news and views

Genetic factors in hepatitis

ALTHOUGH much has been written about the possible mechanisms leading to the establishment of the chronic carrier state of hepatitis B antigen and the remarkable geographical variation in the prevalence of such carriers, which may number in some areas many hundreds of thousands, the genetic hypothesis promulgated by Blumberg and associates (*Proc. natn. Acad. Sci. U.S.A.*, **62**, 1108; 1969) remains a contentious issue among students of viral hepatitis.

Examples of inherited susceptibility to infection have been described in several animal species including man and it is recognised, of course, that many other factors in the environment such as sex, age at exposure, state of nutrition, immunological factors, socio-economic circumstances and so on also affect susceptibility and resistance to infection. The discovery of hepatitis B antigen resulted from the interest of Blumberg and associates in inherited polymorphisms. Family studies carried out in the islands of Cebu and Bougainville in the Pacific, and on a more limited scale elsewhere, seemed to be consistent with the hypothesis that a gene designated *Au*^{1} is responsible for persistence of hepatitis B antigen once infection with hepatitis B virus has occurred. This gene is considered to be common in tropical areas but rare in temperate zones. Individuals homozygous for this gene (phenotype Au^1/Au^1) would have persistent antigen without overt manifestation of hepatitis, although they may remain as carriers of the associated infectious agent, whereas the heterogygotes (phenotype Au^1/Au) and individuals without the gene (Au^0/Au^0) would not remain as carriers. Persistence of hepatitis B antigen in certain other diseases such as leukaemia, lepromatous leprosy and Down's syndrome (mongolism) is believed to be of a different nature, namely an inherited susceptibility to infection not only with hepatitis B but with the agents responsible for these other diseases (Blumberg, *Ann. N.Y. Acad. Sci.*, **197**, 152; 1972). This would explain the association of the antigen with other diseases in circumstances in which the individuals with the susceptibility gene were exposed to hepatitis B virus; and absence of the association when exposure did not occur.

Ceppellini and colleagues (Convegni Farmitalia, *Antigene Australia ed Epatite Virale*, Minerva Medica, Torino, 53; 1970) also studied the segregation of the postulated trait for persistence of hepatitis B antigen among 165 families in Sardinia. A similar conclusion on the presence of an autosomal recessive locus was reached, although with some distinct qualifications. First, there was a sharp decline in the carrier rate of the antigen after the age of 20, an observation which has also been reported from many other high prevalence areas. Second, all of the reported matings, excepting one family, were between parents where only one parent was antigen-positive or where both parents were negative. In the family in which the antigen was detected in both parents, only two of the seven children were also positive. This finding on its own would rule out a simple hypothesis of recessive inheritance with complete penetrance of the homozygous recessive genotype. Ceppellini considered this fact, but decided to disregard the critical mating.

Now Vyas has reported (*Nature*, **248**, 159; 1974) a second critical mating which also fails to support the postulated inherited susceptibility to persistence of hepatitis B antigen. A pedigree with antigen-carrying parents and their progeny of three children were tested for hepatitis B antigen and hepatitis B antibody by several methods including the most sensitive techniques currently available—radioimmunoassay and passive haemagglutination. The antigen was not found by repeated testing of the serum of the three children. Hepatitis B antibody was, however, detected in the serum of the eldest son, aged 10 years, and so provides unequivocal evidence of past exposure to the antigen resulting in a normal immune response to infection. This is crucial evidence against susceptibility to the chronic carrier state inherited as a simple autosomal recessive trait.

Lederberg (*Hepatitis and Blood Transfusion*, edit. by Vyas, Perkins and Schmid, Grune and Stratton, New York, 89; 1972) previously summarised the position by stressing the alternative hypothesis to the genetic factor—that familial clustering may be entirely a function of an increased opportunity for environmental exposure to the virus. Furthermore, it stands to reason that if a parent is excreting the virus this will augment the chance that any of the offspring may acquire it, particularly if the mother is the transmitter.

Another aspect of the genetic basis of susceptibility to hepatitis is implicit in the finding that the frequency of certain genetic markers on the heavy chains of immunoglobulin G (Gm types) was always greater in multiply-transfused Italian patients with thalassaemia who were persistent carriers of hepatitis B antigen than in those with hepatitis B antibody (Blumberg and associates, *Nature*, **236**, 28; 1972). With respect to Gm types, individuals who are heterozygous for Gm factors are less likely to encounter Gm types different from their own and are therefore less likely to develop anti-Gm. Such persons when infected with hepatitis B virus, which incorporates certain host components in its protein coat, would be likely to develop persistent antigenaemia and minimal liver damage. On the other hand, individuals who are homozygous for Gm types (that is, they have fewer Gm types) are more likely to encounter Gm types different from their own and thus develop antibodies to them. Such persons, when infected with hepatitis B virus, would be more likely to have an acute infection and an increased probability of developing hepatitis B antibody. Schanfield and colleagues (*Nature new Biol.*, **243**, 81; 1973) examined for Gm allotypic markers samples from blood donors submitted routinely for testing for hepatitis B antigen in San Francisco and Minneapolis. The frequency of the various Gm phenotypes did not vary significantly among the Caucasian donors investigated according to the presence or absence of hepatitis B antigen or its antibody. Similarly, there was no significant excess of anti-Gm among individuals with hepatitis B antibody when compared with those with persistent hepatitis B antigenaemia. These findings are not in accord, at least in a normal adult population, with the hypothesis of a direct association betwen the polymorphisms of the Gm types and hepatitis B antigen.

It does not follow, of course, that the hypothesis of a genetic predisposition to hepatitis did not have a productive impact, since it did generate much discussion and considerable experimentation.

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