DISEASES OF THE LIVER AND BILIARY SYSTEM

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16 · Virus Hepatitis

The first reference to epidemic jaundice has been ascribed to Hippocrates. The earliest record in Western Europe is in a letter written in 751 AD by Pope Zacharias to St Boniface, Archbishop of Mainz. Since then there have been numerous accounts of epidemics, particularly during wars. Hepatitis was a problem in the Franco–Prussian War, the American Civil War and World War I. In World War II huge epidemics occurred, particularly in the Middle East and Italy [144].

There are three main varieties [137]. Hepatitis A is a self-limited, faecal-spread disease. Hepatitis B is a parenterally transmitted disease that often becomes chronic. Non-A, non-B hepatitis is ill-defined. It contains many types, some faecally, others parenterally transmitted. It has a high chronicity rate.

Hepatic pathology

The basic pathology of virus A, B and non-A, non-B hepatitis is virtually identical [32, 59].

The essential lesion is an acute inflammation of the entire liver [32]. Hepatic cell necrosis is associated with leucocytic and histiocytic reaction and infiltration. Zone 3 shows the necrosis most markedly and the portal tracts the greatest cellularity (figs 16.1, 16.2 16.3). The sinusoids show cellular infiltration, polymorphs and eosinophils. Surviving liver cells retain their glycogen. Fatty change is rare. Zone 3 liver cells may show eosinophilic change (*acidophil bodies*), ballooning pleomorphism and hyalinization, and giant multi-nucleated cells may be present. Mitoses are sometimes prominent. Zone 3 cholestasis may be found. Focal 'spotty' necrosis may be seen. Bile duct proliferation is usual and damage is an occasional feature [98]. Hepatitis is found even before the development of jaundice.

The reticulin framework is usually well preserved even in the midst of extreme disorganization. This framework provides a scaffolding when the liver cells regenerate. Inflammatory cells disappear gradually from the portal zones, and some new portal connective tissue can often be found for many months (fig. 16.4). During recovery reticulo-endothelial activity increases throughout, apparently a 'scavenger' phenomenon. A slight increase in stainable fat is seen. The Kupffer cells contain lipofusein pigment and iron.

Occasionally the necrosis may be *confluent* (sub-massive), affecting substantial groups of adjacent liver cells, usually zone 3.

In massive fulminant necrosis the whole acinus is involved. Macroscopically the liver is reduced in size, being smallest in those who die the soonest. It is flaccid and shrunken and the left lobe may be disproportionately atrophied. Nodular regeneration is seen in those surviving for more than two weeks (fig. 16.5). The cut surface shows a 'nutmeg' appearance, red areas of haemorrhage alternating with

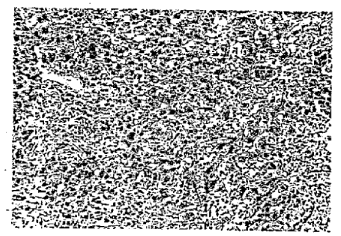


Fig. 16.1. Virus hepatitis: zone 3 (central) (arrow) shows marked loss of liver cells. Zone 1 (portal) shows expansion with cellular infiltration and bile ductular proliferation. (H & E ×40.)

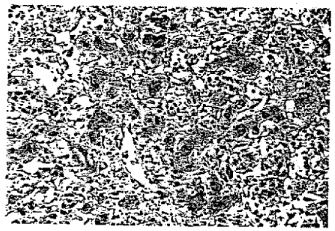


Fig. 16.2. Virus hepatitis: zone 3 shows swollen cells, mitoses and acidophilic bodies. (H & E × 80.)

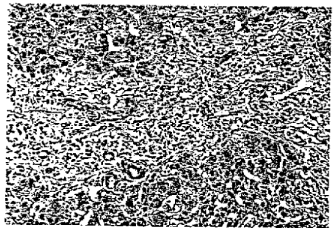


Fig. 16.3. Virus hepatitis: zone 1 (portal tract) shows an acute inflammatory reaction with ductular proliferation. (H & E ×50.)

yellow patches of necrosis. Necrosis in life is always less than that seen in autopsy material as autolysis proceeds particularly rapidly in the presence of acute hepatitis.

If the confluent necrosis extends from zone 3 to zone 1 the reticulum collapses leaving connective tissue septa. This is termed *bridging* (fig. 16.6). Such bridging may be followed by the development of active fibrous septa nodules and cirrhosis. More usually it is followed by scar formation (*post-necrotic scarring*) (fig. 16.7).

Acute viral hepatitis may be followed by chronic persistent or chronic active hepatitis (Chapter 17).

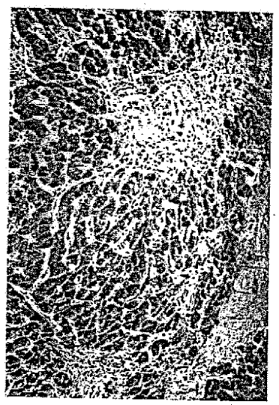


Fig. 16.4. Residual portal zone scarring seen 33 days after the onset of jaundice. (Best's carmine ×100) (Sherlock, 1946).

Electron microscopy

This shows non-specific changes. The rough endoplasmic reticulum is disrupted into vesicles and adherent ribosomes become detached. Large and irregular lysosomes develop which form autophagic vacuoles. The light cells represent ballooned cells and dark cells the eosinophilic bodies and dehydrated remnants of hepatocytes. Mitochondria are clumped, forming hyaloplasmic blebs. Macrophages have approached the sinusoidal cell surface.

During healing, the many polyribosomes form new profiles of endoplasmic reticulum and the smooth endoplasmic reticulum hypertrophies.

Changes in other organs

Regional lymph nodes are large. Splenomegaly is related to cellular proliferation and venous congestion. The bone marrow is moderately hypoplastic, but maturation is usually normal.

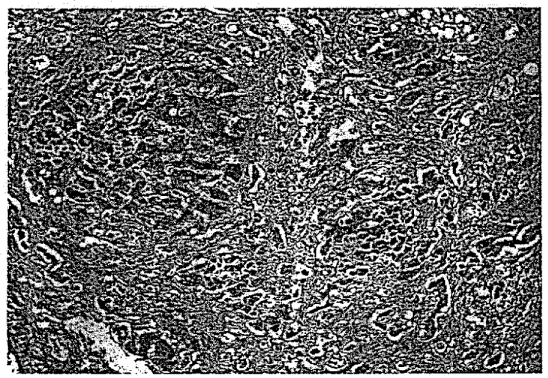


Fig. 16.5. Acute virus hepatitis. Sub-acute massive necrosis with nodular regeneration. (H & E ×120.)

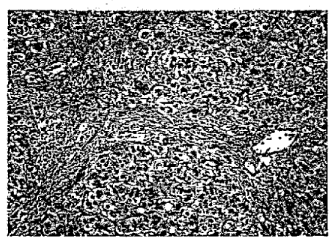


Fig. 16.6. Acute virus hepatitis. A passive septum (bridge) (arrow) has formed between zones 1 and 2. (H & E ×40.)

Fatal marrow aplasia has, however, been reported [54]. The pathogenesis is obscure. In about 15% of fatal cases there is ulceration of the gastrointestinal tract—particularly caecal.

The brain shows an acute non-specific degeneration of ganglion cells. Because of the short duration, the cerebral lesions of hepatic coma (Chapter 7) are rarely evident. Occasionally acute pancreatitis and myocarditis have

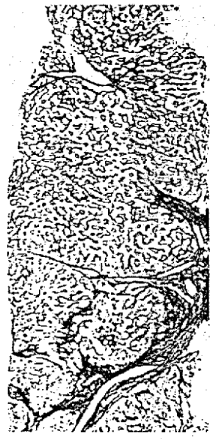


Fig. 16.7. Post-necrotic scarring. The liver biopsy specimen shows scarring, involving and extending from portal tracts. (Reticulin ×34.)

been noted. Haemorrhages are found in most organs.

Virus hepatitis is a multi-system infection involving many organs.

Clinical types

ACUTE HEPATITIS

Note is taken of ethnic origin, jaundiced contacts, recent travel, injections, tattooing, dental treatment, transfusions, homosexuality or ingestion of shellfish. All drugs taken in the previous two months are listed.

The picture varies widely, ranging from anicteric with only slight malaise to a severe and fatal disease culminating in hepatic coma.

In general, type A, type B and non-A, non-B hepatitis run the same clinical course. Type B and non-A, non-B tend to be more severe and may be associated with a serum sickness-like syndrome.

The mildest attack is without symptoms and marked only by a rise in serum transaminase levels. Alternatively, the patient may still be anicteric but suffer gastrointestinal and influenza-like symptoms. Such patients are likely to remain undiagnosed unless there is a clear history of exposure or the patient is being followed up after a blood transfusion. Increasing grades of severity are then encountered ranging from the icteric, from which recovery is usual, through to fulminant, fatal viral hepatitis.

The usual icteric attack in the adult is marked by a prodromal period, usually about three or four days, even up to two or three weeks, during which the patient feels generally unwell, suffers digestive symptoms, particularly anorexia and nausea, and may, in the later stages, have a mild pyrexia. Rigors are unusual. An ache develops in the right upper abdomen. This is increased by jolting movements. There is loss of desire to smoke or to drink alcohol. Malaise is profound and increases towards evening; the patient feels wretched.

Occasionally headache may be severe and, in children, its association with neck rigidity may suggest meningitis. Protein and lymphocytes in the CSF may be raised.

The prodromal period is followed by darkening of the urine and lightening of the faeces. This heralds the development of jaundice and symptoms decrease. The temperature returns to normal and there may be bradycardia. Appetite returns and abdominal discomfort and vomiting cease. Pruritus may appear transiently for a few days.

The liver is palpable with a smooth, tender edge in 70%. Heavy percussion over the right lower ribs posteriorly causes sickening discomfort. The spleen is palpable in about 20% of patients.

The adult loses about 4 kg weight. A few vascular spiders may appear transiently.

After an icteric period of about 1–4 weeks the adult patient usually makes an uninterrupted recovery. In children, improvement is particularly rapid and jaundice mild or absent. The stools regain their colour. The appetite returns. After apparent recovery lassitude and fatigue persist for some weeks. Clinical and biochemical recovery is usual within six months of onset. However, chronic hepatitis may follow types B and non-A, non-B.

Neurological complications, including the Guillain–Barré syndrome, can complicate all forms of viral hepatitis [127].

PROLONGED CHOLESTASIS

Occasionally, prolonged jaundice is of cholestatic type. Onset is acute, jaundice appears and deepens but, within three weeks, the patient starts to itch. After the first few weeks the patient feels well, gains weight and there are no physical signs apart from icterus and slight hepatomegaly. Jaundice persists for 8–29 weeks and recovery is then complete [115]. It is particularly associated with hepatitis A (fig. 16.8) [48].

Liver biopsy shows conspicuous cholestasis which tends to mask the definite, usually mild, hepatitis that is also present.

This type must be differentiated from surgical obstructive jaundice [48]. The acute onset

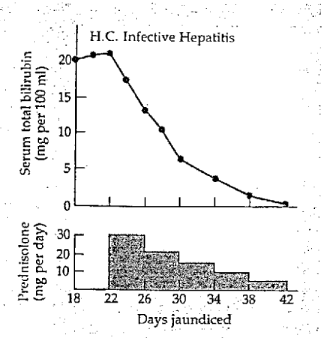


Fig. 16.8. Cholestatic, type A virus hepatitis. Prednisolone therapy was associated with a fall in serum bilirubin values.

and only moderately enlarged liver are the most helpful points. Cholestatic drug jaundice is excluded by the history.

If doubt remains needle biopsy is helpful. Surgical exploration is to be avoided as it may precipitate hepato-cellular failure.

The prognosis is usually excellent with complete clinical recovery and restitution of a normal liver [115].

RELAPSES

These occur in 1.8–15%. In some the original attack is duplicated, usually in milder form. More often, the relapse is simply shown by an increase in serum transaminases and sometimes bilirubin. The relapse may be precipitated by premature activity or by taking large amounts of alcohol. Multiple episodes may occur. Recovery after relapses is usually complete. In some patients relapses may indicate progression to chronic hepatitis.

FULMINANT HEPATITIS (see Chapter 8)

This rare form of the disease usually overwhelms the patient within 10 days. It may develop so rapidly that jaundice is inconspicuous and the disease is confused with an acute psychosis or meningo-encephalitis. Alternatively, the patient, after a typical acute onset, becomes deeply jaundiced. Ominous signs are repeated vomiting, fetor hepaticus, confusion and drowsiness. The 'flapping' tremor may be only transient, but rigidity is usual. Coma supervenes rapidly and the picture becomes that of acute liver failure. Temperature rises, jaundice deepens and the liver shrinks. Widespread haemorrhages may develop.

Leucocytosis may be found in contrast to the usual leucopenia of virus hepatitis. The biochemical changes are those of acute liver failure (Chapter 8). The height of the serum bilirubin and transaminase are poor indicators of prognosis. Transaminase levels may actually fall as the patient's clinical condition worsens. Blood coagulation is grossly deranged and a test of prothrombin is the best indicator of prognosis.

The time relationships and the course depend on whether the cause is A, B or non-A, non-B (table 16.1) [47].

The frequency of the fulminant course in the various types of viral hepatitis depends on the type of patient and the prevalence of hepatitis B carriage. In the United Kingdom and California [86], the non-A, non-B type is more frequent, whereas in Denmark and Greece, hepatitis B predominates [86, 93].

There are clinical differences in the fulminant course of the three types [47]. Pyrexia is most frequent with hepatitis A. The duration of illness before encephalopathy is longer with non-A, non-B. The prothrombin time is greatest with hepatitis B. The bad prognosis in those with a longer duration from onset of illness to encephalopathy is probably related to the greater number of non-A, non-B patients in that group (table 16.1).

POST-HEPATITIS SYNDROME

Adult patients feel below par for variable periods after acute hepatitis. Usually this is a matter of weeks but it may extend to months. This is termed the post-hepatitis syndrome

[117]. It is particularly common in the intelligent, perhaps because of their knowledge of the possible sequelae of hepatitis. Features are anxiety, fatigue, failure to regain weight, anorexia and alcohol intolerance, and right upper abdominal discomfort. The liver edge may be palpable and tender.

Serum transaminases may be raised up to three times normal. Too much attention should not be focused on them and they should not be repeated frequently. This exacerbates the anxiety and a 'transaminitis' is engendered. Serum globulin levels are normal.

Hepatic histology shows only mild, residual, portal zone cellularity and fibrosis with perhaps some fatty change in the liver cells. These features do not differ from those found in patients recovering normally who are now symptom-free. They rarely persist for longer than one year after the acute attack. In general, liver biopsy should not be performed too soon after acute hepatitis, certainly not less than six months, because of the difficulty in distinguishing the usual residual changes from a developing chronic hepatitis.

Treatment consists of reassurance after full investigation. If the acute attack has been type A, chronicity is excluded.

Investigations

URINE AND FAECES

Bilirubin appears in the urine before jaundice. The urinary threshold for bilirubin varies. It is found before the serum level is raised: later it disappears although serum levels remain elevated.

Urobilinogenuria is found in the late pre-icteric phase. At the height of the jaundice, very little bilirubin reaches the intestine, so urobilinogen disappears. Its reappearance indicates commencing recovery. It persists in excess in gradually diminishing amounts until final recovery.

The onset of jaundice is marked by lightening of the faeces. There is moderate steatorrhoea. Reappearance of stool colour denotes impending recovery.

BLOOD CHANGES

Total serum bilirubin levels range widely. Deep jaundice generally implies a prolonged clinical course. An increase in conjugated pigment is early, even when the total bilirubin level is still normal.

Serum alkaline phosphatase level is usually less than three times the upper limit of normal. Serum albumin and globulin are quantitatively unchanged. The serum iron level is raised.

Serum immunoglobulins G and M are raised in about one-third of patients during the acute phase.

Serum transaminase estimations are useful in early diagnosis, in detecting the anicteric case, and for detection of inapparent cases in epidemics. The peak level is found one or two days before or after onset of jaundice. Later in the course the level falls, even if the clinical condition is worsening. The estimation cannot be used prognostically. Values may remain elevated for six months in those who are recovering uneventfully.

In both type A and type B hepatitis antibody against smooth muscle is present, usually in low titre. Mitochondrial antibody is absent.

HAEMATOLOGICAL CHANGES

The pre-icteric stage is marked by leucopenia, lymphopenia and neutropenia. These revert towards normal as jaundice appears. Some 5–28% show atypical lymphocytes (virucytes), resembling those seen in infectious mononucleosis. Acute Coombs' test positive haemolytic anaemia is a rare complication. Haemolysis is commonly precipitated in patients with glucose-6PD deficiency [21].

Aplastic anaemia is very rare [54]. It appears weeks or months after the acute episode and is particularly severe and irreversible. It is not usually associated with A or B infection and may be due to a hitherto unidentified non-A, non-B type. It has been treated by bone marrow transplantation.

The *prothrombin time* is lengthened in the more severe cases and does not return completely to normal with vitamin K therapy.

The *sedimentation rate* of the red cells (ESR) is high in the pre-icteric phase, falls to normal with jaundice, and rises again when the jaundice subsides. It returns to normal with complete recovery.

NEEDLE LIVER BIOPSY

This is rarely indicated in the acute stage. It may ocasionally be needed in older patients to differentiate from extra-hepatic or other forms of intra-hepatic cholestasis and from drug jaundice. It may be used to diagnose the presence and type of chronic complications but should not be performed less than six months after the acute episode else the distinction between the picture of normal recovery and chronic hepatitis may be impossible.

Differential diagnosis

In the *pre-icteric stage*, hepatitis can be confused with other acute infectious diseases, with acute surgical abdomen, especially acute appendicitis, and with acute gastroenteritis. Bile in the urine, tender enlargement of the liver and a rise in serum transaminase values are the most helpful points. The distinction from infectious mononucleosis is outlined in table 16.10. Viral markers are essential.

In the *icteric stage*, the diagnosis must be made from surgical cholestasis. This is outlined in Chapter 12.

The diagnosis of acute virus hepatitis from the drug-related disease depends largely on the history.

Needle liver biopsy is valuable in the problem case. Attempts at a surgical diagnosis are disastrous.

The distinction from Weil's disease is discussed in Chapter 27.

In the *post-icteric stage*, the diagnosis of organic from non-organic complications necessitates routine investigations for the diagnosis of chronic hepatitis, and these may include needle biopsy.

Prognosis (table 16.1)

Type B infection is said to have the highest mortality. In a survey of 1675 cases in a group of Boston hospitals, one in eight sufferers from transfusion hepatitis (B and non-A, non-B) succumbed whereas only one in 200 died with the type A disease. As many non-icteric cases are not included in the statistics the overall mortality rate is undoubtedly very much lower. In the United Kingdom, non-A, non-B hepatitis had the poorest survival [47].

Those who are elderly or in poor general health clearly have a poor prognosis. Fulminant hepatitis is rare in those less than 15 years old. The non-A, non-B patients tend to be more than 45. Survival rate is the same for males as for females.

Treatment

Prevention

Compulsory notification leads to earlier detection and hence identification of methods of infection, for instance food or water contamination, sexual spread or carriage by blood donors.

Treatment of the acute attack

Treatment has little effect in altering the course. At the outset this is unpredictable and it is wise to treat all attacks as potentially fatal and to insist upon bed rest with bathroom privileges. Traditionally this is enforced until the patient is free of jaundice. A less strict regime may be possible if the patients are young and previously healthy. They can be allowed up when they feel well, regardless of the degree of jaundice. They rest after each meal. If symptoms return, the patient is immediately returned to bed rest. Selected patients treated along these

Table 16.1. Fulminant virus hepatitis in the United Kingdom: aetiology, duration from onset to fulminant and survival (Gimson *et al.* 1983)

	A	B	Non-A, non-B
Frequency (%)	31.5	24.7	43.8
Duration from onset (days)	10	7	21
Survival (%)	43.4	16.6	9.3

liberal lines do not show an increased incidence of later complications.

Convalescence is not allowed until the patient is symptom-free, the liver no longer tender, and the serum bilirubin is less than 1.5 mg/100 ml. The period of convalescence should be twice the period spent in hospital or in bed at home.

The traditional low-fat, high-carbohydrate diet is popular because it has proved the most palatable to the anorexic patient. Apart from this, no benefit accrues from the rigid insistence upon a low-fat diet.

When the appetite returns, high protein intake may hasten recovery. Excess protein, however, is harmful to the severely ill patient in impending hepatic coma. The usual diet in hepatitis is composed of the food most appetizing to the patient. Supplementary vitamins, amino acids and lipotrophic agents are not necessary.

Corticosteroids do not alter the degree of liver necrosis, accelerate the rate of healing or assist in immunity in virus hepatitis. Hepatitis tends towards spontaneous recovery and any benefit is not sufficient to justify the use of this treatment. The drug must be continued into convalescence, for premature withdrawal leads to relapse. A usual course is 30, 20, 15, 10 and 5 mg prednisolone, each dose being given for five days (duration of course 25 days). It should be reserved only for the patient with prolonged cholestasis (fig. 16.8) or the non-B patient who seems to be passing into a subacute stage with persistent jaundice, high serum globulin and transaminase values. The steroid 'whitewash' improves the morale of both patient and physician but probably has little effect on the healing of the liver [115].

Patients showing signs of acute hepatocellular failure with pre-coma require more active measures and the regime described in Chapter 8 must be instituted.

FOLLOW-UP

The patient should be seen 3–4 weeks after discharge, and if necessary at monthly intervals for the next three months. Special attention should be paid to recurrence of jaundice and to the size of the liver and spleen. Tests should include serum bilirubin, globulin and transaminase levels and hepatitis B markers if originally positive.

The patient should not be questioned too closely about symptoms and feelings of weakness, for the 'post-hepatitis syndrome' can readily be induced by the physician. Exercise must be undertaken and within the limits of fatigue. Alcohol must be denied for six months and preferably one year afterwards. The patient often has little inclination for it and excessive consumption leads to relapses. Diet can be unrestricted.

Virus A (HAV) hepatitis

Hepatitis A accounts for 20–25% of clinical hepatitis in the developed world [79]. It is due to a small 27 nm, cubically symmetrical RNA picorna virus (type 72) (figs 16.9, 16.10) [41].

Like other picorna viruses (small RNA viruses) it has four capsid polypeptides, virus protein (VP 1–4) [131]. Only a single serotype has been identified. However, the genome has been cloned and characterized and a number of minor differences have been identified among isolates from different parts of the world.

The virus has been transmitted to marmosets and chimpanzees and cultivated *in vitro*. It is noncytopathic and grows in a variety of epithelial cell lines. DNA complementary to genomic hepatitis A virus RNA has been cloned in *E. coli*. The mode of elimination of the virus

Table 16.2. Serological viral hepatitis markers and their significance

Marker	Significance
Hepatitis A	
IgM anti-HAV	Acute hepatitis A
IgG anti-HAV	Immune to hepatitis A
Hepatitis B	
HBsAg	Acute or chronic hepatitis B carriage
IgM anti-HBe	Acute hepatitis B (high titre) Chronic hepatitis B (low titre)
IgG anti-HBc	Past exposure to hepatitis B (with negative HBsAg) Chronic hepatitis B (with positive HBsAg)
Anti-HBs	Immune to hepatitis B
HBeAg	Acute hepatitis B. Persistence means continued infectious state
Anti-HBe	Convalescence or continued infectious state
HBV DNA	Continued infectious state
Delta	Acute or chronic infection with delta agent
IgM anti-delta	Chronic delta infection (high titre with + ve IgM anti-delta)
IgG anti-delta	Past delta infection (low titre with − ve IgM anti-delta)

from the liver is unknown, but cytolytic T-cells probably play a part [134].

A serum antibody (anti-HAV) appears as the stool becomes negative for virus, reaches a maximum in several months and is detectable for many years (fig. 16.10). IgG anti-HAV probably gives immunity from further infection with hepatitis A. The appearance of serum IgM anti-HAV is more helpful diagnostically and implies a recent infection. This antibody persists for only 2–6 months (figs 16.11, 16.12) and rarely, in low titre, up to one year [64].

Chronic carriers have not been identified.

Epidemiology

The disease occurs sporadically or in epidemic form and has an incubation time of 15–50 days. It is usually spread by the faecal–oral route. Parenteral transmission is extremely rare, but can follow transfusion of blood from a donor who is in the incubation stage of the disease [56].

Age 5–14 is the group most affected and adults are often infected by spread from children.

Spread is related to overcrowding, poor hygiene and poor sanitation. With an improved standard of living the prevalence is decreasing world-wide. In urban areas, 29% (Switzerland)

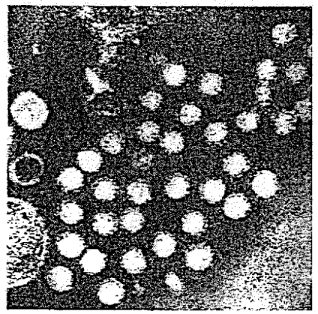
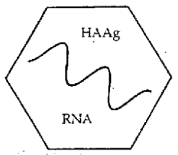


Fig. 16.9. Electron microscopy of hepatitis A antigen particles in faeces. These are shown as 22 nm spheres. (×250 000.)



Hepatitis A

Fig. 16.10. Diagram of the hepatitis A virus shown as a hexagonal body containing single stranded RNA.

Table 16.3. Type A, type B and transfusion-related non-A, non-B hepatitis contrasted

	A	B	Transfusion-related non-A, non-B
Virus	RNA	DNA	
Incubation (days)	15–20	50–60	42–56
Spread			
Blood	No	Yes	Yes
Faeces	Yes	No	No
Saliva	Yes	Yes	?
Vertical	No	Yes	?No
Intra-family	Yes	Yes	?No
Acute attack	Depends on age	Mild or severe	Usually mild
Rash	Yes	Yes	Yes
Serum diagnosis	IgM anti-HAV	IgM anti-HBc. HBsAg	Awaited
Peak SGPT (ALT)	800–1000	1000–1500	300–800
Waxing and waning	No	No	Yes
Treatment	Symptomatic	Symptomatic ? Anti-virals	Symptomatic
Prevention	Vaccine Immunoglobulin	Vaccine Immunoglobulin	None
Antibody prevalence	40–60% (urban areas)	10–80% (geographic variations)	?
Chronic hepatitis	No	10%	60%
Liver cancer	No	Yes	Rare

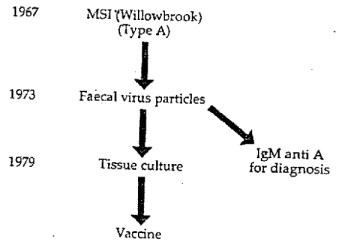


Fig. 16.11. Landmarks in hepatitis A (Sherlock, 1984).

to 96.9% (Yugoslavia) of adults show circulating IgG anti-HAV. In underdeveloped countries, 90% of children have the antibody by the age of 10. Young people not previously exposed, and visiting endemic areas, are increasingly becoming affected. Medical staff in developed countries are at risk. A large outbreak among nurses and mothers in a nursery spread from acute hepatitis A in a neonate with an ileostomy [3].

Most sporadic cases follow person-to-person contact. Children in day-care centres and promiscuous homosexuals are at risk.

Explosive water-borne and food-borne epidemics are described. Use of human sewage for soil fertilization can result in frozen fruit-related epidemics.

Ingestion of raw clams and oysters from polluted waters is known to have caused four epidemics. Steaming the clams may not kill the virus, for the temperature achieved inside the clams is not sufficiently high.

Contamination during preparation has resulted in transmission via other foods, including sandwiches, orange juice, potato salad and meat.

Clinical course

The hepatitis is usually mild, particularly in children where it is frequently subclinical or passed off as gastroenteritis. The disease is more serious and prolonged in adults.

The rare fulminant course may be related to the dose of virus or impaired antibody responsiveness.

Needle liver biopsy in patients with acute type A hepatitis shows a particularly florid portal zone lesion with expansion, marked cellular infiltration and erosion of the limiting plate [129]. Cholestasis is marked. It is therefore surprising that hepatitis A infection never leads to ongoing chronic hepatitis or cirrhosis.

Cholestatic hepatitis A affects adults [48]. The jaundice lasts 42 to 110 days and itching is severe. Serum IgM anti-HAV is positive. The prognosis is excellent. A case can be made for cutting short the jaundice and relieving the itching by a short course of prednisolone 30 mg reducing to zero over about three weeks (fig. 16.8).

Relapsing hepatitis A. Occasionally after 30 to 90 days the patient relapses. The serum transaminase levels have never returned to normal. The relapse resembles the original attack clinically and biochemically and virus A is found in the stools [122]. The relapse may last several months but recovery eventually ensues.

Rarely, the relapse can be associated with arthritis, vasculitis and cryoglobulinaemia [58].

PROGNOSIS

This is excellent, and recovery is usually full. Mortality in large epidemics is less than 1 per 1000 and virus A accounts for less than 1% of cases of fulminant viral hepatitis. The average adult with icteric hepatitis can anticipate six weeks illness and this will rarely exceed three months.

Chronicity does not develop. Follow-ups of large epidemics in World War I [26] showed no long-term sequelae. Viral carriage is transient in faeces. Antibodies develop and the patient becomes immune.

Prevention

The virus is excreted in the faeces for as long as two weeks before the appearance of jaundice. The anicteric patient may excrete the virus for a similar period. Virus is therefore disseminated before the diagnosis is made. For this reason, isolation of patients and contacts cannot be expected to influence significantly the spread of hepatitis.

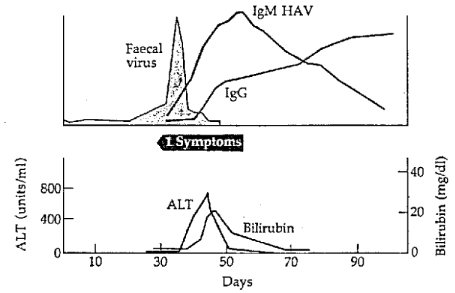


Fig. 16.12. The course of acute hepatitis A. ALT is alanine transferase (GPT) HAV is hepatitis A virus.

Virus A is relatively resistant to inactivation by heat, ether or acid, but is inactivated by formalin 1 in 4000 at 37°C for 72 hours and chlorine 1 ppm for 30 minutes.

IMMUNE SERUM GLOBULIN (ISG) PROPHYLAXIS (table 16.6)

If possible, any candidate for ISG should be tested for anti-HAV. If present, the ISG is not necessary.

Efficacy depends on the antibody content and hence the source of the plasma.

ISG should be given to close personal contacts of sufferers. Casual contacts in office and work do not need ISG. Routine prophylaxis of hospital staff is not indicated but sound hygiene should be insisted upon.

When a common source of infection is identified, for instance food or water, ISG should be given to all those exposed. This particularly applies to epidemics in schools, hospitals, prisons and other institutions.

HEPATITIS A VACCINES

These are under development (fig. 16.13). A live attenuated vaccine has been prepared from hepatitis A growing in fetal monkey kidney cell cultures and human lung cell cultures [100]. It is effective in human volunteers but doubt remains concerning its safety and there is difficulty in getting fully attenuated strains.

Inactivated vaccines have been prepared from cultures of virus A adapted on human fibroblasts [10, 43, 99]. These will be costly and duration of protection is uncertain.

A recombinant vaccine has been prepared using the viral protein (VP1) of the virus. Finally, a synthetic vaccine is being considered.

Where available, hepatitis A vaccines will replace immune globulin for travellers and for the military proceeding abroad. Children in nursery schools, homosexuals and workers handling faeces will also be candidates.

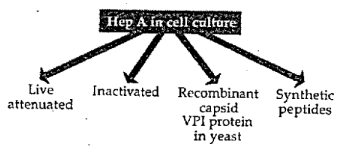


Fig. 16.13. Possible vaccines against hepatitis A.

Type B (HBV) hepatitis

In 1965, Blumberg and colleagues in Philadelphia found an antibody in two multiply-transfused haemophiliac patients which reacted with an antigen in a single serum in their panel which came from an Australian Aborigine (fig. 16.14) [11]. Later the antigen was found in patients with viral hepatitis. Because of its discovery in an aboriginal serum the antigen was called Australia antigen. In 1977, Blumberg was awarded the Nobel prize for his discovery. Australia antigen is now known to be the surface of the hepatitis B virion and is termed hepatitis B surface antigen (HBsAg).

Three types of particle can be seen in hepatitis B serum: small 20 nm spheres, tubules 20 nm in diameter and 100 nm long, and the more complex 42 nm Dane particles (fig. 16.15) [27]. The Dane particle is the complete hepatitis B virus

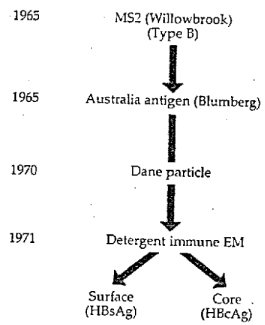


Fig. 16.14. Landmarks in hepatitis B (Sherlock, 1984).

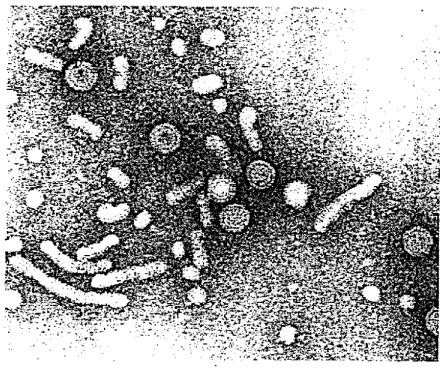


Fig. 16.15. Electron microscopy of hepatitis B antigen particles in blood. These are shown as spherical and tubular forms and the large Dane particles. ×250 000. (Courtesy J.D. Almeida.)

(HBV), whereas the small spheres and tubules are excess viral protein (HBsAg) (fig. 16.16).

The core of the Dane particle is formed by the hepatocyte nucleus whereas the smaller, surface particles are produced in the cytoplasm.

The core of the virus particle contains a DNA polymerase and the DNA has a molecular weight of $1.8-2.3 \times 10^6$. The DNA structure has been characterized and shown to be double stranded and circular. It is approximately 3200 nucleotides in length and has a single stranded gap of 600–2100 nucleotides. The DNA polymerase reaction appears to repair the gap. The core contains a core antigen and another antigen, called little 'e', is a protein sub-unit of the core.

DNA recombinant technology has allowed cloning and sequencing of the double-stranded DNA genome of HBV. The open reading frames coding for putative proteins have been identified (fig. 16.17). The genome contains four major polypeptide reading frames. The S-gene codes for an HBsAg polypeptide. The C-gene codes for viral core polypeptide (HBcAg). The third, the putative DNA polymerase 'P-gene', overlaps the S-gene and the fourth reading frame is designated X. The pre-S (S1 and S2) region is a nucleic acid sequence preceding the gene coding for the major hepatitis B surface antigen polypeptide [88]. It may be concerned with the ability of the hepatitis B virus to interact with the host hepatocyte.

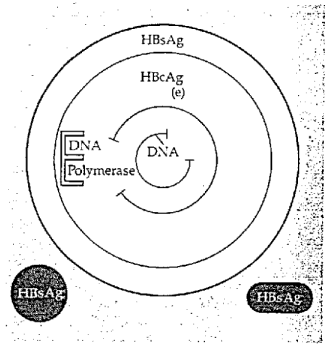


Fig. 16.16. Diagram of the virion of hepatitis B (HBV: Dane particle). The core contains DNA polymerase, double-stranded DNA, core antigen and e antigen. The surface consists of HbsAg. Spheres and tubules of HbsAg are free in serum.

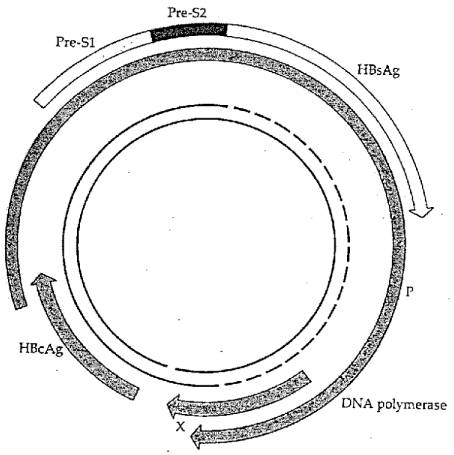


Fig. 16.17. Organization of the genome of the hepatitis B virus showing the four open reading frames, P, HBsAg, HBcAg and X.

A similar disease affects woodchucks, ground squirrels and Peking ducks, and these animals have been extensively used for research [92, 97]. The whole group of agents have been termed *hepadna viruses*.

SUB-TYPES OF HBsAg

HBsAg particles have surfaces that are antigenically complex and this had led to the recognition of antigenic determinants [76]. A common determinant is *a*. The other subdeterminants are designated *d*, *y*, *w* and *r*. The four major determinants are therefore *adw*, *adr*, and *ayr*. They breed true and are very helpful epidemiologically.

SEROLOGICAL DIAGNOSIS (table 16.2)

HBsAg appears in the blood about six weeks after infection and has disappeared by three months (fig. 16.18). Persistence for more than six months implies a carrier state.

Anti-HBs appears late, some three months after the onset, and persists. Anti-HBs levels are rarely high and 10–15% of patients with acute type B hepatitis never develop the antibody. Anti-HBs accounts for recovery and immunity. In the past, HBsAg and HBsAb were believed to be mutually exclusive. However, as many as one-third of carriers of HBsAg also have HBsAb. The mechanism is uncertain, but it has been attributed to simultaneous infection with different sub-types.

HBeAg correlates with ongoing viral synthesis and with infectivity. It is transiently present during the acute attack. It is present for a shorter time than HBsAg. Persistence for more than ten weeks strongly suggests the development of chronicity (Chapter 17).

Anti-HBe is a marker of relatively low infectivity. The appearance of anti-HBe is strong evidence that the patient will recover completely.

HBcAg cannot be detected in circulating blood, but its antibody (anti-HBc) can. High

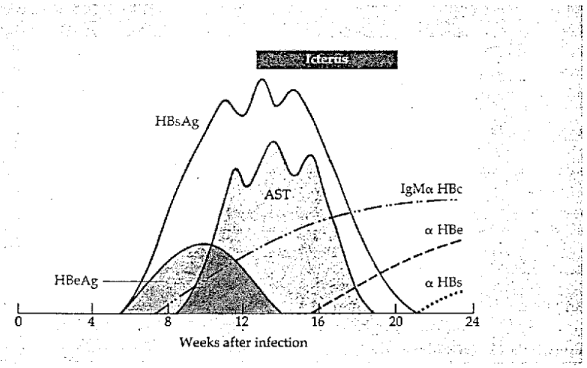


Fig. 16.18. The course of acute type B hepatitis. HBsAg = hepatitis B surface antigen, HBeAg = hepatitis Be antigen, AST = aspartate transaminase, IgMαHBc = IgM antibody against hepatitis B core antigen, αHBe = antibody against hepatitis e antigen, αHBs = antibody against hepatitis B surface antigen.

titres of IgM anti-HBc mark present acute virus hepatitis [22]. This antibody is detected after HBsAg has been cleared from the serum. This is true of 5–6% of cases with acute hepatitis B and is encountered particularly in fulminant hepatitis [120]. It is also useful in determining whether an acute attack of hepatitis is due to virus B or to superinfection with another virus. Persistence of *IgM anti-HBc* implies ongoing virus B-related chronic disease, usually chronic active hepatitis. Lower titres of *IgG anti-HBc* with anti-HBs mark hepatitis B infection in the remote past. Higher titres of IgG anti-HBc without anti-HBs indicate persistence of viral infection.

HBV DNA is the most sensitive index of viral replication. This can now be assessed by molecular hybridization using the Southern blot technique [83, 112]. It can be present in anti-HBe positive sera when it indicates severe ongoing disease [12]. Routine testing for serum HBV DNA will undoubtedly replace tests for HBeAg.

Hepatitis B markers in hepatocytes

HBsAg may be stained orange with orcein (fig. 16.19) in the hepatocytes of carriers and chronic hepatitis patients, but not in those in the acute stage [18]. Electron microscopy and immune histochemistry demonstrate the HBcAg to be in nuclei and the HBsAg in the membranes of liver cells [34]. Core markers are not found in the liver in the acute stage.

INFECTIVITY OF BODY FLUIDS

HBV-containing blood or any body fluid contaminated with blood is infectious. Mere positivity of a fluid for HBsAg is not synonymous with infectivity. However, concentrated samples of saliva, urine and seminal fluid from HBeAg-positive males have shown the presence of HBV-DNA by molecular hybridization [65]. HBV-DNA has also been found in monocytes and leucocytes [51, 96]. The hepatitis B virus probably replicates in extra-hepatic sites.

Fig. 16.19. Orcein staining shows liver cells containing HBsAg (brown).

Bone marrow cells have been infected by HBV [142] and light microscopy has shown hepatitis B viral antigens in the human pancreas [121].

Epidemiology (tables 16.3, 16.4 16.5)

The disease is transmitted parenterally or by intimate, often sexual, contact.

Epidemiological methods have proved particularly important in identifying hepatitis B virus infection, indicating its relationship to hepato-cellular carcinoma and in evaluating the effect of vaccine [84].

The carrier rate of HBsAg varies worldwide from 0.1 to 0.2% in Britain, United States and Scandinavia to more than 3% in Greece and Southern Italy and even up to 10 to 15% in Africa and the Far East. If anti-HBs is measured the rate of exposure to hepatitis B in any community is much higher [75]. Carriage of HBsAg is even higher in some isolated communities, 45% in Alaskan Eskimos [87], and 85% in Australian Aborigines.

In high carriage-rate areas infection is probably acquired by passage from the mother to the neonate. The infection is usually not via the umbilical vein, but from the mother at the time of birth and during close contact afterwards. The chance of transmission increases as term approaches and is greater with acute than chronic carriers. The mother is HBsAg positive

Table 16.4. Approximate percentage carrier rate or HBsAg (by RIA) in 'healthy' blood donors

Scandinavia	0.1
United Kingdom	0.1
United States	0.1
Holland	0.2
Switzerland	0.2
Belgium	0.5
France	0.5
Spain	2.0
Southern Italy	3.0
Japan	3.0
Greece	5.0
South Africa	11.3
Taiwan	15.0
Singapore	15.0
Hong Kong	15.0

Table 16.5. Groups in which acute and chronic type-B hepatitis should be suspected

Immigrants from Mediterranean countries, Africa or the Far East
Drug abusers
Homosexuals
Neonates of HBsAg positive mothers
Hospital staff
Patients with:
Renal failure
Reticuloses
Cancer
Organ transplants
Staff and patients of hospitals for mentally retarded
Post-transfusion

and also usually, but not always, HBeAg positive. Antigenaemia develops in the baby within two months of birth and tends to persist.

In other areas the peak incidence is in childhood rather than in neonates. In such areas, including Africa [13], Greece and Hong Kong intra-family spread seems particularly important. This may be by close contact such as kissing. Shared utensils, toothbrushes and razors may also be important. In the family group the sexual contacts of carriers are at risk.

Homosexuals are at risk of contracting type B hepatitis. In one multi-centred trial, conducted in the United States, 61% of 3816 'gay' men had

markers of hepatitis B (6% HBsAg, 52% HBsAb, and 3% HBcAb) [111]. Infection was related to duration of homosexual activity, number of sexual contacts and anal contact.

Blood-sucking arthropods such as mosquitoes or bed bugs may be important vectors, particularly in the tropics. However, there is no evidence that the virus replicates in the arthropod.

Blood transfusion continues to cause hepatitis B in countries where donor blood is not screened for HBsAg by radioimmunoassay. Transmission is more likely with blood from paid donors than when volunteer blood is transfused.

Opportunities for parenteral infection include the use of unsterile instruments for dental treatment, ear piercing and manicures, neurological examination, prophylactic inoculations, subcutaneous injections, acupuncture, and tattooing (fig. 16.20).

Parenteral drug abusers develop hepatitis from using shared, unsterile equipment. The mortality may be very high in this group. Multiple attacks are seen and chronicity is frequent. Liver biopsy may show, in addition to acute or chronic hepatitis, foreign material, such as chalk, injected with the illicit drug.

Hospital staff in contact with patients, and especially patient's blood, usually have a higher carrier rate than the general community. This applies particularly to staff on renal dialysis or oncology units. Patients are immunosuppressed and, on contracting the disease, become chronic carriers [67]. Danger to the patient's attendant comes from contact with blood parenterally, such as from pricking or through skin abrasions. Surgeons and dentists are particularly at risk in operating on HBsAg-positive patients with a positive HBeAg (fig. 16.20). Holes in gloves and cuts on hands are common. Wire sutures may be a particular hazard in penetrating the skin. Four surgeons developed hepatitis 80–105 days after performing proctocolectomy (with wire sutures) on a patient who developed a positive HBsAg [106]. Checks of 75 additional medical personnel who cared for the patient revealed no other cases of hepatitis. Other methods of casual contact in hospital are much less likely causes of infection.

Using standard cleansing procedures there is no evidence that HBV infection is spread by endoscopes [136].

Special care must be taken in transporting and handling *all* blood samples, but especially those coming from patients with hepatitis.

Institutionalized mentally retarded children (especially with Down's syndrome) and their attendants have a high carrier rate [73].

Clinical course

The course may be anicteric. The high carriage rate of serum markers in those who give no

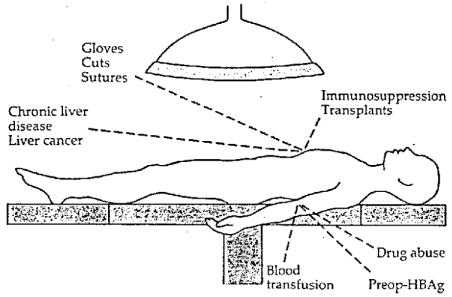


Fig. 16.20. The hepatitis hazard for hospital workers and particularly surgeons. This comes from skin lacerations and pricks when handling blood from a patient with a positive hepatitis B antigen test, especially those with chronic liver disease or cancer, those on immuno-suppression or having organ transplantation or abusing drugs. Care in handling all blood specimens is emphasized.

history of an acute hepatitis B attack suggests that subclinical episodes must be extremely frequent. The non-icteric case is more liable to become chronic than the icteric one.

The usual clinical attack diagnosed in the adult tends to be more severe than for virus A or non-A, non-B infections. The overall picture is, however, similar. The self-limited, benign icteric disease usually lasts less than four months. Jaundice rarely exceeds four weeks. Occasionally, a prolonged benign course is marked by increased serum transaminase values for more than 100 days. Relapses are rare. Cholestatic hepatitis with prolonged deep jaundice is unusual.

There may be features suggesting immune complex disease. This is shown in the prodromal period by a *serum sickness-like* syndrome. This develops about a week before the onset of jaundice. It can be associated with an icteric or an anicteric attack. The syndrome has also been described with chronic hepatitis B [138]. Fever is usual. The skin lesion is urticarial, and rarely, in children, a papular acrodermatitis may be seen. [45].

The arthropathy is symmetrical, non-migratory and affects small joints. Serum rheumatoid factor is negative. It is usually transitory but can persist.

These events can be related to circulating immune complexes containing HBsAg, anti-HBs and complement [130]. Serum complement levels are reduced. Immunoglobulins, complement and HBsAg can be shown in vessel walls.

A fulminant course of hepatitis B in the first four weeks may be related to an enhanced immune response. There is more rapid clearing of virus. Antibodies to surface and 'c' antigen increase, and multiplication of virus ceases [15]. In fulminant hepatitis B, the surface antigen may be in low titre or undetectable and hepatitis Bs antigen is less frequently found. The diagnosis may be made only by finding serum IgM anticore titres.

Another viral hepatitis, superimposed on the symptomless hepatitis B carrier, may precipitate a fulminant course. The new agent may be A [95] or delta; non-A, non-B has also been postulated [93].

Subacute hepatic necrosis is marked by increasing severe disease evolving over one to three months.

Chronic hepatitis can develop insidiously (see Chapter 17).

Extra-hepatic associations

These conditions are often associated with circulating immune complexes containing HBsAg. The accompanying liver disease is usually mild, at the most a chronic persistent hepatitis. The liver disease itself is not due to immune complex injury. Turnover of the C_3 component of complement is not increased in acute type B hepatitis, and is less in chronic active than chronic persistent hepatitis [130]. Acute and chronic type B hepatitis can develop in patients with agammaglobulinaemia.

Polyarteritis (systemic necrotizing vasculitis). This multi-system disease affects the gastrointestinal tract, peripheral and central nervous system. The course is similar to other types of polyarteritis, 31 to 54% have mononeuritis multiplex [127].

Immune complexes containing HBsAg, IgG and complement have been found in the vascular lesions [89]. The presence of circulating complexes correlates with disease activity. As the lesions become less active, evidences of viral infection disappear [89].

The importance of hepatitis B virus in the whole picture of polyarteritis is probably low, perhaps representing some 10% of cases.

Glomerulonephritis. Membranous or membrano-proliferative glomerulonephritis has been found either isolated or as part of a generalized vasculitis [17]. The association is a rare one. Circulating HBcAg antigen–antibody complexes are found in the capillaries [128].

The patient usually has no clinical features of acute or chronic liver disease [74]. The course is indolent but relentlessly progressive.

Polymyalgia rheumatica has been connected with hepatitis B infection [4].

Essential mixed cryoglobulinaemia. A patient

with peripheral neuropathy and cryoglobulinaemia showed a cryoprecipitate with a high concentration of HBsAg. However, anti-HBsAg and complement were not found [82]. The relationship of hepatitis B to this condition has not been proved [35].

The *Guillain–Barré syndrome* has been reported with HBsAg-containing immune complexes in serum and cerebrospinal fluid [94].

Myocarditis may have an immune complex basis [133].

Hepatitis B carriers

There are an estimated 300 million hepatitis B carriers in the world.

Approximately 10% of patients contracting hepatitis B as an adult and 90% of those infected as neonates will not clear HBsAg from the serum within six months (fig. 16.21). Such patients become carriers and this is likely to persist. Reversion to a negative HBsAg is rare but may develop in old age. Males are six times more likely to become carriers than females.

The dilemma of a person, such as a hospital worker, carrying the antigen and coming from an area where it is prevalent is a very difficult one. The HBsAg carrier of today must not replace the leper of yesterday. Hospital staff who develop HBsAg-positive hepatitis and clear the antigen from the blood are immune to type B hepatitis. If they become carriers, the position is difficult. The extent of the infectivity of surgeons, dentists or indeed any hospital worker to patients and casual contacts has not been established but cannot be very great.

'Healthy' carriers may show changes on liver biopsy ranging from non-specific minimal abnormalities through to chronic active hepatitis and cirrhosis [103]. The extent of the changes is not reflected by serum biochemical tests and may only be revealed by liver biopsy. The carrier presenting by chance is likely to have minor hepatic changes compared to the patient presenting to a gastroenterology department where more serious liver disease is likely. In a survey of patients found to be HBsAg positive at blood donation, 95% had near normal liver

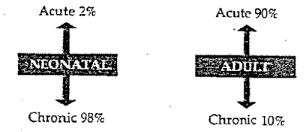


Fig. 16.21. The course of acute hepatitis B in the neonate and adult.

biopsies and only 1.6% proceeded to chronic active hepatitis or cirrhosis [37]. Ninety per cent were serum HBeAg negative and anti-HBe positive.

In a carrier, a positive serum HBV-DNA and HBeAg indicate infectivity and ongoing disease. Mechanisms of chronicity are discussed in Chapter 17.

Chronic organic sequelae

Exposure to HBV can have different results (fig. 16.22). Some are immune and have no clinical attack; they presumably have anti-HBV. In others, an acute attack develops varying from anicteric to fulminant. Previously normal persons usually clear the antigen from the serum within about 4–6 weeks from the onset of symptoms. Chronic liver disease is associated with persistent antigenaemia. In general, the more florid and acute the original attack, the less likely are chronic sequelae.

If the patient survives a fulminant attack of viral hepatitis, ultimate recovery is complete without the development of chronic residuals. Chronicity is more likely after the mildly icteric, anicteric or relapsing episode and in those with immunological incompetence such as neonates, homosexuals, sufferers from AIDS, leukaemia and cancer, renal failure or those receiving immunosuppressive treatment (see Chapter 17) [39].

Prevention

HEPATITIS B IMMUNOGLOBULIN (HBIG)

HBIG is a special hyperimmune serum globulin

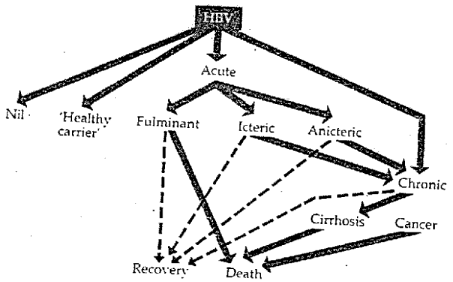


Fig. 16.22. The effect of exposure to hepatitis B virus (HBV).

with a high antibody titre. It is effective for passive immunization against hepatitis B if given prophylactically or within hours of infection [113]. If hepatitis vaccine is available it should always be given with the HBIG, particularly if the subject is at risk of re-infection. It is indicated for sexual contacts of acute sufferers, babies born to HBsAg-positive mothers [8, 141], and victims of parenteral exposure (needle stick) to HBsAg-positive blood (tables 16.6, 16.7, 16.8).

Pre-exposure HBIG, for instance before a blood transfusion, is of possible value.

HEPATITIS B VACCINES

Vaccines are prepared from the uninfectious outer surface of the virus (HBsAg) (fig. 16.23).

The *plasma-derived vaccine* comes from plasma of hepatitis B carriers. It is highly effective in preventing hepatitis B in high risk groups. It is completely safe and no evidence of AIDS has occurred in over one million vaccinees at low risk of exposure to AIDS. The only side-effects are an occasional sore arm and pyrexia, probably due to the alum preservative. Recombinant DNA technology has been used to express HBsAg in yeast cells. The resultant *recombinant yeast vaccine* is free of human plasma. It is safe and as effective as the plasma derived one [16, 125].

Hepatitis B vaccines have been shown to be effective in preventing hepatitis B in promiscuous homosexuals [126], haemodialysis patients [31], Down's syndrome and other mentally retarded patients [55], health care workers [36],

Table 16.6. Immunoprophylaxis of virus hepatitis A and B

Type	Immunoglobulin	Indication	Regime
A	Conventional	Close exposure to virus Travel to 'dirty areas'	3 ml within 14 days 6 ml every six months
B (adults)	HBIG	Exposure to HBsAg +ve blood Sexual consorts	0.06 ml/kg as soon as possible combined first dose of vaccine*
Neonates	HBIG	HBsAg +ve mother	0.5 ml as soon as possible combined first dose of vaccine†

* Full course of vaccine given if subject is anti-HBc negative.
† Full course of vaccine given.

Table 16.7. Indications for hepatitis vaccination

- Surgical and dental staff including medical students
- Hospital and laboratory staff in contact with blood
- Patients and staff in departments of oncology and haematology, kidney, mental subnormality and liver disease
- Mental subnormality
- Accidental exposure to HBsAg + ve blood
- Close family and sexual contacts of HBsAg + ve carriers
- Babies born to HBsAg +ve mothers
- Children in high risk populations
- Drug abusers
- Homosexually active men
- Travellers to high risk areas

Table 16.8. Prophylaxis of persons accidentally exposed to possibly infectious blood

Check donor blood for HbsAg; victim's blood for HBsAg and HbcAb
Give at once 0.06 ml/kg HBIG plus first dose hepatitis B vaccine

	HbsAg	HBcAb	Further action to victim
Victim	+ve	+ve	None: immune
Donor	+ve		Continue vaccine course
	−ve		None or continue vaccine course if victim is at risk of further hepatitis B exposure

babies born to HBsAg-positive mothers [8, 141], in children in Africa [24] and susceptibles in Alaska [87].

In healthy individuals the recombinant vaccine is given in a dose of 10 μg (1 ml) intramuscularly at 0, 1 month and a booster at 6 months (fig. 16.24). This induces sufficient antibody response in 94%. The reason for the failure of some healthy individuals to respond is uncertain. These persons should be given a further booster of 20 μg before failure is admitted. Older patients, renal dialysis patients or those who are immuno-suppressed for any reason may have a reduced antibody response and the

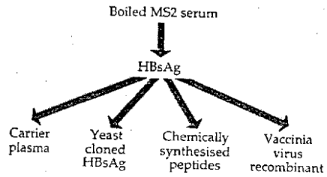


Fig. 16.23. The stages of hepatitis B vaccine production.

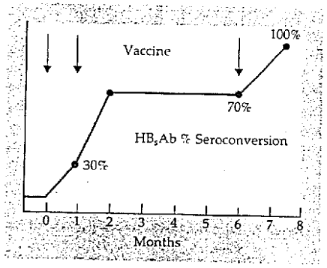


Fig. 16.24. The use of hepatitis B vaccine. Three injections result in about 93% seroconversion at eight months in young healthy subjects.

larger dose of 20 μg intramuscularly should be given.

The vaccine is usually given intramuscularly into the arm. Intradermal administration is effective although antibody titres are not so high as with the intramuscular route [143].

Pre-testing. Vaccination is unnecessary if the person has a positive HBsAb or HBcAb.

The cost-effectiveness of pre-testing to save vaccine depends on the prevalence of serum B markers in a community.

The finding of an isolated serum anti-HBs does not mean immunity to hepatitis B. A positive serum anti-HBc is preferable as this detects infected as well as immune persons.

This test is done in high-risk populations such as homosexuals, drug abusers and spouses of chronic carriers. In low-risk groups, such as health-care workers, it is unnecessary to perform preliminary tests.

Antibody response

The long-term protection depends on the antibody response which is 85–95% in healthy young subjects. Anti-HBs should be measured one to three months after completion of the basic course of vaccine.

Non-responders have peak anti-HBs levels of ≤ 10 IU/l and lack of protection.

Low responders have peak anti-HBs levels of 10–100 IU/l and generally lack detectable anti-HBs levels within about 5–7 years. They may respond to a further booster of double the dose of vaccine.

Good responders have peak anti-HBs ≥ 100 IU/l and usually have long-term immunity.

Failure to develop adequate antibodies may be related to freezing the vaccine or giving it into the buttocks rather than the deltoid region [20].

A poor antibody response is seen in the aged and in the immuno-compromised. These should be given doses of 20 µg.

Approximately 5–10% of normal persons have absent or poor antibody responses. Some may respond to a booster [25].

Duration of protection. This remains unknown. Immunity may persist even after anti-HBs has declined to undetectable levels [53]. Until more data are available, one might consider revaccinating individuals once again, five to seven years after the initial course. Immuno-compromised individuals should be re-vaccinated more frequently.

Indications (table 16.7)

The need for vaccination depends on the chance of that person being exposed to hepatitis B. Vaccination is mandatory for health care staff in close contact with hepatitis B patients, particularly those working on renal dialysis units, liver units, haemophilia and oncology units, genitourinary departments treating homosexuals or those working in homes for the mentally retarded. Surgeons and dentists and their assistants, medical students and laboratory workers regularly exposed to infected blood are also candidates. The vaccine should be given to medical personnel proceeding overseas to areas where the prevalence of hepatitis B is high and where they will be directly involved in patient care.

Acute sufferers from hepatitis B are highly infectious and their sexual contacts should be vaccinated and given hyperimmune-globulin. Sexual and family contacts of hepatitis B carriers should also, if at all possible, be vaccinated after their antibody status has been determined.

Promiscuous homosexuals requesting vaccine should be screened for HBsAg and HBcAb and, if they are not carrying the virus and are not immune, should be vaccinated. The same rules apply to drug abusers.

Babies born to HBsAg-positive, and particularly HB 'e' antigen-positive mothers should be vaccinated and given immune globulin at birth (table 16.7). In countries with a high carrier rate it may be cost-effective to vaccinate all babies without the expense of testing the mothers for HBsAg.

Even in countries with a low carrier rate, it is essential to screen *all* pregnant women for HBsAg and not only those with a high risk of being carriers [63].

The problem of the health care worker, accidentally exposed parenterally to blood which may be infectious, demands special consideration (table 16.8).

The possibility of eliminating hepatitis B and its attendant chronic liver disease and hepato-cellular cancer depends on mass vaccination, particularly of neonates and children in the high carrier areas of the third world. This is turn depends on supplies of an inexpensive vaccine.

OTHER VACCINES

The most simple is derived from *heat-inactivated plasma containing HBsAg* and is based on the original observation of Krugman who boiled infectious hepatitis B-positive serum and showed it protected against hepatitis B [31]. This vaccine is relatively crude and highly immunogenic. It has proved effective in neonates in Hong Kong [141], and in dialysis patients [31].

The cost could be reduced to as little as one dollar per dose.

Polypeptide vaccines are composed of specific immunogenic antigenic determinants of HBsAg. So far they have not proved potent antibody stimulants and are uneconomical to produce.

Hybrid virus vaccines. The coding sequence for HBsAg has been inserted into the vaccinia virus genome and a live vaccine against hepatitis B produced. This has protected chimpanzees against hepatitis B [91]. Vaccinia is clearly not the most satisfactory choice. Other recombinant viruses, such as adenoviruses, are under investigation.

Hepatitis B core antigen [60]. Hepatitis B virus clearance from infected hepatocytes may well require the activity of cytotoxic T-lymphocytes specifically reactive against HBcAg. In chimpanzees, protection against hepatitis B can be induced by immunization with hepatitis B core antigen in adjuvant. This may be useful in the design of further vaccines.

The pre-S region. The hepatitis B virus has a second surface antigen which is coded for by the pre-S region of the HBV-genome (fig. 16.17). Pre-S is important for immunological clearance of hepatitis B viral particles [18]. Recombinant yeast vaccines are now under investigation which will contain pre-S (pre-S1 and pre-S2) [69]. It remains to be determined whether they will be more effective.

Delta virus (hepatitis D virus, HDV)

In 1977, Rizzetto and colleagues, working in Turin, recognized a new antigen–antibody system in the hepatocyte nuclei of HBsAg-positive patients and called it 'delta' [104]. Delta agent is a very small RNA particle coated with HBsAg (figs 16.25, 16.26). It is not able to replicate on its own, but is capable of infection only when activated by the presence of hepatitis B virus. It resembles satellite viruses of plants which cannot replicate without another specific virus. The interaction between the two viruses is very complex. Synthesis of delta may depress the appearance of hepatitis B viral markers in infected cells and even lead to elimination of active hepatitis B viral replication [72].

Delta virus is a single-stranded circular antisense RNA of 1.7 kilobases [70, 139]. It is highly infectious and can induce hepatitis in a HBsAg positive host. It has been transmitted to chimpanzees carrying hepatitis B [42].

Hepatitis B and delta infection may be simultaneous (*co-infection*) or delta may infect a chronic HBsAg carrier (*super-infection*).

EPIDEMIOLOGY

Delta virus infection is not a new disease. Prospective analysis of stored blood shows it among the American army in 1947, in Los Angeles since 1967 [28], and in liver specimens from Brazil in the 1930s.

Delta infection is strongly associated with intravenous drug abuse, but can affect all groups at risk of acquiring hepatitis B infection including homosexuals [124], health care workers, transfusion recipients [80, 107],

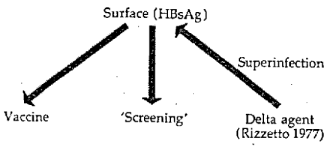


Fig. 16.25. Hepatitis B surface antigen (HBsAg) is the source of the hepatitis B vaccine. It is used for screening for hepatitis B and is superinfected with the delta agent.

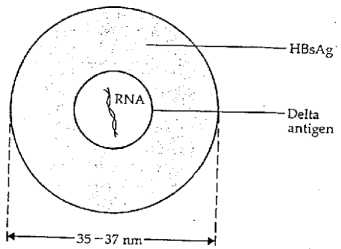


Fig. 16.26. Delta antigen is a small RNA particle coated by HBsAg.

haemophiliacs, immigrants [119] and institutionalized patients. Delta can be spread heterosexually [80]. Intra-family spread with clustering has been noted in Southern Italy [12]. Children can be affected [40]. Delta infection may be reactivated if the sufferer develops HIV infection [116].

Delta infection is world-wide, but particularly in Southern Europe, the Balkans, Middle East [132], South India, and parts of Africa [118]. In general, it is rare in the Far East (including Japan), Brazil, Chile, and Argentina. However, epidemics of delta infection have been reported from the Amazon Basin, Brazil (Labrea fever) [9], Colombia (Santa Marta hepatitis) [19], Venezuela [52] and Equatorial Africa. In these areas children of the indigent population are affected and mortality is high.

DIAGNOSIS (table 16.9)

Serum delta antigenaemia is present only for the first few days of illness.

Co-infection is diagnosed by the finding of serum IgM anti-delta in the presence of high titre IgM anti-HBc. These markers appear at one week, and IgM anti-delta is gone by five to six weeks but may last up to twelve weeks [1]. When serum IgM anti-delta disappears, serum IgG anti-delta is found. There may be a window period between the disappearance of one and

Table 16.9. Diagnosis of delta hepatitis

	Acute	Chronic
Delta antigen		
Serum	+ (transient)	–
Liver	+	+
IgG anti-delta	+ (rising titre)	+ (high titre)
IgM anti-delta	+	+
Delta RNA	+	+

the detection of another. Loss of IgM anti-HDV confirms resolution of delta infection, persistence predicts chronicity.

HBsAg is positive, but often in low titre and may seem negative. Serum IgM anti-HBc is also suppressed by acute delta infection. Unless delta markers are sought, the patient may be misdiagnosed as acute non-A, non-B hepatitis.

Superinfection of a hepatitis B carrier with delta virus is marked by the early presence of serum IgM anti-delta, usually at the same time as early IgG anti-delta and both antibodies persist. These patients are usually IgM anti-HBc negative, but may have low titres of this antibody. Sufferers of chronic delta infection with chronic active hepatitis and active cirrhosis usually have a positive serum IgM anti-delta.

Serum and liver HDV-RNA are found in IgM anti-delta positive patients with acute and chronic delta infection [123].

CLINICAL FEATURES (figs 16.27, 16.28)

With *co-infection*, the acute delta hepatitis is usually self-limited as the delta cannot outlive the transient HBs antigenaemia. The clinical picture is usually indistinguishable from hepatitis due to hepatitis B alone. However, a biphasic rise in aspartate transaminase may be noted, the second rise due to the acute effects of delta [50].

The attack may be fulminant and about a third of fulminant hepatitis B is related to coincidental delta infection. There are marked geographic differences in severity [118].

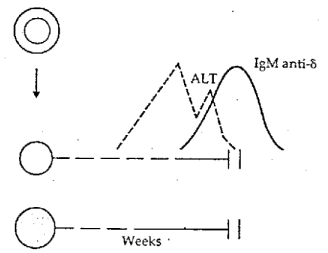


Fig. 16.27. Simultaneous infection with hepatitis B and delta results in acute hepatitis B with rise in ALT (alanine transaminase). Delta infection follows with a second peak of ALT and the appearances of IgM anti-delta in the blood. Clearing of HbsAg is associated with clearing of delta (Rizzetto 1983).

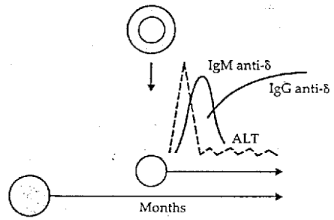


Fig. 16.28. Delta infection in an HBsAg carrier results in an attack of acute hepatitis with the appearance of IgM anti-delta followed by IgG anti-delta in the blood (Rizzetto 1983).

With *super-infection*, the acute attack may be severe and even fulminant, or may be marked only by a rise in serum transaminase levels. Delta infection should always be considered in any hepatitis B carrier, often clinically stable, who has a relapse.

Delta infection reduces active hepatitis B viral synthesis and patients are usually HBeAg and HBV-DNA negative. Two to 10% lose HBsAg. However, chronic delta hepatitis is usual and this results in acceleration towards cirrhosis [140].

Hepato-cellular cancer seems less common in HBsAg carriers with delta. Whether this represents inhibition by the delta virus or such rapid progression of the liver disease that death occurs before cancer can develop remains uncertain. However, when delta is found with late stage chronic liver disease it does not seem to influence survival and hepato-cellular cancer may be a complication in these patients [132].

Delta super-infection modifies the course of healthy B carriers rendering the liver disease more severe.

HEPATIC HISTOLOGY

There may be difficulty in distinguishing the effects of delta virus from those of hepatitis B [135]. However, there is increased histological severity in delta positive patients compared with the usual hepatitis B carriers. Inflammatory activity is greater being particularly marked in intra-lobular portal and peri-portal zones. Focal confluent and bridging necrosis may be seen. Eosinophilic change is noted in the hepatocytes with the formation of acidophilic bodies.

The South American and Equatorial African epidemics are marked by microvesicular fat in hepatocytes, intense eosinophilic necrosis and large amounts of delta antigen within the liver [19]. These changes have also been noted in a New York drug abuser with delta infection [78]. Morula (plant-like) cells may be seen.

Using immunoperoxidase-linked anti-delta serum, delta antigen may be shown in the hepatocyte nuclei. This is reduced in acute delta hepatitis but increases with chronic active liver disease and becomes low in the late stage of cirrhosis (fig. 16.29).

Immune electron microscopy shows nuclear delta as irregular granular structures with aggregates of 20–30 nm similar to those described for non-A, non-B hepatitis [68].

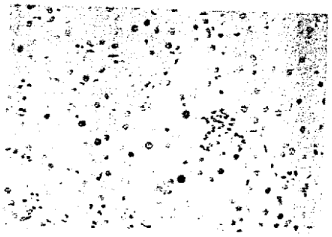


Fig. 16.29. Delta virus hepatitis: immuno peroxidase staining shows delta in hepatocyte nuclei (×100).

PREVENTION

Vaccination against hepatitis B, by rendering the recipient immune to hepatitis B virus infection, protects against delta virus infection. Patients likely to contract delta infection should be encouraged to have hepatitis B vaccine.

Hepatitis B carriers must be educated concerning the risks of acquiring delta by continued drug abuse. A vaccine against delta virus infection is urgently needed.

TREATMENT

This is unsatisfactory. Delta virus infection is unaffected by immunosuppressive therapy. Clinical trials with interferon show inhibition of delta replication with clearance or reduction of serum HBV-RNA and a fall in serum transaminases. Unfortunately delta usually returns to the liver and serum transaminases increase again. More clinical trials are needed, perhaps with larger doses and for a longer time.

Hepatic transplantation of delta infected patients has given disappointing results as delta virus usually returns to the transplanted liver [105].

Non-A, non-B hepatitis

In 1977, on the basis of multiple episodes of viral hepatitis it was suggested that a third variety of acute virus hepatitis existed and this was called non-A, non-B [90]. Diagnosis is made after exclusion of infection with known hepatitis viruses including A, B, cytomegalo- and Epstein–Barr [33, 34]. Non-A, non-B hepatitis has been transmitted to chimpanzees immune to both hepatitis A and B, so confirming a carrier state.

There seem to be two main types, *a blood-borne variety* associated with blood transfusion and drug abuse and an *enteric type* that may be epidemic or sporadic [61]. A possible third type is associated with the administration of blood products such as factor VIII.

PARENTERAL

The causative agent(s) has not hitherto been identified. Under electron microscopy, particles have been seen in the hepatocytes of both chimpanzees and man; their significance is uncertain. Filtration studies give the size of the agent as between 27 and 31 nm [14].

A *viral genomic clone* has been isolated from infected plasma and liver. This encodes the antigen associated with non-A, non-B viral hepatitis in man and chimpanzees [57]. The antibody to it can be measured by radioimmunoassay and has been shown in blood donors and acute and chronic sufferers from parenteral non-A, non-B hepatitis. This opens the prospect of diagnosing chronic non-A, non-B hepatitis and of detecting blood donors carrying the disease.

Hepatic pathology [109]

Various features are suggestive but not diagnostic of non-A, non-B hepatitis. They include sinusoidal cell infiltration, eosinophilic granulomas with acidophilic bodies, giant cells and microvesicular fat. Portal and peri-portal lesions and mild. Bile duct lesions, if present, suggest non-A, non-B hepatitis. Lymphoid follicles may be seen (fig. 16.30).

Epidemiology

The incubation period is about seven weeks.

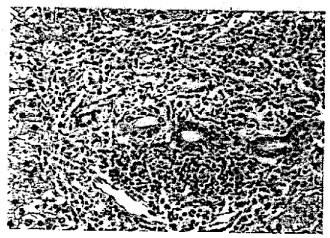


Fig. 16.30. Non-A, non-B hepatitis. Zone 1 (portal) shows cellular infiltration, bile ducts with damaged epithelium and a lymphoid follicle. (H & E ×100.)

Non-A, non-B hepatitis accounts for over 90% of post-transfusion hepatitis in areas where donor blood is screened for hepatitis B. In the United States, it is estimated that 1.6% of volunteer donor blood and 6% of commercial blood carry the virus. In other countries the carrier rate may even be higher, up to an estimated 15% in Brazil.

Recipients of blood products such as Factor VIII and IX are at risk of contracting non-A, non-B hepatitis. In these patients the incubation period may be markedly shortened to 3–21 days. This type may be due to a different virus or to a difference in the infectious dose. Cross-challenge experiments in non-human primates suggest at least two distinct non-A, non-B viruses. The disease has been spread by intravenous immunoglobulin given to agammaglobulinaemics [81].

Non-A, non-B hepatitis also affects dialysis and renal transplant patients and drug abusers. Intra-familial spread is unusual. There is no evidence of heterosexual or homosexual transmission. The high carrier rate in those who give no history of blood transfusion implies that there must be various modes of spread.

Clinical picture

This rather resembles hepatitis B infection. In 73% the patient is completely asymptomatic [23]. In 25%, the picture is that of any other acute virus hepatitis. There may be serum sickness-like prodromata. Rarely the hepatitis is severe and even fulminant (table 16.1).

Serum transaminase values are only moderately elevated, with the peak serum alanine transaminase being about 15 times the upper limit of normal [23]. 60% of patients will have raised serum transaminases one year later. In 68% the disease becomes chronic and in 20% cirrhosis develops [10%] (see Chapter 17).

Hepato-cellular carcinoma, often of clear cell type, is a rare complication [46, 77]. Marrow aplasia may be fatal [7].

Prevention

The use of volunteer instead of commercial blood donors reduces the prevalence. Blood transfusions should be used only when absolutely necessary and blood substitutes are often adequate. The use of free, donated blood will further reduce the risk.

Surrogate tests are being used to identify the donor carrying non-A non-B hepatitis. If blood with an alanine transaminase level exceeding 50 is discarded 30% of non-A, non-B hepatitis would be prevented with a donor loss of 1–3%. The usual cause of the raised transaminase is obesity or alcohol abuse and only 20% are presumptive carriers of non-A, non-B [44]. Serum hepatitis B core antibody can also be used for screening [71]. Those exposed to B are likely to have been exposed to non-A, non-B. This test would reduce post-transfusion hepatitis by 37% with a donor loss of 4–8%.

Factor VIII may be rendered non-infectious by heat inactivation [110]. The risk of factor VIII transmission will disappear when factor VIII is prepared by genetic engineering.

The use of prophylactic immune-globulin before a blood transfusion is given has given good results [108].

A radioimmunoassay test which will diagnose, and hopefully prevent, at least one type of transfusion-related non-A, non-B hepatitis will shortly be available [57].

Treatment of chronic non-A, non-B virus hepatitis (see Chapter 17)

EPIDEMIC (ENTERIC) [101]

In general, this resembles hepatitis A. It affects young adults and has a self-limited course. The mortality is very high in women in the last trimester of pregnancy. The course can be cholestatic, hepatic histology showing marked cholestasis. Epidemic non-A, non-B hepatitis has been reported from India, Pakistan [66], Mexico, Central and South East Asia, North Africa and in travellers returning from these areas [29, 85].

Virology

The disease has been transmitted to Macaque monkeys with recovery of 27–34 nm virus-like particles from the faeces [2]. 27 nm virus particles have been found in the stools of human sufferers and these are aggregated by antibody in acute and convalescent sera from epidemic, but not sporadic, enteric non-A, non-B hepatitis [2]. It is an RNA virus of the calissi group.

Prevention

This depends on improved hygiene and the provision of a clean water supply.

Immunoprophylaxis may be possible using immunoglobulin prepared from donors from countries with a high prevalence of the disease. This may be especially valuable in pregnant women.

SPORADIC (ENTERIC)

This occurs in the general population in the absence of identifiable modes of transmission. Non-A, non-B hepatitis accounts for about 20–30% of acute hepatitis in the Western World [5]. A non-parenteral route of infection, perhaps involving an agent resembling that of epidemic non-A, non-B hepatitis remains possible.

It has a predominance in young men. It is a commoner cause of fulminant hepatitis than either virus A or virus B (table 16.1). The fulminant disease is of slow onset.

Chronicity is uncertain, but is not frequent.

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