# Hepatitis-Associated Antigen, Cirrhosis and Hepatoma in Rhodesia

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## SUMMARY

**Since the discovery of hepatitis-associated antigen (HAA) in 1963 its relationship to chronic liver disease has been quite extensively researched. Cirrhosis and hepatocarcinoma are commonly diagnosed in the Rhodesian Black and the association between HAA and these two liver diseases was investigated.**

**HAA was detected in 6,6% of cases of cirrhosis but was not associated with any case of hepatoma. This finding, in Rhodesian Blacks, where HAA is detected in the sera of 2,5 - 3,6% of the normal population, is of considerable significance, implying that HAA (and the serum hepatitis virus) is of little or no aetiological importance.**


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Hepatitis-associated antigen (HAA, Australia antigen, or serum hepatitis antigen) was discovered in 1963 in the serum of an Australian aboriginal.[2] It can be detected in the serum of patients with infective hepatitis, and the relationship between this antigen and long-incubation hepatitis after blood transfusion was demonstrated by Prince.[31] Since then there has been much experimental and epidemiological evidence to further confirm the association between HAA and serum hepatitis.

More recently reports have been appearing in the medical literature dealing with the relationship between HAA and chronic liver disease and hepatoma, based upon earlier studies which linked cirrhosis of the liver with antecedent infective hepatitis.

We should like to present our findings in respect of two series of patients with cirrhosis and hepatoma, both conditions being extremely common in the Rhodesian Blacks in our experience.

## METHODS AND MATERIALS

The sera of 25 patients with cirrhosis and 30 patients with hepatoma were tested for the presence of HAA, using hyperimmune anti-Australia antigen baboon serum and crossed-over immuno-electrophoresis. In all patients the diagnosis of hepatoma or cirrhosis was confirmed histologically, Menghini needle biopsy of the liver being performed upon each patient. Patients who were thought too ill to undergo liver biopsy, or whose platelet count and/or prothrombin time were outside the usually accepted safe limits, were excluded from this study.

All patients were Blacks admitted to the University medical wards of Harare Central Hospital, Salisbury, during 1972 and 1973.

Of the patients with cirrhosis, which proved to be predominantly of macronodular pattern (Table I), only 2 were found to have HAA in the serum. In no patient in whom the diagnosis of hepatoma was established on liver biopsy could HAA be detected in the serum.

**TABLE I. INCIDENCE OF HAA IN CIRRHOSIS AND HEPATOMA IN RHODESIAN BLACKS**

| Diagnosis | No. of patients | Incidence of positive HAA |
|---|---|---|
| **Cirrhosis** | | |
| **Macronodular 19 (63%)** | **30** | **2 (6,6%)** |
| **Micronodular 11 (37%)** | | |
| **Hepatoma** | **30** | **0 (0%)** |

## DISCUSSION

Following a great deal of confusion regarding chronic liver disease, it emerges that infective hepatitis may follow essentially one of 3 courses:

1. It may resolve completely, leaving the liver undamaged.

2. It may persist with continued clinical and histological evidence of hepatic inflammation. Thus there is persistence of jaundice, or at least continued elevation of bilirubin and SGOT levels for several months, while serial liver biopsy shows chronic inflammatory infiltrates involving principally the portal areas, but with preservation of normal liver architecture. Ultimately the inflammation subsides, with no residual functional or histological change in the liver.

3. It may progress in an aggressive manner characterised by continued hepatitis clinically, and histological changes occur which have been outlined by Klatskin[9] and De Groote *et al.*,[4] namely chronic inflammatory infiltration involving the portal tracts and zones of necrosis which, unlike typical viral hepatitis, tend to be larger and cross lobular boundaries, either bridging adjacent portal triads and central veins or involving whole lobules or groups of lobules. Architecture is disturbed, with the eventual development of postnecrotic (macronodular) cirrhosis.

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To such persistence of hepatic inflammation the terms 'chronic persistent hepatitis' in course (2), and 'active chronic hepatitis' in course (3), have been applied. These 2 categories of disease have been shown to be associated with a persistence of HAA in the serum.[8]

Sutnick,[18] reviewing the relationship between HAA and chronic liver disease, wrote rather provocatively: 'There is a group of individuals who are susceptible to persistence of an agent (HAA) which causes acute hepatitis, resulting in chronic hepatitis and some postnecrotic cirrhosis. These individuals and their damaged livers are also susceptible to some *other* agent in the environment, either infectious or non-infectious, which has the potential of causing malignant hepatoma. This agent does not cause hepatoma in the general population, but only in the susceptible individual. It may only cause the disease in those susceptible individuals who already have chronic liver damage.' Perhaps by so writing he has crystallised the thoughts of the many workers who, in the past 5 years or so, have investigated the link between HAA and the development of cirrhosis and hepatoma. Thus the literature abounds with reports of the experiences of researchers in various countries of the world, this cumulative experience having been extensively reviewed by Prince.[13]

In relation to cirrhosis of the postnecrotic (posthepatitic) type, Australia antigen has been reported in from 4 to 44% of cases in Europe and the USA.[3,5,9,15,21] In Africa Maynard *et al.*[10] found HAA in 33% of cirrhotic patients in Uganda, while Bagshawe *et al.*[1] report HAA in 20,5% of their patients with cirrhosis in Kenya. A similar experience emerges in relationship to hepatoma.

The results of this present study stand out in sharp contrast to those of workers in Africa outside Rhodesia. They are especially significant when one considers that HAA is detected in a relatively high (2,5 - 3,6%) proportion of normal rural Blacks and Black blood donors.[19] It has been suggested that this high detection rate, compared with a European blood donor detection rate of only 0,2%, is a consequence of infection by the serum hepatitis virus during tattooing or cutting of the skin as a tribal or witchdoctor ritual, both practices being extremely common among the Rhodesian Blacks.

Hepatoma constitutes one of the most prevalent malignancies encountered in Rhodesian Blacks according to Harare Hospital records;[16] cirrhosis, predominantly of the coarse postnecrotic type, is extremely common. HAA was not detected in the serum of any patient with hepatocarcinoma and was detected in only 2 (6,6%) patients with cirrhosis. The Rhodesian experience, as outlined in this article, and earlier by Swanepoel and Cruikshank,[19] parallels more closely the experience of workers in the USA[17] and Northern Europe[15] than that of workers in Southern Europe[3,9] and Africa north of Rhodesia.

The hepatitis-associated antigen, and by implication the serum hepatitis virus, appear to play little or no aetiological role in the development of cirrhosis or hepatoma in Rhodesia. Other aetiological factors must therefore be considered. It may be that cirrhosis (upon which hepatoma is almost invariably superimposed)[6] in Rhodesian Blacks has an alcoholic aetiological basis. Prince's review article shows that HAA has seldom been demonstrated in relation to alcoholic cirrhosis.[13] Many of our patients give a history of heavy alcoholic intake over many years, in the form usually of home-brewed beer, and the relationship of chronic liver disease and alcoholic intake in Rhodesian Blacks is the subject of formal study at the present time.

The theory that the carcinogen aflatoxin is important in the genesis of hepatocarcinoma is an old and popular one. Evidence of its aetiological relationship with hepatoma comes largely from the Far East, but recently strong evidence has been accumulating in Africa also, and Van Rensburg[20] reported at the International Liver Conference with special reference to Africa, held in Cape Town in early 1973, that 'the experimental evidence for incriminating aflatoxin as the main cause of "epidemic" liver cancer in Africa is rapidly becoming overwhelming'.

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