

590

TECHNOLOGY IN SURGERY

The status of liver transplantation

by Thomas E. Starzl, MD, FACS, Pittsburgh

The status of liver transplantation

by Thomas E. Starzl, MD, FACS, Pittsburgh

The number of medical centers that perform liver transplantations in the United States is small but growing. About a dozen centers have had experience in performing half a dozen or more liver transplants. Other centers with lesser experience are now beginning to spring up—in Phoenix, Jackson, Birmingham, Madison, Milwaukee, Boston, and Philadelphia. Some of these have attained outstanding results.

In Europe there are now almost a dozen medical centers as well that have experience with a half a dozen or more cases, and some other centers are beginning to develop—a second center in London, one in Oslo, in Helsinki, Innsbruck, Milan, Nice, and Rome. This extraordinary growth in the number of centers affords the possibility of establishing a European network similar to what we hope to develop in the United States.

As of September 1984, a total of 568 orthotopic liver transplantations had been carried out in the United States over the past 20 years. Almost half of the recipients are still alive. In 1983 alone, 145 liver transplants were performed, more than the number done the previous year. It is difficult to collect accurate survival figures from the various centers because of the differences in data collection and, perhaps more importantly, the differences in when these programs were begun.

Until the advent of cyclosporine in 1980, survival prospects for liver transplant patients were poor. In my own experience at the University of Colorado with an initial series of some 120 patients, two-thirds of the patients had died by the end of the first year. In a later series, the one-year survival rose to 50 percent, but a third series of patients had a one-year survival rate of about 40 percent. The limiting factor in these operations was that there was no margin of safety between toxicity and therapeutic levels of drugs in either the double-drug (azathioprine-prednisone) or triple-drug programs, the latter including antilymphocyte globulin.

The only really encouraging thing about that early dreary experience was that patients who lived for one or, especially, two years had an extraordinary chance of living for a long time afterward. About one in five of the patients who received liver trans-

plants at the University of Colorado between 1963 and 1980 are still alive.

Cyclosporine has had a tremendous influence on survival. Better than two-thirds of patients treated with cyclosporine-steroid therapy since early 1980 survived for one year. Among patients I treated at the University of Colorado in 1980, survival was about 80 percent. In 1981, my first year at Pittsburgh, patient survival was almost as good. Then in 1982, one-year survival went down to 50 percent. This was the first year of truly mass production of liver transplantation operations. In one year, we treated 62 new patients plus some 20 who underwent retransplantation.

It also was a year of intensive training of multiple teams to perform donor hepatectomies, and a time when several younger faculty members were gaining experience with the recipient operation. The payoff came in subsequent years in which the survival went up to its present rate of over 80 percent.

Perioperative mortality

We have found that perioperative mortality can be reduced in a number of ways:

- By using venovenous bypasses, almost always done in adults, but also for selected pediatric patients.
- With double-route therapy, i.e., administering cyclosporine intravenously until the degree of gastrointestinal absorption of this important drug can be accurately assessed.
- And finally, with a policy of aggressive retransplantation.

Retransplantation in the past, under conventional therapy, was extremely unsuccessful. Only about one in six or one in seven patients undergoing retransplantation lived as long as six months and most of those died shortly after one year. Under cyclosporine steroid therapy, particularly because heavy steroids are not necessary, the number who survive more than six months is almost half. And those results are slowly edging up toward the success rate achieved after primary transplantation. Incidentally, there have been two or three patients who have received three grafts and are still alive.

The effectiveness of oral administration of cyclo-

Dr. Starzl is professor of surgery in the department of surgery at the University of Pittsburgh and is on the staff of Presbyterian Hospital of Pittsburgh, Children's Hospital of Pittsburgh, and the Veterans Administration Hospital of Pittsburgh, Oakland, PA.



sporine can be determined, as the pioneering work done in London, Ontario, and in Houston by Kahan has shown, by measuring cyclosporine levels in the blood. Double-route therapy is rather complex, but competent internists are accustomed to the technique in assessing therapy with other drugs. If cyclosporine levels are not adequate, alternative therapy can be used. I believe that the discriminating use of monoclonal antibody therapy is going to provide a tremendous advantage to recipients of extra-renal organs, such as the liver and the heart. We are, among others, working on this possibility at the present time.

Venovenous bypasses were used in the laboratory development of liver transplantation a quarter of a century ago, but have not been used clinically for almost 20 years because they were thought to be unnecessary. The bypasses return blood to the upper half of the body and thus to the heart during the obligatory occlusion of the vena cava and portal vein while the new liver is being sewn in. And although most patients can survive this insult, it is a major insult, leading to third-party fluid sequestration, swelling of the gut, a high incidence of renal failure and the necessity for preloading, and then subsequent pulmonary edema during the post-operative period. The physiologic advantages of the bypass were reported by Shaw at the American Surgical Association meeting last spring and published in the *Annals of Surgery* (200:524, 1984). Bypass systems are advantageous to the patient and should not be avoided in any adult or even large pediatric patient.

Technical problems

A couple of technical problems had to be resolved before the field of transplantation could move forward. Biliary tract reconstruction has been the most perplexing problem until relatively recently. The present methods of biliary tract reconstruction are duct-to-duct anastomosis over a stent, usually a T-tube stent, or if that fails, a duct-to-Roux limb anastomosis over a stent. These are almost, but not quite, foolproof methods of reconstruction. And in England, Calne still uses a procedure originally in-

troduced by Waddell of Colorado: the gallbladder itself is used as a conduit between the common duct, which is anastomosed to it, and the recipient common duct or intestine. Calne is pleased with this method of reconstruction, but it is more complex than conventional methods and I think that the use of this operation will probably decline.

With the number of cases increasing along with the number of new centers entering the field of liver transplantation, altruistic cooperation among cities and groups has led to a standardization of procurement procedures designed to remove not only the liver but also the kidneys and, in many instances, the heart from the same donor. These multiple organ procurement procedures have in common mobilization of the central abdominal vessels (the aorta) and control of the vena cava, which allows for controlled infusion of cold fluids into specific organs.

Vascular grafts should be removed in every organ procurement procedure because there are so many anomalies among liver transplant recipients that in about a third or a fourth of the cases, large iliac grafts must be used to plug into the recipient aorta and act as conduits in order to revascularize the donor liver. It would be a great tragedy to find such a situation in the recipient and realize that these grafts were in the morgue with the donor.

An alternative method of organ removal that can be used for non-heart-beating donors is to put cold fluids up into the aorta. These fluids immediately pass into the splanchnic circulation and almost immediately infuse the liver. This method protects the kidneys as well as the liver and it can be performed quickly.

With this method, body temperature drops into the cryoprotective range within one minute and then drifts down into the deeply cryoprotective range over a period of five minutes or so. The explanation for the quick and effective liver preservation is that the hematocrit level of the portal vein drops so quickly that within two minutes preservation fluid, after passing through the splanchnic capillary bed, perfuses the liver. The temperature of the kidney also falls quickly. This method could be used in those countries in Europe, principally Scandinavian countries, in which brain death has not yet been legally defined.

Indications for transplantation

The indications for liver transplantation—what Dr. John Najarian has colorfully termed the textbook of liver disease—represent a very long list. However, the principal indication is liver failure. Within the past year, three other diseases—Crigler-Najjar's syndrome (a glucuronyl transferase deficiency), congenital oxalosis, and familial hyper-

cholesterolemia—have all been treated with liver transplantation despite the fact that the removed livers were seemingly normal.

The future of liver transplantation is encouraging because so many bright young surgeons can now perform the procedure. As the field grows, so will the expertise of its practitioners and the benefits to the patient.