At the third Eular Workshop on Rheumatology Research, held at Mainz, West Germany, on 17-18 February 1983, the following abstracts were submitted.

**Induction of SLE-like disease in normal mice**

**I. Types of autoantibodies and pathological lesions produced.** E. Gleichmann, F.M. van Rappard-van der Veen. Central Lab. of the Netherlands Red Cross Blood Transf. Serv., Amsterdam, the Netherlands.

A chronic graft-versus-host reaction (GVHR) was induced in adult nonirradiated (B10 x DBA/2)F1 mice by I.V. injection of live DBA/2 (H-2d/d) lymphocytes. Although both a class I (K/D) and a class II (I-A/I-E) incompatibility existed in the F1 recipients, DBA/2 donor cells were unable to induce the severe lympho-hemopoietic depletion characteristic of acute GVHD; in this DBA/2 differs from most other strains of mice, such as B10 and B6. Instead, DBA/2 cells induced an SLE-like GVHD which included the following symptoms: 1) autoantibodies to thymocytes, erythrocytes, nuclear antigens, dsDNA, and other less well-defined self-antigens; 2) increased serum titers of antibodies to the surface antigen (gp70) of endogenous murine leukemia viruses; 3) a 10- to 50-fold increase in spontaneous IgG formation and a 4-fold increase in IgM formation in the spleen, these were accompanied by hyper-γ-globulinemia; 4) a ubiquitous periarteritis; 5) the deposition of IgG and IgM antibodies along the basement membrane of the skin; and 6) a severe immune-complex glomerulonephritis; significant amounts of anti-gp70 antibodies and antinuclear antibodies were eluted from diseased kidneys.

In spite of the tremendous increase in spontaneous Ig production and the spontaneous formation of very high titers of SLE-like autoantibodies, however, we failed to detect a spontaneous formation of antibodies to non-self, such as SRBC, HRBC, TNP, levan, bacteriophage fd, and plasmodium berghei. Upon planned immunization with SRBC, the specific antibody response of SLE-like GVH mice was even decreased. Interestingly, there was no autoantibody formation to organ-specific antigens, such as thyroglobulin. Thus, the increased antibody formation in these SLE-like GVH mice was preferentially, if not exclusively, directed against self-antigens involved in SLE. We propose that due to their intrinsic structure these self-antigens are more apt than others to trigger the corresponding autoreactive B cells in the presence of unspecific T cell help.


The spectrum of pathological symptoms induced by the GVHR comprises "stimulatory" as well as "suppressive" pathological symptoms. Stimulatory GVH symptoms include hyper-γ-globulinemia, autoantibody formation, lymphoid hyperplasia, and various inflammatory lesions reminiscent of collagen vascular disease, which can overlap to a considerable extent. Suppressive GVH lesions, by contrast, consist of pancytopenia, which includes a disappearance of plasma cells in the gut and is accompanied by aplastic anemia and hypo-γ-globulinemia. Previous studies, all of which were performed in nonirradiated F1 recipient mice, have established that the induction of both the stimulatory symptoms (chronic GVHD) and suppressive symptoms (acute
GVHD) require T lymphocytes in the donor cells inoculum and an H-2 incompatibility in the recipient. Using the same system, we now report that stimulatory GVH symptoms are induced by class II (I-A/I-E)-reactive Lyt 1+2- donor T helper (T^H) cells, whereas suppressive GVH symptoms are caused by class I (K/D)-reactive Lyt 1+2+ donor T suppressor (T^S) cells. For the optimal induction of alloreactive donor T^S cells, however, an alloactivation of donor T^H cells was also required. The activated donor T^S cells appear to release anti-mitotic factor(s) by which they prevent the physiological proliferation of lymphohemopoietic cells and thus cause the pancytopenia of acute GVHD.

These findings might help us to understand the associations of MHC structures with spontaneously arising GVH-like diseases. Various etiologic agents, such as viruses or drugs, that would render class II MHC structures of lymphohemopoietic cells and/or macrophages "foreign" might thus activate T^H cells and cause the "stimulatory" pathological symptoms. This might explain why so many of the collagen vascular autoimmune diseases in man are associated with HLA DR alleles. By contrast, if the same, or other, etiologic agents would render class I (plus class II) MHC structures "foreign" this might activate T^S cells and lead to the suppressive pathological symptoms mentioned above.

**Analysis of immunoregulatory defects in MRL-Lpr/Lpr mice.** J.D. Waterfield, R.N. Maini. Clinical Immunology Division, Kennedy Institute of Rheumatology, London W6., Great Britain.

The immune system is a network of clonally distributed cells homeostatically balanced by positive and negative signals (messages) passed among the different sub-sets of lymphocytes. Effective interaction amongst these sub-sets is a prerequisite for preventing autoimmune reactions and associated disease.

SLE is an autoimmune disease found in both the human and the mouse. Serologically the disease is characterized by oligoclonal increases in immunoglobulins such as anti-nuclear antibodies, anti-double stranded DNA antibodies and anti-single stranded DNA antibodies.

In individuals presenting with SLE it is apparent that there is activation of antibody producing cells with specificity for self antigens - a finding that does not normally occur in healthy individuals. We postulate that such activation reflects a failure in "correct" interactions of sub-sets of lymphocytes responsible for maintaining homeostasis.

There are two possibilities:

1) The activation of autoantibodies is a result of too much help being delivered to select clonally distributed self-reactive B lymphocytes.

2) The activation of autoantibodies is a consequence of a defect in the regulatory (suppressor) T cell population failing to "damp down" an otherwise transient autoimmune episode.

At present we are investigating the first possibility in MRL-Lpr/Lpr mice, mice that spontaneously develop SLE-like disease. We have set up three

**Animal model: Spontaneous lupus erythematosus associated with rheumatoid arthritis in MRL mice.** G. Trautwein, M. Hewicker. Tierärztliche Hochschule, Institut für Pathologie, Hannover, W. Germany.

MRL mice have been developed by MURPHY and ROTHIS (1978) at the Jackson Laboratory, Bar Harbor (Maine, USA). Of this inbred strain, two substrains designated MRL-Lpr/lpr and MRL-+/+ are available. These substrains differ as to their life span, the severity of disease and the occurrence or absence, respectively, of lymphoproliferation (symbol "lpr"). We have studied two aspects of disease in MRL mice: (a) The natural evolution of immune-complex-mediated glomerulopathy in mice of different age. The glomerular lesions were classified as mesangio-proliferative, membranoproliferative, mesangiosclerosing, intra- and extra-capillary proliferative, and epimembranous glomerulonephritis. Glomerular immune deposits consist of retroviral gp 71 antigen, IgG, IgM, and C3. Glomerulopathy is frequently associated with panarteritis in the kidney and in other organs.

(b) The occurrence of rheumatoid arthritis-like joint lesions. Polyarthritis which develops predominantly in older MRL-Lpr/lpr mice has many of the histological characteristics of human rheumatoid arthritis: proliferation of synovial lining cells, subsynovial infiltration with lymphocytes, plasmacytes and macrophages, pannus formation, cartilage erosion, and tendovaginitis, esp. at the phalangeal joints. In addition, there is vasculitis in the subsynovium, the periarticular connective tissue, the skeletal musculature, and in perineural locations. Affected mice develop significant levels of rheumatoid factor.