Primary biliary cirrhosis is a disease with progressive granulomatous destruction of small intrahepatic bile ducts. It is of unknown aetiology. The disease is associated with a profound immunological disturbance and this has been related to bile duct destruction (Table 8.1). The final event seems to be an attack by cytotoxic lymphocytes on biliary epithelium. The antigen might be the individual’s own human leukocyte antigens (HLA-ABC glycoproteins) which are present in high concentration on biliary epithelium. It is unclear why the reaction should be to normal rather than foreign proteins. Perhaps the patient’s own lymphoid system is at fault so that self and self antigens are not recognized. This could be due to failure of schooling by cytotoxic T-cells in the thymus. These cells are regulated by suppressor cells which have been shown to be diminished both in number and function in primary biliary cirrhosis. Alternatively, and perhaps more likely, the HLA proteins may have become foreign due to an extrinsic environmental factor. The identification of such a factor is an ongoing challenge to all those investigating primary biliary cirrhosis.

In many respects, primary biliary cirrhosis is analogous to the graft-versus-host syndrome as seen, for instance, after bone marrow transplant and where the immune system has become sensitized to foreign HLA proteins. Structural changes in the bile ducts are similar. Other ducts with a high concentration of HLA antigens on their epithelium, such as the lachrymal and

Table 8.1 Immunological changes in primary biliary cirrhosis

<table>
<thead>
<tr>
<th>Depressed skin energy</th>
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<tr>
<td>Granuloma formation</td>
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<tr>
<td>Circulating immune complexes</td>
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<td>Complement activation</td>
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<td>Reduction regulator suppressor cells</td>
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L. Bianchi et al. (eds.), *Trends in Hepatology*  
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pancreatic\(^3\), are involved. The condition can be viewed as a dry gland syndrome\(^2\). Ultrastructural changes in the bile ducts are similar.

The granulomas might be related to immune complexes, and indeed complement has been identified within them. However, they consist predominantly of cytotoxic T-cells, monocytes and macrophages, which suggest cell-mediated tissue injury. Patients with many granulomas are usually seen early in the disease where bile duct destruction is not prominent and the prognosis better. Such patients have normal or only slightly decreased concentrations of suppressor cells in the peripheral blood. This might be related to the rarity of diffuse bile duct destruction and the good prognosis\(^4\).

Copper is retained in the liver, but in a non-hepatotoxic form\(^5\).

**EPIDEMIOLOGY AND GENETICS**

The disease has been reported from all parts of the world. Asians, Caucasians, Jews, Negroes and Orientals are affected. There is family clustering and the prevalence of circulating mitochondrial antibodies is increased in relatives of patients. There is no excess of any particular ABO blood group, HLA antigen, or rhesus negativity\(^6\).

**PRESENTATION**

The patient is usually female, only 10\% being male. Presentation is usually between 40 and 60 years old. The usual onset is as pruritus. Jaundice may appear at the same time or later. The patient is usually pigmented. The liver is variably enlarged. The spleen is often palpable.

**The asymptomatic patient**

The widespread use of automated biochemical screening has resulted in an increasing number of patients being diagnosed when asymptomatic\(^7\). Similarly, the diagnosis may be made in patients under investigation for a condition known to be associated with primary biliary cirrhosis such as thyroid or collagen disease or in the course of family surveys. Such patients tend to be younger and abnormal physical signs may be absent. Mitochondrial antibody is always positive. Serum alkaline phosphatase and bilirubin may be normal or only minimally increased. Serum cholesterol and transaminases can also be normal.

**ASSOCIATED DISEASES**

Non-hepatic disorders are found in about two thirds especially the collagenoses, and autoimmune thyroiditis is also frequent. Primary biliary cirrhosis may be associated with scleroderma and with the whole CREST