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Chronic viral hepatitis B and C: an argument against the conventional classification of chronic hepatitis

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Abstract The classification of chronic hepatitis distinguishing benign chronic persistent hepatitis from severe chronic active hepatitis was constructed without knowledge of well-defined aetiological factors. Better understanding of the different hepatitis-viruses has shed new light on this subject. Chronic viral hepatitis B and C each show typical histological patterns. The validity of the conventional classification has been evaluated by a comparative study of chronic viral hepatitis B and C. 130 biopsies from 110 patients with chronic hepatitis C (CH-C) proven serologically by antibodies (second generation testing) were compared with 105 biopsies from 73 patients with chronic hepatitis B (CH-B). These were scored semi-quantatively. In CH-C, lymphoid follicles and / or aggregates were found in 88.5%, fatty degeneration in 51%, bile duct lesions in 46.2%, and Mallory body-like material in the hepatocytes in 9.2%. The portal lymphocytic infiltration generally predominated over the necro-inflammatory lesions of the parenchyma. Chronic persistent hepatitis (defined by the presence of portal hepatitis) was present exclusively in CH-C. Chronic lobular hepatitis was found exclusively in CH-B. We conclude that the histological criteria described for CH-C are highly suggestive of the diagnosis, that the artificial subdivision of chronic hepatitis into CPH and CAH is obsolete and that the histological assessment of chronic hepatitis should consist of a grading of inflammatory activity (minimal, mild, moderate, severe) and staging of fibrosis (extent of distortion of architecture). The final diagnosis should be based on the demonstration of the aetiological agent.

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Introduction

During the 1960's, the significance of the hepatitis viruses in chronic hepatitis was a matter of debate. While Heinz Kalk had postulated the occurrence of chronic viral hepatitis in soldiers returning from the Soviet Union shortly after World War II [17], some authors questioned whether chronic viral hepatitis existed at all [7, 9]. This was largely because there were no cases of chronic hepatitis or post-hepatitic cirrhosis in follow-up investigations of large scale hepatitis epidemics [9, 10].

The classification of chronic hepatitis in use today was first proposed in 1966 [36], and officially accepted by an international group in 1968 [12]. This classification distinguishes between chronic persistent hepatitis (CPH) and chronic aggressive hepatitis. The term "aggressive" was chosen to emphasize the typical morphological changes while chronic "active" hepatitis (CAH) was reserved for the clinical entity of autoimmune chronic liver disease [19, 26]. However, chronic aggressive hepatitis was later renamed chronic active hepatitis (CAH) [3]. CAH was subsequently associated with the clinical features and pathological changes of polyaetiological chronic active hepatitis. Hans Popper added chronic lobular hepatitis as a third and separate disorder [29].

Jürgen Ludwig's recent review article "The nomenclature of chronic active hepatitis: an obituary" provided a stimulating discussion concerning chronic active hepatitis [25]. It is apparent that the advances in molecular virology have changed the concept of chronic hepatitis [11, 15, 34]. This better understanding of hepatitis virology and immunology provided the evidence that chronic hepatitis was caused by a DNA-virus in hepatitis B (HBV), and a RNA-virus in hepatitis C (HCV) [8, 39].

It has been shown that CPH, defined by the histological changes confined to the portal tracts, occurs only in

viral hepatitis [4, 16]. However, chronic hepatitic diseases of non-viral origin, including drug-induced, autoimmune, Wilson's disease, and in alpha1-antitrypsin deficiency are not restricted to the portal areas and are referred to as chronic active hepatitis [1, 27, 38, 40]. Therefore, the identification of portal hepatitis implies chronic viral hepatitis.

The diagnosis of chronic hepatitis B (CH-B) is most often made by light-microscopic demonstration of orcein-positive ground-glass cells [4, 13]. Conversely, the histology of chronic hepatitis C (CH-C) is characterized by dense lymphocytic infiltrates or lymphoid follicles in portal tracts, bile duct lesions, and steatosis [1, 23, 35].

The purpose of this study is to confirm and extend the results of previous studies, demonstrating that the present classification of chronic hepatitis is no longer adequate. A new classification should be based on the histological findings of necro-inflammatory activity, structural distortion by fibrosis and aetiology.

Materials and methods

Between 1980 and 1992, 130 liver biopsies were performed on 110 patients with serologically proven CH-C. These patients were found to have elevated serum aminotransferases at least 6 months prior to the biopsy. The sera had been stored deep-frozen in a serum bank and all samples were positive for antibodies to hepatitis C (anti-HCV) of the second generation enzyme-linked immunosorbent assay (ELISA, Ortho) and the immunoblot assay (RIBA) (Chiron Ng Emeryville). Forty-two samples were tested with polymerase chain reaction (PCR) and these all produced positive results. The majority of the patients (64%) were sporadic cases and 27% were in those identified as IV drug users. In 9% of the cases, the hepatitis was thought to be transmitted by blood product transfusion. All patients were seronegative for all hepatitis B markers (HBsurfaceAG, Anti-HBcore, HBeAG, Anti-HBe) and other causes of a seronegative hepatitis. Auto-antibodies such as antinuclear, anti-smooth muscle, anti-mitochondrial and LKM-antibodies (liver/kidney/microsomal auto-antibodies) were also assayed and were negative in all except 12 patients, who were found to have low titre antinuclear antibodies (maximum 1:80).

The reference group for CH-B consisted of 105 biopsies from a total of 73 patients with CH-B. All patients were positive for HBs antigen, anti-HBc and HBe antigen, but negative for anti-HCV. Eleven additional patients with concurrent HBV and HCV infection and 19 patients with delta hepatitis (HDV) were excluded from the study.

In the CH-C group, there were 68 male and 42 female patients with a mean age of 47 years (range 16–81 years). The CH-B group consisted of 53 males and 20 females with a mean age of 53.5 years (range 18–73 years).

All biopsies were fixed in 10% neutral buffered formalin and stained with haematoxylin-eosin, diastase-periodic acid Schiff, Berlin blue reaction for iron and chromotrope aniline blue. The sections of the CH-B group were also stained with Shikata's modified orcein stain. A biopsy was considered adequate only if its length was at least 15 mm and if it included at least eight portal tracts. The histological diagnoses were made independently by two pathologists without prior knowledge of the clinical data or biopsy dates in patients with more than one biopsy.

A semi-quantitative system was used to define the degree of portal inflammation, the extent of piecemeal necrosis, and lobular necro-inflammatory changes according to Knodell's Histological Activity Index (HAI) [18]. In contrast to Knodell's HAI, porto-portal bridging necrosis was considered to be a result of portal expansion of piecemeal- or sleeve-necrosis and rated with a lower score than the porto-central bridging necrosis, since only the latter are true bridges with the vascular consequences of shunt formation [5, 13]. The porto-central necrosis was therefore registered as confluent lytic intralobular liver cell necrosis (see Table 1). Deviating from Knodell's HAI, but in keeping with Scheuer's proposition, fibrosis and architectural distortion were evaluated by a separate score [25, 34]. This was because the fibrous score signifies a staging of the disease, whereas the HAI represents a grading of necro-inflammatory activity.

The histological diagnosis was made in accordance with the international classification [3, 13]. Definitions were used as indicated in Table 2.

The following histological parameters were considered and graded semi-quantitatively: Ground glass cells were scored 0: absent, 1: small numbers, 2: moderate numbers, 3: large numbers. Lymphoid follicles/aggregates in portal tracts: were present or absent, or described as lymphoid follicles with a germinal centre, either isolated in the centre of the portal tracts or as part of a diffuse portal infiltrate, lymphoid aggregates (dense accumulation of

Table 1 Histological activity index

Grading (HAI)	
1. Portal inflammation	SCORE
A. None	0
B. Mild: Sprinkling of inflammatory cells in <1/3 of PT	1
C. Moderate: Numerous inflammatory cells in 1/3–2/3 of PT	3
D. Marked: dense inflammatory infiltrates in >2/3 of PT	4
2. Periportal piece-meal necrosis (PMN)	SCORE
A. None	0
B. inimal: One or few tongues in single PT	1
C. Moderate: PMN involving <50% of circumference of most PT	3
D. Marked: PMN involving >50% of circumference of most PT	4
E. Severe: portal-portal bridges by PMN	5
F. Very severe: As in D plus septal PMN	6
3. Lobular necro-inflammatory lesions spotty/confluent necrosis / inflammation (SN/I)	SCORE
A. None	0
B. Mild: SN/I in <1/3 of lobules or nodules	1
C. Moderate: SN/I in 1/3–2/3 of lobules or nodules	3
D. Marked: SN/I in >2/3 of lobules/nodules and/or bridging portal-central confluent necrosis	6
E. Severe: Pan- or multilobular confluent necrosis	10
Staging	
4. Fibrosis/cirrhosis	SCORE
A. None	0
B. Mild: Only portal fibrosis	1
C. ortal fibrosis plus incomplete septa	2
D. Septa bridging portal-portal	3
E. Septa bridging portal-central and/or focal incomplete cirrhosis	4
F. Diffuse incomplete and/or focal complete cirrhosis	5
G. Diffuse complete cirrhosis	6
5. Bile duct lesion	Absent/Present
Total score	
Classification	

Table 2 Assessment of chronic hepatitis

Grading of	Necro-inflammatory activity	Staging of fibrosis	Conventional classification
Minimal	Mild portal and acinar inflammation with sprinkling of inflammatory cells in less than one third of portal tracts and small granuloma-like accumulation of macrophages and focal hepatocellular necrosis in the absence of fibrosis and perivenular liver cell loss	No fibrosis	Non-specific reactive hepatitis (NRH)
Mild	Predominantly lymphocytic inflammation restricted to the widened portal tracts leaving the parenchymal limiting plate preserved. Minimal intra-acinous changes. We prefer the term *"portal hepatitis"*	No fibrosis or fibrosis confined to enlarged portal tracts	Chronic persistent hepatitis (CPH)
	Spotty necrosis (inflammation as in mild acute hepatitis) lasting for more than six months in the absence of substantial portal inflammation	No fibrosis	Chronic lobular hepatitis (CLH)
Moderate	Dense inflammatory portal infiltration with extensive piecemeal necrosis involving substantial parts of the perimeter of portal tracts, but still restricted to periportal areas. Porto-portal bridging by extensive piecemeal necrosis may occur.	Periportal fibrosis with or without incomplete septa formation, ev. portal-portal septa.	Chronic active hepatitis (CAH, moderate activity)
Severe	Piecemeal necrosis in the periportal region and along fibrous septa (pericentral piecemeal necrosis) or confluent zonal necrosis usually portocentral bridging hepatic necrosis (eventually sublobular of panlobular necrosis) in addition to the piecemeal necrosis.	Periportal and septal fibrosis (portal-portal and portal-central septa) Septal fibrosis with incomplete (focal) or complete cirrhosis	Chronic active hepatitis (CAH, severe activity)
Cirrhosis	Chronic active hepatitis with cirrhosis of mild or high activity, extending over the whole scale of HAI	Complete cirrhosis	

small lymphocytes lacking a germinal centre) or loose diffuse lymphocytic infiltrates. Bile duct lesions were noted to be: present or absent, and when present were characterised by degenerative changes of the epithelium of small-sized bile ducts in portal tracts, such as vacuolation or acidophilic cytoplasm with nuclear pyknosis [32]. The damaged bile ducts were surrounded by a lymphocytic infiltrate. Migration of lymphocytes across the epithelium was often seen. Fatty change was: microvesicular or macrovesicular and scored as 0: absent, 1: mild or 2: marked. Activation of the sinusoidal lining cells and Kupffer cells with lymphocytes arranged along the sinusoids in a beads-on-a-string pattern similar to infectious mononucleosis was scored as 0: absent, 1: mild, 2: moderate or 3: pronounced.

The type of hepatocellular degeneration whether acidophilic necrosis or ballooning degeneration was noted as was the degree of intralobular inflammation in proportion to the extent of hepatocellular necrosis and whether this was proportionate or disproportionate.

Hepatocyte dysplasia was present or absent, defined as enlarged hepatocytes with nuclear atypia including hyperchromasia, several cell nuclei, some with several nucleoli.

Mallory body-like material in hepatocytes of the acinus periphery (23) was noted if present.

Results

Figures for the HAI are shown in Table 3. The major differences between CH-C and CH-B in the HAI were found to be a lower mean total score in CH-C than in CH-B. A preponderance of portal inflammation compared with necro-inflammatory and piecemeal necrosis was seen in CH-C (Figs. 1, 2).

Table 3 HAI Grading of chronic hepatitis (CH)-C versus CH-B

HAI	CH-C (n=130)	CH-B (n=105)
mean of total score	5.8	7.2
Relation of mean portal to lobular inflammation	3.2:2.2	2.6:3.6
Relation of portal inflammation to piecemeal necrosis	3.2:2.2	2.6:3.6

Quantitatively, the intensity of the portal inflammation assessed by HAI seemed not strikingly different in CH-C and CH-B. In CH-C dense (grade 3) and very dense (grade 4) infiltrates were found in 47 (36%) cases each, whereas in CH-B these were seen in 51 (48.5%) and in 30 (28.5%) cases respectively. The quality of portal inflammation (in contrast to these quantitative features) however was found to be fundamentally different in CH-C and CH-B. In CH-C the infiltrates were mainly lymphocytic, plasma cells were either absent or present

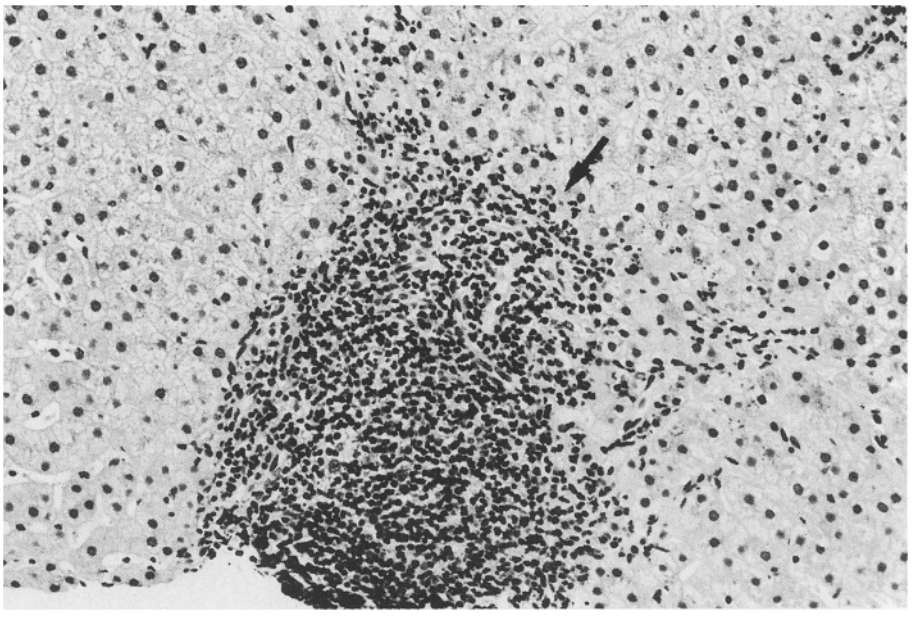

Fig. 1 *Chronic hepatitis C:* preponderance of a dense lymphocytic portal infiltration as compared to the relatively mild lobular necroinflammatory lesions. Rather mild piecemeal necrosis *(arrow).* H&E; original magnification × 150

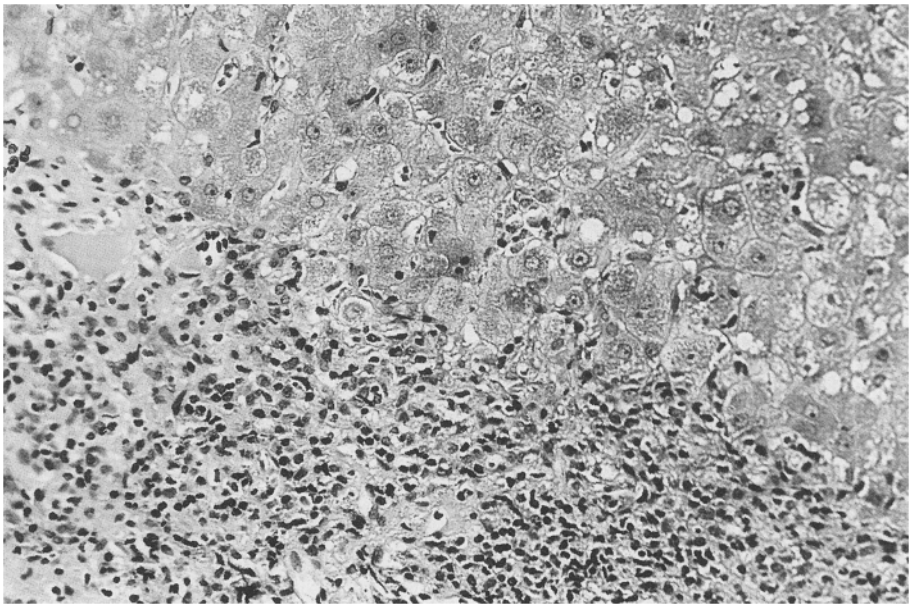

Fig. 2 Chronic hepatitis B: marked disarray of liver cell plates due to ballooning and conspicuous liver cell damage. Note the relatively loose and mixed cellular portal infiltration. H&E; original magnification × 175

only in a small number at the margin of the infiltrate. A considerable sampling error may occur in CH-C (especially in cases of mild activity) because dense lymphocytic infiltration was present only in part of the portal tracts. In CH-B a mixed cell infiltrate with lymphocytes, histiocytes and plasma cells was spread out over almost all portal tracts.

Important histological features, differentiating between CH-C and CH-B (Table 4A) were identified as follows: in CH-C lymphoid follicles or lymphoid aggregates were found to be common and prominent in the portal tracts in all stages of the disease. They were either the core of a diffuse inflammatory infiltrate or were interspersed with a few inflammatory cells in the centre of a portal tract. Lymphoid follicles with germinal centres were present in 85 (65%) biopsies, whereas densely packed lymphoid aggregates lacking germinal centres only were demonstrated in 30 (23.1%).

In CH-B lymphoid follicles were absent. Lymphoid aggregates were seen in only two biopsies, whereas diffuse lymphocytic infiltrates were found more often. Eleven biopsies with both lymphoid follicles and ground glass cells were subsequently proven to be infected with both HBV and HCV and were excluded from the study.

Bile duct lesions were often conspicuous in CH-C, but uncommon in CH-B. The lesions were restricted to the small-sized bile ducts within a single portal tract or less often in several portal tracts (Fig. 3). They were most prominent in CH-C of mild activity. Nevertheless, the few bile duct lesions in CH-B were registered exclusively in highly progressive forms. Loss of bile ducts was observed in only 5 cases of CH-C.

Steatosis was more frequently observed in CH-C than in CH-B. In CH-C it was often focal rather than diffusely disseminated and macrovesicular. However, steatosis was absent in 63 (48.5%) of CH-C cases, especially in highly active inflammation. A correlation of the presence or extent of steatosis with degrees of activity of CH-C could not be demonstrated.

Table 4A Prevalence of important histological features in CH-C versus CH-B

Characteristics	CH-C (n=130) Total number / %	CH-B (n=105) Total number / %
Lymphoid follicle/aggregate	115 / 88.5%	2 / 1.9%
Diffuse lymphocytic infiltrates	7 / 5.4%	19 / 18.0%
Bile duct lesion	60 / 46.2%	10 / 9.5%
Steatosis	67 / 51.5%	27 / 26%
Mallory body like material	12 / 9.2%	none
Ground glass cells		
total	–	68 / 64.8%
scantily scattered	–	44 / 41.9%
numerous	–	15 / 14.3%
abundant	–	9 / 8.6%

Table 4B Non-characteristic histological features

Acidophilic necrosis		
absent	11 / 8.5%	10 / 9.5%
widely distributed	63 / 48.5%	56 / 53.4%
numerous	38 / 29.2%	33 / 31.4%
abundant	18 / 13.8%	6 / 5.7%
Ballooning degeneration		
absent	90 / 69.2%	24 / 23%
moderate numbers	35 / 27.0%	39 / 37%
very numerous	5 / 3.8%	42 / 40%
Activation of sinusoidal lining cells in a beads-on-a-stringpattern	85 / 65%	42 / 40%
Activation of sinusoidal lining cells proportional to degree of lobular hepatocyte damage	67 / 51.5%	82 / 78.0%
Activation of sinusoidal lining cells disproportional to the extent of liver cell injury	63 / 48.5%	23 / 22.0%

If present, ground glass cells were the hallmark of an HBV infection and were never seen in CH-C. These cells were most numerous in minimally active chronic hepatitis. They were absent in the acute episode of highly active CAH and were also lacking in 6 cases of minimally active or mildly active CAH. However in the latter, the cell nuclei of the hepatocytes displayed "sandy degeneration" [4].

Mallory body-like material in hepatocytes of the acinus periphery was uncommon and occurred exclusively in CH-C.

Non-characteristic histological features, which did not help in differentiating CH-C from CH-B (Table 4B), included the following: differences in acidophilic liver cell necrosis were not significant, ballooning degeneration of hepatocytes was much more common in CH-B. There was more pronounced disarray of the liver cell plates in CH-B than in CH-C (Fig. 2). In contrast to Dienes et al. [14] we found naked acidophilic bodies in both CH-C and CH-B.

There were no periportal necroses in 32 (24.6%) cases of the CH-C group, whereas fresh and old piecemeal necroses were present in virtually all cases of CH-B (99=97%). In CH-C, the distribution of piecemeal necrosis was patchy, often involving only parts of the circumference of a portal tract. These changes were absent in portal tracts with isolated lymphoid follicles or aggregates lying in their centres.

Activation of the sinusoidal lining cells with lymphocytes and Kupffer cells in a beads-on-a-string-pattern occurred in both groups, with higher frequency in CH-C. In almost half of CH-C specimens, the pronounced intralobular inflammation was completely out of proportion to the relatively slight hepatocellular damage, whereas in the majority of the CH-B specimens, the activation of the sinusoidal lining cells corresponded closely with the degree of lobular parenchymal damage.

Small clusters of dysplastic hepatocytes with hyperchromatic nuclei (often with several nucleoli) were registered in 20 (15.4%) CH-C and 17 (16.2%) CH-B biopsies.

The results of staging are shown in Table 5. CPH (evidenced by portal hepatitis) was diagnosed in 32 (24.6%) of the CH-C biopsies, but in only 7 (6.7%) of the CH-B biopsies. CPH-HCV cases showed a true portal hepatitis

Table 5 Staging of chronic hepatitis according to the conventional classification of chronic hepatitis, compared to proposed grading of activity

Staging classification	CH-C (n=130) Total number/%	CH-B (n=105) Total number/%	Chronic hepatitis: proposed grading of activity
Non specific reactive hepatitis NRH	7 / 5.4%	3 / 2.8%	minimal
Chronic portal hepatitis CPH	32 / 24.6%	7 / 6.7%	mild
Chronic lobular hepatitis CLH	0 / 0%	2 / 1.9%	mild
Chronic active Hepatitis CAH (total)	91 / 70%	93 / 88.6%	
moderate activity	62 / 47.7%	47 / 44.8%	moderate
severe activity	29 / 22.3%	46 / 43.8%	severe
Cirrhosis	19 / 14.7%	28 / 26.7%	

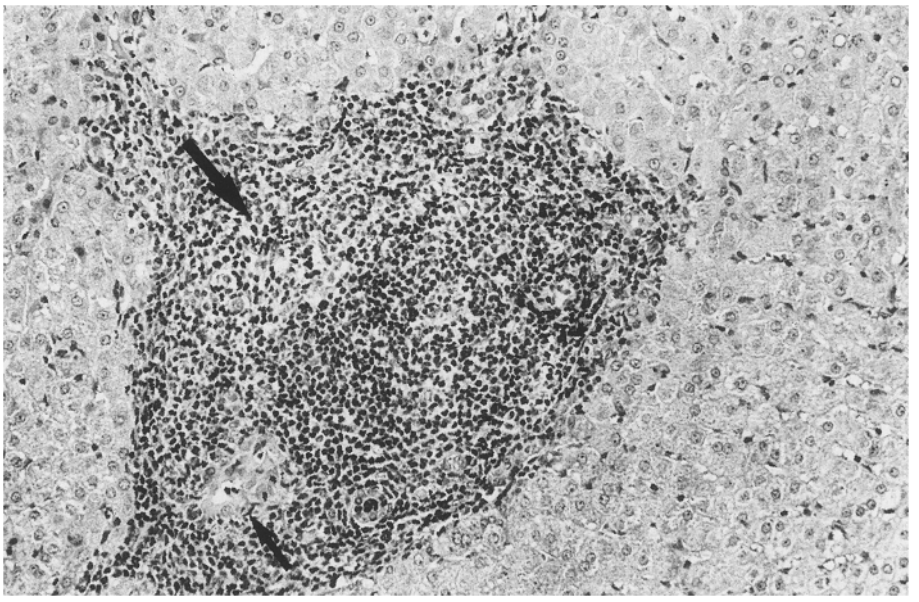

Fig. 3 Chronic portal hepatitis in a biopsy of a patient with hepatitis C infection. Bile duct lesions. Acidophilic and vacuolated duct epithelium *(small arrow)*. Dense portal infiltration with lymphoid follicle and germinal centre *(arrow)*. A previous liver biopsy two years ago showed an identical histological picture. H&E; original magnification × 175

with only minimal lobular lesions (Fig. 3). Dense lymphocytic infiltrates were seen encasing damaged bile ducts in one quarter of CH-C biopsies. They rarely affected all portal tracts in the biopsy, but were most often seen in a patchy distribution. This virtually pure portal hepatitis was associated with normal values of aminotransferases at the time of biopsy in one third of CH-C cases, whereas in all CH-B cases, at least slightly elevated aminotransferases were registered.

The few CH-B biopsies which had first been interpreted as CPH showed homogeneous involvement of all portal areas. The inflammatory infiltrate was mixed and diffusely distributed. The bile ducts were invariably intact. In contrast with CH-C, mild lobular inflammatory lesions were always present in every case, so that the term "portal hepatitis" would hardly be appropriate. This would be better interpreted as a "non-specific reactive hepatitis" (NRH). Orcein-positive ground glass cells confirmed the diagnosis of CH-B in the majority of these cases.

Complete follow-up over a period of 4 to 10 years (clinical findings and two or more biopsies) was available in only 12 of 32 CH-C patients with CPH. The diagnosis of CPH was originally made on the basis of the histological pattern of pure portal hepatitis; 1 patient returned to normal, 3 improved to a minimal change hepatitis (NRH), 4 remained unchanged (CPH) (Fig. 3) and in 4 patients transition into CAH was registered, with progression to cirrhosis in 1 case.

CAH of severe activity was found only in 29 (22.3%) of CH-C but in 46 (43.8%) of CH-B. A higher HAI in CH-B may also be reflected by the greater frequency of cirrhosis in CH-B and by the generally milder course of CH-C. Fully developed cirrhosis was found in only 19 cases (14.6%) in the CH-C group whereas it was seen in 28 CH-B biopsies (26.7%).

Discussion

The histological picture of CH-C is virtually identical to the previously described findings in non-A, non-B hepatitis [20, 23, 35, 37]. Lymphoid follicles, bile duct lesions and steatosis are the hallmarks of CH-C. However, in this series, lymphoid follicles and/or lymphoid aggregates in the portal tracts were not only the most striking qualitative feature but occured far more frequently (88.5%) than in other series in the literature. They were observed in all stages of HCV infection (from acute hepatitis to cirrhosis) and were absent only in a few highly active cases of CAH. They were also absent in all NRH cases. Lymphoid follicles in portal tracts may often persist, even though the aminotransferases return to normal levels, as seen in this series. One can think of persisting lymphoid follicles as a "time bomb", leading to the frequent undulant course of HCV-infection.

Diffuse lymphoid infiltration of portal tracts was demonstrated in only 18% of CH-B cases. Two isolated cases of CH-B showed lymphoid aggregates. It is important to note that lymphoid follicles and a mixed-cell portal infiltrate (in addition to ground-glass cells) were found in 11 patients who were excluded from the study. HBV and HCV double-infection was presumed in these cases, on the basis of morphology. This was subsequently verified by detection of HCV antibodies and of HCV-RNA by PCR (Schmid, unpublished observation). Lymphoid follicles can also occur in autoimmune CAH in rare cases [1]. Clusters of plasma cells, confluent liver cell necroses leading to parenchymal collapse with rosette formation, and multinuclear hepatocytes all indicate the presence of autoimmune CAH but not CH-C [1, 21].

The close relationship of bile duct damage with lymphoid follicles appears to be particularly characteristic for CH-C [1, 23, 35, 37]. In fact, the appearance of primary biliary cirrhosis may be simulated. However, in most cases of primary biliary cirrhosis, there are numer-

ous plasma cells and epithelioid-cell granulomas in the portal tracts or in the parenchyma. The chronic cholangitis results ultimately in the destruction of the bile duct ("vanishing"). Vanishing bile ducts were only occasionally found in CH-C (in agreement with Lefkowitch et al. [23]. The combination of bile duct lesion and lymphoid follicles is considered a manifestation of an immune reaction in both diseases (CH-C and primary biliary cirrhosis). In CH-C, this might be caused by viral infection of the bile duct epithelia, either directly by a viral antigen or indirectly by a virus-induced antigen. In CH-B, bile duct lesions were found exclusively in very severe necrotizing CAH without any topographical association to lymphoid aggregates.

Steatosis, predominantly macrovesicular, was ascribed to be an important feature of CH-C in the literature. Nancy Bach and collaborators described large droplet fat in 72% of their CH-C biopsies [1]. Lefkowitch et al. found fatty change even in 97.6% (large droplets in 68.9%, small droplets in 28.7%) [23]. Scheuer et al. however recorded steatosis in 29 out of 45 cases of CH-C [35]. In our material steatosis was recognised only in half of the CH-C biopsies. It was conspicuously absent in biopsies with high inflammatory activity. In several publications steatosis is attributed to a cytotoxic effect of the virus, analogous to the course of inflammation in HCV-infected chimpanzees. This conclusion is controversial. On the one hand in the chimpanzee model steatosis was observed in an early cytotoxic phase [30]. Steatosis was also found in the biopsies of HDV epidemics in Indian tribes in South America [6, 31] as well as in sporadic acute HDV [22]. In steatoviral hepatitis B the steatosis of the hepatocytes is likely to be attributable to the cytotoxicity of HBV surface material (HBs) on the virus burden hepatocyte [28]. On the other hand an unequivocal relationship between the steatosis and the phase and activity of the disease could not be inferred in our material. The hypothesis of the steatosis as a cytotoxic effect of the virus is controversial in our opinion and needs further investigation.

Lefkowitch et al. drew attention to Mallory body-like material in the periportal hepatocytes [23], which in the present study was noted in CH-C, but never in CH-B. This characteristic although rare feature of CH-C has not yet been explained. However, it is probably not associated with Bouin's fixation, as postulated by the authors of a multicentric study [33], since it has also been described in formalin-fixed material [23].

A further difference between CH-B and CH-C is the frequent occurrence of ballooning degeneration of hepatocytes in CH-B, often resulting in a marked disarray of liver cell plates. The activation of sinusoidal lining cells exceeded the degree of hepatocyte damage in almost half of the biopsies of CH-C, whereas the ratio in CH-B appears to be balanced. Overall, the preponderance of portal inflammation compared to the lobular necro-inflammatory lesions is conspicuous in CH-C, while the opposite is true in CH-B. (Figs. 1, 2)

Portal inflammation is most prominent in CPH, which is defined by portal hepatitis with or without minimal lobular lesions [16]. In the strict sense of the term, we found CPH exclusively in CH-C, occuring in 32 (24.6%) of our cases (Fig. 3). It may be difficult to discriminate between CPH and mild CAH in the presence of superficial piecemeal necroses involving only part of the circumference of the portal tract or occasional tongue-like infiltrations into the limiting plate.

In 7 CH-B biopsies initially interpreted as CPH, portal inflammation was most prominent. The mixed-cell portal infiltrate was diffusely distributed in all cases. However, mild lobular lesions were invariably present. With strict application of the definition, a pure portal hepatitis was not present. In the literature, the term CPH is applied generously, often deviating from the strict definition [25]. In therapeutic trials, CPH was thus regarded as a remission stage of CAH [2, 24]. However, remission is histologically characterized by portal fibrosis and an irregular undulant contour of the restored limiting plate, which is often combined with trapping of isolated hepatocytes within fibrous scars. Portal fibrosis with stellate contours is a strong argument against a CPH, because it indicates a previous lesion of the limiting plate (piecemeal necrosis).

We suggest that the diagnosis given by the pathologist includes a grading of necro-inflammatory activity (HAI) and, as proposed by Scheuer and Ludwig [25,34], a staging of the degree of fibrosis (see Table 2). However, the definitive diagnosis should include an aetiological designation [25]. Indeed, these data suggest that an aetiology can be recognized or at least suggested by the histological pattern. The final diagnosis requires serological and/or biochemical confirmation in every patient.

Strictly speaking, portal hepatitis occurs exclusively in hepatitis C. As the prognosis of HCV-infection is uncertain the conventional classification of chronic hepatitis in which the term CPH implies a good prognosis has become meaningless. Therefore, the present classification is obsolete.

The histological appearance of CH-C is not diagnostic but highly suggestive of the diagnosis. The most reliable criterion is the presence of lymphoid follicles or lymphoid aggregates. If present, bile duct lesions, steatosis and Mallory body-like material in hepatocytes of the periportal region support the diagnosis. CH-C differs from CH-B in the preponderance of portal inflammation when compared to the extent of necro-inflammatory lesions. In mild cases, CH-C appears as a chronic portal hepatitis and thus fulfills the criteria for CPH. Sampling errors due to irregular inflammatory involvement of the portal tracts make it frequently impossible to distinguish CPH from mild CAH. According to the strict definition, no cases with pure portal hepatitis were found in CH-B, but several cases were noted in CH-C. Thus, the conventional classification of chronic hepatitis into CPH and CAH creates an artificial boundary which appears arbitrary by stringent consideration. We therefore consider the conventional classification obsolete. It should be replaced by an assessment on a morphological basis, including grading of necro-inflammatory activity (HAI), staging of fibrosis and evaluation of the architecture. The

final diagnosis must include the aetiology of the hepatitis.

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