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Abstract

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THE AUSTRALIA (Hepatitis-associated) ANTIGEN

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"Most great discoveries are accidental"
Sir Henry Dale

"Discovery comes to the mind prepared"
Louis Pasteur

INTRODUCTION

The accidental discovery of the Australia antigen (HAA) in 1963 by Blumberg and his coworkers is a classical example of biomedical serendipity. Its recognition not only stimulated a substantial amount of research into viral hepatitis, thereby adding considerably to our knowledge about this important disease, but has had far-reaching implications in the understanding of several other hepatic and systemic diseases. Indeed, its discovery may well be seen in the future to have been the all-important breakthrough in attempts at culture of the virus as a means of vaccine prepartion for future prophylactic usage.

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It was some time before it became apparent that the Australia antigen was closely related to, or might be located directly on, a hepatitis virus. It was found in the serum of some 30 per cent of patients institutionalised because of Down's syndrome (mongolism) but did not occur in out-patients with this disease or in hospitalised patients with other causes of mental retardation. In these institutionalised mongoloid patients antigenaemia was associated with chronic anicteric hepatitis, as shown by liver biopsy and elevated S.G.P.T. levels (6). The antigen was isolated by density-gradient sedimentation, and under the electron microscope was found to be a particle of 200 A° in diameter with knob-like subunits of some 30 A° on the surface. Agglutination of these particles occurred on addition of anti-HAA antiserum. The liver cells of patients whose blood contained the antigen was then shown to have striking fluorescent granules in or on their nuclei when fluorescent anti-HAA was added (7), a phenomenon not seen in patients without hepatitis or in those who do not have the antigen in their blood (3). Clinical hepatitis was then found to result in a high proportion of patients given transfusions of blood from donors who carried the Australia antigen (8). Epidemiological studies suggested that the antigen was an infective agent, and supported the conclusion that the Australia antigen was intimately associated with a virus that caused hepatitis. Subsequent studies suggested that the antigen was associated with clinically different forms of hepatitis, the form depending on the immune status of the patient (9). The antigen was also shown

to be rare in North America and the United Kingdom (0.1 per cent) but was common in people living in the tropics (2-20 per cent). Indeed, these patients seemed to be susceptible to chronic infection with the hepatitis virus (10), a point that will be more fully discussed later.

THE NATURE OF THE ANTIGEN

The Australia antigen was shown by the Blumberg group to differ from the serum beta-lipoproteins which they had previously described in that it had a high molecular weight and contained proteins with minimal amounts of lipid. Electron microscopic studies of antigen-positive serum, prepared by sucrose density-gradient centrifugation and a negative-staining technique, revealed virus-like particles (11). These particles were about 200 A° in diameter with knob-like subunits of 30 A° diameter. Some had a central core while others were elongated their length varying from 500 A° to 2 300 A°. The addition of specific rabbit antiserum to the Australia antigen resulted in agglutination of the particles. The unusual degree of pleomorphism was the only feature incompatible with firm acceptance of the particles as viral in origin. Nucleic acid has, however, never been demonstrated in these particles, another somewhat unusual feature, although it is possible that the virus contains little or no nucleic acid. A wide variety of particles can be detected in serum by electron microscopy and Australia antigen particles are so pleomorphic that they may only be recognised with confidence in the presence of tubular forms (12). Small antigen particles seem to predominate in acute hepatitis, while large particles and tubular forms occur in carriers of the antigen, or in patients with chronic hepatitis. Certainly, there is now wide acceptance that the presence of particles of 22 A°, with little substructure, and those of 42 A° with a dense outer coat about 7 A° across and an inner body of 28 A° in association with HAA, is indicative of infection with the S.H. virus. Since the specific antibody to Australia antigen will cause clumping of both these particles (13) it is now generally agreed that the particles themselves constitute the antigen)14).

Almeida and Waterson (13) have described three patterns of Australia antigen as observed under the electron microscope in relation to clinical features.

1. In the patient with fulminant hepatitis, large amounts of antibody separate the aggregated particles;
2. in the patient with chronic active hepatitis, unattached particles of antigen were seen, together with immune complexes with antigen excess; and
3. in symptom-free carriers of the antigen, randomly distributed spherical and tubular particles were observed without clumping by antibody.

It has been suggested by Dane et al (1970) that the large (42 A°) particles are the virus itself, while the tubular forms are surplus virus coated material (15). These particles have some features in common with arborviruses. It has, however, been variously suggested that the virus associated with the Australia antigen may be a variant of the cowpea-chlorotic virus, or a member of the picornavirus family, which cause duck hepatitis. Almeida and her colleagues have further suggested that the Australia antigen may be an aggregation of protein subunits derived from the virus (13, 16). Zuckerman, working with Almeida, has described particles found on electron microscopy that displayed the characteristics of the coronavirus group, and suggested that the particles appeared to consist of antigen-antibody complexes (17, 18). More recently this group have reported the apparantly successful propagation of the serum hepatitis virus in human embryo liver organ cultures, confirming their results on electron microscopy. Material harvested from these cultures has been successfully passaged, so that the full elucidation of the virus, and the antigen with which it is inextricably associated, may now not be far away (19).

DETECTION OF THE ANTIGEN

The earlier workers elicted the presence of the Australia antigen in serum using the micro-Ouchterlony immunodiffusion technique (1). Since then, more sensative methods have become available. These include complement fixation, immunoelectrophoresis, haemagglutination, haemagglutination-inhibition, radio-immunoassay, and electron microscopy using negative-staining techniques.

The immunodiffusion method is simple to perform, but not sensitive. Complement fixation is more sensitive, and is amenable to quantitative determination of both Australia antigen and specific antibody. Immunoelectro-osmophoresis is a rapid and comparatively simple technique which is less sensitive than complement fixation but more sensitive than immunodiffusion. Haemagglutination and haemagglutination-inhibition are highly sensitive for detection of antibody to the antigen.

Electron microscopy is relatively elaborate to perform, but is a rapid and sensitive method. Radio-immunoassay is about twice as sensitive as complement fixation, while immunofluorescence is amenable to detection of the Australia antigen in liver biopsy specimens. The more recently developed methods include an immune adherence-haemagglutination technique which lends itself to automation, and a latex agglutination test which is simple and rapid to perform, and sensitive.

The Australia antigen has been found, not only in serum, but in liver biopsy specimens, where it can sometimes be demonstrated by immunofluorescence when negative in the serum. Faecal antigens have also been described (20, 28) while urinary spread seems probable, for chronic carriers of the antigen may excrete it in their urine. The antigen has also been detected in bile, and may well be present in saliva, as serum hepatitis can apparently be spread by kissing.

PREVALENCE OF THE ANTIGEN

Community studies have shown that the Australia antigen is rarely found in the healthy population of North America and the United Kingdom (0.1 per cent), and is exceptionally rare here in those under 18. In tropical countries, however, the antigen is found far more frequently in the serum of apparently normal people. Figures quoted by Blumberg (3) for these countries include Costa Ricans (2 per cent), Australian aborigines (2.1 per cent), Brazilians (2.5 per cent), Melanesians (3.6 per cent) Filipinos (4.8 per cent), Vietnamese (6.3 per cent), Micronesians (7.2 per cent), Ghanaians (9.5 per cent), Taiwanese 13 per cent and Peruvian Indians (20.2 per cent).

The Australia antigen is also commonly found in patients with acute myeloid leukaemia, and with acute and chronic lymphatic leukaemia. Most of these patients, however, have received blood transfusions as part of their therapy, and few have hepatitis. Patients with lepromatous leprosy also have an unusually high incidence of positivity in relation to their fellows in the community and in comparison with patients with tuberculoid leprosy. This is presumably due to their altered cellular immunity, favouring persistence of the antigen, together with a high incidence of antigen in the community.

Patients on chronic renal haemodialysis programmes, who also have altered cellular immunity due to their uraemia, and may in addition be receiving immunosuppressive therapy, have an usually high incidence of positivity in comparison with other hospitalised patients often becoming chronic carriers of the antigen after incidents of mild hepatitis.

High carriage rates have more recently been reported in "mainline" drug addicts in Europe and America, figures of 7 per cent being recorded in one recent survey.

The association between Australia antigen and Down's syndrome has long been recognised, and was reported by Blumberg in 1967 (2). Figures of between 27.7 and 35.1 per cent have been variously reported for mongoloid patients in institutions. Many of these patients have histological evidence of chronic active hepatitis, and their age at time of exposure seems to determine long-term antigen carriage. The chronic carriage of the antigen in these patients may also be related to immunological deficiency.

SERUM HEPATITIS

Although Blumberg and his workers recognised that the Australia antigen was intimately associated with a virus causing hepatitis and that its presence in serum was indicative of the presence of that virus (21), it was not until later that the clear association of the Australia antigen with serum or long incubation period hepatitis was shown.

Prince (22) reported a close association between the Australia antigen and long incubation period hepatitis in 1968, calling the antigen SH or serum hepatitis antigen. It is identical with the Australia antigen and is absent from the serum of patients with common source outbreaks of short incubation period infectious hepatitis. The finding of Australia antigen in patients with presumed infectious hepatitis has been reported and is due to the diagnosis being made solely on clinical grounds.

Unequivocal evidence for the presence of two quite distinctive clinical, epidemiological and immunological types of viral hepatitis was provided by the work of the Krugman group at Willowbrook State School for mentally retarded children in Staten Island, New York (23, 24). Whatever one may think of the ethics of these experiments — and they certainly provoked a world-wide outcry — the work was brilliantly conceived and methodically and scientifically done. By infecting these children shortly after their admission to the school with serum from patients known to have infective and serum hepatitis and taken from these patients shortly before the development of jaundice a considerable amount of clinical, bio-

chemical, and other data was collected. The trials were done with the acquiescence of the children's parents and were defended on the grounds that viral hepatitis was endemic at the school and that the children, most of whom could not be toilet trained, would almost inevitably acquire hepatitis by the faecal-oral route while resident in the school. The experiments were condoned and sanctioned by committees set up in America to monitor human experimentation, and were conducted in accordance with the World Medical Association's Draft Code of Ethics on human experimentation.

The data accumulated during those studies has contributed immeasurably to the understanding of viral hepatitis. Two quite distinctive varieties of infectious hepatitis were shown to exist. One type resembled classical infectious hepatitis (IH) and was characterised by an incubation period of 30-38 days, a relatively short period of liver function test abnormality and a high degree of infectivity. The second type resembled serum hepatitis (SH) and was characterised by a longer incubation period, a more protracted and severe clinical and biochemical upset and moderate infectivity. On reinfecting the patients it was shown that one attack of IH protected the child from a second and that patients who had been given the SH type were in no way immune from the IH variety of infection. They subsequently showed also that IH could be transmitted parenterally as well as orally and SH orally as well as parenterally. The mode of transmission did not affect the incubation period of the IH virus, this being essentially the same after oral and parenteral exposure. The incubation period for the SH virus however was longer following oral than parenteral inoculation. They also showed that gammaglobulin protected against the infectivity of IH but not against that of SH serum.

The discovery of the Australia antigen allowed the Krugman group then to extend their studies using the antigen as a marker. They tested 25,000 specimens of serum, collected and stored during their earlier experiments on 700 patients with viral hepatitis, for the Australia antigen. This showed that the Australia antigen was consistently present in sera from patients with long incubation period hepatitis (SH) but was not present in sera from patients with short incubation period infective hepatitis (IH). Moreover, the antigen was detected earlier after a parenteral exposure to SH than to oral exposure, appearing jaundice. The antigen was also found to be two weeks to two months before the onset of transient in 65 per cent of the children given SH, lasting a mean of 49 days. It persisted for many months, however, in the remaining 35 per cent of children. In addition, the children given SH infection were immune following re-exposure to SH virus one year later. Their observations amply confirmed that the Australia (hepatitis-associated) antigen was specifically related to serum and not to infective hepatitis and showed that if the antigen was present for more than four months it was likely to persist indefinitely. They also showed that serum containing the antigen and obtained from patients who had never had overt hepatitis, was capable of causing serum hepatitis. Indeed, it has been shown that less than 0.001 ml. of serum containing the Australia antigen was infectious (25) although the severity of the resultant hepatitis may depend on the dose of the antigen (26). Barker et al (1970) have also shown that the transmission of serum hepatitis was associated with the administration of an HAA-positive plasma pool containing virus-like particles of approximately 20 A° diameter. This is further strong support for the hypothesis that the Australia antigen (HAA) is an integral part of the serum hepatitis virus.

SEQUELAE OF INFECTION WITH THE AUSTRALIA ANTIGEN

(1) Sources of Infection

In the clinical context, the classical mode of infection with the serum hepatitis virus and the Australia antigen is parenteral by the transfusion of infected blood or blood products, or by contaminated equipment, especially needles or syringes.

The increasing incidence of drug abuse exposes larger numbers of the community to potential syringe-borne infection. Close contacts with addicts, who are not themselves "mainliners" can contract the disease. It is probable on clinical grounds that kissing and sexual contact with antigen positive persons may well lead to serum hepatitis. It has, of course, also been shown in the Willowbrook experiments that the disease may be spread by the faecal-oral route. Hospital-acquired disease, for example in uraemic patients on chronic renal dialysis, may also spread to the community. Indeed, cases have been reported where the spouse of such a patient has contracted a fatal serum hepatitis illness.

The importance of mass screening of blood donors is apparent in this context, especially

as the antigen has been shown to have persisted over 20 years in a patient who has remained apparently entirely well over that period (27). Shaving brushes, razors, toothbrushes, hairdressing implements, dental instruments and tatoo needles contaminated with Australia antigen positive blood have all been implicated in the spread of serum hepatitis.

The identification of the Australia antigen in faeces (28) and urine and bile creates further obvious possible sources for the spread of the disease.

(2) Consequences of Infection

This depends on the dose, virulence of the strain, previous exposure to the antigen, and the immune status of the individual. In the latter context, depression of cellular immunity is particularly important. The patient who is immunocompetent is likely to get severe or fulminant hepatitis, while the patient who is immunodepressed by disease or iatrogenically is likely to have mild hepatitis. The former patient, should he survive, will probably rid himself of the antigen within two months of the onset of clinical hepatitis. The immunodepressed or immunosuppressed patient is, however, likely to have mild hepatitis with persistence of the antigen, often indefinitely. Some of this group will become apparently healthy long-term carriers of the antigen, while others may develop chronic active hepatitis that may proceed to cirrhosis. This has been well shown in the outbreaks of serum hepatitis in renal dialysis units. The patients tended to have mild hepatitis followed by persistent antigenaemia while the staff had severe and often fatal hepatitis, but cleared the antigen from their blood.

The Australia antigen is detectable in the serum some weeks before there is subjective or clinical illness and may be detcted in the liver after recovery, when the patient is seronegative. Some antigen positive patients show allergic manifestations during the late incubation period or early in the phase of active hepatitis with urticaria, arthralgia, angioneurotic oedema and sometimes migrainous headaches. This may be related to the presence of circulating immune complexes of Australia antigen, its antibody, and complement.

The antigen becomes demonstrable in the hepatic parenchymal cells at this stage and can be nicely shown by immunofluorescent or EM studies. The patient may then develop the fulminant picture, which is similar to that of acute massive necrosis from any cause. There is a high mortality rate in this group despite intensive therapy with colomycin, lactulose, parenteral glucose, heparin and fresh frozen plasma followed by extracorporeal perfusion, or exchange transfusion. More often, however, the patient will recover after a protracted period of cholestatic jaundice. Most who are immunocompetent will clear the antigen within four to ten weeks (29). These are the group, however, who run the risk of destroying their liver, presumably by a vigorous antigen-antibody reaction. Many will have no lasting hepatic damage, although some may proceed to chronic hepatitis of the mild persistent or even the severe aggressive varieties. Chronic persistent hepatitis often follows the classical attack of acute serum hepatitis, leading to cirrhosis, while chronic aggressive hepatitis tends to follow a mild or subclinical attack of antigen positive hepatitis. Certainly, cirrhosis is most likely when the Australia antigen remains positive after the acute attack. This persistent antigenaemia is probably related to immunological defects, especially in cellular immunity. It is at least possible that the SH virus may gain in virulence by passage through patients who are immunosuppressed either by uraemia or by azathiprine (Imuran), cyclophosphamide and antilymphocytic serum, causing very severe or fulminant hepatitis when an immunocompetent person is infected. This is, however, conjectural.

CELLULAR IMMUNITY AND THE ANTIGEN

It has been postulated that a complex series of interactions between the Australia antigen, the serum hepatitis virus and the immune response of the host, both cellular and humoral, follows infection with HAA positive material although immune complexes of HAA and antibody are important in producing some of the varied clinical manifestations that follow infection, the cellular immune response seems to determine the severity and persistence of the associated liver damage. It has recently been suggested that the competence of the cell mediated (T-lymphocyte dependent) immune system determines whether the infection is self-limiting or persists with varying degrees of damage (30).

Krugman and his associates showed that inoculation of children with standard preparations of Australia antigen-positive serum resulted in a spectrum of clinical outcomes (24). Although transient antigenaemia was usual in association with either overt or anicteric hepatitis, persistence of the antigen could occur in association with either chronic active hepatitis,

or without apparent disease. The actual course is dependent on many variables, including genetic predisposition, immune competence, the virulence of the virus, its dose and mode of transmission. The host response to the infective agent is, however, probably all-important in determining the clinical course followed by the individual patient.

Although the presence of immune complexes of HAA correlate poorly with the degree of liver damage, deposition of these complexes may play a role in the development of the serum-sickness like syndromes which sometimes precede serum hepatitis. Only a mild persistent hepatitis is seen in the presence of complexes in HAA positive polyarteritis, while acute and chronic hepatitis can occur in patients with agammaglobulinaemia. Immune complex disease is therefore unlikely to be the mechanism by which HAA causes liver cell damage (30).

It is more probable that liver cell necrosis is related to the cellular immune response of the host to the infecting agent. This response is controlled by thymus-dependent lymphocytes, and variations in their function could determine the clinical course that follows infection with HAA positive material. This is supported by the fact that impairment of the cellular immune systems results in mild hepatitis after HAA infection — with persistence of the antigen. People who are immunologically normal, however, develop severe hepatitis when infected, but clear the antigen rapidly from their blood (3). Persistence of the antigen is seen frequently in patients with impaired T-lymphocyte function (lymphoproliferative disorders, lepromatous leprosy, chronic lymphatic leukaemia). The high frequency of antigen in mongolism may also be related to an abnormal immunological status.

Dudley et al (30) have suggested that the Australia antigen, on gaining entry to the body, comes into contact with susceptible cells — possibly in the liver. Here it proliferates, producing further infective particles plus excess virus coat material, both of which are released from the cell without having caused cell necrosis. During transit out of the liver cell antigens specific for the infective agent become incorporated in the surface membrane of infected cells. The circulating foreign antigens are then recognised by immunocompetent T-lymphocytes which proliferate to produce a number of sensitised lymphocytes. These then recognise and react with the antigens on the surface of infected liver cells. This lymphocyte/antigen interaction results in destruction of the infective agent, and necrosis of the liver cell. Modification of this pattern can explain the various forms of Australia antigen positive liver disease.

It follows from this postulate that, in the presence of a normal immune response the patient's T-lymphocytes will react in this manner, leading to extensive liver cell necrosis — but with clearance of the antigen, i.e. the infective agent. If all the liver cells are involved, severe fulminant hepatitis will result. If few cells are infected, the hepatitis will be mild or subclinical. The outcome, therefore, with normal immunological status, is fulminant hepatitis, or complete recovery. Conversely, if the patient's immunological state is abnormal, little or no liver damage will result, but the patient would become a healthy antigen-positive carrier. An intermediate course would likewise result in a mild hepatitis followed by continuing liver cell damage and persistent antigenaemia (30). It follows from this hypothesis that immunosuppression will modify the clinical course after HAA infection the therapeutic possibilities of this being offset by the likelihood of producing persistent antigenaemia.

CYTOPLASMIC LOCALISATION OF THE ANTIGEN IN LIVER

Recently, immunofluorescent and electron microscopic techniques have demonstrated the Australia antigen in the cytoplasm of hepatocytes. Haynes et al (14) have shown hepatocytes. in antigen sero-positive patients to contain characteristic particles with membrane bound cytoplasmic vesicles. The appearances of these particles was similar to that of the Australia antigen particles found in the serum. Two sizes of cytoplasmic particles were observed, with average diameters of 26 and 46 A°. Particles of both sizes often had a membrane-like outer component and a moderately electron-dense inner component. They differed in both size and structure from the mainly intranuclear particles described by previous authors (31).

Although a direct connection between the two types of particles described above has yet to be established, it seems likely that the different types are related to stages in the development of the serum hepatitis virus. It has been shown that there is apparent intranuclear replication of 22 A° particles, with considerable disruption of the nucleus, and sometimes also with cytoplasmic replication, occasionally

with the production of rather different particles within the cytoplasmic vesicles. Others have shown no intranuclear replication or damage, but enormous production of particles, within the cytoplasm, of the larger type — and a much greater degree of cytoplasmic damage. Whether these two situations represent different stages of a single process or are alternative manifestations of infection by the SH virus is uncertain. It seems unlikely, however, that either one could lead directly to the other. Another possibility is that they are related to the immunological status of the patient (14).

CHRONIC ACTIVE HEPATITIS (C.A.H.) AND CIRRHOSIS

The remarkable specificity of the Australia antigen for serum hepatitis and chronic active hepatitis in comparison to other forms of liver disease suggests that persistence of the antigen may be aetiologically important in some cases of chronic active hepatitis and cirrhosis.

Chronic active hepatitis is characterised by a prolonged course and the presence of persistent hepatic inflammation with fibrosis which may progress to cirrhosis. Some patients develop polyserositis, hypergammaglobulinaemia, and positive serum antinuclear factors and even L.E. cells. The pathogenesis of C.A.H. is unknown, but may have its origins in infection with the Australia antigen, superimposed upon primary, or complicated by secondary immunological factors (32). Although one study showed an association with HAA, several others have failed to do so. Some reports have shown progression, on liver biopsy, from serum hepatitis to cirrhosis, so that the HAA may have a role to play in some cases of C.A.H. and cirrhosis. In these cases it seemed probable that persistent viral infection, as judged by antigenaemia, has contributed to the pathogenesis of C.A.H. Other cases may conceivably be initiated by infection with the SH virus and HAA, but be perpetuated by some other mechanism, possibly auto-immune, after clearance of the antigen (12). Zuckerman et al (33) have, however, detected particles by electron microscopy (EM) in the serum of a patient with C.A.H. and cirrhosis whose serum was HAA negative, so that the apparent anomaly may lie in the sensitivity of present methods of testing for antigen.

PRIMARY BILIARY CIRRHOSIS AND THE ANTIGEN

Particles identical to those associated with the Australia antigen were found by EM in the sera of 11 out of 12 patients with primary biliary cirrhosis. Antigen and/or antibody to Australia-antigen was also found in 9 out of 10 of these cases by sensitive immunological methods (34). These findings remain to be confirmed, but the suggestion is that the liver damage in primary biliary cirrhosis may be due to either continuing replication of the SH virus, or be the result of the patient's immune response to persistent antigenaemia. The presence of autoimmune (smooth muscle and anti-mitochondrial) antibodies in this condition has led to the suggestion that the condition is either due to or associated with abnormal immune reactivity, the trigger possibly being the SH virus.

HEPATOCELLULAR CARCINOMA AND THE ANTIGEN

There has recently been worldwide interest in the possible oncogenic properties of the SH virus and HAA. In Uganda (35) 40 per cent of patients with hepatocellular carcinoma had the Australia antigen in their blood. These workers found a tendency for HAA positive individuals with hepatocellular carcinoma to be alpha-fetoprotein positive, and to have underlying cirrhosis of the posthepatic type. Young patients tended to be HAA positive more frequently than the older ones who were often alpha-fetoprotein negative. This data certainly suggests an association between persistent antigenaemia and the pathogenesis of hepatoma — at least in Uganda, especially as only 4 of their 122 controls (3 per cent) were antigen positive. It is certainly tempting to speculate that antecedent viral hepatitis plays a causative role in the neoplastic transformation of the liver cell. Other workers have lent support to this theory, with marked differences across the globe. In Singapore 3 per cent of 114 patients with hepatomas were HAA positive, in Japan 5 per cent of 19, in India 63 per cent of 11, and in Twaiwan 80 per cent of 55. Alternatively, in South Vietnam HAA was not found in any of the patients with hepatoma that were studied, but was present in 4 per cent of their controls! (36)

POLYARTERITIS AND AUSTRALIA ANTIGEN

A most interesting survey of 11 patients with biopsy-proven polyarteritis nodosa showed 4 of them to be Australia antigen positive. The four HAA positive patients exhibited a typical polyarteritis syndrome, but differed from the antigen negative patients in having evidence of mild hepatic damage. The presence of circulating immune complexes in the sera of 3 of the 4 anti-

gen positive patients was demonstrated by serological, ultracentrifugal, and EM studies, and were shown to be composed of Australia antigen and immunoglobulin. Immunofluorescent studies of tissue from one of the patients revealed deposition of Australia antigen, IgM and BiC in blood vessel walls. The suggestion is that the syndrome of diffuse vascular damage observed in these patients was due to deposition of immune complexes in the blood vessel walls, and that these deposits were composed of Australia antigen, homologous IgM antibody, and complement components (37).

THE HUMAN BEING AND HIS AUSTRALIA ANTIGEN

During the recent tragic Edinburgh serum hepatitis outbreak, the community in general and hospital staff in particular came face to face with a new and terrifying reality — inoculation with antigen positive material might herald a fatal illness. This transformed people, and created problems that are only now being fully realised as the immediate danger seems past. Patients were sometimes treated as were lepers, and many are still aware of being ostracised, despite a long-standing negative Australia antigen. Many doctors and nurses did, however, behave in a manner that does them very great credit, and signs are around that medicine, in its broadest sense, is coming to terms with the discovery that Blumberg fell upon quite by accident almost a decade ago. He could hardly have realised then that he had, in truth, perhaps created more problems in his discovery than have been solved by the now clear cut delineation of the two forms of viral hepatitis by the recognition of the Australia antigen.

"Knowledge comes, but wisdom lingers."
Lord Tennyson

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