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Viral Hepatitis, the B Antigen, and Liver Cancer

Review

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The role of viral hepatitis in the pathogenesis of chronic liver disease has been the subject of debate for many years. Viral hepatitis represents an acute inflammation of the liver caused by one of at least two immunologically distinct infectious agents; hepatitis A is the etiological agent of infectious, epidemic, or short-incubation hepatitis, while virus B is responsible for the so-called serum hepatitis, or long-incubation hepatitis. (Inflammation of the liver caused by yellow fever virus, as well as the hepatitis frequently associated with other common viral infections such as cytomegalovirus (human herpes virus 5) and EB virus (human herpes virus 4) are generally excluded from the common definition of viral hepatitis.)

The discovery in 1965 by Blumberg, Alter, and Visnich of the Australia antigen, now known as hepatitis B antigen, has provided a specific serological marker of infection with (or carriage of) type B hepatitis virus. This finding has altered our previous concepts about the nature of type B infection and has resulted in considerable progress in defining the epidemiology and immunology of this form of hepatitis. The hepatitis B antigen is a protein associated with a varying amount of lipid. It is immunologically distinct from normal low-density lipoproteins, and the buoyant density of the antigen-bearing particles is intermediate between that of serum lipoproteins and most other serum proteins.

Molecular Nature of Hepatitis B Antigen

The molecular nature of the hepatitis B antigen is mysterious. It is uncertain whether it represents incomplete virus particles, aggregates of protein subunits, excess virus coat material, overproduction of unstable virus-like particles, or a modified cellular component whose synthesis is specified or specifically derepressed by the hepatitis B virus (see Zuckerman, 1972). The observation of Jozwiak et al. (1971) that antigen partially purified from serum contains about 5% RNA, and the detection by Hirschman, Vernace, and Shaffner (1971) of a reverse transcriptase activity in pellets of antigen concentrated by ultracentrifugation from sera of patients with hepatitis have not yet been confirmed.

These observations have led to suggestions that hepatitis B antigen is associated with a unique type of infectious agent, which also has the properties of a serum protein polymorphism, that the infectious agent may be classed among the subviral agents termed viroids (see Zuckerman, 1973), or that hepatitis B virus consists of a very small amount of RNA-enzyme complex with an amount of host protein far in excess of the protein coat of most recognized viruses. Popper and MacKay (1972) have suggested that these host proteins might include various pre-existing structures of the liver cell.

Based on this premise, acute type B hepatitis may be regarded as a restricted immunological response to the proteins in the hepatitis B antigen-virus complex. Such models predict that any hepatitic antecedent of chronic liver disease should be associated with hepatitis B antigen positive infection. This chronic liver disease may then be the result of one of two processes: either continued restricted immune reactions against the virion or, more probably, reactions to the protein of the whole antigen-virus entity, with infectivity that persists because of the presence of the virion and with a characteristic distribution of antigen at other sites, resulting in a continuing autoimmune reaction to specific host components of broken-down hepatitis B antigen particles (Popper and MacKay, 1972).

The discovery of a new antigen-antibody system in antigen-positive hepatitis B (Almeida, Rubenstein, and Stott, 1971) has added an important new dimension to definition of the nature of the infectious agent. Detergent treatment of pellets of hepatitis B antigen obtained by ultracentrifugation of whole serum containing the large 42-nm spherical (Dane) particles results in separation into an outer coat of antigen and an inner component some 27 nm in diameter. The morphology of the inner core resembles that of a rhinovirus.

Antibody present in the serum of patients after recovery from hepatitis B reacts with the inner core, but not with the outer hepatitis B antigen component, yielding immune aggregates resembling those seen in homogenates of liver taken postmortem from patients with type B hepatitis. An important observation was that antibody to the inner core is absent from the prehepatitis sera from the same convalescent patients. This suggests that antibody to hepatitis B develops in this type of hepatitis but is subsequently cleared from the serum with clinical improvement, while a normal immune response is produced to the inner core of the 42-nm particle. These findings have since been confirmed and lend support to the view that the inner component may indeed represent the infectious agent of type B hepatitis, although final confirmation must await the successful cultivation of the infectious agent.

Etiology of Viral Hepatitis

Both type A and type B hepatitis take the form of frequent and widespread infections in the Tropics. The apparently high prevalence of hepatitis B antigen in chronic liver diseases and especially mac-

ronodular cirrhosis and primary liver cell cancer in many regions in Africa and Southeast Asia implies the possibility of some form of etiological association. But there are varying and conflicting reports from different regions on the frequency of detection of hepatitis B antigen in patients with liver cell carcinoma (see WHO Report, 1973).

As in the case of other liver diseases, it is not known whether the discrepancies between different areas are due to genuine geographical differences or to variations in the techniques and reagents used to assay the antigen, differences in sensitivity or differences in titre of circulating antigen. And any geographical differences may be environmental rather than genetic in nature, for while there is a similar low incidence of hepatocellular carcinoma in the Negro and white populations in North America, the native African displays a very much higher incidence. That only tentative conclusions about the link between hepatitis B antigen and liver cancers can be drawn at present is emphasized by observations that hepatitis B is not uncommon in countries where liver cancer is very rare, even though hepatitis B antigen is prevalent in patients with chronic active hepatitis and cirrhosis in many areas.

One suggestion has been that an important factor in the possible etiological association between hepatitis B infection and liver cell carcinoma may lie in an early age of exposure to infection; and repeated exposure in very early life has been proposed as an important element. But although it is impossible to deny that the risk of infection in early life, before the defense immune mechanisms have fully developed, is much greater in tropical countries—for example, as a result of poor socioeconomic environment and mechanical or passive transmission of hepatitis B infection by the bites of blood-sucking arthropod vectors—infection of children in other geographical regions also seems to occur not infrequently, especially in institutions and occasionally as a result of family clustering.

Is Hepatitis B Transmitted Vertically?

Transplacental transmission of hepatitis B infection does not appear to be common, even when sensitive techniques are used for detecting hepatitis B antigen (see WHO Report, 1973). But transmission of hepatitis B antigen from mother to infant is relatively common when the mother suffers from hepatitis B infection between the eighth month of pregnancy and the end of the second month postpartum. Transmission during the passage in the birth canal or postnatal infection as a result of close contact seems likely, although the transplacental route may also be involved, at least in a few instances. Transmission of the antigen seems to be infrequent when maternal hepatitis occurs early in pregnancy or from mothers who are asymptomatic carriers of the antigen.

A particularly interesting study in Japan has been reported by Ohbayashi, Okochi, and Mayumi (1972). Sera collected from 54 members of 3 families with chronic liver disease or primary liver cancer were tested for hepatitis B antigen by immune adherence haemagglutination. The antigen was detected in 14 of 15 affected members of the families and their siblings and in 20 of the 24 children of the female siblings. In contrast, the antigen was detected in only 1 of the 8 children of the male siblings, and the homologous antigen was found in the serum of his mother. The antigen has not been demonstrated in the 6 spouses of the siblings so far tested.

The finding of hepatitis B antigen in these three families coincided remarkably well with the distribution of severe chronic liver damage or primary hepatoma in the family tree. Familial clustering of cryptogenic cirrhosis has been reported in 10 families in Japan since 1963. Of the 39 affected members of these families, 11 died of cirrhosis and 9 died of cirrhosis combined with primary liver cancer. It is notable that successive occurrence of liver disease for two generations was recognized in 7 of the 10 families, and the mother or her siblings were affected in each of the 7 families.

In spite of these results, however, it is too early to assess with any certainty the relative importance of horizontal and vertical transmission of type B hepatitis in relation to chronic liver damage, for which further genetic studies are needed.

Links between Hepatitis B and Liver Cancer

Preliminary tests have indicated that the frequency of antibody to hepatitis B antigen may be reduced in patients with primary liver cancer. This observation suggests an immunological difference in the host response to hepatitis type B infection; and failure to produce sufficient antibody may be one of the factors that leads to persistence of the antigen. However, another study of patients with hepatocellular carcinoma revealed no defect in either the humoral or cellular immune responses.

On the other hand, it is important to note that the epidemiology of liver cancer does not display the properties of an infectious disease. Unambiguous data are required to establish the progression of hepatitis to primary liver cancer. After all, type B hepatitis is ubiquitous, particularly in Africa and Southeast Asia, and who can say whether the infectious agent is the driver or the passenger? The kind of evidence that is needed must show that infection precedes the development of the cancer, that the tumor cells contain virus-specific molecules or antigens, that the cancer cells produce the agent, and that the virus can transform cells in cul-

ture or induce hepatomas in experimental animals; and, most important of all, it must be shown that immunization against the infectious agent, when it becomes available, will lower the incidence of cancer as a result (assuming that the responsible human virus is not transmitted until after birth).

Chemical Induction of Liver Cancer

Those who work with chemical carcinogens tend to believe, of course, that their favorite compounds —such as the polycyclic aromatic hydrocarbons, aromatic amines and amides, azo dyes, selenium or nitrosamines—are the most likely candidates for the principal environmental causes of cancer. Interest in the mycotoxins and the pyrrolizidine alkaloids also continues. The aflatoxins, for example, comprise the most potent hepatocarcinogens known for the rat and also induce hepatic carcinomas in fish, birds, and mammals, although not as yet in primates.

The extensive experimental data gained from animal studies form the basis for the suggested importance of fungal products in the etiology of human liver cancer. It is also known that optimum conditions for the natural production of the aflatoxins and other mycotoxins are found in those areas of the world with a high incidence of liver cancer; furthermore, such toxins have been isolated in some of these areas from human food (Purchase, 1971).

Yet the quantity of aflatoxin that would need to be ingested by an individual in the form of contaminated peanuts, assuming the dose is similar to that needed to cause experimental necrosis of the liver of the type seen in experimental animals, is in gross excess of that likely to be consumed, amounting to several kilograms per day (Higginson, 1970). It remains possible, nevertheless, that the ingestion of low doses of aflatoxin, in conjunction with other stimuli, over a long period of time may be carcinogenic for man. Liver cell cancer is probably the cumulative result of many factors, and the roles of viral and parasitic infections, chemical carcinogens, fungal toxins, and other nutritional and environmental factors cannot yet be defined.

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