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CRITICAL CARE MEDICINE AND LIVER TRANSPLANTATION

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OUTLINE

EDUCATIONAL OBJECTIVES

In this chapter the reader will learn:

1. the development of liver transplantation in its historical context.
2. the developmental methods for immunosuppression leading to cyclosporine and cyclosporine-steroid therapy.
3. the principles of titration of IV and then oral administration of cyclosporine therapy to whole blood concentrations of 800-1000 ng/ml measured by immunoassay.
4. the technical application of veno-venous bypasses and other technical surgical problems during total hepatectomy in adult and pediatric recipients.
5. the problems and outcome for retransplantation.
6. the principles of harvesting the liver from hemodynamically unstable donors.

HISTORICAL BACKGROUND

The pathetic and often hopeless state of victims of end-stage liver disease has been well known to critical care physicians since the beginning of their specialty. All too little could be done. Because of the multiplicity of hepatic functions that can become deranged simultaneously, the symptomatic treatment of such patients in intensive care units has been an exercise in multiple brush-fire control.

From an economic point of view, the magnitude of the problem can be appreciated from the study of O'Donnell et al (1). Five years ago, when the dollar was worth more than today, they cost accounted the treatment of adult patients with end-stage hepatic disease who had a single bout of gastrointestinal bleeding. The bills were more than $35,000 if no surgical procedure was involved, and more than $50,000 if any kind of surgical intervention was carried out. Since hemorrhages and other complications of chronic liver failure tend to occur repeatedly, the cost of dying can be astronomical.

It is quite remarkable to reflect on the change in attitudes of critical care physicians about victims of liver disease that has occurred in the last 5 years; instead of being a nuisance, the mortally ill "liver patient" has become a challenge. It was during these 5 years that the value of liver transplantation became obvious first to those who were evolving the methodology, and then to others. Most of the developments have taken place at the University of Pittsburgh, where the liver surgery team combined its efforts with the remarkable intensive care program headed by Ake Grenvik. Grenvik and his assistants at the Presbyterian-University Hospital, including James Snyder and the pediatric intensivists Richard Orr, Ann Thompson and Richard Schieber have been pivotal figures in making liver transplantation practical.

Experimental Studies

My own experience with liver replacement began in the summer of 1958 when I came to Northwestern University in Chicago from the University of Miami. I had developed a technique for total hepatectomy in dogs which became a widely used method in experimental laboratories (2). While using this preparation in the performance of metabolic studies, it was obvious how simple (at least conceptually) it would be to put a new liver back in the evacuated hepatic fossa. Veno-venous bypass techniques were developed which made the experimental hepatectomy practical for the first canine liver replacement experiments (3).

About 2 or 3 weeks before we performed our first orthotopic liver transplantation in dogs, Moore and his associates (4) using quite different techniques, had undertaken a similar study of liver replacement at the Peter Bent Brigham Hospital in Boston. At first, both our efforts in Chicago and those in Boston failed. At Northwestern University 79 ortho-

topic liver transplantations produced only 19 recipients that survived for as long as 4 days. However, by the end of this experience, the operation had become almost routine. Eight of the last 11 animals survived the operation and, although they were not given immunosuppressive therapy, one of the dogs lived for 20½ days (3,5). Initial efforts at immunosuppression using total-body irradiation were completely unsuccessful (6). It was more than 2 years before long-term survival of canine liver recipients became common, using azathioprine (7,8). Subsequently, the same thing was accomplished using anti-lymphocyte serum (ALS) or its globulin derivative, ALG (9). A further encouraging fact was that it was possible in many animals to discontinue immunosuppressive treatment at a surprisingly early time with very prolonged subsequent survival (7,9,10). These observations suggested that the liver had a biologic advantage in its resistance to rejection, even though it was the most difficult organ to tranplant technically.

CLINICAL TRIALS

The Pre-Cyclosporine Era

The first attempt at liver transplantation in March 1963 failed with the death of the patient on the operating table (11). Four more attempts that year also were unsuccessful, although survival of more than 3 weeks was obtained. Other failures occurred at the Peter Bent Brigham Hospital in Boston and in Paris (12). A 3-year moratorium on further efforts resulted.

The first long-term survival after liver transplantation was not achieved until the summer of 1967 (13). The recipient was a child with a hepatoma. She eventually died of recurrence of her malignancy, but only after 400 days (10). Between then and the end of 1979, the procedure was so unreliable and unpredictable that its potential value could not be exploited. The one-year survival in the first 111 patients was barely 30%. In a subsequent small series of 30 patients, the one-year survival rose to 50% but in a third series of the same size, the survival sank again (14) to almost the original level (Fig. 1).

There were many reasons why the results were so unsatisfactory (15). Surgical errors resulted in hemorrhage, thrombosis of the graft blood supply, the use of poorly preserved grafts, and defects in biliary tract reconstruction. Furthermore, errors of judgment were made both in case selection and postoperative management. There was a tendency in those early days to attribute all postoperative hepatic dysfunction to homograft rejection, when in fact a significant number of patients had biliary tract obstruction and others had developed hepatitis from B virus, cytomegalovirus, Herpes zoster and adenovirus. However, the central problem was that the immunosuppressive treatment available from 1963 through 1979 was suboptimal. The margin between therapeutic and toxic

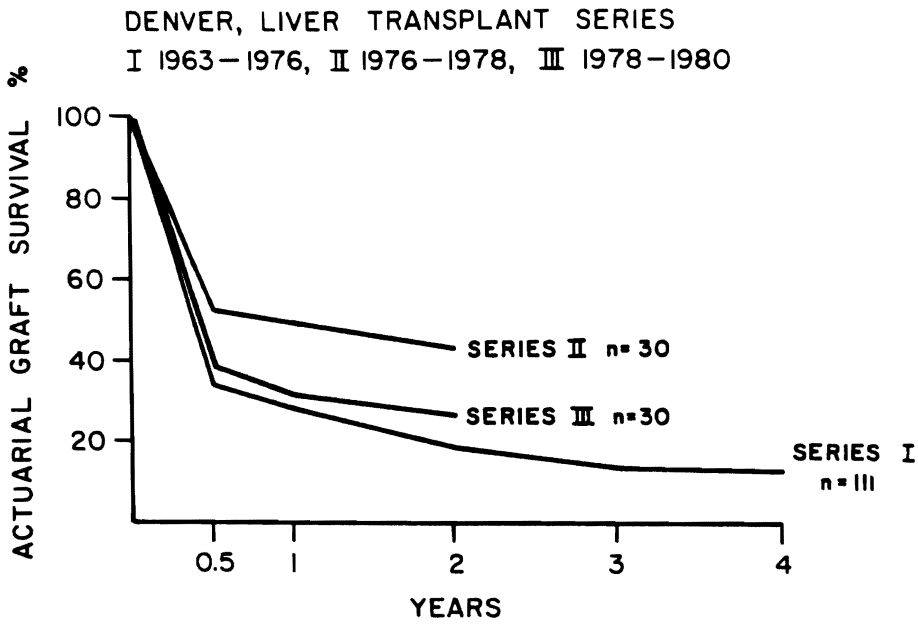

Fig. 1. Patient survival in the pre-cyclosporine era of the orthotopic liver transplantation. Note a slight improvement in the results of a second series which could not be sustained in a third series that was completed just before the introduction of cyclosporine. By permission of Starzl et al (14).

doses of azathioprine and steroids (with or without ALG) was slender at best and did not exist at all in many cases. Thus, it was not until a deeply fundamental change was made in immunosuppression that a major improvement was seen in the prospects for liver transplantation. This occurred in the last days of 1979 and early in 1980.

The Cyclosporine Era

The major steps in pharmacologic immunosuppression are listed in Table 1, beginning with the use of azathioprine as a single agent (16). All of the regimens were worked out with the human kidney transplantation model and subsequently used for the extrarenal organs (9,16-20). The modern era of organ transplantation began with the systematic combined use of azathioprine and steroids (double-drug treatment) introduced in Denver in 1962 and 1963 (17). The most significant further step (in 1966) in the next decade and a half was the addition of antilymphocyte globulin (ALG) as an adjunct to azathioprine and prednisone (triple-drug therapy) (9).

Neither double-drug nor the triple-drug therapy allowed predictable results after transplantation of cadaveric organs. Thus, the introduction of cyclosporine by Calne et al. (21) of Cambridge in 1979 for kidney and

TABLE 1

IMMUNOSUPPRESSIVE DRUG REGIMENS AND ADJUNCTS DEVELOPED FOR KIDNEY TRANSPLANTATION AND APPLIED FOR OTHER ORGANS INCLUDING LIVER

Agents	Year Described and Reported	Place	Deficiences	Used for Livers
Azathioprine	1962 (16)	Boston	Ineffective, dangerous	No
Azathioprine-steroids	1963 (17)	Denver	Suboptimal	Yes
Thoracic duct drainage as adjunct	1963 (18)	Stocknolm	Nuisance; requires 20 to 30 days pretreatment	Yes
Thymectomy as adjunct	1963 (19)	Denver	Unproven value	No
Splenectomy as adjunct	1963 (19)	Denver	No longer necessary	Yes
ALG as adjunct	1966 (9)	Denver	Suboptimal	Yes
Cyclopnospnamide substitute for azathioprine	1979 (19)	Denver	No advantage except for patients with azathioprine toxicity	Yes
Total lymphoid irradiation	1979 (20)	Palo Alto, Minneapolis	Dangerous; extensive preparation; not quickly reversible	No
Cyclosporine alone	1978–1979 (21)	Cambridge	Suboptimal	Yes
Cyclosporine-steroids	1980 (22)	Denver	Under evaluation	Yes

liver recipients was a major event. Although they recommended the use of cyclosporine alone, we quickly learned that the effective exploitation of this new drug required its combination with steroids (22) in the modern day double-drug program that almost overnight became the new standard world-wide for kidney transplantation and for the transplantation of all the extrarenal organs.

With the introduction of cyclosporine, the one-year survival after orthotopic liver transplantation more than doubled (12) as summarized in Figure 2. In a group of 199 patients treated from a few months to more than 5 years ago, the one-year survival expectation rose from 30% to 70%. This improvement caused a tremendous increase in activity in other centers all over the world.

By July 1984, there were 11 major liver centers in the United States and Canada, major being defined as experience with at least five transplantations. The cumulative patient total in North America was 568. Although only five institutions had had experience with more than a dozen cases (Fig. 3), the number of such "large centers" in the ensuing half year has grown to about 20. Other centers than those in Figure 3 have opened. In Europe, nine groups with more than five cases were active as of July 1984 (Fig. 4), and in another seven cities, smaller programs had started. The total European recipients was 424. Both in the United States and in Europe, a network of liver exchange and sharing of patients had already become a practical possibility.

Further Notations on Survival

As already noted, nearly one thousand patients were treated with liv-

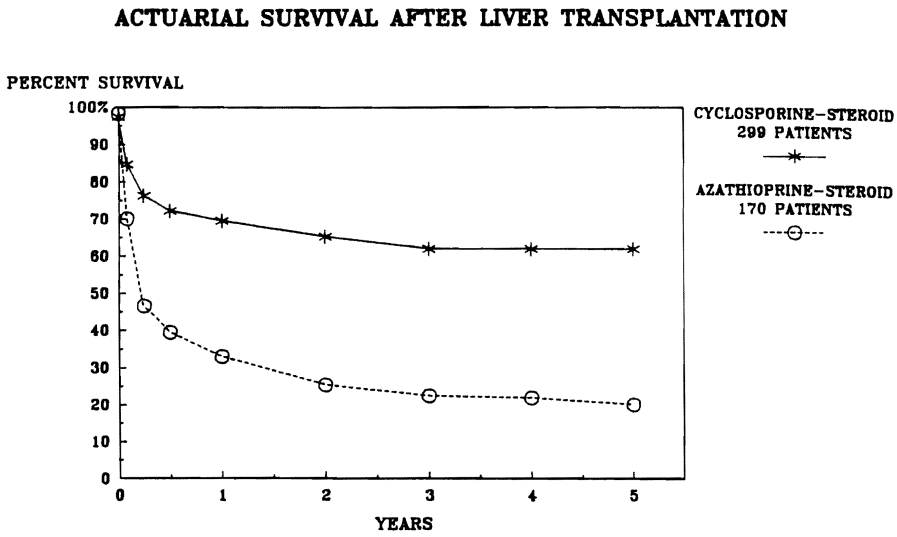

Fig. 2. Life survival curves of patients treated by us with conventional immunosuppression before 1980 (lower curve), versus those treated with cyclosporine and steroids in 1980-1984.

er tranplanation by July 1, 1984. That number probably doubled in the ensuing 6 months. It has been impossible to keep up with survival statistics from all these groups. Consequently, I will concentrate on survival in our own series.

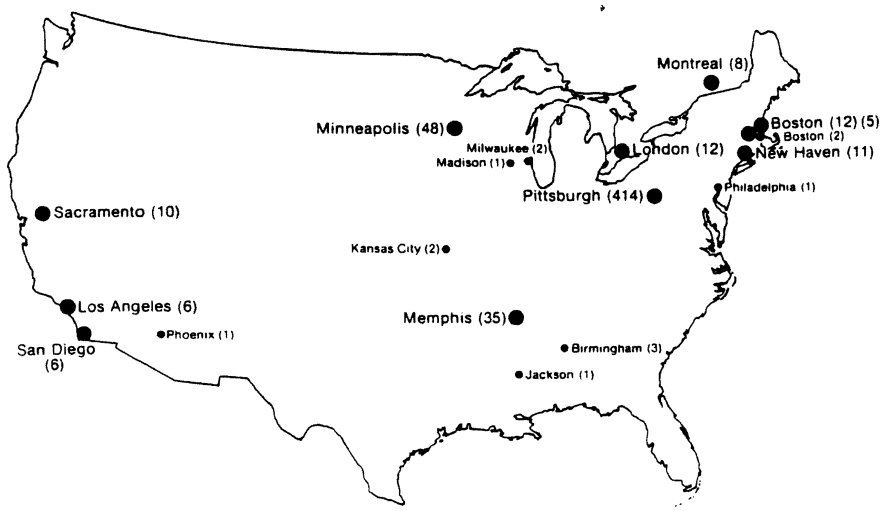

Fig. 3. Liver tranplantation centers in the United States in July, 1984. Teams with five or more cases are designated with large dots. By permission of Starzl et al. (23).

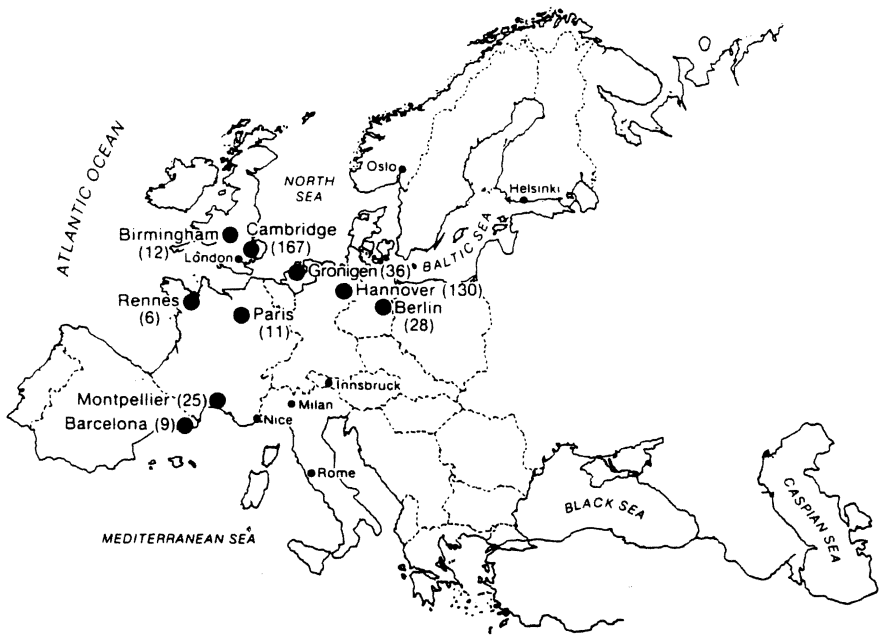

Fig. 4. *European liver transplantation centers in July, 1984. Large dots have the same meaning as in Fig. 3. By permission of Starzl et al (23).*

Using conventional immunosuppression with azathioprine or cyclophosphamide and prednisone to which ALG was usually added, the one-year survival was 55 (or 32.4%) of 170 consecutive recipients treated between 1963 and the end of 1979 (Fig. 2). Twenty-four of the 55 one-year survivors died subsequently, so that of the original 170 recipients, 31 (18.2%) are still alive with followups now of 5 to 15 years. There have been only two deaths after 5 years.

During the 5-year period since the combination therapy with cyclosporine and steroids was instituted, the expectation of one-year survival of 199 consecutive patients treated up to November 1, 1984 rose to 70% (Fig. 2).

In Figure 5, our experience in the cyclosporine era is broken down by calendar years beginning with 1980. In 1980, 14 new patients treated with cyclosporine-steroids were entered. In spite of two deaths on the operating table, 11 (78.6%) of these 14 patients survived for a year. Seven of the 14 still survive, 4 to 5 years later. In 1981, two-thirds of our patients lived for a year and 58% are still living (Fig. 5). 1982 was a special year in that for the first time multiple and interchangeable donor and recipient teams were assembled and trained in response to the need for large case volume. Sixty-two new recipients were enrolled in 1982 with primary grafts and, in addition, 18 retransplantations were performed for a grand

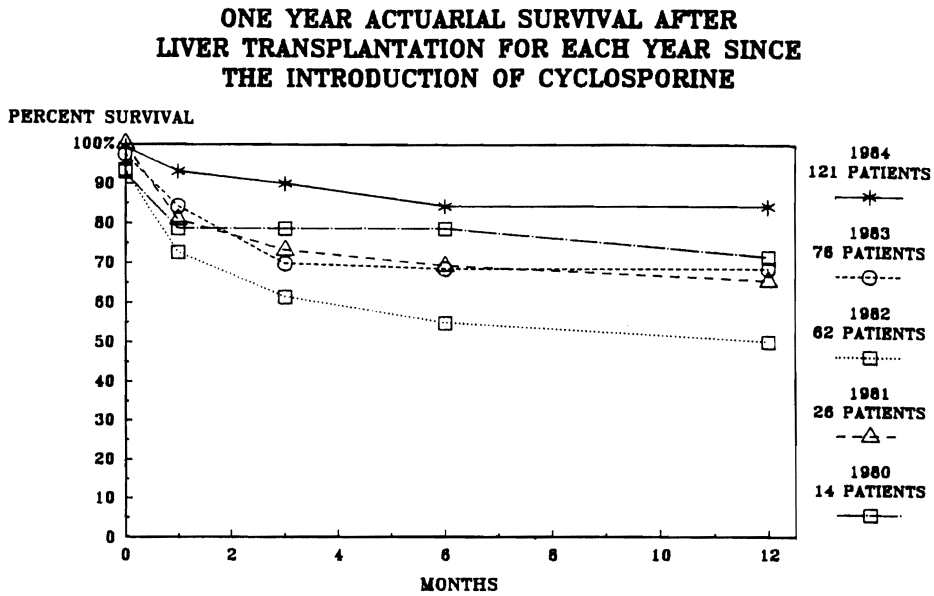

Fig. 5. *One-year survival from year-to-year using cyclosporine and steroids beginning in 1980. 1982 was the first year when multiple donor and recipient teams were trained and the first year of a truly large case load. The statistics from 1984 are for the first 11 months.*

total that year of 80 transplantations. The one-year survival for new patients in 1982 fell to 50% as the multiple teams paid the price of working on a learning curve. The payoff came in 1983 when 76 new patients were entered, and in 1984 during which 121 new recipients were treated in the first 11 months at a pace which projected at about 140 for the full present year. The actuarial or actual survival at one year is better than 80% (Fig. 5). In fact, almost 90% of the patients treated in 1984 are still living. Thus, liver transplantation has become safe to a degree not even easily dreamed of only 2 or 3 years ago.

In assessing these results, an important potential artifact must be examined. Since the beginning of our program, more than two decades ago, pediatric recipients have survived at a higher rate than adults. In Figure 6 is shown the disparity in results between those recipients who were 18 years of age or younger versus those in the adult age group. The divergence of results has become even more striking in the cyclosporine era (Fig. 6). Thus, in looking at the results from any time in the history of our program, stratification of the adult and pediatric cases is necessary.

In the entire pre-cyclosporine era through 1979, about half of the recipients were pediatric (Fig. 7). Since that time, the pediatrics component of the overall case material has ranged from 20% to just under 50% but never as high as in the pre-cyclosporine era. Thus, improved overall sur-

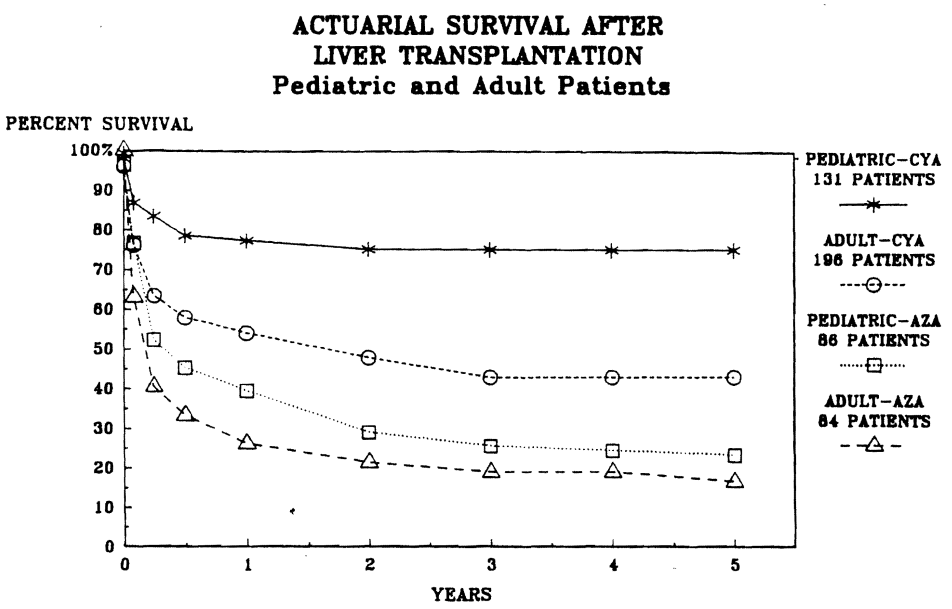

Fig. 6. Life survival of all pediatric patients versus all adults in the pre-cyclosporine era and after the introduction of cyclosporine-steroid therapy.

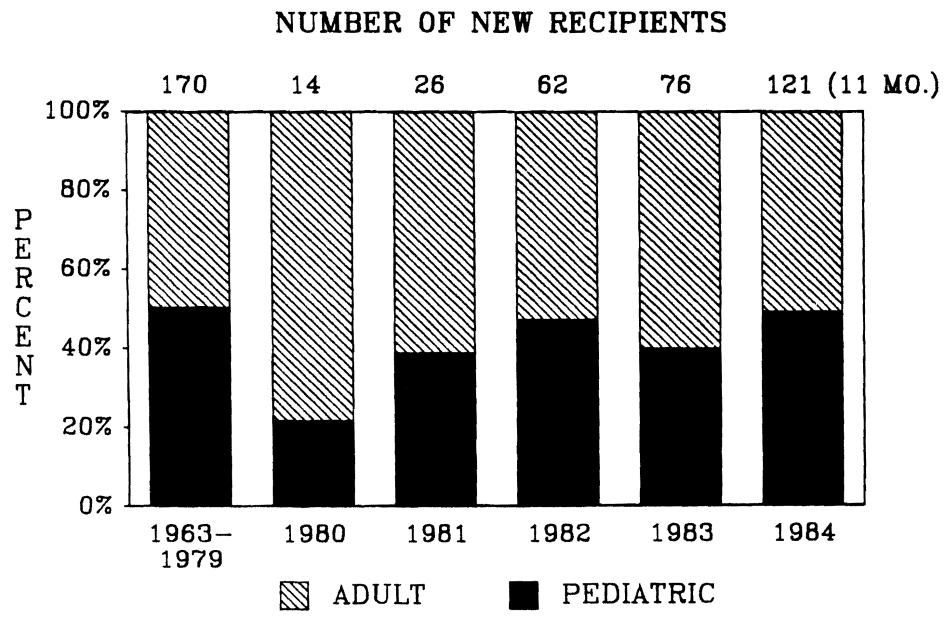

Fig. 7. Percentage of patients in the pediatric (≤18 years) and adult population (≥19 years) in the pooled patients from 1963-1979 and in each calendar year thereafter. Statistics for 1984 are for the first 11 months.

vival after the introduction of cyclosporine has not reflected a major shift downward in the candidate's age spectrum in comparison to the pre-cyclosporine era. However, some of the yearly survival variations since 1980 probably have been influenced by the age factor, especially during 1984 when almost half of the recipients were pediatric.

PROSPECTS FOR FURTHER REDUCTIONS IN MORTALITY

Now that the vast majority of liver recipients can be brought through the operation and the postoperative period, the mortality which remains has been felt more keenly than ever. Further improvements in both graft and patient survival should be feasible almost immediately.

Improvements in Immunosuppression

Almost all liver transplant centers now are using the double-drug program of cyclosporine and steroids. At first, pharmacologic monitoring was not available on a practical basis but there has been increasing dependence on serial measurements of cyclosporine blood levels. The objective usually is to reach whole blood concentrations of 800 to 1000 ng/ml as measured with the radioimmunoassay technique just before the next dose. This is referred to as the trough. In addition, renal function is carefully monitored, and if abnormalities occur, a downward adjustment in the doses is promptly made since cyclosporine's principal side-effect is nephrotoxicity.

The most dangerous time during the recovery is during the first few days or weeks postoperatively. During this time, the intravenous cyclosporine is given while the gastrointestinal tract goes through the expected postoperative ileus, and even after this, the intravenous route is continued until absorption of oral dose can be documented by measuring the trough levels (Fig. 8).

In patients with draining T-tubes, the absorption of the oral drug often has been noticed to increase abruptly with T-tube clamping. This is not surprising since cylosporine is fat soluble. The general objective is to protect the patient from underdosage by using the intravenous route while at the same time working to establish an exclusively enteral route (Fig. 8.).

In the past, the only option that was available if rejection occurred in spite of the foregoing management, was further steroid therapy (Fig. 8). Conventional ALG was sometimes tried, but the results were unpredictable. Often, the only way to save patients undergoing severe rejection was to make a quick decision for retransplantation.

Beginning in the autumn of 1984, a new and powerful tool was added to the immunosuppressive armamentarium, namely monoclonal OKT-3 antibody (Ortho Corporation, Raritan, New Jersey). This agent is a highly standardized ALG made with the mouse hydridoma technique (24).

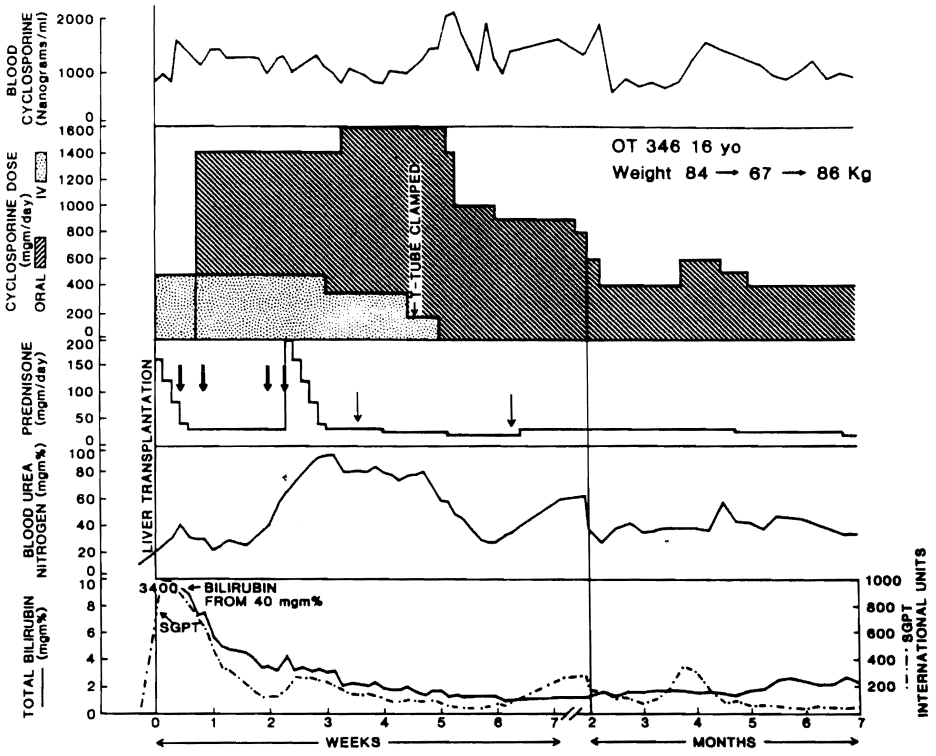

Fig. 8. The use of cyclosporine and steroids. Note that the cyclosporine initially is given intravenously and that the intravenous therapy is continued long after the drug is begun orally. The switch from double-route cyclosporine therapy to the oral route alone is carefully monitored with cyclosporine 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 gram Solu-Medrol. Slender arrows = 1 gram Solu-Cortef. By permission of Starzl et al. (23).

Now, if a rejection occurs which is sluggishly responsive or nonresponsive to steroid therapy, daily intravenous monoclonal antibody is given. The ability of this agent to reverse rejection of renal or hepatic homografts has been little short of spectacular. A further advantage of monoclonal antibody therapy is that cyclosporine doses can be reduced during the period of the ALG therapy. Frequently, patients who develop early and uncontrollable rejection also have renal failure, for which the cyclosporine is deterimental. By using an agent which is effective at reversing rejection, the need for high-dose cyclosporine treatment is reduced or eliminated with consequent relief of the associated renal failure.

During the period of monoclonal antibody therapy (usually 10 to 14

days), an effort is made to tune the ultimate doses of steroids and cyclosporine to those which will be compatible with effective maintenance. When this has been done, there has been a very low incidence of recurrence of rejection after discontinuance of the monoclonal antibody therapy.

Technical Improvements

Veno-Venous 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's vascular anastomoses, veno-venous bypasses are being used without heparinization for almost all adult liver recipients, and for an increasing number of pediatric recipients.

The bypasses which were developed in the last half of 1982 (25) and given extensive clinical trials in 1983 (26,27), have made liver transplantation a very reasonable operation, and one that can be taught to younger surgeons under acceptable conditions. The improved state in which liver recipients are returned to the intensive care unit for convalescence after the introduction of veno-venous bypasses has been documented by Shaw et al (27). The reasons have been several. With veno-venous bypasses during operation, the necessity for volume preloading to keep the patient alive has been drastically reduced, renal function has been protected to an extent not previously possible, and the sequestration of fluids in the obstructed venous beds has been all but eliminated. It has now become quite common to have patients enter the operating room in a nearly moribund state and to have them return from the liver transplantation as if they had undergone a routine procedure.

Retransplantation

Whenever one of our patients is doing badly, we look first to the graft for an explanation. If there is inadequate or questionable liver function because of uncontrolled rejection or other causes, we consider early retransplantation. Before 1980, 21 retransplantations had been attempted in the first 170 recipients under conventional immunosuppression. There were only three examples of subsequent survival for as long as 6 months, and even these three patients died 12, 13 and 16 months after receipt of their second liver. Their extended survival was a nightmare of morbidity from excessive steroid requirements.

With the advent of cyclosporine, it has become obvious that patients after retransplantation often have a trouble-free postoperative period (28) Now the survival after retransplantation is about 50%. Thus, retransplantation has become a major factor in our improved results (24,18).

As it was appreciated that retransplantation could be life-saving, the

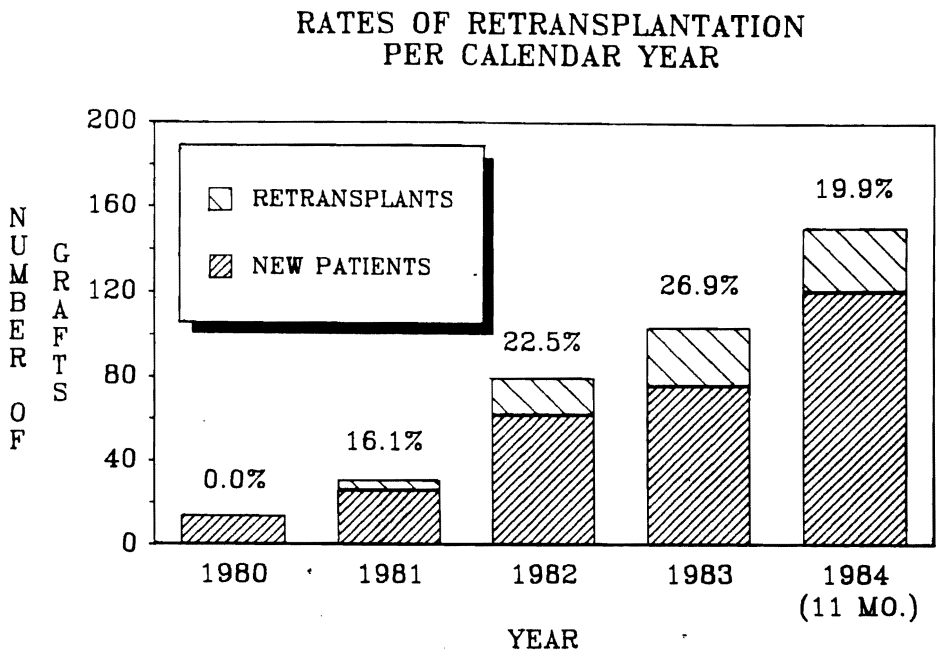

Fig. 9. *Incidence of retransplantation in each year since 1980. Note that about one in five transplantations have been for homograft replacement in the last 4 years.*

number of such attempts increased. Figure 9 shows the year-by-year total from 1980 until the present year. About one out of every 5 hepatic grafts currently being used is for retransplantation.

Other Technical Refinements

One of the greatest advantages of using veno-venous bypasses, is that much more attention during the period of venous occlusion can be paid to obtaining perfect hemostasis in the hepatic fossa. When veno-venous bypasses were not used, the urgency with which the new liver had to be sewn in was comparable to that in cardiac surgery during operations under inflow occlusion. The first objective was to keep the physiologically unstable period as short as possible. The niceties of hemostasis often had to be given second priority.

Under veno-venous bypasses, it is possible to clean up the entire hepatic fossa after the diseased native liver has been removed. The principle which is observed is to try to eliminate entirely the raw areas created by the total hepatectomy. The triangular and coronary ligaments are sewn with continuous hemostatic sutures, and eventually the rows of sutures are connected together to completely eliminate the bare areas.

The classical complications of reconstruction of hilar structures (hepatic artery, portal vein, and ducts) which occurred at a high incidence a

number of years ago have been greatly reduced. Difficulties with biliary tract construction including obstruction or leakage have become rare, as have thromboses of the portal venous and hepatic arterial anastomoses.

THE INTENSIVE CARE PHYSICIAN AND ORGAN PROCUREMENT

Fiction has it that neurosurgeons provide most of the cadaveric donors for organ transplantation. Of course, the cooperation of the neurosurgeons is absolutely vital not only in donor procurement, but also in the application of brain death criteria. Increasingly, however, it has been the intensive care physician with a high degree of social and moral conscience who has set into motion the chain of events leading to organ donation. If a brain dead donor is identified and shown to be stable, evaluation and organ removal can proceed in an orderly way. Multiple organ harvesting that allows the removal of kidneys, liver, heart and other organs from the same donor has become extremely common.

Under ideal circumstances, the organs to be removed are dissected free in the presence of good circulation. They can then be infused with cold solutions, the distribution of which can be controlled by cross-clamping the aorta at different levels (29). These preparations by experienced surgeons require about 2 hours and for those who are slow or inexperienced this time can be doubled or tripled.

If necessary, multiple organ procurement can be accomplished in a few minutes (23). This is important for intensive care physicians to know, since the impression has been created, or it has been explicitly taught by transplant surgeons, that cardiovascular stability is a prerequisite. To do the rapid procurement, 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 as infusion with a cold solution is begun through the distal aortic cannula (Fig. 10.). Eight or ten liters of one of the potassium-rich preservation fluids is allowed to run in as quickly as possible in adults. Smaller volumes are used in children. The lower vena cava is cut or decompressed into a bag on the floor to prevent organ injury from venous distention.

The liver becomes cold to palpation within 1 or 2 minutes and it quickly becomes bloodless at the same time as the intestines become blanched. In animals, it has been shown that the interior of the liver reaches a cryoprotective range below 32°C within 2 or 3 minutes. Blood in the portal vein becomes almost hemoglobin-free within 1 or 2 minutes. Thus, double-flow infusion of the preservation fluid is achieved in a remarkably effective way by infusion into the arterial system (Fig. 10.).

Using this method, dissection of the hilar structures is done only after the liver is blanched and chilled, by which time the kidneys are similarly protected. If the anatomy of the hepatic hilum is familiar to the oper-

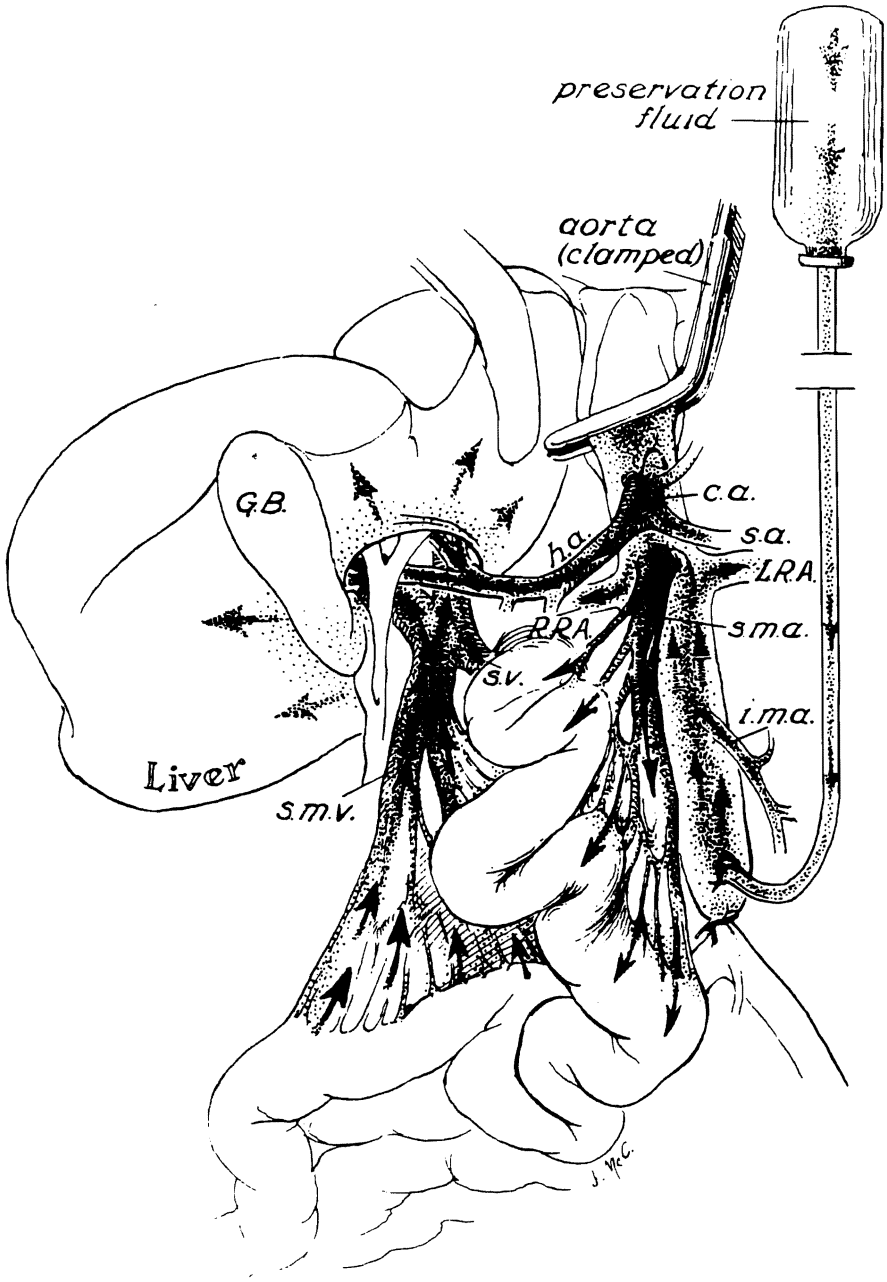

Fig. 10. *Method of rapid liver cooling that can be done without any preliminary dissection except for insertion of a distal aortic cannula and cross-clamping of the aorta at the diaphragm. The infusion fluid quickly gets into the portal system via the splanchnic capillary bed, providing double inflow cooling. By permission of Starzl et al (23).*

ator, the hilar dissection can be done with great speed in a bloodless field. Rapid nephrectomy can also be carried out.

This simplified method of multiple organ removal has been used to retrieve livers and kidneys from unstable donors, from donors who had already undergone cardiac arrest, and from donors whose heart or heart and lungs had already been removed. In Sweden, a country which does not yet have brain death laws, the technique has been applied successfully for organ harvest in non-heart beating cadaveric donors. The hepatic, cardiac and renal grafts have uniformly been of good quality.

SUMMARY

Orthotopic liver transplantation was first carried out in the laboratory almost 27 years ago, and in the human operating theater 22 years ago. Although the procedure was first considered experimental, it has been shown during the last five years how liver replacement can be made an indispensable part of the therapeutic armamentarium in hepatology. The pace at which technical improvements have been made and at which new knowledge has accumulated has been exponential in these recent years.

Much of the recent progress in liver transplantation has been made by effective collaborations with talented critical care teams. Important questions of detail or even concept remain which will be resolved by a new group of talented young men and women working in anesthesia and surgery and in the intensive care units around the world.

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