The History of Lupus Erythematosus

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The history of lupus erythematosus (LE) has been reviewed in two of the major textbooks on this disease1,2 and was the subject of an article in a journal in 1983.3 This article concentrates on developments in the present century which have greatly expanded our knowledge about the pathophysiology, clinical-laboratory features, and treatment of this disorder.

The history of lupus can be divided into three periods: the classical period which saw the description of the cutaneous disorder, the neoclassical period which saw the description of the systemic or disseminated manifestations of lupus, and the modern period which was heralded by the discovery of the LE cell in 1948 and is characterized by the scientific advances noted above.

The history of lupus during the classical period was reviewed by Smith and Cyr in 1988.4 Of note are the derivation of the term lupus and the clinical descriptions of the cutaneous lesions of lupus vulgaris, lupus profundus, discoid lupus, and the photosensitive nature of the malar or butterfly rash.

The term lupus (Latin for wolf) is attributed to the thirteenth century physician Rogerius who used it to describe erosive facial lesions that were reminiscent of a wolf's bite.1,3 Classical descriptions of the various dermatologic features of lupus were made by Thomas Bateman, a student of the British dermatologist Robert William, in the early nineteenth century; Cazenave, a student of the French dermatologist Laurent Biett, in the mid-nineteenth century; and Moriz Kaposi (born Moriz Kohn), student and son-in-law of the Austrian dermatologist Ferdinand von Hebra, in the late nineteenth century. The lesions now referred to as discoid lupus were described in 1833 by Cazenave under the term "erythema centrifugum," while the butterfly distribution of the facial rash was noted by von Hebra in 1846. The first published illustrations of lupus erythematosus were included in von Hebra's text, Atlas of Skin Diseases, published in 1856.

The Neoclassical era of the history of lupus began in 1872 when Kaposi first described the systemic nature of the disorder:

"... experience has shown that lupus erythematosus ... may be attended by altogether more severe pathological changes ... and even dangerous constitutional symptoms may be intimately associated with the process in question, and that death may result from conditions which must be considered to arise from the local malady."5

Kaposi proposed that there were two types of lupus erythematosus; the discoid form and a disseminated form. Furthermore, he enumerated various symptoms and signs which characterized the disseminated form including (1) subcutaneous nodules, (2) arthritis with synovial hypertrophy of both small and large joints, (3) lymphadenopathy, (4) fever, (5) weight loss, (6) anemia, and (7) central nervous system involvement.5

The existence of a disseminated or systemic form of lupus was firmly established by the work of Osler in Baltimore6 and Jadassohn in Vienna7 in 1904. Over the next thirty years, pathologic studies documented the existence of nonbacterial verrucous endocarditis (Libman-Sacks disease)8 and wire-loop lesions in patients with glomerulonephritis;9 such observations at the autopsy table lead to the construct of collagen disease proposed by Kemperer and colleagues in 1941.10 This terminology, collagen vascular disease, persists in usage now fifty years after its introduction.

The sentinel event in the mid 1900s which heralded the modern era was the discovery of the LE cell by Hargraves and colleagues in 1948.11 The investigators observed these cells in the bone marrow of patients with acute disseminated lupus erythematosus and postulated that the cell "... is the result of ... phagocytosis of free nuclear material with a resulting round vacuole containing this partially digested and lysed nuclear material ..." This discovery ushered in the present era of the application of immunology to the study of lupus erythematosus.

Two other immunologic markers were recognized in the 1950s as being associated with lupus: the biologic false-positive test for syphilis12 and the immunofluorescent test for antinuclear antibodies.13 Moore, working in Baltimore, demonstrated that systemic lupus developed in 7 percent of 148 subjects with chronic false-positive tests for syphilis and that a further 30 percent had symptoms consistent with collagen disease.12 Friou applied the technique of indirect immunofluorescence to demonstrate the presence of antinuclear antibodies in the blood of patients with systemic lupus.13 Subsequently, the

recognition of antibodies to deoxyribonucleic acid (DNA) 14 and the description of antibodies to extractable nuclear antigens (nuclear ribonucleoprotein (nRNP), Sm, Ro, La), and anticardiolipin antibodies; these autoantibodies are useful in describing clinical subsets and understanding the etiopathogenesis of lupus.

Two other major advances in the modern era have been the development of animal models of lupus and the recognition of the role of genetic predisposition to the development of lupus. The first animal model of systemic lupus was the F1 hybrid New Zealand Black/New Zealand White mouse.16 This murine model has provided many insights into the immunopathogenesis of autoantibody formation, mechanisms of immunologic tolerance, the development of glomerulonephritis, the role of sex hormones in modulating the cause of disease, and evaluation of treatments including recently developed biologic agents such as anti-CD4 antibodies among others. Other animal models that have been used to study systemic lupus include the BXSB and MRL/lpr mice, and the naturally occurring syndrome of lupus in dogs.17

The familial occurrence of systemic lupus was first noted by Leonhardt in 1954 and later studies by Arnett and Shulman at Johns Hopkins.18 Subsequently, familial aggregation of lupus, the concordance of lupus in monozygotic twin pairs, and the association of genetic markers with lupus have been described over the past twenty years.19 Presently, molecular biology techniques are being applied to the study of human lympho-cyte antigen (HLA) Class II genes to determine specific amino acid sequences in these cell surface molecules that are involved in antigen presentation to T-helper cells in patients with lupus. These studies have already resulted in the identification of genetic-serologic subsets of systemic lupus that complement the clinico-serologic subsets noted earlier. It is hoped by investigators working in this field that these studies will lead to the identification of etiologic factors(e.g.,viral antigens/proteins) in systemic lupus.

Finally, no discussion of the history of lupus is complete without a review of the development of therapy. Payne, in 1894, first reported the usefulness of quinine in the treatment of lupus.20 Four years later, the use of salicylates in conjunction with quinine was also noted to be of benefit.21 It was not until the middle of this century that the treatment of systemic lupus was revolutionized by the discovery of the efficacy of adrenocorticotrophic hormone and cortisone by Hench.22 Presently, corticosteroids are the primary therapy for almost all patients with systemic lupus. Antimalarials are used principally for patients with skin and joint involvement on the one hand and cytotoxic/immunosuppressive drugs are used for patients with glomerulonephritis, systemic vasculitis, and other severe life-threatening manifestations on the other.23 Currently, newer biologic agents are being investigated in treating patients with lupus.

Thus, the history of lupus, although dating back at least to the Middle Ages, has experienced an explosion in this century, especially during the modern era over the past forty years. It is hoped that this growth of new knowledge will allow a better understanding of immunopathogenesis of the disease and the development of more effective treatments.

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