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LIVER

Orthotopic Liver Transplantation in 1984

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SINCE THE MEETING in Brighton, the status of hepatic transplantation has changed drastically. Liver replacement has become accepted as a patient service in many countries and programs are either in effect or planned for all of the continents except Antarctica.[1,2]

CASE NUMBERS

Some idea of the worldwide activity can be obtained by looking at the numbers in the European and American centers. In the United States and Canada (Fig 1), there are at least 11 centers (defined by experience, with at least five transplantations) with an accumulated patient total through June 1984 of 568. Although only five institutions have had experience with more than a dozen cases, the number of such "large" centers is apt to be closer to 20 by the time we meet in 1985. Additional isolated and successful trials have been made in Phoenix, Kansas City, Birmingham, Ala., Philadelphia, Boston, Milwaukee, Madison, Wis., and Jackson, Miss.

In Europe, nine groups with more than five cases are active (Fig 2), and these nine teams have treated 424 recipients by July 1, 1984. Early and more limited trials have also been carried out before July 1984 in another seven cities. Clearly, a European network of liver exchange is already a practical possibility.

In spite of this intense activity, not all aspects of liver transplantation have been agreed upon, and today we will focus upon some, although not all, of the controversial issues.

PATIENT SURVIVAL

Before doing so, we should remark that patient survival in many of the new series has been outstanding. In North America, a survey completed recently showed that 269 (47.3%) of the 568 known liver recipients treated in the last 21 years are still alive. However, it proved impossible to get cumulative survival data

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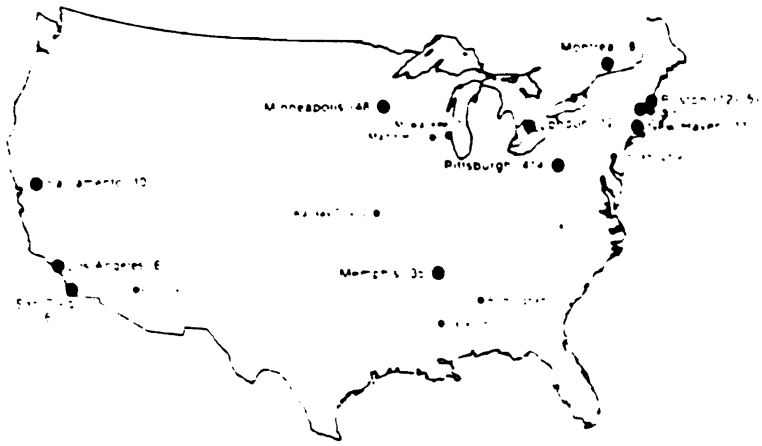

Fig 1. Liver transplantation centers in the United States. Teams with five or more cases are designated with large dots.

with complete accuracy because of the different starting times of these programs and for a variety of other reasons. Consequently, we will present our own series to illustrate what was the historical record until 1980, compared with the expectations today.

From 1963 Through 1979

Using conventional immunosuppression with azathioprine or cyclophosphamide and prednisone, to which antilymphocyte globulin (ALG) usually was added, the one-year survival (32.4%) was in 55 of 170 consecutive recipients (Fig 3). Twenty-four of the 55 one-year survivors died subsequently, so that of the original 170 recipients, 31 (18.2%) are still alive with follow-ups now of 4¾ to 14¾ years. There have been only two deaths after five years.

From 1980 Onward

In early 1980, combination therapy with cyclosporine and steroids was instituted. During the ensuing 4½-year period, the expectation of one-year survival for 244 consecutive recipients treated up to July 1, 1984, rose to 68% (Fig 3).

It is worth breaking down our experience in the cyclosporine era by calendar years beginning with 1980, during which 14 new patients were treated with cyclosporine and steroids (Fig 4). In spite of two deaths on the operating

Fig 2. European liver transplantation centers. Large dots have the same meaning as in Fig 1.

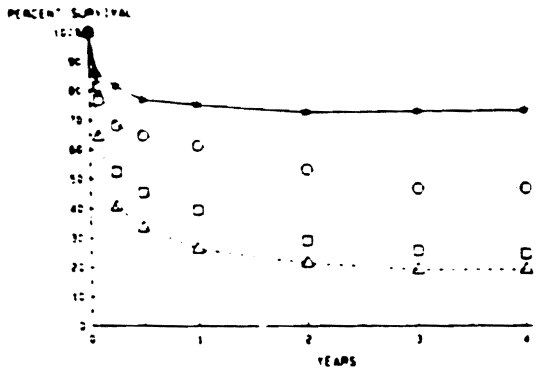

Fig 5. Four-year actuarial survival of all pediatric liver transplant patients v all adults in the precyclosporine era and after the introduction of cyclosporine-steroid therapy. —●—, pediatric cyclosporine (n = 104). --○--, adult cyclosporine (n = 140); ··□··, pediatric azathioprine (n = 86); --Δ--? adult azathioprine (n = 84).

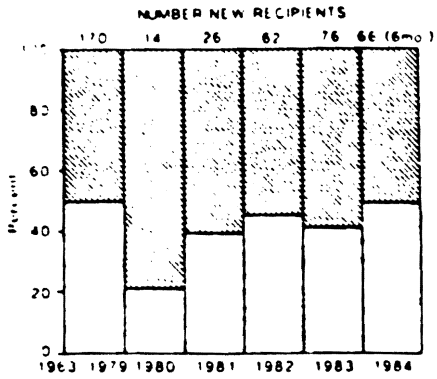

Fig 6. Percentage of patients in the pediatric (≤18 years) and adult population (≥19 years) in the pooled patients from 1963 to 1979 and in each calendar year thereafter. ▨, adult recipients; □, pediatric recipients.

OPTIMAL IMMUNOSUPPRESSION

All of the American liver transplant centers are using double-drug treatment with cyclosporine and steroids. The details vary but a common program is shown in Fig 7. The patients are started on the day of operation on 2 mg/kg every eight hours of intravenous (IV) cyclosporine, given each time over a 1½ to two-hour period. An effort is made with pharmacologic monitoring to reach whole blood trough concentrations of 800 to 1,000 ng/mL, as measured with the radioimmunoassay technique. If serious abnormalities in renal function occur, a downward adjustment in the IV dose is promptly made, even in the first postoperative day. The patient is also given a five-day burst of methylprednisolone beginning in adults at 200 mg/d and ending on the sixth postoperative day with 20 mg, providing rejection has not supervened. The steroid doses are reduced for children.

As soon as the patient is able to eat, oral cyclosporine is begun at a dose of 17.5 mg/kg/d. The IV and oral cyclosporine doses are continued under pharmacologic monitoring until it can be determined with certainty that absorption of the enteral drug is good enough to sustain therapeutic blood levels (Fig 7). Then the IV cyclosporine doses are weaned and discontinued. In patients with draining T-tubes, the absorption of the oral drug often has been noticed to increase suddenly with T-tube clamping (Fig 7). Further reductions in oral cyclosporine and steroid doses are individualized. Some element of nephrotoxicity is accepted in adults at all levels of convalescence until the first half-year has passed (Fig 7). In children, significant nephrotoxicity is quite unusual.

If rejection occurs, a second five-day burst of steroid therapy is given (Fig 7), sometimes stopping in adults at a level of 30 mg/d of prednisone (Fig 7). If this kind of immunosuppression cannot control rejection, a course of antilymphocyte globulin may be considered, but failure to have a prompt response to ALG or intensified steroid therapy should lead to a decision for retransplantation as quickly as possible.

There has been far greater variability of immunosuppression in the European centers. At Cambridge, cyclosporine is not given by Calne until after several weeks of triple-drug therapy with azathioprine and prednisone (and more recently, monoclonal ALG). McMaster, a former associate of Calne, uses the same general method in Birmingham. At Krom's Dutch center and in Berlin, most of the experience has been with conventional azathioprine-prednisone therapy. In Hannover, FRG, Barcelona, Spain, and Montpellier,

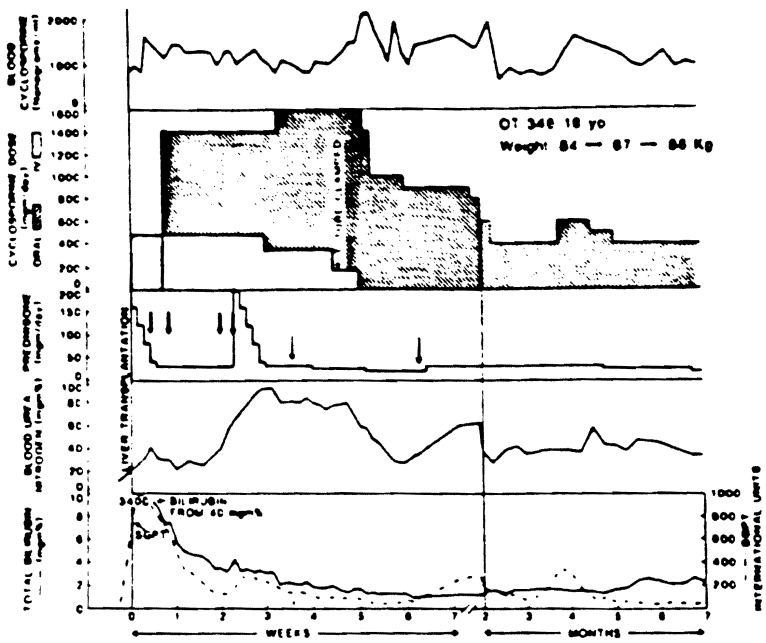

Fig 7. The use of cyclosporine and steroids. Note that the cyclosporine initially is given intravenously (IV) and that the IV therapy is continued long after the drug is begun orally. The switch from double-route cyclosporine therapy to the oral route alone is carefully monitored with cyclosporine blood levels. Note the seeming increase in enteral absorption after clamping of the T-tube, the insistence upon maintaining high blood levels of cyclosporine in spite of obvious low-grade nephrotoxicity, and the intensification of steroid therapy with either a cycle or intermittent bolus administration with suspicion of rejection. Large arrows, 1 g Solu-Medrol (Upjohn, Kalamazoo, Mich); small arrows, 1 g Solu-Cortef (Upjohn).

France, the technique of management has been similar to that in the United States.

Cyclosporine-steroid therapy from the outset has been a simple and effective way to provide therapy, especially after accurate provisions were made for tight dose control by pharmacologic monitoring. The possibility of using monoclonal ALG to reverse rejections that are refractory to "reasonable" cyclosporine-steroid therapy will be evaluated by three collaborating centers in the United States in a randomized trial this autumn.

TECHNICAL MATTERS

Biliary Reconstruction

In the early days of liver transplantation, cholecystoduodenostomy or cholecystojejunostomy were commonly used, with a high incidence of complications. Our eventual policy was to perform duct-to-duct anastomosis, and if this was not possible, to use choledochojejunostomy.[1] The early and late results have been satisfactory with both techniques. As an option, Calne has developed and recommended a conduit procedure with which the graft common duct is anastomosed to the graft gallbladder, which in turn can be connected either to a recipient bile duct or a piece of intestine.[2] The conduit procedure is still being used routinely only in Cambridge and Birmingham, England.

Venovenous Bypasses

During the period of vena caval and portal occlusion that is necessary during the final stages of total hepatectomy and during the construction of the graft vascular anastomoses, venovenous bypasses are being routinely used without heparinization for most adult recipients treated in the United States. The recent physiologic studies reported by Shaw et al[3] have demonstrated how a number of metabolic derangements secondary to venous stasis can be minimized with bypasses. Equally important, the procedure of liver transplantation in adults has become a less stressful operation and one that can be taught to younger surgeons under reasonable conditions. In England, Calne, who described a venous-to-arterial bypass under heparinization some years ago for patients who became unstable during venous occlusion,[2] has recently refined his technique so that heparin is no longer required (personal communication).

It is a curious fact that small children and

infants usually do not seem to have serious injury during the anhepatic period, and thus the bypass may not be so important in the pediatric population. Nevertheless, much further study will be necessary before concluding that the bypass technique is superfluous in pediatric recipients.

Retransplantation

Whenever one of our patients is doing badly, we look first to the graft for an explanation. If there is inadequate or questionable function because of rejection or from other causes, we consider early retransplantation. Before 1980, 21 retransplants were attempted in the first 170 recipients under conventional immunosuppression. There were only three examples of subsequent survival for as long as six months.[1] Even these three patients were not well served by this extraordinary effort, since their survival of 12, 13, and 16 months was a nightmare of morbidity from excessive steroid requirements.

With the advent of cyclosporine, it soon became obvious that patients after retransplantation could often have a trouble-free postoperative period.[1] Between March 1980 and March 1984, 52 patients were retransplanted under cyclosporine (nine received three organs). Patients undergoing retransplantation under cyclosporine and steroids six months to 3¼ years ago have had an overall survival of 48%, a major factor in our improved results; of the nine patients undergoing three transplantations, five are alive. The possibility of retransplantation tends to reduce the zeal with which immunosuppression is pursued in attempts to rescue primary grafts, and thus, infections and other morbidity are commensurately reduced.

Other workers have had gratifying results with retransplantation, including those in Cambridge who recently rescued a child whose graft had a clotted blood supply and who could not have lived longer than a few more hours had not an organ been found. Efficient retransplantation is dependent upon the kind of interinstitutional networks that have sprung up in North America and in Europe.

PROBLEMS OF ORGAN PROCUREMENT

Multiple-organ harvesting that allows the removal of the kidneys, liver, heart, and other organs from the same donor has become common. If a brain-dead donor is stable, preliminary dissection of the liver and kidneys as well as the aorta and vena cava is performed. The organs to be removed can be infused with cold solutions, the distribution of which can be controlled by cross-clamping the aorta at different levels.[4] Preparation for the infusions by experienced surgeons requires about two hours, and for those who are slow or inexperienced, this time can be doubled or tripled. At best, the delay can be annoying to collaborating procurement teams, and at worst, there can be destabilization of a frail donor.

If necessary, multiple-organ procurement can be accomplished in a few minutes. One of the common iliac arteries or the terminal aorta is dissected free, encircled, ligated, and cannulated with a large-bore catheter after total body heparinization. The aorta is encircled again just above the diaphragm and cross-clamped at the same time that infusion with cold solution is begun through the distal aortic cannula (Fig 8). Eight or ten liters of one of the potassium-rich preservations is allowed to run in as quickly as possible in adults, with smaller volumes in children. At the beginning of infusion, the lower inferior vena cava is decompressed to prevent the injury of venous distention.

With this technique, the liver becomes cold to palpation within one or two minutes, and it quickly becomes bloodless at the same time that the intestines become blanched. In animals, it has been shown that the interior of the liver reaches a cryoprotective range below 32 °C within two or three minutes (Fig 9). If the intestines have not been dislodged from their normal position, the blood in the portal vein, which has passed through the intestinal capillary bed, becomes almost hemoglobin-free within one or two minutes (Fig 9). Double

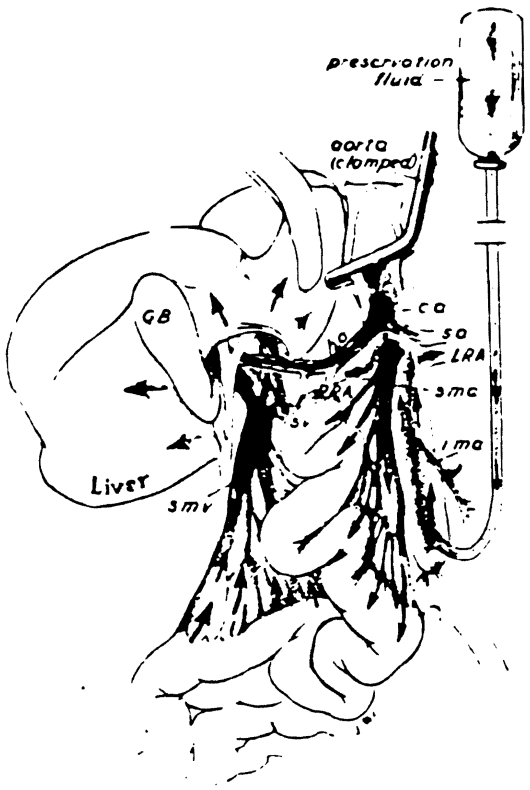

Fig 8. A method of rapid liver cooling that can be done without any preliminary dissection except for insertion of a distal aortic cannula and cross-clamping of the aorta at the diaphragm. The infusion fluid quickly gets into the portal system via the splanchnic capillary bed, providing double inflow cooling (Fig 9).

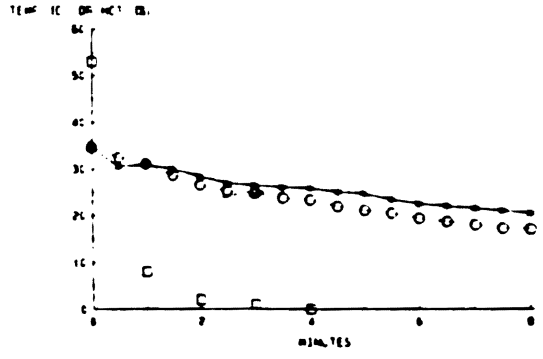

Fig 9. Rapid aortic perfusion for organ preservation: organ core temperature and portal vein hematocrit. Cooling curve of the liver and kidneys with the technique shown in Fig 8. Note that the kidney is fully protected with this in situ technique. The portal venous blood becomes hemoglobulin free within one or two minutes, providing double inflow infusion and cooling. —●—, kidney core temperatures; —○—, liver core temperature; □, portal vein hematocrit.

inflow infusion of the preservation fluid is thereby achieved in a remarkably effective way (Fig 8).

If this method is used, dissection of the hilar structures can be put off until the liver is blanched and is felt to be chilled, by which time the kidneys are similarly protected (Fig 9). The aortic infusion is continued but at a somewhat reduced rate, while the organs to be used are rapidly dissected free and removed in the same general way as if this were done with an intact circulation. If the anatomy of the hepatic hilum is familiar to the operator, this can be done with great speed since the staining from minor hemorrhagic sites does not occur. Similarly, nephrectomies with the en bloc technique can be performed expeditiously as the result of the dissection that has been performed before and with the liver out of the field. Removal of the heart, liver, and both kidneys can be completed within 30 to 45 minutes.

The simplified method of multiple-organ removal has been used to retrieve livers and kidneys from unstable donors, from donors who had undergone cardiac arrest, and from donors whose heart or heart and lungs had already been removed. The hepatic and renal grafts uniformly have been of good quality.

NEW INDICATIONS FOR TRANSPLANTATIONS

Metastatic Disease

A few patients with hepatic cancers have been cured by liver transplantation, and metastases have been rare from small incidental malignancies in livers destroyed by biliary atresia, tyrosinemia, alpha-1-antitrypsin deficiency and the sea-blue histiocyte syndrome.[1] However, a disappointing high rate of tumor recurrence has been well documented in patients whose main reason for liver replacement was primary hepatic or duct cell malignancy. Even patients with slow-growing fibrolamellar hepatomas have had a 50% recurrence rate.[5] The poor results have been attributed in part to an adverse effect of the immunosuppressive drugs.

In view of this, attempts to treat localized hepatic metastases from extrahepatic primaries might be considered bold. Yet Huber and Margreiter and their associates[6] from Innsbruck, Austria, Basel, Switzerland, and Seattle have achieved a remarkable success in a 43-year-old woman with hepatic metastases from the breast. They replaced the liver, gave toxic doses of cyclophosphamide and irradiation, and carried out hematopoietic rescue with autologous marrow. The patient was free of disease more than two years later (personal communication). Recent efforts also have been made by Calne (Cambridge) and Busuttil (Los Angeles) to treat hepatic metastases with liver transplantation but without adjuvant therapy (personal communication). Two of their three patients quickly developed widespread metastases, and the third is alive only five months postoperative. The approach is still experimental.

More Metabolic Engineering

A number of inborn errors of metabolism have been effectively treated with liver replacement.[1] However, the metabolic correction obtained with the phenotypically normal homografts has been incidental to the larger objective of treating hepatic failure, with the possible exceptions of an infant with Crigler-Najjar syndrome who was unsuccessfully treated by us several years ago with an auxiliary liver graft[7] and an 8-year-old child with the same disease whose anatomically normal liver was replaced by H.O. Wolff of Berlin. Wolff's patient is well more than two years later (personal communication).

There have been at least two examples in 1984 of replacement of an anatomically normal liver for the sole purpose of treating a liver-based inborn error that had resulted in damage or destruction of an extrahepatic organ system. In February, a child with homozygous familial hypercholesterolemia was given a new heart by Bahnson of Pittsburgh because of irreparable damage to the coronary arterial system. After the heart was in place and while on the same cardiopulmonary bypass, Shaw removed the seemingly normal liver and replaced it with the liver of the same donor. The result has been a spectacular success in terms of the cardiac function and because the new liver has been able to bring the serum cholesterol down by more than 70%. In this case, in which the fundamental enzymatic explanation for the disease had not been known precisely, the liver transplantation itself became a remarkably powerful research tool with which unanswered questions of the most sophisticated basic nature are now being probed.

In Cambridge, Calne and his associates replaced the liver of a young man whose oxalosis and consequent oxalate crystal formation had destroyed his kidneys and had threatened the cardiovascular system. Calne had described the eerie feeling of removing a liver that looked at least as healthy as the one that was to be transplanted. As the reliability of liver transplantation improves, and that time has already arrived in selected circumstances, other liver transplantations will be performed solely for metabolic objectives. It is interesting that the vision of the Consensus Development Committee that met in Bethesda, Md. in 1983, was broad enough to identify and even to condone this possibility.[8]

SUMMARY

The last four years have been the most exciting in the 26-year period since liver replacement was first attempted in Francis D. Moore's Boston laboratories and in our Chicago laboratories. Important questions have been answered and those that remain will be resolved by a new crop of talented young men and women who have acquired more physical skills and more knowledge than any other surgeons in history. Their contributions about transplantation of the liver and other organs will enliven our meetings for decades to come.

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