PRIMARY BILIARY CIRRHOSIS

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Primary biliary cirrhosis (PBC) is a chronic, usually progressive, often relentless, cholestatic liver disease of unknown etiology which has intrigued and interested hepatologists far beyond its frequency.[1-3] It is somewhat unfortunate that a name including the term cirrhosis has been rather universally accepted. In most patients with PBC, cirrhosis is not present at the time of diagnosis, and the designation chronic destructive intrahepatic cholangitis is far more descriptive of the pathologic findings.[4-6] For many patients who are in the early, often asymptomatic stages of the disorder, the label of cirrhosis carries a major emotional impact.

Our recognition and understanding of PBC is of quite recent vintage. The initial modern descriptions of PBC were made in the early 1950's in patients with advanced disease in whom biliary cirrhosis was present with sequelae of deep jaundice, xanthomata, and hepatic decompensation [7].

PBC is found predominantly in females and is characterized by the progressive destruction and disappearance of small interlobular hepatic bile ducts.[1-3] Extrahepatic bile ducts are not affected. The clinical manifestations of PBC result from the destruction and subsequent loss of bile ducts (cholangitis) thereby leading to a diminished flow of bile.

PBC must be distinguished from extrahepatic bile duct obstruction; from tumors or biliary stones; and from other established causes of prolonged cholestasis including drug-induced cholestasis and sclerosing cholangitis.

There is little question that increased awareness and availability of diagnostic tests has led to the diagnosis of PBC being established at an early stage during which cholangitis is the major histologic finding.[8-12]

As PBC progresses, bile duct destruction leads to bile duct disappearance (vanishing bile ducts). The later stages of PBC are characterized by the development of portal to portal bridges of fibrosis and subsequently cirrhosis.[4-6]

Early descriptions of PBC emphasized the clinical and histologic features of patients with advanced disease in whom there was often unrelentingly increasing jaundice, pruritus, extreme weakness, and muscle wasting, as well as the presence of xanthomas and bone fractures.[7] Bleeding from esophagogastric varices, ascites, and hepatocellular failure resulted from the biliary cirrhosis. Occasionally a patient with PBC in whom there is no previous history suggesting the disorder will present with bleeding from esophagogastric varices.[13]

At present, the diagnosis of PBC is most often established in a patient who is asymptomatic or only minimally symptomatic. Many early diagnoses result from increased awareness of the disorder and confirmation by detection of antimitochondrial antibodies, liver biopsy, and imaging techniques to evaluate (and exonerate) a bile duct problem as the cause of cholestasis.[14]

In my experience, the majority of patients with PBC are diagnosed early in the illness before jaundice and signs of chronic liver disease have appeared. Therefore, reconsiderations of the natural history of PBC appreciating a much longer course are underway.[1-3,8-12] There is mounting evidence that the stage of the illness and the presence or absence of symptoms are important in predicting the course and eventual outcome in patients who are diagnosed as having PBC at an early stage.

DEMOGRAPHIC FEATURES

Primary biliary cirrhosis is predominantly a disorder of females (90%) with onset after the age of 20 years.[1-3] Most often the diagnosis is established between the ages of 30 and 60 years. Occasionally PBC is initially diagnosed in patients beyond the age of 80. Evidence of PBC may first occur during pregnancy at which time the diagnosis of pruritus of pregnancy may be considered. There is no evidence that the course of PBC in a male differs from that found in females.[15] PBC has been diagnosed throughout the world in patients of many races.

OCCURRENCE OF PBC IN FAMILIES

PBC has been detected in more than one member of a family in a few instances.[16-20] A role for a genetic predisposition while intriguing, is uncertain. Family members of patients with PBC have an increased incidence of circulating autoantibodies as well as an apparent increase in the incidence of other autoimmune disorders.[18-20]

There are a few reports of an increased incidence of HLA-DR8 in patients with PBC.[21,22] However, others have not found specific HLA associations and the issue remains uncertain.[23]

CLINICAL FEATURES

Early Signs and Symptoms

Patients with PBC often complain of a gradual often insidious progressive loss of energy and decreasing interest in life. These patients, who are frequently women in

mid-life, are not readily diagnosed as having a liver disorder. Unexplained weight loss and anorexia may be present early in the course of the illness.

Pruritus is often found early in PBC, well before jaundice appears.[1-3] Pruritus may appear very insidiously. In addition, the skin often becomes progressively dry, thickened and darker. The hyperpigmentation is most likely due to deposition of melanin derivatives in the skin with later accentuation by the addition of bilirubin when jaundice develops. Jaundice preceding pruritus is unusual. Once pruritus appears in a patient with PBC, it rarely spontaneously remits. In the fatigued, depressed patient, pruritus may be initially considered to represent neurodermatitis.

An enlarged liver is found in more than half of patients with PBC at the time of diagnosis. Abdominal pain is unusual, although occasionally the liver may be tender when palpated. Splenomegaly may be detected even in an asymptomatic patient with apparent early disease. Occasionally corneal Kayser-Fleischer rings are found and presumably result from accumulation of copper secondary to impaired copper excretion in bile.[3,24]

Late in the course, accelerated weight loss may result from steatorrhea secondary to a decreased delivery of bile salts to the intestine or, in some patients, to an associated pancreatic insufficiency.[25,26]

Clinically apparent jaundice is often absent early in the course. Once primary biliary cirrhosis enters a progressive phase, the level of bilirubin begins to rise, xanthelasma and xanthomata develop from the accumulation of lipids, and signs of hepatocellular failure with portal hypertension and ascites develop. Wrist drop and foot drop may result from deposition of lipids around nerves (xanthomatous neuropathy). Rarely bleeding from esophagogastric varices are the initial clinical manifestation of liver disease in a previously asymptomatic patient.[13]
Such patients with considerable hepatosplenomegaly, portal hypertension, and no evidence of jaundice or pruritus may not readily be diagnosed as having PBC.

LABORATORY FINDINGS

Biochemical Tests:

Almost all patients with PBC have an elevation in serum alkaline phosphatase level at the time of diagnosis and throughout the course reflecting the obstruction to bile flow from the loss of interlobular bile ducts.[1-3] The 5′ nucleotidase and gamma glutamyl

transpeptidase (GGTP) levels are increased to similar extents as are the levels of serum alkaline phosphatase.

Serum bilirubin level is normal or only slightly elevated in asymptomatic patients and early in the course of many individuals who subsequently develop progressive disease. A progressive rise in serum bilirubin is an ominous prognostic sign; when the serum bilirubin rises rapidly over several months, trouble lies ahead.[27,28]

Serum cholesterol is elevated in the majority of patients with symptomatic disease and, in those with xanthomas, may exceed 1000 mg/dl. The HDL cholesterol level is usually increased in patients with mild to moderate PBC and falls in later stages of the disease.[3] A falling cholesterol in a patient with advanced PBC, especially when associated with an increasing serum bilirubin and decreasing serum albumin, is an ominous sign suggesting failure of overall hepatic synthesis. The serum aminotransferase levels are usually only slightly increased.

Steatorrhea

Some degree of steatorrhea is frequent in patients with PBC and is usually present in those with advanced (stage 3 and 4) disease, most of whom are jaundiced. Steatorrhea correlates most closely with the decreased intraluminal bile acid content resulting from a failure of delivery from the liver to the gut.[25] Severe steatorrhea (greater than 25 gms of fecal fat/24 hours) may be associated with diarrhea and rapid weight loss as well as with malabsorption of the fat soluble vitamins (A, D, E, and K) resulting in metabolic bone disease, decreased dark adaptation, and a prolonged bleeding time.

Small Intestine and Pancreatic Studies

Patients with PBC usually have normal small bowel histology, d-xylose tests, and intraluminal concentrations of pancreatic lipase and bicarbonate. However, in a few patients, an association has been reported between celiac disease and PBC.[29,30] In some, there is a submaximal lipase and trypsin output response following the intraluminal infusion of essential amino acid indicating impaired exocrine pancreatic secretion.[26]

IMAGING STUDIES

Demonstration that the extrahepatic bile ducts are not obstructed is important in the differential diagnosis of conditions causing chronic cholestasis. In PBC, the

extrahepatic bile ducts are characteristically normal. Bile duct patency may be evaluated noninvasively by ultrasonography; although, if there is any doubt, an endoscopic retrograde cholangiogram may be required. Transhepatic cholangiography is less frequently performed when PBC is suspected. Since the bile ducts in PBC are not dilated and are fewer in number, there is less likelihood that a duct will be entered by the transhepatic route.

Technetium liver scans are of little value in the evaluation of patients with PBC and most often show only non-specific nonhomogeneous uptake of tracer. Late in the course of PBC, there is evidence of splenomegaly and translocation of the technetium to extrahepatic sites, especially the bone marrow.

SEROLOGIC AND IMMUNOLOGIC TESTS:

Determination of the serum IgM and antimitochondrial antibodies are two laboratory studies of considerable value in the diagnosis of PBC.[1-3,31,32]

Serum IgM

The serum IgM is increased in approximately 75% of patients with PBC.[1-3] IgG and IgA levels may also be increased but usually to a lesser extent than is IgM. It has been shown by immunofluorescent studies using antisera to detect Ig subclasses that plasma cells in and around the damaged bile ducts in patients with PBC are predominantly producing IgM.[33] The IgM in patients with PBC is unusual in that it is cryoprecipitable and quite immunoreactive.

FEATURES OF IgM IN PATIENTS WITH PBC

Increased level > 75%
Cryoprecipitable
Immunoreactive
Spontaneously activates classical complement pathway
Features resembling immune complex

The immunoreactive IgM has been shown to promote spontaneous conversion of complement C3 to C3b and C3c by activation of the classical complement pathway.[34-36] The effects of the immunoreactive IgM on the complement system may explain the rapid turnover (hypercatabolism) of complement which is characteristically found in PBC. There is evidence that the immunoreactive IgM is

produced by a small population of B cells with the over-production of IgM presumably resulting from a defect in T suppressor cell function.[37,38]

Antimitochondrial Antibodies

The discovery in 1965 of antimitochondrial antibodies (AMAs) and recognition of the high (> 90%) incidence of these antibodies in patients with PBC was a milestone in the history of the disorder.[31,32] The detection of AMAs offers an excellent, reproducible test which has led to the diagnosis of many patients with PBC well before there is any evidence of symptomatic liver disease. Detection of AMAs is the most important diagnostic test in PBC.

There has been a marked increase in knowledge regarding AMAs over the past several years. The role of these antibodies has intrigued and thus far baffled investigators. The significance of the finding of AMAs remains unknown and is an area of continuing considerable interest. Hopefully, study of the AMAs will provide a clue to the pathogenesis of PBC. However, there is as yet no evidence that antimitochondrial antibodies per se are important in the pathogenesis of PBC.[39-42] The issue remains unsettled as to whether AMAs represent a response to the cause of PBC or occur as a secondary rather nonspecific epiphenomenon.

Early studies indicated that the antigen target for the AMAs in patients with PBC was a component of a trypsin sensitive inner membrane of mitochondria and was neither organ nor species specific.[39] AMA titer does not generally correlate with clinical, laboratory, or histologic severity of disease.

AMAs were initially identified by use of immunofluorescent testing.[31,32] Subsequently more refined tests such as ELISA analysis have largely supplanted immunofluorescent methods and are much more accurate. The ELISA test appears to be the most sensitive accurate widely available assay for detection of AMA.[39]

The antimitochondrial antibody (AMA) test is positive in greater than 90% of patients with PBC.[1-3] AMAs are rarely found in patients with mechanical obstruction of the biliary tract, and therefore the test is most useful in differentiating mechanical obstruction of the bile duct from PBC. In addition AMAs are rarely detected in patients with primary sclerosing cholangitis or in other forms of chronic cholestatic liver disease such as sarcoidosis of the liver or drug-induced cholestasis.[43] AMAs are found in 5-15% of patients with idiopathic chronic active hepatitis, and in some patients, a clear distinction between PBC and idiopathic autoimmune chronic active hepatitis is not possible. There is hope that subtypes of AMAs will prove helpful in

distinguishing PBC from idiopathic autoimmune chronic active hepatitis, but the epitope towards which the subtypes are directed have not been extensively tested nor are the tests widely available.[44] Usually in patients with chronic active hepatitis in whom there are detectable AMAs, the titer is lower (1:40 to 1:80) than are the levels characteristically found in patients with PBC.

Subtypes of Antimitochondrial Antibodies

There are several rather increasingly characterized members of the AMA family.[41,42,44-49] There has been remarkable progress in the identification of the antigenic targets for AMAs. There are multiple AMAs which recognize different antigenic sites. Hopefully, further characterization will assist in answering such basic questions as to the cause of PBC and whether there are prognostic implications which should be attributed to the presence of the subtypes.

The most prevalent AMA in PBC, designated M2, is directed against a trypsin sensitive antigen of the inner mitochondrial membrane.[41,42,44,46] The M2 antigenic site has been characterized and cloned. This antigen is an approximately 70-72 kD proline-rich polypeptide which is found in 90% of patients with PBC.[41,42,44,46,49] More recently it has been established that anti-M2 is directed towards enzymes which are in the pyruvate dehydrogenase and branched chain α keto acid dehydrogenase complexes.[41] One antibody (70-72 kD) is directed against E2 of PDH and a 52 kD antigen against E2 of the branched-chain α keto acid dehydrogenase. An additional antigen (39 kD) is directed against an uncertain epitope.

The PDH complex consists of three enzymes which sequentially catalyze the oxidative decarboxylation of pyruvate to acetyl coenzyme A. Both PDH and branched chain α keto acid dehydrogenase complexes have three components: El, a decarboxylase; E2, an acyltransferase; and E3, a lipoamide. The E2 components of each enzyme are similar and each has a lipoic acid binding site. The 70-72 kD and 52 kD antigens have been cloned and provide the basis for research ELISA tests. Even more specifically, it is thought that the lipoic acid binding regions on the E2 regions are the binding sites for the AMAs.

Alpha-keto-oxo-acid dehydrogenase is synthesized in the cytoplasm of the cell under the control of nuclear DNA. After synthesis, the enzyme is transported into the mitochondria and is located on the inner membrane. One hypothesis as to how AMAs might play a role in the pathogenesis of PBC suggests a misdirection of the enzyme away from the mitochondria and into the plasma cell membrane.[50] If such occurred,

there might be cell surface expression of an antigen normally restricted to deep within the mitochondria.

Therefore, there is considerable evidence that M2 antigenic sites are components of PDH, α-keto-oxo-acid dehydrogenase, and other structurally related enzymes with the active sites where lipoic acid is bound.

Ninety-six percent of 752 patients with clinical and histologic evidence of PBC had anti-M2 antibodies when tested by an ELISA method.[44] There were no positive anti-M2 tests in sera from a variety of other hepatic and nonhepatic disorders. Eighty-six percent of the M2 positive sera were also positive for AMAs detected by immunofluorescent techniques. ELISA tests utilizing the 72 kD and 52 kD antigen were positive in 84 of 93 samples from patients with PBC.[49] Thirty-five of 93 reacted only against the 74 kD antigen whereas only 5 reacted exclusively to the 52 kD antigen. Forty-four of 84 patients reacted to both antigens.

Other disorders in which AMA have been found and shown to be directed against different target antigens include syphilis (anti-M1); pseudolupus syndrome (anti-M3); collagen diseases (anti-M5) iproniazid-induced hepatitis (anti-M6) and cardiomyopathies (anti-M7).[39] In these other conditions, the AMAs do not react with the PBC specific M2 antigen.[39,44,46]

A most interesting additional AMA has been identified and designated M9.[51] M9 is directed towards an antigenic site on submitochondrial particles. Forty percent of patients with PBC who are anti-M2 positive react with M9. Anti-M9 antibodies are most often found in patients with early PBC and are generally not found in later stages of advanced disease. Of note has been the detection of anti-M9 AMA in 50% of 70 relatives of 11 patients with PBC.[51] Furthermore, anti-M9 AMAs was found in 63% of technicians working in immunopathologic laboratories compared to only a 17% incidence found in technicians in a general hematologic laboratory. These observations, as yet unconfirmed suggest that a contagious agent may be involved in the pathogenesis of PBC and that AMAs may represent markers shared with a causative agent. However, there have been no reported instances of PBC developing in these M9 positive technicians or spouses.

Most AMAs are globulins which are either of the IgG3 or IgM subclasses.[52] Most antimitochondrial antibodies apparently are IgG3 class.[52,53] Serum levels of IgG3 are markedly elevated in patients with PBC accounting for 17.4% of the total serum IgG (nl < 4.5%).[52] The significance of an elevated IgG3 is unknown. Similar elevations

in serum IgG3 are found in patients with herpes simplex I, cytomegalovirus, rubella, and hepatitis B virus infections suggesting that there may be a viral antigen which either causes or cross reacts with the mitochondrial antigen leading to B cell activation and IgG3 production.[53] Furthermore, IgG3 may be important in mediating antibody-directed cellular cytotoxicity.

Antigen bound IgG3 and IgM may activate the classical complement pathway leading to the hypercatabolism of complement which is characteristically found in PBC.[38] As a result of formation of products resulting from complement activation, mononuclear and polymorphonuclear cells may be recruited leading to an inflammatory response.

Role of Antimitochondrial Antibodies in Primary Biliary Cirrhosis

Therefore, at present the detection of AMAs is of major importance in the diagnosis of PBC. In fact, the diagnosis of PBC is suspect if AMAs are not found. The widespread use of the ELISA test with its increased sensitivity should increase the percentage of patients with PBC in whom positive tests are found. Whether use of a panel of subtypes of AMAs defined by molecular histological techniques will add measurably to the assessment of prognosis in PBC remains to be established. The possibility that AMAs represent shared antigens with an infectious agent which initiates the process leading to PBC in a susceptible individual is intriguing and deserves further consideration.

Anticentromere Antibody

The anticentromere antibody is an antinuclear antibody initially described in patients with scleroderma and also found in patients with CREST variant of PBC therefore suggesting an overlap of the two disorders.[54-56] The target for the anticentromere antibody is a 140 kD polypeptide.[55] I have observed patients with typical PBC in whom there has been relentless progression of quite typical scleroderma.

ASSOCIATED DISORDERS

Many disorders which have features suggesting immunologically mediated mechanisms of damage are found in association with PBC.[57,58] Major among these are Sjogren's syndrome, polymyositis, polyarthritis, renal tubular acidosis, Hasimoto's thyroiditis, hypothyroidism, celiac disease, primary pulmonary hypertension, vasculitis and interstitial pneumonitis.[29,30,57-64] Non-Hodgkin's lymphomas and breast cancer have also been reported to be more frequent in patients with PBC.[65]

CREST Syndrome

Of particular note is the association between PBC and the CREST syndrome - calcinosis, Raynaud's phenomenon, esophageal motility disorders, sclerodactyly and telangiectasia.[54,56,66,67] The telangiectasias are most often found on or around the lips, fingers and palms. The telangiectasias resemble those found in Osler-Weber-Rendu disease and differ from vascular spider angiomas in that "legs" are not present.

CREST syndrome has been reported to be present in 3-17% of patients with PBC.[54] Evidence of Raynaud's phenomenon or scleroderma may precede evidence of liver disease and are detected only when evidence of liver injury is sought in patients with these problems. Calcinosis is the least constant component of the syndrome and in many the designation would more appropriately be the REST syndrome.

The anticentromere antibody, a specialized antinuclear antibody, has been identified on a serologic marker for patients with the CREST variant.[54,55] Detection of the anticentromere antibody may be useful in identifying patients with PBC who have or will develop changes of scleroderma. Anticentromere antibodies are not found in patients with Osler-Weber-Rendu disease.[67]

It has been suggested that the concept of the CREST syndrome in association with PBC be expanded to include the PACK syndrome representing primary biliary cirrhosis, anticentromere antibody, CREST syndrome, and keratoconjunctivitis sicca.[54]

In a survey of 558 patients with PBC, 22 had evidence of scleroderma (3.9%).[54] All 22 patients were female with an age range of onset of 48.1 years (range 30 to 73 years). In 13 of the 22, signs and symptoms of scleroderma preceded the apparent onset of PBC. Anticentromere antibodies were found in all 12 patients from whom serum was available.

Celiac Disease

Celiac disease (gluten-sensitive enteropathy) has been described in a few patients with PBC.[29,30,64] Small bowel biopsy changes typical of gluten-sensitive enteropathy have been reported, and there have been favorable clinical responses to a gluten-free diet.

Sarcoidosis

Occasionally patients have clinical and laboratory manifestations suggesting PBC,

sarcoidosis or both disorders.[43,68,69] Since both conditions are of unknown etiologies and are characterized by granulomas raises the possibility of a relationship.

Bacteriuria

In one series, significant bacteriuria was found in 19% of 87 women with PBC as compared to only 7% of 89 women with other types of chronic liver disease.[59,62] Although there are no reports of a general increased susceptibility to infection in patients with PBC, these observations may indicate a special predilection to urinary tract infections. The significance of increased urinary tract infections is unknown. Interest in the observation is heightened by the considerations of possible shared epitopes between antimitochondrial antibodies and some gram-negative bacteria.[59,62]

Hypothyroidism

Hypothyroidism, usually subclinical, has been reported in approximately 20% of patients with PBC.[57] Determination of the TSH level may therefore be useful in the evaluation and management of patients with PBC.

Hepatocellular Carcinoma

Rarely hepatocellular carcinoma has developed in patients with long-standing PBC.[70,71] The incidence of the tumor is much lower than in patients with hepatitis B-related cirrhosis or hemochromatosis.[72]

HISTOLOGIC FINDINGS

The liver is usually enlarged early in the course in PBC and has a smooth surface. The enlargement results in part from swelling secondary to retention of bile. As bile duct destruction progresses, the liver becomes scarred and in the late stage, a dark-green grossly cirrhotic organ is found.

Percutaneous liver biopsy is helpful in establishing or confirming the diagnosis of PBC. The histologic stage of PBC may also be useful in judging prognosis. Most often the findings on liver biopsy are considered compatible or confirmatory rather than diagnostic of PBC.[4-6]

The principal early lesion of PBC is that of a cholangitis involving small interlobular bile ducts.[4-6] The earliest evidence of damage is to interlobular ducts which measure 80-100 um.[73] The bile duct lesions are often focal and may involve only a segment of

the duct wall. The predominant inflammatory cells are lymphocytes and plasma cells which accumulate in the portal triads. Similarities between the lesions of PBC and graft versus host disease have been noted.[74]

Granulomas are often found around affected bile ducts but may also be found elsewhere in the hepatic parenchyma.[4-6,75]

Liver biopsy findings in patients with PBC have led to a histologic classification of the disorder into 4 broad stages.[6,76] The classification is quite arbitrary and features of several stages may co-exist. There is no predictable transition from stage to stage. Even though there is often poor correlation between clinical and histologic manifestations of disease, efforts at classification of PBC appear to be somewhat useful. In advanced PBC, as in other chronic liver diseases with extensive scarring and cirrhosis, there may be considerable sampling error in a percutaneous liver biopsy.

Stage I: Florid duct lesion with damage to the small interlobular bile ducts characterizes this stage. The ductular lesion may be quite patchy and asymmetrically affect the bile duct. The injured ducts are often surrounded by a dense infiltrate of lymphocytes and plasma cells. The infiltrating lymphocytes have been shown to be T cells. The principal T cell types is the CD4 (helper/inducer) cell, although it appears that the lymphocytes immediately around the injured bile duct are CD8 (suppressor-cytotoxic) cells.[77] Granulomas are found near the damaged ducts in 40% of patients with Stage 1 lesions.[75]

Therefore, in the histologically early PBC, the injury is confined to the portal area with evidence of focal bile duct destruction. The pattern of inflammation may resemble chronic persistent hepatitis or pericholangitis found in patients with chronic inflammatory bowel disease (especially ulcerative colitis) who later develop sclerosing cholangitis.

Stage II: Ductular proliferation occurs with continued inflammation and early fibrosis which spills over into periportal areas. Occasionally Mallory's alcoholic hyaline is found. Periportal inflammation, cell destruction, and cholestasis may be prominent. Evidence of periportal fibrosis is often present.

Stage III: Septal fibrosis is found with bands of fibrosis bridging from portal to portal areas and evidence of architectural remodeling of the liver. In this stage there is a progressive diminution in the number of identifiable normal bile ducts.

Stage IV: The late histologic manifestation of PBC is that of cirrhosis with regenerative nodules. Often by this phase of the illness, the more characteristic early features have disappeared and few intact interlobular bile ducts are found (vanishing bile duct syndrome).

DIAGNOSIS

PBC should be suspected in any patient in whom there is evidence of chronic cholestatic liver injury and especially sought in a middle-aged female patient who has fatigue, pruritus, and an elevated serum alkaline phosphatase.[1-3,14] The diagnosis is established by finding a positive AMA test and a compatible liver biopsy which demonstrates nonsuppurative cholangitis often associated with the additional presence of granulomas. High titer AMA levels (> 1:160) are rarely found in any other condition. In addition, it is important to determine that there is no evidence of extrahepatic bile duct obstruction. In a patient with apparently typical PBC, real-time ultrasonography may be sufficient to exclude bile duct obstruction. If there is doubt regarding possible obstruction in the extrahepatic bile ducts, endoscopic retrograde cholangiography is indicated and is characteristically normal. Transhepatic cholangiography is less frequently used in diagnosis because the bile ducts may be small and few in number. The major alternative diagnoses to be considered include: chronic drug-induced cholestasis (especially that induced by phenothiazines), sclerosing cholangitis, chronic active hepatitis, and bile duct carcinoma. In a rare patient with sarcoidosis, the clinical and histologic picture may closely resemble PBC, and the differentiation of the two conditions may be difficult or impossible.[43]

A careful drug history should be obtained since it is established that chlorpromazine and other phenothiazines may cause (or unmask) a syndrome similar or identical to PBC.[78] Usually in patients with phenothiazine-induced cholestasis. AMAs are not found. I have also seen a PBC-like illness follow an apparent reaction to thiabendazole.

Antimitochondrial antibody negative PBC is rare but does occur.

COURSE OF PBC

There is no evidence that the course of these patients with otherwise typical PBC differs from that found in the much larger number of patients who have AMAs. The apparent considerable increase in the number of patients diagnosed as having PBC over the past decade has resulted from an increased awareness of the condition and the widespread use of liver biopsy and the antimitochondrial antibody test in the

evaluation of patients with elevated serum alkaline phosphatase levels. The identification of many patients at very early stages of the illness has led to an appreciation of the quite variable clinical course. The disorder may pursue a progressive relentless downhill course. However, many patients with clinically apparent symptomatic disease survive for more than a decade.[9-11,79,80]

In a follow-up study of 243 symptomatic patients from the Yale Liver Study Unit, the average survival was 11.9 years which is much longer than that earlier thought usual for PBC.[10] In 37 patients who were asymptomatic at the time of diagnosis, there was no difference in survival from a control population during a 12 year interval. In a further long term follow up study of 36 asymptomatic patients with PBC who were followed for a median of 11.4 years, there were no differences in survival when these patients wee compared to survival expectations for the general population.[11] However, 15 (42%) of the 36 patients developed signs or symptoms of liver disease. The most frequent symptom which developed was pruritus (8 patients) followed in incidence by jaundice (3 patients), bleeding from esophagogastric varices (2 patients), fatigue (1 patient) and ascites (1 patient). The presence of granulomas on initial liver biopsy was the only factor which was identified to be associated with a favorable prognosis. Patients with concomitant manifestations of an autoimmune disorder such as thyroiditis, sicca syndrome, or the CREST syndrome fared less well. Seven patients in this series had a history of having had estrogen therapy which may have unmasked or induced the PBC followed a relatively benign course.

Many patients are asymptomatic or have only minimal nonspecific symptoms such as fatigue at the time of diagnosis. The histologic findings in these asymptomatic patients may be quite similar to those found in patients with symptomatic PBC. Whether all asymptomatic patients will eventually progress to symptomatic PBC is unknown but likely.[79,80] I have followed several patients for longer than 15 years with no apparent progression. However, the weight of the evidence suggests that most patients with PBC will progress and eventually develop clinically apparent liver disease.

FEATURES OF PROGNOSTIC VALUE

There have been extensive searches for prognostic factors which might prove helpful in determining the likely course for a patient with PBC. The successes resulting from liver transplantation in patients with PBC have increased interest in developing predictive models in order to time liver transplantation at a point in the illness when the risk-benefit ratio is favorable and before major complications have occurred.[81]

The finding of granulomas on liver biopsy has been suggested to be a favorable prognostic sign indicating earlier disease.[75] However, in one large multicenter study, granulomas were found at all stages of PBC and were not considered indicative of early disease.[5] An increasing serum bilirubin is recognized as a sign of poor prognosis.[27] The presence of associated autoimmune disorders including thyroiditis, CREST syndrome, and Raynaud's phenomenon is associated with a decreased survival. As in any other type of chronic liver disease, progressive weight loss and evidence of decreased muscle mass are ominous signs.

PATHOGENESIS

The cause of PBC remains unknown.[1-3,36,82,83] Several interesting and ingenious hypotheses have been presented. All are interesting but none is proven. The major theories consider a possible infectious etiology versus an immunologic etiology. However, no specific viral, bacterial, or infectious agent has been identified.

INFECTIOUS ETIOLOGY HYPOTHESES

The finding of an elevated serum IgG3 level in patients with PBC similar to that found in a variety of viral disorders led to the speculation that a virus might cause PBC or at least set in motion the disorder in a genetically susceptible individual. However, thus far, no homologous sequences of any known virus has been reported in patients with PBC, although it would be a safe wager that such will be found. There is no evidence of an increased incidence of present or past hepatitis B infection in patients with PBC.[84]

Antimitochondrial antibodies from patients with PBC have been reported to recognize antigens localized in the ribosomal and membrane fractions of several species of Enterobacteriaceae.[85] These antigens are known components of the inner mitochondrial membrane of the bacteria. In addition, two PBC-specific mitochondrial antigens (70 kD and 50 kD) were recognized by rabbit antisera against mutants of Salmonella minnesota but not by antisera against the wild-type bacteria. These observations have lead to the further consideration that infection with certain types of bacteria may cause or trigger PBC in a susceptible host.

IMMUNOLOGIC ABNORMALITIES

Many features of PBC suggest that the injury is mediated by immunologic mechanisms.[36,82] Whether these abnormalities relate to the cause of PBC or occur in response to some more proximal event is unknown. These features include the

presence of lymphoid aggregates and granulomas in the liver; the presence of antimitochondrial and other autoantibodies; the increased serum IgM, the frequent finding of skin test anergy, and the association with other disorders which are thought to be caused by immunologic mechanisms.[86]

Immune Complexes

For several years considerable attention has been directed towards a possible role for immune complexes in the pathogenesis of PBC.[36,82,83,87] Several groups reported finding circulating immune complexes, and it has been suggested that the inciting antigen might be in the wall of the bile ductule.[87] One suggestion is that deposition of the IgM containing immune complexes might have a role in causing PBC.[88] However, other investigators have been unable to detect immune complexes by more specific methods, and quite likely false positive immune complex tests caused by the presence of immunoreactive IgM were responsible for the earlier findings.[89] Most likely the immunoreactive IgM in PBC itself leads to a false positive test for the presence of immune complexes using the Raji cell assay.

Lymphocyte Abnormalities

Another theory of pathogenesis suggests a defect in T lymphocyte function with a decreased ability to appropriately activate suppressor T cells.[36,82]

There is a progressive decrease in the number of circulating T lymphocytes as PBC advances.[90] Furthermore, there is evidence of decreased in vitro T suppressor cell function in patients with PBC and in 25% of their healthy first-degree relatives.[91] As with other immunologic abnormalities thus far detected in PBC, the significance of these findings is unknown.

The finding of suppressor/cytotoxic T cells at the site of bile duct injury strongly suggests a role for these T cells in causing the injury.[77] It has been established that bile ducts in PBC have surface expression of Class I (HLA-A, HLA-B, and HLA-C) histocompatibility antigens as well as Class II antigens (HLA-DR).[92] Normal bile ducts and hepatocytes do not express HLA histocompatibility antigens. Bile duct antigens are the likely target for cytotoxic lymphocytes in the rejection of a transplanted liver and in graft versus host disease. There are similarities between PBC and transplant rejection which most likely result from lymphocytic attack on bile ducts which express an HLA target. What is not known is what influence (genetic or environmental) may have led to the initial alterations in the bile duct. It is appealing to consider either an

infectious etiology, or overproduction of a toxic product, initiating changes in a genetically susceptible host.

Impaired Sulfoxidation in Patients with Primary Biliary Cirrhosis

An impaired ability to carry out sulfoxidation reactions has been found in patients with PBC and has been postulated to be important in the pathogenesis or progression of the disorder through the accumulation of toxic products normally disposed of as sulfoxide metabolites.[93]

Impaired sulfoxidation has been suggested to be important in the production of chlorpromazine-induced hepatotoxicity based on observations that sulfoxide metabolites of chlorpromazine are less likely to produce cholestatic and hepatotoxic liver injury than are hydroxyl metabolites of the drug.[94,95] Because of the similarities between chlorpromazine-induced liver injury and PBC, sulfoxidation capacity was evaluated in patients with PBC and found to be abnormal. In 44 patients with PBC, there was evidence of impaired sulfoxidation in 84%.[93] The impairment was not related to histologic stage of disease nor to the level of serum bilirubin. There was an inverse correlation between the age of the patient and the degree of the sulfoxidation defect suggesting that those with the most severe impairment might be a increased risk of developing PBC at a younger age. Patients with other forms of liver disease were much less likely (24%) to have an impaired ability to produce sulfoxidation products. The defect in sulfoxidation was corrected by liver transplantation.

One interpretation of these observations is that the patients with PBC are susceptible to hepatic injury from any of a number of environmental or endogenous substances (such as female sex steroids) which are normally rendered harmless by sulfoxidation. The several patients in whom PBC has apparently been caused (or unmasked) by use of chlorpromazine are of particular interest.[78,96,97] Of further note is the observation that an impaired sulfoxidation capacity is associated with an increase in adverse reactions to d-penicillamine which may explain in part the many side effects to d-penicillamine therapy in patients with PBC.[98]

THERAPY

In the absence of a specific effective therapy for PBC, management must emphasize general support of the patient with the addition of measures designed to relieve symptoms and minimize the effects of complications. With the availability and relatively widespread utilization of liver transplantation, many of the late complications

of advanced PBC such as recurrent bleeding from gastroesophageal varices and severe hyperlipidemia are (or should be) less frequently encountered.

PRURITUS

Pruritus is often a major disabling and distressing problem which occurs in the majority of patients with symptomatic PBC. Pruritus may be noted early in the course of PBC, well before there is evidence of jaundice. Often pruritus has been present for months or even years before the diagnosis of PBC is considered and established.[1-3] The substance (or substances) which accumulates in the skin presumably because of an impaired excretion into bile is unknown.[99] There is no evidence to support bile acids as the pruritogen. While bile acid accumulation is an obvious candidate pruritogen, concentrations of bile acids measured in the skin have not been shown to be elevated. An accumulation of opiate agonists which then act centrally has also been suggested as the cause of pruritus in PBC. Proof that these substances are involved would open new approaches to therapy.[99]

A number of therapeutic approaches have been tried to control the pruritus. The multiplicity of the approaches attests to the often unsatisfactory results. Continuous and worsening pruritus may prevent sleep, promote skin infections in excoriated areas, and lead to considerable depression.

Exchange Binding Resins

The use of the non absorbed quaternary ammonium exchange resin cholestyramine (4-24 g per day) is an often effective treatment for the pruritus of PBC.[100] Cholestyramine therapy is most successful in patients in whom the serum bilirubin level is normal or only moderately increased indicating that continued flow of bile containing the pruritogen(s) into the bowel is necessary to allow capture.

The presumed mechanism of action of cholestyramine is through binding of a bile based pruritogen. Therefore, it is logical to expect little or no therapeutic benefit once PBC has advanced to a stage of diminished bile ducts and scant flow of bile into the intestine. Cholestyramine stimulates hepatic synthesis of bile acids as the result of interference with enterohepatic circulation of bile acids with sequestration of such bile as is available in the gut.

Of course there are many other potential pruritogens which may be captured. There is possibly an advantage to giving a large part of the daily dose of cholestyramine early in the morning when the concentration of bile in the intestine is at its peak after

early morning emptying of the gall bladder.[101] Patients should be informed that the anti-pruritic effects of cholestyramine appear gradually over several days as the concentration of the pruritogen (or pruritogens) is decreased, and there should be no unrealistic expectation of immediate relief. Patients often become distressed if there is no immediate (1-2 days) favorable effect but should be encouraged to persist with the medication.

There are generally no adverse side effects from the use of cholestyramine. Either mild diarrhea or constipation may develop in some patients. The potential adverse effects of cholestyramine is resin binding of vitamins or other therapeutic medications. Cholestyramine may be given with food but should not be given within one to two hours of the use of any other medication.

Colestipol hydrochloride is another ammonium binding resin which appears to be equally as effective as cholestyramine in the treatment of pruritus.

Antihistamines

Occasionally addition of an antihistaminic compound is helpful in the management of pruritus.[102] However, antihistamine therapy does not appear to have a major role in therapy of the pruritus.

Phenobarbital

Phenobarbital occasionally is a useful adjunctive therapy for pruritus through its choleretic effects.[103,104] The response to phenobarbital in my experience has been quite variable. Some patients do very well and others have no benefit at all. The dose of phenobarbital should be initially quite low and gradually increased especially if the drug is used in patients with advanced disease in whom excessive sedation and even encephalopathy may be induced.

Ultraviolet Phototherapy

Ultraviolet phototherapy is an experimental mode of therapy for pruritus which has proven of little (if any) value despite early reports suggesting efficacy.[105]

Plasmapheresis

In intractable pruritus, plasmapheresis may be useful, and in patients with desperately severe pruritus, may produce rapid, most appreciated relief.[106,107] However,

plasmapheresis is expensive; has to be repeated frequently; and has not been shown to have any effect on the progression of the underlying disorder. Despite these problems, plasmapheresis remains the most effective rapid method to control severe pruritus.

Rifampicin

There are several reports that rifampicin, an antibiotic with established properties of inducing microsomal enzymes, may be effective in the treatment of the pruritus associated with PBC.[108,109] In a randomized crossover trial, a group of 22 patients with PBC and pruritus were given courses of rifampicin (10 mg/kg a day) and phenobarbital (3 mg/kg a day).[108] Each drug was given 14 days with an interval of 30 days between treatments. Rifampicin was found to be beneficial in 19 patients with 9 having a disappearance of pruritus and 10 more noting some improvement. One patient developed hemolytic anemia and renal failure presumably related to the drug. There was partial improvement in pruritus in 8 of the 21 patients. Three patients in the treated group developed skin rashes within two weeks of beginning therapy which led to discontinuation.

The mechanism by which rifampicin might exert an antipruritic effect is uncertain. Improvement was noted usually only after a week of therapy. The drug is an enzyme inducer but is no stronger an inducer than is phenobarbital. Whether rifampicin affects the intracellular bile acid pool size or composition leading to less injury while promoting the flow of bile remains to be established. It is noteworthy that there was a significant fall in serum alkaline phosphatase and fasting bile acid concentrations in patients during the rifampicin phase of the study. Whether rifampicin has a favorable effect on pruritus by reducing the pool of toxic bile acids is unknown. There is even the possibility that long-term therapy with rifampicin will favorably affect the course of PBC. Whether long-term therapy with rifampicin will prove safe is an important unknown. Undoubtedly, more will be heard on the rifampicin front.

Fat Soluble Vitamin Deficiencies

Deficiencies of the fat-soluble vitamins A, D, E and K is often present in patients with PBC and presumably result from steatorrhea and malabsorption.[110-112] Vitamin replacement therapy should be based on serum levels. Additional consideration should be given to the known toxic effects which may occur from excess vitamin A and D.

Vitamin A and Zinc

Vitamin A deficiency with decreased serum levels and impaired dark adaptation is frequent in patients with PBC.[110] However, overt symptoms of night blindness are unusual but may be identified with careful questioning. Oral vitamin A (10,000-50,000 u per day - check dose) usually corrects the deficit. In some patients with vitamin A deficiency, there is coexistence of zinc deficiency which must also be corrected in order to reverse abnormal dark adaptation.[110] It is important to occasionally determine serum vitamin A levels in patients receiving supplementation in order to avoid hepatotoxicity from excessive vitamin A.

Vitamin D

Vitamin D deficiency is quite regularly found in patients with PBC. Serum 25-OH vitamin D levels are usually decreased in patients with moderate and advanced PBC. Hepatic osteodystrophy is a major problem for many patients with PBC.[111-115] The bone disease is predominantly osteoporosis with a loss of bone matrix.[111,113,114] In some patients there is a component of vitamin D responsive osteomalacia but such is unusual. Bone fractures are frequent especially in patients with advanced disease.

The cause of the hepatic osteodystrophy is unknown and is not apparently related to vitamin D deficiency. It appears that patients with advanced PBC have an inhibition of osteoblast function as evidenced by a reduction in bone gia protein (osteocalcin levels).[114,116] Osteocalcin levels have been reported to increase following liver transplantation.[116] Patients with PBC usually have normal urinary 25-hydroxy proline excretion.

It is important for the patient with PBC to avoid prolonged immobilization which may promote further bone deterioration. There are no convincing studies that administration of vitamin D to these deficient patients leads to any measurable reversal of the bone disease. Furthermore, it is not known if the rate of progression of osteoporosis is slowed by vitamin D therapy. We administer vitamin D replacement therapy to deficient patients in order to prevent or treat any possible component of osteomalacia. 25-OH cholecalciferol (50-100 mcg orally daily) usually leads to a normal serum vitamin D level even in a patient with steatorrhea. Serum 25-OH cholecalciferol levels should be monitored in order to prevent generation of excessive levels. In addition we administer a daily supplement of approximately 1 gram calcium.

Vitamin K

Vitamin K deficiency as indicated by a prolonged prothrombin time and bleeding tendency may respond to daily oral vitamin K (5-10 mg per day).

Other Vitamins

Folic acid (1 mg per day), and a general multivitamin may be helpful in ensuring that no deficiencies develop especially in a patient receiving cholestyramine.

Nutritional Support

In the occasional patient with severe steatorrhea and weight loss, medium chain triglyceride oil (up to 60 ml in divided dose) may be administered as a high caloric, well-absorbed dietary supplement.[25] Restriction in dietary fat may reduce steatorrhea. In some patients iron deficiency anemia develops even in the absence of evidence of bleeding. Probably most of these patients have had unrecognized bleeding from the gastrointestinal tract. In addition, any patient with PBC and weight loss should be evaluated to determine the status of the small bowel (looking for celiac disease) and the pancreas (looking for pancreatic insufficiency).[26] Progressive wasting with loss of weight and weakness, often associated with hypoalbuminemia, may be an important consideration in deciding the timing for liver transplantation.

Management of Hyperlipidemia

The extraordinary high levels of serum lipids occasionally found in patients with PBC may lead to xanthoma formation and xanthomatous neuropathy.[7] Cholestyramine therapy may be useful. Administration of clofibrate has been disastrous with a paradoxical increase in serum cholesterol.[117,118] Experimental approaches to the hyperlipidemia include lowering of serum lipids by plasmapheresis.[106,107] Such therapy while temporarily effective, provides only short-term relief and is expensive. Liver transplantation reverses the hyperlipemia.

Experimental Therapies for Primary Biliary Cirrhosis

Corticosteroids: The many features of PBC suggesting immunologically mediated damage suggests a role for corticosteroid therapy. One randomized controlled trial has been reported in which patients who received prednisolone therapy obtained some benefits as regards liver tests.[119] However, corticosteroids are generally not used (nor

likely to be used) in patients with PBC because of concern that bone disease may be accelerated.

Azathioprine: The immunosuppressant, azathioprine (50-100 mg per day) has been reported in a multinational prospective, double-blind, randomized trial of 248 patients (127 azathioprine; 121 placebo) with PBC to improve survival.[28] The use of azathioprine apparently reduced the risk of death to 59% of that observed with placebo treatment ($p = 0.01$). It was determined that azathioprine improved survival on average by 20 months. Side effects from azathioprine were relatively few and included rash, nausea, vomiting, and bone marrow depression.

From this trial, a prognostic index was developed for PBC based on five variables which were independently found to indicate poor prognosis - high serum bilirubin, increasing age, presence of cirrhosis, low serum albumin, and central (zone III) cholestasis. When the derived prognostic index was included in the analysis, there was evidence that azathioprine slowed the rate of developing incapacitating manifestations of PBC. If the derived prognostic index is validated in other series, it may prove useful in more precisely indicating the optimal timing for hepatic transplantation. Unfortunately, many of the clinical, laboratory and histologic details of the trial have not been reported.

An earlier small controlled trial of azathioprine versus no treatment had not found evidence of a favorable azathioprine effect.[120] Overall, there is scant enthusiasm for the use of azathioprine in PBC.

d-Penicillamine: Extensive clinical trials from Europe and the United States evaluated the use of d-penicillamine in the treatment of PBC.[121-128] In fact, d-penicillamine is likely the most extensively studied drug for the treatment of PBC. Potentially favorable actions of d-penicillamine which led to initiation of the trials included the opportunity to reduce the elevated hepatic copper level characteristically found in patients with PBC; the established antifibrotic effect; a favorable effect on reduction of immune complexes, and a reduction in circulating T lymphocytes.[24,121-129]

Following assessment of the results of the trials, it has been generally concluded that d-penicillamine is ineffective in improving survival or in decreasing complications, and its use was often complicated by the development of toxic reactions. The use of d-penicillamine has been abandoned following demonstration in several trials that the drug was poorly tolerated and was generally ineffective. Side effects from the drug were frequent (20-25%) and often severe with the most frightening neutropenia, optic

neuritis and renal tubular damage. The most frequent side effect encountered was proteinuria which usually reversed upon drug withdrawal.

The most extensive randomized, double-blind trial of d-penicillamine was that performed at the Mayo Clinic in the 1980s.[24] Initial reports were encouraging and suggested that there was improved survival in treated patients who entered the study with early (stage 1 or 2) histologic lesions. Furthermore, there was an early trend noted towards improved survival even in treated patients who entered the trial with more severe disease. d-Penicillamine therapy apparently led to significant improvements in aminotransferase, alkaline phosphatase and IgM levels as well as inducing a fall in sedimentation rate in patients who received d-penicillamine. Hepatic copper concentration decreased significantly. However, subsequently, the Mayo Clinic Group concluded from further follow up of 227 patients (111 d-penicillamine; 116 placebo) that use of the drug did not result in any improvement in survival.[24] Moreover there were no differences seen in the final review of the 10 year study in the rate of progression of PBC nor morphologic changes on sequential liver biopsy. Major side effects of d-penicillamine led to permanent discontinuation of the drug in 22% of those receiving the agent.

Therefore, despite early enthusiasm for the use of d-penicillamine in the therapy of PBC, there is now scant evidence or hope that the drug will prove useful.

Colchicine: There is at present considerable enthusiasm for the use of colchicine therapy in patients with PBC.[130-134] Colchicine has been reported by three groups of investigators to produce significant improvement in bilirubin, alkaline phosphatase, and aminotransferase levels in patients with PBC. In one randomized, double-blind trial, survival four years after entry was 53% in the placebo group and 79% in the colchicine treated patients.[134] There were significant differences in survival at the end of two years of the study after which time the investigators placed all patients on colchicine for the remainder of the trial. In addition to the favorable effect on survival in the colchicine treated group, decreases were noted in serum bilirubin, alkaline phosphatase, and aminotransferase levels.

In a study of 57 patients with PBC who received oral colchicine (0.6 mg twice a day), there was less of a rise in the serum IgM levels in a control group.[131] There were no significant differences in survival for the two groups. The trial was carried out over five years with the average duration of therapy of 33 months. However, there was no evidence on follow-up liver biopsies that colchicine reduced fibrosis or inflammation.

Therefore, colchicine therapy may prove useful in PBC if these preliminary observations are confirmed. The mechanism (or mechanisms) by which colchicine may lead to improvement is unknown. Colchicine may favorably affect the course of PBC through its anti-inflammatory effects, anti-mitotic effects, or through inhibition of intracellular microtubular assembly. Colchicine has been used successfully as an anti-inflammatory drug in such diverse conditions as Familial Mediterranean Fever and its time honored role in acute gout. Colchicine apparently reduces fibrosis both by decreasing collagen synthesis and by increasing collagenase activity.

There has been widespread acceptance and use of colchicine therapy if PBC and in other chronic liver disorders in part because of its minimal toxicity. Dose-related diarrhea is the only frequent undesirable effect; therefore colchicine appears suitable for long-term use. However, it must be recognized there are, as yet, no studies which demonstrate histologic improvement in patients who have received colchicine. Colchicine may find its greatest use in combination therapies.

Ursodeoxycholic Acid (UCDA)

UCDA is a hydrophilic bile acid which has proven useful in dissolution of gallstones and is apparently free of hepatotoxid effects.[133-140] There is evidence that the intracellular accumulation of bile acids which occurs when bile flow is impaired secondary to bile duct destruction and disappearance may lead to cellular toxicity. UCDA therapy has not itself been associated with any evidence of hepatocyte injury such as was recognized during trials of chenodeoxycholic acid (CDCA) therapy in patients with gallstone. Combinations of CDCA and lithocholic acid cause hepatocellular injury when incubated with hepatocytes.[141] Therefore, UCDA has been administered long-term to patients with PBC in efforts to reduce intracellular concentrations of toxic bile acids by alterations of the composition of the bile acid pool. Administration of UDCA does not raise the total bile acid level.[136]

After one year of therapy of UCDA (13-15 mg/kg) in 9 patients with PBC, there were no changes in the size of the total bile acid pool, but marked alterations in serum bile acid composition.[136] There were significant increases in total UCDA and the glycine conjugates of UCDA. In addition, there were significant decreases in the concentrations of primary bile acids (cholic and chenodeoxycholic) and their glycine conjugates and no significant changes in the levels of conjugates of secondary bile acids (lithocholic and deoxycholic acid). These observations suggest the benefits from UCDA therapy may be related to changes in the primary bile acids rather than in the secondary bile acids.

Early results from use of UCDA in a few patients with PBD have been promising.[135-140] The incidence and severity of pruritus has been reduced. In addition, there has been improvement in bilirubin, aminotransferase, alkaline phosphatase and gamma glutamyltranspeptidase levels. In a follow-up analysis of 95 liver biopsy specimens, there was a significant improvement in the mean histologic score in treated patients.[139] In several patients, discontinuation of UCDA has been followed by deterioration of the liver biochemical tests. There was no effect of UCDA on serum IgM level. UCDA appears to be safe and is therapeutically promising, no effects on histologic evidence of long-term survival has been yet reported.

Chlorambucil

The immunosuppressive alkylating agent chlorambucil has been evaluated in a small randomized controlled trial of patients with PBC who were followed for 2-6 years.[142] The dose of chlorambucil was adjusted to keep the blood lymphocytes at approximately half the pre-treatment value. The patients in the chlorambucil treated group (13 patients) either maintained or had an improvement in serum bilirubin, aminotransferases and albumin levels as compared to deterioration in the patients in the placebo group. Serum IgM levels decreased to normal in all the chlorambucil treated patients. Of most interest was a decrease in the inflammatory cell infiltrate, fibrosis and stage of disease in liver biopsies from treated patients as compared to the control group. Despite the apparent favorable effects of chlorambucil, toxicities from the drug are frequent and severe. Four of the 13 patients who received chlorambucil in the trial had evidence of bone marrow depression which led to discontinuation of the drug. No instances of leukemia were found. It is unlikely that chlorambucil will be used in the treatment of PBC.

Cyclosporine A

An additional candidate therapy for use in patients with PBC is cyclosporine A.[143] Cyclosporine A has been demonstrated to inhibit T helper cell function.[144,145] In a randomized, double-blind study, 17 of 19 patients who received cyclosporine A therapy had improvement or stability in the degree of fatigue and in 18 a decrease in pruritus. There was generally a drug-related reduction in bilirubin, aminotransferase, alkaline phosphatase and GGTP levels.[143,146] There was evidence of histologic progression in biopsies before and after two years of treatment in only 1 of 13 cyclosporine treated patients as compared with 5 of 7 in the placebo group.[143] However, the well-recognized toxicities of cyclosporine A including a progressive use of serum creatinine and induction of hypertension has thus far limited widespread enthusiasm for the use of cyclosporine A.[143,146] There remains the possibility that

very low-dose cyclosporine A may favorably affect the course of PBC and not lead to significant toxicity.

Methotrexate

Low-dose oral-pulse methotrexate has been reported to lead to improvement in fatigue, pruritus, and biochemical tests in two patients.[147-149] In one, there was evidence of histologic improvement and in the other there were no histologic changes noted. It is suggested that in low doses, the known hepatotoxicity of methotrexate is minimized or absent. Little in the way of hepatotoxicity has been reported in patients receiving low dose (15 mg/week) methotrexate for a variety of rheumatologic disorders. One possible favorable action of methotrexate is to inhibit interleukin 1 therapy reducing the number of activated T cells which have been implicated in causing bile duct damage in patients with PBC. Further studies are underway evaluating methotrexate; for now the approach should be considered experimental and used with caution and only in clinical trials.

Liver Transplantation

Patients with primary biliary cirrhosis are considered especially good candidates for hepatic transplantation.[1-3,150]

INDICATIONS FOR LIVER TRANSPLANTATION IN PATIENTS WITH PBC

- Hepatic decompensation
- Bleeding from esophagogastric varices
- Rising serum bilirubin to level > 10 mg/dl
- Inanition and advanced muscle wasting
- Severe metabolic bone disease
- Recurrent spontaneous bacterial peritonitis

These patients often are women in mid-life in whom there is scant evidence of damage to other organ systems. With the progressive improvement in postoperative survival following liver transplantation, the operation is being considered earlier in the course of the illness.[81]

The generally excellent results with liver transplantation make it unlikely that a randomized, controlled clinical trial comparing liver transplantation to any alternative form of therapy will be available. A trial might be carried out if one (or more) of the candidate therapies proves dramatically effective. At present, such appears unlikely.

A most interesting model predicting survival in patients with PBC has been developed at the Mayo clinic.[81] Five readily available, non-invasive factors have been combined in a Cox regression model to produce an equation which appears to give an accurate assessment of prognosis.

Mayo Clinic Prognostic Index: Variables and Equation

- Age
- Total Serum Bilirubin
- Serum Albumin
- Prothrombin Time
- Clinical Severity of Edema*

Edema assessed as requiring therapy

0 = Absence of edema or edema not

0.5 = Moderate; edema which resolved after diuretic therapy or for which no diuretic used

1.0 = Severe; persistent edema despite therapy

$$R = 0.871 \log_e(\text{bilirubin in mg/dl}) + -2.53 \log_e(\text{albumin in g/dl}) + 0.039(\text{age in years}) + 2.38 \log_e(\text{prothrombin time in seconds}) + 0.859\,\text{edema}$$

The Mayo model was used as a surrogate for a control group in assessment of results of liver transplantation in a large number (161) of patients who underwent liver transplantation at the University of Pittsburgh program. The patients who were transplanted had a significantly improved survival at all points after the initial three postoperative months. Survival was better for each subgroup of patients who were transplanted in categories ranked regarding the severity of the liver disease at the time of surgery. The expected improved survival for patients transplanted at an earlier, less decompensated state of illness was confirmed. The Mayo model may become useful in assisting in the decision for optimal timing for proceeding to transplantation in a patient with PBC. There is no question that the earlier the transplant is performed, the better as far as overall survival.

The issue is to decide when to proceed to a still dangerous transplantation operation at a time medical therapy might be equally effective.

Liver transplantation can restore to patients with PBC to health and a long life. In a follow-up of the large series from Pittsburgh, more than 90% of long-term survivors returned to full or part-time work.[150] The effect in sulfoxidation found in the liver of patients with PBC is reversed.[93] Antimitochondrial antibodies persist in the blood of patients with PBC after liver transplantation although often in decreased titer.

Apparent recurrence of primary biliary cirrhosis in the transplanted liver has been reported.[151] The importance of these occasional patients is difficult to assess because of the similarities between the histologic findings in primary biliary cirrhosis and those found in graft versus host disease.

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