have put forward models with more than one non-thermal component. They use the synchrotron self-Compton mechanism as their basic process. Variability observations can be used to test these possibilities. The necessary multiwavelength simultaneous observing programmes are notoriously difficult to arrange and can be frustrating when the fickle objects of study fail to perform on cue. We must work hard to find other ways to test Malkan's interpretation. Perhaps the few objects in which the UV excess is dominant will provide the key. □

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Immunology

Aetiology of autoimmunity

from Alfred D. Steinberg

IT is very common for the sera of patients with autoimmune diseases to contain autoantibodies against several different tissues. It has however been difficult to determine whether the pattern of reactivity of the antibodies with different tissues reflects a range of autoantibodies with different specificities, or autoantibodies with the same specificity reacting with a common determinant on different tissues. This kind of question can be resolved, at least in part, by immortalizing large populations of B cells from patients with autoimmune diseases and analysing in detail the monoclonal antibodies they produce. One such study has recently been conducted by Haspel *et al.*, who report in this issue of *Nature*[1] that mice with a polyendocrine autoimmune disease induced by reovirus infection produce autoantibodies reacting with related or identical determinants in different tissues.

These results may have interesting implications for human autoimmune disease. For example, suppose patient A has a defect leading to the production of thyroid autoantibodies. Those antibodies happen to cross-react with gastric determinants. A defect in patient B leading to production of thyroid autoantibodies might result in molecules which can react with pituitary cells. Why should the specificities of the anti-thyroid antibodies produced by patients A and B differ? Several explanations are possible: patients A and B may, for example, have produced antibody in response to different antigenic determinants on the same structure; or they may have been immunized by different structures — modified 'self' determinants, viruses, bacteria and so on. Thus, although patients A and B both have anti-thyroid antibodies, their antibodies have different specificities and therefore have different cross-reactivities. As a result of cross-reaction with secondary organs, the anti-thyroid antibodies might also react with and induce damage in the secondary organ. Therefore, a similar abnormality leading to the production of anti-thyroid immunoglobulins in patients A and B might result in molecules which react with determinants in different secondary organs by virtue of the unique specificities of the antibodies. If the antibody molecules are capable of inducing damage in both the primary and secondary organs, what might appear to be different diseases might, in fact, be quite closely related. The common involvement of the thyroid could suggest such a relationship. The common features of the illnesses of patients A and B would of course be harder to trace if the damage occurred only in the secondary organs.

A recurrent problem in the interpretation of studies with monoclonal antibodies is however that of cross-reactions. Reactivity of a single monoclonal antibody with apparently unrelated ligands has been demonstrated on several occasions[2-5]. A monoclonal autoantibody has been found to react with both human immunoglobulin and DNA–histone complexes[6]. Other monoclonal autoantibodies react with both DNA and cardiolipin, apparently by virtue of similar spacing of phosphodiester groups[7,8]. Such findings help to explain some of the unusual properties of antibodies previously observed in patients with autoimmune rheumatic diseases; they also help to define the specificities of the antibodies. However, they serve only to complicate attempts to assess autoantibody heterogeneity in patients with autoimmune diseases. There is evidence that non-autoimmune organisms are capable of producing a range of monoclonal autoantibodies[1] whose production in harmful quantities is presumably normally suppressed by regulatory mechanisms[9]. This suggests that autoimmune animals may be expected to produce a heterogeneous range of autoantibodies. There is moreover evidence that the sample represented by antibodies from hybridomas may be atypical: for example, most anti-DNA molecules in the serum of patients are IgG but the anti-DNA hybridomas produced from such patients are preferentially IgM[10].

It has been suggested that studies of monoclonal autoantibodies might yield information regarding the 'immunogen(s)' responsible for autoantibody production; for example in cases of immunization by self determinants modified by viral infection, or with a microbial agent which cross-reacts with self determinants. It is however possible that the autoantibody specificity in such cases will bear very little relationship to the 'immunogen'[4], or represent only a small determinant on a larger structure from which one could not easily deduce the whole[11]. Finally, when autoantibody production reflects polyclonal B-cell activation primarily, and the specific expansion of subsets of B cells only secondarily, analysis of specificity may bypass certain critical pathogenetic mechanisms[9].

Despite their limitations, studies of monoclonal autoantibodies force us to re-examine our basic concepts of autoimmune diseases. The paper by Hazel *et al.*[1] provides clues to a unifying concept of the pathogenesis of multiple endocrine autoimmune disorders. □

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100 years ago

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CHOLERA PROSPECTS

THE early history of cholera is involved in a good deal of obscurity, and it was not until 1817, when the disease caused a terrible mortality amongst our troops in India, and subsequently spread into different parts of the Asiatic continent, that any noteworthy attention was given to it by European observers. It is very possible that even previous to the present century cholera had made its way into Europe, but the first trustworthy record of its course westwards was in 1831, when it travelled by way of Russia and the Baltic, and, as far as we know, made its appearance for the first time in England. In 1866 the disease became epidemic in the metropolis, and its special incidence in the East End was shown to be in the main due to the polluted character of the water delivered to that part of London. The disease is once more prevalent in Egypt; it has already caused over 2000 deaths in a few towns in the delta of the Nile, and the prospect of its spread to the several ports of Europe is regarded with universal concern.

The etiology of cholera, in so far as relates to its influence in this country, does not admit of much doubt. The infection must be actually imported into our midst; it has never yet been imported except through human agency. In all essential respects the disease appears to spread under much the same conditions as favour the spread of enteric or typhoid fever, and, like that disease, it has in this country mainly been associated wioth the use of water supplies, which have been subjected to the risk of receiving the specific infection. What that infection consists in is not yet known, but judging from analogy it is a definite organism capable of reproducing its own kind under those conditions of filth which we have adverted to as being associated with the spread of the disease. In the case of anthrax, which causes the so-called wool-sorter's disease in man, and in the case of relapsing or famine fever, the microscope has succeeded in showing the organisms which lead to the production of those specific affections; but in the case of cholera no such results have as yet been attained, and this notwithstanding the laborious microscopic and other researchers which have been made in India and elsewhere.

M. Pasteur has been appointed head of the Sanitary Commission formed in Paris in view of the dreaded visitation of cholera.

A French scientific periodical puts forward the idea of a joint occupation of Mecca by the several European powers for the purpose of stopping pilgrimages thither and thereby preventing the further dissemination of cholera through the crowding of people in so pestilential a city, especially when the Ramadan falls in summer.

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