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A Clinical Analysis

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Lloyd H. Smith, Jr., M.D., *Editor*

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FOREWORD

Over the past 150 years the concept of systemic lupus erythematosus (SLE) has gradually emerged as a disease entity or perhaps as a group of closely related disorders which aggregate uncomfortably under that awkward barbarism of medical terminology. As has been the case with a number of systemic diseases, the first descriptions of SLE are found in the literature of dermatology. It was Osler's patient observation and genius which first elucidated and emphasized the generalized disorder. Before the end of the last century he wrote: "By exudative erythema is understood a disease of unknown etiology with polymorphic skin lesions, hyperemia, edema, and hemorrhage-arthritis occasionally, and a variable number of visceral manifestations of which the most important are gastrointestinal crises, endocarditis, pericarditis, acute nephritis and hemorrhage from mucosal surfaces. Recurrence is a special feature of this disease and attacks may come on month after month or even throughout a long period of years. The attacks may not be characterized by skin manifestations. The visceral symptoms may be present and to the outward view the patient may have no indications whatever of erythema exudativum."[1] That astute summary, made without benefit of pathological studies, was quoted with admiration by A. McGehee Harvey and his collaborators in their classic monograph of 20 years ago in which their analysis of the Johns Hopkins Hospital experience with 138 patients with SLE brought the disease from comparative obscurity to more general attention.[2] Their own work was built upon earlier contributions, such as the pathological studies of Klemperer, Pollack and Baehr, which introduced the concept of "collagen vascular disease" in 1941 and the extraordinarily important discovery of the LE cell by Hargraves in 1948.

What has been added in these last two decades since the Harvey monograph? The modern tools of immunology and immunopathology have demonstrated an array of aberrations. In fact, SLE has been facetiously described as "immunologic epilepsy." Are these abnor-

malities of primary etiologic importance or do they represent merely epiphenomena reflecting some more basic pathogenetic mechanism? Whether primary or secondary, they are useful diagnostic and clinical markers of disease activity. Few would deny that immune complexes also contribute directly to tissue injury. There is evidence, mostly through animal disease models such as the spontaneous SLE-like disease which occurs in New Zealand black mice, that viral agents are capable of producing similar disorders and may yet be implicated in human SLE. These theories are reviewed in succinct fashion by Fries and Holman in this monograph.

Approximately 140 years ago Pierre-Charles-Alexandré Louis introduced the numerical method for the study of human disease. Prior to that, seminal innovation statements about disease were based on reference to dubious historical authority or on the fallible whim of personal impression. The major contribution of *Systemic Lupus Erythematosus* lies in its modern extension of the Louis method, with the analysis of clinical and laboratory data on 187 patients with SLE followed for over 1000 patient years by the authors at the Stanford University Hospital. The emphasis of the monograph is on the natural history of the subsets of lupus manifestations, both clinical and laboratory, as a guide to prognosis and to individualized therapeutic intervention. SLE seems to be increasing in both incidence and prevalence and can no longer be considered a rare disorder in internal medicine. The care of the patient with SLE taxes the ingenuity of the physician, but the results of such therapy can be impressive in improved survival and reduced morbidity. This monograph, based on a large personal experience, will be of specific assistance to the internist who undertakes the care of patients with this baffling and serious disease.

LLOYD H. SMITH, JR., M.D.

1. Osler W: On the Visceral Complications of Erythema Exudativum Multiforme. Am J Med Sci *110*:629, 1895.
2. Harvey AM, Shulman LE, Tumulty PA, et al: *Systemic Lupus Erythematosus: Review of the Literature and Clinical Analysis of 138 Cases*. Baltimore, The Williams & Wilkins Company, 1955.

PREFACE

We present in these pages an approach to the clinical understanding and management of systemic lupus erythematosus. This monograph has been internally documented by over 1000 computer searches of our patient experience since 1969. Data emphasize the course and progression of findings with time. The estimation of prognosis is a central theme, and data referable to prediction of future course are provided. A considerable body of clinical data relevant to management decisions is included.

The patient with systemic lupus erythematosus has a much more favorable prognosis now than a few years ago. There are many reasons for this improved outlook. Among those generally recognized are earlier and improved diagnosis, refinements in the use of corticosteroid therapy and introduction of immunosuppressive therapies, improved treatment of septicemia and deep fungal infections, total hip replacement for aseptic necrosis, hemodialysis, and renal transplantation. Further improvement in ability to care for the patient will occur, and we hope to indicate some directions this improvement may take.

Current understanding of SLE indicates the need for a conceptual approach to assessment and management which considers fully the multiple variations of this complex illness. This approach began with the recognition that patients with SLE and nephritis are different in prognosis and in therapeutic needs from patients with SLE and no renal involvement. Further characterization of patient groups by renal histology, central nervous system involvement, and specific immunologic abnormalities similarly has resulted in clinically useful distinctions. In the following discussions, the concept of multiple determinants of severity and prognosis in SLE is expanded. The diagnostic entity, SLE, is not the focus of this book. Rather, subsyndromes within the classic diagnostic entity are separately discussed, and the clinical meaning of individual clinical findings is explored.

This monograph is not an exhaustive review of the literature. It has no photomicrographs or radiographs, no detailed discussion of

histopathology, and only broad allusions to some major areas of investigation not directly related to patient care. In our view, excellent publications on these matters are already available and are listed in the bibliography under "General References." The chapter bibliographies suggest areas for further reading.

The voluminous SLE literature and excellent scientific reviews are not easily translatable into operational principles for patient management. Our data and those of others fail to define therapeutic strategies and tactics in absolute terms. Management decisions, however, require a judgment of probable benefit balanced against possible harmful consequences. In this assessment of the toxicity of the disease versus the toxicity of the therapeutic program, more reliable estimation of prognosis for the individual patient is essential. It is our intent to assist in the development of therapeutic guidelines by providing detailed clinical data about subpopulations of SLE and their synthesis into a program for management of the SLE patient.

The basis for these data is clinical observations of patients seen at our institution. Since 1969, patient data have been carefully and prospectively recorded in quantitative and semiquantitative form using a time-oriented, fixed-format medical record designed for patients with rheumatic disease. Patients are seen on multiple occasions, and detailed observations are made on each visit. These data, computer-stored, have enabled the following dissection of our recent experience with this fascinating disease.

James F. Fries
Halsted R. Holman

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We wish to thank Miss Bonnie Obrig and Ms. Helen Page for their assistance in the preparation of this manuscript, and Ms. Alison Harlow and Mr. Steven Weyl for their creation of the computer programs which made these data available. We are indebted to many colleagues who, as faculty, fellows, residents, and students in the Division of Immunology, made the careful clinical observations which constitute the data base for this volume. Finally our deep respect goes to the patients for their perception and understanding of the disease process.

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J.F.F.
H.R.H.

CONTENTS

CHAPTER 1

INTRODUCTION

EARLY HISTORY

Systemic lupus erythematosus has been widely recognized only in recent decades, although its dermatologic relative, discoid lupus erythematosus, has been known as a mild, chronic skin disease for many centuries. In the latter half of the 19th century, scattered references to systemic complaints accompanying the skin disease were to be found in the literature. The histopathology of endocardial lesions was described in 1924. By the mid-1930's, discussions delineating lupus erythematosus from tuberculosis pathologically began to appear. In 1939, Rose and Pillsbury argued that disseminated (systemic) lupus erythematosus was a systemic disease. In 1941, the classic pathologic description of "collagen vascular disease" was made by Klemperer, Pollack, and Baehr. With these descriptions, the modern history of systemic lupus erythematosus (SLE) began.

Over the past three decades, interest in this fascinating condition has been high. The many manifestations, complicated course, and multiorgan involvement of SLE made the disease a major challenge to available techniques of differential diagnosis. Its regular appearance at Clinical Pathologic Conferences gradually led to its recognition as the modern "great imitator." As immunologic abnormalities were discovered in SLE, it became a model disease for elucidation of mechanisms of immunologic tissue damage. The burgeoning interest led to improved understanding of the disease over relatively short periods of time. The intensive search for the pathogenetic mechanisms has been accompanied by dramatic advances in clinical recognition and management.

RECENT EVOLUTION OF SYSTEMIC LUPUS ERYTHEMATOSUS

In recent years, three important phenomena have occurred, each inadequately understood. First, systemic lupus erythematosus has shown an apparent increase in incidence. Second, there has been an apparent dramatic improvement in survival. Third, there has been an apparent shift in the manifestations of the disease.

No truly reliable figures for the incidence of systemic lupus erythematosus are available, but available data support the major increase in both frequency and discovery rate. In 1939, cases were being recognized at the University of Pennsylvania at a rate of approximately two per year. Over the 15 years from 1938 to 1953, new cases were observed at the College of Physicians and Surgeons in New York at a rate of approximately three patients per year. By 1954, new cases were being seen at Johns Hopkins at a rate of nearly 30 per year. In 1964, a prevalence of 81 per million was estimated in New York City, and in 1968, a prevalence rate of 418 per million was suggested for the city of Rochester, Minnesota. Some investigators have suggested that the incidence of systemic lupus erythematosus is approximately one-fourth that of rheumatoid arthritis. Using a probably reasonable prevalence estimate of 500 per million at the present, over 100,000 persons in the United States are affected. If the figure of one-fourth the prevalence of rheumatoid arthritis is used, at least twice as many persons are affected. In our clinic, which receives many referrals, systemic lupus erythematosus is the most common disease seen. We presently follow approximately 180 patients with SLE. Systemic lupus erythematosus is no longer a rare disease.

Concurrent with the apparent increase in incidence has been a marked improvement in survival. Figure 1–1 demonstrates these changes. In 1953, Jessar, Lamont-Havers, and Ragan counseled relative optimism because 22 per cent of their patients remained alive for periods in excess of 5 years. In 1954, the first large series of patients with systemic lupus erythematosus showed a 50 per cent survival for 4 years at Johns Hopkins Hospital (JHH). By 1964, survival at 10 years was in excess of 50 per cent at the Cleveland Clinic (CC) and by 1969 in excess of 60 per cent at Columbia Presbyterian Medical Center (CPMC). Recent studies, including our own (SUH), have estimated survival from onset of multisystem disease to be from 80 to 95 per cent at 10 years. Equally impressive is the decline in the absolute number of deaths in SLE patients within an institution. At our hospital, a steady decline from eight to ten deaths yearly to a present level of one or two deaths per year has been observed over the past 10 years, despite an enlarging population at risk.

An apparent shift in manifestations of the disease has also occurred, although it is infrequently remarked. The first described

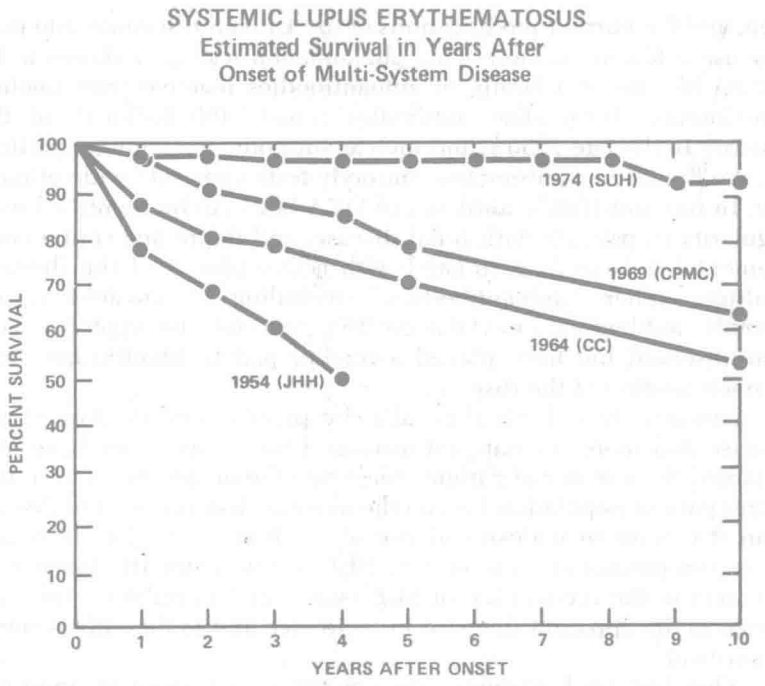

Figure 1–1. (From Fries, J. F., Weyl, S., and Holman, H. R.: Estimating prognosis in systemic lupus erythematosus. Am. J. Med. 57:562, 1974.)

pathologic manifestation other than that involving the skin, the so-called "Libman-Sacks endocarditis," is now very rarely seen. Hemolytic anemia has decreased in frequency. Malar "butterfly" rash remains common but is less frequent than in early series. Infections continue to be a major problem, but fewer common pyogenic organisms are now found, with a concomitant increase in the number of "opportunistic" infections, presumably related to treatment. The picture of renal disease has appeared more variable in recent years, with several subsyndromes of different severity. In general, the apparent shifts in characteristics of SLE parallel shifts in primary diagnostic methods from dermatologic to pathologic to serologic. Therapy, in addition, is more effective in changing some characteristics than others.

MODERN HISTORY OF SYSTEMIC LUPUS ERYTHEMATOSUS

Identification of systemic lupus erythematosus has been greatly facilitated by laboratory aids of reasonably recent derivation. In 1948, Hargraves identified the "LE cell" in a bone marrow speci-

men, and the current modifications of the LE cell test came into popular use a few years later. This phenomenon was later shown to be caused by one of a family of autoantibodies reactive with nuclear constituents. Antinuclear antibodies remain the hallmark of the disease. In the late 1950's, antinuclear antibody detection (in particular, the fluorescent antinuclear antibody test) came into wide clinical use. In the mid-1960's, antibody to DNA began to be identified with regularity in patients with renal disease, and depressed serum complement levels were correlated with active phases of the disease. Multiple other "autoantibodies," including rheumatoid factor, Coombs antibodies, and false-positive reactants for syphilis, were also observed but have played a smaller part in identification and characterization of the disease.

Serologic tests have allowed more precise identification of the disease and more accurate estimation of prognosis. They have also enlarged the number of patients receiving the diagnosis. In turn, this larger patient population has, on the average, had less severe disease than that prior to widespread use of serologic tests. The tests and increased physician awareness of SLE are undoubtedly major contributors to the recognition of SLE earlier and in milder forms, and hence to the apparent increase in incidence and to the improvement of survival.

This historical sequence demonstrates that apparent improvements in course cannot be attributed solely to better management. "Control groups" obtained from earlier years are not relevant comparisons for present patient groups. Controlled, randomized, prospective studies involving patients seen at the same period in time are required to establish the true effects of therapy. Improvement in prognosis has frequently been attributed to therapeutic changes over a period of time, although a major part of the improvement may have been due to identification of milder cases. Overenthusiasm for proposed new treatments and disregard for their complications have ensued.

Three major therapeutic changes have occurred in the past 25 years. In 1949, corticosteroids were first employed, and they have been used in the majority of identified cases through the present time. The greatest enthusiasm for their use in high doses followed favorable reports in the mid-1950's; there has been a tendency toward the use of more moderate doses in recent years. In the 1960's, immunosuppressant therapy with cytotoxic drugs became frequent. Nitrogen mustard was employed earliest; more recently cyclophosphamide, chlorambucil, and azathioprine have been the mainstays of this form of treatment. Strong clinical impressions have supported the use of these agents despite absence of absolutely convincing, controlled demonstration of their efficacy. A third component of modern management has been improvement in antibiotic and supportive ther-

apy. During this period a steady stream of new antibiotic agents has appeared, which now combine with new methods of prompt diagnosis and therapy of severe infections. More effective approaches to gram-negative septicemia, tuberculosis, *Pneumocystis carinii,* and deep fungal infections are now standard. Renal dialysis and renal transplantation are playing an increasing role.

Initial concepts of immunopathology were relatively simple; the autoantibodies were assumed to be responsible for tissue damage. Later concepts suggested that antigen-antibody complexes deposited in tissues were responsible for much of the pathology. The antibody of the immune complex appears not to be immunologically directed against the affected tissues; rather, the damaged organ is essentially an "innocent bystander." Why the offending complex localizes on a particular tissue has not been established.

It is now clear that no single mechanism can explain all the observed clinical phenomena. Initial, simple models have grown more complicated. A variety of mechanisms, including the possibility of protective autoantibodies or an underlying "slow" viral disease and of a dynamic relationship between autoantibody formation, circulating autoantigens, and their removal, may be relevant. It is now known that a low serum complement may indicate decreased synthesis of complement as well as increased deposition into tissues. Therapy may theoretically cause deterioration of status under certain circumstances. Genetic factors, particularly those linked to the HL-A histocompatibility antigen system, appear important. The immunologic phenomenon of tolerance may be involved.

A variety of natural or experimental models of diseases with features of SLE have been described. Best known is the immune complex disease model in rabbits infused with bovine serum albumin, resulting in an immune complex glomerulonephritis closely resembling SLE. The naturally occurring glomerulonephritis in the NZB/NZW hybrid mouse is associated with antibody to DNA and deposition of complexes of DNA and its antibody in glomeruli. Several viral diseases, such as Aleutian mink disease, are marked by a chronic course, hyperglobulinemia, and hyperplasia of the reticuloendothelial system. In humans, a possible model is acute rheumatic fever, in which an initiating bacterial infection causes a serologic response, resulting in immunologic damage to cross-reacting tissues, even though the original infection is eradicated.

It seems likely that each of these models offers clues to understanding certain aspects of SLE. Major concepts such as "innocent bystander" tissue damage from deposited complexes, abnormalities in the genetic control of the immune response, the possibility of latent or chronic viral infections, and suspicion that the "initiating" and "perpetuating" factors in SLE might be different have had their genesis in such models.