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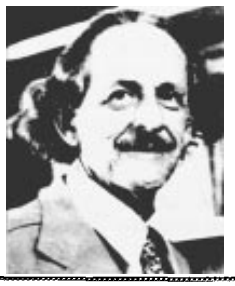

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EUGENE GARFIELD
INSTITUTE FOR SCIENTIFIC INFORMATION®
3501 MARKET ST. PHILADELPHIA, PA 19104

Lupus. Part 2. How Current Research Is Unmasking the Great Imitator

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In this, the second of a two-part survey of lupus, the focus is on the clinical symptoms of this autoimmune disease and the often problematic nature of diagnosis. Included are lists of the most common symptoms and their frequencies as well as criteria for a lupus diagnosis established by the American Rheumatism Association in 1982. Also discussed are the various therapeutic regimens, both standard and experimental, that are prescribed for lupus patients. Finally, we highlight the dozen and a half 1987 research fronts, or specialty areas, identified by ISI®'s co-citation clustering algorithms, that deal with lupus and the key papers for the largest fields.

Clinical Manifestations and Diagnosis

The clinical manifestations of systemic lupus erythematosus (the full name for the most severe form of lupus, abbreviated as SLE) are manifold, as any physician well knows. Rarely will more than a few symptoms appear simultaneously, and there is no telling which ones will surface first. These variable clinical characteristics are what can make the differential diagnosis of SLE so challenging. As one handbook notes, "Meticulous evaluation and long-term observation may be required before the diagnosis is established."[1]

Among the most common symptoms that a person with SLE will notice are fatigue and general malaise, a low-grade fever, weight loss, and—in 9 of 10 cases—joint pain, which is usually transitory and often located in the wrists and elbows, ankles and knees. Many patients experience morning stiffness. Unlike rheumatoid arthritis, joint deformation and disability are uncommon in SLE.

Skin rashes and lesions, especially the "butterfly" rash across the bridge of the nose and on the cheeks, are also frequently encountered symptoms. Forty percent of SLE patients exhibit photosensitivity that can exacerbate skin eruptions. A related problem is alopecia, loss of scalp hair in small patches.

Inflammation of serous membranes in the form of pleurisy and pericarditis is evident in about half of all SLE patients, as is enlargement of lymph glands. Anemia can be detected in 7 out of 10.[2]

Table 1 lists the common clinical abnormalities found in SLE, including those mentioned above and many others that are observed in only a minority of patients. But two other major abnormalities, because of their potential seriousness, deserve special mention.

Involvement of the central nervous system (CNS) in SLE patients can vary from insignificant to disabling. Indications that the CNS is affected include seizures resembling epilepsy, migraine headaches, forgetfulness, and confusion. Personality disorders from mild depression to psychosis (paranoia, mania, schizophrenia) are also encountered in half of all SLE patients.[2] In the past, psychological disorders were thought to arise as a secondary response to coping with SLE; however, today the organic basis of such symptoms is increasingly acknowl-

Table 1: Clinical features of patients with systemic lupus erythematosus.

Abnormality	Frequency (%)
Constitutional	
Fatigue	90
Fever	80
Weight loss, anorexia	60
Musculoskeletal	
Arthritis, arthralgia	90
Myalgia, myositis	30
Skin and mucous membranes	
Butterfly rash	60
Alopecia	50
Photosensitivity	40
Raynaud's phenomenon	30
Mucosal ulcers	30
Discoid lupus	20
Urticaria	10
Edema or bullae	10
Eye (conjunctivitis/episcleritis/sicca syndrome)	20
Gastrointestinal (anorexia, nausea, vomiting, abdominal pain)	30
Serosal (pleurisy, pericarditis, peritonitis)	50
Lymphoreticular	
Lymphadenopathy	50
Splenomegaly	30
Hepatomegaly	30
Hypertension	30
Bacterial infections	40
Pneumonitis	30
Renal	50
Central nervous system	
Personality disorders	50
Seizures	20
Psychoses	20
Stroke or long tract signs	10
Migraine headaches	10
Cardiac	
Myocarditis	30
Murmurs and valvular disease	30
Coronary artery disease	20
Hematologic	
Anemia	70
Purpura	50
Peripheral neuropathy	10

(After Steinberg, p. 2015 [see reference 2].)

edged. In its most severe form, SLE damage to the CNS can cause paralysis and coma.

Renal disease, seen in half of all SLE cases, is likewise potentially grave, although it can also be benign and asymptomatic. Alfred D. Steinberg, National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland, says in a recent comprehensive review that only a minority of SLE patients are threatened with loss of kidney function, but, should it occur, "chronic dialysis and renal transplantation are well tolerated."[2]

No one clinical symptom or set of clinical symptoms is specifically diagnostic for SLE, just as no one laboratory test can unequivocally detect it. The most specific tests, as mentioned in Part 1,[3] are those for antinuclear antibodies and anti-DNA antibodies. A positive finding in both tests along with the presentation of some of the clinical symptoms described above is strongly suggestive of SLE.

As an aid to researchers, the American Rheumatism Association drew up in May 1971 a set of preliminary criteria for SLE. The criteria were published by Alan S. Cohen, Boston University School of Medicine, Massachusetts, and colleagues that same year in a paper that went on to achieve *Citation Classic*® status.[4] In a commentary on the paper published in *Current Contents*® in 1982, Cohen recalled:

> The criteria were created to achieve uniform classification of defined groups of patients in order to compare data from different sources concerning the natural history, evaluation of therapy, and epidemiologic description of SLE.... It seems that the criteria have been widely quoted as they did indeed fill a need [and] because the criteria themselves have been a focus of discussion.... It was apparent when the SLE criteria were published that newer laboratory data such as antinuclear antibodies and complement would have to be considered for inclusion.[5]

The update appeared in 1982.[6] According to this new system, a person is defined as having SLE if any 4 or more of the 11 criteria (listed in Table 2) are observed, either simultaneously or serially. The authors of the revised criteria concluded:

> As with the 1971 criteria, the 1982 revised criteria set should be used mainly for the purpose of classifying patients in reports relating to clinical, serologic, cellular, or pathogenetic studies of SLE. Although it has good discriminating power against

> rheumatoid arthritis, scleroderma, and dermato/polymyositis, its performance against other rheumatic diseases has not been tested. Its potential as a truly diagnostic criteria set in SLE should await the results of more extensive tests against a wider variety of diseases.[6]

The revised criteria set is, in fact, now being tested by Naomi F. Rothfield, Division of Rheumatic Diseases, University of Connecticut, Farmington, according to Joan W. Miller, Terri Gotthelf Lupus Research Institute, South Norwalk, Connecticut.[7]

Treatments

For all forms of lupus, it is advisable to avoid sun exposure that can ignite a flare-up.[8] This is particularly appropriate if one has active skin rashes or lesions. When sun exposure is unavoidable, the patient should apply a sunscreen with a high protective factor rating (at least 15) against long-wavelength ultraviolet light.

The avoidance of exhaustion, both emotional and physical, is also appropriate.[8] Physicians typically advise 8 to 10 hours of sleep every night and a short nap in the afternoon, if possible.

In mild cases of SLE—those that do not involve major organ systems—adequate rest and salicylates, such as aspirin, may be the only treatment necessary. Salicylates are anti-inflammatory drugs that bring relief of joint pain and reduction of fever. For active rashes or lesions, topical application of cortisone cream is appropriate. If a stronger therapy is required, however, antimalarial drugs such as chloroquine and hydroxychloroquine are generally prescribed. Both salicylates and antimalarials have potentially serious side effects if taken in large doses for long periods. For aspirin, gastrointestinal disorders and liver toxicity may appear, whereas for the antimalarials the most damaging side effect, although rare, is irreversible retinopathy, which can cause blindness.[8]

For severe SLE, the cornerstone of therapy is corticosteroids, such as prednisone. They often have a dramatic beneficial effect on SLE symptoms, but their long-term use is to be avoided, if possible, because of their toxicity. A physician will use corticosteroids to bring a flare-up or "crisis" under control, but then slowly decrease the therapy. Frequently, however, such reduction of corticosteroids can open the door to renewed flare-ups.[8] The long-term management of SLE can, thus, prove problematic.

For the most severe forms of SLE—those threatening major organ systems, such as the kidneys—treatment combining corticosteroids and orally administered immunosuppressive drugs, such as azathioprine or cyclophosphamide, is often implemented. But, once again, serious side effects can arise from such therapy—bone marrow toxicity, hemorrhage cystitis, and sterility, to name a few. Intravenous administration of immunosuppressives, which seems to be more effective in treating lupus nephritis, is currently under study.[2]

Experimental treatments, whose efficacy is as yet unproven, include administration of sex hormones such as androgen, total irradiation of the lymph glands,[9] and plasmapheresis—the exchange of the plasma component in a patient's blood—as an adjunct to corticosteroid therapy, among many others.[10]

Research Fronts

The ISI® database of research fronts, which contains information on over 9,000 specialty areas for 1987, contains 18 with lupus or SLE in their titles (see Table 3).

A research front is a currently active specialty area, identified by papers indexed in 1987 and the highly cited publications that those papers consistently cite. The algorithm allows the literature to order itself into intellectually coherent groups of publications that make up frontier areas that we call research fronts.[11]

Table 2: American Rheumatism Association 1982 revised criteria for classification of systemic lupus erythematosus (SLE). A person is said to have SLE if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a physician
5. Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Serositis	a) Pleuritis—convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR b) Pericarditis—documented by ECG or rub or evidence of pericardial effusion
7. Renal disorder	a) Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed OR b) Cellular casts—may be red cell, hemoglobin, granular, tabular, or mixed
8. Neurologic disorder	a) Seizures—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance OR b) Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance
9. Hematologic disorder	a) Hemolytic anemia—with reticulocytosis OR b) Leukopenia—less than 4,000/mm^3 total on two or more occasions OR c) Lymphopenia—less than 1,500/mm^3 on two or more occasions OR d) Thrombocytopenia—less than 100,000/mm^3 in the absence of offending drugs
10. Immunologic disorder	a) Positive LE cell preparation OR b) Anti-DNA: antibody to native DNA in abnormal titer OR c) Anti-Sm: presence of antibody to Sm nuclear antigen OR d) False positive serologic test for syphilis known to be positive for at least six months and confirmed by *Treponema pallidum* immobilization or fluorescent treponemal antibody absorption test
11. Antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome

(After Tan, p. 1274 [see reference 6].)

The most active lupus research front for 1987 is entitled "Lupus anticoagulant, and antiphospholipid and anticardiolipin antibodies" (#87-1263), which contains 321 1987 papers and 31 earlier or "core" documents that are consistently cited by the 321. Identifying subgroups of lupus patients using various blood tests has been and continues to be a major focus for scientists investigating lupus. Graham R.V. Hughes, Lupus Research Laboratory, St. Thomas' Hospital, London, UK, last year described the history of recent work in the area that is the subject of research front #87-1263:

> In 1983 and 1984, having confirmed a strong association between lupus anticoagulant and thrombosis...we devised a sensitive immunoassay for antiphospholipid antibodies, using the readily available antigen cardiolipin. It has become apparent to us that high titres of anticardiolipin antibodies are associated with a distinct syn-

Table 3: The 1987 *SCI®/SSCI®* research fronts on lupus and systemic lupus erythematosus. A = number of core papers. B = number of citing papers.

Number	Name	A	B
87-1263	Lupus anticoagulant, and antiphospholipid and anticardiolipin antibodies	31	321
87-0678	Murine models of lupus nephritis	10	165
87-5880	Autoantibody effect on murine glomerular basement membrane	5	125
87-4415	Antibody DNA immune complexes in SLE	5	115
87-2805	Neurophysiological and cardiovascular involvement in SLE	11	103
87-4193	Reversal of murine lupus through treatment with monoclonal antibody to L3T4	3	92
87-7357	Circulating immune complexes in SLE	4	89
87-3889	Neonatal lupus erythematosus	7	69
87-4945	Natural autoantibodies and monoclonal immunoglobulins in SLE	3	67
87-4875	Interferons in autoimmune conditions, including SLE	3	57
87-2177	Nutrition, immunity, and immune response observed in children in a rural Tanzanian village, and implications for SLE	4	56
87-1526	Thyroid disease in SLE patients	4	47
87-6650	Anticardiolipin antibodies in SLE and Moyamoya disease	7	36
87-1042	Occurrence of renal tubular dysfunction and SLE	6	36
87-5800	Antihistone antibodies in idiopathic and drug-induced lupus	3	34
87-6538	Circulating immune complexes in SLE and C1q solid-phase radioimmunoassay	2	30
87-6033	SLE and Sjogren's syndrome associated with anti-Ts antibodies	3	17
87-1035	SLE and serine proteinases	2	15

> drome—separate from SLE, and characterized by recurrent venous and arterial (especially cerebral) thrombosis, recurrent placental thrombosis and abortion, as well as other features. We have chosen to call this syndrome the anticardiolipin syndrome or, more correctly, the antiphospholipid antibody syndrome.... In lupus, the description of this syndrome has filled in yet another blank in the definition of an "atypical" subset of patients—often DNA-antibody negative—who present with non-inflammatory, but nevertheless disastrous thrombotic disease.[12]

The key paper in this research front describes the detection of anticardiolipin antibodies by radioimmunoassay, a paper that Hughes himself coauthored.[13]

The lupus research fronts for 1987 with the second and third greatest number of citing papers center on kidney damage as observed in the New Zealand mouse strains—"Murine models of lupus nephritis" (#87-0678) and "Autoantibody effect on murine glomerular basement membrane" (#87-5880). A key paper in #87-0678 is a 1985 review of murine, or mouse, models of SLE, written by Argyrios N. Theofilopoulos and Frank J. Dixon, Research Institute of Scripps Clinic, La Jolla, California.[14] For #87-5880, four of five core papers in the front are by Y.S. Kanwar and M.G. Farquhar, Yale University School of Medicine, New Haven, Connecticut.

Of the 18 lupus research fronts listed in Table 3, two-thirds relate directly to the study of antibodies in SLE patients. Clinical manifestations of SLE are highlighted in only four. This probably accurately reflects the current emphasis in lupus research, which is focusing on the fundamentals of autoimmunity at the biochemical level.

Conclusion

The future path of lupus research undoubtedly lies both in rigorous clinical studies and in more advanced immunological investigation. More clinical trials of experimental therapies will likely bring about better treatments, especially for those with the most severe cases of SLE who are now receiving therapies that are highly toxic when administered over long periods.

But the most promising area may be the use of monoclonal antibodies targeted at several cell types. This is an area of current research represented by research front #87-4193, "Reversal of murine lupus through treatment with monoclonal antibody to L3T4." "It might be possible," David Wofsy, University of California School of

Medicine, San Francisco, has observed, "to suppress production of selected autoantibodies by using monoclonal antibodies that recognize the T cells that initiate the response."[15]

This may mark a basic shift in our strategy against lupus: instead of nonspecific therapy aimed at suppressing the immune system, physicians might directly target the exact components of the immune system that cause autoimmunity.

If that day comes, the battle against lupus may be won. That day is not yet here, but the millions of lupus sufferers around the world have good reason for hope. They should know that the effort being expended on their behalf by thousands of dedicated scientists is no less than herculean, as the size and breadth of the scientific literature on this subject makes plain.

* * * * *

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REFERENCES

1. **Berkow R,** ed. *The Merck manual.* Rahway, NJ: Merck Sharpe & Dohme Research Laboratories, 1987. p. 1276.
2. **Steinberg A D.** Systemic lupus erythematosus. (Wyngaarden J B & Smith L H, eds.) *Cecil textbook of medicine.* Philadelphia: Saunders, 1988. p. 2011-8.
3. **Garfield E.** Lupus. Part 1. "When your body attacks itself, there's no place to hide." *Current Contents* (11):3-10, 13 March 1989.
4. **Cohen A S, Reynolds W E, Franklin E C, Kulka J P, Shulman L E & Wallace S L.** Preliminary criteria for the classification of systemic lupus erythematosus. *Bull. Rheum. Dis.* 21:643-8, 1971.
5. **Cohen A S.** Citation Classic. Commentary on *Bull. Rheum. Dis.* 21:643-8, 1971. (Barrett J T, ed.) *Contemporary classics in clinical medicine.* Philadelphia: ISI Press, 1986. p. 83. (Reprinted from: *Current Contents/Clinical Practice* 10(11):24, 15 March 1982.)
6. **Tan E M, Cohen A S, Fries J F, Masi A T, McShane D J, Rothfield N F, Schalier J G, Talal N & Winchester R J.** The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum.* 25:1271-7, 1982.
7. **Miller J W.** Personal communication. 6 May 1988.
8. **Dubois E L & Wallace D J.** Management of discoid and systemic lupus erythematosus. (Wallace D J & Dubois E L, eds.) Dubois' *lupus erythematosus.* Philadelphia: Lea & Febiger, 1987. p. 501-64.
9. **Strober S, Farinas M C, Field E H, Solovera J J, Kiberd B A, Myers B D & Hoppe R T.** Treatment of lupus nephritis with total lymphoid irradiation. *Arthritis Rheum.* 31:850-8, 1988.
10. **Huston D P.** Experimental therapy in systemic lupus erythematosus. (Lahita R G, ed.) *Systemic lupus erythematosus.* New York: Wiley, 1987. p. 947-72.
11. **Small H & Garfield E.** The geography of science: disciplinary and national mappings. *J. Inform. Sci.* 11:147-59, 1985. (Reprinted in: **Garfield E.** *Essays of an information scientist: towards scientography.* Philadelphia: ISI Press, 1988. Vol. 9. p. 324-35.)
12. **Hughes G R V.** Systemic lupus erythematosus. *Postgrad. Med. J.* 64:517-21, 1988.
13. **Harris E N, Gharavi A E, Boey M L, Patel B M, Mackworth-Young C G, Loizou S & Hughes G R V.** Anticardiolipin antibodies: detection by radioimmunoassay and association with thrombosis in systemic lupus erythematosus. *Lancet* 2:1211-4, 1983.
14. **Theofilopoulos A N & Dixon F J.** Murine models of systemic lupus erythematosus. *Advan. Immunol.* 37:269-390, 1985.
15. **Wofsy D.** New approaches to treating systemic lupus erythematosus. *West. J. Med.* 147:181-6, 1987.