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Pointers

B.M.A. Annual Meeting: At Harrogate. Annual Representative Meeting, 25-29 June; Annual Scientific Meeting, 29 June-3 July. Programme (*Supplement*, p. 25).

Australia Antigen: Melbourne workers find that in hepatitis patients Australia antigen is associated with transfusions and older age (p. 259). British workers report presence of virus-like structures on electron-microscopy similar to those of the coronavirus group (p. 262). Leader on this page.

Withdrawal of Chlormadinone: Leader at p. 251. Letters from a manufacturer and others (p. 303).

Antenatal Thromboembolism: Clinical management of anticoagulant therapy in pregnancy (p. 270). Leader at p. 249.

Hay-fever: A study of the effects of methylprednisolone acetate, a slow-release injection, on the hypothalamic-pituitary-adrenal axis (p. 267).

Malignant Hyperpyrexia: A family investigation suggests an association with subclinical myopathy (p. 275).

Alcoholic Hypoglycaemia in Children: Three examples (pp. 278 and 280).

Other Clinical Studies: Role of renin in acute renal failure (p. 253; leader at p. 250), diabetic retinopathy (p. 264), "pugnacious pink buffers" (p. 273), and polyarteritis presenting with leg pain (p. 277).

Influenza Epidemic: Leader on the neurological complications (p. 248); P.H.L.S. report on viral isolations and graph of deaths (p. 311).

Lung Cancer: With endocrine dysfunction. Clinicopathological Conference at Royal Postgraduate Medical School (p. 281).

Haemodialysis and Renal Transplantation: An integrated regional centre (p. 291). Letter on computer scheme at the London Hospital (p. 298).

Developing Countries: Rural medicine (p. 295).

Personal View: Dr. Alex Anthony (p. 297).

G.M.C. Retention Fee: Report of emergency meeting of B.M.A. Council (*Supplement*, p. 29). Letters at p. 305.

G.M.S. Committee: Against admitting press to Annual Conference. Discusses district hospitals, the chronic sick, and nurse attachment (*Supplement*, p. 33).

Hospital Junior Staff: Group Council accepts chairman's resignation (letter at p. 304), appoints Mr. J. S. Elkington in his place, for interim agrees to direct access to the Council, and records opposition to specialist registration (*Supplement*, p. 36).

Australia Antigen and Hepatitis

In the past six months evidence has accumulated identifying the Australia antigen with viral hepatitis.[1] Now scientific communications are appearing at such a rate that it may be helpful to the practising doctor to go back to the beginning of the story.

In 1961 B. S. Blumberg and his colleagues[2-4] reported that patients who had received blood transfusions developed precipitating antibodies against serum beta-lipoproteins. These antibodies were found commonly in patients who had received large numbers of transfusions—for example, patients with thalassaemia. During a search for additional precipitating antibodies an antibody was detected in the serum of a transfused haemophiliac patient which was different from the lipoproteins previously discovered.[5] This serum came from an Australian aborigine, and so the name "Australia antigen" was given to it.[6]

Subsequent studies by B. S. Blumberg and his colleagues[7 8] showed that the antigen was relatively rare in the blood of healthy people in North America and Europe (0·1%) but was found with much higher frequency in apparently healthy people living in the tropics and south-east Asia. It was often found in patients with acute forms of lymphocytic and myelogenous leukaemia (13-18%), but not with chronic myeloid leukaemia. It was also detected in patients with lepromatous leprosy (9%), in patients with thalassaemia and others who had received numerous transfusions, and in patients with Down's syndrome (mongolism), especially those living in institutions.[7 8]

In 1967 Blumberg and colleagues[7 8] reported that the Australia (Au) antigen appeared to be associated with cases of acute viral hepatitis. The antigen was detected in about 20% of cases of acute viral hepatitis, and, moreover, the antigen was detected in an individual after a blood transfusion. Recent studies indicated that the net was closing in on the association between the Au antigen and viral hepatitis,[9] but this is not the complete story.

At first it appeared that Au antigen was present in the blood of patients suffering from both forms of viral hepatitis, serum and infectious.[1 10] Further studies have shown that this is not correct. There is a close association between the presence of the Au antigen and serum hepatitis, and also with the SH antigen, later identified by A.M. Prince.[11] Au antigen and SH antigen are closely related (if not identical) and are related to serum, but not to infectious, hepatitis. What is the reason for these apparent discrepancies?

For the answer one must turn to the work of Saul Krugman and his colleagues.[12] They have now clearly identified two epidemiologically and immunologically distinct forms of viral hepatitis. The first has a short incubation period (MS-1, infectious, or IH) hepatitis; the second has a long incubation (MS-2, serum, or SH) hepatitis. The association between MS-2 infection and SH antigen[13] was independently confirmed by Krugman's group.[14]

The initial discrepancy in the association of the Au antigen and *infectious* hepatitis is almost certainly due, as Krugman has suggested, to difficulties in clinical differentiation between the two forms. Patients with hepatitis without a clear-cut history of parenteral inoculations are likely to be diagnosed as of the infectious type, but this type of infection may be transmitted by the parenteral route. And what is more important, the SH, or serum, infection may be transmitted by the oral route.[13] In this sense the patient's history can be misleading, but at all events the association of Au with SH antigen now seems firmly established. A report by Y. Cossart and co-workers[15] in Britain showed that Australia-SH antigen had been identified by similar techniques in 40% of patients with acute viral hepatitis.

How does this fit in with other forms of liver disease? W. T. London and colleagues[16] found no evidence of the Au antigen in other diseases affecting the liver, including cirrhosis, infectious mononucleosis, and hepatoma. Basically similar results have been reported by R. Wright and colleagues.[17] They identified Au antigen in 46 out of 88 patients (52%) with acute viral hepatitis, in 11 out of 29 (38%) of those with prolonged viral hepatitis, and in 6 out of 24 (25%) of those with chronic active hepatitis, and in only 3 of the remaining 248 patients with acute or chronic liver disease. G. L. Gitnick and co-workers found Au antigen in only 3 out of 31 patients with chronic active liver disease.[18]

Although the Au-SH antigen can be found more readily in the early weeks of the disease it can undoubtedly persist for long periods,[13 17] even for as long as 20 years.[19] That the Au-SH antigen is highly infectious there is little doubt. Studies[8 14] have shown it to be transmissible. Furthermore, workers in Britain[20] have obtained positive tests for SH antigen from affected staff and patients after an outbreak of viral hepatitis in a haemodialysis unit. The antigen persisted for a longer period in affected patients and in one case was still positive after three years.

A study from Melbourne in this week's issue of the *B.M.J.* by Drs. J. D. Mathews and I. R. Mackay (page 259) indicates that Au antigen was detected less often than might have been expected in their patients both in acute and in chronic cases. There appear to be differences in geographical incidence which are unlikely to be due to technical procedures, as most of the results reported have used reference sera from similar sources.

Another report in this week's *B.M.J.* (page 262) takes the story a stage further. This comes from work published by Dr. A. J. Zuckerman, Dr. Patricia E. Taylor, and Miss June D. Almeida, who have contributed much to our knowledge of the subject in this country.[21 22] On electron-microscopy these workers found virus-like structures displaying the characteristics of the coronavirus group. Furthermore, all the particles appeared to consist of antigen-antibody complexes. It must be stressed that this is a single observation and will have to be confirmed, but if confirmation is forthcoming this could be a discovery of the greatest significance. Mouse hepatitis virus belongs to the coronavirus group, and the finding of similar morphological structures in a human serum clearly calls for further study.

Antibodies to mouse hepatitis can be found in human sera,[23] but it is not clear whether these result from infection with rodent excreta, as for example occurs with lymphocytic choriomeningitis virus, or by infection with a human serotype of the mouse hepatitis virus. The latter is a possibility that has to be considered in relation to the aetiology of acute infectious (IH) hepatitis. So far all attempts to isolate the viruses of hepatitis, both IH and SH, have failed except in man but, as Zuckerman and his colleagues have shown by electron-microscopy studies, antigen-antibody complexes are often present. These may be responsible in part for the disease process; the antibody present may also inhibit virus growth in susceptible cells. This is exciting news and it is to be hoped that with the many new and specific techniques that have been developed we shall be hearing more of hepatitis antigens and the viruses responsible for hepatitis. If it can be proved that a corona-type virus is aetiologically related to infectious hepatitis, the next important step will be to isolate it by cultural methods. As well as being a step towards proving its identity this will be essential for developing measures of active immunization. Many have tried their hand at culturing the hepatitis viruses and all have so far failed. It will be interesting to see the outcome of further attempts based on this fascinating work.

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Neurological Complications of Influenza

Epidemics of infectious disease are often accompanied by scattered cases of neurological complications, and the recent outbreak of influenza has been no exception. Meningitis caused by the *Haemophilus influenzae* has of course been recognized for years, with its particular dangers in early infancy, but epidemics of influenza have been of virus origin, with less tendency to cause meningeal inflammation. Viruses seem to cause neurological symptoms in two main ways. These are, firstly, by direct invasion of nervous tissue, such as in poliomyelitis or herpes simplex encephalitis; and, secondly, by starting some form of antigen-antibody reaction which may affect the brain,