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Editorial

The Problem of Histologic Evaluation of Primary Biliary Cirrhosis

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Etiology and pathogenesis of primary biliary cirrhosis remain an enigma. The majority of investigators assume there is a primary immunologic alteration, possibly an abnormal reaction to a preceding injury such as biliary tract disease or hepatitis, viral or drug-induced, since these diseases are often elicited in the history of persons with primary biliary cirrhosis. Others incriminate a primary alteration of the bile acid metabolism with a secondary immunologic response. The demonstrated immunologic abnormalities in family members suggest a genetic basis (Galbraith et al., 1974; Tong et al., 1976).

Growing experience has greatly clarified the evolution, for instance it is now well established that cirrhosis (which is part of the conventional name of the disease) is a very late feature of the disease and is present only for a short time of its duration, which extends over many years. Sometimes, however, this cirrhotic transformation may set in unexpectedly fast and early. As a rule, annual serial biopsies show for years a persistence of one of several morphologic patterns of evolution.

The demonstration of chronic nonsuppurative destruction of bile ducts (Rubin et al., 1975) associated with granuloma formation and sometimes accompanied by the deposition of antigen/antibody complexes around the bile ducts (Paronetto et al., 1967) is now accepted as a diagnostic criterium and has led to wide adaptation of the name 'chronic nonsuppurative destructive cholangitis'. The early investigations considered this histologically characteristic lesion not only a diagnostic criterium but also an indication of the initial stage. From this observation followed the description of a sequence of several stages, eventually terminating in cirrhosis. Three factors, however, complicate the matter. One is the occurrence in late stages of the characteristic florid bile duct lesion, including the proliferation and destruction of bile ductules which had been considered a feature following the bile duct destruction. The florid lesion usually disappears but may persist in consecutive annual specimens or may seemingly reappear in the late cirrhotic stage. The feature is thus denied the characteristic of an initial lesion, though it remains the most important diagnostic

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sign. Secondly, bile duct lesions may occur in acute and in chronic hepatitis of viral or cryptogenic nature, now usually presumed hepatitis non-A-non-B. Histologic criteria (Poulsen and Christoffersen, 1972) are supposed to distinguish the bile duct changes in acute and in chronic hepatitis from those of primary biliary cirrhosis, but sometimes, difficulties arise. Thirdly, the characteristic lesion is best seen and has also been described in surgical specimens and need not be seen in needle specimens. Recent improvements of cholangiographic techniques have reduced the need for exploratory laparotomy to exclude mechanical obstruction. There are indications that surgical exploration of the common duct may not be harmless in this disease, which is characterized by a hyperirritability of the bile duct system. Possibly the now assumed far longer life span of primary biliary cirrhosis reflects the avoidance of surgical exploration.

Improvement of diagnostic laboratory parameters, particularly elevation of alkaline phosphatase activity, mitochondrial antibodies, elevated levels of IgM, and other immunologic reactions (Sherlock, 1976), has facilitated the clinical diagnosis, with the biopsy being confirmatory even without the characteristic bile duct change. As positive indications serve, besides granulomas, absence of cholestasis in the presence of elevated serum bilirubin, activation of sinusoidal lining cells in the absence of hepatocytic injury, and portal and periportal inflammation which sometimes resembles conventional chronic hepatitis but frequently differs by a smaller number of lymphoid cells and predominance of vacuolated mesenchymal cells which accompany a similar erosion of the limiting plate as seen in chronic active or aggressive hepatitis ("biliary piecemeal necrosis"). The deposition of copper, recognized either by specific stains or with Shikata's orcein method (Sipponen, 1976), and, peculiarly enough, portal eosinophiles are other histologic indications of primary biliary cirrhosis.

Features of sometimes typical chronic active hepatitis with the associated changes, including central/portal necro-inflammatory bridges, in substantiated primary biliary cirrhosis present problems, both diagnostic and pathogenetic. Immunologic manifestations, including mitochondrial antibodies and their characteristics (Klöppel et al., 1977), are being proposed for the separation of primary biliary cirrhosis from chronic active hepatitis, particularly when features of both overlap. This differentiation, which is still not possible in all patients, has therapeutic implications since in primary biliary cirrhosis steroid therapy is contraindicated and azothiaprine is probably not effective, while both forms of therapy are beneficial in chronic active hepatitis.

Two different pathways lead apparently to cirrhosis in substantiated primary biliary cirrhosis. One is a dissection of the parenchyma by septa as fibrotic consequence of the ductal and ductular alterations, associated with many vacuolated and pigmented macrophages and limited other inflammatory reaction. Destruction of peripheral layers of hepatocytes can be explained by hepatocellular accumulation of detergent bile acids (Popper et al., 1976) and possibly also of copper. Both are the result of cholestasis in the peripheral portion of the parenchyma (zone 1 of Rappaport) which is caused by the fibrosis and also accentuates it. Thus, the consequences of the initial bile duct lesion, possibly induced by antigen/antibody deposition, lead to cirrhosis, possibly over granulomatous inflammation (Thomas et al., 1977). By contrast, in other patients the cirrhotic transformation seems to develop by the same mechanism as in chronic

aggressive hepatitis. They show the typical features of this disease, such as lymphoid cells surrounding periportal hepatocytes and diffusely infiltrating the septa. In these latter instances, similar immunologic reactions as in chronic active hepatitis, directed against hepatocytes, may be operative as a secondary phenomenon. While thus two different pathogenetic processes with different cytologic features may be responsible for the development of cirrhosis, the destruction of the architecture follows similar pathways in both.

The paper, in this issue, by Ludwig et al. takes a pragmatic approach by using the manifestations of the architectural alterations as a criterium for staging the progress of the disease without regard for the pathogenetic, mainly cellular, features which are helpful in the diagnosis of the disease. They thus separate diagnosis of the disease from morphologic indications of progression. Such an approach, however, is widely used in chronic hepatitis and cirrhosis to provide indications of therapy, regardless of specific differential diagnostic features. The authors indeed apply the same nomenclature which they have used in staging of chronic hepatitis, accepting a recommendation (Popper and Schaffner, 1971) to replace terms like persistent and aggressive by anatomic designations which now have also been approved by the group recommending the original classification of chronic hepatitis (Bianchi et al., 1977). Their proposal results not only in a simplified nomenclature, identical in both chronic hepatitis and primary biliary cirrhosis, but also offers the possibility to recognize these stages in small needle biopsy specimens. In contrast to our previous recommendations (Paronetto et al., 1962), it might be advantageous to consider as criterium for the periportal lesion instead of "piecemeal necrosis" (that means the erosion of the limiting plate which may occur also in acute hepatitis) rather the loss of contiguous layers of hepatocytes around the portal tracts, a "sleeve necrosis" (Popper, 1977). This extension of piecemeal necrosis is characterized by trapping of hepatocytes in acinar arrangement in the periportal fibrotic tissue and is best recognized in connective tissue stains. They permit in both primary biliary cirrhosis and chronic hepatitis the differentiation of the original portal tract from the greatly collapsed peripheral zone of the hepatic parenchyma.

The staging criteria recommended by the authors in established cases of primary biliary cirrhosis appear to be well reproducible. But, in contrast to similar criteria in chronic active hepatitis, they do not provide indications for therapy and only monitor the results of therapy and assist in communication.

The suggestion has been made (Salaspuro et al., 1976) that, regardless of etiology, hepatocellular deposition of copper characterizes conditions which respond poorly to steroid therapy and in whom penicillamine therapy is preferable, at least for removal of copper. Confirmation of this observation would be desirable until either histologic or clinical laboratory methods offer differential diagnostic features which distinguish in all patients primary biliary cirrhosis from chronic hepatitis.

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