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Foundation of America, Inc.
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The Massachusetts Chapter of the Lupus Foundation has been following progress of meetings between the EPA, city government and citizens of New Bedford concerning the construction of an incinerator and its environmental impact.

Attached are two articles which appeared in the most recent issue of Lupus News, the quarterly publication of the Lupus Foundation of America, entitled "A lupus syndrome related to drugs and environmental factors" and "Environmental factors and lupus."

Dr. Hess reports that "over 50 different drugs and other compounds have been reported in association with a lupus-like syndrome called drug-related lupus (DRL)." Dr. Kreig writes that "there are probably many environmental and genetic factors that can cause lupus; in different patients lupus is probably triggered by different causes." He cites vinyl chloride, asbestos, or silica. "A recent study found that patients exposed to hair dyes have a significantly increased risk of lupus. It seems prudent for lupus patients to avoid unnecessary exposure to hydrazine or other aromatic amine-containing compounds.... Environmental factors can clearly have important immune effects."

The LFA would like to reiterate its earlier position that a causal relationship between the environment and lupus should be investigated by epidemiologic studies. The LFA is currently involved in a study in Gardner, MA with the Dept. of Public Health to determine if there is an unusually high incidence of lupus in that area. Further studies may follow to examine environmental conditions which may account for a higher incidence of lupus.

Please call the Lupus Foundation office at 617-332-9014 for further information.

Lupus News

OFFICIAL NEWSLETTER OF THE LUPUS FOUNDATION OF AMERICA, INC.
Volume 11, Number 3, 1991 Circulation 60,000 Henrietta Aladjem, Editor

Environmental Factors and Lupus

by Arthur M. Krieg, M.D., University of Iowa, College of Medicine, Department of Internal Medicine

This Issue of *Lupus News* contains an article from Mr. Neil Duane describing a fairly typical case of drug-induced lupus and an accompanying article by Dr. Evelyn Hess providing the medical perspective on drug-induced lupus. Dr. Hess makes the point that other environmental factors can also trigger lupus. The topic of environmental factors and lupus is one that has recently received national and even international attention because of the autoimmune illness that have affected President Bush, Mrs. Bush and their dog, Millie. It is not yet clear whether these 3 cases are related or coincidental, but we believe the topic is an important one to the readers of *Lupus News*, and have decided to provide additional information in this article.

Decades of research have made it increasingly clear that there is no single cause of lupus or other autoimmune diseases. There are probably many environmental and genetic factors that can cause lupus; in different patients lupus is probably triggered by different causes. This may be one reason that the symptoms and course of disease can vary so much from one patient to another. The genetic factors that may contribute to lupus are discussed in the article by Dr. Arnett in this issue of *Lupus News*.



Arthur M. Krieg, M.D. and youngest daughter

knowledge of the environmental factors that may contribute to lupus. Some of these may be avoided by patients and family members. Of course, it is quite likely that not all of these factors have been identified. Furthermore, patients should bear in mind that what causes lupus in one patient will not necessarily cause lupus in another.

UV light

The role of UV light in lupus has been discussed in *Lupus News* recently (Volume 11, number 1), so the discussion here will be brief. While UV light probably does not cause lupus, at least a third of lupus patients are photosensitive, and may have disease flares following UV exposure. UV light has immune stimula-

erbate lupus. However, UV light also has some immunosuppressive effects that are rather complex, but could theoretically be beneficial under some circumstances. The safest advice for lupus patients at the present time is to avoid all UV light (including the so called "safe" UV-A light). Patients should be aware that uncovered fluorescent bulbs can emit UV light and that some drugs or food containing psoralens can sensitize patients to UV light (see below).

Drugs

The role of drugs in triggering lupus is discussed in the articles by Mr. Duane and Dr. Hess in this issue.

Infectious agents

Many common clinical features of lupus, such as fever, fatigue, malaise and myalgias, are typical of those seen in infections. Epidemiologic studies and searches for infectious agents in lupus indicate that there is not one agent that is unique to lupus. However, it remains possible that different infections could trigger disease in different patients. Many attempts to isolate retroviruses from lupus patients have been unsuccessful, but this remains an active area of investigation, as discussed in a recent *Lupus News* article (see volume 11, number 1). Many bacterial and

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Environmental Factors and Lupus

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viral infections can cause immune activation that could in turn exacerbate lupus. Lupus patients are prone to viral and bacterial infections (see *Lupus News*, vol. 11, number 2), and sometimes have flares after common infections, but this risk has not been documented in clinical studies.

To illustrate the difficulties involved in these studies, lupus patients have been reported to have increased antibody levels to at least 12 different viruses and 4 retroviruses (1,2). Patients with active lupus often have generalized immune activation, resulting in the increased production of many antibodies and autoantibodies. Thus, the significance of the above anti-viral and anti-retroviral antibodies remains unclear and does not necessarily mean that these infections are causing lupus.

Stress

It has been the clinical impression of many physicians caring for lupus patients that severe physical or emotional stress can induce flares. In recent years research in immunology has demonstrated that immune responses can be affected by marked physical or emotional stress. Stress frequently leads to suppression of immune responses — thus accounting for the observation that college students have an increased incidence of colds during final exams. In lupus patients the affects of stress could be more complicated, and lead to immune activation. Some patients feel that their lupus symptoms worsen with stress, but others report no difference. This question has yet to be studied clinically in lupus patients, so it is unclear how often stress aggravates lupus.

Diet

There has been little research on the possible role of diet in human lupus. Several strains of mice spontaneously develop a disease very similar to human lupus. These "lupus mice" have been studied extensively to better understand how autoimmunity arises and how best to treat it. In lupus mice, severe vitamin deficiencies can exacerbate disease, which is improved by vitamin supplementation (3). In human patients eating well-balanced diets vitamin supplements are probably harmless but unnecessary. Of course, many patients

do not eat well-balanced diets, so some physicians recommend the use of a multivitamin supplement.

Lupus-prone mice fed large doses of omega fatty acids (present at high levels in fish oil) had decreased disease severity. However, a study supplementing 17 lupus patients with 10-15 capsules daily of a commercial fish oil, MaxEPA, showed no detectable benefit after 6 months of treatment (4). Furthermore, high doses of fish oil are quite expensive and often unpopular (they frequently make patients smell like fish!). Low calorie, low fat diets reduce disease severity in lupus mice, and possible in humans as long as the diet remains well-balanced.

Lupus flares have been reported after eating large amounts of foods containing psoralens (celery or celery salt, parsnips, parsley, figs). Psoralens are chemicals that increase photosensitivity in patients who are sun sensitive. Hydrazines, the chemicals which are believed to be responsible for many cases of drug-induced lupus, are also present in mushrooms, some food dyes (e.g. tartrazine), tobacco smoke, and most cooked foods, especially cooked meats and other fatty foods. While some patients exposed to large amounts of hydrazine have had flares, the amounts present in a typical diet probably have little or no adverse immune effect. A related amine, L-canavanine, is present in alfalfa seeds and sprouts (as well as most other legumes) and has also been implicated in occasional cases of lupus when eaten in large amounts.

Some foods could cause symptoms that mimic lupus, without actually affecting disease activity. For example, lactose intolerance is fairly common among adults and can cause abdominal pain and cramping after ingestion of lactose-containing foods. Food allergies can cause symptoms such as rashes or hives that are similar to lupus symptoms.

Some patients take various "natural" drugs containing bio-active extracts of variable composition. Many natural herbs contain chemicals with known immune effects as well as a complex mixture of uninvestigated compounds. Major research efforts are underway to identify any such compounds that may be useful in

treating disease in the meantime. It seems wisest to avoid such substances.

Other

Antinuclear antibodies (but not lupus) are increased in some workers exposed to high levels of vinyl chloride, asbestos, or silica. Some lupus cases have followed the injection or implantation of silicone polymers, such as those used in breast implants.

Hair dyes contain high levels of hydrazines and other chemicals that are related to procainamide and hydroxyzine and can be absorbed through the scalp. A recent study found that patients exposed to hair dyes have a significantly increased risk of lupus (5). It seems prudent for lupus patients to avoid unnecessary exposure to hydrazine or other aromatic amine-containing compounds.

In theory, routine immunization could cause lupus flares by stimulating the immune system. The studies performed so far have shown no increased risk from immunizations in lupus patients (6), but this area remains controversial.

Conclusion

Environmental factors can clearly have important immune effects. In some patients or predisposed family members, these immune effects could lead to the development or exacerbation of lupus. In different individuals, various environmental factors, or combinations of factors, are probably important. Unfortunately there are no tests available to predict which factors will trigger lupus in any given individual. Therefore patients should know about the factors that can or do trigger lupus, so that they can become aware of whether their symptoms change in response to environmental agents and so that they may modify their habits accordingly. ■

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Lupus News

OFFICIAL NEWSLETTER OF THE LUPUS FOUNDATION OF AMERICA, INC.
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"A Lupus Syndrome Related To Drugs And Environmental Factors"

by Evelyn V. Hess, M.D., F.A.C.P., McDonald Professor of Medicine
University of Cincinnati, Medical Center

Mr. Duane has given us a very interesting report of a lupus syndrome from which he suffered, which was related to a drug used in the treatment of hypertension called hydralazine. His symptoms were many aches and pains in his muscles and joints, a lot of fatigue and his doctor found lupus cells. I have been interested in drugs and other agents which may cause a lupus syndrome for many years and have done research into why and how drugs and other agents could cause lupus.

We now know that over 50 different drugs and other compounds have been reported in association with a lupus-like syndrome called drug-related lupus (DRL). The first report of such a reaction was in 1945 when one of the sulphonamides was the drug that caused the lupus syndrome. Hydralazine was first reported to cause lupus syndrome in 1953 at a time when rather large doses of the drug were being used to treat hypertension. Another important drug which is still a common cause for this syndrome is procainamide, first implicated in 1962. This drug is used to treat various types of heart abnormalities. There have been so many reports of drugs and other agents associated with lupus that investigators who are researching this problem like to divide the drugs into three categories: 1) those where there is a very definite association which has been shown by prospective studies, 2) those with a strong possibility of an association, and 3) those where, as yet, there is lack of definitive proof of association. The drugs and other agents can also be divided into different chemi-



Evelyn V. Hess, M.D., F.A.C.P.

cal classes: Aromatic amines, hydrazines, sulfur containing and the hydralazine anti-convulsants.

Some of the drugs which are quite definitely associated with lupus syndromes include hydralazine, procainamide, quinidine, beta blockers, certain anticonvulsants, chlorpromazine, some sulpha drugs. More recently there has been a great deal of interest in many non-drug compounds and environmental agents which may be related to this syndrome. Certain hydrazine chemicals, other materials such as L-tryptophan associated with eosino-phillic-myalgia syndrome, metals, silicone in breast implants and certain natural plants can be related to the production of antinuclear antibodies. Ultraviolet light has always been known as a possible stimulus to lupus disease activity.

Systemic lupus erythematosus is a disorder affecting many more women than men but drug related lupus occurs only slightly more often in

women. Patients with this syndrome tend to be in the older age group, perhaps because of the higher incidence in the older population of cardiac and other diseases for which many of these drugs are prescribed. However, the true incidence of lupus for many of the drugs is not known as the studies have not been performed. One of the other problems is that there are no established criteria for the diagnosis of DRL. There are classification criteria for SLE but many of the patients with DRL do not fulfill these criteria.

Sometimes the patient may only have one or two of the clinical features of lupus. Often the onset of symptoms is very abrupt. A common symptom complex is fever, myalgias and arthralgias; there may be chest pain indicating inflammation of the lining of the heart or lungs. Various rashes particularly the butterfly rash seen in SLE, is rarely seen with DRL. It is highly unusual to have either the kidneys or the central nervous system involved. Lastly, the symptoms will often clear within days to weeks of stopping the drug. The laboratory tests show that the antinuclear antibody must be positive which it has been in 100% of the patients with these associations. The LE cell is found in a high percentage of these patients. Many of the other antibodies, which are of importance in SLE, are usually not present. A special kind of immune reaction occurs as these patients make antibodies to specific nuclear components termed histones. There is a whole family of these antihistone antibodies for which certain laboratories can assay and thus help the physician make the

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"A Lupus Syndrome Related To Drugs And Environmental Factors"

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diagnosis. Information is available about these antibodies and their association with drugs particularly hydralazine, procainamide and quinidine.

It is important to stress that although varying percentages of patients on these drugs will make the antinuclear antibodies, only a small percentage of those who do will actually have the symptoms and signs of the lupus syndrome. It is not always necessary to stop a needed drug because the antinuclear antibody is positive. However, the physician must follow the patient very carefully and get some baseline studies. If the symptoms do occur, stopping the

drug will very often be sufficient. If there are problems, the physician may prescribe a short course of prednisone or a non-steroidal anti-inflammatory drug.

The consensus of opinion at the present time is that SLE and DRL are not exactly the same disorder. It is not infrequent for physicians to have to give patients with SLE some of the drugs which have been reported to cause DRL. As long as care is taken and the patient followed carefully, there has not been strong evidence to show that the drug will worsen the SLE itself. This has been true when antihypertensive drugs, anticonvulsants, anti-TB drugs, beta blockers

have been given to these patients.

We now know that the metabolites, which are breakdown products of the drugs, are more likely than the drug itself to cause the problem. This may also be true for some chemicals which are found in certain foods and tobacco and basic amino acids present in alfalfa seeds and sprouts and other legumes. It can be seen then that this is an important area of research: if we can find the means, whether biochemical, genetic or immunological by which these compounds cause these lupus syndromes, this will provide important information for our understanding of SLE as well. ■

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1000 Massachusetts Ave., N.W.
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Phone: (202) 331-1111
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