Progress report: Hepatitis-associated (Australia) antigen

This most interesting antigen was discovered incidentally. In 1965, Blumberg, a geneticist, and his colleagues1 were working in Philadelphia on the development of antibodies against human serum lipoproteins using Ouchterlony's double diffusion technique. They found that in two multiply-transfused haemophilic patients, there was a precipitin which reacted with antigen in a single serum in their panel and this came from an Australian Aborigine. The antibody, an immunoglobulin G, was found in many patients who had been multiply transfused. Later the antigen was found in some 20% of patients with viral hepatitis2 and this was confirmed in Japan3. Because of its discovery in an Aboriginal serum, the antigen was originally called Australia antigen. It was later related to serum hepatitis and called SH-antigen, but in view of uncertainty concerning its relationship to the type of hepatitis, the more general term, hepatitis-associated antigen (HAA) has now been adopted.

The antigen is more frequently found in the blood of patients with serum (post-transfusion) hepatitis (34% of 41 patients) than in those suffering from infectious hepatitis (13% of 84 patients)4. If sampling is done more frequently, the incidence of positive results may be increased. Blood samples taken at weekly intervals during the acute phase of serum hepatitis were positive in 46 of 62 patients (74%)5. The antigen has been detected in serum 35 to 120 days after exposure to contaminated blood products and has persisted for one week to three months in 42 patients and for more than 10 months in five patients5. In another study, Gocke and Kavey6 from New York reported that 36 of 48 patients with serum hepatitis gave positive results for the antigen. The percentage of positives increased to 82% (28 of 34 patients) when testing was done within the first 12 days after the onset of symptoms. Seven of 15 patients with possible infectious hepatitis gave positive results, but of the eight patients giving negative results seven were tested more than 12 days after the onset of symptoms. When tested within the first 12 days, five out of six patients (83%) gave positive results. Cossart and coworkers7 found 11 positive sera out of 27 from patients with hepatitis in a London infectious-disease hospital. Wright and coworkers8 from Yale (USA) found 25% of patients with infectious hepatitis positive by this test. These results raise the important issue of whether HAA is related to the virus of serum or infectious hepatitis or indeed whether the two diseases are related in any way. At the present time, this question cannot be answered. Using the Willowbrook strains of hepatitis virus, Giles and coworkers9 from New York, found no antigen in several specimens of serum taken four to 200 days after infection from 31 patients with short incubation period viral hepatitis, in 19 patients with long incubation period hepatitis, however, the antigen appeared regularly, usually well in advance of clinical hepatitis. In approximately half the cases, it was present only transiently (up to 68 days) but in the remainder it persisted throughout the period of intensive observation and for at least three years subsequently. Prince10 in 1968, also in New York, failed to find HAA with hepatitis assumed to be of infectious type, but it was present in 10 of 12 specimens obtained in the early acute phase of serum hepatitis. These observations, together with the increased
incidence with serum hepatitis have led to the relation of Australia antigen specifically to the SH virus; this remains uncertain. Certainly in both forms of the disease, HAA tends to be present only in the early stages and a negative result obtained later does not exclude the diagnosis. The elaboration of more sensitive methods of assay, particularly a complement-fixation test\textsuperscript{11}, may add to the diagnostic usefulness of the method.

Using electron microscopy, the antigen has been identified as definite particles\textsuperscript{12}. They seem to be approximately 190-210 Å in diameter, about the same as virus particles. Addition of specific rabbit gammaglobulin results in agglutination of the particles and this suggests that antigenic sites are present in them. When serum containing Australian antigen is mixed with antibody containing serum and centrifuged, aggregates are found in the antigen antibody precipitates. The standard form of the antigen-antiserum particles is spherical, but numerous tubular aberrant forms are also present\textsuperscript{13}. The particles are indistinguishable whether obtained from patients with infectious or serum hepatitis\textsuperscript{5,13}. A further support for the causal association of HAA with hepatitis seems to have been obtained by a fluorescent antibody technique\textsuperscript{14}. A specific antibody to HAA was conjugated with fluorescein and the conjugate reacted specifically with an antigen which was localized in, or on, the surface of nuclei of hepatic cells obtained by biopsy of the liver from four patients with viral hepatitis, all of whom carried HAA in their serum. Positive results were not obtained in five control patients, four of whom had no evidence of liver disease and whose serum did not contain HAA. These results remain to be confirmed in other laboratories.

Relation to Blood Donors and Transfusion

The incidence of positive tests for HAA seem to vary in different parts of the world. In New York, 16 of 2,211 units of blood tested were found to contain HAA\textsuperscript{15}. In Japan, the antigen was found in 141 of 11,820 blood donors\textsuperscript{3}. Recipients of blood containing HAA may develop hepatitis. In Japan, recipients of such blood either developed antibody in their serum or the antigen itself could be found in the blood when they developed post-transfusion hepatitis. In New York, nine of 12 patients who received blood containing HAA developed hepatitis later; HAA appeared in the serum of seven of these patients during the illness. The development of antibody to the antigen may not be protective for its presence before post-transfusion hepatitis develops does not prevent its later occurrence\textsuperscript{16}. This suggests that either antibody does not completely protect against hepatitis or that the hepatitis was caused by an agent serologically distinct from that associated with HAA. The antigen may survive and persist in the blood for as long as 20 years\textsuperscript{17}. In 1951, a blood donor was identified as a carrier of serum hepatitis and 10 months after the first episode of an infection in a recipient of his blood, a sample of serum led to hepatitis in one of five volunteers into whom it was injected. Fresh samples of serum collected in 1968 and 1969 from this apparently healthy donor contained HAA.

These observations have great practical implications. It will almost certainly be necessary to screen all prospective blood donors for HAA before they are accepted to give blood. This will eliminate many undesirable donors, particularly narcotic addicts. The staff and patients of all renal dialysis units will need to be similarly screened. There are limiting factors in the development of such mass screening programmes. The most important is a current world-wide shortage of antibody. This will be overcome when more persons having antibody in their serum are detected and when greater cooperation exists between different laboratories working on HAA. The
development in Chimpanzees of antibodies to Australia antigen may also solve the serum antibody shortage. A standard of serum antibody must be selected which may be obtained from pooled serum. This must be available to all for central reference. Another difficulty is that the anticoagulant present in the blood used for transfusion can cause difficulties in testing for HAA by the Ouchterlony double-diffusion method.

Relation of Down's Syndrome to Leukaemia and to Renal Failure

Hepatitis associated antigen has been found to persist in the blood of patients with Down's syndrome, particularly those in large institutions, where spread of infection is most likely. It is absent in outpatients and the frequency is very low in patients living in small institutions. The frequency of elevated serum transaminase levels parallels the frequency of HAA and evidence of hepatitis has been found in liver biopsy sections from patients with Down's syndrome having HAA, irrespective of the presence or absence of clinical or laboratory evidence of liver disease. The antigen also persists in the blood of some patients with lepromatous leprosy, and in patients with chronic leukaemia who have received many blood transfusions. Patients with renal failure having chronic dialysis have also been shown to carry the antigen, not only if they have a definite history of hepatitis, but also if they have been multiply transfused. In one patient the test was positive after three years. The blood of these patients was probably the causal agent for outbreaks of hepatitis. These patients also, presumably, have abnormalities of their immune mechanisms in terms of perpetuation of the antigen in the serum. This may be the common factor between Down's syndrome, leukaemia, and lepromatous leprosy.

Relationship to Chronic Liver Disease

There seems to be a connexion between HAA and chronic liver disease. Wright and coworkers from Yale found the antigen persisting for months or years in seven out of 14 cases of unresolved viral hepatitis, four of 15 cases of subacute hepatic necrosis progressing to posthepatitic cirrhosis and six of 24 cases of chronic active hepatitis. Fox and colleagues; from the Royal Free Hospital, London, failed to detect HAA in 32 patients with active chronic hepatitis. The differences between the results from the two centres may be related to criteria for diagnosis of active chronic hepatitis. If results are confined to young females with persistent hyperbilirubinaemia and hypergammaglobulinaemia with multisystem involvement and hepatic histology showing marked plasma cell infiltration, rosette formation, and piecemeal necrosis, then HAA seems to be absent from both centres. There does, however, appear to be a form of aggressive chronic hepatitis which is associated with a positive HAA test. It is unusual in England, but has been encountered in patients from Africa, Greece, and the United States. The entity has been described so recently that its natural history remains to be defined. The mechanism of the chronic hepatic injury related to HAA is also in doubt, although the recent preliminary communication of Almeida and Waterson is of considerable interest. These authors have shown that in a patient with 'chronic active hepatitis' unattached particles of antigen were present, but also immune complexes of HAA with attached antibody. This is characteristic of antigen excess. This may be analogous to what pertains in some forms of nephritis, where glomerular injury has been related to antigen-antibody complexes.
It is generally agreed that HAA is not found in association with primary biliary cirrhosis or alcoholic liver disease\(^8,24\).

**Conclusions**

In spite of the original optimistic reports, it now seems unlikely that HAA does in fact represent the actual virus particles of hepatitis. It lacks some of the properties of virus. It has never been shown to multiply in tissue culture or in experimental animals. It lacks either DNA or RNA and has no protein coat. Electron microscopy shows that it is present in the blood in such large amounts that if it were a virus the effect would be overwhelming. The exact relationship of HAA to virus hepatitis, whether infectious or serum, or both, remains to be determined.

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**References**

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