Essays of an Information Scientist: Creativity, Delayed Recognition, and other Essays, Vol:12, p.74, 1989 Current Contents, #12, p.3-10, March 13, 1989

Current Comments®

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

Lupus. Part 1. "When Your Body Attacks Itself, There's No Place to Hide"

—Terri Gotthelf, who died of lupus on May 11, 1981, at the age of 21.

Number 11 March 13, 1989

This essay discusses lupus, an immune-system dysfunction that affects many, especially young women, but is recognized by all too few. Its multiple manifestations have been baffling to researchers for over 100 years; only recently have the tools of molecular biology and immunogenetics revealed substantial new information on its mechanism of autoimmunity. Still, the ultimate trigger for lupus remains a mystery. In this, the first of a two-part overview of lupus, we look at the history, epidemiology, pathogenesis, and possible etiologies for the disease. Included are lists of lupus associations and the main journals publishing lupus research. In Part 2, the clinical symptoms, diagnosis, and standard and experimental treatments for lupus are surveyed, as are the 18 research fronts from 1987 that involve lupus.

Introduction

Each year thousands of young women contract a disease that is life-changing and often life-threatening. For all it means social isolation and great frustration. It brings pain, fatigue, and other, more serious disabilities. For some—thankfully not all—it means death.

This disease affects more people than do leukemia, muscular dystrophy, multiple sclerosis, cystic fibrosis, Hodgkin's disease, or even AIDS, yet there is great ignorance of its symptoms among the public. Even health professionals still frequently misdiagnose it.

The disease is called lupus.

Lupus is a chronic immunological disorder that, in its most severe form, can impair and destroy major organ systems. Specifically, it is an autoimmune disease that causes the body's defenses to turn upon healthy tissues and organs.

Lupus afflicts an estimated 500,000 to 1 million or more persons in the US alone; 50,000 new cases are reported annually. Worldwide figures are unavailable, but its per capita prevalence in other nations is thought to be approximately the same as in the US. In adults, it is some 10 times more frequent in women than it is in men. The severity of the disease varies greatly, as do its symptoms. It is characterized by flare-ups and remissions that often seem to come and go unpredictably, although certain exacerbating factors—such as sunlight—have been recognized. Because some forms of lupus can affect the joints and bones, the skin, the kidneys, the heart, the lungs, the brain, and other organs and organ systems, it can easily be mistaken for other ailments. In fact, recognition of what is and what is not lupus erythematosus (its full name) is often a good test of a medical student's skill in making an accurate differential diagnosis. Given its multiple manifestations, lupus has earned the moniker "The Great Imitator."

Lupus is the Latin word for wolf, and *erythematosus* is Latin for redness. Thus, the term *lupus erythematosus* (LE), first ascribed to this disease in the mid-nineteenth century, means "wolf red." The disease came to be called "wolf" because of the jagged-edged, butterfly-shaped rash or ulceration across the bridge of the nose and on both cheeks present in more than half of all cases. It has been suggested, alternately, that the facial rash and ulceration resembles a wolf's bite;[1] that the progress of ulceration is ravenous, like a wolf;[2] (p. 3)

and that the facial rash resembles the markings and color of the wolf's face in the same area—across the bridge of the nose and on the cheeks.[3]

There are two types of LE—discoid and systemic. Discoid lupus erythematosus (DLE) is the less serious form of the disease and apparently affects only the skin, causing skin rashes and lesions. It is usually not life-threatening.

The more severe form of lupus, however, systemic lupus erythematosus (SLE), can be fatal, since it extends to and can cripple major organ systems. Skin rashes and lesions, like those of DLE, frequently appear in SLE, but not always. There has been considerable debate over the relationship between DLE and SLE—whether they are opposite ends of what might be called a "lupus spectrum," or whether they are in fact distinct diseases.[2] (p. 302) Although they have much in common (for example, a fundamental immunological dysfunction, skin lesions, photosensitivity, and a high incidence in women relative to men), they are generally exclusive: only about 5-10 percent of those with DLE go on to develop the more generalized lupus, SLE.

There is currently no known cause, nor is there a cure for lupus. There are, however, a number of therapies that, depending upon a patient's condition, can make living with lupus bearable. Advances in our understanding of molecular biology and cellular immunology, and the refinement of standard treatments during the past two decades, have improved the prognosis for many lupus patients. Ten-year survival rates for SLE of over 95 percent are now commonly reported.

Even in this brief overview of lupus, the contributions of physician-scientist Henry G. Kunkel deserve special mention. Until his death in 1983, Kunkel, the Abby Rockefeller Mauze Professor of The Rockefeller University, New York, and senior physician at The Rockefeller University Hospital, stood at the forefront of the scientific vanguard battling lupus. He described many of the important autoantibodies present in SLE and, more generally, established the world's center for studying the immunology of lupus. Much of today's current research stems directly from the achievements of Henry Kunkel.

"No other disease captures the spirit of modern medicine more," writes Kunkel's former student Robert G. Lahita, The Rockefeller University, "than SLE." He continues,

> Essentially...[it can be said], "if you know SLE, then you know medicine." There is something in the study of SLE that appeals to all serious-minded investigators. For the clinician, there is the central nervous system, dermatologic, cardiac, pulmonary, or renal manifestations. For the basic investigator in immunology or biochemistry, there are the variations in cellular regulation or the abnormalities of sex steroid metabolism. For the molecular biologist, there is a continuum of newly discovered antibodies to specific subcellular components that defy explanation. Such antibodies select specific nuclear components or forms of RNA-polypeptide fragments involved in differentiation as antigens for unknown reasons. The veterinarian can be intrigued with either the murine or canine models of the disease, which can mimic the human condition. And the pharmacologist can explore the intriguing association of certain drugs with a form of SLE, a disease manifestation that is limited in severity, resembles the idiopathic variety, and seems to be based on well-known metabolic changes of such drugs in organs like the liver.[4] (p. xvii)

A disease that is as multifaceted and intriguing as lupus, one now pursued by thousands of clinicians and basic researchers in hundreds of hospitals and laboratories around the globe, cannot possibly be treated adequately in this limited space. The aim here is merely to highlight the disease's chief features and, using ISI® 's unique data, to call attention to classic, highly cited papers (*Citation Classics*®) on lupus as well as to the currently active specialty areas (research fronts) in which lupus researchers have recently been focusing their efforts.

For an exhaustive, expert discussion of all aspects of the disease, the recommended works are Daniel J. Wallace, University of California, Los Angeles, and Edmund L. Dubois (1923-1985), Dubois' *Lupus Erythematosus*, third edition (1987);[2] Lahita's

Systemic Lupus Erythematosus (1987);[4] and a chapter on SLE by Alfred D. Steinberg, National Institute of Arthritis and Metabolic Diseases (NIAMD), National Institutes of Health (NIH), Bethesda, Maryland, in a new edition of a standard text of internal medicine.[3] Steinberg's excellent review, which incorporates the work and ideas of many researchers, is quoted extensively throughout this essay. More information on lupus and on current research into lupus can be obtained from the associations, societies, foundations, and research centers listed in Table 1.

I wish to call special attention to the Terri Gotthelf Lupus Research Institute, South Norwalk, Connecticut, which was founded by my good friend Ted Gotthelf after he lost a 21-year-old daughter, Terri, to lupus. This is the only organization that offers research fellowships exclusively for the investigation of lupus. Its Lupus Research Scholar Awards go to postdoctoral researchers who wish to study this disease under the guidance of a leading lupus researcher. The award includes a three-year stipend, and last year three were given out. The intent of this program is to attract some of the best and the brightest minds to lupus research. This program is the highest priority for the institute, whose advisers are concerned that not enough young people are entering this particular area of research. The nonprofit organization is also active in sponsoring conferences on lupus, in encouraging collaborative research efforts, and in better educating the public and physicians about lupus.

Table 2 is a select list of journals reporting research on lupus and the 1987 impact factor of each. Using the online version of the *Science Citation Index®—SCISEARCH®*—and keywords, our research department identified approximately 750 papers on lupus each year for 1987 and for 1988. To help scientists cope with this ever-burgeoning literature, ISI introduced in January 1989 an *ASCATOPICS®* profile on SLE that alerts researchers to new SLE and SLE-related papers every week. As I recently discussed, *ASCA®* and *ASCATOPICS* provide what may be some of ISI's most effective, but least well known, services.[5]

Table 1: Select list of associations, societies, and foundations that increase knowledge, offer support, and encourage research in lupus erythematosus and other autoimmune diseases.

American Lupus Society
23751 Madison Street
Torrance, CA 90505

American Rheumatism Association
17 Executive Park Drive, NE
Suite 480
Atlanta, GA 30329

Arthritis Foundation
1314 Spring Street, NW
Atlanta, GA 30309

Hahnemann University Lupus Study Center
221 North Broad Street
Philadelphia, PA 19107

Lupus Arthritis Research Unit
Rayne Institute
St. Thomas' Hospital
London SE1 7EH
United Kingdom

Lupus Foundation of America
1717 Massachusetts Avenue, NW
Suite 203
Washington, DC 20036

National Institute of Arthritis, Musculoskeletal and Skin Diseases
National Institutes of Health
Bethesda, MD 20892

Terri Gotthelf Lupus Research Institute
50 Washington Street
South Norwalk, CT 06854

University of Connecticut Multipurpose Arthritis Center
Division of Rheumatic Diseases
School of Medicine
Farmington, CT 06032

Vanderbilt University
Arthritis and Lupus Center
B-3219 MCN
Nashville, TN 37232

Following a brief review of the history of lupus research, we will discuss the epidemiology, pathogenesis, and possible etiology of lupus. In Part 2, we will continue this overview by looking at its clinical manifestations and diagnosis, examining the treatment of SLE, and mentioning a few lupus-related *Citation Classics* along the way. Finally, we will review the lupus research fronts for 1987.

Table 2: Select list of journals reporting on various aspects of lupus, autoimmune diseases, and connective-tissue disorders. A = title and first year of publication in parentheses. B = 1987 impact factor.

A	B
Annales de Medecine Interne (1848)	0.26
Annals of the Rheumatic Diseases (1939)	1.98
Arthritis and Rheumatism (1958)	3.82
British Journal of Rheumatology (1983)	1.90
Clinical and Experimental Immunology (1966)	2.45
Clinical and Experimental Rheumatology (1983)	0.73
Clinical Immunology and Immunopathology (1972)	1.81
Journal of Autoimmunity (1988)	—
Journal of Experimental Medicine (1896)	11.08
Journal of Immunology (1916)	6.48
Journal of Rheumatology (1974)	1.43
Scandinavian Journal of Rheumatology (1973)	0.50
Terapeuticheskii Arkhiv (1923)	0.28
Zeitschrift fur Rheumatologie (1938)	0.47

Brief History

Lupus was sporadically described in the early nineteenth century, but it was not until 1851 that the French physician P.L.A. Cazenave dubbed it "lupus erythemateaux," by which it is known today.[6] In 1872 Viennese dermatologist Moritz K. Kaposi, whose name is attached to a form of cancer common in AIDS patients (Kaposi's sarcoma), recognized that lupus was more than just a malady of the skin and could involve internal organs.[7] By the turn of the century American physician William Osler had established that the disseminated, systemic variety was a separate type of lupus.[8] Postmortem pathological studies in the 1920s and 1930s gradually led to a better picture of the internal dimensions of the disease, and in 1936 it was recognized that the disease could be present even when there were no dermatological manifestations.[9]

By 1940 a number of investigators had reported that SLE patients often registered false-positive results on syphilis tests. In the following two decades, close analysis of the sera of SLE patients revealed other, more distinctive abnormalities. In 1948, for example, an LE cell, consisting of a nucleus phagocytized or engulfed by a neutrophilic leukocyte, was discovered in the bone marrow of SLE patients (it was later found in peripheral blood, too).[10] While it indicated the action of an autoimmune disease, the LE cell did not, however, prove to be specifically diagnostic, since LE cells can also be found in the blood of persons who suffer from other connective-tissue inflammatory diseases such as rheumatoid arthritis. Moreover, only about half of SLE patients test positively for LE cells.

Several laboratories independently introduced a better test for SLE in 1957 by using Coons's indirect fluorescent technique to detect autoantibodies. This antinuclear antibody (ANA) test proves to be positive in 95-98 percent of SLE cases. Two years later four research teams detected large quantities of antibodies to native DNA in SLE patients. The DNA antibody test was introduced into clinical settings between 1966 and 1969. For example, in 1969 Theodore Pincus and colleagues, NIAMD, NIH, published a paper that reported the use of the Farr ammonium sulfate technique to measure antibodies to double-stranded DNA found in SLE patients.[11] This methodological paper went on to achieve *Citation Classic* status, and Pincus wrote a commentary about it that was published in *Current Contents®* (*CC®*) in 1983.[12]

While ANA and anti-DNA antibody testing are the best diagnostic screens for SLE, there is still no one specific, 100-percent-foolproof test for the presence of the disease.

Another breakthrough in lupus research occurred in the late 1950s—the discovery in 1959 of a murine, or mouse, model for SLE using the New Zealand Black mouse and the select hybrids produced by mating the New Zealand Black with the New Zealand White.[13] These mice develop a spontaneous, lupus-like autoimmune disease, which has been the object of careful study and experimentation by researchers for 30 years and from which has come a considerable increase in our understanding of this type of immunological dysfunction.

Also important in the history of lupus research are the numerous clinical studies, many including hundreds of SLE cases, that have been issued periodically in the last four decades. One of the earliest rigorous studies, analyzing 138 cases, was published in 1954

by A. McGehee Harvey and colleagues, Johns Hopkins School of Medicine, Baltimore, Maryland.[14] Their paper was identified as a *Citation Classic*, and Harvey wrote a commentary on it for *CC* in 1978, noting that "this review drew attention to the disease at a time when new advances in immunology provided novel approaches to the study of its pathogenesis. [It] provided an important reference for the expanded concept of the clinical pattern of the disease and a complete description of its manifestations."[15]

Other large-scale clinical series were reported by Dubois and D.L. Tuffanelli in 1964,[16] by R.E. Kellum and J.R. Haserick in 1964,[17] by D. Estes and Charles L. Christian in 1971,[18] and by Wallace *et al.* in 1981.[19]

Epidemiology

Such clinical studies have given researchers a good and generally consistent picture of the incidence of SLE by sex, by age, and, to a lesser extent, by race. Before these studies, lupus was thought to be a rare disease; that is no longer the case. As mentioned, approximately 50,000 new cases of lupus are diagnosed each year in the US. Its annual incidence has been calculated at 6-7 per 100,000 among the general population and up to 30-35 per 100,000 in high-risk groups.[3] The overall prevalence of SLE may be as high as 50 per 100,000, but 30 per 100,000 is the more frequently reported figure. Numbers for the incidence and prevalence of SLE have tended to move upward in the last 30 years, but this is probably due not so much to any real increase as it is to better, more consistent diagnosis. As previously mentioned, SLE has a distinct sexual preference, with as many as 90-95 percent of all adult cases being encountered in the female. It also favors relatively young women in their second through fourth decades: over 60 percent have their first symptoms between ages 13 and 40. It is noteworthy that in children with SLE the ratio of female to male is approximately three to one, and that after menopause the high ratio of female to male in adulthood gradually falls back to the childhood levels. The disease in males, while less common than in females, is, however, no less severe.[3]

There is some disagreement among investigators as to whether SLE affects different racial groups differently—whether there are high-risk populations. Steinberg writes that

> the disorder is approximately three times more common among American blacks than American Caucasians. Certain North American Indian tribes (Sioux, Crow, Arapahoe) have an even greater predisposition toward SLE. Orientals have been less well studied; however, the data suggest that they are affected to approximately the same extent as American blacks.... The chance of a black female developing SLE in her lifetime is approximately 1 in 250.[3]

In contrast, Wallace argues that

> even though some studies show an increased incidence of lupus in black Americans, a socioeconomic bias is often evident in these studies. Urban blacks are hospitalized more often and utilize fewer private physicians than whites and may therefore present with more severe disease. SLE is rare in black Africans. At this time, it is impossible to say whether black Americans are at increased risk of developing SLE.[2] (p. 25)

What does not seem in question, however, is the increased correlation of SLE among first-degree family members and especially between identical twins. In the case of the latter, if one has SLE, the other will also have it in 6 out of 10 cases.[20] This is a strong indicator of at least a partial genetic component for the disease (see Etiology below). Such twin studies, a subject I wrote about in 1984,[21] have proven exceedingly useful to scientists.

Pathogenesis

The hallmark of SLE is the immune system's production of autoantibodies that react with nuclear, cytoplasmic, and cell membrane antigens. It is an oversimplification to say that in SLE the body becomes "allergic to itself," since some autoantibodies are produced in healthy individuals. Rather, it seems that SLE "occurs only when anti-self reactions are either excessive or produc-

tive of especially injurious immune responses," explains Steinberg.[3]

Two *Citation Classics* by David Koffler, Hahnemann University, Philadelphia, and colleagues on the pathogenesis of SLE have been highlighted in *CC*. The earlier article, published in 1967, reported the detection of anti-DNA and several other ANAs in the kidneys of SLE patients with glomerulonephritis, frequently found in the SLE patient.[22] Koffler, recalling this research in 1980, wrote, "The evidence obtained...was one of the early demonstrations that a specific antigen (DNA) and antibody were associated with renal glomerular injury. The techniques utilized were of potential importance for the identification of antigens and antibodies in a murine model of human SLE."[23]

Koffler's second *Citation Classic* was a 1973 review of antigen-antibody immune complexes and their association with inflammatory lesions such as those found in SLE.[24] In his commentary Koffler suggested that there was a paucity of significant data for reviews after 1973, which accounted, in part, for the many citations to his review.[25]

Another lupus-related *Citation Classic* on immune complexes is a 1974 paper by Urs E. Nydegger and colleagues, World Health Organization Research Unit, Geneva, Switzerland, describing a technique for measuring and monitoring circulating antigen-antibody complexes in the sera of SLE patients using radiolabeled complement C1q.[26,27]

But exactly what triggers a proliferation of autoantibodies in the person with SLE?

Etiology

Laboratory investigation and clinical studies have implicated a variety of factors that strongly indicate a multifactorial process of initiation. Table 3 lists those factors most likely contributing to the development of SLE.

The high incidence of SLE in women relative to men logically suggests that hormonal effects may be a basis for the disease. In fact, estrogen is known to worsen SLE symptoms, and, in the murine model, androgen ameliorates SLE.[28] Steinberg explains that "males are protected against SLE by their androgens except in a subgroup of males who inherit a Y chromosome accelerating factor from their fathers. Estrogens probably predispose to SLE to a lesser extent than androgens protect against the expression of the illness."[3] But hormones are unlikely to be the sole source of SLE.

There is convincing evidence for a genetic predisposition to the development of SLE. It was mentioned earlier that a higher-than-normal incidence of SLE has been encountered in the first-degree relatives of SLE patients. Moreover, 57 percent of studied identical twins both have SLE, whereas only about 5 percent of studied fraternal twins both have SLE.[20] A genetic factor could certainly cause or incline one's immune system to go awry. On the other hand, a higher-than-normal incidence of SLE has also been detected among nonblood relatives living in the same household, which indicates some type of environmental factor at work.[29]

An environmental factor unanimously recognized as capable of inducing or exacerbating SLE skin lesions is ultraviolet (UV) light. Also, in a minority of SLE patients, UV exposure induces systemic problems. Dov T. Golan, Department of Immunology, Technion-Israel Institute of Technology, Haifa, reported last year that "metabolic disorders following UV light exposure are not yet fully defined in SLE. However, [my] observations may support the notion of a possible role of UV light in the pathogenesis of SLE by being related to a yet undefined defect of DNA repair and other intracellular elements following UV light exposure."[30] Steinberg speculated on the most likely mechanisms in his review:

> UV light induces keratinocytes to secrete interleukin 1, which, in turn, stimulates B cells and induces T cells to produce growth factors (interleukin 2, B cell growth factors, B cell differentiation factors, interferon), which stimulate the immune system; [or] UV light impairs processing of antigen and immune complexes, thereby increasing the load of pathogenic complexes on target organs; [or] UV light induces cytosine and thymine dimer formation, which stimulates immune responses.[3]

Table 3: Etiological factors implicated in pathogenesis of systemic lupus erythematosus.

Sex hormones
Genetics
Environmental factors
  Ultraviolet light
  Drugs, chemicals, toxins
Infectious agents, viral or bacterial (?)

Certain foods and food additives have been the object of study in the etiology of SLE as well. For example, in 1982 M. René Malinow, Regional Primate Research Center, Beaverton, Oregon, and colleagues reported that alfalfa sprouts fed to monkeys (cynomolgus macaques) could induce hematologic and serologic abnormalities similar to those of SLE in humans.[31] The effective agent was found to be L-canavanine, an amino acid found in high concentration in alfalfa. Richard N. Podell, University of Medicine and Dentistry of New Jersey-Rutgers Medical School, New Brunswick, in reviewing the possible nutritional basis for SLE, also drew attention to "two cases...in which ingestion of L-canavanine-containing alfalfa 'health food' tablets was associated with a flare-up of previously quiescent SLE," but he concluded that there is very little firm evidence of the effect of diet, and specifically of alfalfa, in the induction of SLE in humans.[32]

However, certain other chemical substances—prescription drugs—are known to induce SLE-like symptoms in healthy individuals. The main drugs are the antihypertensive compound hydralazine hydrochloride (Apresoline) and the antiarrhythmic procainamide hydrochloride (Pronestyl). It has been estimated that approximately 10 percent of all SLE cases reported are the result of these and other prescription drugs. Drug-induced SLE differs significantly from the idiopathic variety: it is generally milder than spontaneous SLE and usually does not involve the kidneys and the central nervous system. Moreover, SLE symptoms promptly disappear after the drug is withdrawn. While half of all patients with drug-induced SLE test positive for ANAs, the test for antibodies to native DNA is typically negative; that test, along with consideration of a patient's drug intake, helps the physician distinguish drug-induced from spontaneous SLE, notes Dwight R. Robinson, Harvard Medical School and Massachusetts General Hospital, Boston.[33] Still, the similarities between the two are sufficiently striking to consider the hypothesis that "chemicals in our environment *might* play roles like those of drugs in the induction of SLE," says Christian, Cornell University Medical College, New York.[34]

The other major candidate for explaining the etiology of SLE is an infectious agent(s), bacterial or viral, which Lahita calls "the most intellectually satisfying...yet the most elusive of possibilities."[4] (p. 5) He adds, "It seems likely that some unconventional agent, or agents, is behind the illness." "If there is an infectious etiology for SLE," observes Christian, "the responsible agents are most likely either unusual microorganisms not isolatable by standard techniques or agents that although ubiquitous in the population cause atypical disease in only a minority of subjects."[34] He concludes his review, however, by emphasizing that "the notion that lupus is a disease entity with a uniform etiology and pathogenesis is less tenable than the concept that it is a heterogeneous dycrasia, resulting from the expression of host and environmental factors that regulate immune reactions."

The environmental factors and infectious agents that may serve to trigger SLE in those who have an inherited susceptibility to abnormal immune function remain, in Christian's view, "the area of greatest ignorance" in our present knowledge of the etiology of SLE.

Next week, in Part 2, we will examine the clinical manifestations of this disease, its diagnosis and treatment, and the 1987 research fronts that deal with lupus, representing the efforts of today's scientists to unmask the Great Imitator.

* * * * *

My thanks to C.J. Fiscus and David Pendlebury for their help in the preparation of this essay.

REFERENCES

1. **Blotzer J W.** Systemic lupus erythematosus. I. Historical aspects. *Md. State Med. J.* 32:439-41, 1983.
2. **Wallace D J & Dubois E L,** eds. Dubois' *lupus erythematosus*. Philadelphia: Lea & Febiger, 1987. 775 p.
3. **Steinberg A D.** Systemic lupus erythematosus. (Wyngaarden J B & Smith L H, eds.) *Cecil textbook of medicine*. Philadelphia: Saunders, 1988. p. 2011-8.
4. **Lahita R G,** ed. *Systemic lupus erythematosus*. New York: Wiley, 1987. 1000 p.
5. **Garfield E.** We invite you to try *ASCA*, the "ultimate research assistant." *Current Contents* (33):3-7, 15 August 1988.
6. **Cazenave P L A.** Lupus erythemateaux (érythème centrifuge). *Ann. Malad. Peau Syph.* 3:297-9, 1851.
7. **Kaposi M K.** Neue Beitrage zur Kenntiss des lupus erythematosus (New reports on knowledge of lupus erythematosus). *Arch. Dermatol. Syphil.* 4:36-78, 1872.
8. **Osler W.** On the visceral manifestations of the erythema group of skin diseases. *Amer. J. Med. Sci.* 127:1-23, 1904.
9. **Friedberg C K, Gross L & Wallach K.** Nonbacterial thrombotic endocarditis associated with prolonged fever, arthritis, inflammation of serous membranes and widespread vascular lesions. *Arch. Intern. Med.* 58:662-84, 1936.
10. **Hargraves M M, Richmond H & Morton R.** Presentation of two bone marrow elements: the "tart" cell and "L.E." cell. *Proc. Staff Meet. Mayo Clin.* 23:25-8, 1948.
11. **Pincus T, Schur P H, Rose J A, Decker J L & Talal N.** Measurement of serum DNA-binding activity in systemic lupus erythematosus. *N. Engl. J. Med.* 281:701-5, 1969.
12. **Pincus T.** Citation Classic. Commentary on *N. Engl. J. Med.* 281:701-5, 1969. (Barrett J T, ed.) *Contemporary classics in clinical medicine*. Philadelphia: ISI Press, 1986. p. 82. (Reprinted from: *Current Contents/Clinical Practice* 11(2):18, 10 January 1983.)
13. **Bielschowsky M, Helyer B J & Howie J B.** Spontaneous anemia in mice of the NZB/BL strain. *Proc. Univ. Otago Med. Sch.* 37:9-35, 1959.
14. **Harvey A M, Shulman L E, Tumulty P A, Conley C L & Schoenrich E H.** Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. *Medicine* 33:291-437, 1954.
15. **Harvey A M.** Citation Classic. Commentary on *Medicine* 33:291-437, 1954. (Barrett J T, ed.) *Contemporary classics in the life sciences. Vol. 1: cell biology*. Philadelphia: ISI Press, 1986. p. 136. (Reprinted from: *Current Contents* (21):11, 22 May 1978.)
16. **Dubois E L & Tuffanelli D L.** Clinical manifestations of systemic lupus erythematosus: computer analysis of 520 cases. *J. Amer. Med. Assn.* 190:104-11, 1964.
17. **Kellum R E & Haserick J R.** Systemic lupus erythematosus. A statistical evaluation of mortality based on a consecutive series of 299 patients. *Arch. Intern. Med.* 113:200-7, 1964.
18. **Estes D & Christian C L.** The natural history of systemic lupus erythematosus by prospective analysis. *Medicine* 50:85-95, 1971.
19. **Wallace D J, Podell T, Weiner J, Klinenberg J R, Forouzesh S & Dubois E L.** Systemic lupus erythematosus—survival patterns: experience with 609 patients. *J. Amer. Med. Assn.* 245:934-8, 1981.
20. **Winchester R J & Lahita R G.** Genetic susceptibility to systemic lupus erythematosus. (Lahita R G, ed.) *Systemic lupus erythematosus*. New York: Wiley, 1987. p. 81-118.
21. **Garfield E.** Twins. Part 2. The twin study method in behavorial and clinical research. *Essays of an information scientist: the awards of science and other essays*. Philadelphia: ISI Press, 1985. Vol. 7. p. 397-404. (Reprinted from: *Current Contents* (49):3-10, 3 December 1984.)
22. **Koffler D, Schur P H & Kunkel H G.** Immunological studies concerning the nephritis of systemic lupus erythematosus. *J. Exp. Med.* 126:607-24, 1967.
23. **Koffler D.** Citation Classic. Commentary on *J. Exp. Med.* 126:607-24, 1967. (Barrett J T, ed.) *Contemporary classics in clinical medicine*. Philadelphia: ISI Press, 1986. p. 81. (Reprinted from: *Current Contents/Clinical Practice* 8(36):16, 8 September 1980.)
24. **Cochrane C G & Koffler D.** Immune complex disease in experimental animals and man. *Advan. Immunol.* 16:185-264, 1973.
25. **Koffler D.** Citation Classic. Commentary on *Advan. Immunol.* 16:185-264, 1973. *Current Contents/Life Sciences* 30(47):20, 23 November 1987.
26. **Nydegger U E, Lambert P H, Gerber H & Miescher P A.** Circulating immune complexes in the serum in systemic lupus erythematosus and in carriers of hepatitis B antigen: quantitation by binding to radiolabeled C1q. *J. Clin. Invest.* 54:297-309, 1974.
27. **Nydegger U E.** Citation Classic. Commentary on *J. Clin. Invest.* 54:297-309, 1974. *Current Contents/Life Sciences* 30(42):16, 19 October 1987.
28. **Lahita R G.** The influence of sex hormones on the disease systemic lupus erythematosus. *Springer Sem. Immunopathol.* 9:305-14, 1986.
29. **Mannik M & Gilliland B C.** Systemic lupus erythematosus. (Isselbacher K J, Adams R D, Braunwald E, Petersdorf R G & Wilson J D, eds.) *Harrison's principles of internal medicine*. New York: McGraw-Hill, 1980. p. 355-60.
30. **Golan D T.** Exposure to UV light in the pathogenesis of systemic lupus erythematosus (SLE). *Isr. J. Med. Sci.* 24:360-2, 1988.
31. **Malinow M R, Bardana E J, Pirofsky B, Craig S & McLaughlin P.** Systemic lupus erythematosus-like syndrome in monkeys fed alfalfa sprouts: role of a nonprotein amino acid. *Science* 216:415-7, 1982.
32. **Podell R N.** Systemic lupus erythematosus: does diet play a causative role? *Postgrad. Med.* 75:251-4, 1984.
33. **Robinson D R.** Systemic lupus erythematosus. (Rubenstein E & Federman D D, eds.) *Scientific American medicine*. New York: Scientific American, 1988. Vol. 2. Sect. 15. p. IV:1-5.
34. **Christian C L.** Etiologic hypotheses for systemic lupus erythematosus. (Lahita R G, ed.) *Systemic lupus erythematosus*. New York: Wiley, 1987. p. 65-79.