubling that further clinical trials were jeopardized. First was a high incidence of lymphomas. Second, none of the kidney recipients had normal graft function. Third, there had been a high patient mortality. The way in which these adverse findings have been explained or minimized in subsequent trials will be mentioned now.

The Development of Lymphomas. Amongst *Calne's* first 32 kidney recipients, there were 3 who developed malignant lymphomas [27]. The possibility that ciclosporin had a unique capacity to produce lymphomas in humans thus vitiating its value had to be seriously considered.

Fortunately, the lymphoma threat has become less and less ominous as information about the etiology and appropriate treatment of these lesions has emerged. Almost from the outset, it was obvious that the lymphomas were complications of primary or secondary infection with the Epstein-Barr virus [28, 29]. At first, it was speculated that lymphomas which produced a single immunoglobulin (monoclonality) already had become autonomous [28]. Ultimately, this doctrine was overthrown [30]. In a large number of patients followed by us, it was demonstrated that all of the ciclosporin lymphomas could be expected to disappear spontaneously if immunosuppressive therapy was stopped, and often if treatment was only lightened. This involution occurred whether the lesions were polyclonal or monoclonal. In recipients of kidneys, livers and hearts, reduction or discontinuance of immunosuppression was not necessarily followed by loss of the transplanted organ. The point was best made in our kidney recipients in whom therapy with ciclosporin and steroids usually was stopped [30]. Of 7 so treated, 4 retained their grafts which have continued to function for 1½ to 3½ years subsequently. After the tumors had disappeared, therapy at lower doses was reinstituted.

An example of the manipulation of therapy in a liver recipient who developed a lymphoma of the tonsils and pharynx is shown in figure 2. Ciclosporin therapy was cut to about half of the preceding dose and the prednisone doses were brought to even lower levels. The child received an emergency tracheostomy. Within a few days, the fever and other systemic manifestations of the lymphoma had gone, the gross lesions had melted away, and recovery was assured. No changes whatsoever were seen in the liver function at this time, supporting the conclusion that the patient had been over-immunosuppressed.

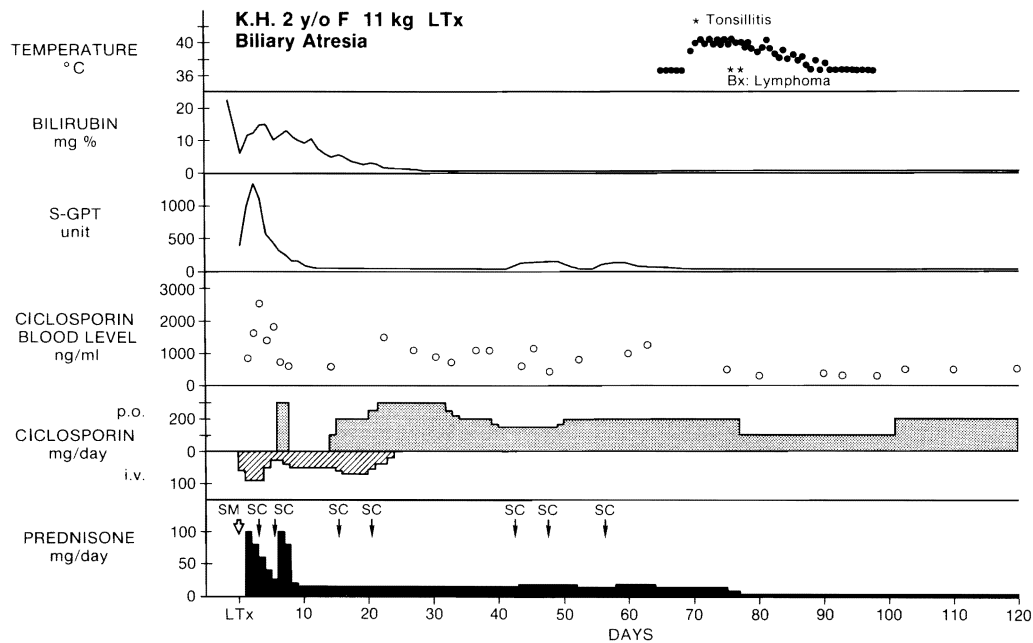


Fig. 2. The treatment of lymphoma in a pediatric liver recipient by reduction of both cyclosporin and prednisone doses. The airway was protected with a tracheostomy, but within a few weeks after lightening immunosuppression, the cervical tumors disappeared. Bx = Biopsy.

The development of de novo malignancies in immunosuppressed patients is not unique to cyclosporin. It has been a well-known complication of therapy with azathioprine and prednisone (with or without ALG) since the 1960s [31, 32]. With conventional immunosuppression there has been an extremely high incidence of epithelial cancers, which have outnumbered the lymphomas by a ratio of about 4:1 [33]. Under cyclosporin-steroid therapy, there has been little or no increase in the incidence of the epithelial tumors. Thus, the risk of the development of malignancies is probably considerably less with cyclosporin than with conventional immunosuppression, even if one considers the lymphomas to be true tumors, a concession that may not be valid [34].

Ciclosporin Nephrotoxicity and Its Prevention. Of the kidney recipients first reported by Calne et al. [27], none had normal renal function, a finding which Calne attributed to universal ciclosporin nephrotoxicity. In retrospect, part of the problem was failure to distinguish rejection from drug toxicity [29]. Nevertheless, many subsequent reports including our own [29, 35, 36] have shown that nephrotoxicity is the most limiting side effect of ciclosporin.

It was immediately obvious in our first trials with ciclosporin in late 1979 that the full exploitation of the drug would not be possible without combining it with other agents, of which prednisone was the most important [29, 36]. By so doing, it was possible to minimize the contribution of homograft rejection to poor renal function, and at the same time to ameliorate the nephrotoxicity by reducing the requisite doses of ciclosporin. Since then, other drugs have been proposed and/or tried in modifications of the 'pharmacologic cocktail' concept [37, 38], but the ciclosporin-steroid combination remains the benchmark. Normal renal transplant function has become the rule.

It is not hard to envision ciclosporin-steroid therapy as the modern analogue of the original double-drug therapy with azathioprine and steroids (table I). As a further analogy, the next logical step may be development of new 'triple-drug' programs analogous to azathioprine, prednisone and ALG (see table I) but with ciclosporin-steroids being the baseline therapy to which one of the monoclonal ALG preparations which are undergoing preliminary clinical trials may be added. Our present opinion is that monoclonal ALG should be used to 'rescue' patients in whom rejection cannot be controlled with ciclosporin-steroid therapy or in whom there are severe limitations for one reason or other to the amounts of ciclosporin that can be safely given. Such limitations are particularly important in applying knowledge about immunosuppression obtained from the kidney transplant model to the transplantation of other organs such as the heart and liver since secondary renal failure is common in patients with cardiac and hepatic disease thereby complicating the use of ciclosporin.

We have used OKT3 monoclonal antibody therapy in a number of our kidney recipients. If rejection has developed despite ciclosporin-steroid therapy, reversal with OKT3 antibody usually has been striking (fig. 3). With the first dose of the monoclonal ALG, the circulating T lymphocytes are practically eliminated (fig. 3). Recurrence of rejection after the monoclonal antibody course has been completed has been far less common using baseline therapy with ciclosporin-steroids than previously reported with azathioprine-prednisone maintenance [17-19].

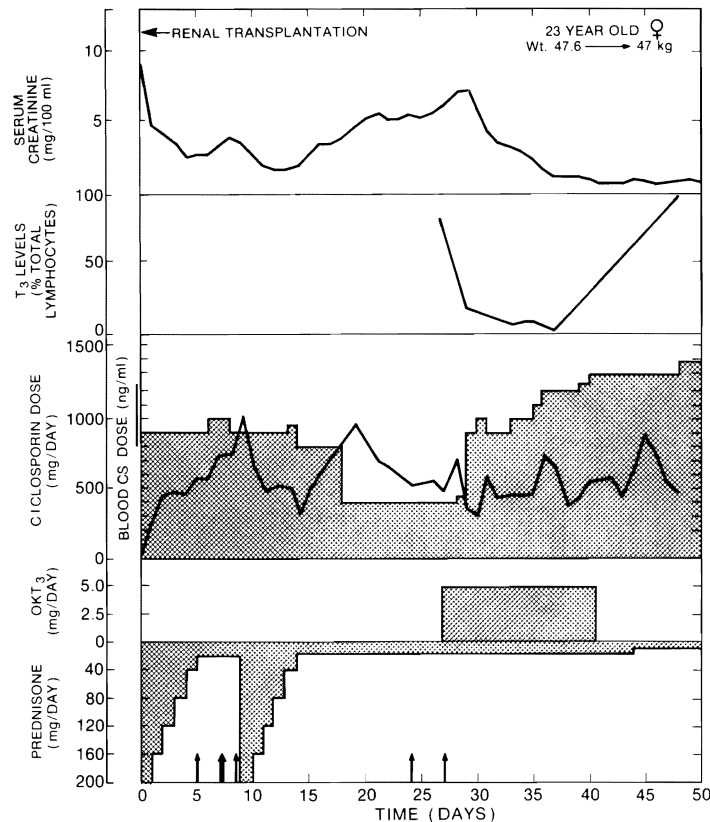


Fig. 3. Course of a patient who developed inexorable rejection in spite of good blood levels of ciclosporin and despite a second burst of high-dose steroid therapy. The rejection was immediately reversed with OKT-3 therapy and with good function for the ensuing 8 months. Note the prompt reduction in circulating T lymphocytes.

High Patient Mortality. The heavy mortality with the first use of ciclosporin [27] apparently was a reflection of a learning experience in which cytotoxic drugs and steroids were combined with ciclosporin with lethal effects. Even in our first trials with the far safer ciclosporin-steroid combination, the 1-year patient mortality was 13.6% [39], but in the following year, the 1-year mortality was reduced to 2% [40]. Since then, most groups using ciclosporin-steroid therapy have had a mortality of less than 5%. Ciclosporin-steroid therapy has been the safest of the therapeutic regimens yet tried.

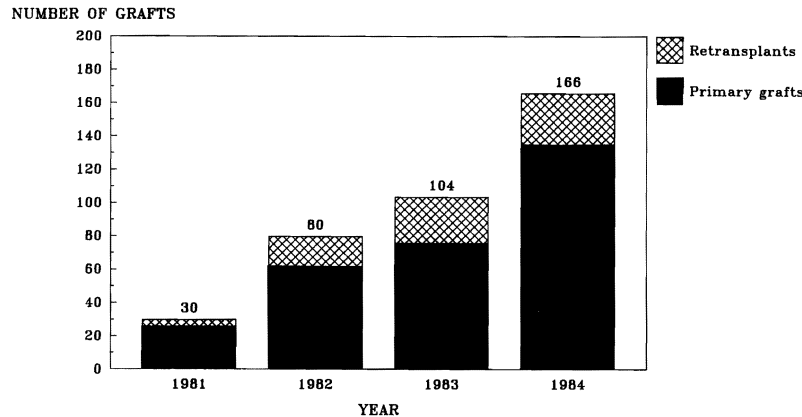


Fig. 4. Increasing numbers of liver transplantations at the University of Pittsburgh between 1981 and 1984. Note the significant number of retransplantations.

With Liver Transplantation

In 1980, ciclosporin and prednisone were used to treat 12 patients undergoing liver replacement. Two other liver recipients died on the operating table for a total patient pool in that year of 14 of whom 11 (78%) lived out the first year. If one counted only those who actually survived the operation to be able to receive drug therapy, the success rate was 11 (91.7%) of 12.

Case Numbers. These improved results became known in 1981 [41] and almost immediately a remarkable effect was seen on the case numbers. Increments occurred year-by-year until in the calendar year of 1984, a total of 166 orthotopic liver transplantations were performed at the University of Pittsburgh (fig. 4). Augmented activity in other centers throughout the world has been documented elsewhere [42].

The Increasing Use of Pharmacologic Monitoring. In our early trials of cyclosporine-steroid therapy in renal transplantation, primary cadaveric kidney graft survival of 80–90% was achieved without knowing what the ciclosporin blood levels were. The clinical judgement in managing such patients reflected a deliberate effort to balance the possibilities of rejection against those of nephrotoxicity [36] and to treat both.

When techniques became available for assessment of whole blood or plasma ciclosporin concentration using radioimmunoassay (RIA) or high

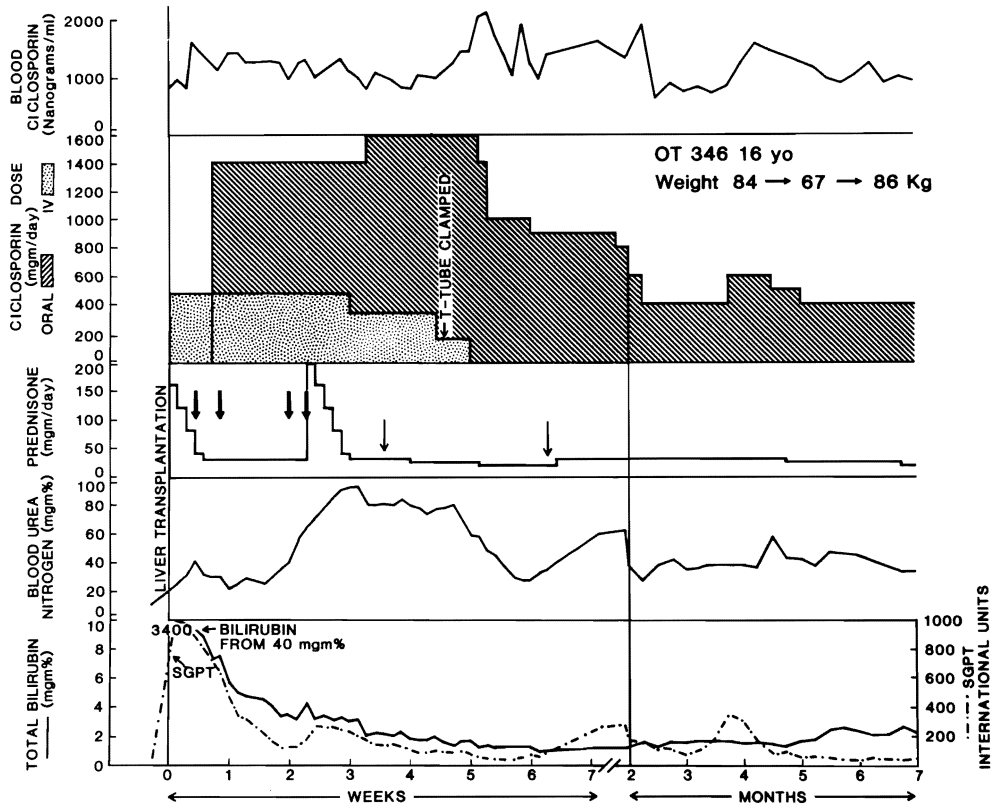


Fig. 5. The use of ciclosporin and steroids. Note that the ciclosporin initially is given intravenously (i.v.) and that the i.v. therapy is continued long after the drug is begun orally. The switch from double-route ciclosporin therapy to the oral route alone is carefully monitored with ciclosporin blood levels. Note the seeming increase in enteral absorption after clamping of the T-tube, the insistence upon maintaining high blood levels of ciclosporin in spite of obvious low-grade nephrotoxicity, and the intensification of steroid therapy with either a cycle or intermittent bolus administration with suspicion of rejection. Large arrows = 1 g Solu-Medrol; small arrows = 1 g Solu-Cortef. By permission of *Starzl et al.* [42].

performance liquid chromatography (HPLC), it became popular to rely heavily on the results of these tests for management decisions. Recipients of liver transplantation have benefited from this practice since intestinal absorption of ciclosporin after liver transplantation has been unpredictable. To assure adequate ciclosporin blood concentrations, it has frequently been necessary to administer the drug both intravenously and by mouth for several

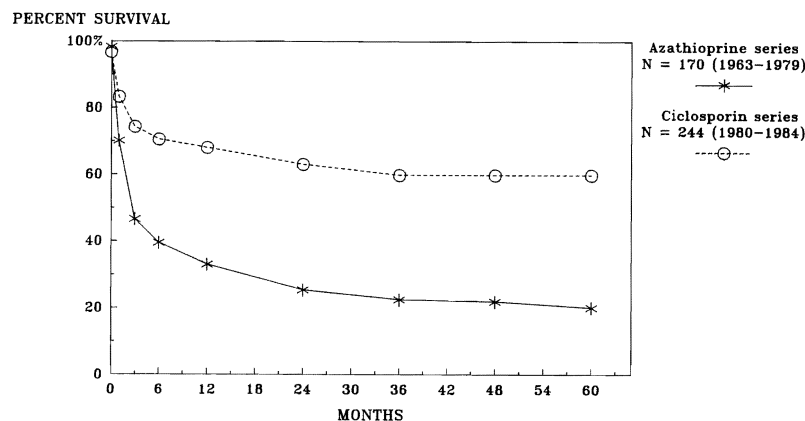


Fig. 6. Marked improvement in results of liver transplantation after the introduction of cyclosporin-steroid therapy in early 1980.

days, weeks or even months postoperatively (fig. 5). As absorption improves with the oral route, the intravenous doses are slowly reduced. However, blind faith in the cyclosporin blood levels cannot be used to replace good clinical judgement since toxicity of the drug including that affecting the liver as well as the kidney does not have an absolute correlation with the blood level.

Survival after Cyclosporin. From 1963 through 1979, 170 patients were treated with conventional immunosuppression. The chances of living for a year after liver transplantation were only about 1 in 3 (fig. 6). Subsequently, 244 liver recipients were provided with cyclosporin-steroid therapy between March 1980 and 1 July 1984, allowing follow-ups 10 months to more than 5 years. The chances of 1-year survival were more than doubled. Actuarial projections beyond 1 year indicate that these gains will be sustained for at least half a decade (fig. 6).

In a later section, more detail will be given of the influence of age and underlying disease upon the outcome. In the meanwhile, other factors that could influence the results will be considered briefly.

The Role of Tissue Typing

In patients treated with cyclosporin-steroids after renal transplantation, the antigen matching at the A, B, or D loci has had little influence on the

results. Such matching has not even been attempted for liver recipients. It is unlikely that this kind of tissue matching will play a significant role in further developments in liver transplantation.

A surprising finding has been the remarkable resistance of the liver to hyperacute rejection [43, 44]. There has been no obvious penalty with transplantation of livers to recipients whose sera contain the cytotoxic anti-graft antibodies that almost invariably lead to immediate loss of kidney grafts. Furthermore, many liver transplantations have been and are being carried out across the ABO blood group barriers which frequently (although not invariably) cause hyperacute rejection of kidneys as the consequence of anti-graft isoagglutinins [13]. These observations have simplified some of the logistic problems of liver transplantation.

Improvements in Technique

The technical principles of liver transplantation have been well worked out for almost 2 decades but 2 highly significant developments have occurred in the last few years. These are perfection of pump-driven veno-venous bypasses and the standardization of biliary tract reconstruction.

The Veno-Venous Bypass

When liver transplantation was first carried out in dogs, an obligatory condition for success was decompression of the vena caval and portal venous systems that had to be occluded while the native liver was removed and the new organ was sewn in [1, 2]. In the first clinical trials, it was found possible to omit this step [5] and for a number of years bypasses were not used. Without bypasses, the urgency with which the transplantation was performed was comparable to that in the early days of heart surgery when open cardiac operations were performed under inflow occlusion.

In the last 3 years, pump-driven veno-venous bypass techniques without heparin have been developed (fig. 7) which have removed this urgency and which have allowed the avoidance of the venous hypertension that otherwise is inevitable during the anhepatic phase [45–47]. The advantages of veno-venous bypasses include: (1) improved intraoperative cardiovascular stability; (2) preservation of renal function by avoidance of the renal-venous hypertension; (3) diminished blood loss; (4) reduced trauma to the gastrointestinal tract by avoidance of the portal venous hypertension, and (5) creation of an operating room ambience compatible with training a new generation

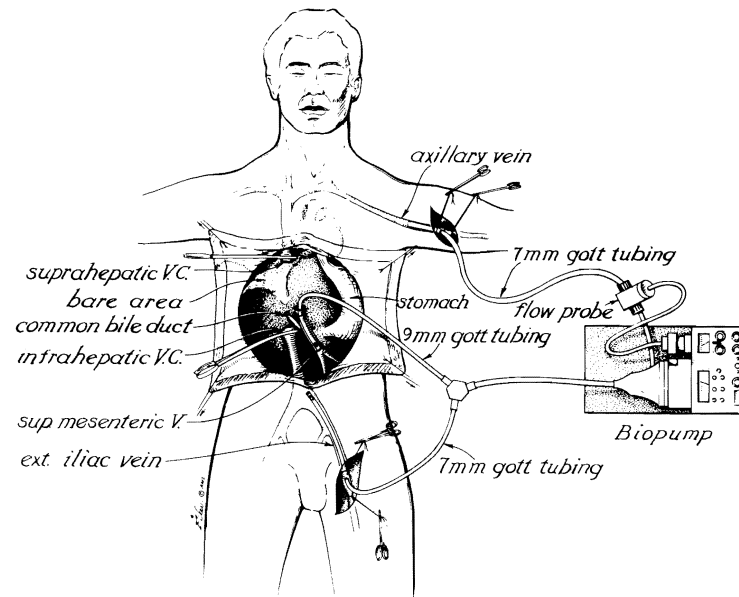


Fig. 7. Pump-driven bypass. By permission of Griffith et al. [46].

of surgeons who in turn will set up numerous new centers in the United States and other countries.

The veno-venous bypass has changed the technical strategy of liver transplantation in important ways. In the past, when time was such a critical factor during the anhepatic phase, it was impossible to obtain meticulous hemostasis in the bare areas opened up by removal of the diseased native liver. Even had there been time, it was often impossible to clean up and make dry the raw surfaces which were exuding blood at a voluminous rate because of venous hypertension. Control of bleeding by mechanical means was frequently impossible until the new liver was in place and until the obstructed venous beds were decompressed by opening the caval and portal venous anastomoses.

If veno-venous bypass is used, the technique shown in figure 8 can be applied whereby most or all of the bare areas are closed by running sutures [48]. Although these maneuvers may require an hour or longer before the anastomoses are started, the investment pays rich dividends later in ease of hemostasis.

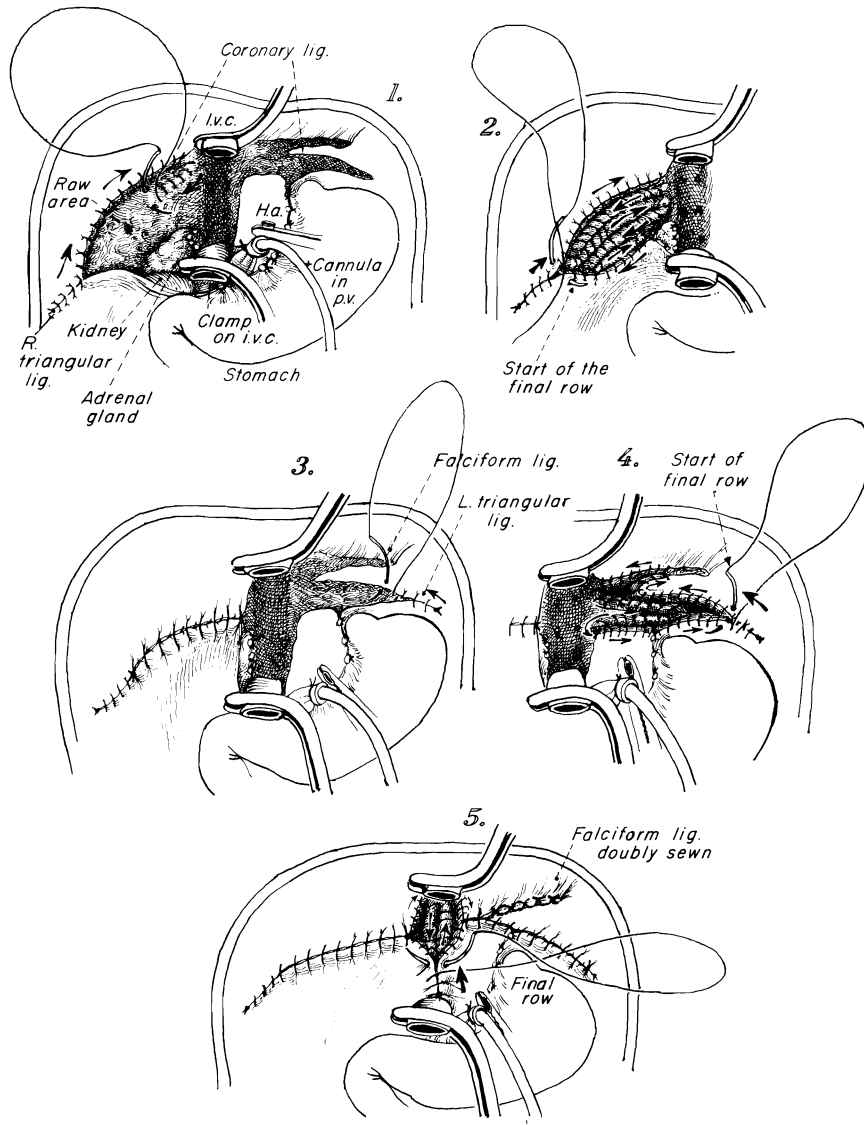


Fig. 8. Elimination of the raw areas in the hepatic fossa with continuous Prolene suturing. See text for details. By permission of Starzl et al. [48].

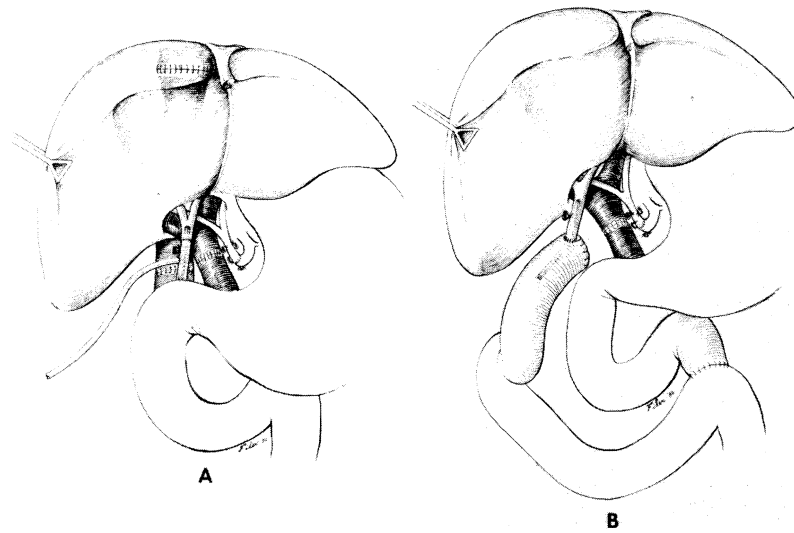


Fig. 9. Completed orthotopic liver transplantation. *A* Biliary tract reconstruction with choledochocholedochostomy. *B* Biliary tract reconstruction with choledochojejunostomy, using a Roux limb. By permission of Starzl et al. [25].

Biliary Tract Reconstruction

Until about 8 years ago, biliary tract reconstruction was called the Achilles heel of liver transplantation with failure rates that were as high as 30–50% [49, 50]. At that time, the gallbladder was usually used for reconstruction, the pathway of bile excretion being from the common duct through the cystic duct and gallbladder and into the intestine. Duct to duct and duct to bowel reconstruction were not employed frequently.

Today, all biliary tract reconstructions are performed by one or the other of the techniques shown in figure 9, namely choledochocholedochostomy with a T-tube stent, or choledochojejunostomy to a Roux limb of jejunum. With these procedures, 90% or more of the biliary tract anastomoses are successful on the first occasion and even when there are complications, these usually are easily rectified.

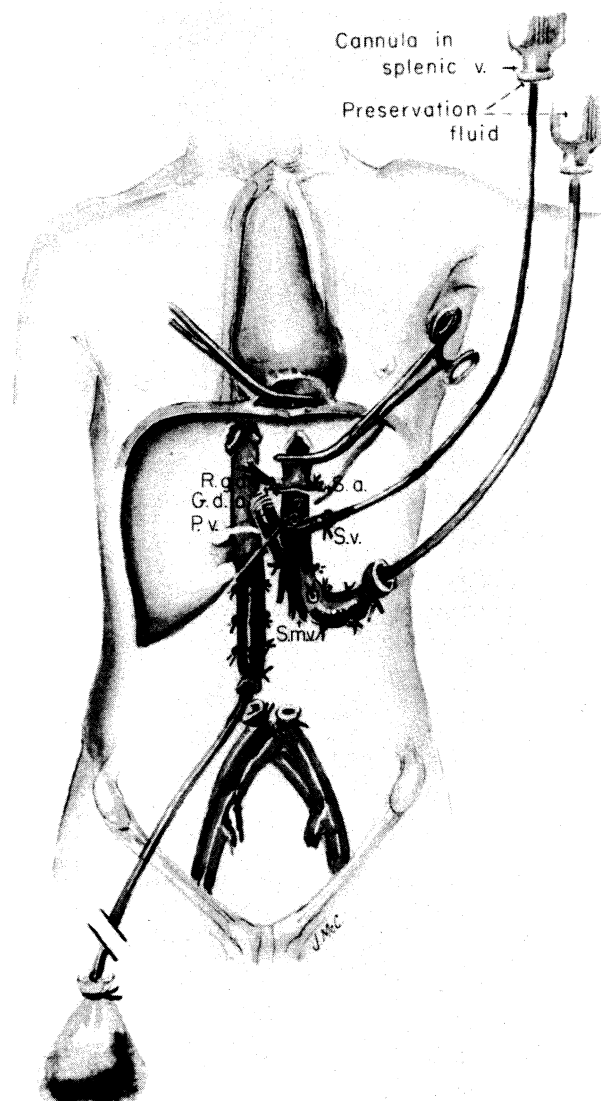


Fig. 10. In situ infusion technique used when the kidneys and liver are removed from the same donor. R.g.a. = Right gastric artery; G.d.a. = gastroduodenal artery; S.a. = splenic artery; S.v. = splenic vein; P.v. = portal vein; S.m.v. = superior mesenteric vein. By permission of Starzl et al. [51].

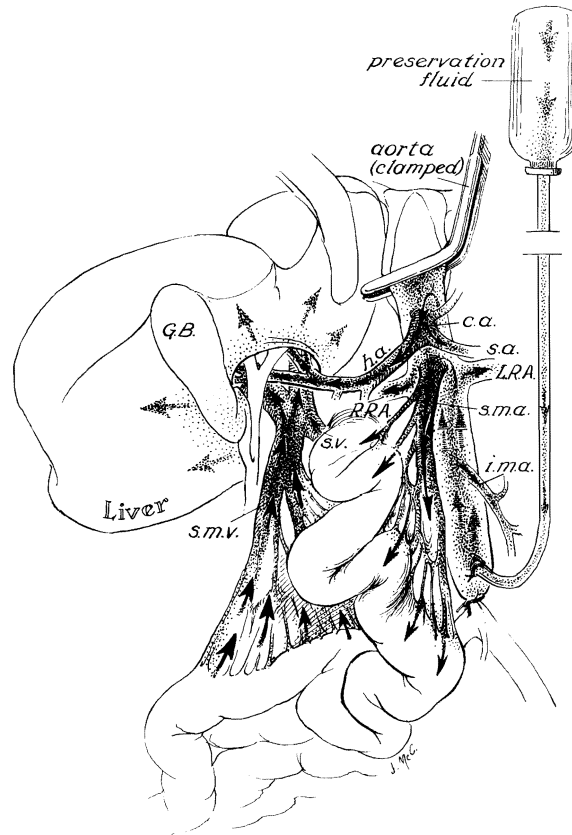


Fig. 11. Method of rapid liver cooling that can be done without any preliminary dissection except for insertion of a distal aortic cannula and cross-clamping of the aorta at the diaphragm. The infusion fluid quickly gets into the portal system via the splanchnic capillary bed, providing double inflow cooling. By permission of Starzl et al. [42].

Organ Removal and Preservation

Great advances have been made in multiple organ removal and a relatively standard procedure is being used throughout most of the United States [51]. The operation is done through a complete midline incision from the suprasternal notch to the pubis, including splitting of the sternum. The prin-

Table II. Indications for liver transplantation in 140 adults

Indication	Number	Percent
Acute hepatic necrosis	3	2.1
Budd-Chiari syndrome	5	3.6
Cirrhosis	46	32.9
Inborn errors of metabolism	11	7.9
Alpha-1-antitrypsin deficiency	6	4.3
Wilson's disease	3	2.1
Tyrosinemia	1	0.7
Primary biliary cirrhosis	36	25.7
Primary hepatic tumors	13	9.3
Secondary biliary cirrhosis	5	3.6
Sclerosing cholangitis	19	13.6
Other	2	1.4

ciple followed is to dissect the aorta for cross-clamping at a level which will allow intraaortic infusion of cold fluids which will pass into the organs to be removed. If the liver is to be one of these organs, dissection of the liver hilum is carried out after which the liver can be infused through both the aorta and portal vein (fig. 10). The kidneys also are cooled by the aortic perfusion. In the example shown in figure 10, the liver and both kidneys are to be removed. With minor modifications, the heart can also be excised.

This procurement technique requires 'brain death' conditions with stable cardiovascular function. An alternative with which we have had recent experience can be done swiftly, and in donors who have had cardiac arrest [42]. With this so-called fast method, a cross-clamp is placed on the aorta near the diaphragm and cold solutions (usually the high potassium, high magnesium concentration Collin's solution) are infused rapidly. Blood enters the liver through the normal celiac axis route but also through the portal vein after passing through the splanchnic capillary bed (fig. 11). The portal venous blood quickly becomes almost red cell free.

The cold ischemia limit which is permissible for a human liver graft has been set arbitrarily at 10 h, but great efforts are made to work within a 5- or 6-hour time frame. One of the most urgent needs in liver transplantation is the development of better methods of preservation. Any technique which would allow safe preservation of livers for the better part of a day would revolutionize the field over night.

Table III. Indications for liver transplantation in 104 children

Indication	Number	Percent
Biliary atresia	56	53.8
Budd-Chiari syndrome	1	1.0
Cirrhosis	10	9.6
Familial cholestasis	7	6.7
Inborn errors of metabolism	23	22.1
Alpha-1-antitrypsin deficiency	15	14.4
Wilson's disease	4	3.8
Tyrosinemia	3	2.9
Neonatal hepatitis	3	2.9
Secondary biliary cirrhosis	1	1.0
Sclerosing cholangitis	1	1.0
Other	2	1.6

Indications for Transplantation and Results

The indications for liver replacement in the developmental phase of this field have been documented elsewhere [25] and will not be mentioned here. Since the beginning of the ciclosporin era, 244 patients underwent this procedure between March 1980 and 1 July 1984. In tables II and III are shown the principal indications for these operations. In about 10% of cases, there were multiple pathologic diagnoses such as the incidental presence of primary hepatic malignancies in livers with a variety of underlying chronic diseases.

The profile of diseases in pediatric patients (less than 18 years) has been different than that in adults. In adults, postnecrotic cirrhosis has been the most important reason for proceeding (table II). Other common diseases in adults have been primary biliary cirrhosis and sclerosing cholangitis (table II). In children, more than half of all the transplantations have been done for biliary atresia, the only other large group being heterogenous collection of inborn errors of metabolism (table III). The inborn errors if they are hepatic-based are cured permanently by liver replacement since the phenotype of the new liver remains that of the original donor [25].

Influence of Age on Survival

Aside from the fact that the disease profiles leading to transplantation are different in children versus adults, another justification for stratification

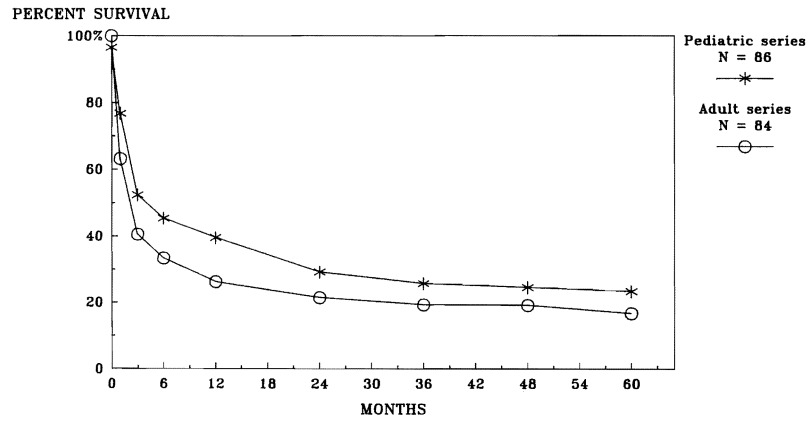


Fig. 12. Results with adult versus pediatric liver transplantation under conventional immunosuppression between 1963 and early 1980.

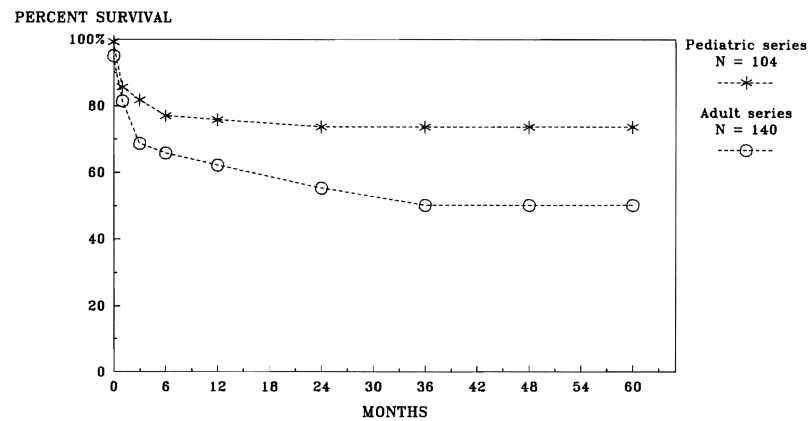


Fig. 13. Comparison of results in adult and pediatric recipients during the ciclosporin era of 1980-1984.

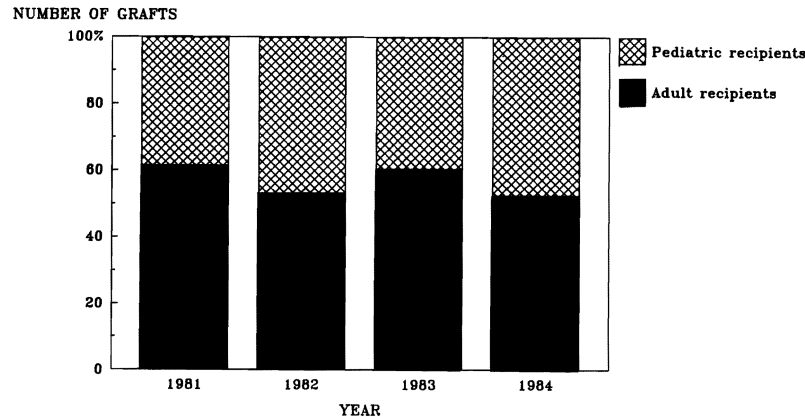


Fig. 14. Percentages of liver transplantations in pediatric versus adult recipients at the University of Pittsburgh from 1981 through most of 1984.

into adult and pediatric categories is the influence of age on survival. It was noted in the days of conventional immunosuppression that the results were better in pediatric recipients (fig. 12). The disparity in results in pediatric versus adult cases has been even more striking during the ciclosporin era (fig. 13). The actuarial 5-year survival in adults is projected at about 50%, compared to more than 70% for the pediatric recipients (fig. 13). In view of the importance of the age factor, it will be important for groups reporting results to stipulate age distribution in their series. In our own experience using conventional immunosuppression from 1963 to 1979, half of the recipients were infants, children and teenagers. In the subsequent years using ciclosporin, the pediatric component has never been this high (fig. 14).

With the appropriate age stratification, meaningful comparisons become possible between what was achievable in the pre-ciclosporin era versus now. In adults, the projected 5-year survival after liver transplantation, while still unsatisfactory, is nearly 3 times better than it was previously (fig. 15). In children, the divergence of results using conventional immunosuppression compared to the present time is even more striking (fig. 16).

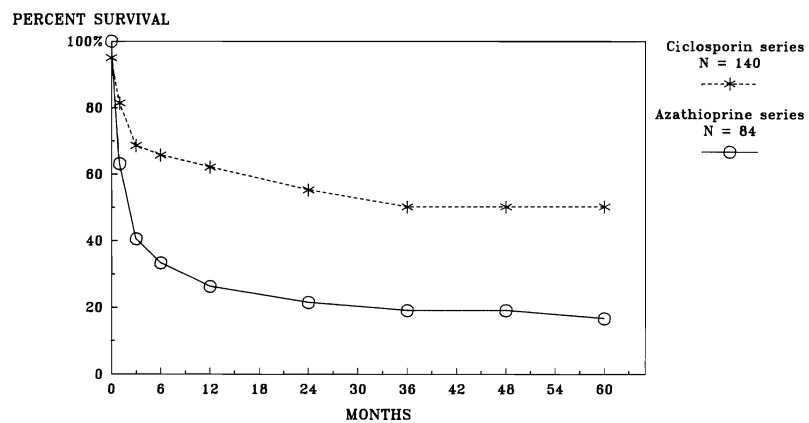


Fig. 15. Survival of adult liver recipients in the pre-ciclosporin versus the ciclosporin era.

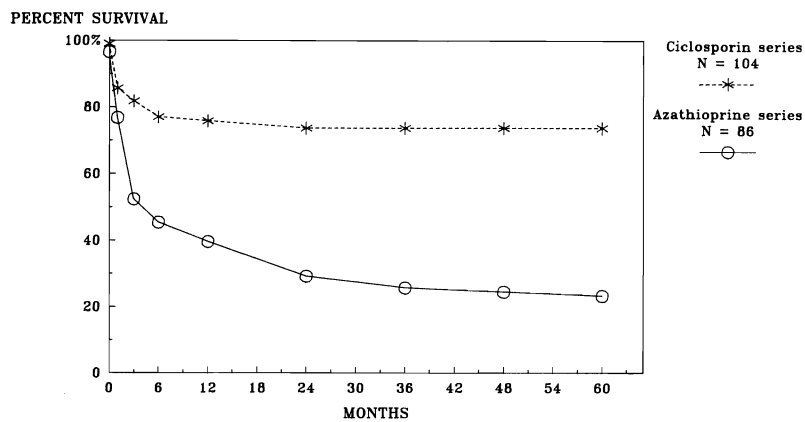


Fig. 16. Survival of pediatric patients in the pre-ciclosporin versus the ciclosporin era. Notice the remarkably high survival of children treated with ciclosporin-steroids during the first postoperative year as well as the fact that subsequent losses were extremely uncommon.

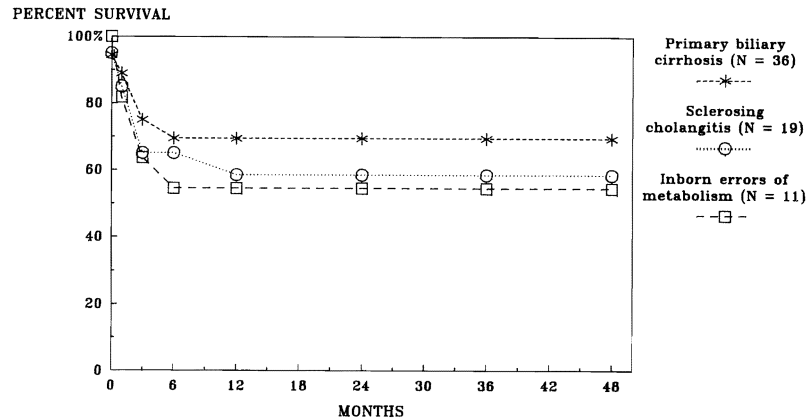


Fig. 17. The lack of influence of the underlying disease in adults treated for primary biliary cirrhosis, sclerosing cholangitis, and inborn errors of metabolism.

The Influence of Diseases Upon Prognosis

There are no diseases for which transplantation has been carried out in the past which can be automatically precluded from future trials. Usually, the nature of the original disease has not profoundly influenced the outcome after transplantation. For example, the results in adults have been similar with such diverse diseases as primary biliary cirrhosis, sclerosing cholangitis, and inborn errors of metabolism (fig. 17). Nevertheless, there may be some high risk diseases. So far, the results with postnecrotic cirrhosis and with primary hepatic tumors have been inferior (fig. 18). With cirrhosis, the principal explanations have been the technical difficulties of the operation caused by the pathologic process, the generally poor condition of the cirrhotic patients, and almost universal recapitulation of their original chronic active hepatitis in B virus carriers.

In patients whose reason for liver replacement was a primary hepatic malignancy which could not be removed by conventional subtotal hepatic resection, the early mortality has been quite low with more than 80% of the recipients being alive at 6 months. The steady decline thereafter (fig. 18) has been caused by recurrent tumor which can be expected in 80% or more of patients who live long enough for metastases to be detected. The only acceptable results thus far have been in patients with the slow-growing and nonaggressive fibrolamellar hepatomas which recently have been recognized to be

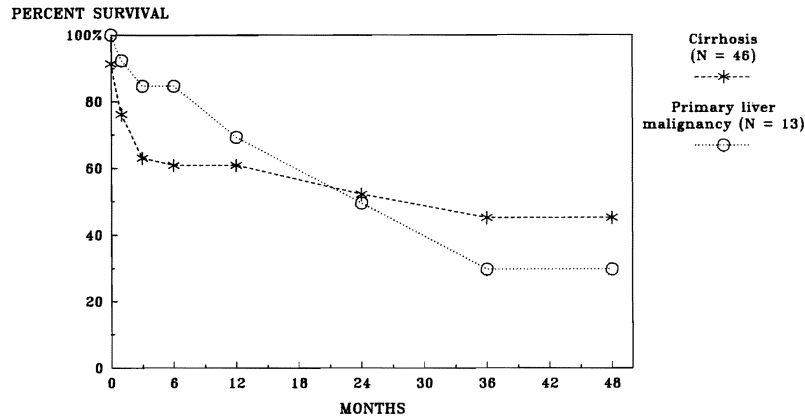


Fig. 18. The life survival curves of patients with 2 'bad' diseases – cirrhosis and primary hepatic malignancy. Note the very high survival of patients with malignant disease during the first half year (85%), but with a steady decline thereafter which was due primarily to the development of metastases.

a favorable variant within the larger hepatoma category [52]. It has been exceptionally disappointing to note that no patient in the world has ever been cured of a duct cell carcinoma by liver transplantation. This has been unexpected since the small duct cell carcinomas at the confluence of the right and left hepatic ducts (Klatskin tumors) were once thought to be an almost ideal indication for liver replacement.

In children, the results have been about the same in all of the main disease categories (fig. 19). It was thought once that the technical problems in frequently reoperated children with biliary atresia would result in an increased mortality. Almost all such infants and children have had portoenterostomies and many have had multiple later surgical interventions in and around the hepatic hilum. Although transplantation is technically much more difficult under such circumstances, there has been no demonstrable penalty in terms either of early or late survival (fig. 19).

The Role of Retransplantation

Before the ciclosporin era, retransplantation in the event of failure of the first liver was almost never successful. Twenty-one patients had retransplantations carried out between 1963 and 1979 under conventional immunosup-

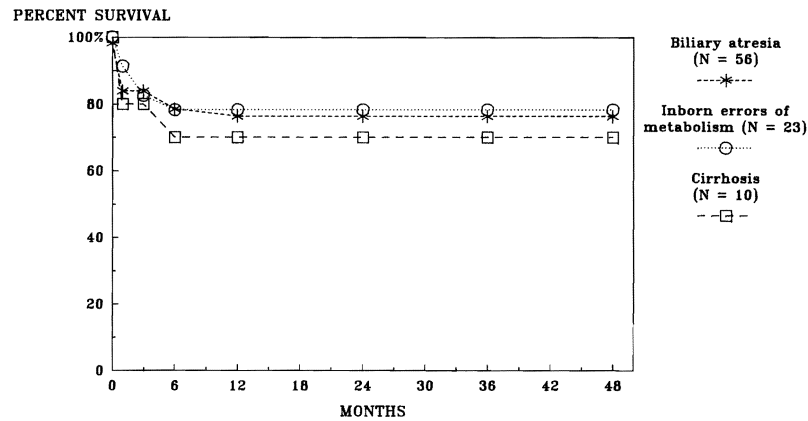


Fig. 19. The lack of influence of underlying disease on the survival of children undergoing liver transplantation.

pression with only 4 patients living for as long as an additional half year. Even these 4 exceptional recipients died 6, 12, 13 and 16 months after retransplantation.

The effectiveness of retransplantation has improved greatly since the introduction of ciclosporin, with a subsequent 1-year survival of almost 50% [53]. The success rate for patients whose grafts have been in place for some time and failed slowly because of rejection has been high. The worst results have been in patients with immediate and serious technical complications and those whose grafts have undergone a rapid and uncontrolled rejection in the first week or two.

The role of retransplantation in the future has been somewhat clouded by the enormous economic ramifications of early technical or other complications serious enough to warrant replacement of the graft. At The University of Pittsburgh hospitals, the costs of liver replacement averaged less than \$100,000 if only one transplantation was performed. In contrast, the bills for patients receiving multiple grafts (usually 2 but as many as 3) have been astronomical and have averaged almost 3 times as much as for patients treated successfully from the beginning.

Both in adults and in children, but particularly the latter, technical

complications have played an important role in necessitating attempts at retransplantation [53]. The lesson has been clear that if a perfect operation is not performed the first time for any reason, the cost will be prodigious and will have to be borne by the patient or more commonly the health insurance carrier. In future years, it will become important to try to identify those patients for whom retransplantation offers little or no chance of survival so that expensive and ineffective attempts can be avoided with some degree of accuracy.

Summary

During the last 5 years, liver transplantation has become a service as opposed to an experimental operation. The most important factor in making this possible has been the introduction of ciclosporin-steroid therapy. At the same time, liver transplantation has been made more practical by improvements in surgical technique, including perfection of intraoperative veno-venous bypasses and the standardization of biliary tract reconstruction. Tissue typing and matching has played no role in improving the results of liver transplantation. With the demonstration that preformed antibody states are irrelevant, even avoidance of positive cross-matches caused by cytotoxic antibodies and observance of ABO blood group barriers have become unnecessary if the recipient's needs are great. With the exceptions of malignancy and cirrhosis, the nature of the underlying hepatic disease has not profoundly influenced the results. Retransplantation has played an important role in improving survival, although the costs of retransplantation have been extremely high. Many aspects of liver transplantation need to be improved including the development of better methods of preservation which will allow the recipient operations to be done in a more leisurely manner and at more convenient times.

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