Progress report

Natural history of the HBsAg carrier

Chronic carriage of the hepatitis B virus (defined as carriage longer than six months) is an important cause of morbidity and mortality worldwide but particularly in Africa and the Far East. Some idea of the scale of the problem can be gauged from the fact that there are estimated to be 800 000 carriers in USA alone and 200 million carriers worldwide. There are said to be 4000 deaths per annum in the USA due to HBsAg positive cirrhosis and up to 250 000\textsuperscript{1} deaths per annum from HBsAg positive hepatocellular carcinoma throughout the world.

Modes of transmission

In Africa and the Far East where the prevalence of infection in the community is high (10–15\% population), the virus is usually spread from mother to infant shortly after birth and between children in the first few years of life.\textsuperscript{2,3} Such early infection is usually asymptomatic and chronic carriage of the virus frequently results. In Western Europe and the USA as examples of areas of low prevalence of HBsAg carriage, infection usually occurs in adult life and is related to either contact with infected blood or blood products in a health care setting or to drug addiction.\textsuperscript{4} There is an increased incidence of infection among household contacts of chronic carriers of hepatitis B,\textsuperscript{5} and sexual contact, either heterosexual or between male homosexuals, has been increasingly recognised as an important route of transmission.\textsuperscript{4,6} This latter route may be more prone to result in chronic liver disease.\textsuperscript{7} The majority of infections in adults whatever the source are inapparent and perhaps only 30–40\% patients become jaundiced.\textsuperscript{8}

Factors favouring chronicity

A number of factors seem to favour the development of a chronic carrier state. These include infection in infancy or childhood (see above) and male gender. Chronicity also tends to follow mild anicteric illness rather than a severe attack with deep jaundice\textsuperscript{9} and this state of affairs may be more likely with a small viral inoculum.\textsuperscript{10} Approximately 10\% of patients with clinically apparent acute hepatitis B can be expected to become chronic carriers.\textsuperscript{11} Impairment of cell mediated immune responsiveness at the time of infection has been held to account for the tendency to chronicity found in patients with Down's syndrome, chronic renal failure, leukaemia, and on corticosteroid therapy.\textsuperscript{12} In a prospective study among cancer patients inadvertently exposed to HBV, however, there was no increased likelihood of patients becoming chronic carriers. This was true even for those patients who were receiving immunosuppressive therapy.\textsuperscript{13} Several immunological mechanisms favouring the development of chronicity have been postulated.\textsuperscript{14,15}
Duration of HBsAg carriage

The carrier state is not necessarily life long and a small proportion, perhaps 1–2% per annum, lose the antigen and seroconvert to anti HBs. In most of these patients the hepatitis B infection has been eliminated. In others the antigen may become undetectable in the serum by current methods but the virus may still be found in the liver by immunological staining or recombinant DNA technology, (see below). Most of these patients have high circulating titres of antibodies to HBc. The use of IgM anti-HBc may be of value in patients with prolonged acute hepatitis B to predict those most likely to become chronic carriers. Similarly, the absence of IgM anti-HBc when a patient is found on screening to be HBsAg positive suggests that the infection is not recent and that he may therefore be a chronic carrier. The precise use of this assay, however, remains uncertain.

Spectrum of disease and natural history

A wide variety of disease states may accompany the chronic carrier state. These include polyarteritis nodosa and glomerulonephritis but as they are not usually accompanied by significant liver disease they will not be considered further in this review. In the other carriers the precise nature of the liver abnormality is of central importance in determining the natural history.

Carriers with normal liver function tests

The great majority of asymptomatic blood donors who are found to be chronic HBsAg carriers have normal liver function tests. On the other hand, when the asymptomatic carrier population is drawn from clinics for sexually transmitted diseases the proportion with abnormal liver function tests is much greater and probably reflects a more serious burden of significant chronic liver disease. Liver histology has been studied in several series of chronic carriers with normal liver function, and in the great majority of cases the appearances are normal or show only minor changes. Around 10–15% have chronic persistent hepatitis and only the very occasional patient has chronic active hepatitis or cirrhosis.

Serial liver biopsy studies have been carried out on patients with normal histology or minimal abnormalities and the appearances are usually improved or unaltered on the subsequent biopsy. Progression to chronic persistent hepatitis or even cirrhosis is documented exceptionally. Because of the very low prevalence of significant liver disease initially or on follow up, however, it is not generally felt necessary to carry out liver biopsy on carriers with normal liver function. It should be noted, however, that such individuals do appear to have a significant risk of developing hepatocellular carcinoma.

Carriers with abnormal liver function tests

In these cases a spectrum of liver pathology is found on liver biopsy (Table 1) ranging from minimal change through chronic persistent hepatitis to
Table 1 Histopathological findings in asymptomatic HBsAg carriers with abnormal liver function tests

<table>
<thead>
<tr>
<th>Reference</th>
<th>Country</th>
<th>Carrier population</th>
<th>No</th>
<th>N/NS/CPH</th>
<th>CAH ± Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>USA</td>
<td>Donors</td>
<td>17</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>28</td>
<td>Canada</td>
<td>Donors</td>
<td>21</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>42</td>
<td>UK</td>
<td>Donors</td>
<td>18</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>43</td>
<td>Taiwan</td>
<td>Military</td>
<td>13</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>44</td>
<td>Chile</td>
<td>Donors</td>
<td>19</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>31</td>
<td>UK</td>
<td>Mainly homosexual men</td>
<td>61</td>
<td>24</td>
<td>37</td>
</tr>
<tr>
<td>45</td>
<td>Canada</td>
<td>Donors</td>
<td>16</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>46</td>
<td>USA</td>
<td>Donors</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>Italy</td>
<td>Not stated</td>
<td>35</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>36</td>
<td>Austria</td>
<td>Donors</td>
<td>85</td>
<td>74</td>
<td>11</td>
</tr>
<tr>
<td>47</td>
<td>Taiwan</td>
<td>Students</td>
<td>26</td>
<td>24</td>
<td>2</td>
</tr>
</tbody>
</table>

N = Normal. NS = Non-specific changes. CPH = Chronic persistent hepatitis. CAH = Chronic active hepatitis.

chronic active hepatitis and cirrhosis. It is not possible to predict the degree of liver damage on the basis of liver function tests, titre of HBsAg, the HBe/anti HBe status, or level of virus replication.12 48–50 The only accurate means of assessment at present is by liver biopsy. The outlook for patients with minimal abnormalities is good (see above). The other types of liver pathology will be considered separately.

**Chronic lobular hepatitis**

This is an unusual but characteristic form of chronic hepatitis. The histological features are confined to the lobules and comprise spotty necrosis and inflammation.51 Clinical and laboratory features are those of prolonged acute hepatitis (more than six months) and the condition may relapse and remit.52 In a series of 54 HBsAg positive cases from Taiwan many of whom had follow up liver biopsies, Liaw et al53 concluded that the prognosis was excellent and there was no evidence of progression to cirrhosis. No specific therapy is indicated.

Similar inflammatory changes within the lobules accompanied by a rise in transaminase levels may be seen during HBeAg seroconversion54 occurring either spontaneously or in response to antiviral therapy.

The same group from Taiwan has recently suggested that liver biopsies showing non-specific histological changes should be classified with chronic lobular hepatitis as patients had the same fluctuating clinical course, usually with a favourable prognosis.55

**Chronic persistent hepatitis**

A number of studies in the literature report serial liver biopsies in patients with HBsAg positive chronic persistent hepatitis (Table 2). Such studies biased by sampling error on liver biopsy but it can be seen that the condition usually shows no progression although in occasional cases chronic active hepatitis or even cirrhosis may develop. There is no way at present of predicting those cases with a progressive course but there is a
Natural history of the HBsAg carrier

Table 2  Serial liver biopsies in HBsAg positive chronic persistent hepatitis

<table>
<thead>
<tr>
<th>Patients (no)</th>
<th>2nd Liver biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>38</td>
<td>6</td>
</tr>
<tr>
<td>39</td>
<td>8</td>
</tr>
<tr>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td>57</td>
<td>6</td>
</tr>
<tr>
<td>58</td>
<td>11 (HBe+)</td>
</tr>
<tr>
<td>58</td>
<td>5 (HBe-)</td>
</tr>
<tr>
<td>59</td>
<td>11 children</td>
</tr>
<tr>
<td>55</td>
<td>12</td>
</tr>
<tr>
<td>6 CPH 1 CAH 1 cirrhosis</td>
<td>5 CPH 1 CAH</td>
</tr>
<tr>
<td>6 CPH 2 CAH</td>
<td>3 CPH 5 CAH</td>
</tr>
<tr>
<td>5 CPH 1 CAH</td>
<td>3 CPH 1 CAH 4 cirrhosis</td>
</tr>
<tr>
<td>3 CPH 1 CAH normal</td>
<td>9 CPH or minor changes 2 CAH</td>
</tr>
</tbody>
</table>

CAH=Chronic active hepatitis. CPH=Chronic persistent hepatitis.

suggestion that this is more likely in those which are HBe positive. There are, however, many other influences which may play an important role (see below).

Chronic active hepatitis

Follow up studies on patients with HBsAg positive chronic active hepatitis (Table 3) show that many progress to cirrhosis and there is a significant death rate from liver failure and hepatocellular carcinoma. In one study, using life table analysis, the authors report an estimated five year survival of 72%. It is not possible at present to predict with any certainty which patients will progress but the prognosis seems to be better in patients with chronic active hepatitis of minor severity on liver biopsy compared with those with bridging necrosis and patients who are anti-HBe positive generally seem to have less inflammatory liver disease (see below).

Cirrhosis

There are few published reports on the detailed long term follow up of patients with HBsAg positive cirrhosis. Many of these patients, however, die from liver failure, bleeding varices, and hepatocellular carcinoma. The risk of developing hepatocellular carcinoma does seem to be greater than with other types of cirrhosis and may occur in up to

Table 3  Prognosis of HBsAg positive chronic active hepatitis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patients (no)</th>
<th>Mean follow up (months)</th>
<th>Clinical or histological change</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>29</td>
<td>44</td>
<td>No clinical change. Repeo biopsy: unchanged (12) CPH (2) Cirrhosis (3)</td>
</tr>
<tr>
<td>61</td>
<td>17</td>
<td>23</td>
<td>No clinical change</td>
</tr>
<tr>
<td>62</td>
<td>37</td>
<td>32</td>
<td>Repeat biopsy: cirrhosis (3)</td>
</tr>
<tr>
<td>63</td>
<td>17</td>
<td>87</td>
<td>34 stable. Deaths from liver failure (2) HCC (1)</td>
</tr>
<tr>
<td>64</td>
<td>52</td>
<td>46</td>
<td>Cirrhosis in 12. Deaths from HCC (3). Varices (1). Gall bladder cancer (1)</td>
</tr>
</tbody>
</table>

CPH = Chronic persistent hepatitis. HCC = Hepatocellular carcinoma.
38.5% of HBV related deaths. Undoubtedly, chronic infection with HBV is the major cause of hepatocellular carcinoma throughout the world. This complication may supervene after a latent period of as little as 10 years from the time of HBV infection, and has been reported with perinatal infection after only seven years.

Factors modifying the natural history

HBe to anti-HBe seroconversion

Longitudinal studies have shown that in the early phases of chronic infection with HBV there is active viral replication accompanied by circulating Dane particles, HBV DNA, HBV associated DNA polymerase and HBe. This phase may last for three to 10 years and then viral replication ceases and the patients seroconvert to anti-HBe. This phase may last for three to 10 years and then viral replication ceases and the patients seroconvert to anti-HBe.72-74 This is often accompanied or followed by a reduction in biochemical and histological evidence of inflammatory activity. The prognosis at this stage probably depends on the degree of liver damage already present and whereas many cases merely have chronic persistent hepatitis others have established cirrhosis. It should also be noted that the development of hepatocellular carcinoma occurs late in the natural history of the disease and almost always after seroconversion to anti-HBe.70 In some patients inflammatory activity and progression of liver damage continue after seroconversion and there may be other damaging factors operative such as alcohol and delta infection (see below). The annual seroconversion rate in the different series ranges widely from 2.6%-25% (Table 4) with a significantly higher rate of seroconversion in female patients.75 76 Such figures need to be remembered when the effects of antiviral therapy are being assessed in uncontrolled trials.

It has been shown in chimpanzee studies that seroconversion from hepatitis Be antigen to antibody is not always accompanied by loss of infectivity.77 In these cases the more sensitive assays of HBV DNA and HBV DNA polymerase are likely to be positive indicating continuing viral replication usually at a low level. In these patients the presence of HBV DNA in serum correlates with detectable HBeAg in liver tissue.81 This pattern of infection appears more common in the Mediterranean patients where persistent delta infection (see below) may also be contributing to continuing liver damage.

Reactivation of viral replication in patients who are hepatitis Be antibody positive has been reported. Immunosuppressive drugs may be

<table>
<thead>
<tr>
<th>Table 4 Seroconversion from HBeAg to anti-HBe</th>
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<tbody>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>73</td>
</tr>
<tr>
<td>48</td>
</tr>
<tr>
<td>54</td>
</tr>
<tr>
<td>75</td>
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</table>
immlicated but it may occur spontaneously, or after antiviral treatment. The frequency and importance of this phenomenon is as yet uncertain.

**Immunosuppression including corticosteroids**

There is now ample evidence that administration of immunosuppressive drugs will allow increased viral replication which is accompanied by an increase in viral antigen both in the liver and the circulation. Not only does this increase the infectivity of the patient, but there is evidence that the histopathological appearances of the liver may deteriorate. Certainly corticosteroids have not been shown to be clinically beneficial in moderate dosage in HBsAg positive chronic active hepatitis and indeed may be harmful, although a recent report in Chinese patients with chronic active hepatitis produced conflicting results. If immunosuppression is reduced or stopped there is also the danger of a sudden flare up of the disease occasionally with a fatal outcome.

**Alcohol**

There is recent evidence that HBsAg carriers are unduly susceptible to the hepatotoxic effects of alcohol. Modest wine consumption in Italy was accompanied by abnormalities in liver function in HBsAg carriers more commonly than in abstinent carriers and HBsAg negative drinkers. Similarly, Japanese workers have shown that the development of both cirrhosis and hepatocellular carcinoma in HBsAg carriers seems to be accelerated by regular moderate alcohol consumption. Although a recent French epidemiological study failed to confirm these results, it seems wise to advise carriers not to become regular alcohol consumers or at least to keep their intake below 40 g/day for men.

**Simultaneous infection with other viruses**

HBsAg carriers may contract a second hepatotoxic virus infection. We have seen three cases of acute hepatitis A in HBV carriers and one of these patients subsequently cleared HBsAg with return of liver function to normal. A similar sequence of events has been noted by other authors with both hepatitis A and delta agent (see below). The mechanism is speculative. It should also be pointed out that an attack of acute viral hepatitis in a patient who already has serious chronic liver disease whatever the cause is a dangerous development attended by a significant mortality.

**Delta agent**

This is an incomplete RNA virus which requires HBV for replication and clinical expression. It is endemic in Italy where it was first discovered but it has now been identified throughout Europe as well as in USA and South America. At present both in the UK and the USA delta infection is largely confined to drug abusers and haemophiliacs but it may in time become established within the homosexual population. Infection
may occur either simultaneously with the hepatitis B virus or a delta infection may be superimposed on a chronic HBV carrier state. In this latter situation there are various possible outcomes. The patient may develop a self-limited attack of acute hepatitis and sometimes this may be followed by loss of the chronic HBV infection. In other cases there may be a fatal outcome. On the other hand, some carriers who had had normal liver function tests previously now go on to develop chronic liver disease.

It is generally accepted that the prognosis for chronic HBV carriers who have superimposed delta infection is probably worse than for those without it. This may explain in part the high rate of progression of HBsAg positive chronic hepatitis in Italian patients who are predominantly anti-HBe positive and might be expected to have inactive disease. Further controlled studies are needed to examine the natural history of chronic delta infection.

Antiviral treatment

The goals of antiviral treatment for chronic hepatitis B infection are to prevent progression of the liver disease and if possible to eliminate the infection. As the antiviral agents are active only against the replicating virus, patients suitable for treatment have circulating HBV DNA polymerase and most will be HBeAg positive. The role of antiviral treatment for the small group of patients with active liver disease who are anti-HBe positive with persisting low level viral replication remains to be determined.

Recent advances in molecular hybridisation and recombinant DNA technology have allowed the detection of HBV DNA both free within liver cells and/or integrated within the host genome. By the use of these techniques it has become clear that after a few years of infection HBV DNA becomes integrated within the host genome. It is not known why this occurs at a particular time but integration may occur within as little as two years of the initial infection. This has important implications for antiviral therapy since complete eradication of the virus may only be possible if treatment is given before integration has taken place.

Previous attempts at treatment of HBsAg positive chronic liver disease have proved disappointing but there is encouraging progress with the anti viral agents Interferon, adenine arabinoside (ARA - A), its monophosphate derivative (ARA - AMP), and acyclovir. These substances will suppress viral replication during the time of administration and this effect persists in a proportion of cases, although in only very few patients has the HBV infection been eliminated. Antiviral treatment has recently been comprehensively reviewed. At the present time the optimal duration of treatment and whether combination therapy is better than single agent therapy is under investigation in controlled trials. So far the best results indicate that viral replication ceases permanently in around 30-40% treated. This is followed by seroconversion to anti-HBe and reduction in biochemical and histopathological markers of hepatic inflammation. It remains to be seen whether the long term prognosis is improved and in particular whether the risk of developing hepatocellular carcinoma is reduced. Unfortunately, initial results from both our own studies and those...
in other centres suggest that the response rate among homosexual HBV carriers is considerably less than among other groups. This observation awaits confirmation but may be related to the recently described impairment of cellular immunity seen amongst some members of this community. Alternative methods of treatment will be needed to eliminate those hepatocytes in which HBV has already become integrated into the host genome. This may include the use of immune modulators but such treatment is at present experimental.

Prevention

While modest progress may be claimed in the treatment of patients with chronic HBV infections, the aim for the future must be prevention. The development of safe and highly effective vaccines now makes this possible. Because concomitant treatment with hyperimmune globulin against HBV does not interfere with active immunisation, both may be given concurrently to achieve immediate and long term protection either to the newborn in areas of high prevalence or to adults at risk from whatever source.

HBV infections are a major source of morbidity and mortality throughout the world. HBV carriage is not necessarily lifelong and 1–2% of carriers lose the HBsAg per annum. The prognosis for the individual depends on the degree of liver damage present and this can be accurately determined only by liver biopsy although the likelihood of significant liver disease being present is very small in patients with normal liver function tests. Chronic persistent hepatitis seldom progresses but chronic active hepatitis often leads to cirrhosis. The prognosis seems to be adversely affected by moderate alcohol consumption, infection with the delta agent and immunosuppressive treatment. Antiviral agents improve the outlook for some patients. Around 40% of HBsAg positive cirrhotics die from hepatocellular carcinoma.

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Natural history of the HBsAg carrier


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