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Changes in the Small Biliary Passages in the Hepatic Localization of Hodgkin's Disease

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Summary. The authors have investigated the behaviour of the small biliary passages in the liver biopsies of six patients suffering from untreated Hodgkin's disease with hepatic localization. No obstruction of the major bile ducts was demonstrated in any patient. Three of the patients were anicteric, while the three others presented with jaundice. In the first three cases typical Hodgkin's granulation tissue appears to be limited to portal tracts and collagen reaction is virtually absent. The three cases with cholestasis showed granulomatous tissue associated with heavy connective tissue rearrangement invading and dissociating the lobular structure. They also show a conspicuous bile-duct proliferation, which is not observed in the three anicteric patients. In these latter cases, however, the small bile ducts running within or near the granulomatous tissue present various morphologic changes, including basal membrane thickening, dilation or constriction of the lumen and alterations of the biliary epithelial lining. Complete disappearance of the bile duct may occur.

Key words: Bile ducts, intrahepatic – Hodgkin's disease – Liver.

Introduction

Alterations of intrahepatic bile passages, other than the commonly occurring bile-duct proliferation, have been reported in various acute and chronic primary liver diseases. Disembryogenetic, suppurative or neoplastic primary diseases of the biliary tree are not considered here.

In acute hepatitis the ductular lesions consist mainly of regressive changes

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and leucocytic infiltration of the epithelial lining. There is also conspicuous reduction of the lumen due to epithelial cytoplasmic blebs or to clumps of cellular debris (Sotgiu et al., 1967a, b; Cavalli et al., 1968, 1971; Blüger et al., 1974). The basal membrane does not appear to be destroyed. At the same time some mitoses are observed in biliary epithelium, probably indicating the replacement of cells undergoing degeneration. It is possible that persisting basal membranes act as a framework in facilitating the reconstruction of damaged segments. Interruptions in the course of fine bile tubules have occasionally been reported (Takahashi and Hayama, 1967; Blüger et al., 1974), especially in those forms presenting with prolonged cholestasis (Sotgiu and Cavalli, 1975). The disappearance of segments of interlobular bile vessels has recently been demonstrated in certain cases of cholestatic hepatitis (Nusinovici et al., 1974).

Alterations of biliary epithelium have also been described in chronic hepatitis. They are characterized by cellular oedema (and sometimes necrosis), infiltration, mainly by lymphocytes and reduction or obliteration of the tubular lumen (Poulsen and Christoffersen, 1969).

Segmental changes of fine biliary branches have been observed in benign idiopathic recurrent intrahepatic cholestasis (Lévy et al., 1965; Sotgiu and Cavalli, 1975) and in recurrent intrahepatic cholestasis of pregnancy. In the latter the lesions seem to occur in the absence of inflammatory infiltration (Cavalli et al., 1969) but some cases evolved to what Albot et al. (1972) define as "isolated chronic cholangiolitis". Inflammatory interruption of fine intrahepatic biliary vessels has been shown to be associated with the typical lesions of major bile ducts in primary sclerosing cholangitis (Cavalli et al., 1971).

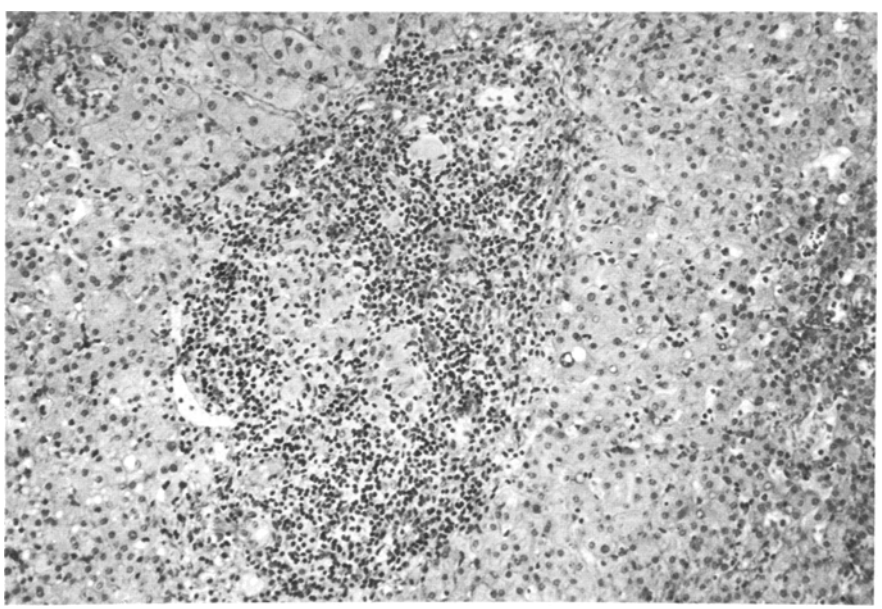


Fig. 1. Hodgkin's disease (case 1, L.B.). Surgical liver biopsy. The granulomatous tissue appears to be circumscribed within the portal tract. Fix.: Bouin. Stain: Azan. ×150

However, the paradigm of the bile duct and ductule destructive lesions is furnished by primary biliary cirrhosis (Lévy et al., 1964; Sotgiu et al., 1967a, b; Cavalli et al., 1968; Albot et al., 1969). The cholangitic alteration is segmentary and typically consists of peritubular crowding of lymphocytes and plasma cells which cross and dissociate the basal membrane. At the same time the epithelial biliary cells present regressive features ranging from oedema, dissociation and detachment from the basal membrane to necrosis. Stereological methods

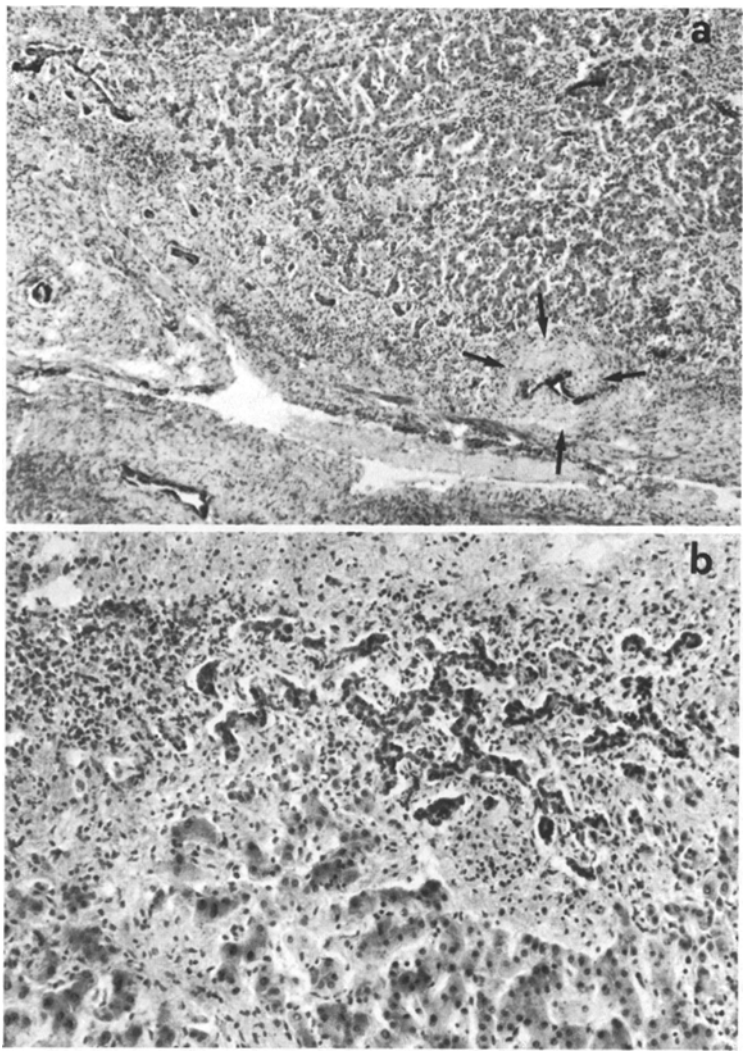


Fig. 2a and b. Hodgkin's disease (case 4, P.B.). Surgical liver biopsy. **a** The hepatic lobules are dissociated by granulomatous tissue which shows prominent collagen production. Conspicuous bile-duct proliferation can also be observed. Some bile ducts (arrows) are surrounded by a heavy collagen coat. Fix.: Bouin. Stain: H & E. ×60. **b** Aspect analogous to those shown in **a**. The higher magnification shows the bile-duct proliferation to better advantage. Fix.: Bouin. Stain: H & E. ×150

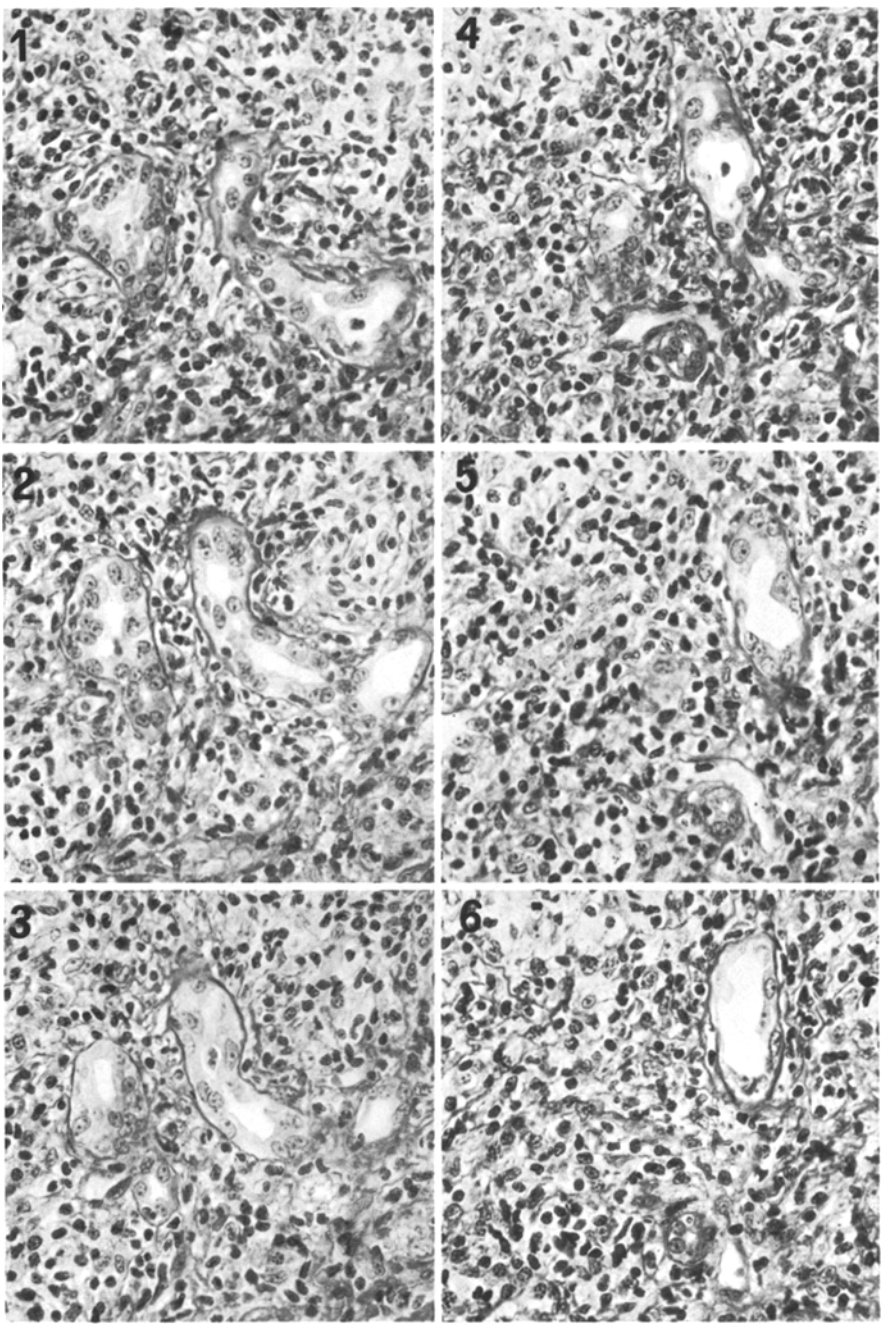
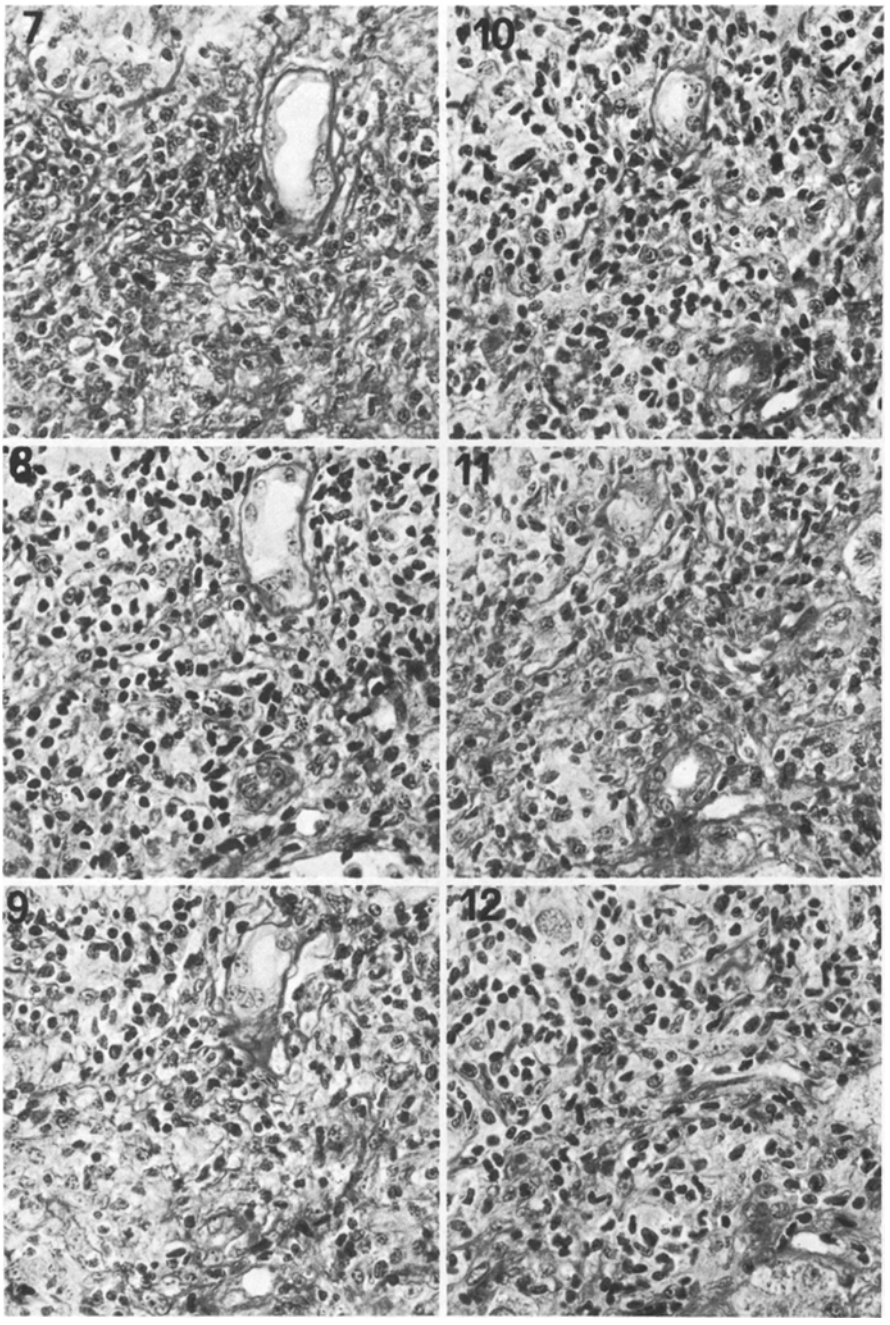


Fig. 3. Hodgkin's disease (case 1, L.B.). Surgical liver biopsy. Reconstruction from serial sections of some small bile ducts, which then disappear along their course. In these bile tubules various alterations can be observed: segments with thickened basal membrane, dilation of the lumen, irregularities in the epithelial lining. Fix.: Bouin. Stain: Azan. ×350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in particular show that the basal membrane becomes more and more ill-defined and the epithelial cells disappear, while inflammatory infiltration increases; finally no morphological signs of the bile tubule persist. Apart from these changes others can be seen, such as ductules with greatly thickened basal membrane and oedema of the epithelium which makes the lumen ill-definable by electron microscopy (Cavalli et al., 1968).

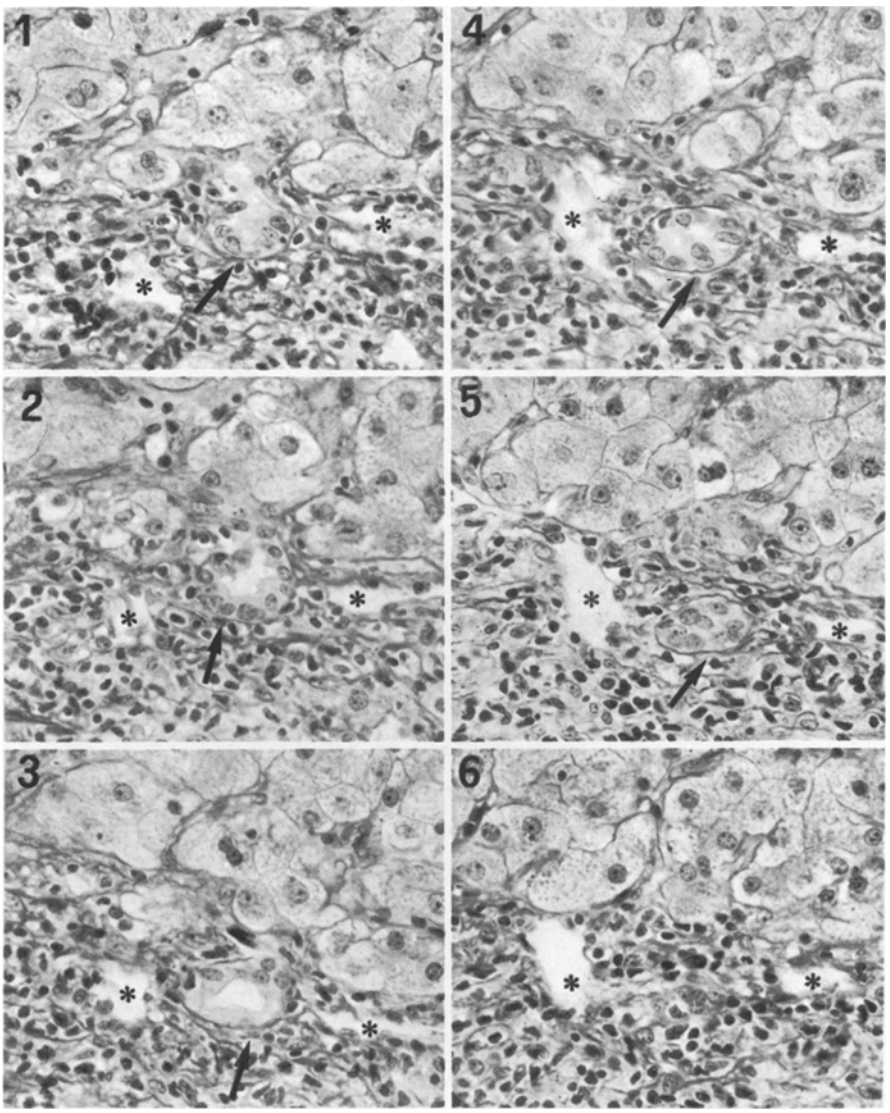

Fig. 4. Hodgkin's disease (case 2, F.G.). Surgical liver biopsy. Reconstruction from serial sections of a small bile duct, which is followed from its origin (*1*). Rapidly it shows irregularities and dilation of the lumen, with epithelial alterations (*2, 3*), then disarrangement of the epithelium (*4*). In *5* the lumen cannot be distinguished and in *6* the bile tubule can no longer be seen. The asterisk indicates two small blood vessels used as landmarks. Fix.: Bouin. Stain: Azan. ×350

Alterations of the intrahepatic biliary tree are not restricted to primary liver disease. It may be that these lesions represent involvement of the biliary tree in various primary or secondary cholestatic, or in non-cholestatic diseases. The disease may affect the liver cells and portal tracts independently or together. We have tried to extend our observations by studying the behaviour of the fine biliary passages in cases of Hodgkin's disease which frequently has hepatic localization with or without cholestasis.

Liver involvement in Hodgkin's disease is estimated to occur in about 70% of cases (Levitan et al., 1961) and is generally manifest as one of the three following features, firstly, clinically isolated hepatic forms of Hodgkin's disease with cholestasis, cytolysis and often splenomegaly; secondly, jaundice in the course of Hodgkin's disease; and finally various histopathologic pictures of the liver (fatty degeneration, amyloidosis, typical Hodgkin's granulation tissue, etc.) evidenced by liver biopsy (Barge and Potet, 1971). In liver biopsies in about 85% of cases it is possible to demonstrate a mesenchymal reaction of the liver independent from the coexistence of typical Hodgkin's granulation tissue (Oehlert and Dischler, 1972). This reaction is non-specific and of varying intensity.

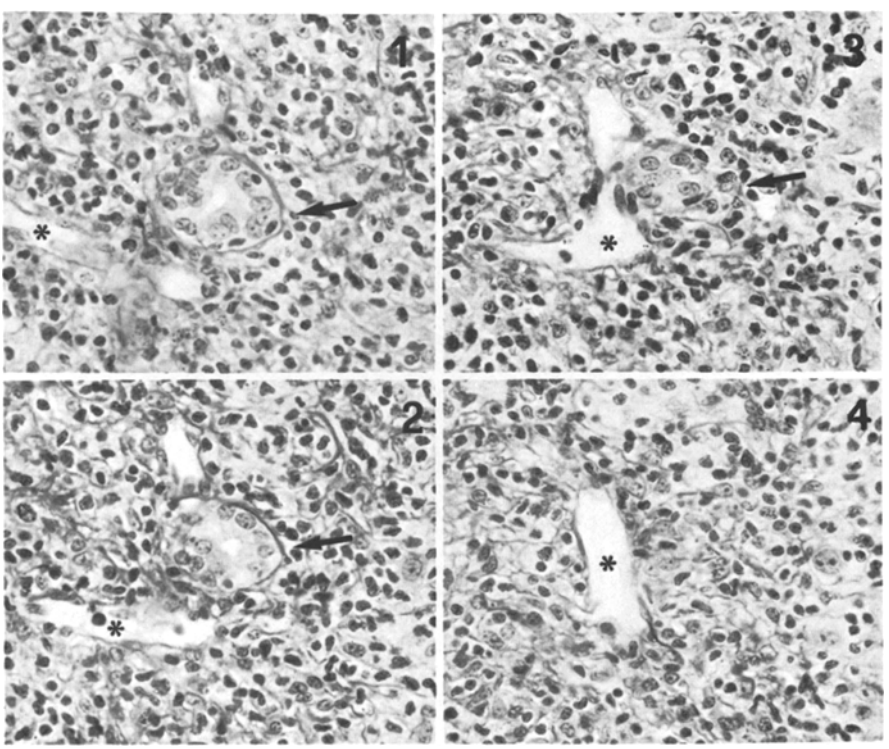

Fig. 5. Hodgkin's disease (case 1, L.B.). Surgical liver biopsy. Reconstruction from serial sections of a small duct presenting alterations along its course. It is possible to see a thickening of the basal membrane, leucocytic infiltration and disarrangement of the epithelium. In *3* the small bile duct is recognizable with difficulty and in *4* it is no longer distinguishable. The asterisk indicates a small blood vessel used as landmark. Fix.: Bouin. Stain: Azan. ×350

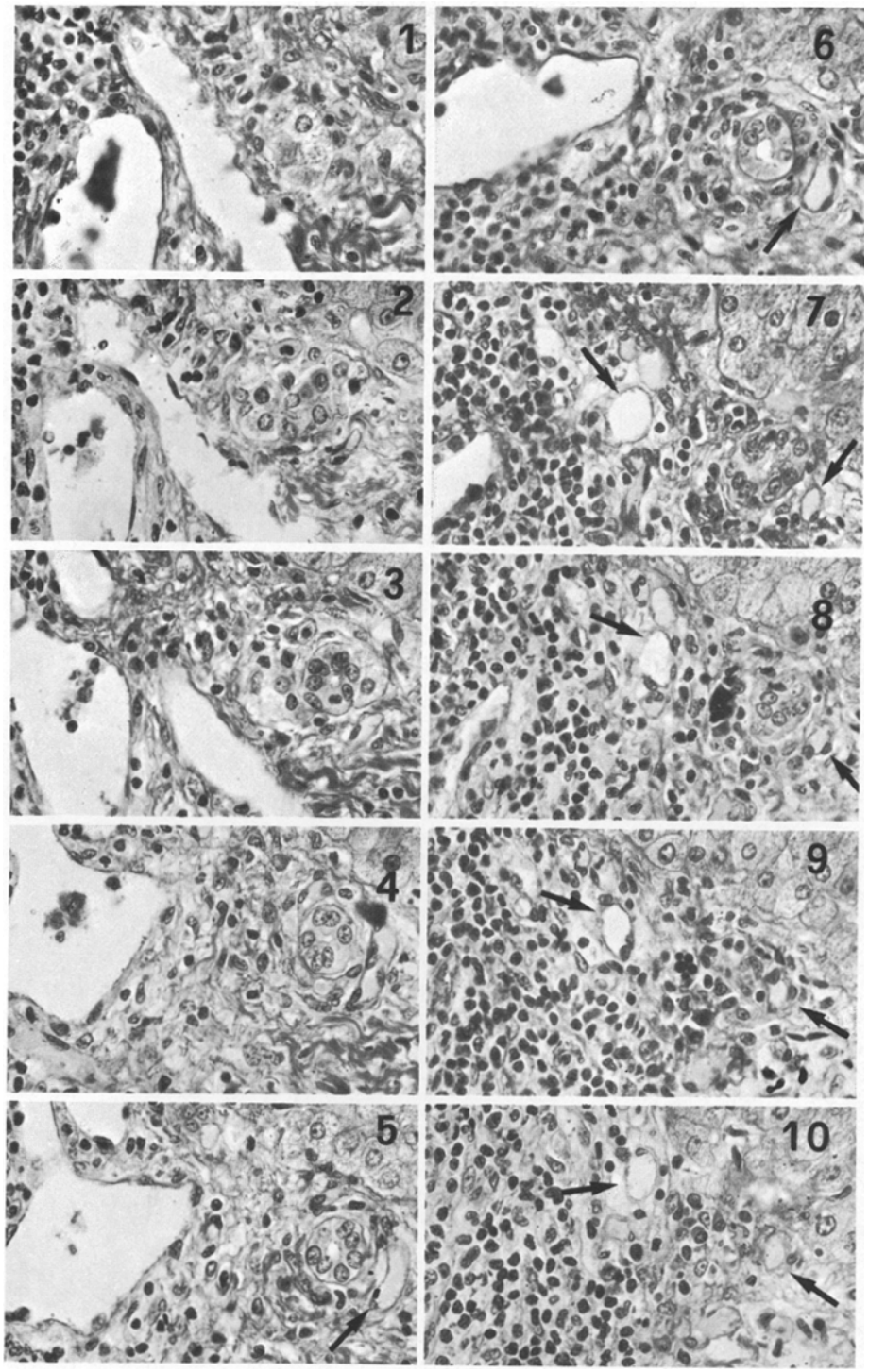

Fig. 6. Hodgkin's disease (case 2, F.G.). Surgical liver biopsy. Reconstruction from serial sections of a small bile duct. It can be followed distally from its origin (*1, 2*) and initially shows dilation of the lumen (*5, 6*), then disarrangement of its epithelium (*7, 8*); in *9* the small duct is difficult to distinguish; in *10* it cannot be seen and its presumptive site is occupied by a cluster of plasma cells. In the last micrographs the arrows indicate the small blood vessels used as landmarks to identify the small bile duct. Fix.: Bouin. Stain: Azan. ×350

Materials and Methods

Segments of the intrahepatic biliary tree were reconstructed from surgical and/or percutaneous liver biopsies in 6 cases of Hodgkin's disease with hepatic localization. Three of these patients presented with jaundice, while the other three were anicteric. Obstruction of the major bile ducts was not demonstrated by intravenous and/or operative cholangiography in any of the cases studied. At the time the biopsy was made the patients were untreated as they were diagnosed only when the disease was already in stage IV.

The study was carried out by means of microphotographic reconstruction of the small biliary passages from serial sections. The sections were 5 μm thick. The percutaneous biopsies were entirely sectioned to obtain about 100 to 120 successive slices, while from the surgical biopsies at least 200 to 250 successive sections have been studied. Preparation for microscopy was made according to the procedures of classical histology.

Results

The granulomatous alterations observed in the liver biopsies of our patients can be summarized essentially into the two following major histological pictures. In the first the granulomatous lesions are localized within portal tracts and the collagen increase is very scanty (Fig. 1). In the second histological picture typical Hodgkin's granulation tissue is associated with a conspicuous and extensive increase of collagen which can also dissociate portions of lobules; at the same time zones of hepatocytic necrosis are present (Fig. 2a and b). These two histopathologic pictures are the same we have observed in our other cases of liver localization of Hodgkin's disease. They are never simultaneously present in the same liver biopsy, but every liver shows one or the other. In our experience the first picture appears to be the more common, while the second has been encountered in only 4 of a total of 18 cases of liver localization of Hodgkin's disease. We have limited our observations on bile tubular changes to untreated cases only.

In general there is no bile-duct proliferation in the first histopathological picture. The granulomatous tissue is composed of closely crowded histiocytes, plasma cells, lymphocytes and Sternberg-Reed cells. Eosinophils are very scanty. Peripheral to these nodules the lymphatic vessels often appear dilated and may have histiocytes or even Sternberg-Reed cells in their lumen. The Hodgkin's granulation tissue does not tend to spread into the lobule and the hepatocytic limiting plate is not interrupted. Small ducts running within or close to the Hodgkin's tissue very often show alterations of the epithelium. This may appear swollen, so that its cells and their nuclei appear much larger than those of the tubules of the same order contained in the intact portal tracts. Elsewhere the epithelium appears flattened. The lumen always appears empty or contains scanty leucocytes. When the epithelium is "oedematous" the lumen can be reduced to a thin slit, while when the epithelium is flattened the lumen appears wide and for short portions small clumps of epithelial cells may protrude into it, the more superficial of these cells being partially detached (Fig. 3). Both changes may be present along the same bile duct. Generally the biliary segments with flattened epithelium and widened lumen also present a thickened basal membrane. Rarely, mitoses may be observed in the epithelial cells close to the damaged portions of the bile duct.

Table 1

Case	Cholestasis	Biopsy	Histopathologic Picture
1. L.B., woman, 57 y	absent	percutaneous and surgical	Granulomatous lesions localized in portal tracts without heavy mesenchymal reaction (Fig. 1)
2. F.G., man, 35 y	absent	percutaneous and surgical	
3. B.P., man, 42 y	absent	percutaneous	
4. P.B., man, 45 y	present	surgical	Hodgkin's granulation tissue associated with conspicuous connective tissue rearrangement and bile-duct proliferation (Fig. 2)
5. G.S., man, 38 y	present	surgical	
6. A.T., man, 46 y	present	surgical	

By reconstruction it is possible to demonstrate the interruption of fine bile ducts, which sometimes appear to terminate blindly (Fig. 4). In others the living epithelial cells become more and more swollen, the basal membrane is progressively permeated with leucocytes which also infiltrate the biliary epithelium and finally the small duct seems to dissolve into the granulomatous tissue (Fig. 5). In this case, the sections immediately next to those where the bile duct can no longer be distinguished often show clusters of plasma cells in the presumptive site of the vanished bile duct (Fig. 6). These morphological changes are not found in bile tubules contained in those portal tracts not affected by the granulomatous process.

In the second histopathological picture a mesenchymal remodelling can be observed within the granulomatous tissue, often with concentric arrangement about bile tubules of a certain diameter (200–300 μm). Bile-duct proliferation is also evident (see Fig. 2b). The bile tubules surrounded by the rearranged connective tissue sometimes present considerable changes of caliber along their course with associated irregularities of the lumen, as if the peritubular connective tissue rearrangement was partly responsible for the limited constrictions. The ductular proliferation is certainly a sign of alteration of the bile passages. Continuity was observed between the newly formed ductular structures and the hepatocytic plates.

Cholestasis was evident in all the cases showing the second of the two histopathological pictures described above in their liver biopsies (see Table 1). In all cases primary biliary cirrhosis could be excluded with certainty on the basis of clinical and serological findings; in particular serum mitochondrial antibodies were absent. In contrast, the liver biopsies of the three anicteric patients consistently presented the first picture.

Discussion

The demonstration of alterations of bile ductules in cases of Hodgkin's disease with hepatic localization shows that lesions of small bile ducts are not exclusively

an expression of primary liver disease. Such lesions, moreover, are not necessarily accompanied by jaundice. Correlation with the clinical features shows that in our cases a syndrome of cholestasis, probably due to intrahepatic obstruction (Perrin, 1970), was present only in those patients whose liver biopsy displayed, apart from Hodgkin's tissue, extensive mesenchymal rearrangement, zones of hepatocytic necrosis and prominent bile-duct proliferation. In contrast, jaundice was not present in the other cases, in whose liver biopsy the granulation Hodgkin's tissue was not spreading out from the portal tracts and ductular alterations were not associated with bile-duct proliferation and collagen increase. In these latter cases it might be suggested that ductular alterations are initially related to metabolic changes produced in the portal tract by the proliferating granulomatous tissue. A possible functional alteration of structures contained in the portal tract may also be inferred from the occurrence of dilated lymphatics with swollen endothelium in the same portal areas.

A syndrome of cholestasis, reported in about 13–14% of cases of Hodgkin's disease (Perrin, 1970), often appears late in the disease (Bouroncle et al., 1962) and is only rarely due to involvement of the extrahepatic biliary tract (Levitan et al., 1961). Nevertheless, according to Perrin (1970), specific Hodgkin's granulation tissue infiltration may often produce partial obstruction of bile passages. However, cholestasis not attributable to therapy may occur in Hodgkin's disease in the absence of granulomatous lesions of the liver or major bile ducts (Sherlock, 1968).

Concerning the two histopathologic pictures observed, the question remains whether they are distinct or whether one can turn into the other in the same case. It is very difficult to answer this question, since natural evolution of the first into the second can only be demonstrated with certainty by subjecting patients excluded from all therapy to successive liver biopsies.

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