32

Hepatic Transplant

A 45-year-old woman is known to have biliary cirrhosis, first diagnosed at age 25. Cholesterol level was elevated, as was the level of alkaline phosphatase, but she was not icteric. Over the past three years, she has gradually become more icteric, with persistent elevation of the level of alkaline phosphatase and with anorexia. Episodes of hepatic encephalopathy become more frequent, responding to protein restriction and finally to catharsis, lactulose, and neomycin. For the past six months, she has noticed a gradually increased protuberance of her abdomen and an umbilical hernia. Two weeks ago, she was hospitalized with increased lethargy, increasing abdominal distention, and failure to eat. She is barely arousable; bilirubin level is 12 mg/dl; alkaline phosphatase, 1600 units/L. Serum albumin value is approximately 1.8 gm/dl and there is peripheral edema.

Consultants: Leonard Makowka, M.D., Ph.D.
Thomas E. Starzl, M.D., Ph.D.

GENERAL COMMENTS

Primary biliary cirrhosis (PBC) or chronic nonsuppurative obstructive cholangitis represents one entity in a spectrum of hepatic disorders termed "chronic cholestatic liver disease" that also includes sclerosing cholangitis in adults and biliary atresia and intrahepatic cholestasis in children. The progressive loss of bile ducts is the feature common to all of these hepatic disorders. (*Editor's note:* This is an unusual but, at least to me, very attractive concept. Evidence as to common etiology is as yet not abundant.) The etiology of PBC is unknown, although it is thought to be an autoimmune disorder, with antimitochondrial antibodies (AMA) being positive in over 90% of the patients. The disease overwhelmingly afflicts middle-aged women (female:male ratio of approximately 10:1), as illustrated by the present case.

The disease is characterized clinically by jaundice, pruritus, hepatosplenomegaly, early fatigability, and malabsorption, with vitamin deficiencies, malnutrition, and bone disease and fractures of varying severity. Once the end-stage of this disease develops, the patient can present with the complications of cirrhosis

and hepatic failure, including ascites, encephalopathy, and variceal hemorrhage that often represent the terminal events. The diagnosis of PBC is based on these clinical findings, accompanied by abnormal biochemical parameters reflecting a cholestatic pattern of liver injury, the presence of circulating autoantibodies, particularly AMA, increased immunoglobulins (IgM), and an increased complement turnover.

The exact histologic characterization of PBC is critical, especially when one considers orthotopic liver transplantation (OLTx) for this entity and as it relates to the differential diagnosis of posttransplant liver dysfunction, as will be described below. The pathologic characteristics have been described to represent the stages and progression of the disease, ranging from the early findings of a chronic inflammatory process, with lymphocytic infiltration of the portal tracts and interlobular bile ducts and granulomata, and finally leading to the end-stage findings of an absolute paucity of bile ducts, fibrosis, and frank cirrhosis.

Previously, medical management has been directed at the prevention, early recognition, and treatment of the symptoms and systemic complications of PBC. The results of therapy with such agents as penicillamine, chlorambucil, colchicine, and cyclosporine have been disappointing. These approaches have had little influence on survival; the progression of the disease is inevitable, and patients succumb to liver failure and its complications such as variceal bleeding.

Orthotopic liver transplantation has revolutionized the approach to and management of patients with end-stage liver disease. The survival results of this procedure have advanced dramatically over the past seven years as a result of improved immunosuppression with cyclosporine and improved methods of multiple organ harvesting and preservation, and with technical refinements in the recipient procedure. Now OLTx should be considered the treatment of choice for patients with PBC. The survival is excellent, with a projected five-year actuarial survival of at least 70% in our group of PBC patients, which represents the largest single series of such patients undergoing OLTx (165 out of the first 1,000 transplant patients during the cyclosporine era). These results are even more striking when one considers the survival of those patients treated by alternate methods or not at all, and the fact that successful transplantation represents a cure allowing the patient to resume, in the majority of cases, a normal life and not one of a chronic and relentless disease. In fact, PBC is currently the second most common indication for OLTx in adults at our institution, being exceeded only by posthepatic cirrhosis, and represents a primary indication for OLTx at most other transplant centers.

The patient described here in many respects typifies the ideal candidate for OLTx. With the current state of the art, one might argue that liver replacement should have been considered at an earlier stage of her disease, prior to the most recent marked deterioration in her condition. The preoperative evaluation, operative approach, and important postoperative considerations pertaining to this case will be outlined.

PREOPERATIVE EVALUATION AND CONSIDERATIONS

Once referred to the transplant center for evaluation as a candidate for OLTx, the patient undergoes a thorough and extensive evaluation to determine the suitability and fitness for the procedure. A careful history and physical examination are carried out. Alcohol and/or drug abuse, prior blood transfusions, concomitant illnesses, prior surgical procedures, medications, and exposure to toxins are important details. Physical examination will offer an estimate of how advanced the liver disease is (i.e., the presence of the stigmata of end-stage liver disease and cirrhosis), and may also offer clues as to the etiology of the liver disease that at times may be very difficult to diagnose (i.e., the presence of xanthomata and Kayser-Fleischer rings in PBC and Wilson's disease, respectively).

The presence and degree of encephalopathy should be documented and graded. The presence of hepatic encephalopathy should initiate a search for precipitating factors such as dehydration, infection, or gastrointestinal bleeding that should all be treated. Spontaneous bacterial peritonitis (SBP) is a very important associated finding and must always be considered and ruled out by appropriate cultures. The SBP can usually be easily managed with appropriate antibiotics. When all other circumstances are appropriate, and the patient is a candidate for OLTx, and a suitable donor organ is available, the presence of a recent SBP should not be considered a contraindication to OLTx since SBP represents a manifestation of end-stage liver disease. Severe cases of encephalopathy should be managed in an intensive care setting, with consideration being given to endotracheal intubation to prevent aspiration. All patients should also receive neomycin and lactulose.

A full battery of blood tests are performed that include blood cell count, full coagulation profile, electrolyte studies, liver function tests, glucose level, and renal function tests, along with more specialized determinations for specific disease entities (i.e., autoantibodies, copper and iron studies, etc.). Any evidence of coagulopathy should be corrected insofar as possible prior to undertaking any invasive procedures. Abnormalities in renal function must be further investigated to distinguish the hepatorenal syndrome from both simple dehydration due to chronic diuretic therapy and ascites, and intrinsic renal disease. This differentiation is extremely important, since renal failure during the posttransplant period increases morbidity and mortality. Hepatorenal syndrome is completely reversible after successful OLTx. However, OLTx candidates with significant preoperative intrinsic renal disease are best managed by combined liver and kidney transplants during the same operative procedure. This combined approach to end-stage liver and kidney disease has now been carried out in 18 patients at our institution with excellent results.

The functional reserve of the liver can be determined further using an indocyanine green clearance study, particularly in patients who are not deeply jaundiced. Endoscopy of the gastrointestinal tract can be performed to detect

esophageal varices and other pathology such as inflammatory bowel disease in patients with primary sclerosing cholangitis. Patients with a history of bleeding esophageal varices undergo injection sclerotherapy.

Doppler ultrasonography is used to determine the patency of the portal vein, hepatic artery, hepatic veins, and vena cava. Selective angiography is reserved for patients whose portal vein cannot be visualized by noninvasive means or for patients with previous portasystemic venous shunts in whom the status of both the shunt and portal vein are very important technical considerations. A general evaluation of pulmonary, cardiac, and renal status is carried out to asssess the surgical risk and to prepare the patient for major surgery.

The patient's weight, height, ABO blood group, and ultrasound and/or computed tomography (CT) scan determination of the liver volume are the most important variables in the selection of a suitable donor. The ultrasound and CT scan are also useful to detect the presence of liver tumors and to exclude extrahepatic extension. Donor-recipient matching is mainly based on blood type and organ size. Although ABO blood group barriers have been violated in emergent situations (i.e., fulminant hepatic failure, retransplantation, or in pediatric patients for whom the supply of donor organs is critical), we recommend that for the elective or semielective OLTx, donors of the same ABO blood group be selected. Knowledge of the recipient liver volume as assessed by ultrasound and/or CT scan has proved to be very helpful in the size matching of the donor organ. The liver volume may be very small in relation to the body weight in certain hepatic disorders such as postnecrotic cirrhosis, and therefore an organ harvested from a donor of similar body weight as the recipient could prove to be too large for that recipient, who would better accept a liver from a smaller weight donor. Conversely, the liver in diseases such as PBC and sclerosing cholangitis is quite large or oversized, and thus such recipients are able to accept organs from much higher weight donors. It is important to remember that whatever the liver size, it can always be easily accommodated by a much larger recipient; however, the opposite situation can result in disaster.

It is important to consider certain "risk factors" and discuss how the approach to these have changed. These risk factors have included age, previous abdominal surgery, previous portasystemic shunt procedures, and the presence of active infection. The presence of extrahepatic acute infection should preclude OLTx at the time of the active infection. However, the presence of intrahepatic sepsis such as cholangitis and hepatic abscesses, as may occur with hepatic artery thrombosis in a transplanted liver, should not be contraindications for liver transplantation. Similarly, as already mentioned, the presence of treated spontaneous bacterial peritonitis, a manifestation of chronic liver disease, should not preclude successful OLTx.

In the past, an age of 55 years or greater was considered a relative contraindication to OLTx. The concept of age has undergone a dramatic reevalu

at our institution over the last two to three years. With careful selection criteria and individualization of patient management, and by establishing accurate criteria for adequate cardiovascular, pulmonary, and neurologic function, the survival results in patients older than 50 years, and even in patients older than 60 years, have approached the results in the younger age groups. In fact, in a recent review of the first 1,000 liver transplants at our institution, who were immunosuppressed with cyclosporine, there were 121 patients between the ages of 50 to 60 years old, 47 patients between 60 to 70 years old, and one patient who was 76 years old at the time of OLTx.

The case of the 76-year-old patient who underwent OLTx illustrates clearly the impact that liver transplantation can have on the delivery of health care to and the management of geriatric patients; it also highlights the importance of considering and evaluating each candidate as an individual. This patient was a 76-year-old woman with primary biliary cirrhosis who was bedridden because of incapacitating bone disease. Jaundice was moderate and the main indication for OLTx was her debilitating bone disease. She was carefully evaluated, both medically and psychosocially, and there was unanimous agreement at the candidate selection committee that she should undergo OLTx. She underwent an uneventful transplant procedure, with an uncomplicated postoperative course, and was discharged at three weeks after transplantation. She is now about 18 months posttransplant, doing extremely well at home, with normal liver function, and has required no readmissions into the hospital.

There is no doubt that previous abdominal surgery can increase the difficulty, morbidity, and mortality of OLTx. Even simple procedures such as an open liver biopsy or a cholecystectomy can influence the blood loss and operative time. However, it is the mutilating procedures in the hilum of the liver, such as bile duct reconstructions for sclerosing cholangitis and portacaval shunt for bleeding esophageal varices, that can convert an otherwise routine and straightforward liver transplant procedure into a nightmare. In fact, any portasystemic shunt procedure will add tremendously to the complexity and morbidity of OLTx, not only because of the consequences of previous abdominal surgery and adhesions, but also because of marked changes in the quality of the portal vein that can occur with any of these shunt procedures. All of these procedures can at best be considered palliative; the progression of the underlying liver disease is not altered, and rarely do the patients become free from the ravages of a chronic and relentless disease state. Liver transplantation is curative, and with the markedly improved results that have been realized over the last few years, many, if not all, of the procedures such as portoenterostomy, bile duct reconstruction, and portasystemic shunts should become obsolete. The results of OLTx will undoubtedly even improve further as candidates are selected at an earlier stage in their disease and as OLTx is offered to younger patients and prior to undergoing extensive upper abdominal surgical procedures.

The indications for OLTx include a major gastrointestinal (GI) bleed, a history of repeated bouts of encephalopathy, progressive neuropathy, refractory ascites, a recent precipitous deterioration in liver function and jaundice, severe fatigue and pruritus, the rapid progression of incapacitating bone disease, and severe wasting.

Considerations regarding the proper timing of OLTx are also constantly changing and, as already mentioned, OLTx continues to be offered at earlier stages of the disease. It has been somewhat easier to time and offer liver transplantation to patients with PBC than for some of the other indications since a set of prognostic indices have been developed and accepted at most centers; these indices employ the common clinical and pathologic criteria of this entity (i.e., age, total bilirubin level, albumin level, encephalopathy, ascites, GI bleed). In our own large series of PBC patients that underwent OLTx, virtually all met the criteria for advanced disease that would predict that death would have been likely in a year or less without the transplant procedure.

The patient described in the present case report represents an ideal candidate for OLTx. This patient exemplifies most of the common features and characteristics of PBC that have already been outlined above. Moreover, the signs and symptoms that she presents will illustrate many common findings in end-stage liver disease of any etiology that require hepatic replacement. This patient has experienced a rather rapid deterioration of her liver function and exhibits the sequelae from it. This type of patient should immediately undergo an evaluation as outlined above and immediately be considered for OLTx once a suitable donor liver is available. One can easily argue that this patient should have been referred for evaluation of liver transplantation at a much earlier stage in her disease. The importance of knowing a patient well, and of being able to follow the course of a patient's liver disease prior to transplantation, cannot be overemphasized.

OPERATIVE CONSIDERATIONS

Liver transplantation for PBC, as for any disease indication, involves the donor hepatectomy (organ procurement), recipient hepatectomy, and implantation of the new liver into the recipient.

Donor Procedure

The techniques for multiple organ retrieval that are currently used are based on the rapid core cooling of solid organs by the aortic infusion of cold electrolyte-containing or colloid-containing solutions, and for the liver, the additional infusion of cold solution through the portal venous system. These techniques, along with careful donor monitoring and management, and synchronous collaboration with other transplant teams, have allowed the successful harvesting o

the liver and/or pancreas, kidneys, and heart or heart and lungs from a single brain-dead, heart-beating cadaveric donor. The suitability of a potential liver donor has been customarily based on traditional indicators of ischemic injury, including liver function tests, parameters of coagulation, oxygenation, blood pressure, level of pressor agent support, the number and duration of cardiac arrests, and the cause of death. We have found that these parameters of donor assessment can be applied too rigorously and, in fact, may be much less reliable in predicting the quality of the liver than has been assumed, thus resulting in a potentially high degree of organ wastage. We have liberalized these conservative criteria for donor acceptance considerably, and have not suffered a discernible penalty.

The conventional method of liver preservation in recent clinical practice has been static, hypothermic (4°C) storage of the liver in Euro-Collins solution. This has necessitated the implantation of the liver within a six- to eight-hour period after aortic crossclamping in the donor. A major advance in liver preservation that has impacted our own clinical practice of liver transplantation has been the development of the University of Wisconsin-Lactobionate solution by Dr. Belzer and his group. (*Editor's note:* A very logical approach to increasing donor organ survival, this is hopefully but the first in a series of metabolic approaches in improving substrate supply to donor organs.) Cold preservation in this new solution has resulted in improved quality of organs after revascularization, after any duration of preservation; however, more importantly, it has allowed us to successfully preserve and transplant livers after more than 20 hours of simple cold preservation.

Recipient Procedure

The recipient hepatectomy in patients with PBC is usually easier to perform than it is in most other instances of adult chronic liver disease. This is especially true in the absence of previous upper abdominal surgery. Specific operative findings include livers that are considerably larger than normal, marked hilar lymphadenopathy, and a minimal-to-moderate degree of portal hypertension. These findings, along with the usual absence of major collaterals in the hepatic suspensory ligaments and the bare areas of the liver, the usually normal consistency and configuration of the suprahepatic and infrahepatic vena cava and the portal vein, and the usual presence of a normal recipient common bile duct, are all features that render the procedure in PBC technically easier than it is for many of the other indications for OLTx.

Veno-venous bypass (without systemic heparinization) was developed for the anhepatic phase of OLTx as a method of decompressing the temporarily obstructed systemic venous (vena caval) and splanchnic venous (portal) systems. The anhepatic phase of OLTx is the most physiologically turbulent period of the

entire procedure. Without veno-venous bypass, there is a massive sequestration of blood volume in the peripheral venous circulation of the lower torso and in the mesenteric venous circulation, resulting in diffuse edema of the gastrointestinal tract, high renal vein pressure with deterioration of renal function, increased bleeding from high pressure in the thin-walled venous collaterals found throughout the abdomen in patients with portal hypertension, and marked hemodynamic instability.

Veno-venous bypass is now routinely employed in most adults undergoing OLTx in order to reduce these risks and to maintain physiologic stability during the anhepatic phase. Blood from the inferior vena cava is drained via a cannula placed through the saphenofemoral junction into the cava near the bifurcation of the common iliac veins. A second cannula to drain the splanchnic venous system is placed end-on into the transected portal vein. These two cannulas are joined by a Y-type connector, and the blood is returned to the heart through a cannula placed in the ipsilateral axillary vein using a nontraumatic, centrifugal pump (Biomedicus Inc.). Using such a bypass, it is possible to maintain stable hemodynamic parameters similar to prehepatectomy levels, to reduce postoperative problems of the bowel and ileus by relieving congestion of the intestinal tract, to avoid renal venous hypertension (thus markedly decreasing the incidence of renal failure requiring postoperative dialysis), and to reduce the blood loss by preventing the development of high pressure in venous collaterals.

The technique of veno-venous bypass allows the surgeon to control the length of the anhepatic phase and, in this way, the recipient hepatectomy can be individualized; certain problems can be addressed such as previous surgery or significant portal hypertension. The bypass is established prior to the completion of the recipient hepatectomy and facilitates the final steps of this procedure, particularly the dissection of the vena cava. Once the liver is removed, the large bare areas created by the hepatectomy are carefully inspected and hemostasis is achieved by oversewing them if necessary. The cuffs of the suprahepatic and infrahepatic vena cava are then carefully fashioned and tailored for anastomosis. The donor liver, appropriately prepared at the back table in cold fluid, is then brought up for implantation. The suprahepatic and infrahepatic vena caval cuffs are anastomosed. Prior to the completion of the infrahepatic caval anastomosis, the liver is flushed free of potassium and air with cold solution infused through a cannula in the portal vein. The portal bypass cannula is then removed, and the splanchnic venous system is clamped for the next 10 to 15 minutes while the portal vein cuffs are appropriately fashioned and anastomosed. The liver is usually revascularized on portal flow, and the bypass is then completely stopped and the cannulas are removed. Once the liver is revascularized on portal blood and initial rapid hemostasis is achieved, we then proceed with the hepatic arterial reconstruction. We prefer an end-to-end anastomosis between the recipient hepatic artery and the donor celiac axis, whenever possible.

Our preferred method of vascular anastomoses for the vena cava, portal vein, and hepatic artery is an end-to-end anastomosis with continuous nonabsorbable monofilament propylene suture. A "growth or expansion factor" is employed to prevent suture line stenoses. The running suture is tied several millimeters or more from the vessel wall such that when the vessel distends under pressure or when vasospasm resolves, the suture can easily be soaked up into the vessel, thus preventing deformity at the site of the anastomosis.

Portal vein thrombosis at one time was considered an absolute or at least a relative contraindication to OLTx. However, as the surgical techniques of OLTx have been refined over the last few years, our approach to abnormalities and thrombosis of the portal vein has become much more aggressive, and these situations no longer preclude successful OLTx. We have used vascular grafts of donor iliac vein, harvested at the same time as the liver, to reconstruct recipient portal vein segments of varying length that are either hypoplastic or thrombosed. We have been able to reconstruct the portal vein as far back as the level of the confluence of the superior mesenteric and splenic veins under the neck of the pancreas, in order to achieve satisfactory splanchnic flow to the liver.

One technical problem that is unique to patients with PBC undergoing OLTx is the fragility and friability of the recipient hepatic artery. The media and subintima have a tendency to separate from the rest of the artery, even with the slightest amount of trauma, including the application of vascular clamps in the preparation for anastomosis and/or the ligation of the gastroduodenal artery or other branches. This can result in fragmentation and intramural dissection of the injured vessel proximal to or beyond the level of the left gastric and splenic arterial branches, resulting in a suboptimal arterial supply that is unacceptable for successful OLTx. In this situation, as in any situation in which the hepatic arterial inflow is poor, we use a conduit usually consisting of a free-standing graft of donor iliac artery that is anastomosed to the recipient infrarenal aorta and is passed through a tunnel posterior to the pancreas and duodenum and entering the hilum so that it can be anastomosed to the donor iliac artery. It should be noted that intimal dissection occurred in about 20% of the cases in our large series of PBC patients and required the use of an iliac graft to prevent subsequent thrombosis.

After completing the four vascular anastomoses and achieving adequate hemostasis, the recipient procedure is completed with the biliary tract reconstruction. In PBC patients, the biliary reconstruction of choice, and one that is usually possible, is a duct-to-duct choledochocholedochostomy over an external biliary stent. The advantages of this method include the preservation of the sphincter of Oddi and the availability of the T-tube to monitor bile production and perform cholangiography. In certain situations, a direct duct-to-duct repair cannot be performed, and in these cases an end-to-side Roux-en-Y choledochojejunostomy over an internal stent should be performed. This technique

should be the primary method of biliary reconstruction in patients with preexisting extrahepatic biliary tract disease such as sclerosing cholangitis, when there is significant size discrepancy between the donor and recipient bile ducts, when there is significant bleeding around the bile duct, and for most cases of liver transplantation for hepatic tumors in which the recipient dissection includes the entire supraduodenal lymph node and bile duct areas. Failures of duct-to-duct repair are usually best managed by conversion to this method of reconstruction.

POSTOPERATIVE CONSIDERATIONS

Postoperative immunosuppression in adults usually consists of a rapid steroid taper, beginning with methylprednisolone at 200 mg intravenously the day after surgery; this is reduced by 40 mg each succeeding day until a maintenance dose of 20 mg per day is reached. Cyclosporine is administered intravenously at a dose of 6 mg/kg/day in three divided doses. As gastrointestinal function normalizes, the therapy is gradually switched from intravenous to oral cyclosporine at 17.5 mg/kg/day. The cyclosporine dose is judged on a day-to-day basis by assaying the blood concentration of the drug. Acute rejection episodes are treated with either steroid boluses and recycles, with monoclonal antibody (OKT_3, Orthoclone, Ortho Pharmaceutical Corporation, Raritan, NJ), or with increased doses of cyclosporine when indicated.

The survival in liver transplant patients treated with cyclosporine has improved dramatically. The overall survival rates of the first 1,000 liver transplant patients treated with cyclosporine-steroid therapy at our institution were three times higher than those of the 170 patients treated with azathioprine and steroids before 1980. The five-year actuarial survival for this overall group of 1,000 patients was 64%. The projected five-year actuarial survival of the group of PBC patients who underwent transplantation at our institution is approximately 70%.

An aggressive attitude toward and the frequent use of retransplantation has had a favorable influence on the overall survival results of liver transplantation at our institution, in particular in the group of patients with PBC. In addition to hepatic dysfunction, important factors determining the feasibility of retransplantation include cardiopulmonary status, renal function, and the presence or absence of infection. Since the overall general condition of PBC patients prior to the initial transplant procedure is usually better than that of patients undergoing transplantation for other indications, retransplantation can often be carried out more readily and with better results in the PBC group. In our own series of PBC patients undergoing OLTx, the incidence of retransplantation was less than 1 in 5, and the survival rate in this particular group was almost 50%.

Most of the mortality after OLTx for PBC occurs within the first six months following transplantation. The causes of death are the same as for OLTx for any disease indication. In the group of PBC patients who underwent transplantation

at our institution, rejection was the single most important cause of death, either because retransplantation was not possible or because retransplantation was not successful. Other causes of death included primary graft nonfunction, hepatic artery thrombosis, and pneumonia due to bacteria or *Pneumocystis carinii*. Although the morbidity after OLTx has decreased considerably over the last few years, numerous postoperative complications are experienced by patients after this procedure, many of which require surgical intervention. Our review of PBC patients undergoing OLTx revealed that wound infection was the most common problem, followed closely by the need for biliary tract revision for anastomotic stricture or leak. Gastrointestinal hemorrhage and hemoperitoneum were also significant postoperative complications in this group of patients.

The only potential controversy regarding the application of OLTx for patients with PBC has arisen from another group's experience with liver transplantation for PBC in 11 patients who were immunosuppressed with azathioprine and prednisone. Clinical and histopathologic evidence for recurrent PBC was reported in 3 of these 11 patients. However, in our own experience in 165 patients, and with follow-up periods ranging from six months to almost 9 1/2 years, we have not been able to document recurrent PBC in any of the patients who underwent transplantation. Furthermore, we could demonstrate no correlation between the presence of AMA titers before and after transplantation and the function of the graft. Many histologic similarities exist between PBC and rejection, as well as graft vs. host liver disease, and this may therefore account for some confusion when diagnosing recurrent disease after transplantation.

The quality of life after OLTx for PBC has been excellent, with 90% of the long-term survivors achieving full rehabilitation. A significant incapacitating problem in patients with PBC is osteoporosis, which is thought to be caused by a low bone turnover state. Significant bone disease was present in about 40% of the PBC patients who underwent liver transplantation at our institution, and approximately 20% of these patients were totally incapacitated. There was marked improvement in either bone pain or fractures following OLTx in these patients, even though some patients required prolonged postoperative rehabilitative programs. A large number of the long-term survivors have returned to either full-time or part-time work, and there are patients who have become pregnant and have given birth to normal children.

There is no doubt that the survival, and particularly the quality of life, of patients with primary biliary cirrhosis who undergo orthotopic liver transplantation is markedly enhanced when compared to that in patients managed with standard medical therapy. It is expected that these results will even improve further in the future with better and earlier preoperative selection of candidates, as immunosuppression improves or becomes more selective, and as the surgical technique and the postoperative management of these patients becomes more refined.

BIBLIOGRAPHY

1. Esquivel CO, Van Thiel D, Demetris AJ, et al: Transplantation for primary biliary cirrhosis. *Gastroenterology* 1988; 94:1207–1216.
2. Gordon R, Iwatsuki S, Esquivel CO, et al: Progress in liver transplantation. *Adv Surg* 1987; 21:49–64.
3. Iwatsuki S, Starzl TE, Todo S, et al: Experience in one thousand liver transplantations. *Transplant Proc* 1988; 20(Suppl 1):498–504.
4. Starzl TE, Iwatsuki S, Van Thiel D, et al: Evolution of liver transplantation. *Hepatology*, 1982; 2:614–636.
5. Starzl TE: Hepatic transplantation. *Semin Liver Dis* 1985; 5:309–419.