J. clin. Path., **31**, Suppl. (Roy. Coll. Path.), **12**, 144-149

Systemic lupus erythematosus—an autoimmune disease?

E. J. HOLBOROW

From the Bone and Joint Unit, The London Hospital, Whitechapel, London

The discovery of the LE cell phenomenon by Hargreaves in 1948, quickly followed by the elucidation of its immunological mechanism (Haserick *et al.*, 1950; Miescher and Fauconnet, 1954), proved to be the curtain-raiser that demonstrated the diagnostic relevance of an undoubtedly autoimmune curiosity, and set the stage for the long-running drama relating autoimmunity to connective tissue disease which has been unfolding ever since.

From these beginnings systemic lupus erythematosus (SLE) has gained general acceptance as the protagonist in the scenario of autoimmune disease, especially as an exemplar of the systemic lesions that may arise as a result of autoimmune reactions. The long list of autoantibodies now identified in this condition seems to justify this assessment to the full, and it might well be wondered why the title of this paper carries a terminal question mark. My purpose is by no means to challenge the concept of SLE as an autoimmune disease but rather to indicate some of the gaps in our knowledge of how these autoantibodies contribute to the immune tissue damage characteristic of lupus and the still wider gaps which become apparent when we attempt to explain how this autoimmunity arises.

I shall first sketch in some present views of how the two constellations of autoantibodies that most often occur in this disease—namely, antinuclear (especially anti-DNA) antibodies (ANA) and lymphocytotoxic antibodies (see Table)—are related to the pathogenesis of the lesions of SLE. Secondly, I shall outline some of the disturbances of function in the immune system which are being sought in SLE in current attempts to throw light on its puzzling aetiology.

Autoimmune tissue damage in SLE

The evidence is strong that immune complex deposition in blood vessels is a major cause of the vasculitic lesions in SLE, whether in the kidney, lung, spleen, liver, intestine, peritoneum, choroid plexus, or elsewhere (Brentjens *et al.*, 1977). The composition of these immune complexes, espcially in lupus glomerulonephritis, has been extensively studied. In choosing which antigenic components to seek investigators have naturally been influenced by the almost invariable presence of antinuclear antibodies in SLE sera, by the frequent presence of high-titre anti-DNA antibodies in active lupus, and by the fact that anti-DNA antibodies, especially antibodies reactive with ds DNA, segregate strikingly in this disease (Holborow, 1977). Therefore not surprisingly both DNA itself and anti-DNA antibodies were identified in eluates from lupus nephritis renal tissue (Koffler *et al.*, 1967). This is generally taken as support for the view that deposition of circulating soluble DNA-anti-DNA immune complexes is a major pathogenetic mechanism in lupus nephritis.

High binding activity of serum for ds-DNA is unquestionably of diagnostic value (Hughes, 1977), but the correlation of levels of such high binding antibodies with clinical activity, with progress of the disease, or sometimes even with renal involvement may be disappointingly erratic (Edmonds *et al.*, 1975). Although anti-ds-DNA antibodies, detected by high binding results in a radioimmunoassay such as the Farr test or by the ability to stain *Crithidia luciliae* kinetoplasts, are found most often in clinically overt SLE they may turn up also in chronic active hepatitis and in rheumatoid arthritis without evident renal disease, as not infrequently happens in SLE itself. We have also seen anti-ds-DNA antibodies developing in juvenile chronic polyarthritis patients during treatment with penicillamine. The complement-fixing properties of these antibodies are presumably important in determining their pathogenetic potential. Again, while the ANAs present in lupus sera, unlike those that may occur in rheumatoid arthritis, are often complement fixing this is not peculiar to SLE: it is also seen with ANAs present in progressive systemic sclerosis.

Little is known of the antigenic components of the circulating immune complexes in SLE. The limited effect of DNAase treatment on the behaviour of

Table *Antibodies (?autoantibodies) in SLE*

Antinuclear antibodies
LE cell factor
Anti-nucleoprotein
Anti-histone
Anti-ds, anti-ss DNA
Anti-nuclear RNA protein
Anti-nuclear RNA
Anti-non-nucleic acid protein (Sm)
Anti-RNA protein (ribosomes)
Anti-RNA protein (cytoplasmic, La)
Anti-ss, dsRNA
Anti-cytoplasmic (Ro)
Lymphocytotoxins
Anti-erythrocytes
Anti-coagulants
Anti-platelets
False-positive WR
Rheumatoid factors

such complexes *in vitro* (Onyewotu *et al.*, 1974) does not necessarily exclude DNA as a component since, as Liebling and Barnett (1975) have shown, DNA complexed with antibody may be protected from the effect of DNAase. Nevertheless, it is interesting that when Fournié *et al.* (1974) injected mice intravenously with bacterial lipopolysaccharides (LPS) this produced a rapid appearance of DNA in the blood and, after an interval of days, the appearance of circulating anti-DNA antibodies.

These authors went on to show that *in vitro* DNA tends to bind spontaneously to isolated glomerular basement membrane and to collagen and that injected radiolabelled DNA showed a very significant degree of binding in the kidneys of LPS-treated mice (Izui *et al.*, 1976). They also identified immune complexes containing DNA in the kidneys of such LPS treated mice (Izui *et al.*, 1977a).

An alternative hypothesis for the immunopathogenesis of the glomerular and epidermal basement membrane lesions and the disseminated immune deposits in lupus might thus postulate that DNA released from cells, bacteria, or viruses is bound by collagen or basement membrane. If at the same time circulating anti-DNA antibodies are present such tissue-bound DNA would act as an immunoabsorbant and give rise *in situ* to DNA-anti-DNA compexes, whose biological properties would determine their inflammatory effects. The recent failure of Izui *et al.* (1977b) to detect circulating DNA-anti-DNA complexes in patients with SLE supports this hypothesis.

There are clearly questions still to be answered about the provenance of the immunogenic DNA in SLE, the site of combination of the anti-DNA antibodies with DNA, and the nature of other antigen-antibody complexes that may contribute to the major pathogenetic mechanism in this disease.

Lymphocytotoxic antibodies

SLE sera often contain antibodies cytotoxic for normal lymphocytes. The presence of the antibodies is strongly correlated with the lymphopenia (Butler *et al.*, 1972). Anti-lymphocyte antibodies, however, occur quite widely in a number of other conditions, including several other connective tissue diseases and some viral diseases, and several attempts have been made to identify features in SLE lymphocytotoxins which may be characteristic. It transpires that they are predominantly IgM complement fixing but cold-reactive antibodies, and that under such conditions they are cytotoxic for both T and B lymphocytes. Nevertheless there is much variation between lymphocytotoxic sera in the precentage of normal lymphocytes killed as well as between the percentage kills obtained in a panel of normal donor lymphocytes with a given lymphocytotoxic serum (Lies *et al.*, 1973; Winfield *et al.*, 1975).

As well as cold IgM antibodies many patients also have IgG lymphocyte-binding antibodies reactive at 37°C and able to block mixed leucocyte culture reactions (Wernet and Kunkel, 1973). Some of these may have specificity for determinant present only on stimulated lymphocytes (Williams *et al.*, 1976). HLA specificities are apparently not involved. No specificity pointing to a special SLE antigen as a common target has so far emerged from investigations of these anti-lymphocyte antibodies. Two striking observations, however, suggest that they may not only play a hitherto unsuspected role in the pathogenesis of some of the characteristic clinical lesions of lupus but also may reflect the operation of environmental factors in the aetiology of the disease.

To take the latter first, de Horatius and Messner (1975) found that more than half the 124 relatives of 28 SLE probands had lymphocytotoxic antibodies as against 3% in controls. When they examined whether the relatives were blood relations or close household contacts it emerged that close household contact correlated much better with the presence of lymphocytotoxins than consanguinity. This suggested an important role for environmental factors in the pathogenesis of SLE. Similar results were obtained by Malavé *et al.* (1976), although Raum *et al.* (1977) found a less pronounced family incidence.

Even more interesting, from the point of view of their pathogenetic role, Bluestein and Zvaifler (1976) have shown that homogenised tissue from normal human frontal cortex absorbs the lymphocyte antibodies from SLE sera, and that eluates from the absorbing brain contain the IgM antibodies cytotoxic for both T and B cells. They also showed that lymphocytotoxicity levels are higher in patients

with central nervous system manifestations of lupus than in other SLE patients.

Dr Bresnihan and his colleagues at Hammersmith have confirmed this finding (Bresnihan *et al.*, 1977b), and have further shown that lymphocytotoxic antibodies in patients with cerebral lupus are absorbed by brain but lymphocytotoxins in patients without cerebral disease are not. Further evidence that lymphocytotoxic antibodies may play a pathogenetic role is the same group's finding that in pregnant lupus patients the presence of these antibodies correlates strongly with spontaneous abortion, while placental trophoblast extracts are effective in absorbing them out from such patients' sera (Bresnihan *et al.*, 1977a).

On the basis of current knowledge of their behaviour the lymphocytotoxic antibodies of lupus are probably a heterogeneous mixture of IgM and IgG cold and warm reactive antibodies directed at a variety of lymphocyte surface determinants—some of them shared between the lymphocyte cell membrane surface and brain and others between the lymphocyte membrane and trophoblast. These antibodies may belong to a wider family of anti-cell membrane antibodies occurring in lupus which includes anti-erythrocyte and anti-platelet antibodies. Whether the tuboreticular structures seen on electron microscopy in lupus blood lymphocytes and sometines also in other connective tissue diseases (Grimley *et al.*, 1973) are evidence of viral infection in these cells is conjectural. Lewis and Schwartz (1976) have produced evidence suggesting that in SLE the lymphocyte membrane shares antigenic determinants with C-type virus particles, as shown by the effect of absorption with purified virus on the reaction of SLE lymphocytes with an anti-lymphocyte antibody found in an SLE patient's serum.

It might therefore be postulated that the effect of such viral modifications of the cell membrane is to increase its autoimmunogenicity, and that this is the stimulus for the production of lymphocytotoxins. It could be further argued that any membrane damage induced by these antibodies would release intracellular components of similarly enhanced autoimmunogenicity, and that this would explain the multiplicity of non-organ specific antibodies directed at nuclear and cytoplasmic components which are commonplace in lupus.

Is the immune system deranged in SLE?

Delayed hypersensitivity to skin test antigens is impaired in SLE (Horwitz, 1972), especially in active disease (Horwitz and Cousar, 1975). Lymphopenia is common in lupus and seems to result from deficiences in all the lymphocyte subpopulations in the blood, especially some T-cells (Messner *et al.*, 1973) and Fc receptor-bearing cells—at any rate those that take part in K cell activity (Scheinberg and Cathcart, 1976). A striking decrease in 'active' E-rosette forming cells—considered by some to be a functionally distinct sub-population—is also reported, again especially in patients with clinically active disease (Rivero *et al.*, 1977). Both normal and depressed responses of SLE lymphocytes to stimulation by plant lectins are reported, and in active disease decreased mitogenic activity seems to be the rule (Rosenthal and Franklin, 1973; Lockshin *et al.*, 1975); but this may in part be an artifact due to lymphopenia in the test cell preparation from the patient (Horwitz and Garrett, 1977).

Lupus sera suppress responses of autologous and homologous lymphocytes to PHA, Con A, and PM but, disappointingly, no clear relationship has so far been demonstrable between these serum inhibitors and the anti-lymphocyte antibodies discussed above (Horwitz *et al.*, 1977). In contrast with the general lymphocyte deficiencies reported the blood of SLE patients contains B lymphocytes that are able to bind DNA at their surface, a property generally interpreted as identifying lymphocytes whose surface Ig is specific anti-DNA antibody. Bankhurst and Williams (1975) who reported this finding also made the interesting observation that such specifically DNA-binding lymphocytes are to be found in the blood of normal people, although in active SLE the number is tenfold higher. This matches the earlier observation of Bankhurst *et al.* (1973) that lymphocytes binding thyroglobulin, a tissue antigen involved in autoimmune thyroiditis, are present in normal human blood.

If these findings are evidence of the presence of potentially anti-DNA and antithyroglobulin producing cells in normal subjects this is inconsistent with an explanation of self-tolerance towards such antigens that postulates depletion of autoreactive cells during developmental contact with antigen—that is to say, the 'forbidden clone' theory of Burnet (1959). We know now that for so-called T-dependent antigens antibody induction requires the co-operation of T cells which perform a helper function for the B cells in question, and that appropriately low doses of these antigens can make such T cells tolerant, vitiating their helper function. This in turn has led to the similar idea that self-tolerance to potentially autoantigenic body components present in low concentrations in the tissues is a T-cell based tolerance (Allison, 1971).

There is now compelling evidence from mouse experiments that T cells express suppressive effects which regulate both humoral and cellular immune

responses (Katz and Benacerraf, 1974) as well as helper functions. The suppressive effects also play an important part in maintaining experimentally induced tolerance to foreign antigens (Gershon, 1975). As Allison *et al.* (1971) have pointed out, self-tolerance based solely on T-cell tolerance is by no means infallible: it is by-passed by antigens in which the relevant determinents are coupled with a different carrier. These workers predicted that suppressor T lymphocytes must play an important supporting role in maintaining self-tolerance. Studies in the autoimmune mouse strain NZB and its related hybrid NZB/W support the concept that autoimmunity can be viewed as a disorder of immune regulation, so that a decrease in the activity of suppressor T cells or an increase in the activity of helper T cells sufficient to disturb the balance could lead to proliferation of B cell clones capable of producing autoantibodies (Talal, 1976).

In mice, the existence of congenic stocks differing at a single locus permits the production of alloantisera which define the surface antigens of lymphocytes. These congenic stocks have been used with great effect to identify functional subsets of lymphocytes. In man this is a more difficult problem, and detection of suppressor cells in normal subjects or in disease, like the detection of K cells, at present relies on indirect methodology. One such approach to the study of suppressor-cell activity in SLE is based on a supposed analogy between mouse and human lymphoid cells in their susceptibility to incubation for 24 hours in culture. The addition of Concanavalin A to mouse spleen cells responding to antigenic stimulation in culture depresses the antibody response, but if the cultures are incubated for 24 hours before the addition of Con A this produces enhanced responses rather than suppression (Dutton, 1972). This seems to imply that suppressor cells are depleted during the 24-hour culture period.

Applying the same procedure to normal human blood mononuclear cell cultures Bresnihan and Jasin (1977), similarly found that the incubation of cultures for 24 hours before adding an appropriately chosen dose of Con A resulted in an enhanced cellular proliferative response to this mitogen. Since Con A responsiveness is a T cell function, and since it was shown that the presence of cells preactivated with Con A abolished this effect of incubation, it was reasonably concluded that normal cells lose their suppressor function in culture. When lymphocytes from active SLE subjects were similarly incubated before addition of Con A no enhancement of its proliferative effect was found, implying that in active SLE suppressor function is already lost *in vivo*.

More direct evidence of a suppressor cell defect is required to support this interpretation. The results lend credence to speculation that the autoimmunity of SLE represents a subtle form of immunodeficiency affecting the functions of a subset of lymphocytes, the suppressor T cells. There is little evidence whether this in turn reflects a genetic effect. In SLE there is among all Caucasians with the disease studied a modest increase in incidence of the HLA antigen B8 (Russell and Barraclough, 1977), an association seen more strongly in several other diseases with autoimmune features (Svejgaard *et al.*, 1975). More striking is the very significantly higher prevalence of C2 deficiency in SLE subjects than in controls (Glass *et al.*, 1976). This has been variously explained as reflecting an impaired immune response caused by an immune response gene linked to the complement deficiency, with resulting persistence of an aetiological agent, but it might equally indicate that C2 is necessary for neutralising or clearing a postulated agent or consequential immune complexes (Ruddy, 1977). Thus genetic studies so far throw little light on the reason for the autoimmune propensities of SLE subjects.

Conclusions

In conclusion, it may be pointed out that autoimmune though the pathogenesis of the lesions of SLE undoubtedly is the fuller understanding of its aetiology needed for more rational therapy is likely to dawn only when the interaction between helper and suppressor T cells in man, and the effects on this of viral or other antigens expressed at cell surfaces, are more clearly defined.

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