histologic appearance while they were receiving long-term corticosteroid therapy. Unfortunately, no data were presented on the effect of corticosteroids on the bone disease that is seen with increasing frequency in patients with PSC. Although the characteristics of these bone abnormalities have not been thoroughly delineated, the cholestatic nature of PSC and previous data on the metabolic bone disease in primary biliary cirrhosis would suggest that the bone abnormalities in PSC are most likely due to osteoporosis.

Azathioprine has been used in at least two patients with PSC without apparent benefit. Use of low-dose methotrexate has recently been reported to cause improvement in results of biochemical studies, in stabilization of bile duct scarring, and in liver histologic appearance in two patients with PSC. The potential hepatotoxicity of this agent and the small number of patients in this report mandate that this drug not be used until results from controlled trials are available. Cyclosporine, a new immunosuppressive drug that inhibits the production of interleukin-2 by T lymphocytes, resulting in decreased T-lymphocyte activation and proliferation, is currently under investigation at our institution in a double-blind controlled trial. Preliminary results are not yet available.

Antifibrogenic Agents

Recently, considerable enthusiasm for the use of colchicine, a drug with putative antifibrogenic effects, has emerged because of several controlled trials suggesting efficacy in several types of chronic liver disease, including primary biliary cirrhosis. To date, there have been no controlled trials of this agent in primary sclerosing cholangitis.

Combination Drug Therapy

We recently reported our preliminary experience in 12 patients with PSC treated with combined prednisone and colchicine therapy compared with 12 untreated patients matched for age, sex, initial biochemical test abnormalities, and liver histology. We observed impressive improvement in bilirubin, alkaline phosphatase, and aspartate aminotransferase levels in treated patients when they were re-evaluated at 6 and 12 months after entry. The long-term effect of this combination in this open trial is currently being evaluated, as is the potential toxicity of both agents when used in this syndrome. A prospective controlled randomized trial employing this combination will begin shortly at the Mayo Clinic.

Anticholestatic Agents

Considerable enthusiasm has recently emerged for the use of ursodeoxycholic acid in the treatment of cholestatic liver diseases, primarily because of uncontrolled but impressive results in a small number of patients with primary biliary cirrhosis. The rationale for the use of ursodeoxycholic acid is to replace bile acids with greater toxic potential (e.g., chenodeoxycholic acid). Although this rationale is theoretically attractive in the treatment of a cholestatic syndrome like PSC, no data are currently available regarding its possible benefit.

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SCLEROSING CHOLANGITIS: LIVER TRANSPLANTATION

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Primary sclerosing cholangitis is a disease of unknown etiology but most likely represents an autoimmune disorder. It has a striking prevalence in young men, ages 30 to 50, and is, more often than not, associated with inflammatory bowel disease, most commonly ulcerative colitis. It has, however, also been seen in association with Crohn's disease. Primary sclerosing cholangitis sometimes precedes but usually follows by several years the onset of the inflammatory bowel disease.

Primary sclerosing cholangitis is most often classified as an autoimmune disorder; it is frequently seen in patients with the HLA-B8 antigen. Contrary to the autoimmune etiology is the fact that attempts at immune modulation have been ineffective in significantly altering the disease process. The incidence of primary sclerosing cholangitis has been increasing either because of an actual increase in the disease or as a result of better diagnostic techniques.

The treatment of sclerosing cholangitis has been slowly evolving as the results of liver transplantation have improved. Current treatment methods fall into noninterventional and interventional modalities.

NONINTERVENTIONAL THERAPY

Nonintervention treatment has included the use of steroids, azathioprine, D-penicillamine, and cholestyramine. Treatment with steroids or azathioprine attempted to alter the course of the disease through immune suppression, but long-term results showed little benefit. D-penicillamine provided some hope, as patients with primary sclerosing cholangitis have been found to have elevated copper content in the liver. However, long-term follow-up has not shown significant beneficial effects. Cholestyramine was used in the belief that the disease was a result of an abnormal bile acid pool; this, too, has proved futile. Another chapter on *Sclerosing Cholangitis* provides details of medical therapeutic maneuvers.

INTERVENTIONAL THERAPY

Radiologic therapy includes percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP) with dilation, with or without stenting. We prefer PTC and ERCP because of long-term access to the biliary tree if needed, and the comfort of the percutaneous long-term stents. Patients with primary sclerosing cholangitis should all have an evaluation of the biliary tree to confirm the diagnosis and to allow the exclusion of cholangiocarcinoma. Any suspicious area of the biliary tree should be biopsied and brushings sent for cytologic examination.

If the primary sclerosing cholangitis is limited to a short segment of the biliary tree (rare), percutaneous dilation and stenting can be attempted. This is preferable to intraoperative stenting as it is just as effective and does not violate the operative field if transplantation becomes necessary.

Operative Intervention

Operative intervention (excluding transplantation) should become more obsolete in the era of better nonoperative diagnostic techniques. Historically cholecystectomy, common duct exploration with biopsies, and the placement of a long-term indwelling T-tube were done in the hopes that the T-tube would serve as a stent until the primary sclerosing cholangitis had run its course.

This, however, has not been the usual course, and the placement of the T-tube only served to violate the operative field and provide a nidus for infection. In addition to this, operative intervention of any type on the biliary tree has been suggested to be the most common cause of cholangitis in these patients, often hastening their demise or need for liver transplantation.

More recent than the simple placement of a T-tube in the gamut of operative interventions has been the use of Silastic stents brought out percutaneously through the liver and into the bowel (choledochojejunostomy or choledochoduodenostomy). This, too, has not proved to be of long-term benefit in most patients and has only served to increase the difficulty of the surgery in the event that transplantation becomes necessary. It offers no real advantage over percutaneous stenting. The chapter *Sclerosing Cholangitis: Surgery for Obstructive Jaundice* is devoted to transhepatic stenting for bifurcation lesions.

External ostomies that provide easy access to the biliary tree, such as Hudson's loops, should not be performed, since access to the biliary tree can now be gained percutaneously. External ostomies cause heavy bacterial colonization of the skin and greatly increase the chance for postoperative infection should any intra-abdominal procedure become necessary.

As primary sclerosing cholangitis usually spares synthetic function of the liver until late in the course of the disease, patients often present with severe portal hypertension but reasonable liver function. Some of these patients have been subjected to elective portal decompressive shunts. This should not be done as an elective procedure because it has no influence on the disease process and only increases the risk of portal vein thrombosis, thereby unnecessarily complicating or preventing liver transplantation if this is required.

None of the above-mentioned surgical procedures does anything to modify the course of this unrelenting, deadly disease. in fact many of these procedures only serve to hasten the terminal stages of the disease and have now become antiquated with the advent of better interventional radiologic techniques and the option of liver transplantation. The most frightening aspect of these pacifying techniques is that what was thought to be "time buying" was, in reality, only serving to promote the development of cholangiocarcinoma, thus sentencing the patient to death.

COLECTOMY

Pretransplant colectomy should not be performed simply for the sake of removing the colon prior to liver transplantation. If the patient develops carcinoma or precarcinomatous changes, then obviously a colectomy must be done. Most patients who come to transplantation with active colitis can usually be fairly well controlled medically. After transplantation most patients enjoy improvement in their colitis symptoms, but they should be closely followed every 6 to 12 months by colonoscopy. There are some patients whose colitis seemingly worsened several months after transplantation. Colectomy post-transplantation can be done in the absence of portal hypertension with much less requirement for blood products.

In patients who require a colectomy prior to liver transplantation, an ileoanal anastomosis should be done when possible. This not only eliminates problems with peristomal varices but also the constant threat of contamination from an ileostomy.

PATIENT MANAGEMENT

When a patient with primary sclerosing cholangitis is evaluated he or she must have an assessment of liver volume, patency of portal vessels, and determination of blood type. The computed tomographic scan for liver volume is also used to rule out intra-abdominal pathology, particularly cholangiocarcinoma. An assessment of the

biliary tree should be made and any suspicious lesions biopsied and brushed for cytologic examination. If the patient has had a portal decompressive shunt, patency must be determined.

Esophagogastroduodenoscopy and colonoscopy should be done, particularly if the patient has ulcerative colitis. Dysplasia and/or carcinoma may be present in some of these patients with long-standing, often quiescent colitis. In addition to the usual blood chemistries, an assessment should be made of liver reserve. As stated earlier, however, liver synthetic function is often preserved until late in the course of this disease and may give a false sense of security, leaving the patient open to repeated bouts of bacterial peritonitis, bleeding varices from portal hypertension, or cholangiocarcinoma.

Recommendations for Transplantation

The timing of transplantation in patients with primary sclerosing cholangitis is difficult at best. Transplantation is recommended for patients with

1. 4+ Varices with hypersplenism,
2. Bilirubin higher than 10 mg per deciliter,
3. History of major variceal bleeding, even with normal liver synthetic function,
4. History of spontaneous bacterial peritonitis,
5. History of repeated bouts of cholangitis, and
6. Loss of synthetic liver function.

These criteria are, however, guesstimates for patients with primary sclerosing cholangitis because of the incidence of undiagnosed cholangiocarcinoma. Unsuspected cholangiocarcinoma was found in 10.6 percent (8 of 75) of the hepatectomy specimens in our series, and one of these patients had only known of his liver disease for 1 year.

Relative Contraindications

A thrombosed portal vein on angiogram that is patent only in the superior mesenteric branches is a relative contraindication to transplantation. Thrombosed portal veins open at the confluence of the splenic and superiormesenteric veins are easily reconstructed.

Contraindications

Contraindications to transplantation are (1) patients with known cholangiocarcinoma, (2) patients with debilitating systemic disease that would preclude such an extensive operation, and (3) nonreformed alcoholics or drug abusers.

RESULTS

Between January 1, 1980, and August 1, 1987, 1,018 primary orthotopic liver transplants were performed at the University of Colorado Health Science Center (through 1980), the University Health Center of Pittsburgh (since 1981), and the Pittsburgh-affiliated Baylor University Medical Center at Dallas (since 1985).

Seventy-five patients received orthotopic liver transplantation for end-stage primary sclerosing cholangitis. Fifty were male (66.6 percent) and 25 were female (33.4 percent). Their ages ranged from 15 to 63 years, with a median age of 37.5 years. Only six patients were older than 50 years.

The indications for transplantation were persistent or recurrent variceal bleeding in 27.2 percent, ascending cholangitis in 27.2 percent, or the symptoms of end-stage liver disease, including encephalopathy, coagulopathy, anorexia, ascites, pruritus, and/or 3 to 4+ varices, in 45.5 percent.

Bowel Disease

Fifty (66.6 percent) of the 75 patients had a history of inflammatory bowel disease. Forty-four had ulcerative colitis, and six had Crohn's disease. Eleven patients (14.6 percent) had undergone prior bowel surgery either for their inflammatory bowel disease or for complicating carcinoma. Ten had undergone partial or total abdominal colectomy; one had had a small bowel resection for Crohn's disease.

Four of the 75 patients (50 of whom had inflammatory bowel disease) had had a carcinoma of the colon removed 11, 11, 4, and 4 years, respectively, prior to liver transplantation without evidence of recurrence. One patient (not included in the above group) had a total colectomy 1 year after transplant for unmanageable ulcerative colitis and was found to have a Duke's B carcinoma. Two of the patients who had pretransplant colectomies died within 3 months after transplantation from sepsis and liver failure, and two are living 20 and 8 months later. Longer follow-up is needed to determine cancer recurrence rate under immunosuppression, but recurrence this long after colectomy would be very surprising.

Management of the Biliary Tract Pretransplantation

Thirty-eight (50.6 percent) of the 75 patients had undergone prior violation of the biliary tract for diagnosis or treatment of the sclerosing cholangitis. Sixteen patients had undergone hepaticojejunostomy, ten cholecystectomy alone, six T-tube drainage of the choledochus, three cholecystectomy and percutaneous choledochal drainage, one choledochoduodenostomy, one choledochojejunostomy, and one cholecystojejunostomy.

Liver Disease Prior to Transplantation

The liver disease was diagnosed 1 to 16 years (mean 5.8 years) prior to transplantation, and the bowel disease, when present, had existed from 2 to 30 years (mean 14.8 years). In all but five of the 50 cases with coexistent inflammatory bowel disease, the bowel disease preceded the sclerosing cholangitis.

SURVIVAL

As of October 1, 1987, there were 52 patients living (69.3 percent) and 23 dead (30.6 percent), with a mean follow-up of 19 months (range 1 to 60 months). The actuarial survival rates were calculated comparing the group including those with cholangiocarcinoma to the same group not including those with cholangiocarcinoma. Actuarial survival rates were calculated using the survival analysis modules in BMDP/PC (BMDP Statistical Software, Los Angeles, CA) on an IBM/PC-AT microcomputer. The data are presented in Table 1.

CAUSE OF DEATH

Thirteen patients died within 3 months of transplantation, all from direct complications of transplantation or the associated immunosuppression. Technical failures, primary nonfunction of the graft, infectious complications, and irreversible acute rejection were the leading causes of death. Three patients died between 3 and 6 months, two from graft failure and sepsis and another from biliary sepsis due to recurrence of cholangiocarcinoma. Between 6 and 12 months, one patient died from an unrecognized lymphoproliferative disorder. Five patients died between 1 and 2 years, three from recurrent cholangiocarcinoma, one from systemic fungal infection, and the other from gastrointestinal bleeding and liver failure due to rethrombosis of the portal and superior mesenteric veins that had been opened with thrombophlebectomy at the time of transplantation. No patients died between 2 and 3 years after transplant. One patient died from liver failure due to chronic rejection more than 3 years after transplantation.

Unrecognized Cholangiocarcinoma

Previously unrecognized cholangiocarcinoma was found in the surgical specimens of eight of the 75 patients (10.6 percent). There were five males and three females with an average age of 44.6 years (range 24 to 61). Three had no history of inflammatory bowel disease; five had a history of ulcerative colitis. The clinically evident liver disease had been present for 1 to 14 years (mean 6.5 years), clearly demonstrating that long-standing liver disease is not a prerequisite for the development of cholangiocarcinoma. Five of these eight patients died as a result of recurrent cholangiocarcinoma 4, 12, 12, 14 and 15 months after transplantation. One patient died of accelerated rejection less than 2 weeks after transplantation. Two patients are alive and well without evidence of recurrence at 21 and 21 months after transplantation. All of the hepatectomy specimens from the patients with cholangiocarcinoma showed separate areas of sclerosing cholangitis, thereby excluding the possibility that any of these patients was wrongly classified as having sclerosing cholangitis instead of only cholangiocarcinoma.

TABLE 1 Post-Transplantation Survival (Percent Survival by Months)

	Including Cholangiocarcinoma	*Excluding Cholangiocarcinoma*
3 months	94%	95%
6 months	85%	85%
12 months	81%	82%
24 months	78%	80%
36 months	67%	73%
48 months	67%	73%

Recurrence of Sclerosing Cholangitis

As primary sclerosing cholangitis is believed to be an autoimmune disorder, the disease process should recur. Only *one* patient who received a transplant for primary sclerosing cholangitis developed chemical and radiologic abnormalities in the graft compatible with sclerosing cholangitis 1 year after transplantation, but the abnormalities have remained stable for the ensuing 2 years. Four other patients whose original liver disease was not sclerosing cholangitis have also developed *similar* abnormalities after histologically proven graft rejection.

DISCUSSION

Sclerosing cholangitis is an enigmatic disease, the incidence of which is increasing. It is a cholestatic disease, probably autoimmune in nature. With an expansion of the diagnostic armamentarium, there may be found a particular subset of patients who have only laboratory abnormalities and minor bile duct changes and whose conditions never progress to end-stage liver disease. However, at this time, primary sclerosing cholangitis must be considered a pernicious disease that is precancerous. It is difficult to determine the number of patients who will actually develop cholangiocarcinoma, but as reported above, 10.6 percent of our transplant population had unsuspected lesions. For every patient receiving a transplant who was found to have cholangiocarcinoma in the hepatectomy specimen, at least one was refused transplantation because of known cholangiocarcinoma. It has been suggested that these patients be followed by serial biopsies until atypical changes suggestive of precholangiocarcinoma are found and then they may receive transplants. However, this should *not* be done, as many of our patients showed only atypical changes on biopsy before transplantation but had terminally advanced cholangiocarcinoma in their hepatectomy specimens.

Timing of Transplantation

The fact that synthetic liver function is preserved in spite of often severe portal hypertension plus the danger of cholangiocarcinoma make the timing of transplantation difficult at best. Many of these patients come to transplantation because of complications from prior surgeries. Even though it is impossible to exactly determine, the ideal time for transplantation is the day before the patient develops cholangiocarcinoma. Until such time that atypical changes on biopsy truly represent preinvasive carcinoma and not

underlying invasive carcinoma, only guidelines such as those presented above can be followed.

In the absence of cholangiocarcinoma, the survival rate for liver transplantation is excellent (73 percent at 4 years), and the patients are able to resume normal lives. Perhaps with the wider application of monoclonal antibodies, a method will be found to identify the earliest changes of cholangiocarcinoma, thus maximizing as much as possible both the timing of transplantation and patient survival.

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SCLEROSING CHOLANGITIS: SURGERY FOR OBSTRUCTIVE JAUNDICE

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Sclerosing cholangitis is a rare disease characterized by fibrous thickening of the walls of the bile ducts that cannot be attributed to other diseases. The cause or causes of sclerosing cholangitis remain unknown, but several etiologic theories such as autoimmune, bacterial, congenital, and viral have been proposed. The disease most closely associated with sclerosing cholangitis is inflammatory bowel disease. Although sclerosing cholangitis has been associated with Crohn's disease, the vast majority of patients with sclerosing cholangitis and inflammatory bowel disease have ulcerative colitis. The incidence of ulcerative colitis in recent series of patients with sclerosing cholangitis ranges from 29 percent to 72 percent and averages about 50 percent. At the time of presentation with sclerosing cholangitis, the colitis is usually mild or the patient has had a prior colectomy.

The clinical course of patients with sclerosing cholangitis may be quite variable. Some patients may be diagnosed because of mild liver function abnormalities and may remain asymptomatic for years. However, other patients have a rapidly progressive course and may die soon after diagnosis from liver failure. Moreover, many patients have exacerbations and remissions, and in some patients the bile ducts have been documented radiologically to revert back to near normal. Because of the variable clinical course and the rarity of the disease, response to treatment has been difficult to evaluate. Nevertheless, a multitude of medical and surgical options has been tried, suggesting that the ideal form of treatment has not yet been found. However, based on our recent experience, we believe that a direct surgical approach to the biliary tree with prolonged transhepatic stenting is the optimal treatment for those patients with severe hilar or extrahepatic stricturing, persistent jaundice and/or recurrent cholangitis, and no biopsy evidence of cirrhosis.

TREATMENT ALTERNATIVES

A summary of treatment options and outcomes is presented in Table 1. Alternatives include drug therapy, nasobiliary lavage, balloon dilation, hepaticojejunostomy in conjunction with postoperative balloon dilation or transhepatic stenting, and hepatic transplantation.

Drug Therapy

No known specific effective medical therapy is available for sclerosing cholangitis, even though numerous approaches with various drug therapies alone or in combination have been tried. Specifically, corticosteroids, azathioprine, and D-penicillamine have been tried in large numbers of patients, but none of these drugs has proved helpful. Colchicine has recently been reported to produce improvement in a few patients, but much more experience is required for efficacy to be proved. Symptomatic relief of pruritus can often be obtained with cholestyramine; however, this bile salt binding agent has not been demonstrated to alter the course of sclerosing cholangitis. Antibiotics may also be beneficial when patients have fever. In general, however, antibiotics effective against biliary flora should be reserved for episodes of cholangitis and not for long-term administration.

Nasobiliary Lavage

Recently, nasobiliary lavage with steroids has been attempted in patients with sclerosing cholangitis. Nasobiliary tubes were placed endoscopically, and patients were randomized to receive continuous biliary lavage with