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Genetic factors in Autoimmune Disease

A. C. ALLISON, D Phil, BM, Clinical Research Centre Laboratories, National Institute for Medical Research, Mill Hill, London

Familial concentration has been observed in several clinical manifestations of autoimmunity. This type of evidence presents difficulties for any formal genetic analysis. It is possible to probe a little further into the genetic background of some autoimmune conditions in experimental animals. Such analyses raise questions about the genetic control of antibody synthesis itself, and the genetic control of susceptibility to infectious agents, especially viruses, which may play a part in the pathogenesis of supposedly autoimmune processes.

FAMILIAL CONCENTRATION OF AUTOIMMUNE MANIFESTATIONS IN MAN

In Graves' disease there is a concordance rate of over 50 per cent in monozygotic, compared with 9 per cent in dizygotic, twins of the same sex (Harvald and Hauge, 1956). Cases have been recorded as discordant when one twin had a goitre without overt thyrotoxicosis, but modern methods might well have shown latent Graves' disease or underlying thyroiditis. Several recent reports reviewed by Doniach and Roitt (1969) show that in monozygotic twins affected by autoimmune thyroid disorders there is a close similarity in the antibodies detected and their respective titres. Hall *et al.* (1964) found thyroid antibodies in 56 per cent of siblings of patients with autoimmune thyroiditis, and concluded that one or both parents could have transmitted the tendency to thyroid autoimmunity in 17 out of 19 families of young patients with thyroiditis. Similar results have been obtained in seven different family studies in Hashimoto's disease and thyrotoxicosis (Doniach and Roitt, 1969). Masi *et al.*

(1965) have criticised studies based on hospital-selected probands, and their criticisms are worth summarising because they are relevant to the interpretation of published data on other autoimmune conditions. Patients attending hospital have the most severe forms of any disease, while the milder cases remain unseen. Social factors influence attendance at a hospital, and families with several affected members are over-represented. When a patient shows an interesting combination of diseases, or autoimmune manifestations, the case report is published, giving a false idea of the frequency of these associations. However, even when attention is paid to these points, there is a significantly greater incidence of thyroid antibodies in the healthy relatives of patients with Hashimoto's disease than in randomly selected controls matched for age and sex (Doniach and Roitt, 1969).

Leonhard (1957) has stressed the familial incidence of systemic lupus erythematosus (SLE). Several families with two or more cases of SLE have been described, and the disease has been reported in at least five pairs of identical twins (*see* review by Miescher and Paronetto, 1969). It would have been of equal interest to know whether SLE could occur in one of a pair of identical twins. Miescher and Paronetto also quote several reports of the increased incidence of hypergammaglobulinaemia, rheumatoid factor, antinuclear factor, and false positive Wasserman reactions in the families of patients with SLE, but the reservations already mentioned are pertinent here.

Genetic influences in rheumatoid arthritis (RA) have been discussed by Lawrence and Wood (1968). In a number of surveys, familial aggregation of rheumatoid arthritis in first degree relatives has varied from none to as much as 16 times the expected rate. Some of the differences may depend on the varying predisposition frequency in different populations, but the method of carrying out the survey and the criteria used are of major importance. The well-controlled data of Lawrence and Wood (1968) show significant familial aggregation in seropositive, but not in seronegative, cases. The results of twin studies are also conflicting. Several small studies have shown no concordance for RA in monozygotic twins, but the large study of Harvald and Hauge (1956)—carried out in Denmark where all twins are registered—shows a striking difference between mono- and dizygotic twins. However, even in this study, data on age distribution are lacking. Lawrence and Wood (1968) estimate by two methods that the heritability factor in RA is approximately 30 per cent.

Enough has been said to underline the tenuous nature of the conclusions that can be drawn. Among the sources of bias are selection of probands and relatives, inadequately matched controls (with populations of diverse ethnic origin this may be nearly insuperable), and the criteria used for classification. Unambiguous information would come only from further extensive studies

which would have to be very carefully designed, and it seems likely that they would merely establish the presence of a genetic component in autoimmune disease and provide some indication of its magnitude. There are no indications that a simple Mendelian type of inheritance is operating, as in straightforward biochemically controlled traits such as alcaptonuria or metabolic polymorphisms. Two more complex explanations suffice to explain observations made so far, although the true situation may be even more complex. There could be a simple genetic factor conferring sensitivity to a relatively uncommon environmental agent—as in the case of glucose-6-phosphate-dehydrogenase deficiency and the consumption of fava beans—or two or more genetic factors could interact in such a way that their coincidence, in the presence of a common environmental agent, is required to produce an autoimmune disease. Purely as a model, one can consider inherited susceptibility to a virus, together with a tendency to hyper-reactivity of immunocompetent cells.

AUTOIMMUNE CONDITIONS IN EXPERIMENTAL ANIMALS

In view of the complex genetic situation in man, it is useful to have animal models of autoimmune diseases in which the genetic component is more readily analysed.

New Zealand Black Mice

The best known model of autoimmune disease is the inbred strain of NZB mice, which were shown by Bielschowski *et al.* (1959) to develop an autoimmune type of haemolytic anaemia. Subsequently, Howie and Hellyer (1968) found that autoimmune phenomena appear in all NZB F_1 hybrids with other strains. In some hybrids the autoimmune disorder was associated with production of autoantibodies against erythrocytes as in the NZB parental strain; in others (e.g. NZB/NZW) antinuclear factors and renal disease like that in SLE were common. Thus, the capacity to produce autoantibody behaves as a dominant factor, and the particular manifestations are conditioned by genetic factors inherited from the other parental strain.

Despite much research, the basic abnormality in NZB mice remains undetected. Autoimmune disorders can be transferred to young syngeneic recipients by grafts of immunocompetent spleen cells from affected animals. Typical disease develops in NZB mice kept germ-free, so that isolation from most pathogenic organisms has no effect on its production. However, NZB mice, even when reared under germ-free conditions, carry in their lymphoid tissues a virus serologically related to Gross leukaemogenic virus, which may play a part in some of the immunopathological changes observed. Thus, the progressive renal glomerular lesions observed in NZB mice follows the deposition of

virus antigen-antibody complexes in the glomeruli (Mellors *et al.*, 1968). In the NZB/NZW hybrids, complexes containing antinuclear factor accumulate in the glomeruli and may play a pathogenic role (Lambert and Dixon, 1968).

The report of Masters and Spurling (1967) that positive antiglobulin tests can be induced in normal mice by NZB thymus grafts enclosed in Millipore chambers is consistent with the possibility of a virus or humoral factor being involved. Thymectomy potentiates NZB disease (Howie and Hellyer, 1968), so proliferation of 'forbidden clones' of cells in the thymus or under its influence is unlikely; however, augmentation of a generalised virus infection could follow thymectomy. Nevertheless, it remains to be shown that a virus is involved in all of the immunopathological changes of the NZB and hybrid mice and, since similar viruses are present in most mouse strains, the hyper-reactivity of the immune system in NZB mice still requires explanation.

Lymphocytic Choriomeningitis Virus (LCM) in Mice

Traub (1939) found that mice infected *in utero* with LCM become, without ill effects, lifelong carriers of virus. However, when older mice are infected they show more severe effects, including runting, lymphocytic infiltration of the meninges, and death. Immunosuppressive treatments such as neonatal thymectomy and administration of anti-lymphocytic serum greatly reduce the severity of the LCM infections in older animals. In cultured cells, LCM multiplies without cytopathic effects. This has given rise to the view that the infection itself is harmless, but the immunopathological consequences of infection of mature mice can be severe (Hotchin, 1962). Mice infected *in utero* or neonatally were thought to be tolerant to the virus, but recent observations (Oldstone and Dixon, 1969) show the presence of antigen-antibody complexes in the renal glomeruli; they produce some antibody, but do not appear to develop cell-mediated immunity. In this case it is supposed that virus on the cell surface is recognised as a foreign antigen and elicits a cell-mediated immune response, which is not strictly auto-immune, although in practice it would be difficult to distinguish from auto-immunity. Tumours induced by oncogenic viruses also have virus-specific antigens that can elicit cell-mediated and humoral immune responses even when the viruses can no longer be recovered. There is evidence that this type of situation is not confined to oncogenic viruses and it could well play a role in certain 'autoimmune' manifestations.

Aleutian Mink Disease

Aleutian disease of mink is a spontaneous condition transmissible by cell-free filtrates, characterised by hypergammaglobulinaemia, plasmacytosis, seg-

mental vasculitis, fibrinoid deposition in arterial walls and glomeruli, and bile-duct proliferation (Padgett *et al.*, 1967). This condition is of interest because it reproduces some of the features of collagen diseases in man. Mink, homozygous for the Aleutian gene, having a pale fur colour and large lysosomes in leucocytes, are more susceptible to the disease than other mink. This is the counterpart of the Chediak-Higashi syndrome in man.

INHERITED SUSCEPTIBILITY TO INFECTIONS

Genetic influences on susceptibility to infections, in man as in experimental animals, are well documented. Single genetic factors, which are easily analysed, make a surprisingly large contribution to susceptibility or resistance. Some of the clearest evidence has come from analyses of virus infections in different strains of mice (Allison, 1965). Only a few examples need be quoted here. A single pair of allelic genes, with resistance dominant, determines susceptibility of mice to arboviruses of the B group; another pair, with susceptibility dominant, determines the effect of infections with murine hepatitis virus, and a third pair is involved in resistance against influenza virus. The genetically determined susceptibility or resistance operates at the cellular level, cultures of macrophages from susceptible animals supporting virus multiplication much better than those from resistant animals. Hence, it is independent of acquired immunity as conventionally defined. Nevertheless, there is synergism with acquired immunity, so that genetically resistant animals can be made susceptible by appropriate immunosuppressive procedures (Allison, 1965; Zisman *et al.*, 1969).

INHERITED DIFFERENCES IN ANTIBODY PRODUCTION

In a recent review, Herzenberg *et al.* (1968) quote evidence of genetically controlled variations in immune responses to numerous antigens, including insulin, diphtheria toxin, foreign erythrocytes, and bacterial and viral antigens. The availability of synthetic polypeptide antigens has made possible a more detailed analysis of genetic control of immune responses. Two examples will illustrate the sort of information available. The response of guinea-pigs to any of four different hapten poly-L-lysine conjugates appears to be transmitted as a single Mendelian dominant character (Levine and Benacerraf, 1964). The marked difference in the immune responses of two inbred strains of mice to a branched multichain synthetic polypeptide, poly-(tyr, glu, ala, lys) is due largely to a single major genetic factor (McDevitt and Sela, 1965). The genetic locus involved is closely linked with the H-2 major histocompatibility locus, which may help with further analysis of the underlying mechanism.

Some genetic differences in response more relevant to autoimmunity can be quoted. In the autoimmune renal disease induced in rats by immunisation with homologous renal tubular proteins, the immune complex circulates and causes nephritis. Sprague-Dawley or Lewis rats readily develop disease, whereas Buffalo rats do not develop autoantibody or nephritis (Watson and Dixon, 1966). Strain differences may also have more complex effects. Paterson (1963), in the course of experiments on the production of allergic encephalomyelitis in several strains of rats, found that Lewis rats form complement-fixing antibody (presumably protective) and do not develop disease, whereas other strains of rats without the protective antibody readily develop experimental allergic encephalomyelitis. Strain differences in the reactivity of tissues, related to mechanisms of production of injury, are also apparent. Thus, there are marked differences in the susceptibility of different animals to immune nephritis after injection of antibodies against renal basement membrane protein, sheep being highly sensitive, rats intermediate in sensitivity, and mice highly resistant. These results parallel those in the induction of autoimmune nephritis. Mouse strains react differently to standard amounts of anti-kidney (Masugi) sera, Swiss and BALB/c mice developing fulminating disease, AKR being intermediate, and A/Jax showing no reaction. When autoimmune renal disease was studied in these strains they all synthesised autoantibodies, but only Swiss and BALB/c mice developed disease (Unanue *et al.*, 1967). These and other observations show that there are genetically controlled differences in production of antibodies, including autoantibodies, and in their effects. There may well be similar differences in man.

AUTOIMMUNITY IN IMMUNE DEFICIENCY SYNDROMES

Autoimmunity has been reported to occur with high frequency in several forms of immunological deficiency, e.g. infantile sex-linked agammaglobulinaemia, primary immunoglobulin aberrations or agammaglobulinaemia, and thymoma (WHO, 1968). Some of these conditions have a clear genetic determination. The incidence of rheumatoid arthritis, dermatomyositis, diffuse vasculitis, and antibody-related haemolytic anaemias in these patients is reported to be about thirty times that in the general population (Good, 1964). First-degree and second-degree relatives of patients with primary immunoglobulin aberrations have shown an unusually high incidence of clinical and/or serological manifestations of autoimmunity. This has not been true of relatives of patients with agammaglobulinaemia.

In Britain, the incidence of rheumatoid arthritis in males with hypogammaglobulinaemia is lower than in the USA but is about ten times the incidence in population samples (Lawrence, 1967). It is difficult to decide on existing

evidence whether the arthritis in hypogammaglobulinaemics is secondary to infection or is an associated genetic effect. Its occurrence in patients with low values for all immunoglobulin fractions favours an infective cause, particularly one that is normally prevented by IgM, A or D globulin, since replacement therapy usually has little effect on these fractions. It is of interest that Cassidy and Burt (1967) have reported eight cases of juvenile arthritis in which only IgA was lacking. Recent discussions of autoimmune haemolytic anaemia in children with immune deficiency syndromes are included in the papers of Robbins *et al.* (1969) and South *et al.* (1969). These associations are remarkable, even though the underlying mechanisms are not yet understood. Again, an infective cause can be considered, but remains to be established. Alternatively, the inherited or acquired abnormality in immunocompetent cells giving rise to the deficiency may be reflected also in immune reactions against host constituents. Only speculative explanations can be offered at present.

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