In this time of environmental concerns, it is appropriate to consider xenobiotics and their role in lupus syndromes. 'Occupational, inadvertent or therapeutic exposure to drugs, environmental chemicals and biological materials are collectively defined as xenobiotics.' In the good old days, the following description was not inappropriate:

'Eye of a newt and toe of frog,
Wool of bat and tongue of dog.'

It is not surprising that we now recognize that, on any given day, the average person may introduce up to 1000 different molecules into his/her body. The recognition and study of occupational and environmental disorders is a well-accepted and important specialty of medicine. Indeed, the regulation and establishment of guidelines for the safety of workers who may be exposed to potentially dangerous agents in the work place is now performed very largely by government. In more recent times, it has become clear that many rheumatological disorders are related to exposure not only to drugs, but also to a variety of environmental agents. The first recognition of a lupus-like syndrome occurring with a drug was in 1945 when Hoffman described such a reaction with sulphadiazine [1]. Since that time, over 70 drugs and medications have been reported in association with various types of lupus syndromes. The well-established drugs include procainamide, hydralazine, various anti-convulsants and psychiatric drugs. Only a few of these reports have consisted of prospective studies of large numbers of patients; the majority are case reports, often describing only one or two patients. Another problem has been that although rheumatology is guided by the classification criteria for systemic lupus erythematosus (SLE) [2], there are no well-defined and accepted diagnostic criteria for these drug and environmental lupus syndromes. The development of positive antinuclear antibodies (ANA) with anti-histone antibody specificity while taking a drug or on exposure to a known environmental agent (EA) with one or two clinical symptoms and signs from the accepted SLE list should be sufficient to alert the physician to the possibility; the disappearance of symptoms and signs and later, often the antibody, on stopping the drug or removal of the EA should clinch the association. There has been considerable study of the pharmacogenetics and molecular structure of many of these drugs and their metabolites, but they lack a commonality of structure. Some of the drugs, including hydralazine, have a strong link to hydrazines which can be found in plastics, rubber, herbicides, pesticides, textiles, dyes and anticorrosives. They are also found naturally in tobacco, mushrooms and penicillin.

Aromatic amines, the basis for a number of drugs, including procainamide, are also present in various azo food dyes such as tartrazine. Another aromatic amine is present in certain hair-dying compounds and provoked some studies of the relationship to SLE. A recent case-control study failed to detect an association between SLE and the use of such hair products [3].

There have been many reviews of drugs and lupus syndromes [4, 5] and I will not dwell further on these aspects, but instead address some of the intriguing possibilities that relate to the environment. Although we know a great deal about the pathogenetic mechanisms of SLE, the specific cause or causes are not yet known. Therefore, study of these ubiquitous environmental factors may well provide important clues. A number of occupational exposures are well recognized. A good example is the association of exposure to polyvinyl chloride and silica dust with scleroderma-tous-like diseases. The possible role of the various types of silicone in breast implants does not need detailing here, except to note that ANA have been reported but the number of reported lupus-like syndromes is very small and may not exceed the expected incidence. Except for one major study [6], any statements about a definitive association cannot as yet be made. Also, in more recent times, two well-recognized syndromes in which autoantibodies occurred include the toxic oil syndrome with exposure to some contaminant in the denatured rapeseed oil and the eosinophilia myalgia syndrome, being most likely a contaminant as yet unconfirmed, present in samples of L-tryptophan health food products. The Bhopal tragedy in India, which resulted in a large number of deaths, also caused chronic respiratory and other systemic disease syndromes with similarities to lupus and with reported positive ANA (unpublished data). Agent Orange-related disorders observed in the Vietnam War and, more recently, the Gulf War syndrome, are further examples of exposure to toxins resulting in many symptoms, some suggestive of lupus and other rheumatic diseases. The specific agent in the Gulf War cases has not as yet been identified, although recent information suggests that it could be a compound given to protect against nerve gas. A study of these well-known events and epidemics can and should provide important data in the study of autoimmunity.

There have been recent reports relating exposure to contaminated groundwater in Arizona, USA, to the appearance of lupus and ANA [7]. However, this study, and another report detailing autoimmune disease and antibodies and symptoms in computer assembly plants in Southern California, have not as yet been confirmed.
and at this time must be regarded as observational [8]. Potential positive chemicals include trichlorethane, benzene, toluene, xylene, perchlorethylene and inorganic chromium. The proposed mode of entry in the first study was through groundwater. There have been other isolated reports from different geographical parts of the USA claiming clusters of lupus secondary to various perceived contaminants. All such reports should alert rheumatologists to endeavour to obtain critical data and, where possible, perform appropriate studies.

We are all aware of the increasing use throughout the Western world of various herbal medicines and food supplements. Many of these have been reported to cause liver damage, thyrotoxicosis, skin, pulmonary and oesophageal problems. The potential for autoimmunity, and particularly for the formation of various antibodies, exists.

Biological agents are used increasingly in many disorders, including rheumatoid arthritis, systemic lupus, systemic sclerosis, multiple sclerosis and psoriasis. Both interferon $\alpha$ and interferon $\beta$ have been associated with autoantibodies to thyroglobulin, thyroid antigen, gastric parietal cells, as well as to nuclear and DNA antigens. Autoimmune-type disorders, including lupus-like syndromes, have been reported with monoclonal antibody to TNF-$\alpha$ [9]. Similar observations are noted with the use of interleukin-2; vasculitis and inflammatory arthritis have been reported [9].

We cannot ignore other dietary components, e.g. the amino acid l-canavanine found in alfalfa seeds and sprouts can induce a lupus-like syndrome in monkeys, and has been reported in association with lupus syndromes and ANA in patients in California. Many complicated manipulations of the diet, such as high-caloric, polyunsaturated fatty acids have been reported to either worsen or improve lupus activity in mice. Such effects are now being studied in human lupus patients. Exactly which component or components of these various dietary constituents is/are the active factor(s) remains unknown.

A number of heavy metals, such as mercury, gold and cadmium, have been associated with the induction of autoantibodies and autoimmune disease in experimental animals and in humans, and are under active study [10].

UV radiation is known to induce and exacerbate cutaneous and systemic lupus erythematosus. The photosensitivity syndrome is associated with a positive ANA in many people, but there are few data on the long-term follow-up of people who acquire these photosensitivity syndromes. Whether the reported low incidence of SLE in Africa has any relationship to the protective effects of skin pigmentation remains conjectural.

Clearly, infectious agents are environmental. Whether or not any specific viral, bacterial or fungal organisms can cause SLE remains unclear, although there is growing evidence of their footprints in the human patient. There have been many observations on possible flares in SLE related to infections. The recent observation of parvovirus inducing a lupus symptom complex is a good example. Human parvovirus B19 (HPV-B19) can present with a malar rash, fever, arthropathy, myalgia, cytopenia, hypocomplementaemia, ANA and anti-DNA. In the patients described, the symptomatology improved within several weeks [11]. We are all aware of other infections, e.g. Epstein-Barr virus (EBV), which can also resemble SLE. This is clearly a very complicated area, but it provides a challenge to physicians to observe and document such associations.

A major question, of course, is whether or not the antibodies, particularly the ANA, which occur so frequently and often without any disease manifestations, play a role. Are they solely markers or do they contribute to the pathogenesis of the disease? Recent work is focusing on the antigen and its role in autoimmunity. A recent study on antibody-mediated autoimmune myocarditis [12] reported that in susceptible mouse strains, the antibodies to myosin can mediate myocarditis. The study also showed that disease susceptibility depended upon the presence of the myosin or at least a myosin-like molecule within the cardiac matrix. Kasturi et al. [13] focused on anti-fibrillarin antibodies, showing that these autoantibodies were against the immunodominant epitopes located at the NH$_2$- and COOH-terminal regions of the fibrillarin. They also showed homology between the NH$_2$-terminal region and the nuclear protein encoded by EBV, the COOH-terminal region and capsid protein P40 encoded by herpes simplex virus (HSV).

What was intriguing was the presence of these anti-fibrillarin antibodies in many connective tissue diseases and the suggestion that molecular mimicry could play an important role in inducing these anti-fibrillarin autoantibodies. It is not too far fetched to speculate that the ubiquitous appearance of the ANA in many of the drug and environmental lupus syndromes could be triggered by a common agent with molecular mimicry, and that disease symptoms occur only in those with the appropriate genetic susceptibility.

The disorder berylliosis, recently shown to have a specific genetic marker, HLA DP.$\beta$1 glutamate, in 32 of 33 exposed subjects [14] reminds us that beryllium is a constituent of ceramics and is found in electronics and dental alloys, and is used in nuclear weapons and the aerospace industry. It is an excellent example of a very specific HLA relationship in which the glutamate instead of a positively charged lysine is present at position 69. Such observations remind us of the importance of the MHC class II alleles, associations which may be very important in some of these lupus syndromes.

Clearly, such a multiplicity of drugs, biologies, environmental factors of many types, does not allow here a consideration of the many specific and non-specific mechanisms. Suffice it to say there is general agreement of the importance of (1) patient risk factors which include sex, race, possible effects of migration,
immunogenetics, genetically determined polymorphisms of metabolic enzymes underlying pathologies/conditions and duration, dose of exposure (these factors could be single, multiple or different at the same time) and (2) the numerous effects directly or indirectly on every aspect of the immune system, with the theories of molecular mimicry coming to the fore. The ever increasing knowledge of alteration of MHC expression and abnormalities within the many cytokines could provide the appropriate mechanisms for any one of these drugs or environmental events.

Many of these factors are addressed in a recently published review which highlighted drug and environmental lupus syndromes [15]. It is hoped that the increasing interest in publications and literature on this subject will stimulate rheumatologists, and indeed all physicians, to take adequate occupational, home and environmental histories so as to seek associations with disease onset. A recent publication on environmental health risks and public policy [16] highlighted five environmental hazards among the many: cigarettes, air pollution, asbestos, lead and electromagnetic radiation. It provides stimulating reading and reinforces the importance of epidemiology in determining causes of disease and their potential prevention. This new interest in environmental epidemiology and xenobiotics has much to offer in helping us determine possible associations to lupus and other rheumatic diseases and autoimmune syndromes.

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REFERENCES


MOLECULAR MARKERS TO MONITOR OUTCOME AND INTERVENTION IN OSTEOARTHRITIS (PROMISES, PROMISES . . . )

OSTEOARTHRITIS (OA) involves the uncoupling of the normal balance between degradation and repair in the cartilage and subchondral bone of the joint. This process results in changes in the structure of the affected joints, and can cause pain and physical disability. OA evolves slowly and is heterogeneous; the patient and the tissues age concurrent with the progression of OA, inducing additional and confounding functional changes in the musculoskeletal system. This creates problems when we want to monitor outcome and intervention in OA, problems which are amplified by a lack of consensus on appropriate methods to assess the disease process. New interventions are now being proposed for treatment of joint disease [1, 2], which may have the ability to alter the rate of joint destruction in OA. Unless improved techniques are developed, standardized and validated, it will not be possible to properly evaluate the role of new and old interventions [3].

There are currently three general ways proposed by which OA might be assessed:

- patient-related measures of joint pain, disability or endpoint (algofunctional scores such as WOMAC [4], index of severity of knee or hip disease [5] or frequency of total joint replacement);