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The place of William Osler in the description of systemic lupus erythematosus

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Introduction

In the pages of *The American Journal of Medical Sciences* more than 100 years ago (1,2) and reprinted in the present issue, famed internist and medical educator William Osler described 29 patients with skin disease without evident systemic or visceral involvement. Much has been written about the life of Osler (3) as well as the history of diseases called lupus or lupus erythematosus (4–11). These terms were originally applied to disease of the skin. Beginning in the middle of the nineteenth century with Kaposi, there was recognition that some patients with lupus erythematosus had involvement of organs other than the skin. Some have given a great deal of credit to Osler in the march towards an understanding of the disseminated nature of lupus erythematosus (6), while others have minimized his contribution (11). With the simultaneous reprinting of Osler's classic article from 1904 (2), we attempt to put the contribution of William Osler into a perspective of the 21st century.

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic disease that can affect almost any organ system. As evidenced the classification criteria (12), phenotypic expression of SLE varies from mild disease with skin involvement and laboratory changes to life-threatening involvement of kidneys, brain, heart, and/or lungs (Table 1). SLE is perhaps the prototypic autoimmune disease by virtue of the universal finding that patients produce antibodies to self-constituents. In fact, despite the wide variety of clinical expression, SLE patients are united by the universality of autoantibodies binding nuclear antigens, i.e., antinuclear antibodies. Similar to other autoimmune diseases (13), these antibodies appear long before clinical illness begins (14). SLE is a familial disease with complex genetics in which many genes individually impart a small risk (reviewed in 15). SLE is a disease of young adult women in that women are affected about 10 times more commonly than men (16). Treatment of SLE consists of glucocorticoid, anti-malarial drugs (17), cytotoxic therapy and more recently biologic agents that act upon key molecules within the immune system (18). In the 1950s the 5-year survival rate was only 5%, but now 5-year survival exceeds 95% (19).

However, before the term lupus was applied to SLE, it was used for diseases involving the skin and the skin alone.

The History of Lupus Skin Disease

The word lupus was first used to describe skin lesions after the fall of the Roman Empire in medieval times. Why the image of the wolf was evoked to describe certain skin lesions is not definitively known, but the lesions having the appearance of having been caused by the gnawing of a wolf as well as the destruction of adjacent skin have been suggested (9). One of the first written references is from 916 A.D. in the description of the healing of Eraclius, Bishop of Liege, at the shrine of St. Martin in Tours (see 8). Later Virchow (1821–1902) would conclude that the meaning of lupus to medieval writers was not clear.

At the beginning of the 19th century, Robert Wilan (1757–1812) of London and his student William Bateman (1778–1821) published his *Manual of Skin Diseases*, which provided an orderly classification of skin diseases based on appearance. The term lupus was reserved for diseases with destructive or ulcerative characteristics that appeared on the face (20 and see 8). This system thus included what would later be called lupus vulgaris and lupus erythematosus. Distinguishing these entities awaited Pierre Cazenave (1795–1877) and Henri Schedel (1804–1856), in Paris at the Saint Louis Hospital for skin diseases (7), who reported their own work as well as that of Laurent Bielt (1781–1840), their mentor and a student of Bateman (8). In several articles and especially in the textbook *Abrégé Pratique Des Maladies De La Peau*, Cazenave and Schedel divided lupus into three types based on the type of visible destruction (7,8). In 1833, Cazenave reported Bielt's work in what is now regarded as the first description of what would become known as lupus erythematosus (7,21).

Ferdinand von Hebra (1816–1880) was in charge of a skin disease clinic at the General Hospital of Vienna beginning in 1841. By 1846 he had described 2 lesions in lupus, 1 consisting of round discs and another of confluent smaller lesions (22, also see 8 and 23). He also invoked the phrase 'butterfly rash' to describe lupus (24). Meanwhile, Cazenave and Schedel continued to publish editions of their textbook, each subsequent version with an expanded description of lupus. In the fourth edition of 1847, the term lupus erythemateux was first used (7,21); thus, dividing lupus into lupus erythemateux, tuberculous lupus, ulcerating lupus and lupus with hypertrophy (7,8,21). From this point on tubercular skin disease of the face (lupus vulgaris) and lupus erythematosus were clearly distinguished from one another (8,25). In 1856, Hebra published the first illustrations and used the Latinized version, namely, lupus erythematosus, in *Atlas of Skin Diseases* (8,23,22). Jonathon Hutchinson (1828–1913), perhaps more noted for his contributions to syphilology, first used the simile of a 'bat wing' to describe lupus erythematosus and also first noted photosensitivity (26 and quoted in 8).

Lupus Becomes a Systemic Disease

Moriz Kaposi (1837–1902) was the first physician to recognize more than skin disease among patients with lupus erythematosus. In an 1872 article (27), which was translated into English in 1880 (28), he stated that "grave and even dangerous constitutional symptoms may be intimately associated with the process in question (lupus erythematosus), and that death may result" (28). In this same passage he also described these constitutional symptoms as swelling of lymph nodes, painful swelling of the joints and pain in the long bones (28 and quoted in 8). Fever, weight loss and anemia were also noted. Fox described mucous membrane involvement in 1880 (29), while Payne noted a "vascular hyperemia" that responded to large doses of quinine (30). In 1902 Sequira and Balean published a treatise on 71 patients with lupus erythematosus, 60 with discoid disease (31). These workers found albumin in the urine of some of these patients and described in detail one such patient - an 18 year girl with a malar rash, peripheral edema and hematuria. She rapidly developed diffuse skin disease, dyspnea, pleural effusion (pneumococcal) as well as urine sediment with albumin, white blood cells and casts along with

red cells (31). She died and underwent an autopsy that showed “glomerulotubular nephritis” (31).

Sir William Osler’s contributions to systemic manifestations come largely in a series of 3 papers. Two were published in *The American Journal of Medical Sciences* (1,2) and 1 in the *British Journal of Dermatology* (33). A total of 29 patients were described. As can be appreciated by reviewing these case reports, several likely had Henoch-Scholein purpura (HSP). Today several of these patients might be diagnosed with erythema multiforme, angioedema or disseminated gonorrhea. The most likely diagnoses we make for each of the 29 are given in Table 2.

Two of the patients; however, appear to have what would today be classified as SLE (2). Case XIX was a 15-year old girl with a photosensitive malar rash, pleuritic chest pain, fever and an enlarged spleen. She eventually developed rash on her hands, and had a waxing and waning course of the rash, arthritis and edema to the point of anasarca. She died after 7 months with albuminuria and falling urine output. Osler concluded that she died of uremia. Thus, even without laboratory data except the presence of protein in the urine, this young woman from more than 100 years ago meets in the 1982 Revised ACR Criteria for the Classification of SLE (12) in that she had malar rash, photosensitivity, pleurisy, renal disease (although proteinuria is not quantified in the manner of the present criteria). Patient XXVI was a 24-year old woman who was said to have lupus erythematosus by the referring physician, Doctor George Fox, Professor of Dermatology at Columbia University, but this rash was not present at the time of Osler’s examination. She had presented earlier with a malar rash, fever, lymphadenopathy and possible pleurisy versus infectious pneumonia. Eventually she developed femoral vein thrombosis, weight loss, and renal disease with red blood cell casts. Her white blood cell count at one point was 6000, but differential count was not reported. Thus, this patient does not overtly meet the present day SLE criteria in that she has only malar rash and renal disease. Nonetheless, to us and to others (8,9), this patient likely had the disease now called SLE.

The Contribution of William Osler to the concept of SLE

The impact of Osler’s papers has been discussed at length (11). Some of this recognition is and was mostly undeserved, as has been well documented (11). For instance, in 2007, Osler was given credit for coining the term systemic lupus erythematosus (6). This is clearly not case. Nonetheless, but just as clearly, the paper reprinted in this issue of *The Journal* and the 2 related manuscripts had an important impact on the field as recognized by Henry Christian as early as 1917 (33). By 1925 one of the most important aspects of Osler’s reports, including the one reprinted in this issue, was appreciated (34). Namely, Osler viewed skin disease, particularly purpuric skin disease, as only a symptom of underlying systemic illness in the ‘erythema group’ illnesses, a concept first advanced by him. In addition, Osler noted the remitting and relapsing nature of these illnesses and was the first to recognize that systemic manifestations might occur without skin disease. Again, this latter idea was a novel view of these diseases.

Clearly, Osler himself, and others (33), knew that he had grouped together disparate clinical syndromes. In fact, he purposely makes no diagnosis in any of the 29 patients presented, even though HS purpura and lupus erythematosus were well described and well known entities at the time. As stated in the first paragraph of the discussion (2), consideration of this ‘motley group of cases’ (to quote Osler) without individual diagnoses was done purposely in order to find commonalities among the various presentations. Today, we recognize that most of the patients in this series have antibody-mediated cutaneous, small vessel vasculitis, and often renal disease. Osler recognized those with more significant systemic or end organ involvement as having exudative skin disease (purpura and non-blanching erythema) and a separate set of patients with more transient urticarial disease. Along this line, Osler definitely noted that

patients XIX and XXVI were similar in that both patients had a facial rash (diagnosed as lupus erythematosus in patient XXVI by an eminent dermatologist), acute renal disease, and fever. In 1937 Keil first suggested that Osler had described lupus systemic erythematosus (35).

Thus, with over a century of perspective, we can say that 2 of Osler's patients had what is today called systemic lupus erythematosus. Only the patient reported by Sequira and Balean in 1902 (32) precedes Osler's description of such a patient. Osler did not make a diagnosis of lupus erythematosus in these patients but he did definitively recognize that diseases theretofore thought to only involve the skin were in fact systemic in nature. This is the most important legacy of this article, and this idea set the stage for systemic lupus to be described over the next several generations in the twentieth century.

SLE Comes of Age after Osler

In 1923, Libman and Sacks first reported 4 patients with non-infectious endocarditis. Two of the 4 had a malar rash characteristic of lupus erythematosus (36,37). Libman and Sacks noted that these patients bore resemblance to the erythema group patients of Osler, but the specific patient or patients are not delineated (36,37). Thirty years after Osler's 1904 paper and after the Libman and Sacks reports, additional patients with what appears to be SLE were described (38,39), but likely because no characteristic rash was present a diagnosis of 'polyserositis with polyarthritis and glomerulonephritis' was given (38). Eventually, in 1935, Baehr advanced the concept of disseminated lupus erythematosus in his report of 23 patients with characteristic skin features of whom 13 had the heart lesions described by Libman and Sacks (39). In addition, Baehr also noted renal disease and glomerulonephritis (wire loop lesions) in 13 of the 23 (40).

Progress has been dizzyingly rapid since then with Hargraves' discovery of the LE cell in 1948 (41) setting the stage for the study of serology among SLE patients. The original description of a familial aggregation of SLE (42) has lead to genomic studies that have identified a myriad of lupus susceptibility genes (43). The finding of a lupus-like illness in NZB/W mice in 1959 launched the study of murine models of disease (44). Finally, the introduction of corticosteroids as treatment of SLE by Hench and colleagues in 1952 (45) can be regarded as the start of immunosuppression as treatment (although anti-malarials were used prior to this), which has evolved into the present use of biologic therapy (18).

Conclusion

Over a century ago William Osler described patients with SLE in *The American Journal of Medical Sciences*, but he refrained from making a definitive diagnosis or definitively grouping the 2 SLE patients together. Instead, he advanced the notion that skin disease, particularly that which manifests as exudative rashes, can be a harbinger of significant systemic illness. Such an idea was a major advance in thinking. This series represents a collection of patients united by immune complex mediated small vessel disease and often glomerular disease. The cases differed in whether they were transient (as in some with HSP and angioedema) or relapsing and remitting (as in the SLE and some of the HSP cases). These observations were made decades before the first description of the gamma fraction of immunoglobulin in 1939 (46) or the attribution of this fraction to LE cell formation (47). By the middle of the twentieth century, SLE was established as a distinct clinical entity by physicians who relied on Osler's legacy. The value of this legacy survives to this day as evidenced by the paper continuing to receive several citations every year.

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Table 1**1997 Revised Classification Criteria for Systemic Lupus Erythematosus (12,49)**

Malar Rash
Photosensitivity
Discoid Rash
Oral Ulcers
Arthritis
Neurological
unexplained seizures or psychosis
Renal
persistent proteinuria >500mg in 24 hours or cellular casts
Serositis
pericarditis or pleurisy
Hematological
otherwise unexplained thrombocytopenia, hemolytic anemia, lymphopenia, or neutropenia
Immunological
false positive serologic test for syphilis, anti-dsDNA, anti-Sm, anti-phospholipid
(APL)*
Antinuclear antibody
4 of 11 criteria allows classification as SLE.

* APL was added as a part of the immunological criterium after 1982, while LE cell was removed.

Table 2

1990 Criteria for the Classification of Henoch-Schonlein Purpura (50).

1	Palpable purpura Slightly raised “palpable” hemorrhagic skin lesions, not related to thrombocytopenia
2	Age at disease onset Patient 20 years or younger at onset of first symptoms
3	Bowel angina Diffuse abdominal pain, worse after meals, or the diagnosis of bowel ischemia, usually including bloody diarrhoea
4	Wall granulocytes on biopsy Histologic changes showing granulocytes in the walls of arterioles or venules

Table 3

Proposed diagnoses for the 29 patients presented by William Osler in the 'erythema group' papers (1,2)

Patient	Probable diagnosis	Comments
I *	Recurring fever, abdominal pain, erythema multiforme	Angioedema or variegate porphyria possible yet symptoms not fully consistent with either
II *	HSP with angioneurotic edema	Unusual splenic sequestration and anemia; arsenic beneficial
III	HSP	Aggressive form – death from uremia
IV	HSP	Older patient – yet resolution without therapy supports HSP rather than ANCA+ vasculitis
V	Gonorrhea with gonococcal arthritis	
VI	HSP	Death from pneumonia
VII	HSP	
VIII	HSP	Father with “rheumatism”, rapid progression to renal failure.
IX *	HSP	
X *	HSP, possible scurvy	Bleeding, swollen gums, responded to lemon juice and arsenic
XI	HSP	Prompts long discussion on the historical descriptions of HSP and peliosis (purpura) rheumatica
XIX	SLE	Malar rash, arthritis, nephritis, fever
XX	HSP	
XXI	HSP	otitis
XXII	HSP	
XXIII	HSP	
XXIV	HSP	
XXV	Angioneurotic edema	
XXVI	SLE	Malar rash, photosensitivity, vasculitis (purpura), nephritis, death – treated with arsenic
XXVII	Possible angioneurotic edema	Blistering as well
XXVIII	HSP	
XXIX	HSP	otitis

* No definite diagnosis clear to the authors