CHAPTER

18

An Overview of Orthotopic Transplantation of the Liver

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The field of liver transplantation has undergone a revolution, beginning around 1980 with the introduction of the immunosuppressant cyclosporine and continuing through the next five years. The improved survival that has occurred has changed the procedure from a rather arduous exercise in surgical exotica to a realistic therapeutic alternative for a large number of patients with advanced liver disease. Enthusiasm for the procedure has spread throughout the world. Aside from the facts that a growing number of patients are being identified as potential recipients of livers and that the ranks of waiting candidates continue to expand more rapidly than the availability of the procedure, the high profile status of transplant recipients in the lay and medical press has infected both academic and private institutions with the belief that developing programs in liver transplantation will garner new prestige for their hospitals, thus strengthening their position in an increasingly competitive battle for health care dollars. It is predictable that many such programs will come and go rather rapidly. Although a revolution has taken place, offering liver replacement to patients is still a complex endeavor. It requires an expensive long-term commitment of resources, which the advertising budgets of most hospitals cannot support.

An understanding of the current status of hepatic transplantation requires a brief review of the history of the field, a general delineation of recipient candidacy requirements, a description of the operative techniques for both donor and recipient procedures, and an accounting of results. Mention should also be made of the costs of the procedure and some estimation of the potential benefits to society. What the future may bring and which research efforts are needed are discussed at the end of the chapter.

HISTORIC NOTES

The technique of transplanting solid, vascularized organs owes much to the pioneering efforts of Alexis Carrel[1] and Emerich Ullman[2] (as does the entire field of vascular surgery). These men demonstrated that removing kidneys from one animal and revascularizing them into another not only was

possible but also worked so well from a technical standpoint that Carrel attributed failures to "biological factors" in the host, rather than to "surgical factors."[3]

Early Experimental Efforts

The first reported efforts at hepatic transplantation involved the heterotopic transfer of the liver in dogs. These experiments were done by Welch,[4] and subsequently by others,[5–7] without the use of immunosuppression. Despite the fact that in this setting the livers were destroyed after several days (most likely by rejection), the observation that they initially looked normal in color and even produced bile supported the technical feasibility of the procedure.

Orthotopic transplantation of the liver in dogs, first reported by Moore and coworkers,[8] at Peter Bent Brigham, and Starzl and colleagues,[9] then at Northwestern University, provided the first test of the methodology, since survival of the animals was solely dependent upon adequate function of the transplanted organs. Once again, these early experiments were on unmodified animals. The failure rate was exorbitant. Characteristically, Starzl and coworkers persisted in their efforts to improve the techniques of surgery and anesthesia and the methods of organ preservation. In 1960, they were able to report a two-day survival of 22 of 23 unmodified dogs, with a six-day survival in 19 of them.[9] These dogs served as the control group for later experiments with immunosuppression. These studies demonstrated the histopathologic nature of liver rejection and eventually proved that rejection could be successfully modified with drugs.[10, 11] The usefulness of these experiments largely depended upon the development of methodology that would eliminate technical errors as a cause for failure. Many of these techniques were directly transferable to early work in humans and, with only minor modifications, serve as the foundation for the clinical procedure practiced today.

Although these early experiments without immunosuppression helped characterize the pattern of rejection of liver grafts, the occasional long-term survival of some of these dogs suggested that in contrast to kidney or skin grafts (which were uniformly rejected), liver allografts might possess the capacity to survive the onslaught of unmodified rejection. This concept received further support when work at other centers showed that pigs possessed an even greater tendency toward survival without immunosuppression than dogs did.[12] In fact, by 1969 in Cambridge, England, Calne and associates[13] were able to demonstrate that these unmodified pigs that survived liver grafting were also rendered hyporeactive to both skin and kidney grafts from the same donor, although full responsiveness to third-party antigens was preserved.[13] Although Starzl's group, working with dogs, and, perhaps more important, Myburgh's group, working with primates, were unable to demonstrate a similar phenomenon in their experiments, Zimmermann and coworkers[15] confirmed the observations of Calne's group using a rat model.

Working with rats, the Cambridge group subsequently showed that the fate of liver grafts is highly dependent upon certain immune response genes of the recipient. They classified individuals as either high or low responders. The former appear to reject liver grafts as readily as they do other organ grafts, whereas the latter group not only do not reject allograft livers but also gain donor-specific tolerance. This phenomenon appears to involve donor-specific clonal deletion. Although they have found no evidence for the development of new populations of either donor-specific or donor–non-specific suppressor cells, the sera of these rats do contain powerful immunosuppressive properties that are donor specific.[16]

Although these findings are fascinating, their direct impact on the clinical situation has yet to be realized. Starzl's group and other early workers realized that the success of clinical liver transplantation would depend upon the availability of safe and effective regimens of immunosuppression. For the most part, these regimens were modeled after those first used in earlier experimental work with kidney transplants and then tested in the canine liver model. One should not underestimate the importance of the experimental successes with azathioprine[10, 17, 18] and various antilymphocyte preparations (antilymphocyte serum [ALS], antilymphocyte globulin [ALG])[10, 19–22] in paving the way for the first clinical trials of liver transplantation.

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The First Human Trials

Starzl and associates recorded the first attempt at transplantation of the liver in a human on March 1, 1963 in Denver, Colorado.[23] Despite an extensive and highly successful four-year experience in the laboratory working with dogs, Starzl's team failed in this first clinical effort. The patient, a three-year-old boy with biliary atresia died on the operating table from hemorrhage. During the ensuing ten months, four more failures in Denver and one each in Boston and Paris (Table 18–1) led Starzl to cease further clinical trials in Denver for the next three years. Two more patients who underwent transplantation in Denver between the fall of 1966 and the spring of 1967 also died. The group then succeeded in obtaining extended survival of a 1½-year-old girl with primary hepatocellular carcinoma who underwent transplantation on July 23, 1967 and lived for 13 months before dying from diffuse metastases.

In May of 1968, under the direction of Professor Roy Calne, the University of Cambridge Department of Surgery at Addenbrooke's Hospital in the United Kingdom formed a consortium with Dr. Roger Williams and the Liver Unit at King's College Hospital in London to embark upon a clinical program of liver transplantation. Calne recently edited a book entitled *Liver Transplantation* that summarizes their experience with 125 patients over a 14-year period ending in May 1982.[24] Calne's experience, in terms of numbers, is second only to Starzl's during the first two decades of clinical hepatic transplantation, and together their two series account for more than three fourths of the world's total experience.

A number of other case reports or small series of human liver transplants from all over the world appeared in the 13 years after Starzl's initial step.[25–37] For the most part, these scattered experiences did not represent the long-term institutional commitments that would lead to the development of large-scale programs. In addition, even at the end of 1979 a critical analysis of the overall results of even the most experienced centers did little to encourage greater involvement in the field. The best one-year survival rate following liver grafting was 50% for a group of 30 patients who were transplanted between 1976 and 1978. These were Starzl's so-called series II patients (Fig. 18–1). Series I consisted of 111 patients with a one-year survival rate of 29%, and series III consisted of 29 patients, of whom 34.5% survived at least one year. The overall one-year survival rate in all 170 patients in series I, II, and III was 33%. Among the first 26 series III patients, only 6 (23%) survived the first year, leading to the publication in 1980 of a paper entitled "Decline in Survival Following Liver Transplantation."[38] Azathioprine and prednisone served as the foundation for immunosuppression in these patients. A number also received adjuvant therapy with various antilymphocyte preparations. Cyclophosphamide was substituted for azathioprine in the treatment of 16 patients in 1971 and 1972, and thoracic duct drainage was employed in 21 patients during 1978 and 1979, but neither offered significant improvements in survival. During this same interval, Calne's group had a 19% one-year survival rate in their first 93 patients.[38]

Although the techniques of surgery and anesthetic management, as well as the methodology for adequate organ preservation,

Table 18–1. THE FIRST HUMAN TRIALS OF ORTHOTOPIC LIVER TRANSPLANTATION

Location	Age (Yr)	Disease	Survival (Days)	Main Cause of Death
Denver	3	Extrahepatic biliary atresia	0	Hemorrhage
Denver	48	Hepatocellular cancer, cirrhosis	22	Pulmonary emboli, sepsis
Denver	68	Duct cell carcinoma	7½	Sepsis, pulmonary emboli, gastrointestinal bleeding
Denver	52	Hepatocellular cancer, cirrhosis	6½	Pulmonary emboli, hepatic failure, pulmonary edema
Boston	58	Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
Denver	29	Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
Paris	75	Metastatic colon carcinoma	0	Hemorrhage
Denver	29	Hepatocellular cancer	7	Hepatic failure, sepsis
Denver	1	Biliary atresia	10	Hepatic failure, sepsis
Denver	1½	Hepatocellular cancer	400	Carcinomatosis

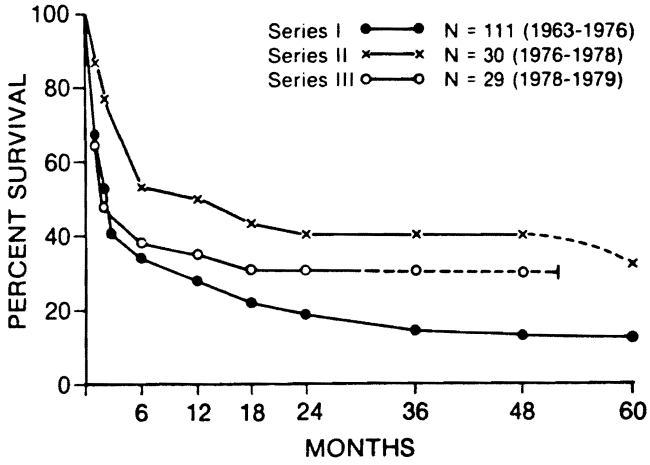

Figure 18–1. Actual survival under azathioprine and prednisone.

had been fairly well worked out, rejection of the liver or infection from immunosuppression had emerged as the major source of mortality. Further improvements in results would require improvements in immunosuppression.

The Advent of Cyclosporine

The early reports of cyclosporine use as an immunosuppressant[39–43] ignited a worldwide enthusiasm for liver transplantation. Starzl's group obtained actuarial one-year survival of greater than 70% in the first 67 patients that they treated between 1980 and 1982.[38, 43] Although patients treated with cyclosporine were not separated from groups not so treated, Calne and Williams also reported an advantage with the use of cyclosporine. Eleven of 18 (60%) patients treated with the drug survived between 3 and 31 months.[44]

The real importance of cyclosporine in improving results is difficult to assess. The argument might be made that other improvements in patient selection, surgical technique, and patient management have supervened to improve the statistical outlook for these recipients. More recently, Calne, in his book, noted that excellent results were obtained by both the Hanover and Groningen groups even before they began to use cyclosporine.[24] Yet if one looks at the single largest series of patients and examines the results of 20 years of effort by a single individual, the most important factor leading to improved patient survival during that era was the introduction of cyclosporine. The importance of careful case selection, improvements in surgical technique, or better management of patient care at some centers cannot be denied. It will become evident throughout this chapter that these factors have operated subsequently to effect even further improvements in the Pittsburgh series.

DONATION AND PROCUREMENT OF LIVERS

Donor Availability

During 1984 fewer than 300 donor livers were procured and transplanted into human recipients in the entire United States. More than half were used by the group at the University of Pittsburgh. In 1986 the number of liver transplants performed in the United States was 924 and by the end of 1987 will have risen to over 1000. Liver transplantation has been performed at more than 40 centers in the United States, and at least seven centers are now performing over 50 procedures annually.

The prospect that mounting demand for liver and other organ transplants will create increasing pressure on the medical profession to battle for rare donor organs conjures up visions which have heretofore arisen only from the imaginations of paperback novelists and Hollywood screenwriters. The very fact that in 1983, a member of the transplant community[46] proposed a system which would encourage wholesale buying and selling of organs, even to the point of compensating unwitting volunteers who might want

to make a few dollars by donating one of their spare kidneys, suggests that the material of bestseller lists may not be all that far off base. However, the reader should take considerable solace from the fact that most of the transplant community has publicly censured all suggestions that direct compensation be provided for organ donation. In addition, Congress passed legislation in 1984 (The National Transplant Organ Act, P.L. 98-507) specifically prohibiting commercial sale of human organs for transplantation.

Since suitable organs for transplantation have remained relatively scarce, other methods for increasing their availability must be sought.[45] The existing system for organ procurement falls short of optimizing the use of available donors. This can best be illustrated by an examination of some numbers.

On the demand side of the equation, The American Liver Foundation has estimated that, conservatively, approximately 5000 people in the United States have liver disease which would be optimally treated with liver transplantation.[47] If a best guess mortality of 50% per year is imposed upon this population of patients, then in order for the number to remain constant, 2500 new cases of terminal liver disease must develop annually. These gross calculations suggest that at fewer than 1000 liver transplants in 1987, the current system in this country provided the option of transplantation to fewer than one half of those people who died of liver disease.

On the supply side, one needs to examine two problems which continue to plague the system. One is the unavailability of the right donor liver at the right time. The other is the unavailability of the liver transplant operation itself.

The first of these problems is being addressed by increasing the usage of available donors as extra renal organ donors. In 1983, more than 3000 cadavers provided kidneys for transplantation in the United States, ten times the number that provided livers. By 1986, although the number of cadaveric kidney donations had risen only slightly, the number of liver donations had nearly tripled. Undoubtedly, new liver transplant centers have stimulated more regional interest in liver donation, and more of these kidney donors have provided livers. However, the approximately 3000 cadavers from which kidneys were obtained represent fewer than 20% of the total estimate of 15 to 20,000 victims of brain death seen annually in hospitals in the United States. Minimizing the wastage of these donor organs continues to be highly dependent upon the efforts of regional transplant and procurement programs to educate both the public and the rest of the medical community about the increasing needs for organs.

Recent advances in organ preservation may allow storage of the liver for up to 24 hours (unpublished observations, University of Wisconsin and University of Pittsburgh). In the more distant future, preserving donor organs for even longer periods of time, exceeding days or weeks, will allow true organ banking and may do much to correct the terrible shortage. This technology is part of the ultimate dream in the field of transplantation. Along with the fantasy of finding the "magic bullet" for immunosuppression, it gives the surgeon hope for a better future in transplantation.

Donor Selection

In making the decision about whether to use a particular donor liver, the surgeon usually must consider a number of variables and can seldom rely upon a single set of laboratory values or one aspect of the donor's history. In addition, the decision must sometimes be tempered by the urgency of the proposed recipient's condition. No clear criteria yet exist to reliably predict whether a donor liver will provide satisfactory function following transplantation. Certain general guidelines are useful only in illustrating the extremes—those conditions under which procurement of a good donor organ is either highly unlikely or highly probable.

Because hypoxia and hypotension seem to represent the most serious threats to the integrity of the liver, a careful review of the donor's history is an essential first step. An initial injury requiring prolonged cardiopulmonary resuscitation or a subsequent course complicated by multiple episodes of cardiac arrest, hypotensive crises, respiratory failure, and hypoxia, or the development of multiple organ failure, usually from sepsis, should make the transplant surgeon wary. Conversely, a stable course in the intensive care unit, especially during a prolonged period without nutritional support, may not always guarantee the quality of the donor liver.

Laboratory values are generally much more meaningful once the overall history has been reviewed. In addition, the more data that one can review, the less handicapped one's overall assessment will be. Liver function test results that appear elevated shortly after an injury but subsequently show a marked trend toward normal levels offer encouragement, especially if the stability of the overall course of the donor supports the impression that things have improved. In contrast, relatively mild but progressive elevation of serum aminotransferase (transaminase) levels may indicate continuing hepatic injury, and a search of the patient's history may reveal evidence of respiratory distress, cardiodynamic instability, or sepsis.

The donor surgeon should make the final decision about whether a donor liver is acceptable. This decision is made after visual inspection of the donor and the liver at the time of recovery. A cyanotic liver (evidence of early cirrhosis), marked edema of the liver, or the presence of direct hepatic trauma should lead to concern about the quality of the organ. If the surgeon sees any evidence that the overall donor condition has changed since the last liver function tests were performed, repeating these tests on an emergency basis may help in the decision of whether to offer the liver for transplantation.

In the end, even the seemingly most predictable situation may offer surprises. In the author's experience with more than 500 liver transplant operations between 1981 and 1987, the number of times that an apparently perfect donor liver has failed to provide adequate function following transplantation is matched only by the number of times that a so-called poor quality graft, used invariably in desperation, has succeeded in saving a patient's life. The science of assessing organ viability prior to transplantation has failed to progress beyond the rather medieval practice of sewing it in, releasing the blood flow through its vessels, and waiting to see what happens. Fortunately, primary failure of a liver graft, as discussed later in this chapter, has been the least common cause for a second transplantation procedure.[48]

The Donor Procedure

A detailed description of the techniques of liver procurement and multiple organ procurement will not be reiterated here. The interested reader should refer to publications that outline these principles and provide detailed step by step illustrations of the procedure.[17, 49–52]

Liver procurement should not be undertaken casually. The donor surgeon has the responsibility of identifying and preserving the arterial blood supply to the graft, avoiding injury to the organ arising from excessive manipulation of the liver or improper management of the donor in the operating room, and minimizing warm ischemia by thoroughly cooling the hepatic parenchymal mass before dearterializing the graft. The techniques that have evolved were designed to serve these purposes. It should be noted that when a donor provides multiple organs for transplantation, the quality of individual organs has not been jeopardized, as shown by several reviews of the authors' experience.[49, 53, 54] Indeed, the need for dialysis in the first week following transplantation among recipients of kidneys procured in concert with livers or hearts, or with both, has been much lower (12–17%) than that reported in other series in which kidneys alone were procured.

Preservation of the Liver

The inadequacies of the present methods of liver preservation are graphically illustrated by the urgency still associated with a liver procurement exercise. If satisfactory preservation of the liver for more than a few hours were possible, the spectacle of an always ready surgical team flying hundreds of miles in the middle of the night in a jet aircraft, in order to obtain the precious organs would be made archaic. Recipient operations could then be scheduled somewhat more electively, or at least could be started after a satisfactory liver was in the hands of the recipient surgical team. The true value of 12- to 24-hour liver preservation (perhaps possible with the recently developed preservation solution from the University of Wisconsin) goes far beyond the simple expediency of converting the transplant procedure from a night-time to a day-time operation.

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of 2 to 12 hours. Any ischemic interval longer than 6 to 8 hours is cause for concern, although quite satisfactory early function has been obtained from a number of organs preserved for even longer periods. In the Pittsburgh program during those years, the use of ischemia times as a predictor of the quality of graft function has been nearly impossible because of the other variables that influence the quality of the liver grafts.

Minimizing the ischemic interval requires starting the recipient procedure before the donor team has returned with the new organ. The amount of time needed for preparing the recipient may also be quite variable, depending upon the diagnosis, a history of previous abdominal surgery, or the level of skill of the operating surgeon. In most cases, the surgeon will prefer not to do anything irreversible to the native liver (such as ligating the artery) until the new liver is in hand.

Interest in improving hepatic preservation has become widespread. Cytoprotection with agents such as prostaglandins,[55-58] somatostatin,[59] calcium channel blockers,[60-62] and coenzyme Q_{10}[63-65] has been one area of focus. The use of various osmotic agents, such as D_2O,[66] or different oxygen free radical scavengers,[67, 68] has also begun to show some promise in the preservation of different organs in certain animal models. The newly developed University of Wisconsin solution takes a number of these principles into account. The solution contains unique polymer sugars (hydroxyethyl starch, lactobionate, and raffinose) as non-ionic osmotic agents, anti-oxidants, and oxygen free radical scavengers (glutathione and allopurinol), and both adenosine and phosphate for more rapid restoration of adenosine triphosphate (ATP) levels following revascularization of the liver. This solution follows the earlier work by Belzer's group in Wisconsin showing the utility of adenosine and phosphate in the preservation of kidneys.[69, 70]

The impact of these studies upon clinical practice has yet to be determined. Methods that offer the prospect of truly long-term organ storage for days to weeks, or even longer are not yet on the foreseeable horizon. Such a leap in preservation technology will likely require the kind of revolutionary changes that make present day thinking obsolete.

THE RECIPIENT

Indications for Transplantation

Figure 18–2 shows the major indications for transplantation in a total of 313 patients (177 adults and 136 children) who underwent transplantation with cyclosporine and prednisone immunosuppression between March

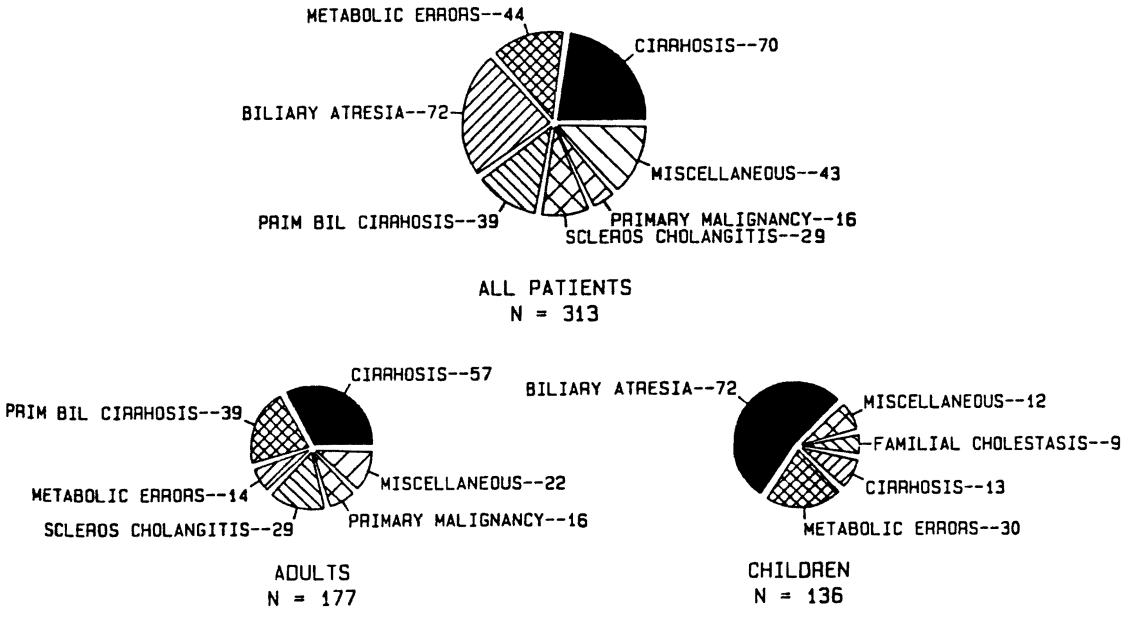

Figure 18–2. Indications for liver transplantation in 313 patients from 1980 to 1984.

1, 1980 and December 31, 1984. Postnecrotic cirrhosis was the most frequent diagnosis in adult patients and biliary atresia was most frequent among those 18 years or younger. Primary biliary cirrhosis and sclerosing cholangitis represent two other major diagnostic categories in adults.

Candidacy

Clear criteria for selecting patients for liver transplantation are not yet available (mainly because of a lack, until recently, of enough patients to provide a valid retrospective analysis of risk factors). With improvements in results, and a situation in which demand far outstrips the current availability of the procedure, optimal selection of recipients has become not only justifiable but also mandatory.

Any patient whose life is threatened by advanced liver disease or whose lifestyle is seriously affected by that disease and for whom other medical or surgical therapy offers no reasonable hope for improvement is a candidate for liver transplantation. Contraindications include the presence of sepsis, extrahepatic malignancy, or severe disease of other organs that would not be expected to improve with liver replacement. The difficulty arises in increasing the criteria for exclusion beyond these simple, rather self-evident criteria.

Three Pittsburgh studies indicate what some of the risk factors that might obviate transplantation are.

The first was a simple analysis, done in mid-1983, of what effect location of the recipient prior to transplantation had on ultimate survival. Six-week survival in those who went to the operating room from the intensive care unit was 42% compared with 84% for those who were in the hospital but on the ward and 68% for those who were outpatient care dependent.[71]

The second was a study of the effect of venous bypass on survival of adult patients undergoing liver transplantation.[72] Overall survival at 30 days was found to have been improved by the use of venous bypass, but these patients appeared to no longer have an advantage by 90 days when compared with a group of historical controls transplanted without the use of venous bypass. The reasons became more evident when these patients were classified into one of three groups, depending upon preoperative risk factors. Those in the high-risk group were patients who were deeply encephalopathic or who had frequent episodes of stage III or IV coma and patients with marked nutritional depletion, massive ascites, severe coagulopathy, renal failure, or recurrent episodes of massive variceal bleeding. Also included were patients who were thought to be at increased risk because of a history of extensive abdominal surgery involving the liver. The use of venous bypass appeared to offer the advantage of a greater chance of survival to those patients in the low- and medium-risk groups at both the 30- and 90-day intervals following transplantation. The high-risk group, on the other hand, experienced a marked improvement in survival at 30 days compared with another group of high-risk patients transplanted without venous bypass, but they went on to experience an inordinate mortality during the next 60 days so that by 90 days, their mortality was the same as the group without venous bypass. In fact, the only long-term survivors in the high-risk, venous bypass group were those few patients so classified for technical, rather than physiological, reasons.[72]

The third study was a multivariant analysis of a variety of patient characteristics in an attempt to develop a mathematical formula for assigning relative risk scores to patients preoperatively.[87] An empirical scoring system was created which accounts for the patient's preoperative serum bilirubin, prothrombin time, amount of ascites, history of encephalopathy, degree of nutrition, renal failure, and age. Following transplantation, this preoperative score should be modified by a blood loss factor, which increases the overall score if total operative blood loss is excessive. The relationship between this empirical score and the probability of the patient surviving at least six months following liver transplantation is best described by a sigmoid shaped curve (Fig. 18–3). Depending upon their score, patients could be separated into one of three major groups: low, indeterminate, and high risk. The risk for those with scores falling on the steep part of the sigmoid curve were felt to be difficult to estimate. However, of nine patients with high-risk scores (7 or above) only two (22%) survived at least six months, whereas 79 of 82 (96%) patients with low-risk scores (3 or below) were alive at six months.

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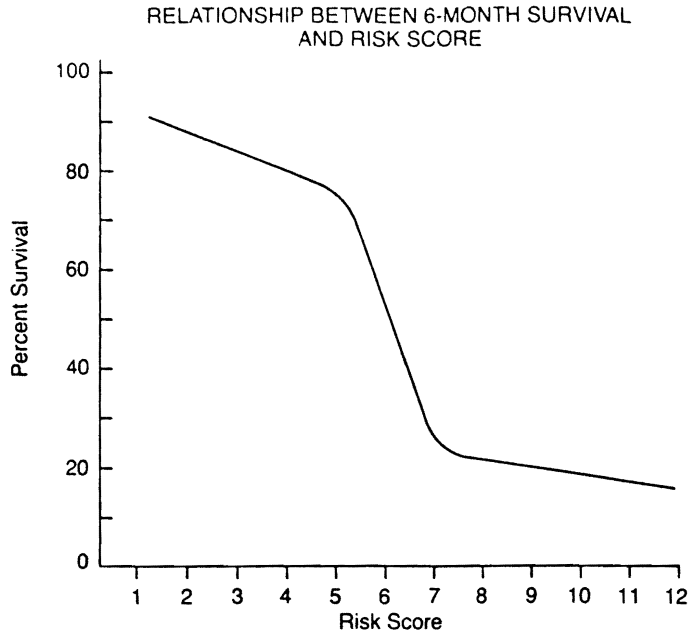


Figure 18–3. Curve showing theoretical relationship between prospective risk score and an adult patient's probability of surviving at least 6 months following liver transplantation.

The major implication from these studies should not be ignored. Technical improvements have done much to improve the perioperative survival of liver transplant recipients, but beyond the immediate interval after surgery, the impact of this progress is lost entirely on the physiologically high-risk patient. Patients should be referred for consideration for liver transplantation long before the ravages of their liver disease make survival highly improbable. Justification for this attitude comes from an understanding of current survival statistics.

RESULTS

Survival

Survival curves based upon life table analysis of 313 patients (177 adults and 136 children) with a minimum follow-up of six months are shown in Figure 18–4. As in previous studies, the survival rate in children (77% at two years) is greater ($p < .0001$) than that for adults (59% at two years). The increased mortality in adults occurs mainly within the first 90 days after surgery (84% 90-day survival in children versus 70.6% in adults). One- and two-year survival rates are 71 and 67%, respectively, for the entire group of 313 patients. The actuarial four- and five-year survival rate is 64.3%, with 37 patients at risk at the beginning of the fourth year.

A further breakdown of these patients into diagnostic categories and the resultant survival curves for adults are shown in Figure 18–5 and for children in Figure 18–6. At two years, adults with sclerosing cholangitis have a better chance of survival ($p = 0.027$) than all other adults (71.5% versus 56.8%, respectively). Patients with primary biliary cirrhosis also have somewhat better two-year survival than all other adults (64% versus 56.6%), but the difference is not significant ($p = 0.184$). Adults wtih postnecrotic cirrhosis had a 55.5% two-year survival rate. The differences in survival rates among all diagnostic groups are not statistically different at one and two years.

Children, the largest group of patients (72 with biliary atresia), have a survival curve that reaches 78% at one year and remains flat thereafter, with four patients at risk at the beginning of the fifth year. Thirty children with metabolic disorders compose the second largest group, and they had an 83% chance of survival after one year ($p = 0.347$ versus the remainder of children), with 25 children alive and at risk after the first year, and 18 children at risk at the start of the second year.

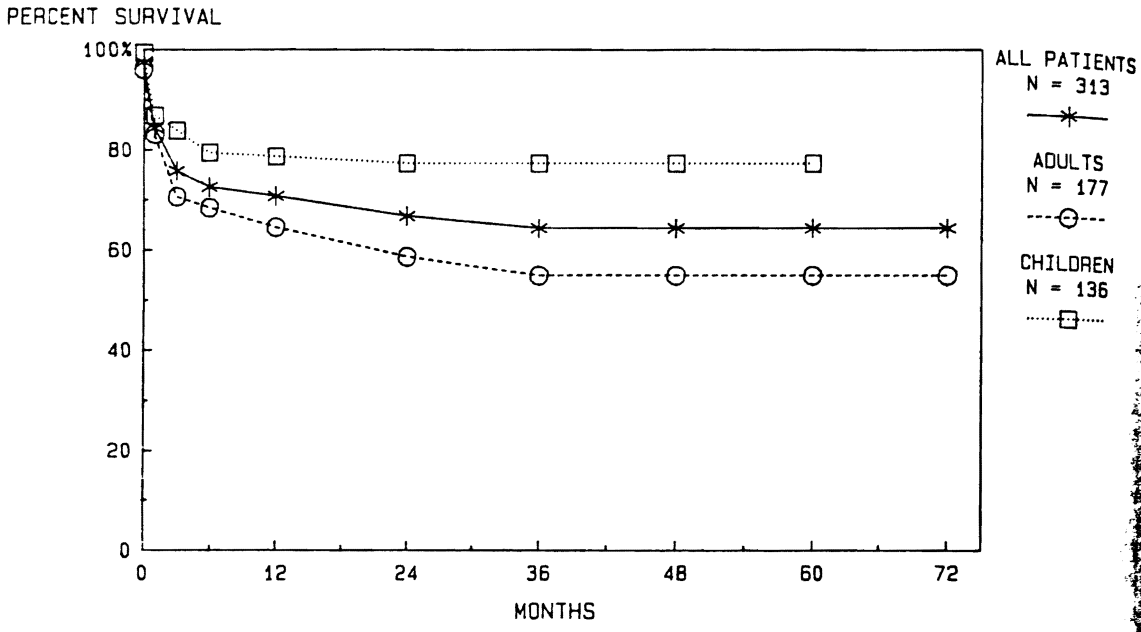


Figure 18–4. Actuarial survival of 313 liver transplants in 177 adults and 136 children between 1980 and 1984.

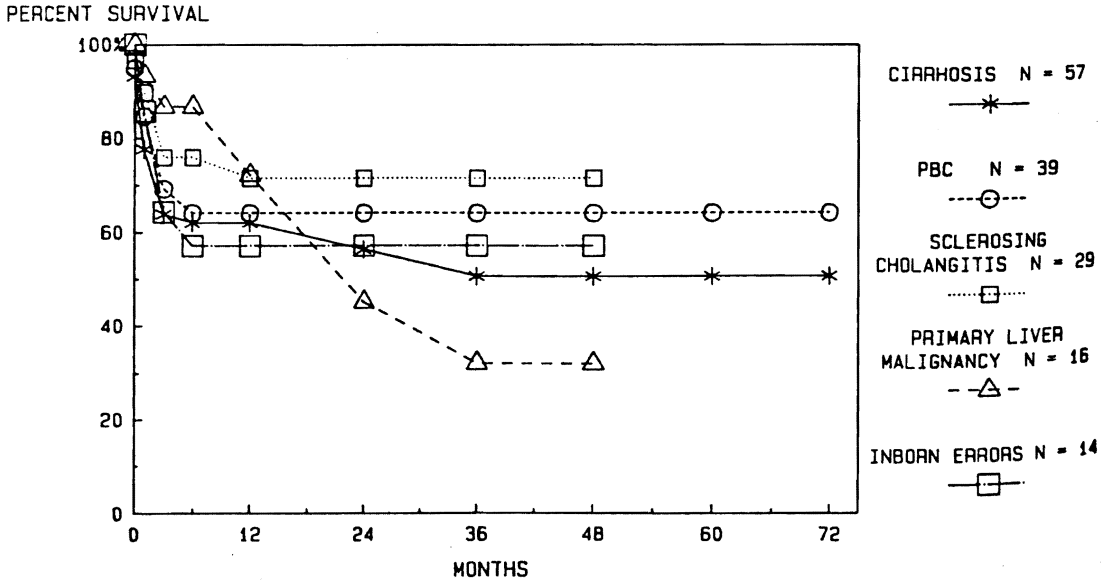
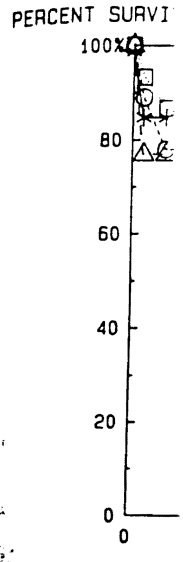


Figure 18–5. Actuarial survival after liver transplantation in adults based on the primary indication for liver replacement.



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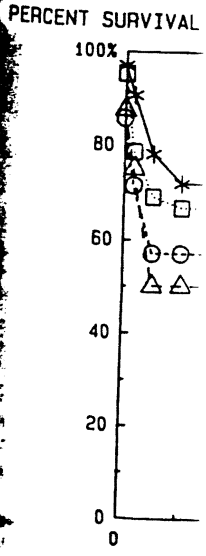

Figure 18–7. Actuarial su
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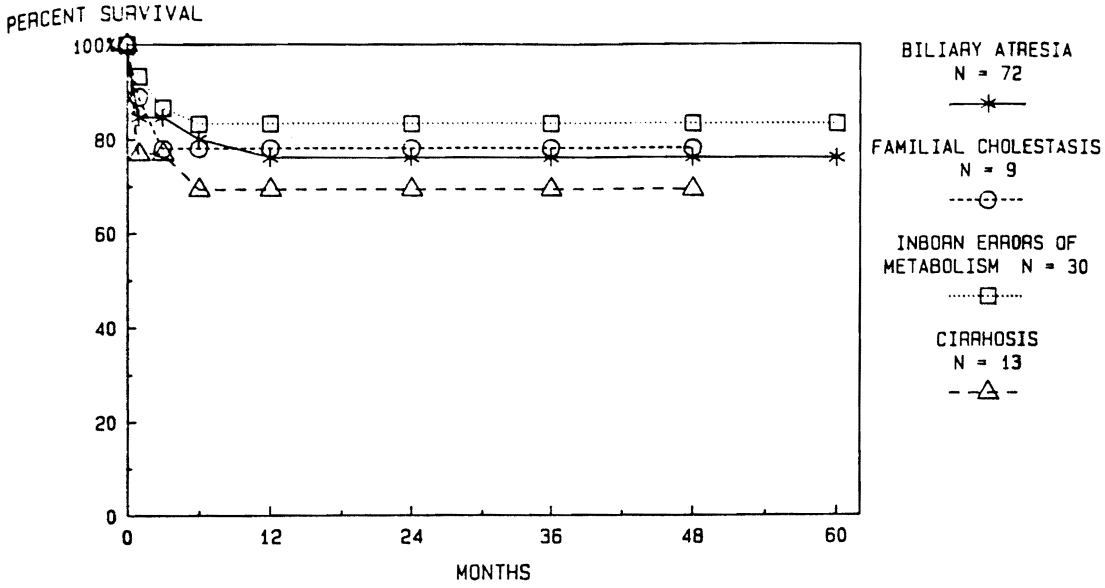


Figure 18–6. Actuarial survival after liver transplantation in children based on the primary indication for liver replacement.

A total of 15 patients in the series were aged 50 years or older. The one- and two-year survival rates in this older group were 67 and 54.5%, respectively. The greatest effect of age upon survival was seen in those with cirrhosis (Fig. 18–7). Among the 57 adult recipients with cirrhosis, 41 were less than 40 years of age and 16 were greater than 40 years. At one year following transplantation, survival in the younger group (66%) was significantly better ($p = 0.039$) than for the older group (50%). The difference was even more marked at two years (66 versus 21%, $p < 0.0001$). The seven patients with primary biliary cirrhosis aged 51 years or older also had a lower two-year survival rate (57%) than the 32 patients who were 50 years or younger (71.9%), although this difference was not significant ($p = 0.22$). Age was not a factor in determining survival in the overall group

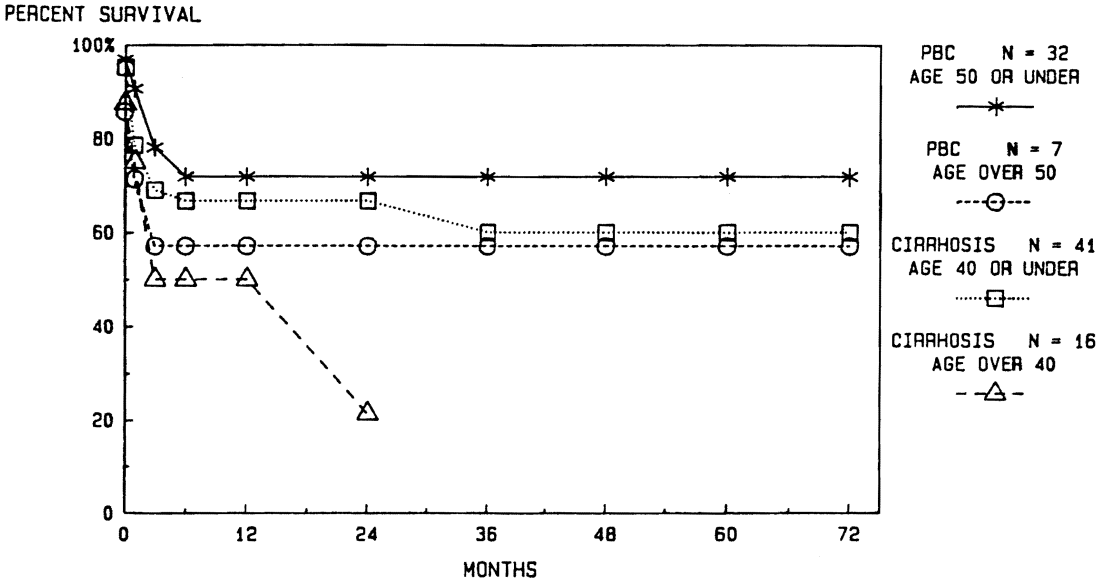


Figure 18–7. Actuarial survival after liver transplantation for postnecrotic cirrhosis or primary biliary cirrhosis based on age.

of adults, using age 40, 45, or 50 years as the cutoff point.

Patients with primary hepatic malignancies have one-year survival rates that compare quite favorably with the remaining group of adults (74% versus 64%, respectively, $p = 0.238$). However, at two years, their survival decreased significantly ($p = 0.015$ for one versus two years) to 48%, which was worse (but $p = 0.08$) than the remainder of adult patients (60.5%). Figure 18–5 reveals this eventual rapid decline in survival that occurs as the result of tumor recurrence. The issue of whether transplantation should be offered to these patients and how tumor type might affect that decision was the subject of a recent report by Iwatsuki,[73] which compared transplantation with resection therapy. With rare exceptions (e.g., the fibrolamellar type of hepatoma), the use of transplantation in the treatment of primary hepatic malignancies may be justified only when combined with experimental protocols employing adjuvant therapy in ways that represent a radical departure from current standard approaches.[74]

Quality of Life

Previously, the authors reported that of 33 transplant patients of the precyclosporine era who survived five years or more following transplantation, two subsequently died and 29 others are managing households, attending school, or employed full time.[75] A look at 90 patients treated after the introduction of cyclosporine and surviving six months or more reveals that all but nine are fully rehabilitated. Among the nine exceptions, two have recently undergone a second transplant, two have required hospitalization for treatment of rejection, and five others require continuing physical rehabilitation or are receiving adjuvant tumor therapy.

IMPROVEMENTS, 1982 TO 1985

Technical Improvements

The basic technique of the recipient hepatectomy and the transplantation of the donor liver has remained principally unchanged (Fig. 18–8). Detailed descriptions are available from a number of other sources and will not be repeated here.[17, 76–78] What will be covered are the recent changes in technique resulting from the development of the venous bypass technique and better management of patients by anesthesiologists.

The technique of venous bypass, which does not require systemic anticoagulation, was developed in the laboratory and first reported by Denmark in 1983,[79] and later modifications for its first clinical use were the subject of a paper by Griffith and associates[80] (submitted and accepted in mid-1983 but unfortunately not published until nearly two years later). The technique was employed routinely in the transplantation of all adult patients in Pittsburgh starting in February 1983 (Fig. 18–9). Shaw and associates were able to report in 1984 that the routine use of venous bypass resulted in a marked decrease in mean intraoperative blood loss, an improved cardiodynamic stability during the anhepatic phase, a significant improvement in renal function after surgery, and a reduction in early mortality, including a virtual elimination of operative deaths.[72]

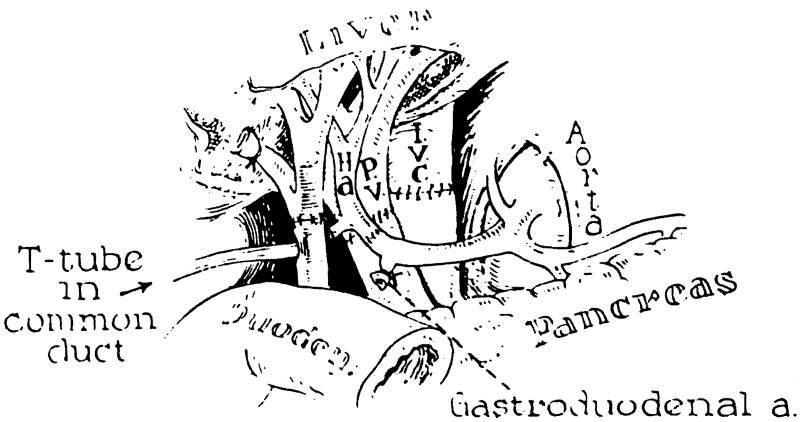
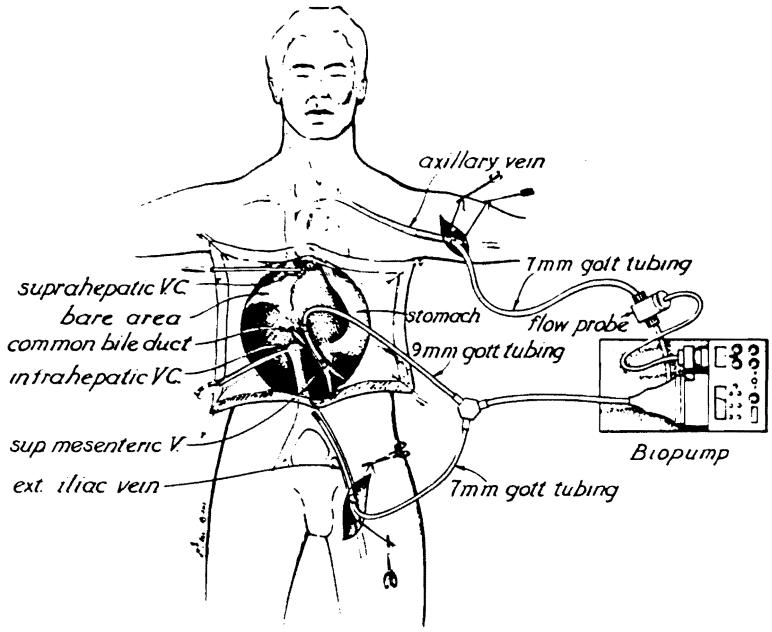


Figure 18–8. The most frequently used methods of vascular and biliary reconstruction in orthotopic liver transplantation. Most often, the arterial anastomosis is made in an end-to-end fashion between the donor celiac axis and the recipient common hepatic artery, proximal to the take-off of the recipient gastroduodenal artery.

Figure 18–9. Anhepatic orthotopic liver transplantation using the use of venous bypass circuits that are heparin-bonded are commercially available, obviating Gott shunts.

One must not underestimate the impact of several recently improved techniques. Not the least of these is the role of a liver team by anesthesiologists in improving the intraoperative importance of monitoring ionized calcium levels, thromboelastography, product replacement, etc. There are only two results following this same interdisciplinary team's experience that also may have contributed toward improving survival. Finally, the more widespread transplantation practice has also led to more patients at the first anniversary of operation. Approximately 80% of patients will remain alive and in the author's center obtain about a 50% one-year survival, thus accounting for the group who survive. Excellent results are obtained when transplant is planned on an elective basis, such as follows. Worst results are obtained in emergency basis, such as dysfunction of a new graft or technical failure such as



igure 18–9. Anhepatic phase of orhotopic liver transplantation showg the use of venous bypass. Tubg circuits that are completely eparin-bonded are now commerially available, obviating the use of ott shunts.

One must not underestimate, however, the impact of several other factors that undoubtedly improved the overall results during this time. Not the least of these was the formation of a liver team by a number of enthusiastic anesthesiologists who had an interest in improving the intraoperative course. The importance of monitoring and maintaining ionized calcium levels and the ability to use the thromboelastograph to optimize blood product replacement therapy for coagulopathies are only two results of this interest.[81, 82] During this same interval, the fact that the surgical team's experience expanded dramatically also may have had a beneficial effect toward improving results.

Finally, the more aggressive use of second transplantation procedures during this time also led to more patients surviving beyond the first anniversary of their transplant operation. Approximately 20% of a large series of patients will require second transplants, and in the authors' experience, they will obtain about a 50% one-year survival rate, thus accounting for about 10% of the overall group who survive long-term. The best results are obtained when the second transplant is planned on a more or less elective basis, such as following rejection, and the worst results are when it is done on an emergency basis, such as for primary lack of function of a new graft or following a technical failure such as arterial thrombosis.[48]

Improvements in Immunosuppression

The most significant change in the management of immunosuppression in Pittsburgh arose from the availability of daily cyclosporine blood levels. Evidence quickly became overwhelming that absorption and metabolism of cyclosporine were highly variable in this group of patients. Absorption has been shown to be dependent upon diet, and bowel habits and whether the patient has diversion of bile through a T tube in the bile duct.[83–85]

The regimen of immunosuppression employed in Pittsburgh in mid-1985 consisted initially of the same taper of steroids reported previously[86] (in adults, 1 g methylprednisolone succinate at the time of transplantation, then a taper of 40 mg of steroid/day starting at 200 mg and leveling off at 20 mg daily by the sixth day, and in children, 500 to 250 mg methylprednisolone bolus and a daily taper by 20 mg from 100 to 10 mg), combined with 2 mg/kg of intravenous cyclosporine three times daily. As soon as the patient's ileus had resolved, oral cyclosporine was started at 8.75 mg/kg twice daily.

The dose of cyclosporine is adjusted daily in order to maintain a trough whole blood level of 1000 ng/ml, as measured by radioimmunoassay. This normally requires an initial reduction of the intravenous dose (usu-

ally by decreasing the frequency of intravenous dosing to twice daily) on about the third or fourth postoperative day. If a T tube is in place, care should be taken to observe cyclosporine blood levels for 24 to 48 hours after clamping the tube, since absorption may be markedly enhanced.

In other patients, particularly in children, the development of diarrhea usually heralds an episode of rejection accompanied by low blood cyclosporine levels. In these patients, uncertainty exists about whether the diarrhea leads to malabsorption of the drug, which then leads to low levels and the subsequent emergence of rejection, or whether the diarrhea may develop as the result of poor bile output secondary to liver malfunction, which is itself the result of rejection. In the latter scenario, an insidious rejection episode may serve to amplify itself by causing less bile dependent absorption of cyclosporine.

Interactions with other drugs that may alter cyclosporine blood levels must also be borne in mind. In the authors' experience, phenytoin, barbiturates, and combinations of trimethoprim and sulfa antibiotics are the drugs most frequently used in liver recipients that can markedly lower cyclosporine levels.

Rejection episodes are treated with an intravenous bolus of steroid (usually 1 g methylprednisolone in adults) followed by a cycle of prednisone that is comparable to that given over the first six days after surgery. More recent additions to the basic immunosuppression regimen include the occasional use of antithymocyte globulins (ATGAM, manufactured by Upjohn and the monoclonal globulin, OKT_3, manufactured by Ortho) or azathioprine in steroid resistant rejection. Thus far the results with these other modalities are too preliminary to be reported, but prompt reversal of aggressive, otherwise unresponsive rejection has been obtained with all three drugs or combinations thereof. The fact that rejection remains the most prominent cause for failure in liver transplantation only serves to underscore the need for continuing to improve the armamentarium against it.

CONCLUSION

The future of liver transplantation as a viable form of therapy for the treatment of a variety of liver diseases seems more certain than at any time since Starzl's first attempts at the operation in the winter of 1963. Performing more than 400 transplant procedures on more than 300 patients during a four-year period from 1981 through 1984, and without the use of any formal process of selection of low- or even medium-risk patients, the group in Pittsburgh was able to obtain one-year survival rates of greater than 70%, with actuarial five year rates near 65%. The prospects for patients at less risk are even brighter.

Since this chapter was written in early 1985, a number of other centers have begun reporting one-year survival rates that range from 65% to 85%. These reports represent a truly successful diffusion of the technology and skills necessary for beginning to address the greater need for liver transplant therapy that has evolved in this country during the past seven years.

This optimism should not be mistaken as a license for every curious surgeon or institution to dabble in the field. Effective use of precious donor organs to treat the large number of waiting recipients nationwide requires full time involvement in the field by institutions committed not only to providing the procedure as a service but also to investigating new inroads into improving the field. The next five years will likely see the emergence of 15 to 20 centers performing 25 or more transplants per year in the United States, with at least 10 centers capable of performing 50 or more operations.

In the near future, immunosuppression will continue to involve the use of cyclosporine doses that are more tailored to the individual patient, with the addition of other agents such as azathioprine or antithymocyte preparations of various types, or both. Cyclosporine analogues may prove less toxic and replace the current cyclosporine A. The recent First International Workshop on FK-506, entitled "A Potential Breakthrough in Immunosuppression," revealed that this newly discovered macrolide, with immunosuppressive action very similar to that of cyclosporine, but at concentrations at least 100-fold lower, may add a significant new weapon to the polypharmaceutical armamentarium. The drug also has serious toxic side effects at doses which, when the drug is used alone in animal models, are not immunosuppressive. Most likely, the drug will prove to be most useful because of its apparent profound sy-

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ergism with cyclosporine, since comparatively low doses of both drugs have tremendous immunosuppressive effects.[88]

Much work is under way, and a great deal of interest has been sparked in the field of hepatic preservation. As mentioned previously, a number of approaches show promise of significant improvements. Paramount to all of this work will be the development of some method of accurately assessing graft viability prior to the actual transplant.

The issue of costs has not been mentioned in this chapter thus far. The mean cost in Pittsburgh during fiscal 1983 to 1984 was about $105,000/case (median costs were closer to $75,000). With inflation and an exponential increase in the number of cases performed there, the costs have no doubt risen even more in the last several years. The impact upon the national health care system of this new enthusiasm for the procedure will not be trivial. However, overall costs of liver transplantation therapy will only decrease with greater participation in the field by a number of centers all striving to improve results through better technique, better patient selection, and better immunosuppression.

Finally, one cannot ignore the greater impact that these programs may have upon improving health care for an even larger portion of society. Advances in the field of transplantation undoubtedly will have important "spin-off" effects upon the ability to treat other disorders, such as cancer, autoimmune diseases, and even viral illnesses.

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