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613

TRANSPLANTATION OF THE LIVER

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INTRODUCTION

Within the past three to four years perhaps no other surgical endeavor has attracted more renewed attention, both from the lay and medical communities, than that of transplantation of solid organs. To discover the single most important cause for this sudden burst of interest one need look no further than the introduction of the new immunosuppressant, cyclosporine. This claim in no way denies that many other important advances have been made in the field over the past 20 to 25 years. Several renal transplant centers were already obtaining outstanding graft and patient survival rates well before cyclosporine came along^{1,2}. No doubt judicious use of new knowledge regarding the value of tissue matching in the Dr histocompatibility loci, and the discovery that deliberate blood transfusion protocols in kidney recipients could enhance graft survival, as well as careful management and selection of recipients all contributed to improvements in results. The assertion over the importance of cyclosporine also should do nothing to diminish the importance of certain other improvements, both technical and conceptual, made in the fields of heart, heart-lung, liver and pancreas transplantation where several groups had continued to struggle for the kind of advances without which cyclosporine would have had a lesser impact^{3,4,5}.

The importance of the arrival on the scene of a new, more effective immunosuppressive agent cannot be properly interpreted without an understanding of the larger history of the field of transplantation. This will become particularly evident in the early part of this chapter on hepatic transplantation. That cyclosporine is far from a "magic bullet" for the

prevention of rejection will also become evident as we discuss the various difficulties and short-comings encountered with its use.

The recent literature is replete with articles about liver transplantation, many of which can serve as comprehensive reviews of the subject ⁶⁻⁹. In addition, virtually every major textbook of surgery or transplantation written within the past ten years contains a chapter or section concerning hepatic transplantation. The major purpose of the present chapter, then, is to serve not just as a general review of the subject, but also to share with the interested reader some of the issues currently facing those physicians who are actively involved in offering liver transplantation as an effective approach to the treatment of a large variety of disorders of the liver.

COSTS AND BENEFITS OF THERAPY

Assessing the various costs involved in providing a form of therapy can be a formidable job. Furthermore, any form of therapy with which those costs run high naturally raises concern over whether the benefits accrued justify the costs. On the other hand, these questions are seldom posed by and they are difficult issues to address for those physicians who may have devoted a life time toward developing and refining the particular therapeutic modality under scrutiny. Until recently, transplantation of the liver was such a rarely performed procedure, being done in the United States on a continuous basis at only one center and at an average rate of less than 20 cases annually, that these issues seldom attracted much attention outside the relatively small brotherhood of health care personnel intimately involved with these procedures. But the improvement in results attending the introduction of cyclosporine in late 1979 and early 1980, as will be further emphasized throughout this chapter, stimulated such a renewal of interest in the procedure that major medical centers throughout the country, prodded by the professional and lay communities alike, began to look into the various cost-benefit ratios of providing liver transplantation as a service.

By the time the first symptoms of the national liver transplant fever had become undeniable in late 1982, the key question repetitively raising its head was "who pays?" Although several major health insurance companies had decided in favor of covering the steep costs of the procedures for their policy holders, a far greater number denied any such obligations by maintaining that the procedure was still experimental in nature. The various

state welfare agencies were equally disparate in answering the question of payment.

In an effort to address some of these issues as well as others, the National Institutes of Health convened a consensus conference in Washington, D.C. during June of 1983. The various opinions, facts and data presented by the wide ranging group of specialists invited to speak at the conference as well as a consensus statement have been published.¹⁰ When interpreting some of this information, one must keep in mind both the speculative as well as the ephemeral quality of its accuracy. Nevertheless, the most important single conclusion of the conference was quite simply that liver transplantation is a viable therapeutic modality for a variety of disorders. Although one express intention of the conference was to steer clear of any opinions about who should pay, or for that matter how much should be paid or to how many or which centers, the official statement quite clearly removes the label "experimental" from hepatic transplantation therapy.

Formal debate of the question of payment is beyond the scope of this chapter. No doubt in the years to come, as liver transplant services begin to sprout in medical centers around the world, the issues involved will become more popular topics for discussion in a wide variety of venues (Figure 1).

Accurate information is available, however, regarding some of the costs involved with the procedure. These are illustrated in Table 1 for 31 adult patients selected at random from 1984 and for the total 55 pediatric patients transplanted during the 1983-84 fiscal year in Pittsburgh. The mean costs for all patients have a tremendous standard deviation because of the wide range

of costs. The median figures give a more realistic accounting of "average" costs. Costs were lower for children overall than for adults. The median cost for all patients (\$75,691) is virtually identical to the median costs for all children (\$75,927) and for all adults (\$75,691). The lowest costs were for pediatric patients who only required one graft, and highest for those 11 children who needed two or more livers.

One must keep in mind that these figures are being generated by a surgical service that, though the most experienced in the world, is constantly pushing the acceptable limits of patient candidacy for the procedure. If the number of high risk patients could be minimized either by earlier consideration for transplantation or by designation into other tracts of therapy, these costs could no doubt be lowered significantly. More will be said about the question of candidacy later in this chapter.

Attempting to compare these costs with alternative methods of care is, in most cases, a mute point since no such alternatives exist. In these instances one must compare the costs of liver transplantation with the costs of death. Although the analysis begins to stretch beyond the intended scope of this chapter, a look at the numbers in terms of how many patients survived the treatment and how many are restored to a productive life is worth accounting.

Table 2 shows that in the pre-cyclosporine era, of the 25 patients surviving five years or more and still living, 20 are employed full time, attending school, or involved in managing households. Although cyclosporine therapy has not been available for more than four years, Table 2 also shows similar information about 81 adult patients surviving 6 months or more after

transplantation under the new drug. Of the 7 patients in the cyclosporine era who are disabled, 4 require recurring hospitalization for continued physical rehabilitation and 2 for adjuvant tumor therapy. Virtually all children are either back in school or otherwise doing well.¹¹

HISTORICAL PERSPECTIVE

The transplantation of vascularized, solid organs was a logical extension of the development of the techniques for vascular anastomoses. Alexis Carrel has been credited with showing that blood vessels could be sewn together with a reasonable expectation that blood would continue to flow through them for extended periods of time.¹² Emerich Ullman, in 1902 demonstrated that the removal of a kidney from one animal and revascularization in another was a technical feasibility.¹³ Other early experiments revealed that auto transplants could be done successfully, but that even by using the same surgical techniques, allotransplants failed. This led Carrel in 1910 to claim that "the physiologic disturbance could not be considered as brought about by surgical factors. The changes undergone by the organ would be due to the influence of the host, that is the biological factors."¹⁴ Thus with these technical successes, Carrel also demonstrated an observance, if not an understanding of the phenomenon of tissue rejection. No less so with the liver, the early history of organ transplantation can be broken down into that dealing with advances in surgical methodology and that involving developments in immunology.

Early Experimental Techniques

The early work with *heterotopic* liver transplantation in dogs, reported first by Welch ¹⁵ and subsequently by others¹⁶⁻¹⁸ was done without immunosuppression. These organs were destroyed after several days, apparently as a result of rejection. Nevertheless, the observation that they produced bile,

at least for an initial period of time, and appeared normal in color and texture was encouraging.

But the real test for the methodology for removal of a liver from one animal and revascularization into another took place when, in the late 1950's, Moore¹⁹ at Peter Bent Brigham Hospital and Starzl²⁰, then at Northwestern University in Chicago, developed their techniques for *orthotopic* transplantation in dogs. Survival following *orthotopic* replacement of an unpaired, vital organ requires, by definition, that a certain high level of organ function be obtained. In these early experiments on unmodified canine recipients, the death rate was exorbitantly high. Despite these discouraging results, Starzl persisted in his efforts to improve the surgical technique, the methods of organ preservation, and the management of anesthesia so that by 1965, he could report that 22 Of 23 unmodified dogs survived at least two days following surgery, with 19 surviving at least six days. These animals served as one of the control groups in a series of elegant experiments which were presented in a landmark paper at the 26th annual meeting of the Society of University Surgeons in 1965.²¹

These studies demonstrated not only the course and nature of rejection of liver grafts in dogs, but also proved that, just as with renal allografts, rejection could be modified successfully with immunosuppression. In the same paper, Starzl only casually mentions the improvements in techniques responsible for the virtual elimination of perioperative mortality in these animals, an accomplishment which he modestly attributes to having gained "considerable experience". The paper belies the kind of Herculean effort required from Starzl and his colleagues to develop a whole new technology, perhaps the most

complex and demanding in the field of surgery, technology that was necessary simply in order to get animals to survive long enough to approach the next great hurdle, that of tissue rejection. Without belaboring the point further, suffice it to say that what Starzl refers to as "gaining considerable experience" was responsible for his developing most of the techniques which are used today in the clinical transplantation of the liver. This will become more evident as we enter the discussion of operative techniques.

Early Experimental Immunology

The early observation that unmodified canine liver recipients would eventually succumb to rejection of their livers in a way not dissimilar to that seen with renal allografts was less surprising than the observation that sometimes the liver grafts failed to obey these so-called normal rules. Starzl reported occasional long term survival in unmodified dogs in 1961²². Later, Garnier²³ observed even greater acceptance of liver grafts in unmodified pigs. These results were in contrast to those seen with random skin or kidney grafts, both of which were promptly rejected in all unmodified dogs or pigs. In 1969, Calne went on to show that unmodified pigs who failed to reject their liver allografts were subsequently rendered hyporeactive to skin or kidney grafts from the same donor²⁴. Although a similar immunosuppressive effect of liver grafts were not found in dogs by Starzl²¹ or in primates by Myburgh²⁵, Zimmermann²⁶ demonstrated an identical phenomenon in rats.

Early theories proposed to explain the apparent "privileged status" of liver grafts as well as the immunosuppressive effects in some animals were

largely speculative.³ One thought was that since the liver is such a large organ, the large antigenic mass simply overwhelmed the immune system of the recipient. Another theory was that since the liver itself comprises a large part of the reticuloendothelial system, a grafted organ replaced a large part of the machinery necessary for the organism to mount an immune response. A third proposal held that the transplanted liver released soluble factors into the serum which helped to block its own rejection.

Subsequent work with the rat model by the group at Cambridge has resulted in an increased understanding of the possible mechanisms for this so-called "privileged status"²⁷. These authors conclude that the fate of liver grafts is primarily determined by immune response genes of the recipient. Accordingly, so-called high responders reject livers as readily as they do other organ grafts whereas low responders not only fail to reject livers, but also appear to develop profound systemic tolerance to donor specific antigens. They have shown that this specific tolerance is accompanied by deletion of specific clones of cells normally responsible for reaction to the specific donor antigens, while those clones responsive to other antigens are retained. In addition, they found powerful and specific immunosuppressive molecules in the sera of liver grafted rats. They have found no evidence for the development of populations of either donor specific or non-specific suppressor cells in these tolerant rats.

The direct impact of these studies upon clinical liver transplantation is undetermined. Since, as yet, no similar mechanisms have been delineated in humans. On the other hand, working with the canine model, Starzl was eventually able to obtain prolonged survival using immunosuppression with

azathioprine ^{3,21,28} and anti-lymphocyte serum or its globulin derivative (ALG)^{3,29-32}. These early successes using immunosuppressive agents to treat rejection of the liver in animals, combined with the massive experience accumulated with the operative technique led to the first human trials of hepatic transplantation.

Early Clinical Trials

On March 1, 1963, Starzl performed the first transplantation of the liver in a human.³³ But that winter day in Denver, Colorado is more important to the field as the day on which Starzl finally broke the ice than as the date on which liver transplantation became a clinical reality. This first attempt was the logical next step in the progression of the intensive research efforts started in the Denver and Boston dog laboratories over four years earlier. Nevertheless, the first patient, a three year old boy with biliary atresia, died of uncontrollable hemorrhage on the operating table. Over the next ten months, four more attempts in Denver and one each in Boston and Paris were also unsuccessful (Table 3), thus halting further clinical trials for three more years. Starzl's sixth attempt in November, 1966 and seventh in May, 1967, also failed to provide prolonged survival. The first patient to obtain extended survival was a 1 1/2 year old girl transplanted on July 23, 1967 as treatment of primary hepatocellular carcinoma. She died thirteen months later of diffuse metastases.

In May, 1968 in the United Kingdom, Calne of the University Hospital at Cambridge and Williams of King's College in London embarked upon their series which, together with the Denver series of Starzl, account for the overwhelming

majority of cases performed in the world during the subsequent decade. During that interval, however, single cases or small series of liver transplants in humans were also reported from Boston^{34,35}, Los Angeles³⁶, Montreal³⁷, Bonn^{38,39}, Sao Paulo⁴⁰, Calgary⁴¹, New York City⁴², Richmond⁴³, Minneapolis⁴⁴, Manchester⁴⁵, and Oslo⁴⁶. The importance of these early trials and the experience that they generated with the use of a variety of regimens of immunosuppression, originally developed for treatment of kidney recipients (Table 4) cannot be over estimated.

Yet by the end of 1978, little progress had been made toward significantly improving survival following hepatic transplantation. The best patient survival reported during this decade was a 50% one year rate reported by Starzl for his so-called Series II patients, a group of 30 patients transplanted between 1976 and 1978. However, the subsequent 26 patients were the subject of a paper entitled "Decline in Survival Following Liver Transplantation" and published in 1980⁴⁷. Of these 26 cases, only six (23%) survived beyond the first year following transplantation (Figure 2). Of particular note, most of the techniques of the operative procedure, of anesthesia management and postoperative care as well as those of organ preservation had been developed to a point where rejection or over immunosuppression in an attempt to control it were the major causes of death in a majority of patients during that era. Clearly the field lay open and fertile for the introduction of a new, more potent and hopefully more specific immunosuppressant.

The Beginning of the Cyclosporine Era

An editorial in the July 11, 1981 issue of the British Medical Journal declared: "Liver transplantation has come of age: It gives a chance of excellent rehabilitation for patients with no other treatment available and the operation is probably less costly than prolonged care of a patient dying of liver disease in the hospital." The journal was responding to the reports from both Denver and Cambridge of marked improvements in survival of liver recipients following the introduction of the then new immunosuppressive agent, cyclosporin A.⁴⁸⁻⁵² In particular, Starzl's initial report of 71% one year survival was startling and compared quite notably with previous results (Figure 3).

The ultimate impact upon the whole field of liver transplantation of these early reports has been a rebirth of enthusiasm for the procedure of epidemic proportions. At the end of 1980, after 17 years of clinical transplantation of the liver, the total number of cases performed in the world was probably less than 350. Most of these had been done at two centers (Denver and Cambridge), with steadily increasing involvement by two other institutions (Hanover⁵³ and Gronigen⁵⁴). In four years following the introduction of cyclosporine, the world total will soon exceed 800 cases and the number of centers around the world planning active involvement in the field is expanding on a weekly basis. Figure 4 shows the location of institutions participating at the mid-point of 1984, along with the number of cases at each center up to that time. The annual rate of cases in Pittsburgh has swollen step-wise from 30 in 1981 to over 175 in 1984. The coming years will no doubt witness the emergence of other centers able to take an active

role and share the burden of providing liver transplantation to the increasing population of potential recipients.

THE LIVER DONOR

Several surveys have revealed that approximately 1 to 1.5% of all in-hospital deaths that occur annually in the United States are the result of irreversible brain damage.⁵⁵⁻⁵⁸ Thus the potential pool of donors has been estimated to be between 10,000 and 20,000 annually. Yet fewer than 3,000 donors per year provide organs for transplantation. The criteria which define a satisfactory kidney donor have become fairly standardized.⁵⁹ For the most part, many of these kidney donors would also be satisfactory donors for livers as well as hearts, pancreases and other extrarenal organs. Yet probably fewer than 25% of kidney donors are actually utilized as extra-renal organ donors. The reasons for this under utilization of organ donors has been related largely to the lack of knowledge in both the medical and non-medical communities about the tremendous increase in demand for extra-renal organs following the improvement in results with these transplants which attended the introduction of cyclosporine. The demand for donor livers at the end of 1984 remained concentrated in only a few centers across the country, with the University of Pittsburgh program continuing to utilize the vast majority of available organs. The high volume of liver transplant operations performed at Pittsburgh has been dependent upon the referral of donors to Pittsburgh by a large number of other medical centers all across the country, most of which are not involved, as yet, in liver transplantation. But, as more medical centers enter the arena of liver transplantation, increasing the local availability of donor organs will become critical to meeting the needs of these transplant programs. This, in turn, will require continuing efforts on the part of transplant programs at making both the public and the rest of the

medical community more aware of these needs so that fewer donor organs are wasted.

The techniques for procurement of multiple organs from a single donor have been described in many previous publications.⁶⁰⁻⁶⁴ These methods have been designed to minimize or eliminate damage done to the various organs by warm ischemia. The basic principals of liver procurement are outlined herein. More detailed descriptions are available elsewhere.⁶⁰⁻⁶⁴

Donor Maintenance

Organ donors are heart beating cadavers. Prior to the declaration of death, the care of a brain injured patient is the sole responsibility of the patient's primary physician(s) and should not be altered in any way which might be detrimental to the patient just because that patient is viewed as a possible organ donor. On the contrary, the functional quality of transplanted donor organs depends, to some degree, on how successful the primary physician(s) has (have) been in maintaining the normal physiology of the patient. Once a patient has been declared dead as the result of the complete and irreversible cessation of all brain function and permission for organ donation has been granted by the appropriate next of kin, then usually, the care of that cadaver is turned over to the transplant organ procurement agency.

At this point, the task of the procurement officer in charge of the donor is to assess the overall status of the donor in terms of its state of hydration, its cardiodynamic stability and ultimately, the level of end organ

function. Any overt abnormalities are corrected and an attempt is made to maintain a steady urine output of 2 mls./ kg. per hour or more. Diabetes insipidus, if present, is treated with judicious use of vasopressin and fluid losses are replaced with a solution of extracellular composition (such as lactated Ringers solution). Care must be exercised to avoid over hydration as well, especially if consideration is being given to procurement of the heart and lungs. A central venous or pulmonary artery catheter is usually required for this purpose.

Hypoxia and hypotension are the two greatest dangers to the donor liver. Yet the liver is unique in its capacity to regenerate following injury. How extensive a period of hypoxia or hypotension a liver will tolerate and still provide satisfactory function in the recipient following transplantation is difficult to determine. A donor with a prolonged history of arterial hypoxia as evidenced by serial blood gas determinations warrants careful examination of the liver function tests. Likewise, a history of multiple or repeated cardiac arrests, of prolonged hypotension requiring the use of high doses of pressor agents for longer than brief periods of instability may have caused unacceptable degrees of hepatic injury. On the otherhand, low doses of dopamine or inotropic agents may prove useful for maintaining good renal function and enhancing cardiac output.

The major point of this discussion is that in making the decision about whether to use a particular donor liver, one must take into account a number of variables. As an isolated set of values, liver function tests, whether entirely normal or grossly abnormal, are not particularly useful. Large elevations in serum transaminase levels as the result of a brief period of

hypotension or of a recent episode of cardiopulmonary resuscitation often do not indicate an hepatic injury significant enough to preclude transplantation of the organ. On the other hand, a donor with extensive hepatic necrosis and in which massive fluid shifts have occurred may exhibit grossly normal serum transaminase levels. Serum bilirubin may be elevated secondary to the transfusion of blood, although usually with a higher than normal indirect fraction. A prolonged prothrombin or partial thromboplastin time should alert one to the possibility of the development in the donor of disseminated intravascular coagulation (DIC). Donor DIC may develop as the result of massive brain or other tissue necrosis secondary to multiple trauma or may indicate overt sepsis. In either case, an uncorrectible or unexplained coagulopathy should be considered a relative contraindication to liver donation, particularly if other evidence points to the presence of a significant hepatic injury.

Ultimately, responsibility for the decision about whether to use a particular liver for transplantation is borne by the surgeon performing the transplant. In making that decision, the surgeon may also take into account the condition of the recipient as well as the size, age and blood type of the donor in terms of the relative frequency with which such a donor becomes available. For example, small pediatric donors are quite rare and the number of waiting candidates large. The number of such patients which die waiting for the appropriate sized donor is still greater than the number that get transplanted. Hence, when they become available, these donors are only infrequently deemed to be unsatisfactory.

Technique of Donor Hepatectomy

The heart beating cadaver is placed on the operating table in a supine position. A heating blanket placed under the body is useful in maintaining donor core temperature above 34°C and thus avoiding premature development of cardiac arrhythmias. An experienced anesthesiologist is invaluable in maintaining the integrity of donor cardiodynamic and pulmonary stability. An arterial catheter and a central venous or pulmonary artery catheter often have proven useful for the intraoperative management of the donor.

The donor abdomen is opened through a long midline incision combined with midline sternotomy. This provides excellent exposure to the abdominal viscera and allows for the option of removing the heart and/or lungs as well. In general, the liver procurement team performs the dissection of the hepatic hilum first. The hepatic arterial supply is identified and traced back to its origin from the aorta. The common bile duct is divided as close to the duodenum as possible, thus providing maximum length for anastomosis in the recipient. An incision is made in the gallbladder and bile flushed from the biliary tree with a bulb syringe. The portal vein is cleaned and the confluence of the splenic and superior mesenteric veins isolated. The latter is facilitated by dividing the pancreas between mass ligatures. A cannula for infusion of cold fluid is inserted into the portal vein via the splenic or mesenteric vein.

Once the hepatic hilar dissection has been completed, the nephrectomy team proceeds with isolation of the kidneys. The authors prefer *in situ* flush of the organs. Large bore cannulas are inserted into the distal aorta and

inferior vena cava at the level of the iliacs, the former for infusion of cold preservation solution into the arterial tree and the latter for drainage of blood and fluid from the venous system.

The so-called precooling step can be started at any time after the hepatic hilar dissection has been completed. The cannula in the distal vena cava is useful for draining off central venous volume as cold (4-10° C) lactated Ringers solution is infused through the liver via the portal vein cannula. This is important to avoid central venous hypertension which may cause swelling of the liver. The precooling step serves to cool the liver while it is still being perfused with oxygenated blood via the hepatic artery. In this way, warm ischemia is virtually eliminated. Infusion of cold lactated Ringers is continued until donor core temperature falls to 28-30° C or until cardiac arrhythmias develop. In practice, a stable donor will accept 3 to 5 liters of portal infusion over approximately 45-60 minutes, with an attendant release via the vena caval cannula of 2 to 4 liters.

The *in situ* flush of the aorta with preservation fluid (Collins or another fluid of intracellular composition) is started as soon as pre-cooling is thought to be complete or at any time that cardiodynamic instability causes arterial perfusion pressures to become unsatisfactory. The aorta is clamped at the diaphragm, above the celiac axis, and the flush begun via the cannula in the distal aorta. At the same time, the vena caval cannula is opened and the fluid infusing through the portal vein is changed from lactated Ringers to preservation solution for an additional liter of flush. The aorta is re-clamped below the celiac axis after about 200-500 mls. have been infused through the artery. While the kidneys continue to be flushed, the aorta is divided

between the celiac axis and renal arteries and the liver is removed. The supra-hepatic vena cava is divided at the base of the atrium and a small cuff of diaphragm left on the specimen. The hepatic ligaments are rapidly divided, the infra-hepatic vena cava divided just above the renal vein and the liver lifted out of the abdomen. The organ is placed in plastic bags, packed in an ice slush solution and transported to the recipient hospital.

Liver Preservation

The average time interval at Pittsburgh between devascularization of a liver in the donor and revascularization in the recipient is 4 1/2 hours with a range of from 60 minutes in locally procured organs to over 12 hours in those flown in from the west coast. In general, an effort is made to limit the cold ischemia time to less than 6 to 8 hours. This usually means starting the recipient procedure approximately two to three hours before the arrival of the donor organ at the recipient operating room. The timing is varied according to the anticipated degree of difficulty of the recipient hepatectomy.

Much research is currently being devoted to improving the methods of hepatic preservation. These efforts have centered around three main areas.

One involves attempts at cytoprotection and is founded on the principal that the major injury to the liver caused by hypotension or hypoxia in the donor or by the period of cold ischemia can be minimized by treatment of the liver or the donor with so-called cytoprotective agents. Different authors have proposed the use of calcium channel blockers⁶⁵⁻⁶⁷, somatostatin⁶⁸, coenzyme Q⁶⁹⁻⁷¹ and various prostaglandins.⁷²⁻⁷⁵

Protection may also be afforded to cells by a new method of cold storage called vitrification. This technique is being studied by the MRC Medical Cryobiology Group in Cambridge.⁷⁶ It involves very slow cooling of tissue under conditions of high atmospheric pressure with the intent being to avoid crystallization of tissue water while at the same time lowering tissue temperatures well below the freezing level, thus effectively arresting tissue metabolism.

A second area involves developing various methods of perfusion of the liver. Cold perfusion of the liver has been attempted by several authors.^{77,78} The extensive experiments of Brettschneider, *et al* showed that these methods of cold perfusion, even if combined with oxygenation of the perfusate, allowed no significant prolongation of preservation times beyond those allowed by simple cold storage. The extensive experience with cold perfusion for preservation of the kidney has demonstrated that these methods yield no clear advantage over simple cold storage, as witnessed by the general lack of agreement among kidney transplant centers over which is the preferred technique.^{79,80} The situation might change, however, if cold perfusion were to prove to be the preferred method for continual delivery of a cytoprotective agent.

The use of a warm, oxygenated perfusate may eventually prove a superior method for preservation of the liver. Rather than cool the liver in order to minimize its metabolic demands during a period of requisite ischemia, perhaps a better approach would involve eliminating the ischemic period altogether and providing the liver with everything that it needs during the time interval that it is between donor and recipient. Removal of the liver and

placement of the organ into an extracorporeal circuit which employs a blood pump, oxygenator, and heat exchanger is combined with the administration into the circuit of appropriate metabolic substrate (glucose and amino acids) and the occasional use of a dialysis membrane. An even simpler solution may involve removal of the various organs to be preserved *en bloc* with placement into a preservation box. Such a circuit might include the heart and lungs, liver, small bowel, pancreas, and kidneys. Critical to these techniques will be minimizing blood loss from leaks and hemolysis, avoiding thrombosis or the development of coagulopathies, and eliminating contamination with bacteria, fungi or other infectious agents which could lead to sepsis in the recipient.

At the present time, the only method of assessing the quality of a liver graft after it has been procured is to revascularize it in the recipient and then wait to see if it provides function adequate to support life. As will be discussed later in this chapter, although inadequate function of a grafted liver is the least common of the three major reasons for retransplantation, it is nevertheless the most devastating. Eliminating primary non-function as a cause of failure of a liver graft would result in decreasing the overall retransplantation rate by 25%.⁸¹ Clearly, one can begin to understand the importance of developing *ex vivo* methods for measuring the degree of damage sustained by a liver either in the donor, at the time of procurement or during the subsequent period of cold storage. Histological examination by either light or electron microscopic techniques have been inadequate for this purpose.

THE LIVER RECIPIENT

Indications for Liver Transplantation

The list of diseases leading to liver failure which can be corrected by hepatic transplantation reads like a textbook of hepatology. Table 5 shows the major diagnoses of 244 patients transplanted under cyclosporine therapy from March 1, 1980 to June 30, 1984, a period of time which will allow for a minimum followup (at the time of this writing) of six months. The most frequent indication for liver replacement in adults is post necrotic cirrhosis, usually following chronic active hepatitis. In children, if one includes with biliary atresia other congenital disorders of intrahepatic bile ductule formation, one can account for over 60% of patients 18 years old or younger who undergo liver transplantation.

A comparison of the indications for transplantation before and after the introduction of cyclosporine therapy reveals some important differences. Among adults, alcoholic cirrhosis and hepatic malignancies have become less frequent indications for liver replacement while the diagnoses of primary biliary cirrhosis and sclerosing cholangitis have become much more common. The list of metabolic disorders for which liver transplantation is indicated also has become more diverse. The reasons for these changes will become more evident later in this chapter, but in general, the survival rate following liver transplantation now exceeds that for other forms of therapy for virtually all causes of liver failure and this has had a major impact upon the selection of recipients.

Figure 5 shows actuarial survival curves for adults and children. The actuarial survival rate for all patients combined is 68% at one year and remains at 60% after the third year. Children have a 76% one year and a 74% five year survival rate, compared to 62% and 50% for adults at the same milestones, respectively.

post necrotic cirrhosis

Most of these patients have so-called non A, non B hepatitis of a chronic nature and have developed cirrhosis with all of its sequelae. The actuarial one year survival rate in the overall group of patients in this category is 62% (see Figure 6). The best results have been obtained in patients in whom nutritional depletion or prior immune depression with steroid therapy has not taken place. The one year survival rate in 45 of these patients who are aged 39 or less is 66.5% (Figure 7). Only five of 11 patients over 40 years of age survived the first year. Three of these patients are alive at 6, 9 and 12 months. Three others lived beyond one year, but all later died within 2 1/2 years of transplantation. On the other hand, in patients with disabling complications of cirrhosis, delaying transplantation in an attempt to temporize with other forms of therapy may seriously hinder long term survival.

Five patients transplanted under cyclosporine therapy had positive sera tests for hepatitis B surface antigen and for E antigen. All were treated with various regimens of human anti-hepatitis B immune globulin and attempts have been made to actively immunize all patients transplanted since vaccine (Heptavax-B, Merck, Sharp & Dohme) has become available. One patient became

antibody positive and antigen negative for over 6 months. A second patient became antigen negative for a brief period following surgery. All patients eventually reverted to their original hepatitis serology (positive for surface antigen and negative for antibody). Three of these patients died at 5, 14 and 14 1/2 months after transplantation. One of these three died with entirely normal liver function. The other two patients died of septic complications attending the development of recurrent liver failure, both with histopathological evidence of recurrent hepatitis. The other two patients are presently alive 1 and 3 years after transplantation. The latter patient, although remaining antigen negative for over six months, eventually became antigen positive and has recently recovered from an episode of acute hepatitis. This limited experience suggests that hepatitis B positive patients remain at high risk for developing recurrent disease in the transplanted organ. Further attempts to transplant these patients must be accompanied by renewed efforts at eradicating the virus and preventing recurrent infection.

Because of the lack of serum markers for non A, non B hepatitis, the incidence of recurrent disease among patients transplanted for this entity is not known. Only two of these patients developed episodes of what appears to have been acute hepatitis and both have recovered fully. Overall, the results in these patients are quite good and they remain a group for which transplantation should be considered early.

primary biliary cirrhosis

Virtually all of these patients are women in their fifth or sixth decade who have had documented disease for ten to twenty years or more. Many are

deeply jaundiced with bilirubin levels in the 20 to 30 mg./dl. range and have ascites, portal hypertension, and severe bone disease. Recurrent bleeding from esophageal varices, repeated episodes of encephalopathy, or a sudden and relentless rise in bilirubin above 10 mg./dl. are the most frequent reasons for referring these patients for transplantation. Although liver replacement can be a relatively easy operative procedure in many of these patients, advanced age, advanced liver disease or a history of previous abdominal surgery are all factors which not only can markedly increase the operative risks, but also may complicate recovery following transplantation.

The actuarial survival rate in these patients is 69.4% at one and five years (Figure 6). Because of severe, pre-existing osteoporosis, complicated by immunosuppressive therapy, 10 of these 36 patients developed vertebral body compression fractures of a severity which required them to be hospitalized in rehabilitation centers following discharge from the hospital.

The question of recurrence of PBC in the transplanted liver has been raised before.⁸² In virtually all of these patients, the anti-mitochondrial antibody titers remain positive following transplantation. In addition, the histological appearance of chronic rejection of an hepatic allograft is extremely difficult to distinguish from primary biliary cirrhosis. The authors have seen chronic rejection in this group of patients, but do not believe they have seen recurrent PBC.

sclerosing cholangitis

Until recently, patients with sclerosing cholangitis (SC) had not obtained survival rates following liver transplantation as high as those for other diseases. The major reason for this has been the fact that the vast majority of these patients have had multiple operative procedures designed to treat extra-hepatic bile duct obstruction. The presence of extensive, dense adhesions in the face of portal hypertension can lead to inordinate blood loss during the transplant operation. Furthermore, pre-existing infection in obstructed bile ducts greatly increases the risk of developing sepsis following surgery. Finally, in the past, because of the temptation for surgeons to treat the disease with repeated sundry procedures, many of these patients were referred for transplantation long after becoming moribund from advanced hepatic failure.

A recent analysis of survival statistics reveals that 13 of the overall group of 21 (62%) SC patients transplanted in Pittsburgh are still alive from 6 to 36 months following transplantation, with only one death occurring after six months. (The actuarial survival curve is shown in Figure 6.)

In making the diagnosis of sclerosing cholangitis, one must be wary of the possibility that the patient has a duct cell tumor. The absence of a history of ulcerative colitis or initial presentation of the disease in an older patient should increase the suspicion that malignancy may be the primary diagnosis. In addition, some evidence suggests that a long history of SC may predispose to development of duct cell tumor.

The treatment of colitis in these patients requires careful individualization. Those patients with a significant risk for developing colonic malignancy by virtue of having a long history (greater than 10 years) of active colitis are theoretically at even greater risk when under immunosuppression therapy following transplantation. Whenever possible, if liver transplantation is a consideration for a patient, total proctocolectomy should be delayed until after the transplant. The presence of intra-abdominal adhesions and/or an ileostomy significantly increase the operative risk and may complicate recovery. If colitis is active following liver transplantation, definitive surgical therapy should be contemplated three to six months later when recovery is complete. The risk for recurrence of SC in the transplanted liver in patients with or without active colitis is not known, but no such cases have been reported thus far.

malignancies

When discussing the results of liver transplantation for malignancies, one needs to distinguish between primary and metastatic lesions and between incidental and diffuse primary lesions. The initial determination must be that tumor is confined strictly to the liver and the assumption, therefore, is that a cure can be affected by total hepatectomy.

Until recently, the only reports involving metastatic lesion came from Calne at Cambridge. All five of their patients died from recurrent tumor within one year of transplantation and their conclusion has been that metastatic malignancy should not be an indication for transplantation of the liver.⁸³ On the other hand, Huber, Margreiter and their associates from

Innsbruck, Basel and Seattle reported the successful treatment of a 43 year old woman with hepatic metastases from breast carcinoma by liver replacement combined with toxic doses of cyclophosphamide and irradiation followed by reconstitution with stored autologous bone marrow.⁸⁴ The patient is alive and free of tumor over two years later (personal communication). This novel approach, though still experimental, nevertheless belies exciting possibilities for the future.

Primary hepatocellular tumors are found in association with diseases that also cause cirrhosis and liver failure. In the combined Denver and Pittsburgh series under cyclosporine immunosuppression, three patients with chronic active hepatitis, four with hereditary tyrosinemia, one with alpha-1-antitrypsin deficiency and one with sea blue histiocyte syndrome had such associated hepatomas. In all but one of these patients, the existence of the tumor was either known or strongly suspected prior to the transplant operation. In all of these cases, resection was not an alternative because of the presence of hepatic failure or extensive cirrhosis from other causes. A resection had been attempted in one patient with hereditary tyrosinemia with subsequent development of deep hepatic failure being the cause for referral of the patient for transplantation. Among the nine patients who survived, with follow up of from ten months to 3 1/2 years, (eight of whom are still alive), none have developed recurrent tumor.

Primary hepatic malignancies with diffuse involvement of the liver have been the major cause for liver transplantation in a total of 32 patients, (exclusive of those with cirrhosis or hereditary tyrosinemia), treated with

transplantation from March, 1963 to September, 1983. Table 6 lists the tumor types for both groups of patients.

Twenty of these patients were treated before the introduction of cyclosporine, twelve of whom survived long enough to observe them for evidence of recurrent tumor. Seven of these patients died between 2 and 11 months, four more between 13 and 54 months following transplantation. Metastatic disease was present in all 11 and was a major factor in the death of 7 of these patients. One patient transplanted for a sarcoma of undetermined cell type, and who had miliary abdominal metastases at the time of transplantation, is alive 8 years after later with no evidence of active growth of residual tumor.

An actuarial survival curve is shown in Figure 6 for the twelve patients with tumors treated in the cyclosporine era. Eight survived at least one year and five are still alive between 1 1/2 and 3 1/2 years postoperatively. Two of the five long term survivors have known metastatic disease, one of whom has had a positive response to chemotherapy.

The fibrolamellar type hepatoma has been described as a particularly slow growing variant of hepatoma.^{85,86} Our experience suggests that these tumors represent a group of patients for whom transplantation may offer both reliable palliation and a reasonable chance for cure. This variant was originally described in 1956 by Edmondson⁸⁷, and further elucidated by Peters in 1975 ⁸⁸. Five patients in the cyclosporine era have been identified as having this type of tumor. Three patients are alive and tumor free, one over three years, the other two over one year after transplantation. One of the remaining two died after 2 1/2 years and the other is alive after 31 months,

having undergone chemotherapy for treatment of pulmonary metastases. This patient is remarkable for having originally undergone a right trisegmentectomy for her tumor in 1977, with transplantation having been undertaken 4 1/2 years later for recurrence of tumor in the residual liver.

Three patients in the cyclosporine group had epithelioid heman-gioendothelial sarcomas. Two died, one of sepsis at 79 days, the other of metastatic disease after 16 months. A total of seven patients had cholangiocarcinomas, five of which were Klatskin's tumors. All three Klatskin's tumor patients from the pre-cyclosporine era died, one at two months with no evidence of metastatic tumor and two of metastatic disease at 24 and 54 months. One of two patients with Klatskin's tumors treated under cyclosporine survived the perioperative period, eventually succumbing to metastatic disease after 8 1/2 months. The two other patients with non-Klatskin's cholangiocarcinomas died at 12 and 20 months of metastatic tumor.

This experience is similar to that reported from other centers. Calne reported 24 patients with primary hepatoma, 20 of whom did not have cirrhosis and therefore, presumably had tumors which were unresectable by virtue of their extensive involvement of the liver.⁹³ Five of these patients obtained survival for two years or more, two of whom then died of disseminated tumor, three of whom lived five years or more without evidence of recurrence. Of all 120 cases in the Cambridge-Kings College series, 26 survived for six months or more and although 15 (58%) of these died as the direct result of tumor recurrence, Calne concludes that transplantation improved the quality of life in these patients, therefore providing worthwhile palliation.

Since in our experience, with the exception of about 50% of patients with fibrolamellar hepatomas, virtually all hepatic malignancies have recurred, many in less than one year and often with such an aggressive behavior that death occurred very rapidly after the appearance of the recurrence, further attempts to treat tumor patients with malignancies are justifiable only if combined with other therapeutic modalities. More experience needs to be obtained in this arena to determine whether transplantation will become a satisfactory form of treatment for tumor patients.

Budd-Chiari syndrome

Thrombosis of the hepatic veins has presented as an indication for liver transplantation in both the acute and chronic setting. Six of the seven patients in the authors' series were treated after the introduction of cyclosporine. The one patient from the pre-cyclosporine period and three from the current series are still alive at 10 and 4 1/2 years and 54, 9 and 8 months. One patient died of sepsis in less than one month after transplantation, but two others obtained long term survival of 16 and 20 months. The latter of these two patients died following retransplantation for liver failure secondary to chronic rejection. The other died of recurrent Budd-Chiari syndrome when chronic coumadin therapy was discontinued in preparation for an elective surgical procedure.

The two most recently treated patients were women who presented with acute thrombosis of both the intrahepatic vena cava and the hepatic veins. One also had complete thrombosis of the portal vein, both renal veins and both ilio-femoral systems. These patients required extensive thrombectomies

during the transplant procedure and both have now survived on chronic anti-coagulation therapy with no recurrent thromboses.

biliary atresia and related disorders

These disorders account for over 60% of all children who have received liver transplants in the cyclosporine era at Pittsburgh and Denver (Figure 8). Biliary atresia, *per se*, is the diagnosis in fully 54% of children, making it the single most frequent diagnosis among all patients receiving liver transplantation in this series.

Most biliary atresia patients have had a Kasai procedure and many have had subsequent attempts at modification of the original procedure in order to obtain drainage of bile. For the most part, a single attempt at a Kasai procedure, even with an attempted revision does not pose an increased operative risk to the recipient at the time of liver transplantation. On the other hand, multiple reoperations for revision of jejunal limbs, creation of stomas, and other repeated attempts designed to obtain better drainage may seriously complicate removal of the recipient liver.

Bylers disease, congenital biliary hypoplasia, and Alagille's syndrome are other disorders of bile ducts which lead to hepatic failure in childhood and require consideration for transplantation. Some of these patients may also have had attempts at correction through biliary drainage procedures, usually because of some confusion about the true diagnosis.

One and five year actuarial survival in this group is 76%. Twenty six of the total 56 patients are alive one year or more, and twelve two years or more following transplantation. The major impediment to adequately treating all potential candidates with this disorder, as has been pointed out earlier in this

chapter, is the lack of availability of appropriate donors. Biliary atresia and related disorders are cured by liver replacement. Many patients who are accepted for transplantation die while waiting for a donor to become available.

metabolic disorders

Under cyclosporine therapy, a total of 34 patients with inborn errors of metabolism have been treated with liver transplantation, all for cirrhosis rather than solely for correction of the metabolic disorder (Table 7). Twenty three of the 34 patients were 18 years old or younger at the time of surgery.

The most common metabolic disorder treated by liver transplantation is alpha-1-antitrypsin (A-1-A) deficiency. Patients with Pi_{zz} phenotype can develop macronodular cirrhosis that is sometimes confused with post necrotic cirrhosis. Replacement of the liver results in restoration of serum A-1-A levels to normal and conversion to Pi_{mm} phenotype.⁸⁹ Suitability for transplantation is somewhat dependent upon the patient's pulmonary status in that severe obstructive airway disease may preclude survival following the procedure. In general, patients with this disorder are excellent candidates for liver replacement. They usually have not had multiple previous abdominal procedures. Because transplantation cures the underlying disorder, they are generally referred for the procedure soon after they begin to manifest signs of significant liver failure, usually before serious physiological deterioration and malnutrition have developed. Of the 21 patients with A-1-A, 15 were children, 6 adults. The actuarial one and four year survival rate is 67% (Figure 9).

Wilson's disease is the second most common diagnosis among the metabolic disorders. These patients suffer from markedly reduced copper excretion and decreased serum ceruloplasmin levels and experience increased copper deposition in liver and brain tissue. Medical treatment consists of strict adherence to low copper diets, oral potassium sulfide to reduce enteral absorption of copper and, more recently, the use of D-penicillamine. Liver replacement corrects the disorder of copper metabolism and is indicated when hepatic involvement with the disease becomes significant. Patients may present for the first time in hepatic failure or in acute hemolytic crisis.⁹⁰ In the authors' series, seven patients have been transplanted with four surviving between 6 months and 13 years (Figure 9). In general, waiting for recovery from the acute hemolytic crisis and then planning for liver transplantation on a semi-elective basis is the preferred route to take.

Hereditary tyrosinemia is another hepatic based disorder of metabolism which is corrected by replacement with a normal liver. The accumulation of abnormal metabolites of tyrosine which are carcinogenic results in a high incidence of malignancies in patients who present with this disorder, although the major indication for transplantation is usually cirrhosis.⁹¹ All four patients treated for tyrosinemia in this series after the introduction of cyclosporine are alive from 7 to 37 months following transplantation.

The two other patients with metabolic disorders include a 17 year old girl with Type IV glycogen storage disease and a 41 year old man with hemochromatosis. Both are alive at 35 and 12 months respectively.

More recently, the authors had an opportunity to treat a 10 year old girl with homozygous familial hypercholesterolemia (FH) who had developed cardiac failure and intractable angina despite three different attempts at coronary artery reconstruction. This patient underwent a combination heart and liver transplantation procedure. The patient underwent liver replacement solely to correct the underlying disorder, since the native liver was anatomically and otherwise outwardly normal. The procedure appears to have been a success since serum cholesterol levels were markedly reduced from over 1000 mg/dl prior to transplantation down to less than 300 mg/dl following liver transplantation.⁹² With the continuing improvement in the success rate with liver transplantation, the future will undoubtedly see an increasing role for the operation in the treatment of not only FH but for a growing list of other metabolic disorders which may prove to be hepatic based.⁹³ As an example, at Cambridge recently, a young man with severe complications of oxalosis was transplanted with no indication other than treatment of the metabolic defect.

alcoholic cirrhosis

Results of transplantation for patients with cirrhosis secondary to alcohol abuse are difficult to assess. Since the introduction of cyclosporine, only three patients have been treated and two are dead. Both of these must be considered technical failures since they died on the operating table. One patient, a 52 year old businessman, is alive and well, leading a productive life one year following surgery. Before the advent of cyclosporine, 15 alcoholics were transplanted, four of whom lived over one year, three of whom are still alive. One patient returned to his former ways following surgery and 56

months later was found unconscious in a roadside ditch in Florida, eventually dying of pneumonitis. The most difficult issue in deciding to treat these patients with liver replacement will continue to be the satisfactory definition of reformation from alcoholism.

THE RECIPIENT OPERATION

Although the development of the surgical techniques necessary for the successful completion of an orthotopic transplantation of the liver began in the laboratory in the late 1950's, the operation in normal dogs often bears little resemblance to the operation in a cirrhotic human. The presence of severe portal hypertension, particularly in the face of adhesions resulting from previous surgical procedures or liver biopsies, can present a markedly different kind of challenge. Much of the inherent difficulty of the procedure lies in the recipient hepatectomy. Failure to carry off this initial step in reasonable safety can jeopardize all of the steps that must follow.

The recipient operation can be divided into three distinct phases, each with its own special problems. The first phase encompasses those steps necessary for the removal of the recipient liver. The second phase begins after the recipient liver has been removed and the new organ is being sewn into place: the so-called anhepatic phase. Restoring blood flow to the new liver in the recipient begins the third phase, a phase which also involves the sometimes arduous process of obtaining complete hemostasis.

The Recipient Hepatectomy

The abdomen is generally opened through bilateral subcostal incisions with a vertical extension in the midline toward the xyphoid. Excision of the xyphoid provides for greater expansion of the midline wound. Alternatively, a Reynolds flap type of incision often provides adequate exposure. A self-

retaining retractor which attaches to the operating table and can effectively spread the rib cage is an indispensable tool for maximizing exposure.

The recipient operation is begun early enough to allow the surgeon sufficient time to exercise meticulous care in removing the diseased liver. Liberal use of the electrocautery to make the incision and elsewhere in the dissection can help minimize blood loss, but is not a suitable substitute for careful surgical technique. Lymphatics and collateral blood vessels in the hepatic hilum are ligated and divided to expose the common bile duct, portal vein and hepatic arterial supply. The supporting ligaments of the liver can be divided with the electrocautery, care being taken to ligate larger blood vessels to avoid bleeding later. The retrohepatic vena cava can be freed from the diaphragm superiorly down to a point just above the right renal vein. Alternatively in adults, if exposure to the hepatic ligaments or the vena cava is limited, either because of the extreme size of the liver or because retraction of the liver out of the hepatic fossa causes hemodynamic instability, the dissection behind the liver can be delayed until after the patient has been placed on venous bypass. In this case, hemostasis can be obtained readily after the native liver has been removed and before implanting the new liver.

Bleeding during this initial phase can also be minimized by aggressive treatment of pre-existing coagulopathy with blood components. In Pittsburgh, the use of the thromboelastograph has allowed the anesthesiologists to constantly monitor the status of the patient's coagulation and to react accordingly.⁹⁴ This technique has proven more useful in the operating room than repeated measurements of conventional coagulation factors.

The Anhepatic Phase

Once dissection of the liver has been completed and the organ is ready to be removed, preparations are made for the anhepatic phase. In the past, this has always been the most critical phase, from a physiological standpoint, for the recipient. Venous return from the inferior vena cava to the heart is completely interrupted. At the same time, both the portal and caval venous beds are completely obstructed. Patients tolerate this stage to varying degrees. Children in general fare much better than do adults. A venous bypass technique which does not require anticoagulation of the recipient was developed in the laboratory in Pittsburgh in late 1982⁹⁵ and has been used routinely in all adults undergoing liver transplantation since February, 1983. The details of the technique and the improvements in results attending its routine use were the subjects of earlier reports.⁹⁶ In short, the method of venous bypass involves cannulating the divided portal vein and the femoral vein through a saphenous vein cut down in order to provide decompression of the respective venous beds through a closed system which employs a centrifugal force pump to return blood to the superior vena cava by way of the axillary vein (see Figure 10). Venous bypass results in the maintenance of normal physiology during the anhepatic phase, a virtual elimination of intraoperative mortality, a lower incidence of postoperative renal failure or gastrointestinal bleeding, and lower blood loss during the transplant operation. The technique also markedly reduces the difficulty of those cases wherein exposure to retrohepatic structures is impossible or inadequate, by allowing one the option of extending the anhepatic phase in order to obtain hemostasis in the hepatic fossa after the native liver has been removed.

In children, the decision about whether to use bypass can usually be made after performing a test clamping of the inflow to the liver and the suprahepatic vena cava. Those who experience a marked fall in central venous or pulmonary arterial wedge pressure and a resultant decrease in cardiac output may require venous bypass. This can be accomplished in most children weighing more than 20 kg. without the need for systemic anticoagulation because flow rates in the bypass circuit will be adequate to prevent activation of clotting mechanisms. More recently, work has begun in the laboratory which no doubt will redefine the acceptable lower limits of flow rate so that venous bypass without systemic anticoagulation of the recipient may soon be an option for all high risk children undergoing the procedure.

The native liver is excised by dividing the inflow vessels and the vena cava above and below the liver. The upper vena cava and hepatic veins are transected as distally as possible in order to maximize length of the upper cuff. The septa between these vessels can be cut or one or more of the hepatic vein ostia oversewn in order to tailor the diameter of the upper cuff to that of the donor upper cava (Figure 11). The lower cava is cut as long as possible as well and excess length trimmed to fit the donor organ.

Once the liver has been removed, some time can be spent obtaining hemostasis in the hepatic bed. If bypass is employed, this time is well spent because decompression of the caval and portal beds prevents the kind of increasing venous congestion that would normally make such attempts futile.

The Revascularization and Hemostasis Phase

The sequencing of the vascular anastomoses requires careful judgement on the part of the operating surgeon. In general, the liver should be revascularized within 60 to 75 minutes after it has been removed from cold storage and brought up to the recipient. Usually all four anastomoses can be accomplished in that period of time so that the liver receives its complete blood supply all at once. Normally the upper vena caval anastomosis is followed by that of the lower cava. In adults on venous bypass, the arterial anastomosis can be done next since the portal vein is decompressed. Following that, if clamping the portal vein side of the venous bypass, (in order to remove the bypass cannula and perform the portal vein anastomosis), results in diminution of bypass flow to less than 800-1000 mls per minute, the arterial inflow to the liver can be restored, the caval clamps removed and the patient removed from venous bypass before starting the portal vein anastomosis. Most often, however, clamping the portal vein cannula does not seriously jeopardize bypass flow. If one anticipates that the arterial anastomosis will be particularly difficult or that the inflow from the artery may be unreliable, the portal venous anastomosis should be done first. This is particularly the case in children or in any patient not benefitting from venous bypass. In these instances, the effort should be directed toward completing the portal vein anastomosis and releasing the obstructed caval and portal systems as rapidly as possible, and then completing the arterial anastomosis thereafter.

Before completing the lower vena caval anastomosis, the donor liver is flushed out with cold (4-10° C) lactated Ringers solution through the cannula

which was placed into the donor splenic vein during the procurement procedure. This precaution washes the preservation solution, high in potassium, out of the organ, at the same time evacuating air from the donor hepatic veins and vena cava, thus lessening the chance of hyperkalemic cardiac arrest or massive air embolism at the time that flow is released to the new liver.⁹⁷

What usually will prove to be the longest stage of the operation follows the revascularization of the new liver. The degree of difficulty in obtaining hemostasis at this point is largely dependent upon how successful the team has been in controlling the bleeding during the performance of the recipient hepatectomy. But following revascularization of the donor liver in the recipient, a period of fibrinolysis often occurs. This period can be quite short, even clinically unnoticeable, but may sometimes last for several hours if it is not anticipated, looked for and effectively treated. The thromboelastograph has proven to be particularly useful in this regard. The appearance of clot lysis is an indication to use cryoprecipitate and/or judicious use of epsilon aminocaproic acid (Amicar). Ultimate control of bleeding requires persistence upon the parts of both the surgical team in managing so-called surgical bleeding and the anesthesia team in reversing coagulopathies. Closing the abdominal incision too early, with the attitude that improving hepatic function or some other feat of "Nature" will take care of the problem of persistent hemorrhage is a trap which the surgeon should avoid.

Bile duct reconstruction is delayed until after hemostasis has been completed. This allows thorough exposure to all hilar structures while looking

for bleeding points and at the same time allows full manipulation and retraction of the liver without fear of disrupting the biliary anastomosis.

biliary reconstruction

If the liver recipient has a normal native bile duct, the preferred method of reconstruction is a duct to duct anastomosis over a T-tube. With this method, the advantage of an intact sphincter of Oddi is preserved. In small pediatric patients or in any situation in which either recipient or donor bile duct is too small to allow the use of a T-tube, (the smallest normally available is # 8 French), a Roux-en-Y loop of jejunum is constructed and a choledochojejunostomy performed. In those patients in whom the bile duct is diseased (eg. sclerosing cholangitis or biliary atresia and related disorders) or damaged (eg. secondary biliary cirrhosis or previous bile duct surgery), a Roux-en-Y choledochojejunostomy is the method of reconstruction preferred by the authors. The anastomosis is stented with an appropriately sized plastic (polyethylene) tube. The authors have had limited experience using the method of reconstruction employed by Calne⁹⁸ and have not found the technique to offer any advantage over conventional methods of reconstruction.

At the completion of the biliary anastomosis, a cholangiogram is obtained,, either through the T-tube, or via a catheter in the cystic duct. Routine cholangiography confirms both patency and competency of the duct anastomosis and also serves to assure proper positioning of the T-tube or stent.

Auxiliary or Heterotopic Transplantation

The possibility of successfully treating some patients with a new liver without the need to remove the native organ has remained an intriguing possibility. But the world experience, as summarized by Fortner⁹⁹, has been rather discouraging, with only one of 50 cases reviewed obtaining unequivocal success. Houssin and associates from Paris later reported a second success.¹⁰⁰ The major problems have been the frequency of thrombosis of the venous outflow and assuring satisfactory portal venous inflow. Optimal revascularization of a liver graft appears to require inflow from the native portal system, as demonstrated by previous work.^{101,102}

Nevertheless, if a satisfactory technical solution were forthcoming, heterotopic transplants would offer the best alternative for patients suffering from metabolic disorders with otherwise normal livers, patients with hepatic dysfunction of a temporary nature, or in patients at high risk for removal of their native liver secondary to a history of extensive surgery in the area or from portal vein thrombosis.

RETRANSPLANTATION

Until recently, few patients were offered a second transplant for treatment of a failing hepatic graft. Figure 12 shows the yearly rate of retransplantation and Figure 13 the survival following retransplantation before and after the introduction of cyclosporine. The 19% one year survival rate for those given second grafts in the azathioprine era did little to justify its increased application. Since 1980, however, survival has begun to exceed 50%, and the rate of retransplantation has been between 20 and 25% annually.

Details of this group of patients given retransplantation were the subject of a previous report.⁶¹ Rejection of the graft continues to represent the most common cause of graft failure leading to retransplantation, with technical failures (mostly arterial thromboses), and primary non-function of a graft being the other two major categories (Figure 14). Technical failures occurred with a frequency that was significantly greater in children than adults.

A total of nine patients in the Pittsburgh series have received three liver transplants, five of whom have obtained greater than one year survival. As with secondary transplants, timing and the setting under which the retransplant occurs are major determinants of ultimate survival. When retransplantation is performed in an emergent setting and in the face of severe liver failure, the chances of success are much lower than in the more elective situation. Likewise, hepatic dysfunction as the result of failure to reverse rejection is an indication to consider retransplantation rather than to subject the recipient to the greater risks of increasing immunosuppression.

FUTURE PROSPECTS

Both 1983 and 1984 saw marked improvements in survival rates for liver recipients over those for 1982 (Figure 15). Aggressive retransplantation, more enlightened use of the new drug, cyclosporine, and the routine use of venous bypass for adults are the major reasons for the better results.

Further improvements could be obtained through better selection of patients for the procedure. An examination of the group of adults transplanted using venous bypass revealed that bypass had a significant effect upon 30 day survival in high risk patients, but that these patients went through a period of increased mortality thereafter such that their 90 day survival was similar to that of those patients transplanted without the use of bypass. High risk factors included recurrent episodes of severe encephalopathy, massive ascites, severe coagulopathy, recurrent episodes of massive gastrointestinal hemorrhage, marked malnutrition and muscle wasting, renal failure or a history of multiple previous abdominal surgeries. In another analysis, patients were assigned to one of three groups, solely dependent upon their physical location at the time they were called to the operating room for the transplant. Six week survival in those who were in the intensive care unit was 42% compared to 84% for those in the hospital, but on the ward and 68% for those who were called in from home.

The survival curves in the Pittsburgh series have been obtained without any formal process of patient selection. Better results would follow the institution of even the most lenient process of patient selection. In general, when assigning priorities to recipients of a service as difficult to obtain in

this country (and the world) as liver transplantation, careful consideration must be given not just to which patient is the most ill, but also to the question of which patient will most likely be benefited by the procedure.

Suitability for survival of a liver transplant operation is often seriously jeopardized by the ravages of advanced hepatic failure. Unlike the field of kidney transplantation, transplantation of the liver has had to be developed without the benefit of a form of dialysis which would allow for stabilization and proper preparation of recipients prior to surgery. The development of an effective and practical technique of hepatic dialysis undoubtedly would markedly enhance survival for those recipients currently classified as high risk for physiologic reasons.

The increasing participation in the field by a number of new centers promises to provide both greater availability of the procedure as a service and greater diversity of results. Liver transplantation has become a high profile news item, leading some institutions to view the procedure as one which might enhance their prestige. Other programs may view a liver transplantation service as a means of filling unoccupied hospital beds. But to be successful, a liver transplant program requires a tremendous commitment of resources, both financial and human. Providing that natural selection rather than governmental assignment is allowed to operate, the next few years will undoubtedly see the emergence of between fifteen and twenty active centers from out of the initial milieu of institutions now starting up programs.

Major research efforts will center around improving immunosuppression. In the near future, a better cyclosporine (cyclosporin G) which is less

nephrotoxic may be forthcoming. In addition, the use of antilymphocyte preparations, especially monoclonal antibodies, may prove to be useful additions to the armamentarium against rejection. On the other hand, the ultimate goal of inducement of donor specific tolerance still appears to be beyond the current horizon.

Developing better methods for liver preservation as well as for assessing viability of a liver graft before implantation were mentioned earlier as areas in which much research is needed. The future will also see multiple organ transplants (such as heart-liver transplants for familial hypercholesterolemia or liver-kidney grafts for polycystic disease) receiving greater application now that the initial trials with these procedures have begun.

The field of liver transplantation is in its infancy in terms of the potential for development that remains ahead. The first twenty years, largely as the result of the unflagging efforts of a few men, saw the technical refinement of one of the most difficult of all surgical procedures to the point that it could be taught successfully to other surgeons. The availability, beginning in 1980, of a new and better immunosuppressant led to better control of what yet remains the greatest single source of failure, cell mediated rejection of the liver allograft. The future offers physicians involved in the field the challenge of making the next chapter one of even greater success in the treatment and ultimate prevention of hepatic failure.

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Table 1: Total hospital costs for 31 adults and 55 children undergoing liver transplantation in Pittsburgh during fiscal 1983-1984.

Table 2: Rehabilitation of liver transplant recipients.

Table 3: First clinical trials of orthotopic transplantation of the liver.

Table 4: Regimens of immunosuppression developed in kidney transplantation and used in liver transplantation.

Table 5: Indications for 244 primary liver transplants performed between March 1, 1980 and June 30, 1984.

Table 6: Types of primary tumors in which patients received liver replacement therapy.

Table 7: Types of inborn errors of metabolism treated with liver replacement.

TOTAL HOSPITAL COSTS
FISCAL 1983-84

	Adults All n=31	Children 1 graft n=44	Children multiple n=11	All Children n=55	All Patients n=86
Mean	\$111,062	\$ 83,459	\$196,998	\$106,167	\$107,931
Std. Dev.	\$ 91,213	\$ 60,006	\$ 97,321	\$82,689	\$ 85,891
Median	\$ 75,691	\$ 69,659	\$164,762	\$75,927	\$ 75,691
Range	\$ 45,339 - \$477,766	\$ 30,937 - \$430,956	\$ 93,209 - \$391,753		

[Table 1]

REHABILITATION FOLLOWING
LIVER TRANSPLANTATION

	Pre-cyclosporine	Cyclosporine
Working	4	34
Housewife	6	34
School	10	4
Lost job, but able	5	2
Disabled	0	7
Totals	25	81

{Table 2}

THE FIRST TRIALS OF ORTHOTOPIC LIVER TRANSPLANTATION

<u>No.</u>	<u>LOCATION</u>	<u>AGE/DISEASE</u>	<u>SURVIVAL DAYS</u>	<u>MAIN CAUSE OF DEATH</u>
1	Denver	3/ Extrahepatic biliary atresia	0	Hemorrhage
2	Denver	48/ Hepatocellular cancer, cirrhosis	22	Pulmonary emboli, sepsis
3	Denver	68/ Duct cell carcinoma	7½	Sepsis, pulmonary emboli, GI bleeding
4	Denver	52/ Hepatocellular cancer, cirrhosis	6½	Pulmonary emboli, hepatic failure, pulmonary edema
5	Boston	58/ Metastatic colon carcinoma	11	Pneumonitis, liver abscesses, hepatic failure
6	Denver	29/ Hepatocellular cancer, cirrhosis	23	Sepsis, bile peritonitis, hepatic failure
7	Paris	75/ Metastatic colon carcinoma	0	Hemorrhage
8	Denver	29/ Hepatocellular cancer	7	Hepatic failure, sepsis
9	Denver	1/ Biliary atresia	10	Hepatic failure, sepsis
10	Denver	1½/ Hepatocellular cancer	400	Carcinomatosis

CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION

<u>AGENTS</u>	<u>YEAR DESCRIBED AND REPORTED</u>	<u>PLACE</u>	<u>USED FOR LIVER TRANSPLANTATION</u>
Azathioprine	1962	Boston	No
Azathioprine - Steroids	1963	Denver, Boston, Richmond, Edinborough	Yes
Thoracic Duct Drainage as Adjunct	1963	Stockholm	Yes
ALG as Adjunct	1966	Denver	Yes
Cyclophosphamide Substitute for Azathioprine	1970	Denver	Yes
Total Lymphoid Irradiation	1979	Palo Alto, Minneapolis	No
Cyclosporin-A Alone	1978-79	Cambridge	Yes
Cyclosporin-A - Steroids	1980	Denver	Yes
Cyclosporine, Steroids, Monoclonal OKT*3	1984	Boston	Yes

INDICATIONS FOR 244 PRIMARY
LIVER TRANSPLANTS PERFORMED BETWEEN
MARCH 1, 1980 AND JUNE 30, 1984

INDICATION	ADULT	PEDIATRIC	TOTAL	PERCENT
Acute hepatic necrosis	3	0	3	1.2%
Biliary atresia	0	56	56	23.0
Budd—Chiari syndrome	5	1	6	2.5
Cirrhosis	46	10	56	23.0
Familial cholestasis	0	7	7	2.9
Inborn errors of metabolism	11	23	34	13.9
Neonatal hepatitis	0	3	3	1.2
Primary biliary cirrhosis	36	0	36	14.8
Primary liver tumors	13	0	13	5.3
Secondary biliary cirrhosis	5	1	6	2.5
Sclerosing cholangitis	19	1	20	8.2
Others	2	2	4	1.6
Totals	140	104	244	100 %

PRIMARY LIVER TUMORS

	Before Cyclo- sporine	After Cyclo- sporine
Hepatoma	12 (0)	6 (5)
fibrolamellar	1 (0)	5 (4)
Klatskin's	5 (0)	2 (0)
Cholangio- carcinoma	1 (0)	2 (0)
Sarcomas	2 (1)	3 (1)

() number currently alive over one year

{Table 6}

INDICATIONS FOR 34 PRIMARY
LIVER TRANSPLANTS PERFORMED FOR
INBORN ERRORS OF METABOLISM

INDICATION	ADULT	PEDIATRIC	TOTAL
Alpha-1-antitrypsin deficiency	6	15	21
Wilson's disease	3	4	7
Tyrosinemia	1	3	4
Glycogen storage disease	0	1	1
Hemochromatosis	1	0	1
Totals	<u>11</u>	<u>23</u>	<u>34</u>

Figure 1: By permission of the Los Angeles Times Syndicate, 1983.

Figure 2: Survival of patients given liver transplants in Denver under prednisone and azathioprine immunosuppression. by permission of Hepatology (6)

Figure 3: Survival curves from initial reports of results of liver transplantation using cyclosporin-A and prednisone. by permission of Hepatology (6)

Figure 4: Locations of active liver transplant centers in the United States and Europe as of July 1984. by permission of Transplant Proceedings (7)

Figure 5: Actuarial survival for 244 liver transplants done between March 1, 1980 and June 30, 1984.

Figure 6: A comparison of actuarial survival in adults based upon disease classification.

Figure 7: A comparison of actuarial survival of 56 patients transplanted for post-necrotic cirrhosis based upon age.

Figure 8: A comparison of actuarial survival in children based upon disease classification.

Figure 9: Actuarial survival for 34 patients transplanted for inborn errors of metabolism.

Figure 10: Anatomy of venous bypass for anhepatic phase of orthotopic liver transplantation.

Figure 11: Development of upper vena caval cuff in recipient. by permission of Surgery, Gynecology, and Obstetrics (103)

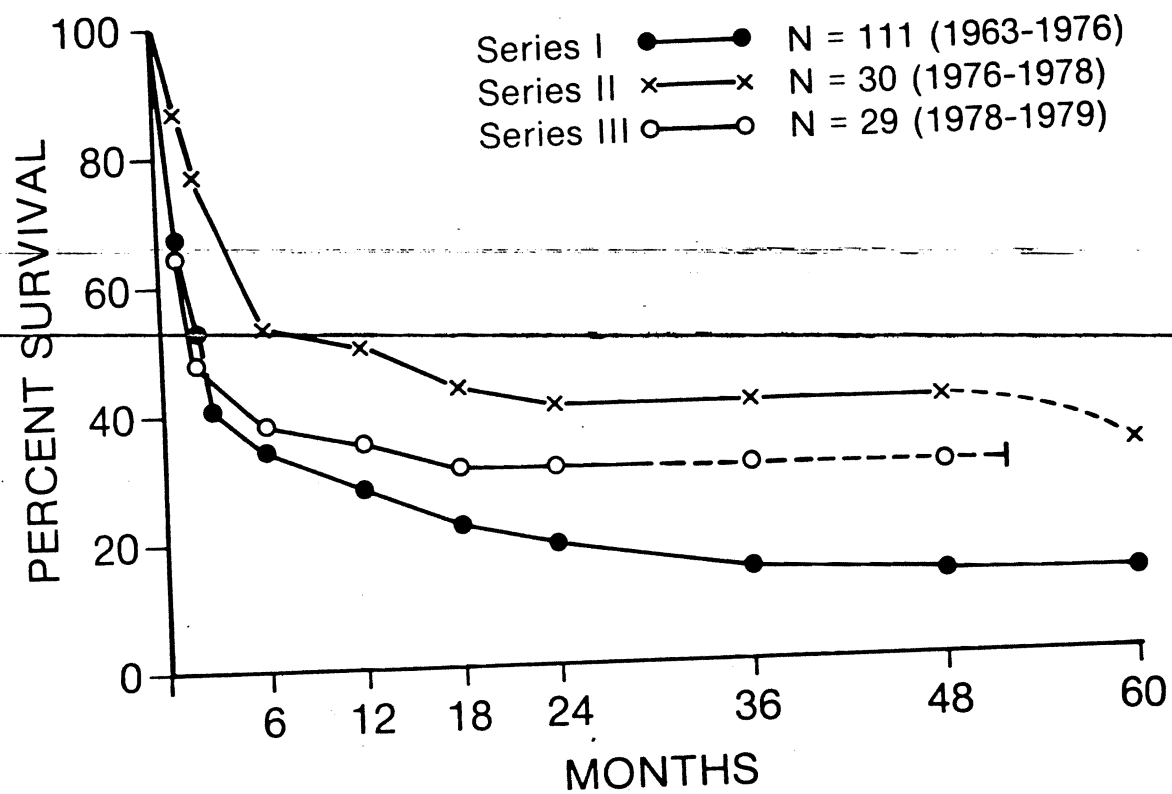
Figure 12: Yearly rate of transplantation and retransplantation in Pittsburgh. by permission of Transplant Proceedings (81)

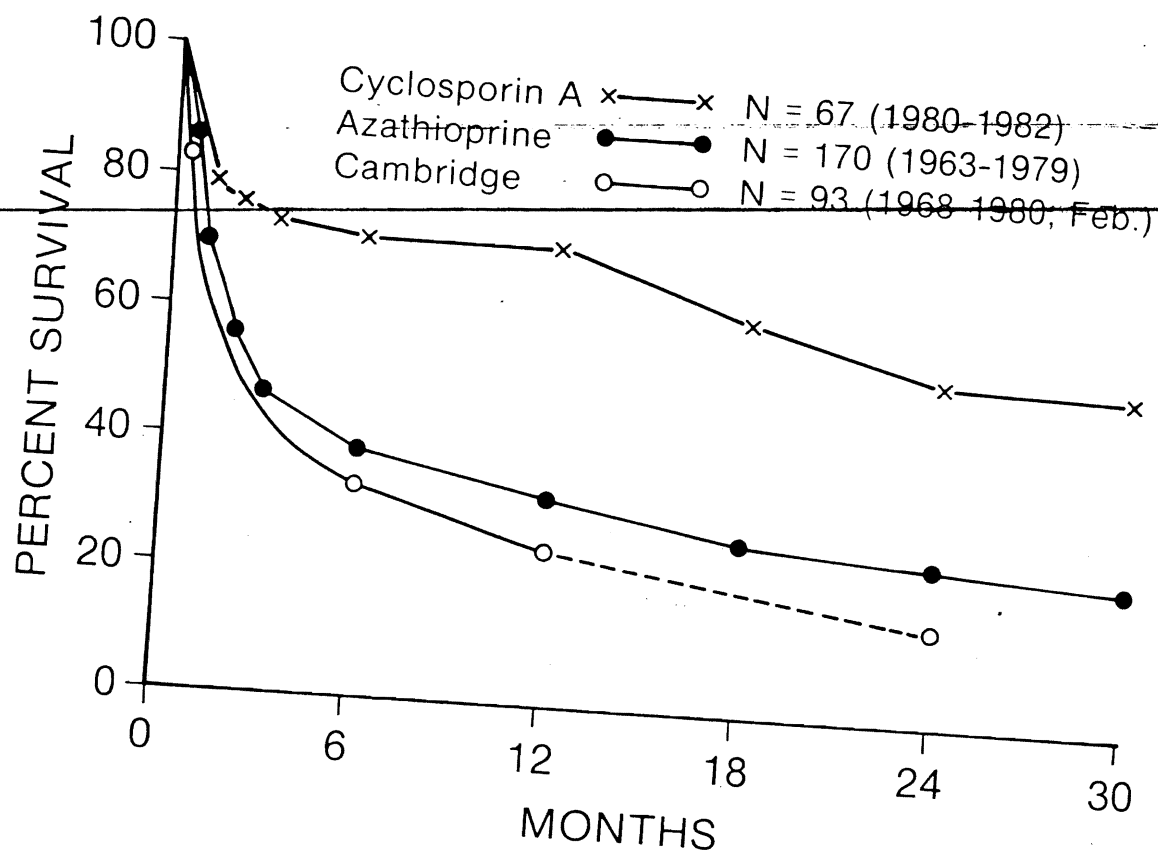
- Figure 13: A comparison of survival following hepatic retransplantation before and after cyclosporine. by permission of Transplant Proceedings (81)
- Figure 14: Indications for hepatic retransplantation under cyclosporine and prednisone. by permission of Transplant Proceedings (81)
- Figure 15: Yearly actuarial survival curves since the introduction of cyclosporine.
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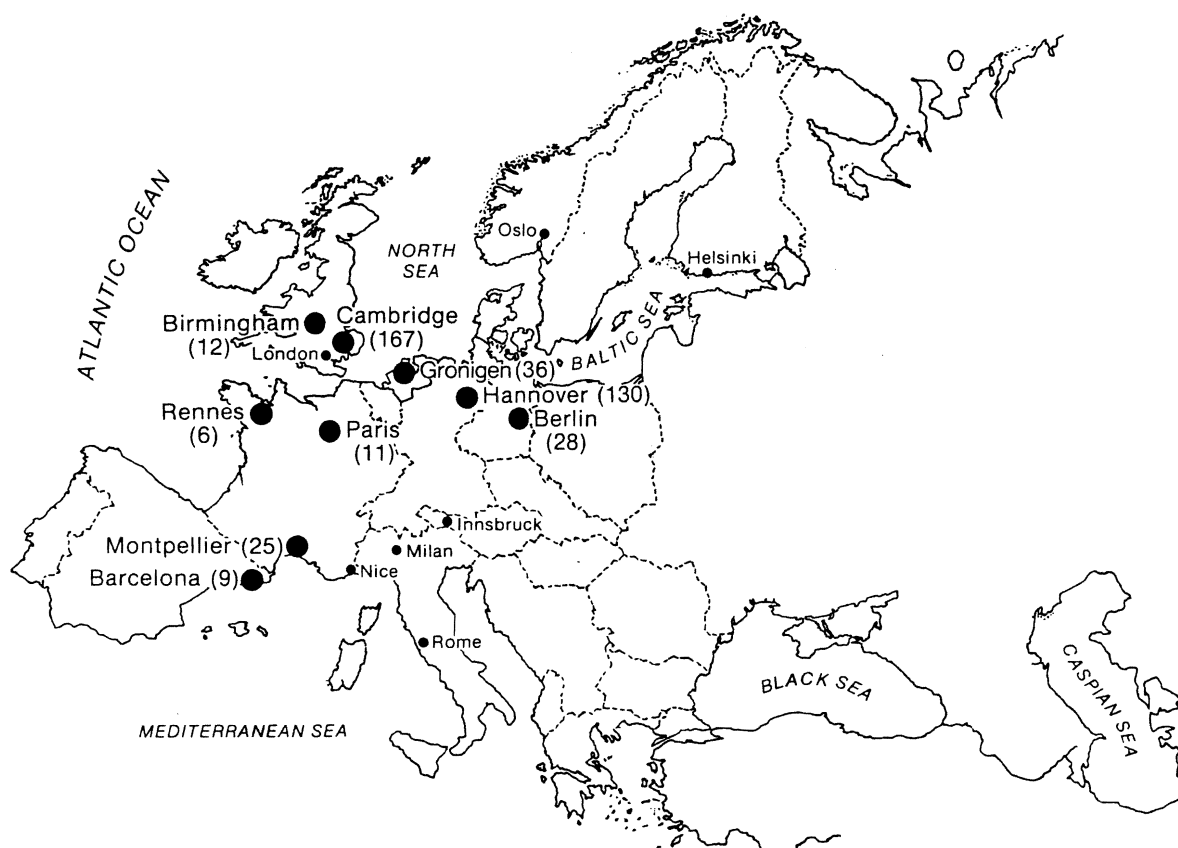
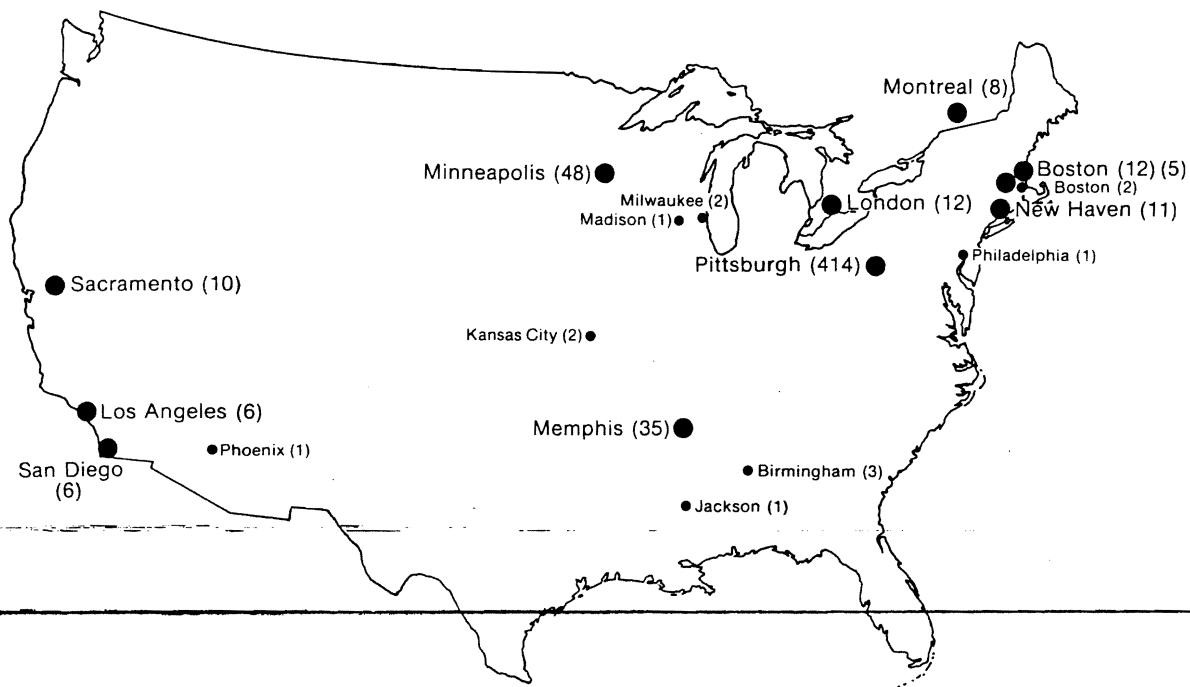


"CAN'T YOU SEE WE'RE BUSY WITH THIS HUMANITARIAN LIVER TRANSPLANT?"

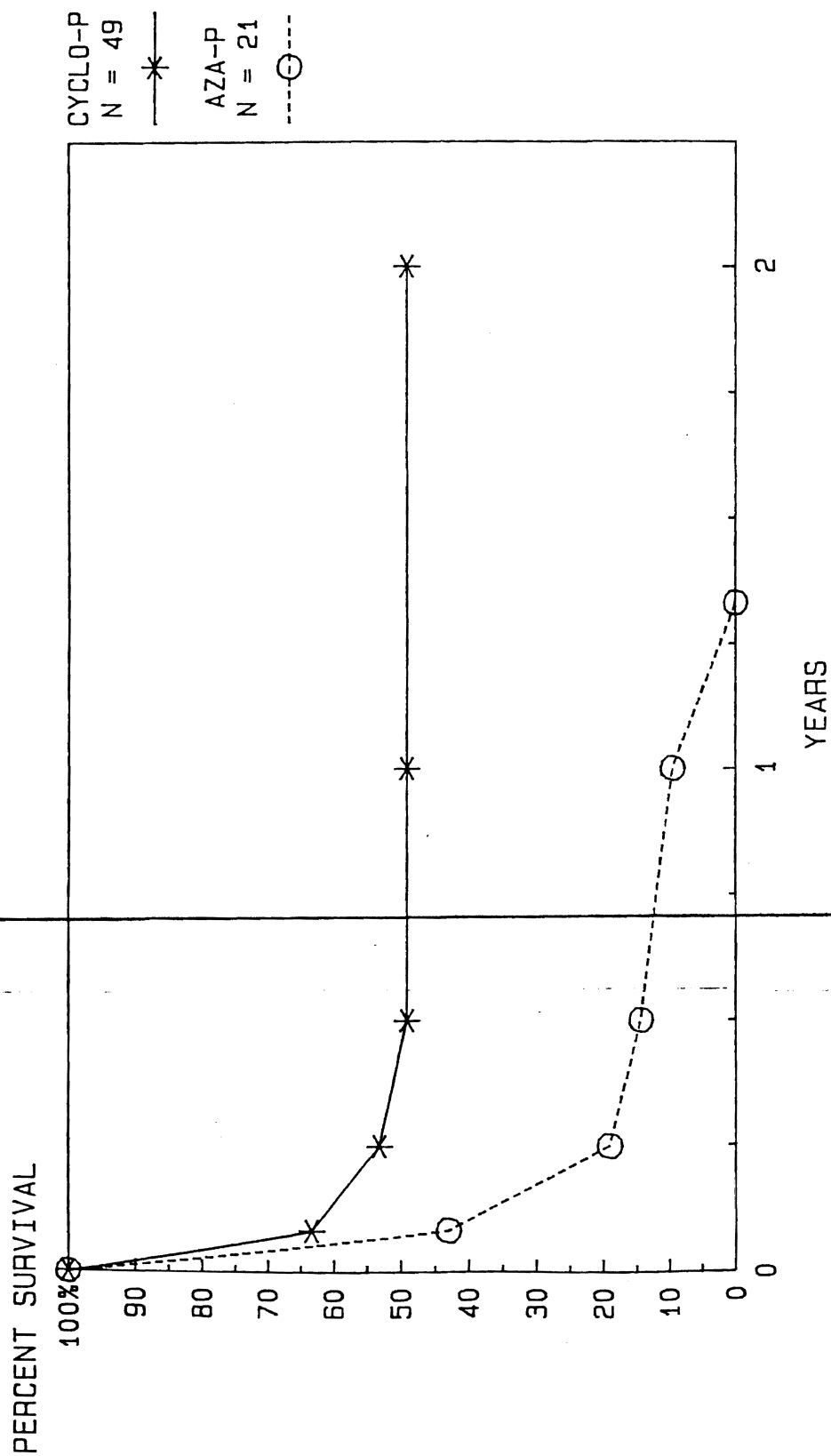
Tim Merries is on vacation



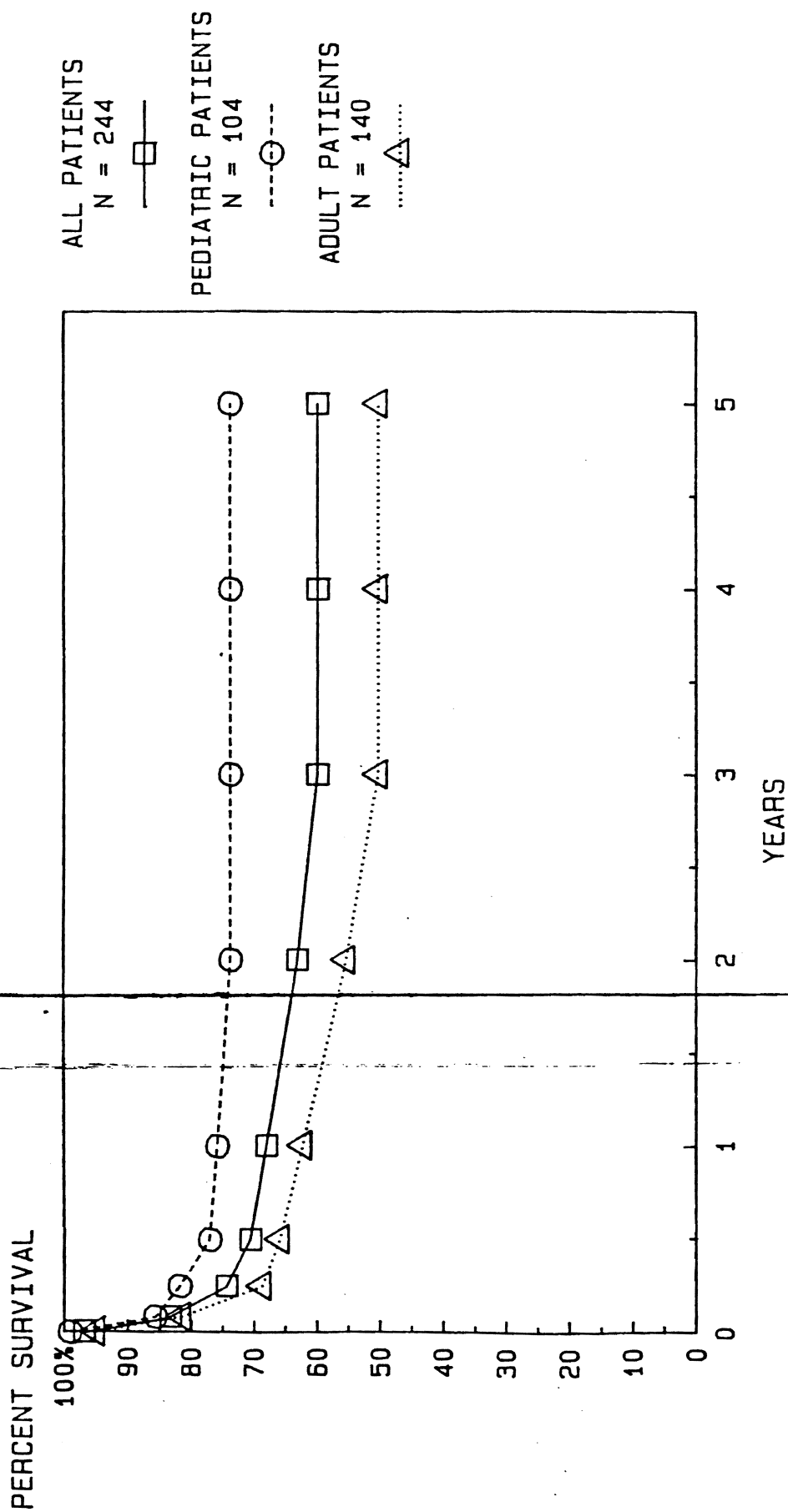




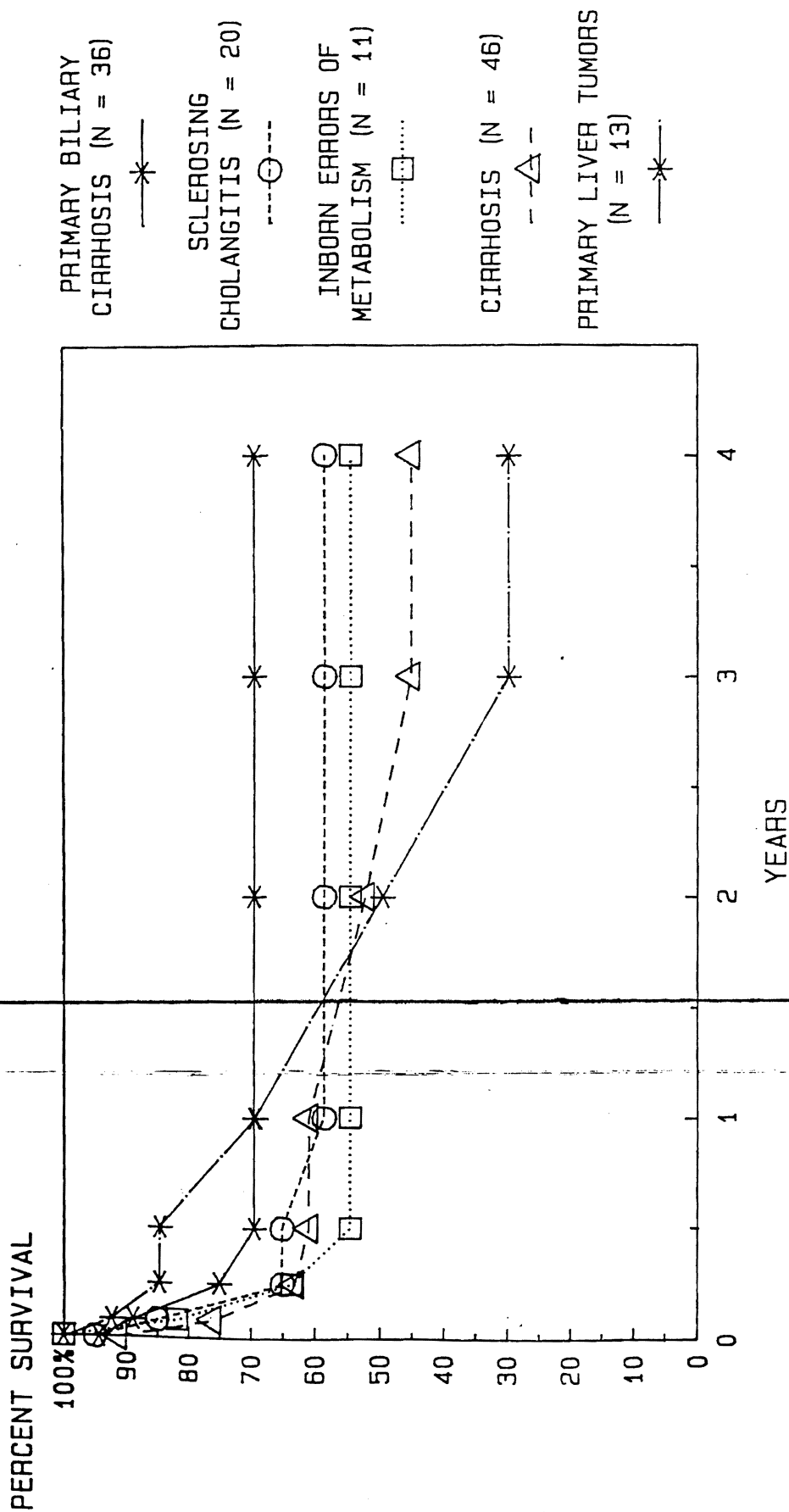
ACTUARIAL SURVIVAL AFTER LIVER RETRANSPANTATION BEFORE AND AFTER THE INTRODUCTION OF CYCLOSPORINE-PREDNISONE THERAPY



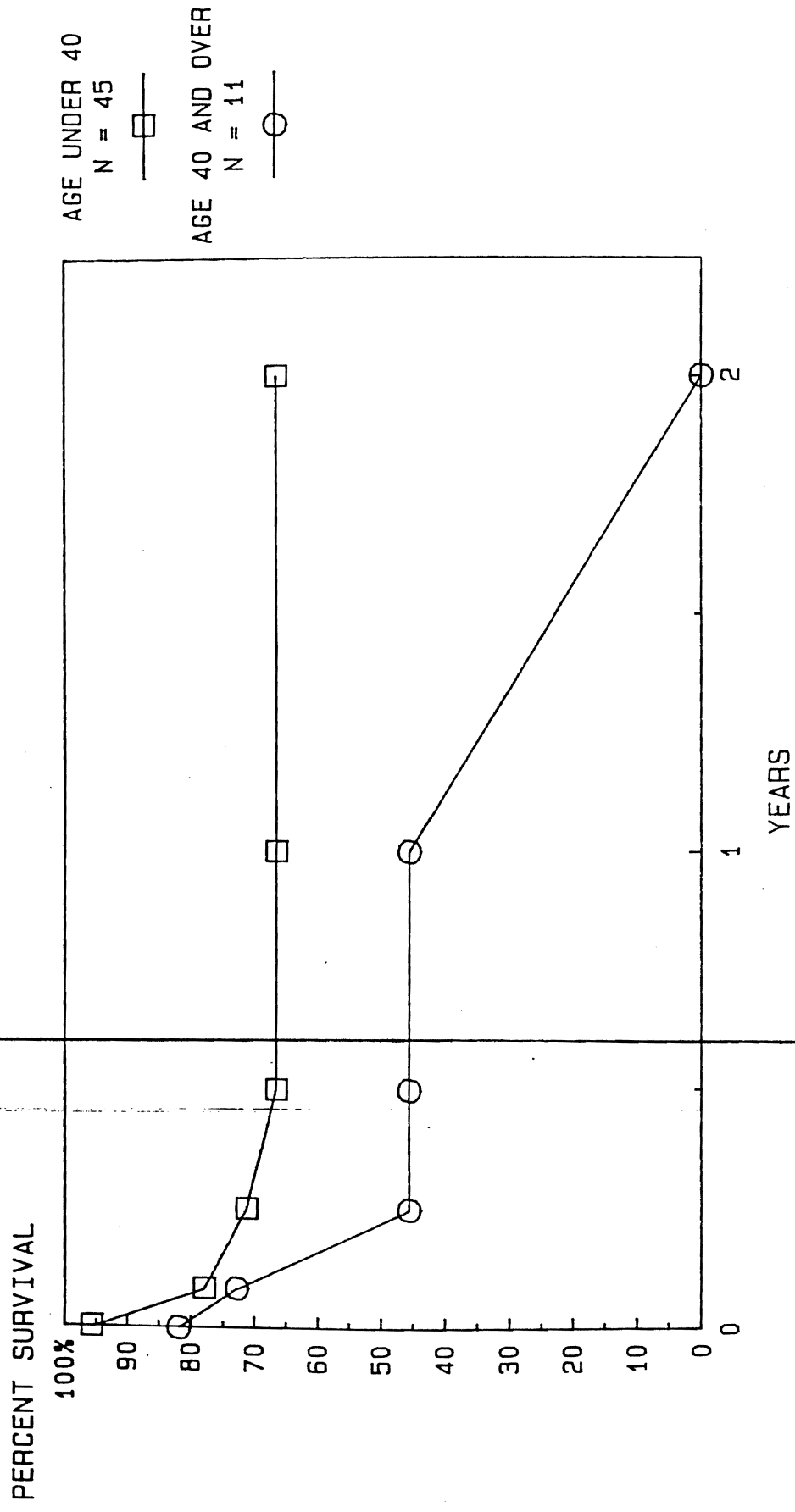
ACTUARIAL SURVIVAL FOR 244 LIVER TRANSPLANTS DONE BETWEEN MARCH 1, 1980 AND JUNE 30, 1984



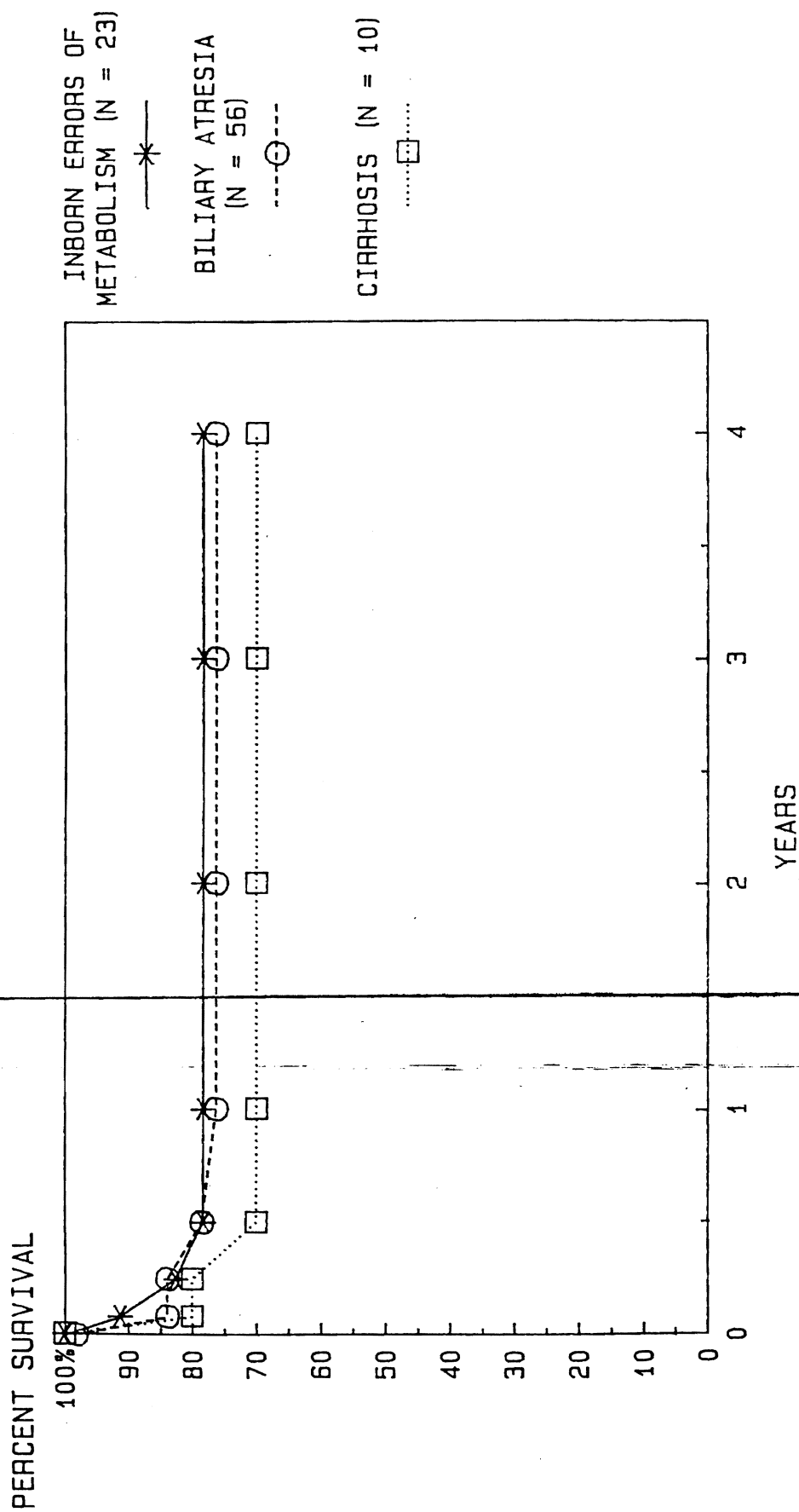
ACTUARIAL SURVIVAL AFTER LIVER TRANSPLANTATION IN ADULTS BASED ON DISEASE CLASSIFICATION



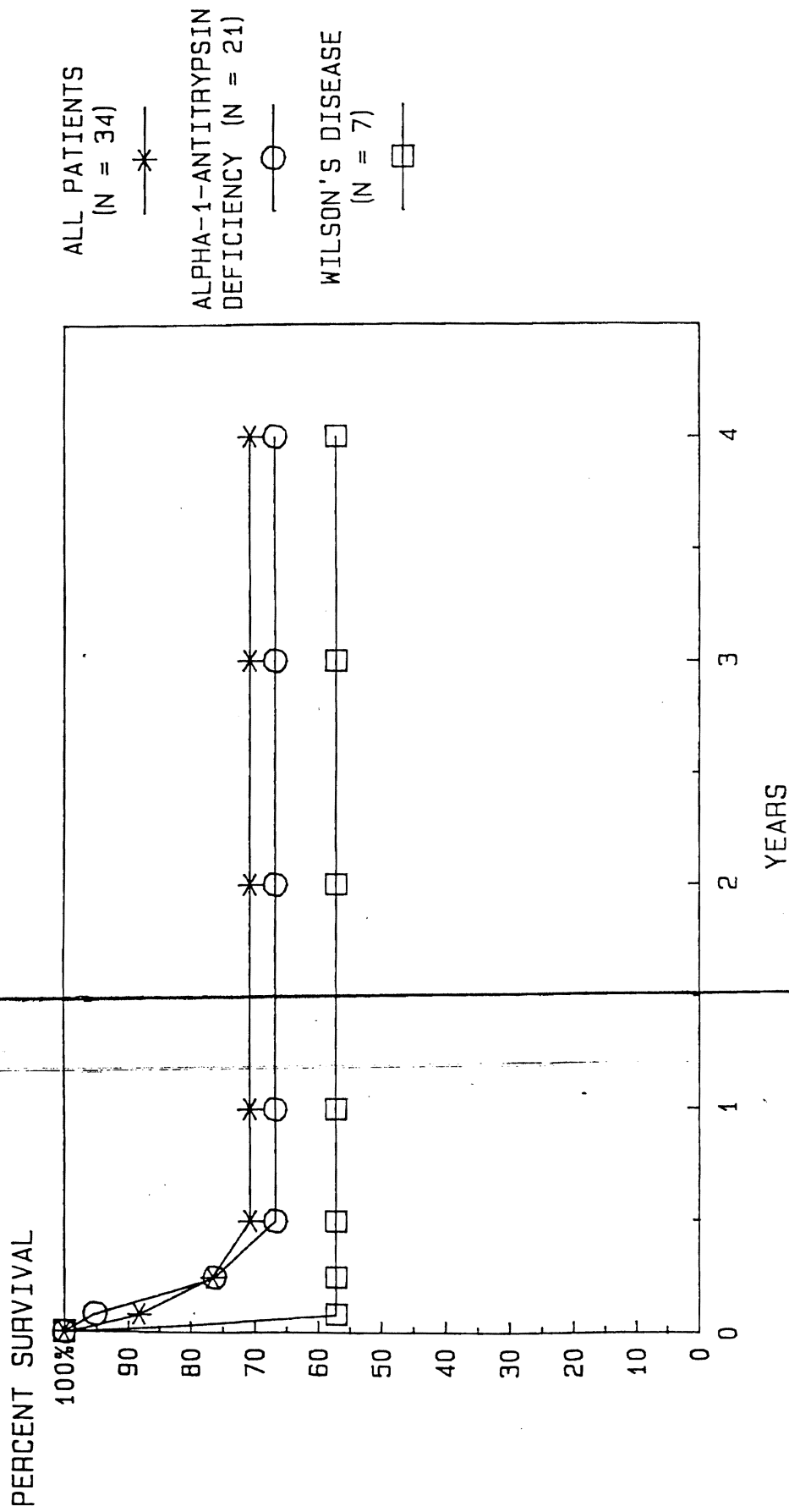
TWO YEAR ACTUARIAL SURVIVAL AFTER LIVER TRANSPLANTATION FOR CIRRHOSIS BASED ON AGE AT TIME OF OPERATION

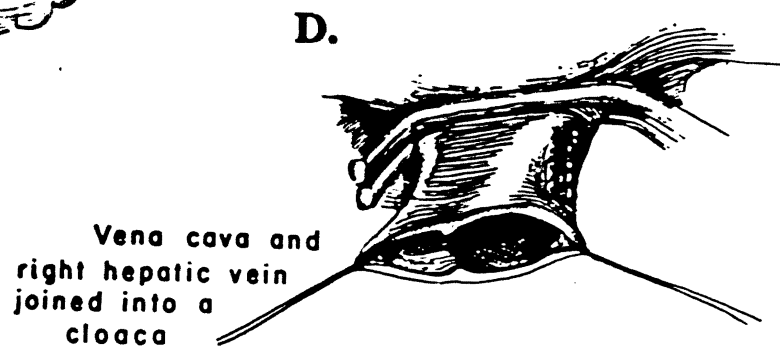
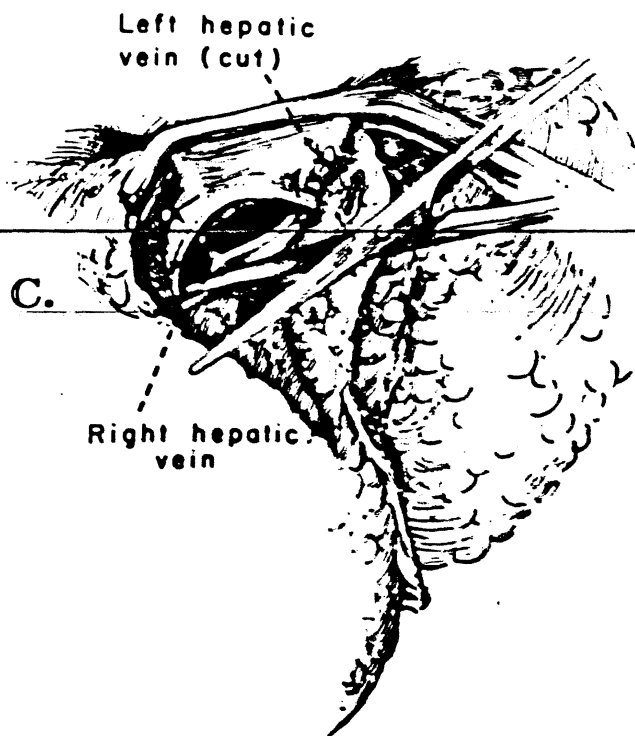
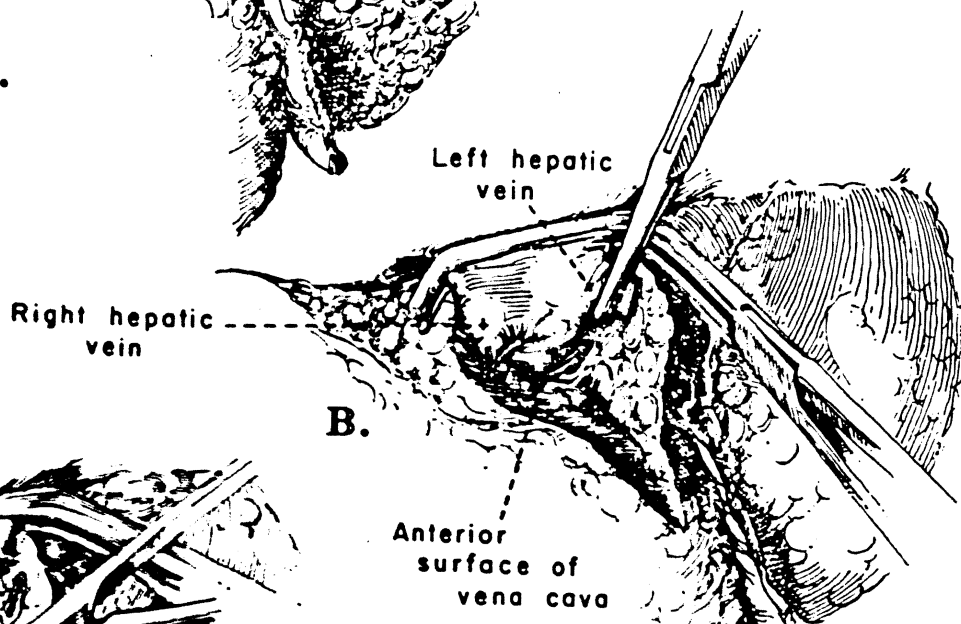
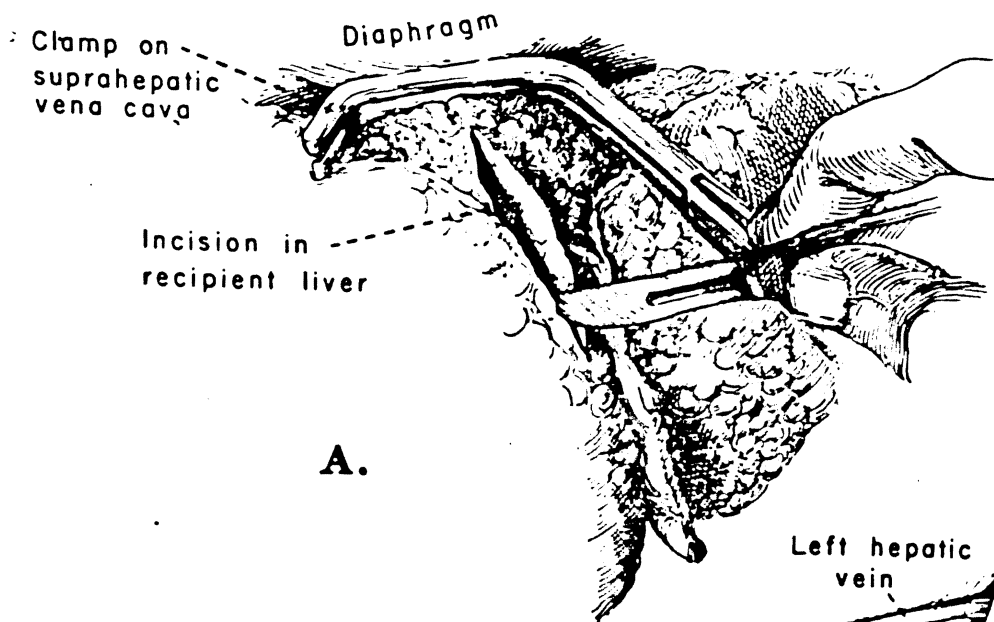


ACTUARIAL SURVIVAL AFTER LIVER TRANSPLANTATION IN CHILDREN BASED ON DISEASE CLASSIFICATION

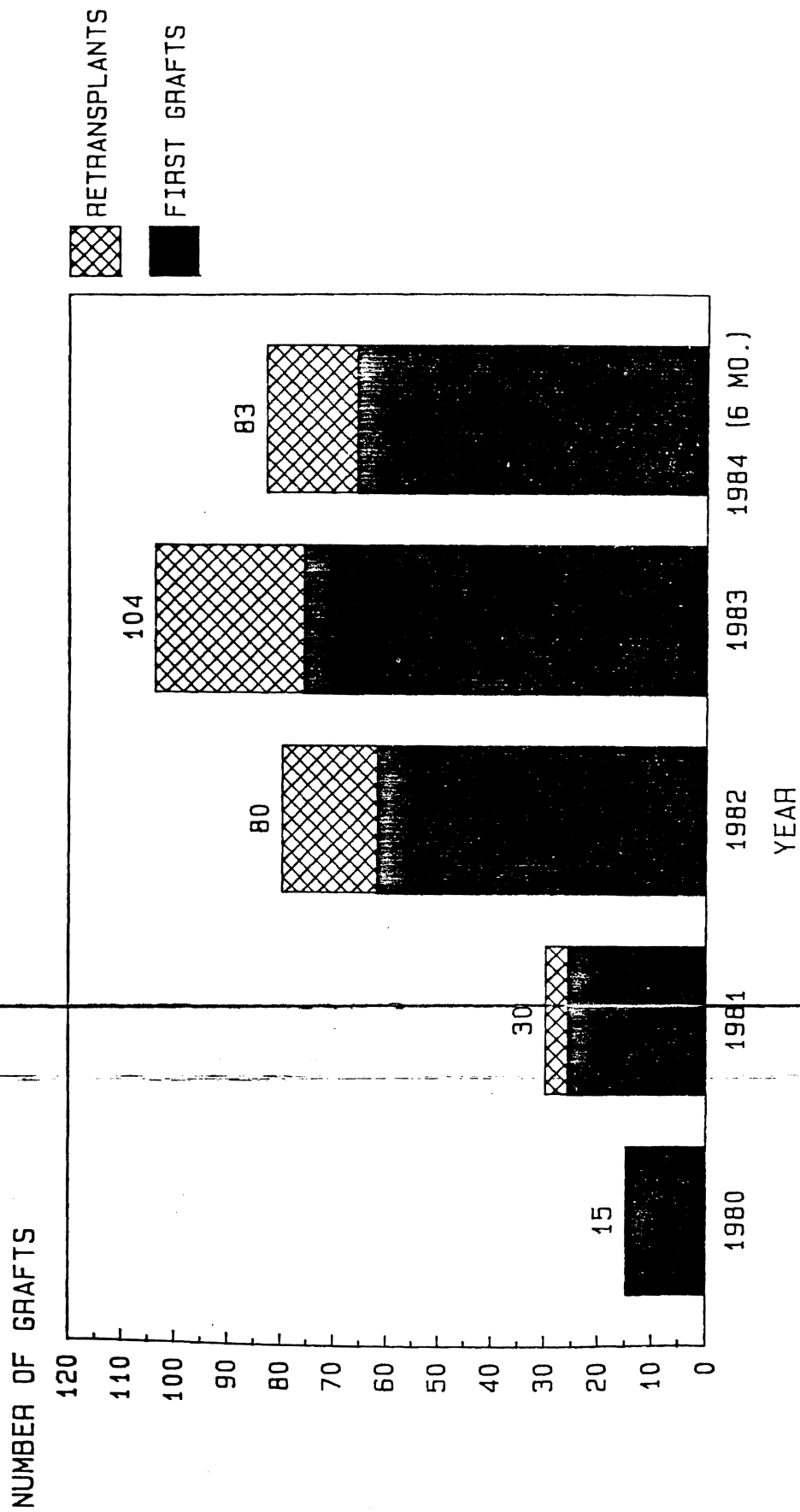


ACTUARIAL SURVIVAL FOR 34 LIVER TRANSPLANTS FOR INBORN ERRORS OF METABOLISM

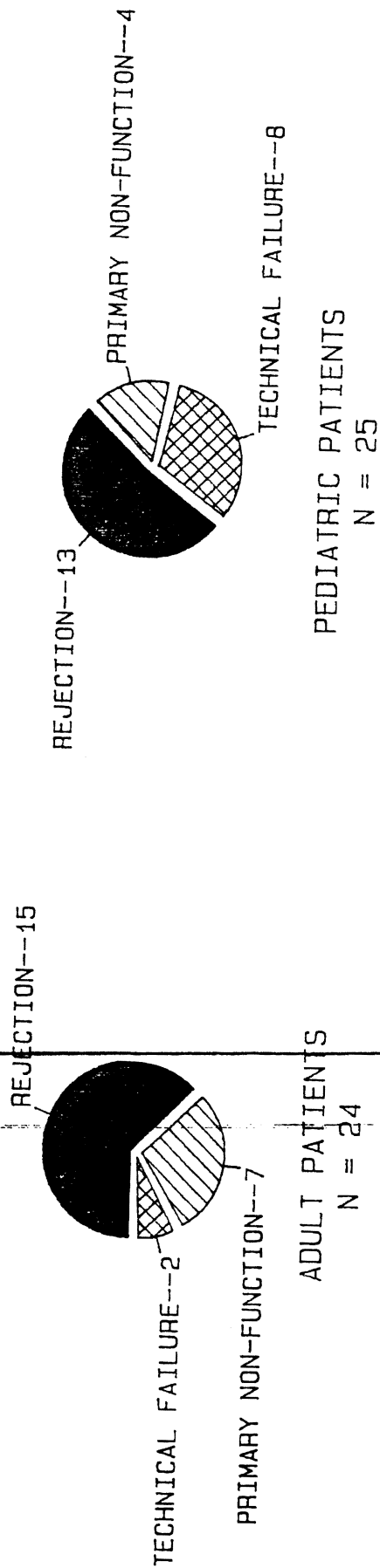
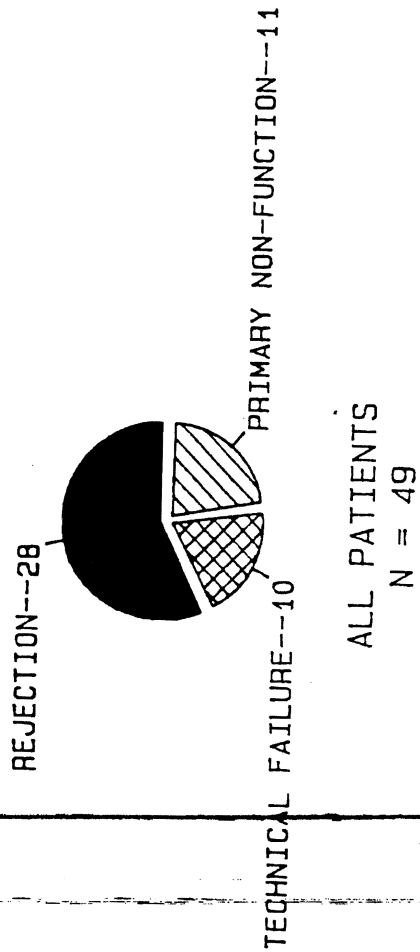




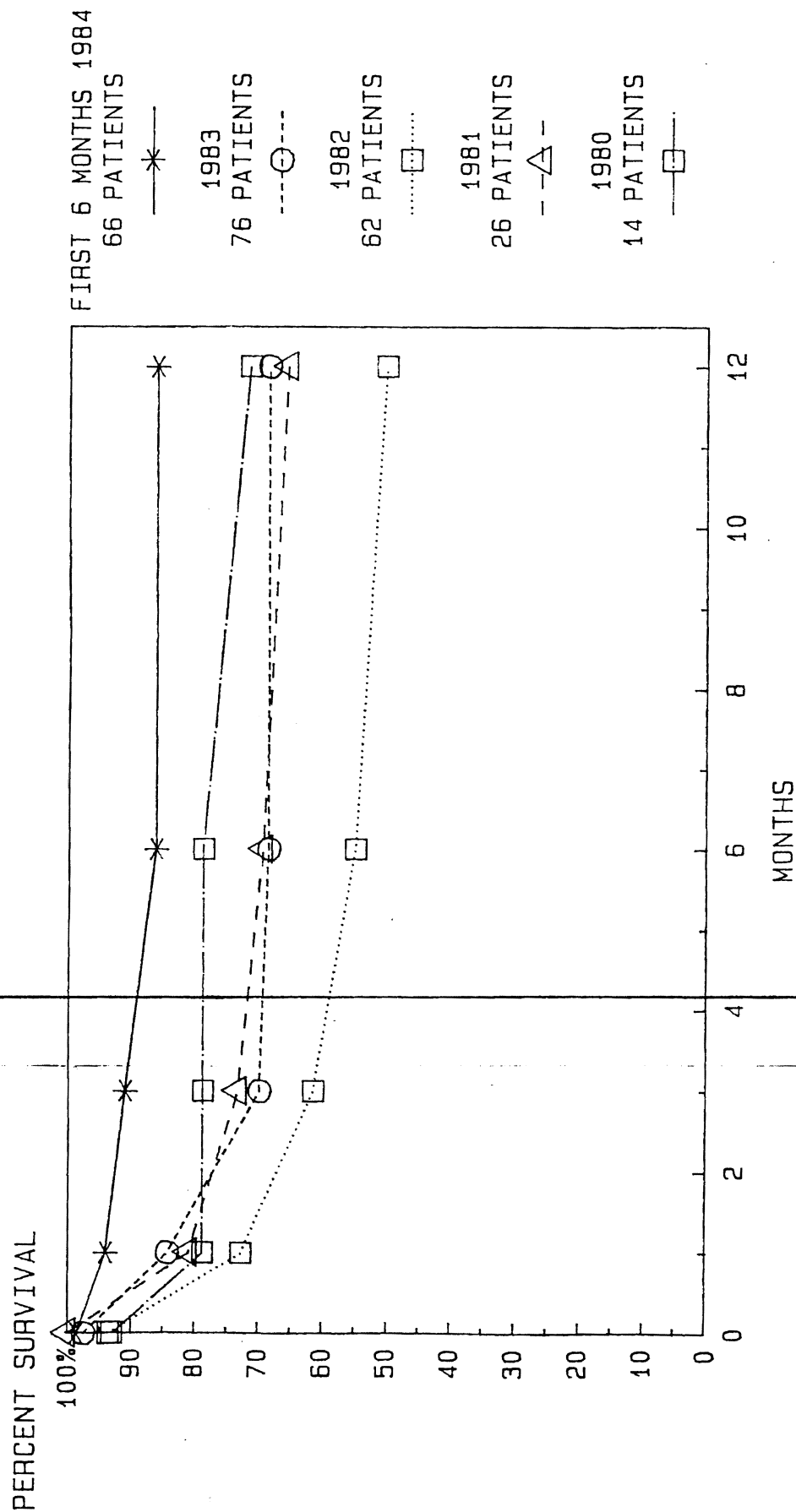
LIVER TRANSPLANTS PER CALENDAR YEAR 1980 - 1984



INDICATIONS FOR RETRANSPLANTATION



ONE YEAR SURVIVAL AFTER LIVER TRANSPLANTATION RESULTS FOR EACH CALENDAR YEAR SINCE 1980



CLINICAL IMMUNOSUPPRESSIVE DRUG REGIMENS DEVELOPED WITH KIDNEY TRANSPLANTATION

<u>AGENTS</u>	<u>YEAR DESCRIBED AND REPORTED</u>	<u>PLACE</u>	<u>USED FOR LIVER TRANSPLANTATION</u>
Azathioprine	1962	Boston	No
Azathioprine - Steroids	1963	Denver, Boston, Richmond, Edinborough	Yes
Thoracic Duct Drainage as Adjunct	1963	Stockholm	Yes
ALG as Adjunct	1966	Denver	Yes
Cyclophosphamide Substitute for Azathioprine	1970	Denver	Yes
Total Lymphoid Irradiation	1979	Palo Alto, Minneapolis	No
Cyclosporin-A Alone	1978-79	Cambridge	Yes
Cyclosporin-A - Steroids	1980	Denver	Yes
Azathioprine - Steroids - Adjuvant OKT*3	1981	Boston	No
Cyclosporine - Steroids - Adjuvant OKT*3	1984	Pittsburgh	Yes

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INDICATIONS FOR 244 PRIMARY
LIVER TRANSPLANTS PERFORMED BETWEEN
MARCH 1, 1980 AND JUNE 30, 1984

INDICATION	ADULT	PEDIATRIC	TOTAL	PERCENT
Acute hepatic necrosis	3	0	3	1.2%
Biliary atresia	0	56	56	23.0
Budd—Chiari syndrome	5	1	6	2.5
Cirrhosis	46	10	56	23.0
Familial cholestasis	0	7	7	2.9
Inborn errors of metabolism	11	23	34	13.9
Neonatal hepatitis	0	3	3	1.2
Primary biliary cirrhosis	36	0	36	14.8
Primary liver tumors	13	0	13	5.3
Secondary biliary cirrhosis	5	1	6	2.5
Sclerosing cholangitis	19	1	20	8.2
Others	2	2	4	1.6
Totals	140	104	244	100 %