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HEPATITIS ASSOCIATED ANTIGEN AND THE ANTIBODY TO IT CESP/TS (70) 25.

In the last 12 months advances of greatest importance have been made in the knowledge of the antigen designated, in 1965, by Blumberg, Alter and Visnich, as Australia antigen. It is also called Australia/SH or Au/SH, or hepatitis antigen. The term, hepatitis associated antigen (HAA), proposed at a meeting in the USA in 1969 (McCollum 1969) is probably preferable, certainly until it is known with certainty whether the antigens so far described are in fact identical and until the relationship of the antigen (or antigens) with infectious hepatitis (hepatitis A or IH or short incubation hepatitis), serum hepatitis (hepatitis B or SH or long incubation hepatitis) and other forms of hepatitis has been worked out. Some reports (see, in particular, Giles et al 1969) claim that HAA is found mainly or exclusively in patients with so-called serum hepatitis, others that it occurs both in this form of hepatitis and in so-called infectious hepatitis. But patients with the latter disease were sporadic cases in hospitals and not properly documented from an epidemiological standpoint. Sera from well-documented outbreaks have, like those examined by Giles et al, been negative (see, for example, Mosley et al 1970 and Zuckerman, 1970(a)). The generally observed distinction between these forms of hepatitis may, of course, be artificial. What is clear, however, is that the antigen is present during viral hepatitis as well as in the blood of patients suffering from certain other diseases.

Hirschman et al (1969) were able to examine sera collected prospectively from patients who had received known ictergenic blood products in 1952-54 and who ultimately developed clinical hepatitis. Of 62 patients whose sera were tested, samples from 46 (75 per cent) contained antigen. Among the latter, antigen first appeared between 35 and 120 days after administration of the icterogenic blood product, and in 42 subjects persisted from 1 week to 3 months and then disappeared; in 4 subjects it persisted for up to 10 months. In those patients with detectable antigen, who had jaundice, the antigen was present during the jaundice. The antigen was present in 7 patients with anicteric hepatitis.

Certain individuals are apparently carriers of the antigen which may persist in their blood for long periods (see Zuckerman and Taylor (1969)). Transfusion of blood containing antigen was shown by Gocke et al (1969) to be followed by hepatitis (anicteric or icteric) in 9 out of 12 patients; 4 patients out of 75 surveyed, who were given antigen-negative blood, developed hepatitis. These authors found 16 antigen-positive donations among 2,211 donations tested, and incidence of 1/147; they do not say whether the donors of this blood were paid or unpaid.

Although a close association between hepatitis and HAA has been demonstrated, a similarly close association between hepatitis and the antibody to HAA is less well established. Taylor et al (1969) and Almeida and Waterson (1969) described the finding of antigen-antibody complexes in patients with serum hepatitis. Hepatitis following transfusion may in fact occur while antibody is present in the blood (Holland et al 1969). Similarly there are very few reports of the development of antibody following hepatitis. Antibody is usually found in the blood of multiply transfused persons. Experience in the UK suggests that antibody carriers among multiply transfused patients are considerably fewer than in the USA. This observation may be related to the fact that only blood from voluntary donors is used in the UK. See for example Walsh et al (1970), whose report provides further evidence that the hepatitis carrier rate among paid donors in the USA is considerably greater than among unpaid donors. In a prospective

survey they observed hepatitis in 42 (51 per cent) of 82 patients undergoing open heart operations who were given blood from paid donors and no hepatitis in 26 patients, undergoing similar operations, who received blood from unpaid donors.

Turner and White (1969) in the UK and London et al (1969) in the USA reported the detection of HAA in haemodialysis unit staff and patients. In staff the antigen was usually present for not more than a few weeks and was associated with an acute form of the disease. In patients the antigen tended to persist for months or years. Both groups described control measures; among these were priming of the equipment with saline and limitation of blood transfusion to patients in whom the PCV fell below 20 per cent. Sever limitations of the use of blood in haemodialysis unit, in which no cases of hepatitis had occurred among patients or staff, was reported by Dathan et al (1970).

The most recent publication concerning the nature of the antigen is that of Dane et al (1970) who suggested that the 40 nm particles detected by them in sera of cases of serum hepatitis were the virus and that the more numerous 20 nm particles were non-infectious surplus virus coat material; proof must await culture of the antigen. The 40 nm particles may on the other hand consist of assembled protein (Zuckerman, personal communication).

Detection of Antigen

The very close association of HAA with hepatitis and the fact that the administration of blood and blood products containing the antigen may be followed by hepatitis in the recipients suggest that donors should be routinely screened for the presence of antigen and that those in whose blood it is detected should be debarred from giving blood. It is important to remember, however, that screening by the techniques at present available would certainly not detect all donors with icterogenic blood.

Because of the obvious implications of routine screening, it should be considered whether introduction of routine screening should not be deferred until more is known about the nature of the antigen or antigens and the corresponding antibody or antibodies and their relationship to hepatitis. The introduction of screening in a piecemeal manner has obvious disadvantages. In any case routine screening cannot at present be adopted until supplies of antisera are assured.

(a) Agar gel diffusion is a relatively coarse method of detection in which high concentrations of virus or virus product are necessary to form precipitate. In most viral diseases antigen has to be concentrated several hundredfold in order to demonstrate precipitation. It is a matter for remark that positive reactions can be obtained with sera containing HAA without first concentrating the sera. It is, therefore, perhaps to be expected that this antigen is not always detected in sera from cases of hepatitis. It follows that positive reactions in donor blood will only be obtained using this technique when HAA is present in high concentration and that, therefore, the absence of a positive reaction does not necessarily indicate that the blood will not transmit hepatitis. In addition to its insensitivity this technique has the further diadvantages of requiring at least three days before the results can be read and of being associated with a high level of operator fatigue. This insensitive technique is not really suitable for screening large numbers of donors.

(b) The complement fixation technique described is much more sensitive (Purcell et al (1969) and Shulman and Barker (1969)). Use of such a technique would allow results to be read with less delay, avoid operator fatigue and might be suitable for mechanisation.

(c) In order to screen donors routinely, assured supplies of suitable antisera are necessary. Human antisera are scarce, of varying potency and not necessarily suitable for use with both the diffusion and CFT techniques. The availability of human antisera in a country is presumably an expression of the frequency of HAA in the donor population. Susceptibility to infection with HAA may itself be genetically determined (Blumberg et al 1969). The availability of sera is therefore unlikely to alter quickly and, as antigen-positive donors are discarded, will presumably become less.

The production of antisera in animals becomes therefore a matter of the greatest importance.

(d) Whether human or animal antisera are used it is desirable, if not essential, that these should be compared with a reference preparation of antiserum so that users are aware of the potency of their antisera. Attempts are being made in the UK to establish such a preparation. Some of the differences in published results may be attributable to the use of sera of different potencies and, possibly, of different specificities.

REFERENCES

Blumberg B S, Alter HJ and Visnich S. J Amer Med.Assoc. 1965, 191, 541.

Blumberg B S, Friedlaender,J A, Woodside, A, Sutnick,A I and London, W T, Proc.Nat.Acad.Sci.(USA) 1969, 62, 1108

Dane, D S, Cameron, C H, and Briggs M. Lancet, 1970, 1, 695

Dathan, J R E, Frankel R J, Goodwin F J, Marsh F P, Murray M, Thompson J M A, and Young G R. Brit.Med.Jour. 1970, 2, 102.

Giles, J P, McCollum R W, Berndtson L W and Krugman S. New Eng.J.Med.1969,281,119

Gocke D J, Greenberg H B, and Kavey N B.Lancet 1969, 2, 248.

Hirschman R J, Shulman N R, Barker L F and Smith K O. J Amer.Med Ass.1969,208,1667

Holland P V, Walsh J H, Morrow A G, and Purcell R H Lancet,1969, 2, 553

London W T, DiFiglia M, Sutnick A I and Blumberg,B S. New Eng.J Med,1969,281,571.

McCollum R W, J Infect.Dis. 1969, 120, 641

Mosley,J W, Barker L F, Shulman N R and Hatch M H. Nature 1970 225,953.

Purcell R H, Holland P V, Walsh,J H., Wong,D., Morrow A G and Chanock R M. J Infect.Dis. 1969, 120, 383

Shulman N R, and Barker L F. Science 1969, 165, 304.

Turner G C, and White G B B. Lancet 1969, 2, 121.

Walsh J H, Purcell R H, Morrow A G, Chanock R M and Schmidt,P J. J.Amer.Med.Assoc. 1970, 211, 261.

Zuckerman A J Virus Diseases of the Liver. Butterworth, London 1970

Zuckerman A J and Taylor P E, Nature 1969, 223, 81.