Chronic Hepatitis B Antigen Disease

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Exposure to the hepatitis antigen (HBAg, Australia, HAA) can have different results (Fig. 1). Certain persons are immune and have no clinical attack; presumably they have been infected previously. Others become healthy carriers. In others, an acute attack develops varying from fulminant to anicteric.

In discussing the development of chronic hepatitis, the mechanism of the persistent antigenaemia that is associated with chronicity and the type of acute attack that is followed by chronic hepatitis and cirrhosis must be considered.

Previously normal individuals who contract HBAg-positive virus hepatitis usually clear antigen from the serum in about four to six weeks of the onset of symptoms. Chronic antigenaemia is associated with different sets of circumstances. It usually implies chronicity, however mild, even if the patient is an apparently healthy carrier. A mild hepatitis is probably not uncommon even in apparently healthy persons detected in the course of screening donors for blood transfusion. In some, the chronic hepatitis follows a clinically diagnosed acute attack. In 88 of one series of patients with HBAg-positive hepatitis studied in Copenhagen the antigen was clear within thirteen weeks but in 11 patients it persisted. In 10 of those with persistent antigenaemia, liver biopsies showed some form of chronic hepatitis (Nielsen et al., 1971). Other workers in Germany (Klinge et al., 1970) and the United States (Prince et al., 1969) have also shown chronic changes in the liver in patients with persistent antigenaemia. In general, the more florid and acute the original attack, the less likely are chronic sequelae to develop. The patient with fulminant hepatitis will probably die but if he recovers, the liver resumes virtually normal structure and function.

The type of acute attack and the development of chronicity could be related to the dose of antigen received. Certainly, a larger amount is likely to come with a blood transfusion than with a needle prick. However, there is no evidence that this determines chronicity. There is no relationship between the blood levels of HBAg and severity. The chronic carrier with the mildest liver damage shows the highest levels (Dudley et al., 1971). Moreover, immuno-
fluorescent studies have shown antigen in liver cells in quantities unrelated to the severity of the underlying lesion; the liver cells of the carrier have particularly large amounts (Hadziyannis et al., 1972).

Virulence is important, as is shown by the terrible results of the outbreak of hepatitis in the renal unit in Edinburgh where there were 10 deaths among patients and staff. This contrasts with outbreaks in other renal units where there have been virtually no fatalities. The aspect of virulence requires further investigation.

![Diagram of hepatitis B antigen and its effects](image)

**Fig. 1.** The possibilities on coming into contact with the Au (HBAg) antigen.

HBAg particles have surfaces that are antigenically complex. This has led to the recognition of four antigenic determinants (subtypes) (LeBouvier, 1971). Subtype a is shared by all HBAg-positive sera. Subtype x is present in almost all positive sera and is probably a host factor. Subtype y and subtype d are mutually exclusive. These subtypes are proving useful epidemiologically. At one time it was thought that a particular subtype was more likely to be associated with development of chronicity, particularly the subtype y. This now seems unlikely as the subtype runs true to a particular epidemic whatever the clinical association. Moreover, geographical differences exist in the predominant subtype. In Greece the main subtype encountered is y, whereas in France the main subtype is a. This again is irrespective of clinical associations, whether asymptomatic, acute, or chronic disease.

Using electron microscopy, hepatitis B antigen is seen as tubules, spheres, and the larger Dane particles which may represent the entire virion, the others
being fragments of the outer coat. It has been suggested that excessive numbers of Dane particles in the blood are associated with chronicity but this cannot be confirmed.

Genetic factors may determine chronicity but they have been little investigated. Certainly there are very great differences in the carrier rate of HBAg in various parts of the world. The incidence is about 1 in 500 blood donors in the UK, whereas in such countries as Greece the incidence is 5 per cent. Moreover, family studies in Sardinia have suggested that HBAg may be inherited as an autosomal recessive. Whether these differences are genetic or environmental remains unknown.

The most important association with chronicity is the immunological status of the recipient of HBAg. Patients in renal units, suffering from renal failure and often receiving immunosuppressive therapy, have a mild attack of type B hepatitis but often become chronic carriers of antigen and develop chronic liver disease. Staff on the same renal unit, with presumably normal immune mechanisms, develop a florid acute attack but rarely chronic disease (Knight et al., 1970). Similarly, those having renal transplants, patients with Hodgkin's disease receiving immunosuppressive therapy, and patients with lepromatous leprosy or Down's syndrome are all liable to develop chronic antigenaemia and chronic hepatitis when exposed to HBAg. These patients have in common a depression of immunity.

The liver injury could be related to primary disturbance of humoral immunity. Antibody is produced to HBAg and this, with the antigens, forms complexes which, in the presence of complement, can cause a lysis, and so death. Several reports support this concept of immune complex liver injury (Almeida and Waterson, 1969). Immunofluorescent studies show immune complexes involving immunoglobulin, HBAg and complement in the tissues of patients with chronic HBAg disease (Gocke et al., 1970). There are, however, points against this hypothesis. If immune complexes are important in the pathogenesis of liver cell injury, complement will be utilised; hence a low serum complement will be expected in patients in whom the liver damage is greatest. The serum level of the third component of complement, which closely reflects the total complement activity, is within the normal range in the majority of patients, but in those with massive necrosis of the liver it is always low (Fox et al., 1971). This marked depression in fulminant hepatic necrosis occurs whatever the aetiology of the liver injury and is likely to be due to reduced synthesis of complement. Moreover, the presence of complexes correlates poorly with the degree of liver damage; only a mild persistent chronic hepatitis is seen in the presence of complexes in HAA-positive polyarthritis, and both acute and chronic hepatitis can occur in patients with
agammaglobulinaemia. Immune complex disease is thus unlikely to be the mechanism by which HBAg is associated with liver cell injury.

Liver cell necrosis is more likely to be related to the cellular immune response of the host to the infective agent. This response is controlled by T (thymus-dependent) lymphocytes, and variations in their function could determine the different clinical courses that can follow infection (Dudley et al., 1972a). After contact with a specific antigen the development of the cell-mediated immunity to that antigen is dependent on the production of synthesised T-lymphocytes which, on subsequent exposure to the antigen, are capable of recognising and reacting with it. This lymphocyte antigen interaction results in lymphocytes producing a number of soluble factors which lead to inactivation of antigen and tissue damage. The clinical course may then depend on variations in T-lymphocyte function. In the presence of normal T-lymphocyte function an acute hepatitis will be produced which will resolve completely with clearance of the infective agent. When specific T-lymphocyte function against the infective agent is absent, both the infective agent and HBAg will persist, with no evidence of liver cell damage. If T-lymphocyte function is impaired, an intermediate course will result, with incomplete removal of the infective agent and continuing liver cell damage. This view is supported by the relation of the clinical course to the development of chronic hepatitis. In the fulminant case, the patient has normal T-cell function; if he survives he recovers completely without developing chronic hepatitis. In the milder case, T-cell function may be inadequate to clear HBAg from the serum. Tissue necrosis is less but antigenaemia and tissue damage continue and chronic hepatitis develops. Carriers have very poor T-cell function, continuing antigenaemia but very little tissue damage.

It has been shown that patients with chronic HBAg disease have impaired lymphocyte response to phytohaemagglutinin, an index of impaired T-cell function (Giustino et al., 1972). One of the soluble factors produced by T-lymphocyte antigen interaction is macrophage migration inhibition factor. The ability to produce this factor is reduced in lymphocytes from patients with chronic HBAg hepatitis when exposed to HBAg (Dudley et al., 1972b).

The view that chronicity develops in those with poor T-cell function would be compatible with the progression of the disease in patients with renal failure and having immunosuppressive therapy. Similarly, neonates, who are known to have impaired cellular immunity, are liable to develop chronic HB antigenaemia and cirrhosis when exposed to HBAg from their mothers (Schweitzer et al., 1972). Finally, corticosteroids inhibit the cellular immune response and administering these drugs during the acute stage of type B hepatitis seems to favour the progression to chronic disease (Dudley et al., 1972c).
PATHOLOGICAL CHANGES
The classification of the chronic sequelae of HBAg infection is made on a pathological basis and depends on correct interpretation of hepatic histology as shown by needle biopsy of the liver (Scheuer, 1970).

The pathological findings include chronic hepatitis and cirrhosis.

Chronic hepatitis is defined as continuing liver inflammation lasting for more than one year. It is divided into two main types, designated chronic persistent and chronic aggressive hepatitis (De Groote et al., 1968).

Chronic persistent hepatitis is characterised histologically by portal zone inflammatory infiltration, preserved zonal architecture, and slight or absent fibrosis. Piecemeal hepato-cellular necrosis is not conspicuous. The condition is essentially reversible and the prognosis is excellent.

Chronic aggressive hepatitis is characterised by a chronic inflammatory infiltrate involving the portal areas and extending into the parenchyma, with piecemeal necrosis and formation of intralobular septa. Zonal architecture is disturbed but there is no nodular regeneration. This progressive hepatitis undoubtedly proceeds, in some instances, to cirrhosis, and the eventual prognosis is poor.

Cirrhosis is marked by complete disorganisation of the zonal architecture of the liver with hepato-cellular nodule formation and widespread fibrosis.

CLINICAL PICTURE
Fifty-six of 59 patients in one series were male and this disease predominantly affects the male sex, most often the 30- to 50-year age group. This is in striking contrast to the ‘lupoid’ type of active chronic hepatitis, which predominantly affects females, usually of a younger age. The disease is often recognised in physicians, perhaps because they are more likely to seek specialist medical attention and because they are more heavily exposed to HBAg. The chronic disease may follow clear evidence of unresolved acute hepatitis but in about half the cases the condition presents as established chronic liver disease or as primary hepato-cellular carcinoma. Clinical findings and biochemical tests of liver function in the different groups of patients reflect the underlying hepatic histology, whether chronic persistent or chronic aggressive hepatitis, cirrhosis or liver-cell carcinoma. The serum bilirubin, aspartate transaminase and gammaglobulin levels are rarely very high.

Smooth muscle antibody is usually absent or present in low titre (Dudley et al., 1973). This is in contrast to the lupoid type of active chronic active hepatitis where smooth muscle antibody is present in significant titres in two-thirds of patients.
TREATMENT
Corticosteroids are not advised in acute HBAg-positive viral hepatitis, for although they may suppress liver cell damage they may also predispose to persistence of the infective agent and to relapses, making the development of chronic liver disease more likely. However, when HBAg persists and chronic hepatitis is diagnosed the position is different. Corticosteroids have already been shown in a prospective trial to be of benefit in prolonging life in patients with active chronic hepatitis of the lupoid type (Cook et al., 1971). They also undoubtedly suppress liver cell damage in HBAg positive chronic liver disease, perhaps by reducing the injurious effects of sensitised T-lymphocytes. They should probably be used in such patients when there is histological evidence by needle biopsy of active liver cell damage. Serum bilirubin, aspartate transaminase and gammaglobulin levels fall with this treatment and serum albumin levels rise. Maintenance dosage should be sufficient to suppress the activity of the liver cell damage and is usually about 10 to 20 mg prednisolone daily. Therapy should be continued for six months after liver function tests have returned to normal. Slow withdrawal of prednisolone should then be attempted while maintaining close observation for signs of relapse. This recommendation, however, is based on a limited experience of its use in HBAg-positive chronic liver disease; a prospective controlled trial of corticosteroids in this disease has not yet been published.

PROGNOSIS
Progression of the liver disease appears to be slow and insidious. Thirty-three patients were followed up for an average of two years and there was no clinical or biochemical deterioration of any patients with chronic persistent or aggressive hepatitis (Dudley et al., 1972c). Patients with chronic persistent hepatitis are expected to have a good prognosis but in HBAg-negative chronic active hepatitis there is usually a high early mortality. Where clinical and biochemical deterioration occurs, primary liver cell carcinoma must be strongly suspected. There is an undoubted association between primary liver cell cancer and a positive HBAg test. In England, 22 per cent of patients with primary liver cell carcinoma show a positive HBAg test. In tropical areas, where primary liver cell cancer is more common, the incidence is higher. The exact relationship between the two is uncertain. Whether this is simply an association with cirrhosis per se or whether HBAg has oncogenic properties remains uncertain.

This article is based on a paper read at the Conference on Chronic Liver Disease held in the Royal College of Physicians in May 1973.
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Book Review

Clinical Aspects of Thromboembolism. By W. R. Pitney. Churchill Livingstone, 1973. Price £3.00, 194 pages.

So often when a new book appears on the market, one is perplexed in trying to understand who the text is aimed at. In this case there is no doubt that Dr Pitney’s monograph on clinical thromboembolism is aimed at all those who practice clinical medicine, from student to consultant. Thromboembolism is a common clinical problem and, on the whole, is dealt with in a rather uncertain manner. Much recent writing on this subject has increased confusion.

The layout of this book is well-prepared, the first part dealing with the clinical problems, the second with anti-coagulant therapy and thrombolysis, and an excellent final chapter on the guide lines to management. The conclusions at the end of each chapter are founded on a well-balanced text and presentation of the literature, backed up by an excellent bibliography.

For the reasonable price this book can be thoroughly recommended to all clinicians.

D.E.