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CHAPTER 6

Acute Viral Hepatitis

Introduction

Acute hepatitis is not usually an indication for liver biopsy. There are, however, at least three reasons why pathologists sometimes receive liver biopsy samples from patients with acute hepatitis. First, there may be doubt about the clinical diagnosis, or even a mistaken working diagnosis. Second, a diagnosis of hepatitis may be well established but the clinician needs information on the stage of the disease or its severity. Third, the patient may have received a liver transplant and the pathologist is being asked to help decide if symptoms or biochemical abnormalities are due to recurrent (or new) viral hepatitis or to some other cause such as rejection. For all these reasons, a knowledge of the pathology of acute hepatitis is essential. There is a further reason, no less important than the others: without a knowledge of acute hepatitis, the pathologist cannot hope to understand chronic hepatitis and cirrhosis, together the cause of most liver disease in the world. This chapter describes acute viral hepatitis and its immediate sequelae in the immunocompetent patient. The specific problems of diagnosing hepatitis in an immunosuppressed patient after transplantation are reviewed in **Chapter 16**.

The hepatitis viruses are listed in **Table 6.1**. While several other candidates have been extensively investigated in recent years, none has so far been established as a definite cause of viral hepatitis, and most episodes of acute and chronic hepatitis can be attributed to one of the viruses listed, to autoimmune hepatitis (**Ch. 9**) or to a hepatotoxic agent (**Ch. 8**). An exception to this statement is fulminant hepatitis, the cause of which cannot currently be established in a substantial minority of patients,[1–3] including children.[4] Occasionally, a virus more often associated with infection of other organs, such as one of the herpesviruses[5–7] or an adenovirus,[8,9] gives rise to a severe hepatitis. These agents are further discussed in **Chapter 15**. Mild acute hepatitis has been reported in patients infected with the SARS virus (severe acute respiratory syndrome-associated coronavirus).[10,11]

Occasionally, mild serum liver test abnormalities and mild histological hepatitis (bystander hepatitis) with apoptotic bodies, focal necrosis and lymphocytic inflammation are seen in systemic, non-hepatic viral infections such as pulmonary influenza and result from migration to the liver of, and collateral damage by, CD8 T lymphocytes.[12,13]

Pathological features

The essential components of the acute phase of hepatitis are inflammatory-cell infiltration and hepatocellular damage. Other features include cholestasis, Kupffer-cell activation, endotheliitis, bile-duct damage, the ductular reaction and hepatocellular regeneration.

Table 6.1 The hepatitis viruses

Virus	Type	Spread and disease
Hepatitis A (HAV)	RNA hepatovirus	Faecal–oral, acute
Hepatitis B (HBV)	DNA hepadnavirus	Parenteral, acute or chronic
Hepatitis C (HCV)	RNA hepacivirus	Parenteral or sporadic; acute, more often chronic
Hepatitis D (HDV)	RNA deltavirus, defective	Pathogenic when combined with HBV
Hepatitis E (HEV)	RNA virus	Faecal–oral, epidemic or sporadic acute disease

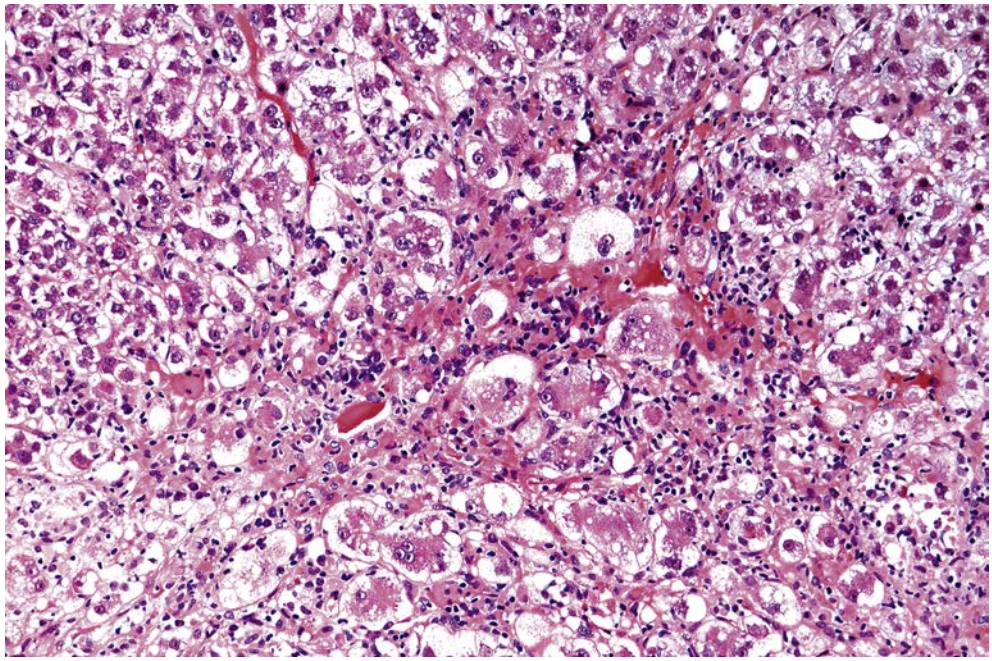

Fig. 6.1 Acute viral hepatitis. Surviving hepatocytes in the perivenular area in the centre of the field are swollen and the area is infiltrated by inflammatory cells. (Needle biopsy, H&E.)

Hepatocellular damage

Changes seen under the light microscope range from minor degrees of cell swelling to cell death. They are accompanied by the inflammatory infiltration described below, reflecting the important role of cellular immunity in the pathogenesis of most forms of hepatitis. Both hepatocellular damage and inflammation are usually most severe in perivenular areas, giving rise to a characteristic histological pattern (**Fig. 6.1**). A periportal pattern of necrosis and inflammation, sometimes seen in hepatitis A, is less common.

The mildest change is cell swelling, and this is probably reversible. The cytoplasm of affected cells is rarified, granular and sometimes finely vacuolated. The more severe degrees of cell swelling are called ballooning degeneration (**Fig. 6.2**). This differs from the feathery degeneration of cholestasis, in which the cytoplasm has a reticular pattern (**see Fig. 5.3**), and from the ballooning in steatohepatitis where the cytoplasm is less granular and more oedematous and 'clarified' (**see Fig. 7.10C**). Other hepatocytes undergo apoptosis, which is an important method of cell death in hepatitis.[14] Shrinkage and increased staining of the cytoplasm, sometimes called acidophilic

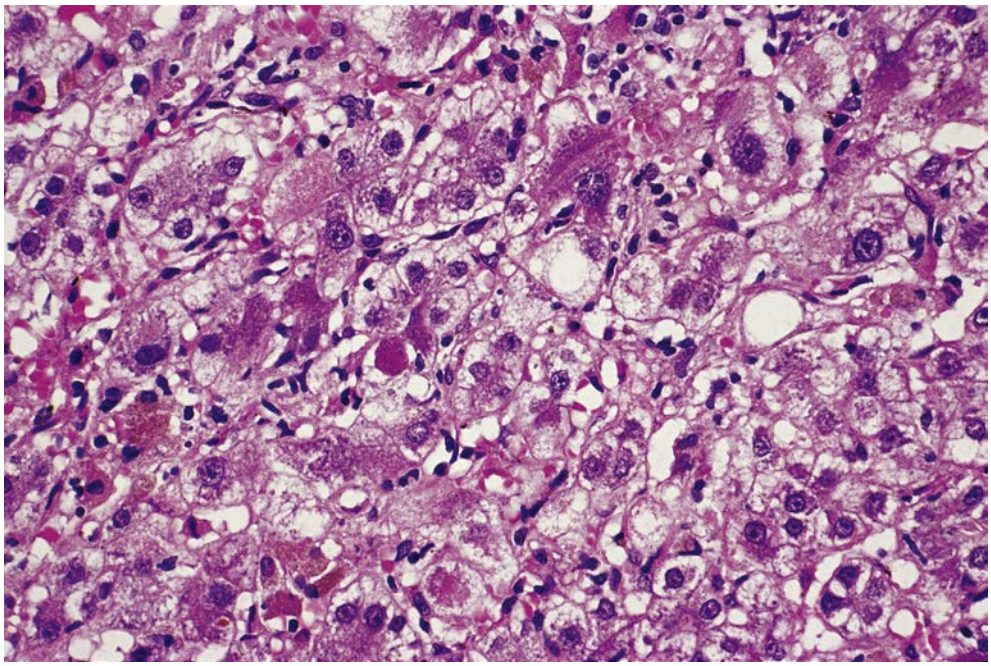

Fig. 6.2 Acute viral hepatitis. Normal liver-cell plate structure is disrupted. Hepatocytes vary in size, and some are ballooned and vacuolated. An apoptotic hepatocyte is seen left of centre. (Needle biopsy, H&E.)

change or degeneration, is probably a precursor of apoptosis, in which the hepatocytes shrink further, become very dense and undergo fragmentation. The apoptotic bodies seen lying free in the sinusoids represent the largest fragments or entire unfragmented apoptotic cells (**Fig. 6.2**). They are also called acidophil bodies or Councilman bodies, Councilman having first described them in yellow fever[15,16] (**Fig. 6.3**). Apoptotic bodies sometimes contain pyknotic nuclear remnants and often appear to bulge beyond the plane of the section. Another form of hepatocellular damage in acute hepatitis is focal (spotty) necrosis, in which liver-cell plates are disrupted or replaced by small groups of lymphocytes and macrophages. Whether these mark a site of necrosis or of apoptosis is not clear; the damage to hepatocytes is deduced from their absence rather than seen. Whatever its mechanism, loss of hepatocytes or liver-cell drop-out, coupled with focal regeneration, leads to a characteristic irregularity of the liver-cell plates, which usually allows acute hepatitis to be distinguished from hepatocellular damage secondary to cholestasis. The loss of hepatocytes also leads to condensation of the extracellular matrix, best seen in reticulin preparations (**Fig. 6.4**).

Hepatocyte nuclei show prominent nucleoli and increased variation in size and may be multiple. When syncytial giant hepatocytes are very prominent, the term giant-cell hepatitis is appropriate.[17,18] This is only rarely of proven viral origin and is also more characteristic of acute hepatitis in neonates. In adults, autoimmune hepatitis and hepatitis C virus with or without human immunodeficiency virus co-infection are important associations.[19–23]

Cholestasis in the form of bile thrombi in canaliculi is common in acute hepatitis but rare in chronic hepatitis, which is diagnostically helpful. It is a result of damage to the bile-secretory apparatus of the hepatocytes, but may also result from interference with bile flow at the level of the portal tracts.[24] The term cholestatic hepatitis is best kept as a clinical description of patients with a prolonged cholestatic course. Mild hepatocellular siderosis or steatosis is occasionally seen.

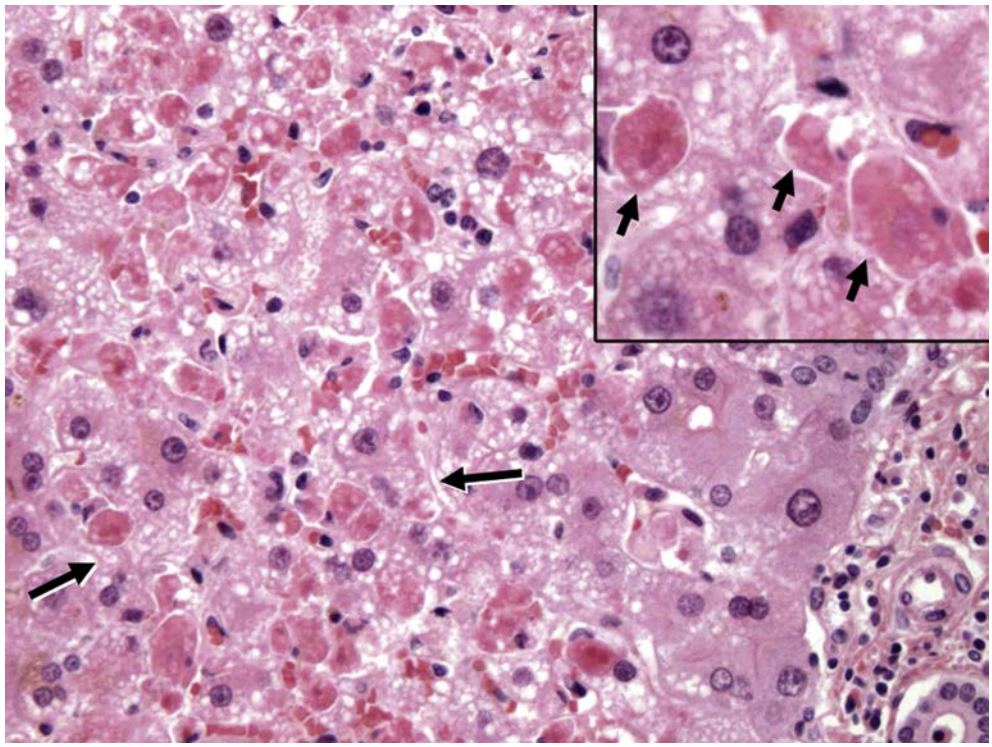

Fig. 6.3 Acute yellow-fever hepatitis. There is prominent mid-zonal necrosis (between arrows) with many apoptotic hepatocytes and scattered lymphocytes. The portal tract at lower right is mildly inflamed and there is relative preservation of periportal parenchyma. Inset: The numerous apoptotic (Councilman) bodies present (arrows) are characteristic of liver involvement in yellow fever. (Case kindly provided by Dr Matthias Szabolcs, New York, NY.)

The inflammatory infiltrate

Unlike classic acute inflammation, viral hepatitis is characterised by a mainly lymphocytic infiltrate within the parenchyma and portal tracts. In acute hepatitis, the most conspicuous inflammation is usually perivenular. The extent of portal inflammation is very variable, and portal tracts may be either normal in size or expanded. The larger conducting tracts are often spared. The edges of small portal tracts may be well defined or blurred by outward extension of the infiltrate. This so-called spillover resembles the interface hepatitis of chronic hepatitis (Ch. 9) and may be difficult to distinguish from it. The parenchymal changes, clinical history and virological findings usually make the correct diagnosis clear.

While most of the infiltrating cells in acute hepatitis are small T lymphocytes,[25] plasma cells may also be prominent,[26] and there are often a few neutrophils and eosinophils. The plasma cells do not necessarily indicate autoimmune hepatitis, nor do a few eosinophils prove a diagnosis of drug injury. Kupffer cells and other macrophages accumulate and enlarge, many of them forming discrete clumps together with lymphocytes. They may contain tan-brown ceroid pigment, staining with periodic acid–Schiff (PAS) agent after diastase digestion (Fig. 6.5). They may also contain stainable iron (Fig. 6.6), but this is less common.

Sinusoidal and venular endothelial cells also take part in the hepatitic process. Sinusoidal endothelial cells become swollen and may contain dense iron-positive

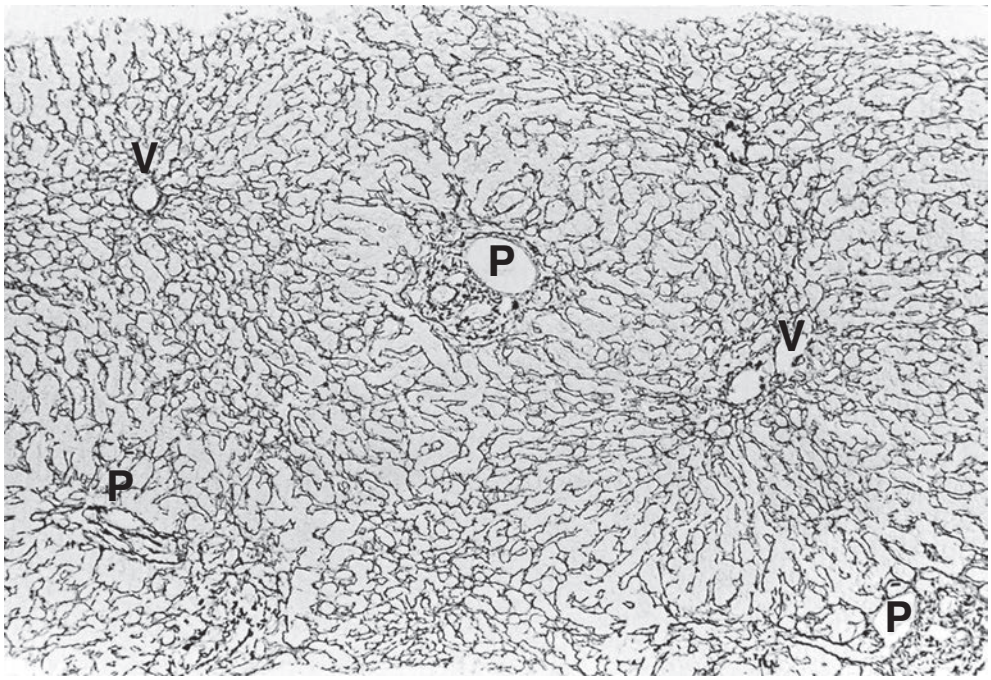

Fig. 6.4 Acute viral hepatitis. The reticulin framework is condensed near the efferent venules (V) but not immediately around the portal tracts (P). (Needle biopsy, reticulin.)

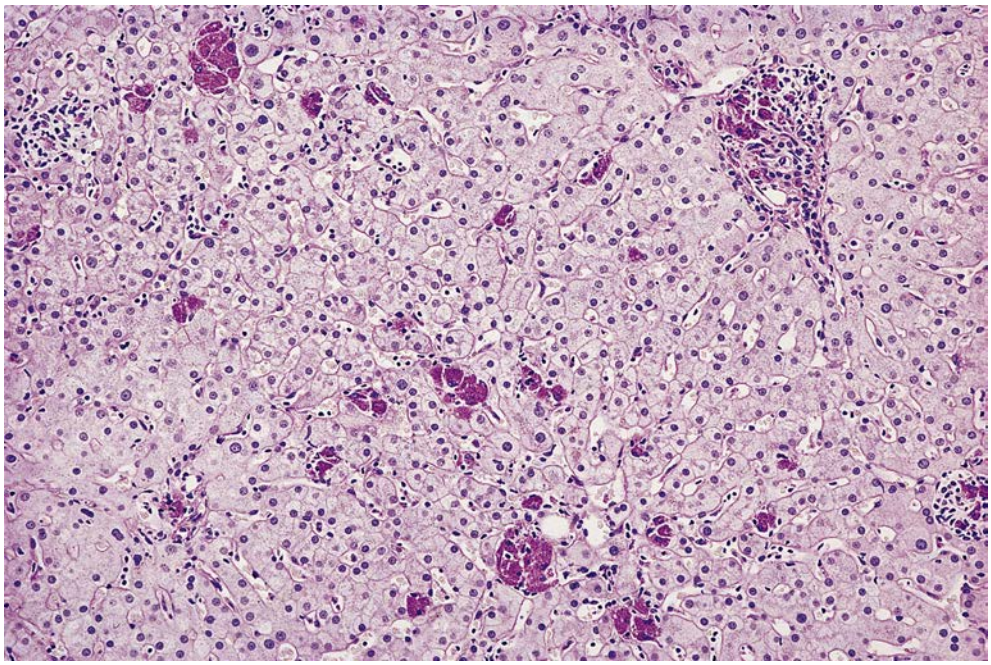

Fig. 6.5 Acute viral hepatitis. Macrophages contain diastase periodic acid–Schiff (PAS)-positive material. (Needle biopsy, diastase–PAS.)

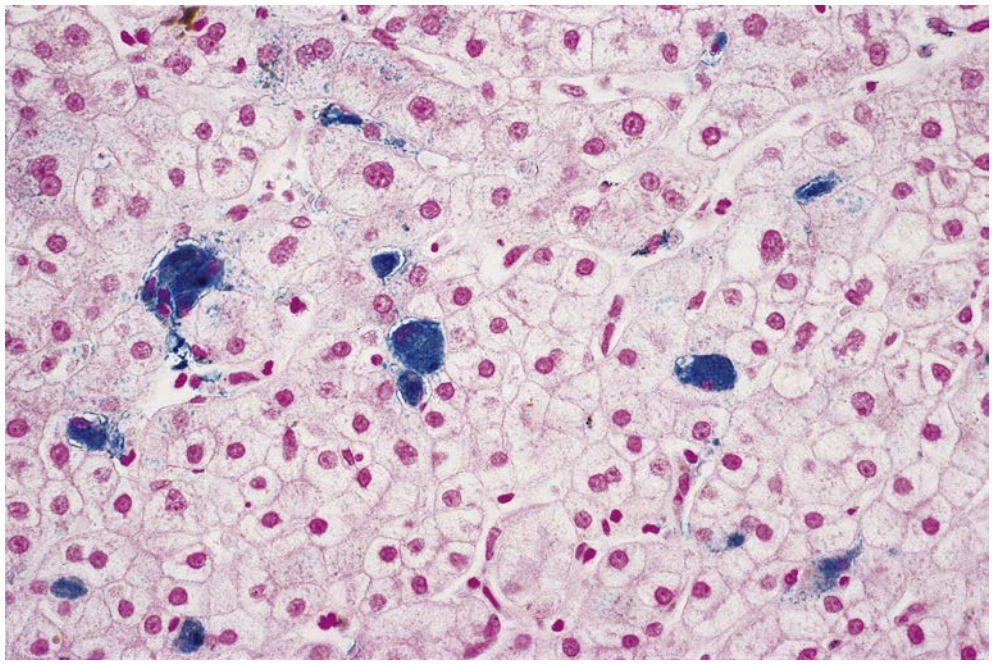

Fig. 6.6 Acute viral hepatitis. Enlarged macrophages are strongly iron positive. Some endothelial cells also contain dense Perls' stain-positive granules. (Section kindly provided by Dr Susan Davies, Cambridge, UK.) (Needle biopsy, Perls' stain.)

granules[27] (Fig. 6.6). Terminal hepatic venules may show disruption of the endothelium and lymphocytic infiltration.

Portal changes

In contrast to chronic hepatitis, the parenchymal changes dominate the picture, but there is always some portal inflammation, affecting most or all of the small portal tracts (Fig. 6.7). The density of the infiltrate varies. Interlobular bile ducts may show abnormalities, including irregularity, crowding and stratification of the epithelium, cytoplasmic vacuolation and infiltration by lymphocytes (Fig. 6.8). These changes, together with formation of dense lymphoid structures (aggregates and follicles), are most often seen in hepatitis C. Bile-duct loss (ductopenia) is very rare.

Histological variants

The histological changes in acute hepatitis are infinitely variable, but a few patterns deserve special mention. These are confluent necrosis, bridging necrosis, necrosis of entire lobules and periportal necrosis.

Confluent necrosis signifies death of a substantial area of the parenchyma. Focal as opposed to zonal areas of confluent necrosis haphazardly distributed in relation to lobular zones are more likely to be due to causes other than acute viral hepatitis; possibilities to be considered include opportunistic infections with herpes simplex or zoster viruses and lymphoma. **Bridging necrosis** (Figs 6.9 and 6.10, **and see** Fig. 4.8) is the term given to confluent necrosis linking terminal venules to portal tracts. A possible explanation for this location is that it represents the entire zone 3 of an acinus, a view supported by the curved shape of many bridges. Bridging necrosis is a manifestation of severe acute hepatitis, but its distribution even within a single biopsy may be irregular. Necrosis and inflammation linking adjacent portal tracts without involvement of terminal venules should not strictly be

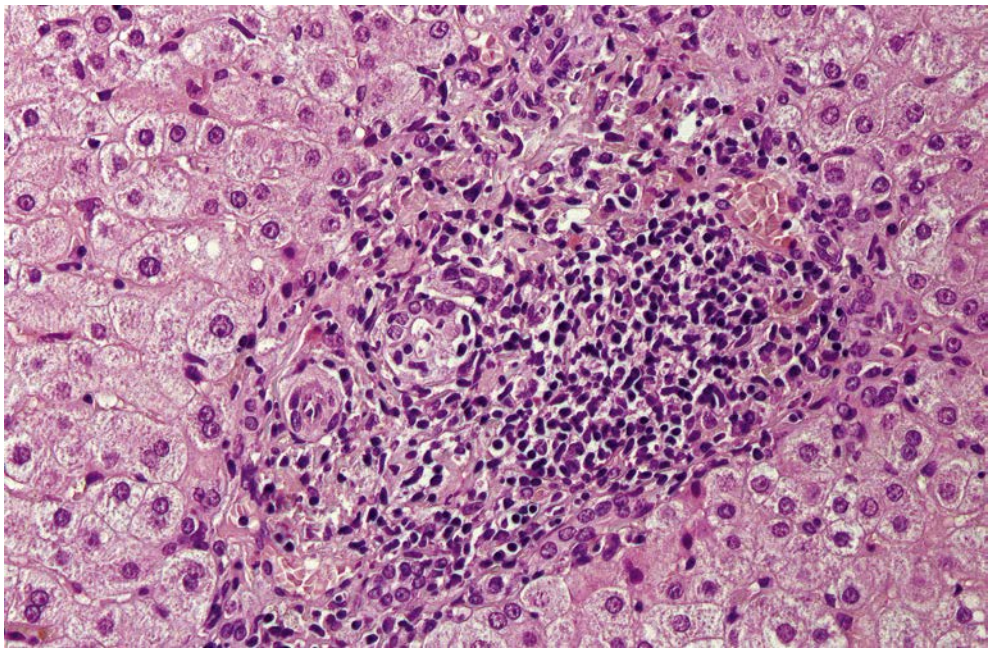

Fig. 6.7 Acute viral hepatitis. A portal tract is infiltrated by inflammatory cells, mainly lymphocytes. In places the infiltrate extends a short way into the adjacent parenchyma. (Needle biopsy, H&E.)

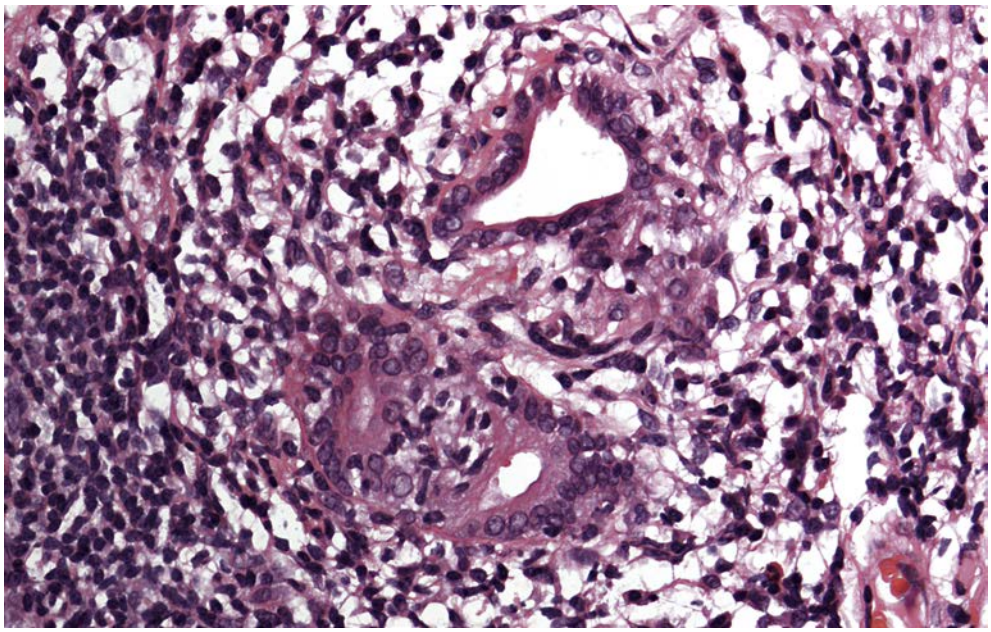

Fig. 6.8 Acute viral hepatitis. Bile-duct epithelium is irregular and infiltrated by lymphocytes. The upper duct profile shows epithelial atrophy and dilatation. (Wedge biopsy, H&E.)

called bridging because it almost certainly has different pathogenetic significance; it results from widening of portal tracts, with or without periportal necrosis.

Bridges of confluent necrosis with subsequent collapse may be mistaken for the septa of chronic liver disease. In making the important distinction between them, the pathologist is often helped by stains for elastic tissue. Unlike stains for collagens, these normally give negative results in the parenchyma, but elastic tissue accumulates as septa age.[28] Recent collapse is therefore negative (**Fig. 6.11**), whereas old septa are positive. Substantial amounts

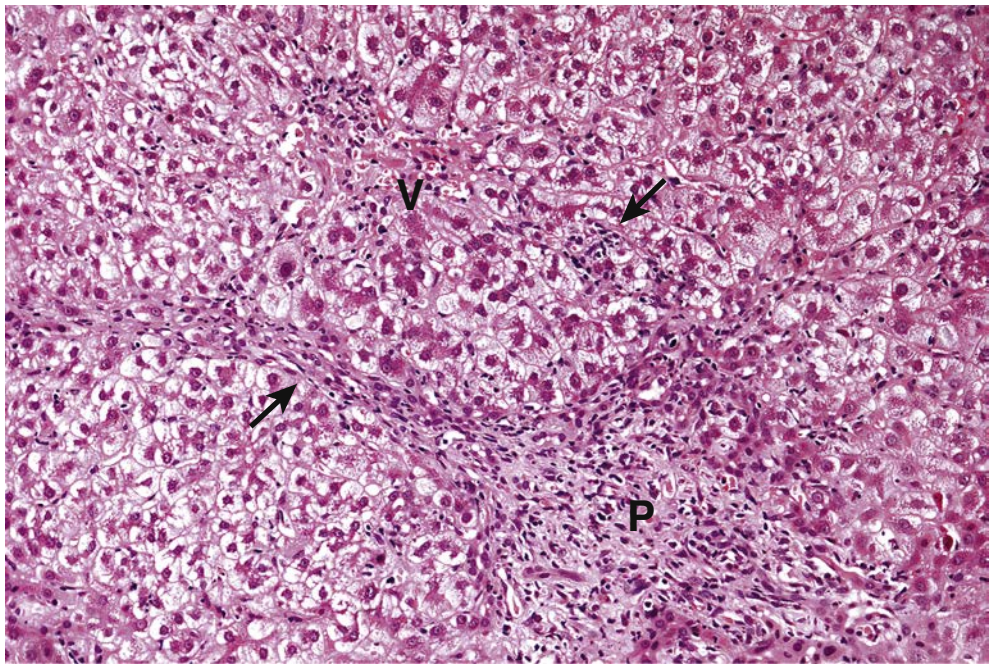

Fig. 6.9 Acute viral hepatitis: bridging necrosis. Two curved lines of collapse (arrows) extend from a portal tract (P). An efferent venule (V) is seen top centre. (Needle biopsy, H&E.)

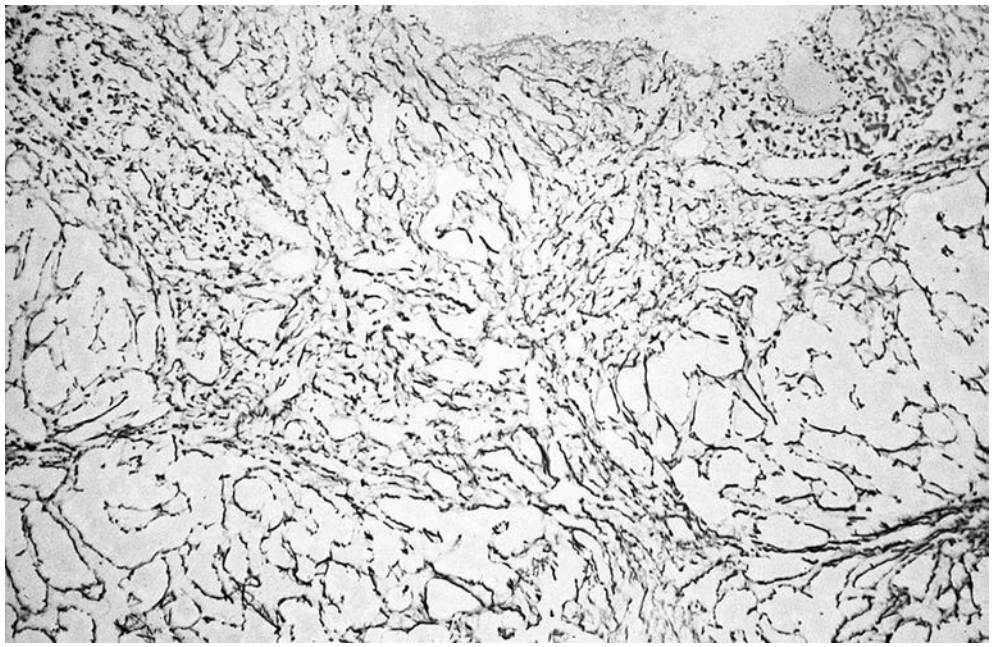

Fig. 6.10 Acute viral hepatitis: bridging necrosis. Recent collapse following confluent necrosis is seen as condensation of reticulin, mimicking fibrosis. (Needle biopsy, reticulin.)

of elastic tissue take months or years to accumulate, but small amounts can be detected by sensitive methods such as Victoria blue as early as 1 or 2 months after onset of hepatitis.[29]

In a minority of patients with acute viral hepatitis, confluent necrosis extends throughout entire lobules or acini (**panlobular** or **panacinar necrosis**) or several adjacent ones (**multilobular** or **multiacinar necrosis**). This is a common feature in patients with

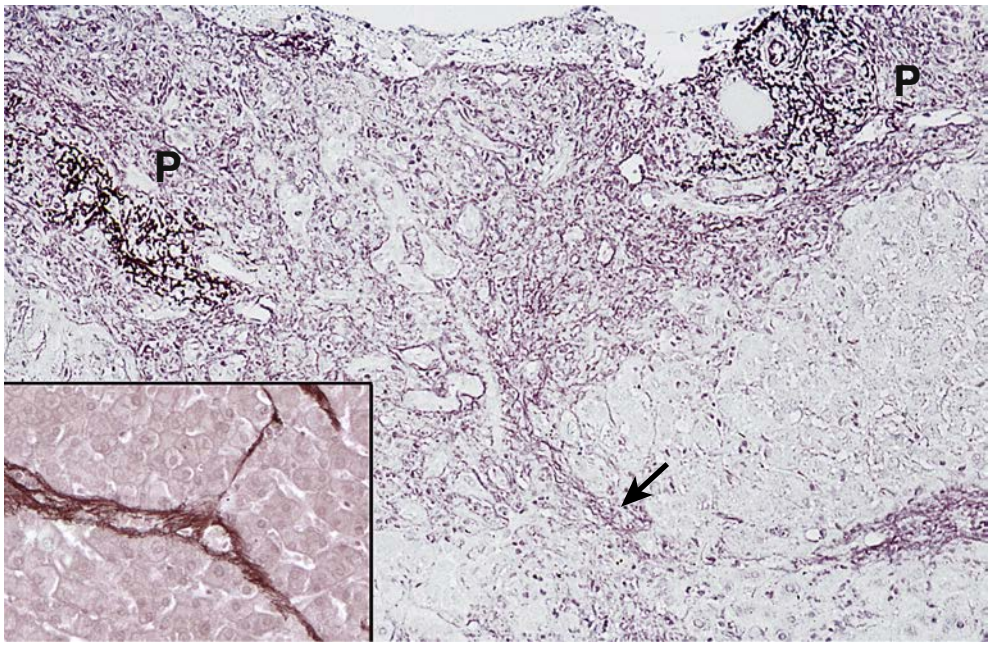

Fig. 6.11 Acute hepatitis: bridging necrosis. The field is the same as that shown in **Fig. 6.10**. A stain for elastic fibres is positive in two portal tracts (P) but not in the intervening area of collapse. A necrotic bridge (arrow) is also negative. Inset: This contrasts with an elastic fibre-rich septum in chronic liver disease. (Needle biopsy, orcein.)

fulminant hepatitis. The term 'massive necrosis' is also sometimes used, but can be misleading in so far as a needle biopsy specimen may not be representative of the liver as a whole and can lead to over- or underestimation of the true extent of liver damage.[30] This throws doubt on the usefulness of liver biopsy as a means of assessing prognosis in severe acute hepatitis. Sometimes multilobular necrosis involves only the subcapsular zone, and a small needle specimen may then give a falsely pessimistic picture (**see Fig. 1.3**). In multilobular necrosis the parenchyma is replaced by collapsed stroma, inflammatory cells and activated macrophages (**Fig. 6.12**). Around the surviving portal tracts there are prominent duct-like structures, some of which probably represent proliferation of pluripotential progenitor cells[31–33] (**see Fig. 4.13D**). 'Late-onset hepatic failure' is a term used for patients developing encephalopathy between 8 and 24 weeks after onset of symptoms.[34] Study of liver biopsies and explanted livers from these patients has shown a consistent pattern of map-like necrosis together with areas of nodular regeneration.

Periportal necrosis rather than the more usual perivenular necrosis is a feature in some patients with hepatitis A (discussed later).

Individual causes of viral hepatitis

There are more similarities than differences between hepatitis types A, B, C, D and E, but certain patterns are more common in one type than another and are described here. They do not allow the pathologist to identify the cause of the hepatitis on histological appearance alone. The picture may be confused by the presence of more than one virus, or by additional damage resulting from alcohol abuse.

Hepatitis A

Two main patterns are described, occurring separately or together.[35–37] One is a histological picture of perivenular cholestasis with little liver-cell damage or inflammation, easily

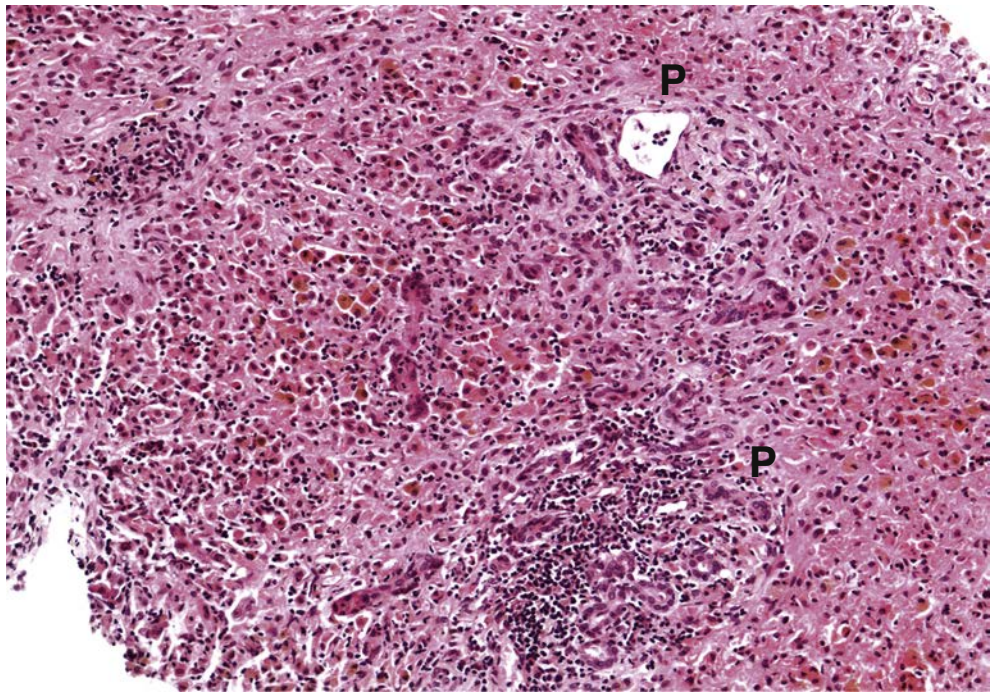

Fig. 6.12 Acute viral hepatitis: multilobular necrosis. Portal tracts (P) can be identified, but the parenchyma has been replaced by inflammatory cells, necrotic debris and duct-like structures. (Needle biopsy, H&E.)

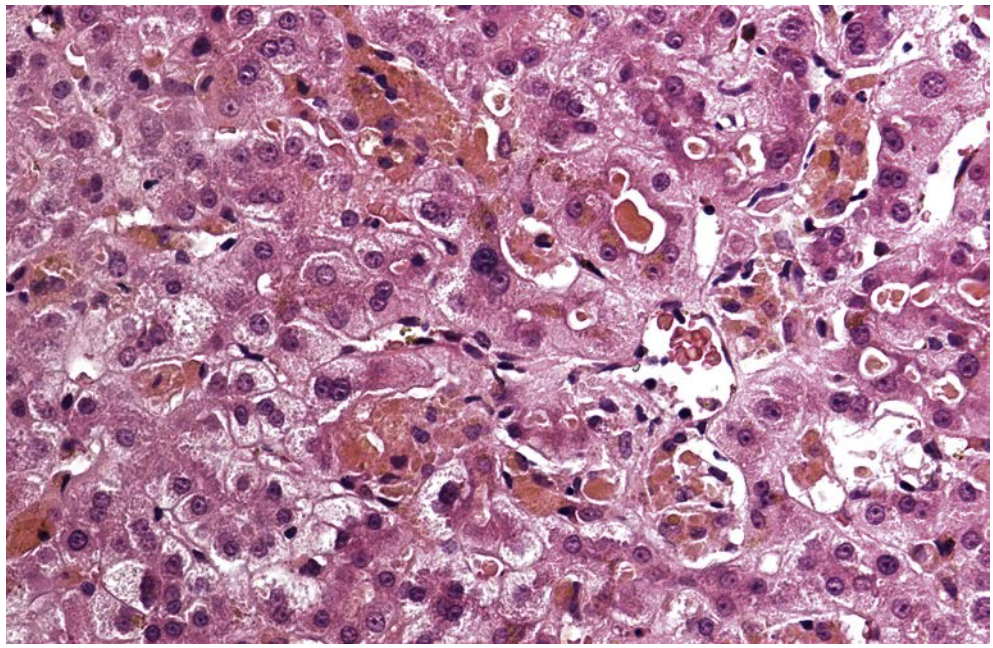

Fig. 6.13 Hepatitis A. Perivenular area showing irregularity of liver-cell plates and cholestasis but only mild inflammatory infiltration. (Needle biopsy, H&E.)

mistaken for other causes of cholestasis (Fig. 6.13). The second is a hepatitis with periportal necrosis and a dense portal infiltrate which includes abundant, often aggregated plasma cells (Fig. 6.14). These two patterns may be related, the cholestasis resulting from interruption of bile flow by the periportal necrosis.[23] Other patterns of hepatitis as described earlier are also found, but fulminant hepatitis with multilobular necrosis is rare. Extensive

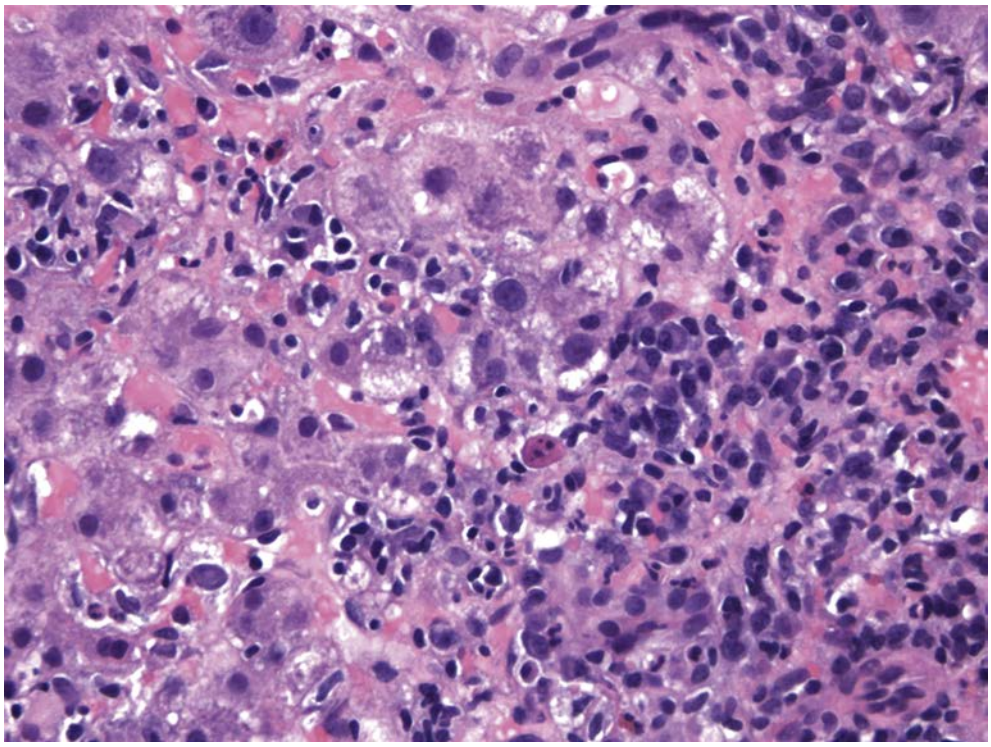

Fig. 6.14 Hepatitis A. The portal area at right is heavily infiltrated by lymphocytes and plasma cells, some of which extend into the adjacent parenchyma. The limiting plate is irregular. The picture resembles that of chronic hepatitis with interface hepatitis. (Needle biopsy, H&E.)

microvesicular change of hepatocytes, previously described in hepatitis D infection, has been seen also in severe acute hepatitis A (**Fig. 6.15**). Fibrin-ring granulomas have been reported.[38,39] A chronic course[40] is very rare.

Hepatitis B

The histological appearances are broadly similar to those of other forms of viral hepatitis. Some of the differences reported in the literature may well reflect patient selection rather than features specific for hepatitis B virus (HBV) infection. However, lymphocytes and macrophages sometimes lie in close contact with hepatocytes (peripolesis) or even invaginate them deeply (emperipolesis), which probably reflects the immunological nature of the cell damage. In a comparative study, periportal inflammation tended to be more severe in acute hepatitis B than in hepatitis C.[41] Liver cells and their nuclei may show a moderate degree of pleomorphism. In most cases of acute hepatitis, the hepatitis B core and surface antigens (HBcAg and HBsAg) are either not demonstrable or very sparse, but in one study of livers infected with an HBV mutant,[42] HBsAg could be demonstrated by immunostaining in over half of the patients and HBcAg in a minority. The presence of ground-glass hepatocytes (**Ch. 9**) or positive staining of surface material with Victoria blue or orcein indicates chronic disease. Recurrence of HBV infection after liver transplantation is an exception to this rule, both antigens being found in large amounts (**see Ch. 16**). In parenterally transmitted hepatitis, including types B and C, birefringent spicules of talc may be found in portal tracts as a result of intravenous drug abuse.[42]

Following clinical recovery of acute hepatitis B, occult infection and mild histological abnormalities including portal inflammation, focal necrosis, apoptosis and fibrosis may persist for at least a decade.[43]

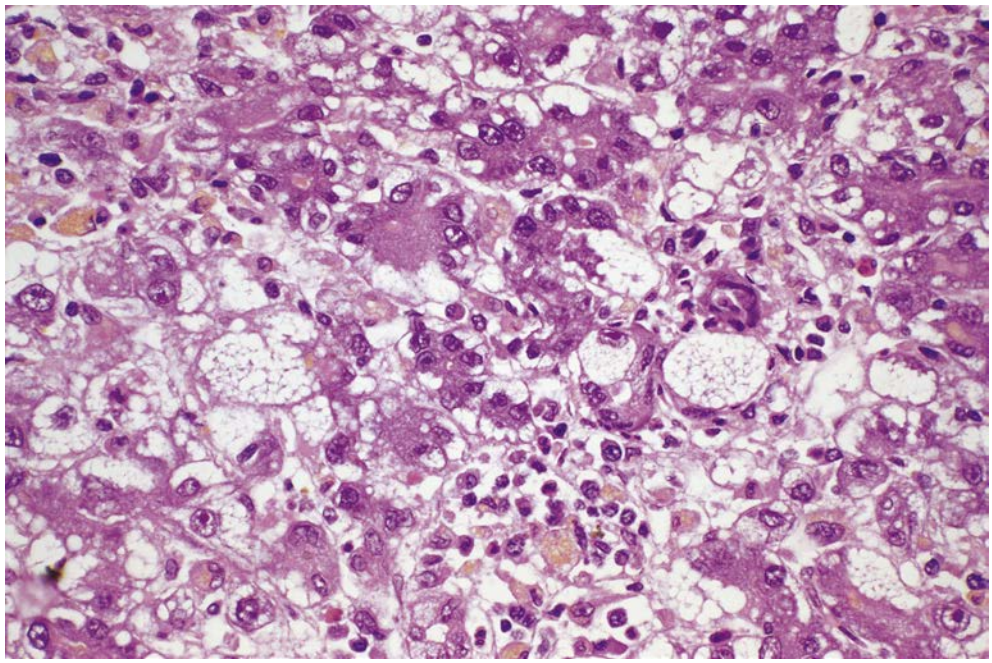

Fig. 6.15 Hepatitis A. In this patient with a clinical picture of fulminant hepatitis, hepatocytes are swollen and microvesicular. There is cholestasis and a lymphocytic infiltrate. (Needle biopsy, H&E.)

Reactivation of a previously occult or quiescent chronic hepatitis B infection may cause changes closely resembling acute hepatitis. In such instances the presence of (1) portal tract lymphoid aggregates, (2) significant lymphoplasmacytic interface hepatitis, (3) any evidence of fibrosis on connective tissue stains and (4) substantial positivity of HBsAg in hepatocytes on immunostaining points to the underlying chronicity of the process.

Hepatitis C

Usually the histological features of hepatitis C are those of any acute hepatitis, but two distinguishing features have been noted. First, there may be prominent infiltration of sinusoids by lymphocytes in the absence of severe liver-cell damage,[44] giving rise to a picture reminiscent of infectious mononucleosis (**Fig. 6.16**). Second, lymphoid follicles and bile-duct damage, features also associated with chronic hepatitis, may be seen within a few weeks or months of onset.[45] There may be cholestasis. The common finding of steatosis in hepatitis C is discussed in **Chapter 9**. Fulminant hepatitis C is very rare in the Western world,[3] but may be commoner in parts of Asia.[46]

Hepatitis D (delta hepatitis)

Co-infection or superinfection with the hepatitis D virus (HDV) alters the course of type B hepatitis. It encourages chronicity and enhances severity,[47–49] except after liver transplantation. The antigen, HDAg, can easily be demonstrated immunohistochemically in paraffin sections and is mainly found in hepatocyte nuclei (**Fig. 6.17**). These may have finely granular eosinophilic centres (so-called sanded nuclei[50]). Cytoplasmic and membrane-associated staining is also sometimes seen.

Severe acute hepatitis in a patient with markers of HBV infection may be due to superinfection by HDV of a chronic HBV carrier.[51] In an outbreak of HDV infection among Venezuelan Indians, notable features included early small-droplet fatty change, sparse lymphocytes and abundant macrophages in the parenchyma, and substantial portal

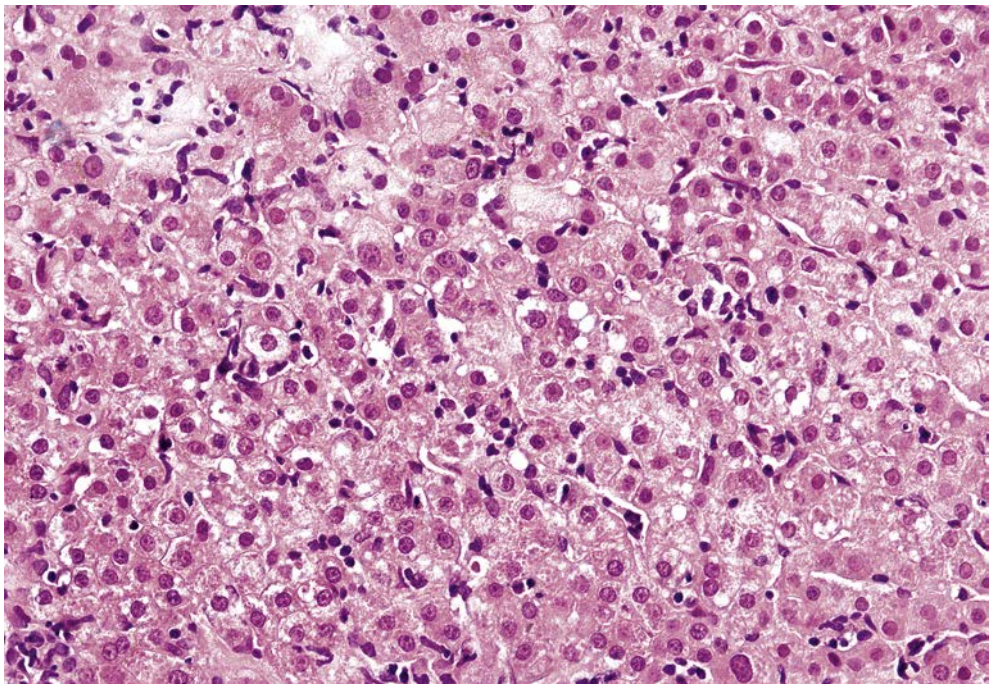

Fig. 6.16 Acute hepatitis C. In this example the main abnormality is infiltration of sinusoids by lymphocytes. (Needle biopsy, H&E.)

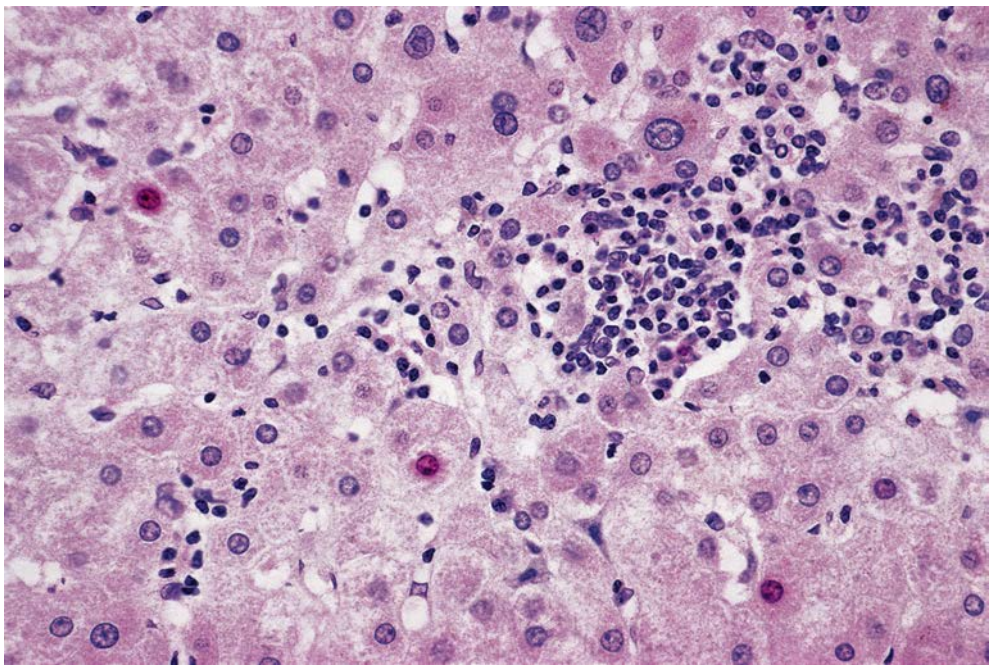

Fig. 6.17 Delta hepatitis (HDV). Some hepatocyte nuclei contain the delta antigen and are stained red. There is a substantial lymphocytic infiltrate. (Needle biopsy, specific immunostain, alkaline phosphatase method.)

infiltration.[52] Later in the attack, there was extensive necrosis and collapse. Microvesicular fatty change and acidophilic necrosis of hepatocytes have been reported from Colombia[53] and North America.[54] In non-immunosuppressed patients with current HDV infection, liver biopsy is likely to show substantial necrosis and inflammation. However, there are HDV-endemic regions where the virus produces little significant disease.[55] Following liver

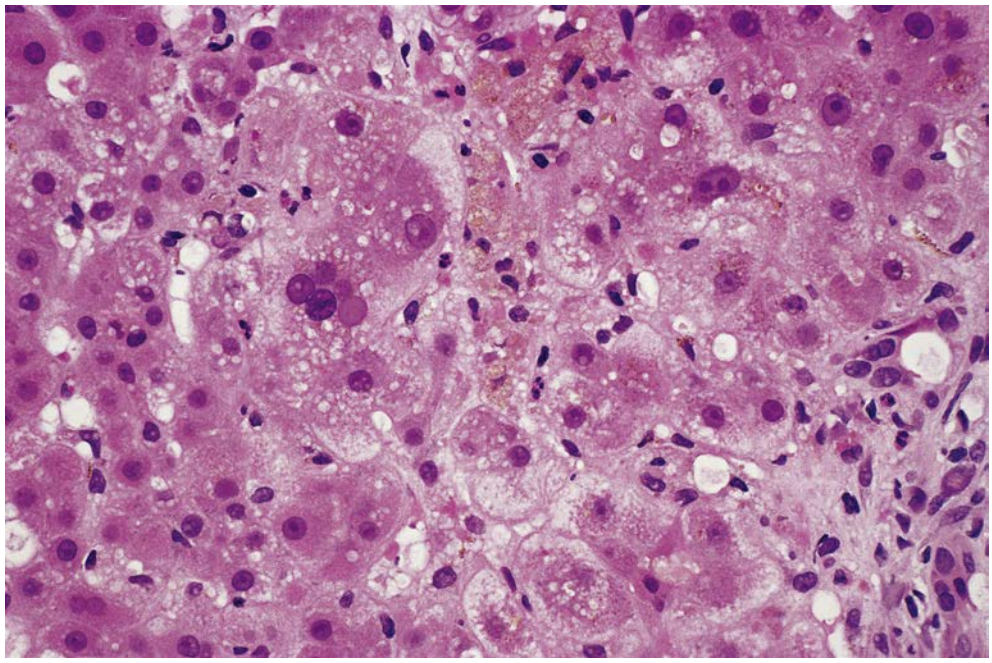

Fig. 6.18 Hepatitis E. Hepatocytes are vacuolated and one to the left of centre is greatly enlarged and multinucleated. There is a mixed infiltrate, and macrophages contain brown ceroid pigment. (Needle biopsy, H&E.)

transplantation, by contrast, HDV without HBV is sometimes demonstrable in the absence of hepatitic changes, indicating that HDV can survive in the absence of HBV. It does not then appear, however, to be capable of causing liver damage.[56]

Hepatitis E virus

Hepatitis E virus (HEV) is an RNA virus with eight currently described genotypes, five of which can infect humans (genotypes 1, 2, 3, 4, and 7).[57,58a] Genotypes 1 and 2 are restricted to higher primates and humans and are associated with epidemic outbreaks and an oral-faecal transmission mode, while genotypes 3-8 show a broad mammalian phylogenetic reservoir including pigs, boar, deer, rodents, ferrets, bats, cattle, sheep, foxes, dromedary camels and horses and cause zoonotic, autochthonous (i.e., acquired regionally) infections, typically through poorly or undercooked meat.[58b,58c] HEV has caused epidemics in Asia and has also been found in Africa, North and South America and Europe. Infections with genotypes 1 and 2 resulted in an estimated >3 million symptomatic cases and 70,000 fatalities in endemic regions in 2005.[59a,59b] Autochthonous HEV infections, among which genotype 3 is the most common, have caused acute hepatitis in North America and Europe[57,60] but sometimes is misdiagnosed as drug-induced liver injury.[61a,61b,61c] Chronic hepatitis E has been described in organ transplant recipients and other immunosuppressed individuals.[62,63a,63b]

Information about the pathology of HEV infection in humans is emerging,[58a,61a,63c] although many of the histological features are similar to those seen in other types of viral hepatitis or in autoimmune or drug-induced hepatitis.[58a,61a] The morphology depends on the HEV viral genotype and on the clinicopathological setting[58a,63a-67] (see Box 6.1). Foci of lobular necroinflammation with intrasinusoidal pigmented, ceroid-laden Kupffer cells are prominent in the acute infection (**Fig. 6.18**).[58a] *Epidemic (genotype 1 or 2) hepatitis E* is well known for its potential for severe hepatic disease, acute liver failure and massive hepatic necrosis, but some cases have shown prolonged clinical cholestasis with bile canalicular cholestasis and cholestatic rosettes on biopsy. The changes may resemble those of hepatitis A, with prominent cholestasis

Box 6.1 Major clinicopathological settings of HEV infection

- Acute, epidemic (genotype 1 or 2) hepatitis E
- Acute autochthonous (genotype 3 or 4-7) hepatitis E
- Acute hepatitis E superimposed on pre-existing chronic liver disease (acute-on-chronic liver disease)
- Acute or chronic hepatitis E in immunocompromised host (e.g., organ transplant recipients; chemotherapy administration; HIV positivity)
- Chronic hepatitis E

and a predominantly portal and periportal inflammatory infiltrate.[68] In one study, a pregnant woman with fatal epidemic hepatitis E the liver showed little portal inflammation, much cholestasis with prominent portal vein and central vein endotheliitis and viral particles were identified in bile ductules by electron microscopy.[69] *Cases of autochthonous hepatitis E (usually genotype 3)* have shown portal lymphoid aggregates and periportal ductular reaction with neutrophilia at the edges of portal tracts.[60] In immunocompromised subjects with organ transplants, immundeficiencies or corticosteroid therapy, *chronic hepatitis E* manifests with the classical features of chronic hepatitis (i.e., interface hepatitis with variable lobular necroinflammation), but portal tract neutrophilia with bile duct damage, or even destruction, may be prominent.[70]

Detection of HEV infection in liver tissue can be accomplished by polymerase chain reaction (PCR) assessment for HEV RNA, or by immunohistochemistry for open reading frames (ORFs) 1-3 (especially ORF 2) and by in situ hybridization for HEV RNA.[71,72] Recent efforts to produce a vaccine have shown promise, but the only existing vaccine (vaccine 239) is currently only licensed in China.[73-76]

Differential diagnosis of acute viral hepatitis

The distinction of acute hepatitis from bile-duct obstruction rests mainly on the finding of typical hepatitic changes in the parenchyma. The portal tract oedema of duct obstruction is absent. Drug-related hepatitis may be indistinguishable from viral hepatitis and should always be suspected if the cause of the hepatitis is in doubt. Features more common in drug-induced than in viral hepatitis include sharply defined perivenular necrosis, granulomas, bile-duct damage, abundant neutrophils or eosinophils and a poorly developed portal inflammatory reaction. Cholestasis may overshadow the hepatitic features. Autoimmune hepatitis may have a clinically acute onset, histologically indistinguishable from viral hepatitis or alternatively with histological features of chronic disease. This is discussed more fully in **Chapter 9**. In steatohepatitis there is usually conspicuous fatty change. Mallory bodies may be present in ballooned hepatocytes, and the infiltrate typically includes neutrophils. The key to the diagnosis is the presence of pericellular fibrosis in affected areas. The differentiation of acute from chronic hepatitis is briefly discussed under bridging necrosis in **Chapter 4**. While the parenchymal changes predominate in acute hepatitis, especially in perivenular areas, portal and periportal changes predominate in chronic disease. The distinction is sometimes difficult to make, especially when extensive lobular changes are found during an exacerbation of chronic hepatitis or in reactivated chronic hepatitis B, as described earlier.

Fate and morphological sequelae of acute viral hepatitis

Resolution

As far as can be deduced from the available evidence, most examples of hepatitis A, B and E are followed by complete or near-complete resolution and a return of the liver to normal.

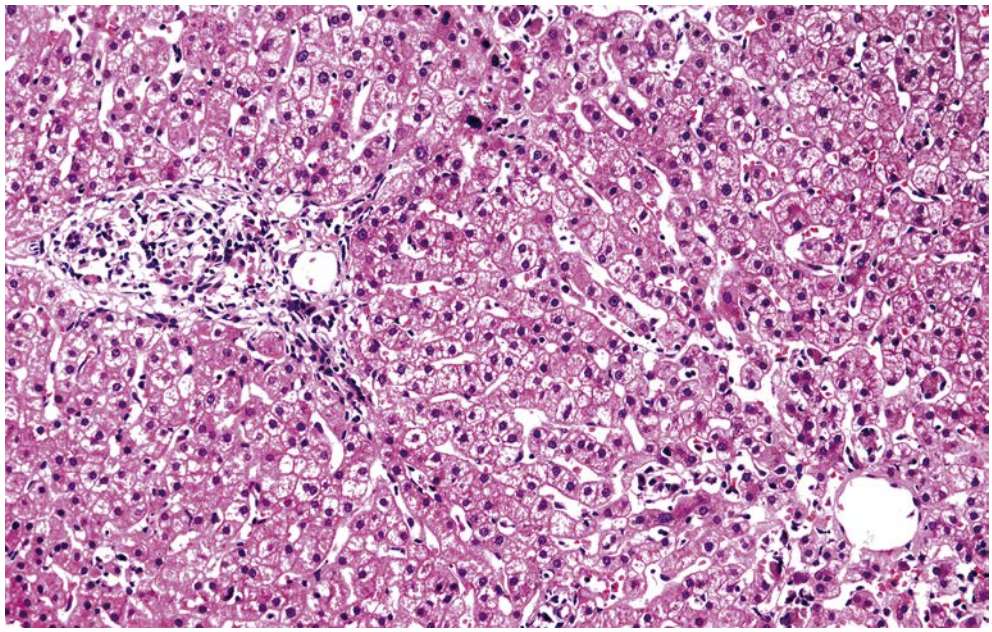

Fig. 6.19 Acute viral hepatitis: residual changes. Short septa extend from the mildly inflamed portal tract to the left. Minimal inflammation and irregular liver-cell plates are seen around the efferent venule below right. (Needle biopsy, H&E.)

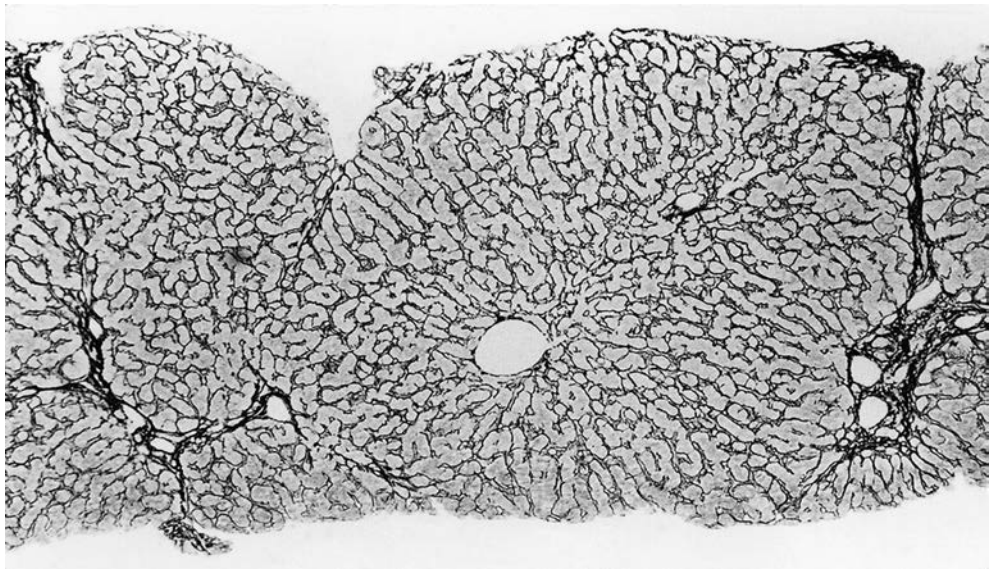

Fig. 6.20 Acute viral hepatitis: residual changes. Slender septa link portal tracts (left and right), but the perivenular area (centre) is unaffected and architectural relationships are preserved. (Needle biopsy, reticulin.)

A chronic course is probably more common when hepatitis B is complicated by delta infection than otherwise, and in hepatitis C the risk of chronicity is high. Even in patients whose hepatitis resolves, some residual changes may persist for many months after clinical recovery (Figs. 6.19 and 6.20).

Scarring

Localised collapse, scarring and regeneration following severe hepatitis with bridging or panlobular necrosis sometimes produce a histological picture indistinguishable from cirrhosis.

Fatal outcome or need for liver transplantation

Necrosis is usually severe. Regenerative hyperplasia of surviving hepatocytes or progenitor cells may be seen.

Chronic hepatitis

In regions where HBV vaccine programs have not been instituted, many individuals will develop chronic hepatitis B. The availability of direct-acting antiviral agents to treat acute hepatitis C virus infections is likely to dramatically reduce the prevalence of chronic hepatitis C in the future.

Cirrhosis

Cirrhosis resulting from infection with a hepatitis virus almost always follows a period of chronic hepatitis, with repeated or continuous hepatocellular necrosis and regeneration. Occasionally it may follow directly after a single episode of severe acute hepatitis where it is termed 'postnecrotic cirrhosis'.

Hepatocellular carcinoma

This may develop on the basis of cirrhosis in patients infected with HBV or hepatitis C virus. Occasionally, however, hepatocellular carcinoma is found in the absence of cirrhosis, usually after a prolonged period of chronic liver disease[76] (although the risk appears to be even greater in non-cirrhotic patients with non-alcoholic steatohepatitis).[77,78]

References

1. Ben-Ari Z, Samuel D, Zemel R, et al. Fulminant non-A-G viral hepatitis leading to liver transplantation. *Arch Intern Med*. 2000;160:388–392.
2. Petrovic LM, Arkadopoulos N, Demetriou AA. Activation of hepatic stellate cells in liver tissue of patients with fulminant liver failure after treatment with bioartificial liver. *Hum Pathol*. 2001;32:1371–1375.
3. Schiødt FV, Davern TJ, Shakil AO, et al. Viral hepatitis-related acute liver failure. *Am J Gastroenterol*. 2003;98:448–453.
4. Kirsch R, Yap J, Roberts EA, et al. Clinicopathologic spectrum of massive and submassive hepatic necrosis in infants and children. *Hum Pathol*. 2009;40:516–526.
5. Peters DJ, Greene WH, Ruggiero F, et al. Herpes simplex-induced fulminant hepatitis in adults: a call for empiric therapy. *Dig Dis Sci*. 2000;45:2399–2404.
6. Pinna AD, Rakela J, Demetris AJ, et al. Five cases of fulminant hepatitis due to herpes simplex virus in adults. *Dig Dis Sci*. 2002;47:750–754.
7. Collin L, Moulin P, Jungers M, et al. Epstein–Barr virus (EBV)-induced liver failure in the absence of extensive liver-cell necrosis: a case for cytokine-induced liver dysfunction? *J Hepatol*. 2004;41:174–175.
8. Wang WH, Wang HL. Fulminant adenovirus hepatitis following bone marrow transplantation. A case report and brief review of the literature. *Arch Pathol Lab Med*. 2003;127:e246–e248.
9. Longerich T, Haferkamp K, Tox U, et al. Acute liver failure in a renal transplant patient caused by adenoviral hepatitis superimposed on a fibrosing cholestatic hepatitis B. *Hum Pathol*. 2004;35:894–897.
10. Chau TN, Lee KC, Yao H, et al. SARS-associated viral hepatitis caused by a novel coronavirus: report of three cases. *Hepatology*. 2004;39:302–310.
11. Ng W-F, To K-F, Lam WWL, et al. The comparative pathology of severe acute respiratory syndrome and avian influenza A subtype H5N1: a review. *Hum Pathol*. 2006;37:381–390.
12. Polakos NK, Cornejo JC, Murray DA, et al. Kupfer cell-dependent hepatitis occurs during influenza infection. *Am J Pathol*. 2006;168:1169–1178.
13. Adams DH, Hubscher SG. Systemic viral infections and collateral damage in the liver. *Am J Pathol*. 2006;168:1057–1059.
14. Lau JYN, Xie X, Lai MMC, et al. Apoptosis and viral hepatitis. *Semin Liver Dis*. 1998;18:169–176.
15. Klotz O, Belt TH. The pathology of the liver in yellow fever. *Am J Pathol*. 1930;6:663–689.
16. Dias Jr LB, Alves VAF, Kanamura C, et al. Fulminant hepatic failure in northern Brazil: morphological, immunohistochemical and pathogenic aspects of Lábrea hepatitis and yellow fever. *Trans Roy Soc Trop Med Hyg*. 2007;101:831–839.
17. Phillips MJ, Blendis LM, Poucell S, et al. Syncytial giant-cell hepatitis. Sporadic hepatitis with distinctive pathological features, a severe clinical course and paramyxoviral features. *N Engl J Med*. 1991;324:455–460.

18. Fimmel CJ, Guo L, Compans RW, et al. A case of syncytial giant cell hepatitis with features of a paramyxoviral infection. *Am J Gastroenterol*. 1998;93:1931–1937.
19. Devaney K, Goodman ZD, Ishak KG. Postinfantile giant-cell transformation in hepatitis. *Hepatology*. 1992;16:327–333.
20. Lau JYN, Koukoulis G, Mieli-Vergani G, et al. Syncytial giant-cell hepatitis – a specific disease entity? *J Hepatol*. 1992;15:216–219.
21. Protzer U, Dienes HP, Bianchi L, et al. Post-infantile giant cell hepatitis in patients with primary sclerosing cholangitis and autoimmune hepatitis. *Liver*. 1996;16:274–282.
22. Ben-Ari Z, Broida E, Monselise Y, et al. Syncytial giant-cell hepatitis due to autoimmune hepatitis type II (LKM1+) presenting as subfulminant hepatitis. *Am J Gastroenterol*. 2000;95:799–801.
23. Micchelli STL, Thomas D, Boitnott JK, et al. Hepatic giant cells in hepatitis C virus (HCV) mono-infection and HCV/HIV co-infection. *J Clin Pathol*. 2008;61:1058–1061.
24. Sciot R, Van Damme B, Desmet VJ. Cholestatic features in hepatitis A. *J Hepatol*. 1986;3:172–181.
25. Volpes R, van den Oord JJ, Desmet VJ. Memory T cells represent the predominant lymphocyte subset in acute and chronic liver inflammation. *Hepatology*. 1991;13:826–829.
26. Mietkiewski JM, Scheuer PJ. Immunoglobulin-containing plasma cells in acute hepatitis. *Liver*. 1985;5:84–88.
27. Bardadin KA, Scheuer PJ. Endothelial cell changes in acute hepatitis. A light and electron microscopic study. *J Pathol*. 1984;144:213–220.
28. Scheuer PJ, Maggi G. Hepatic fibrosis and collapse: histological distinction by orcein staining. *Histopathology*. 1980;4:487–490.
29. Thung SN, Gerber MA. The formation of elastic fibers in livers with massive hepatic necrosis. *Arch Pathol Lab Med*. 1982;106:468–469.
30. Hanau C, Munoz SJ, Rubin R. Histopathological heterogeneity in fulminant hepatic failure. *Hepatology*. 1995;21:345–351.
31. Demetris AJ, Seaberg EC, Wennerberg A, et al. Ductular reaction after submassive necrosis in humans. Special emphasis on analysis of ductular hepatocytes. *Am J Pathol*. 1996;149:439–448.
32. Roskams T, De Vos R, van Eyken P, et al. Hepatic OV-6 expression in human liver disease and rat experiments: evidence for hepatic progenitor cells in man. *J Hepatol*. 1998;29:455–463.
33. Zhang L, Theise N, Chua M, et al. The stem cell niche of human livers: symmetry between development and regeneration. *Hepatology*. 2008;48:1598–1607.
34. Ellis AJ, Saleh M, Smith H, et al. Late-onset hepatic failure: clinical features, serology and outcome following transplantation. *J Hepatol*. 1995;23:363–372.
35. Teixeira Jr MR, Weller IVD, Murray AM, et al. The pathology of hepatitis A in man. *Liver*. 1982;2:53–60.
36. Abe H, Beninger PR, Ikejiri N, et al. Light microscopic findings of liver biopsy specimens from patients with hepatitis type A and comparison with type B. *Gastroenterology*. 1982;82:938–947.
37. Okuno T, Sano A, Deguchi T, et al. Pathology of acute hepatitis A in humans. Comparison with acute hepatitis B. *Am J Clin Pathol*. 1984;81:162–169.
38. Ponz E, Garcia-Pagan JC, Bruguera M, et al. Hepatic fibrin-ring granulomas in a patient with hepatitis A. *Gastroenterology*. 1991;100:268–270.
39. Ruel M, Sevestre H, Henry-Biabaud E, et al. Fibrin ring granulomas in hepatitis A. *Dig Dis Sci*. 1992;37:1915–1917.
40. Inoue K, Yoshiba M, Yotsuyanagi H, et al. Chronic hepatitis A with persistent viral replication. *J Med Virol*. 1996;50:322–324.
41. Chu CW, Hwang SJ, Luo JC, et al. Comparison of clinical, virologic and pathologic features in patients with acute hepatitis B and C. *J Gastroenterol Hepatol*. 2001;16:209–214.
42. Uchida T, Shimojima S, Gotoh K, et al. Pathology of livers infected with 'silent' hepatitis B virus mutant. *Liver*. 1994;14:251–256.
43. Yuki N, Nagaoka T, Yamashiro M, et al. Long-term histologic and virologic outcomes of acute self-limited hepatitis B. *Hepatology*. 2003;37:1172–1179.
44. Bamber M, Murray A, Arborgh BA, et al. Short incubation non-A, non-B hepatitis transmitted by factor VIII concentrates in patients with congenital coagulation disorders. *Gut*. 1981;22:854–859.
45. Kobayashi K, Hashimoto E, Ludwig J, et al. Liver biopsy features of acute hepatitis C compared with hepatitis A, B and non-A, non-B, non-C. *Liver*. 1993;13:69–73.
46. Chu CM, Sheen IS, Liaw YF. The role of hepatitis C virus in fulminant viral hepatitis in an area with endemic hepatitis A and B. *Gastroenterology*. 1994;107:189–195.
47. Govindarajan S, De-Cock KM, Redeker AG. Natural course of delta superinfection in chronic hepatitis B virus-infected patients: histopathologic study with multiple liver biopsies. *Hepatology*. 1986;6:640–644.
48. Verme G, Amoroso P, Lettieri G, et al. A histological study of hepatitis delta virus liver disease. *Hepatology*. 1986;6:1303–1307.
49. Lin H-H, Liaw Y-F, Chen T-J, et al. Natural course of patients with chronic type B hepatitis following acute hepatitis delta virus superinfection. *Liver*. 1989;9:129–134.
50. Moreno A, Ramón Y, Cahal S, et al. Sanded nuclei in delta patients. *Liver*. 1989;9:367–371.
51. Smedile A, Farci P, Verme G, et al. Influence of delta infection on severity of hepatitis B. *Lancet*. 1982;ii:945–947.
52. Popper H, Thung SN, Gerber MA, et al. Histologic studies of severe delta agent infection in Venezuelan Indians. *Hepatology*. 1983;3:906–912.
53. Buitrago B, Popper H, Hadler SC, et al. Specific histologic features of Santa Marta hepatitis: a severe form of hepatitis delta-virus infection in Northern South America. *Hepatology*. 1986;6:1285–1291.
54. Lefkowitch JH, Goldstein H, Yatto R, et al. Cytopathic liver injury in acute delta virus hepatitis. *Gastroenterology*. 1987;92:1262–1266.
55. Rizzetto M. Hepatitis D: thirty years after. *J Hepatol*. 2009;50:1043–1050.
56. Davies SE, Lau JYN, O'Grady JG, et al. Evidence that hepatitis D virus needs hepatitis B virus to cause hepatocellular damage. *Am J Clin Pathol*. 1992;98: 554–558.
57. Nimgoonkar I, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. *Nat Rev Gastroenterol Hepatol*. 2018;15:96–110.

58a. Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. *J Hepatol*. 2008;48:494–503.

58b. Woo PCY, Lau SKP, Teng JLL, et al. New hepatitis E virus genotype in camels, the Middle East. *Emerg Inf Dis*. 2014;20:1044–1048.

58c. Kenney SP. The current host range of hepatitis E viruses. *Viruses*. 2019;11(5):452. https://doi:10.3390/v11050452.

59a. Rein DB, Stevens GA, Theaker J, et al. The global burden of hepatitis E virus genotypes 1 and 2 in 2005. *Hepatology*. 2012;55:988–997.
59b. Hakim M, Wang W, Bramer WM, et al. The global burden of hepatitis E outbreaks: a systematic review. *Liver Int*. 2017;37:19–31.
60. Malcolm P, Dalton H, Hussaini HS, et al. The histology of acute autochthonous hepatitis E virus infection. *Histopathology*. 2007;51:190–194.
61a. Chen EY, Baum K, Collins W, et al. Hepatitis E masquerading as drug-induced liver injury. *Hepatology*. 2012;56:2420–2423.
61b. Davern TJ, Chalasani N, Fontana RJ, et al. Acute hepatitis E infection accounts for some cases of suspected drug-induced liver injury. *Gastroenterology*. 2011;141:1665–1672.
61c. Memon A, Miranda J. Hepatitis E virus infection in a patient with suspected drug-induced liver injury. *BMJ Case Rep*. 2017. https://doi.org/10.1136/bcr-2016-218387.
62. Lenggenhager D, Weber A. Hepatitis E virus and the liver: clinical settings and liver pathology. *Gastroenterol Clin N Am*. 2017;46:393–408.
63a. Hamid SS, Atiq M, Shehzad F, et al. Hepatitis E virus superinfection in patients with chronic liver disease. *Hepatology*. 2002;36:474–478.
63b. Lee G-H, Tan B-H, Chi-Yuan E, et al. Chronic infection with camelid hepatitis E virus in a liver transplant recipient who regularly consumes camel meat and milk. *Gastroenterology*. 2016;150:355–357.
63c. Lenggenhager D, Weber A. Clinicopathologic features and pathologic diagnosis of hepatitis E. *Hum Pathol*. https://doi:10.1016/j.humpath.2019.10.003.
64. Ramachandran J, Eapen CE, Kang G, et al. Hepatitis E superinfection produces severe decompensation in patients with chronic liver disease. *J Gastroenterol Hepatol*. 2004;19:134–138.
65. Kamar N, Selves J, Mansuy J-M, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. *N Engl J Med*. 2008;358:811–817.
66. Kamar N, Mansuy J-M, Cointault O, et al. Hepatitis E virus-related cirrhosis in kidney- and kidney–pancreas-transplant recipients. *Am J Transplant*. 2008;8:1744–1748.
67. Aggarwal R. Hepatitis E: does it cause chronic hepatitis? *Hepatology*. 2008;48:1328–1330.
68. Dienes HP, Hütteroth T, Bianchi L, et al. Hepatitis A-like non-A, non-B hepatitis: light and electron microscopic observations of three cases. *Virchows Arch A Pathol Anat Histopathol*. 1986;409:657–667.
69. Asher LVS, Innis BL, Shrestha MP, et al. Virus-like particles in the liver of a patient with fulminant hepatitis and antibody to hepatitis E virus. *J Med Virol*. 1990;31:229–233.
70. Beer A, Holzmann H, Pischke S, et al. Chronic hepatitis E is associated with cholangitis. *Liver Int*. 2019;39:1876–1883.
71. Lenggenhager D, Gouttenoire J, Malehmir M, et al. Visualization of hepatitis E virus RNA and proteins in the human liver. *J Hepatol*. 2017;67:471–479.
72. Prost S, Crossan CL, Dalton HR, et al. Detection of viral hepatitis E in clinical liver biopsies. *Histopathology*. 2017;71:580–590.
73. Innis BL, Lynch JA. Immunization against hepatitis E. *Cold Spring Harb Perspect Med* 2018;8(11). https://doi:10.1101/cshperspect.a032573.
74. Li Y, Huang X, Zhang Z, et al. Prophylactic hepatitis E vaccines: antigenic analysis and serological evaluation. *Viruses*. 2020;12:109. https://doi.org/10.3390/v12010109.
75. Melgaço JG, Gardinalli NR, Motta de Mello, Leal M, Lewis-Ximenez LL, Pinto MA. Hepatitis E: update on prevention and control. *Biomed Res Int*. 2018:5769201.
76. Desai A, Sandhu S, Lai J-P, Sandhu DS. Hepatocellular carcinoma in non-cirrhotic liver: a comprehensive review. *World J Hepatol*. 2019;11:1–18.
77. Boyle M, Anstee QM. Editorial: hepatocellular carcinoma in non-cirrhotic NASH—a troubling reality. *Aliment Pharmacol Ther*. 2018;48:1021–1023.
78. Stine JG, Wentworth BJ, Zimmet A, et al. Systemic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. *Aliment Pharmacol Ther*. 2018;48:696–703.

General reading

Kim BY, Kim WR. Epidemiology of hepatitis B virus infection in the United States. *Clin Liver Dis*. 2018; 12:1–3.
Lenggenhager D, Weber A. Hepatitis E virus and the liver: clinical settings and liver pathology. *Gastroenterol Clin N Am*. 2017;46:393–408.
Morozov VA, Lagaye S. Hepatitis C virus: morphogenesis, infection and therapy. *World J Hepatol*. 2018;10: 186–212.
Nimgaonkar I, Ding Q, Schwartz RE, Ploss A. Hepatitis E virus: advances and challenges. *Nat Rev Gastroenterol Hepatol*. 2018;15:96-110.
Schmid R. History of viral hepatitis: a tale of dogmas and misinterpretations. *J Gastroenterol Hepatol*. 2001;16:718–722.
Theise ND, Bodenheimer Jr HC, Guido M. Viral hepatitis. In: Burt AD, Ferrell LD, Hűbscher SG, eds. *MacSween's Pathology of the Liver*. 7th ed. Philadelphia, PA: Elsevier; 2018:372–415.