



The History of Lupus Erythematosus and Discoid Lupus: From Hippocrates to the Present

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Abstract

Lupus erythematosus is an autoimmune disease that affects primarily women and whose cause is unknown. The diagnosis arises from a patient that may show singular signs or signs of a multisystem disease; there is a presence of autoantibodies, and other diseases with similar properties are ruled out. Two main forms of the disease exist; the discoid and the disseminated forms. Hippocrates was the first to document symptoms consistent with that of lupus erythematosus in the year 400 BC. Many physicians have studied and added to the current day knowledge of lupus erythematosus. The history of lupus erythematosus is divided into three categories: the classical period, the neoclassical period, and the modern period. Each period is marked with important discoveries that have allowed a better understanding of this disease.

Introduction

Lupus erythematosus (LE) is an autoimmune disease that affects primarily women and whose cause is unknown. The diagnosis arises from a patient that may show singular signs or signs of a multisystem disease; there is a presence of autoantibodies, and other diseases with similar properties are ruled out. Two main forms of the disease exist; the discoid and the disseminated forms. Antimalarials were used in the past primarily for lupus skin and joint involvement and are now recognized to prevent the occurrence of flares, the accumulation of damage, and the occurrence of early mortality. Cytotoxic/immunosuppressive drugs are utilized for glomerulonephritis, systemic vasculitis, and other severe life-threatening manifestations of lupus. Newer biologic agents are now used either off-label or after approval by regulatory agencies and potential drug products are being investigated as new disease pathways are being discovered. Lupus research and treatment has risen dramatically during the modern era over the past 60 years. The history of LE is divided into three categories: the classical period, the neoclassical period, and the modern period. The classical period saw the description of the cutaneous disorder, the neoclassical period witnessed the description of the systemic or disseminated manifestations of lupus, and the modern period was heralded by the discovery of the LE cell in 1948 and is characterized by recent scientific advances. Each period is marked with important discoveries that have allowed a better understanding of this disease.

The Classical Period

The term lupus comes from the Latin, meaning wolf. The origin of this name comes from two different ideas; one being the wolf-like bite the facial rash resembles and the other thought being the way that the rash seems to gnaw away at the flesh of the victim [1,2]. A biography of St. Martin gives us the first example of when the term lupus was used. St. Martin lived in the 4th century and treated The Bishop of Liege. The description of the disease is consistent with lupus.

“He was seriously afflicted and almost brought to the point of death by the disease called Lupus. The location of the disease was not to be

seen, nonetheless, a sort of thin red line remained as a mark of the scar”[3].

The history of lupus goes back even further than the 4th century. The first known documented case of lupus was recorded by Hippocrates in the year 400 BC. Many skin diseases in this time were classified under the category of herpes. It is believed that Hippocrates may have grouped lupus in with herpes esthiomenos [4]. The fall of the Greek empire was followed by the rise of the Roman Empire, although most of the Greek medicine and Greek medical terminology continued to be used because most of the physicians were Greek [3]. The term *noli me tangere*, which is latin for “touch me not” was given to the facial lesions and ulcers associated with lupus and this is credited to the Salernitan surgeon Rogerius Grugardi in the 12th century. This term changed as the location of the disease changed. For example if the ulcers were located on the torso, the term *cingulum*, girdle, was used. If the ulcers were located on the lower body, the term *lupula*, or little wolf, was used. It was at this time that physicians kept ulcers on the face in a separate category than ulcers elsewhere. Although the term “lupus” was first noted to describe an ulcerative skin disease, it was not until the mid-nineteenth century that two specific skin diseases were classified as Lupus erythematosus and Lupus vulgaris. The term “lupus” may derive from the rapacity and virulence of the disease; a 1590 work described it as “a malignant ulcer quickly consuming the neather parts; very hungry like unto a wolfe”[5].

Roland of Parma, a student of Grugardi, clarified Grugardi further.

“In the early stages it [cancer] is called *scliosis* [hardening] or *negrosis* [blackening], after it begins to rot it is called *cancrena* [gangrene]; finally it is called *carcinoma* [cancer]”[6].

Lupus continues to be used to describe any ulcerated lesion of skin, primarily of the face, but also of the legs. Most physicians considered lupus to be a distinct disease, rather than the evolving disease that it is known to be today. Paracelus (1493-1541) had this to say about this problem:

“The art of medicine resides in recognizing the site wherein lies the cure [7].

Neoclassical Period

For many years, it was debated as to whether or not lupus was a manifestation of tuberculosis, another disease that was just being defined at the time. The confusion arose because in this time, tuberculosis was thought of much different in the pre bacteriological days. Erasmus Wilson (1809-1884) described lupus as:

“Destruction, then, we may take as the leading character of lupus. A further inquiry into the nature of lupus served, however, to show that this destructive disease was preceded by a circumscribed thickening and prominence of the skin, commonly termed a tubercle, hence, lupus is considered as a tuberculosis affection of the skin. Now, the destructive action implied by the term lupus, was, in the first instance, intended to be restricted to that form of tubercle which commonly issues in destructive ulceration; but as cutaneous diseases came to be more carefully observed, it was perceived that there existed a kind of tubercle which did not of a necessity ulcerate, which was chronic and lasting in its nature, and which left behind it a deep pit or a strongly marked cicatrix. This form of cutaneous disease has been distinguished by Cazenave under the name of lupus erythematosus” [8] (Figure 1).



Figure 1: LE by William Bagg from Wilson's Atlas 1855.

Wilson later confused lupus with lesions that were caused by syphilis. Up until this point, the classification of lupus was dependent almost entirely on the presence of lesions. Physician Robert Willan (1757-1812) was the one that brought order to the naming of skin disorders. He wanted to use clinical observations in the classifying of skin disorders. Using previous work of Mercurialis, Turner, and Von Planke, he accomplished this in 1790 and published it in his Manual on Skin Diseases. Lupus, herpes, and noli me tangere were all differentiated in this book [9]. Along with his student, Thomas Bateman (1778-1821), they defined lupus as:

“to comprise, together with the "noli me tangere" affecting the nose and lips, other slow tubercular affections, especially about the face, commonly ending in ragged ulcerations of the cheeks, forehead, eyelids, and lips, and sometimes occurring in other parts of the body, where they gradually destroy the skin and muscular parts to a considerable depth”[9].

After Willan's death, his student Thomas Bateman continued his work. Thomas Bateman grouped together several cutaneous disorders under the term of lupus, including lupus vulgaris and lupus erythematosus (LE). What was most remarkable about their system was that it was successful based on pure and direct observation [10]. Just, as Thomas Bateman succeeded after Willan's death, so too did the

Paris School of Dermatology. The St. Louis Hospital was constructed in 1612 and was originally intended for plague victims. In the year 1801 this hospital became specialized in treating chronic skin ailments. Two prominent figures came from this school-Laurent Theodore Biett (1781-1840) and Cazenave (1802-1877). Biett introduced into France the anatomical and analytic approach to skin disorders first developed by the two English physicians Willan and Bateman. Biett described LE as Erythema centrifugum.



Figure 2: Lupus Vulgaris, from Cazenave and Schedel 1838.

Biett, a student of Bateman, and Alibert, co-founded the Dermatological Saint Louis Hospital [3]. It was the pupils of Biett that published his findings, as Biett mostly observed different cases. Both Cazenave and another pupil of Biett, Henri Schedel, published the textbook *Abrege Pratique Des Maladies De La Peau* in 1828 (Figure 2). The text was highly influential in the mid-19th century, and as noted earlier by Wilson, it was here that Casanave coined the term lupus erythematosus. Casanaves was the editor of *Annales des Maladies de la Peau et de la Syphilis*, a journal dedicated to scientific dermatology. Willan's lupus findings were broken down into three different types: (1) Lupus qui detruit en surface, or lupus which destroys on the surface, (2) lupus qui detruit en profondeur (lupus which destroys at the depth), and (3) lupus avec hypertrophie (lupus with hypertrophy)[11]. This was one of the most important works of the 19th century and also led to the famous Willan-Bateman diagnosis system of skin diseases that was used in Europe. In it was the description of LE:

“It is a very rare occurrence, and appears most frequently in young people, especially in females, whose health is otherwise excellent. It attacks the face chiefly. It generally appears in the form of round red patches, slightly elevated, and about the size of a 30 sous piece: these patches generally begin by a small red spot, slightly papular, which gradually increases in circumference, and sometimes spreads over the greater part of the face. The edges of the patches are prominent, and the centre, which retains its natural colour, is depressed. The causes of this variety are unknown it is an essentially chronic affection” [12].

A Viennese physician by the name of Ferdinand von Hebra (1816-1880) was the first credited with describing the two different rash patterns associated with LE, one being the small disc like rash and the other being the smaller confluent rashes. Von Hebra was also the first to describe the facial rash as a butterfly-like rash. Hebra classified this disease under the name of lupus erythemateux [13].

“At the beginning of this disease one can see [changes] mostly in the face, on the cheeks, and on the nose in a distribution similar to a butterfly and finally presents with sharply demarcated, vividly red and scaling lesions non-itching, non-oozing, and non-eroded”[13].

Hebra was also the first to publish illustrations of lupus erythematosus. Anton Elfinger is credited with these paintings. Some believe that some of the pictures are of lupus vulgaris instead of lupus erythematosus [14]. Jonathon Hutchinson (1828-1913) noted the photosensitivity of the rashes of lupus erythematosus[15,16]. The systemic nature of the disease was first described by Kaposi in 1872 and this ushered in the neoclassical period of lupus. He reported:

“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”[15,16].

Hutchinson also described the difference between the major members of the lupus family. He stated that:

“The features which distinguish these two diseases are useful rather for the purposes of clinical diagnosis and arrangement than as implying essential differences. The two are closely allied and ... are in a general way induced by a similar kind of causative influences ... In the lupus family vulgaris and erythematosus stand as brother and sister, having many essential resemblances and many marked but superficial differences”[15,16].

Hutchinson also went on to describe Hebra’s “butterfly” as “bat wing form.” Six years after the discovery of the tubercule bacterium, Hutchinson found that they were not present in patients with lupus erythematosus. He was still a strong advocate of a tuberculosis etiology of lupus erythematosus and figured it was only a matter of time until it was found true. A compromise was made in that “LE was a chronic inflammatory process produced by toxic substances of tuberculous origin”[17,18]. It was later confirmed from Goeckerman and later Keil that tuberculosis being found with patients having LE was merely coincidental. Goeckerman studied data from the Mayo Clinic and found that tuberculosis was found equally in patients with lupus erythematosus and with other dermatoses[19]. Keil, in 1933, observed that active tuberculosis was found in only 20% of his autopsy findings of systemic lupus erythematosus [20].

Moriz Kaposi (1837-1902 born Moriz Kohn), student and son-in-law of von Hebra, was the first to propose the two types of lupus discoid and disseminated lupus [21]. After Kaposi proposed this idea, many case descriptions of systemic lupus erythematosus emerged. He, like Wilson, observed that lupus erythematosus occurs more frequently in women, and is also more severe. Unlike Wilson, Kaposi knew that lupus erythematosus and tuberculosis could occur in the same patient, but that they were of separate entities [22]. To summarize his views he said:

“be restricted to that form of tubercle which commonly issues in destructive ulceration; but as cutaneous diseases came to be more carefully observed, it was perceived that there existed a kind of tubercle which did not of a necessity ulcerate, which was chronic and lasting in its nature, and which left behind it a deep pit or a strongly marked cicatrix. This form of cutaneous disease has been distinguished by Cazenave under the name of lupus erythematosus”[23].

Kaposi believed that discoid lupus erythematosus and systemic lupus erythematosus stemmed from the same disease, though this was argued both ways. JH Macleod said “lupus erythematosus of the acute disseminated type has from time to time been found to occur in association with more or less general toxæmia. The circumscribed cases have probably a different etiology from those of the acute

disseminated type”[24]. It was shown in the pre-1938 cases of SLE diagnosed at the Mayo Clinic that 47% of them were associated with discoid LE, but by the next decade, this number dropped to 17%, most likely because of more knowledge of the disease [25]. Keil believed that it was probable the two forms were from the same disease, but Baehr stated in 1951 that “disseminate lupus erythematosus bears no relationship whatever to the benign indolent skin lesion known to dermatologists as discoid lupus.” This debate was finally resolved by Burch and Rowell who hypothesized that the discoid LE and SLE come from two separate predispositions to the disease. They concluded that if a patient did present both forms of LE then they were predisposed to both forms of LE [26,27].

During the years of 1866-1871, Kaposi diagnosed 22 different patients with lupus erythematosus, while lupus vulgaris (tuberculosis luposa) was diagnosed in 279 patients. Lesions that expanded from single foci were termed discoid, and lesions that enlarge by the merging of multiple, pinhead size regions were described as discrete and aggregate although this was later changed to disseminate and aggregate. Kaposi used the term disseminate when lesions were not limited to the head, but his caused some confusion [21,22]. He went on to say:

“Lupus erythematosus may occur and progress with manifestations of a disseminated or universal acute or subacute febrile eruption, and may then frequently involve the entire body with intense local and general symptoms, indeed to endanger and destroy life”[21].

Kaposi continued to find other diseases that were prevalent in his patients. In 1872, he described 11 cases and 4 of them had pneumonia, 3 of them had arthralgias, and 3 of them had major adenopathy. Three more were brought to autopsy and 2 more had pneumonia and 1 had tuberculosis. None of these patients had any renal disease. Kaposi was unsure of whether the cutaneous symptoms and these other symptoms were related or merely coincidental [23]. Kaposi described a condition in 1869 where a nodular lesion was found in the deeper portion of the skin but was not really found in the epidermis of the patient [21]. Samuel Irgang called this lupus erythematosus profundus and together this syndrome was labeled Kaposi-Irgang syndrome [28]. This syndrome was at first misdiagnosed as sarcoid, but later changed. Quinine was first used as a treatment option for lupus in 1894, by the physician Payne [29]. Philip S Hench began to use ACTH and cortisone to treat patients with LE [30]. Even more treatment options were discovered by Sulzberger and Witten with their discovery of hydrocortisone. Hydrocortisone proved to be effective in patients with discoid LE [31]. In 1951, quinacrine, an antimalarial drug, was used to treat discoid LE. It was the first time that an antimalarial drug was used to treat LE. Later on, immunosuppressants were used to treat LE. The first immunosuppressant was used in 1952 and was nitrogenous mustard.

Sir William Osler (1849-1919) wrote three papers during the years 1895-1904 in which he described systemic lupus erythematosus. Although he studied many skin conditions, only a few were actually lupus erythematosus [32].

In 1895, Osler defined lupus as:

“of unknown etiology with polymorphic skin lesions-hyperaemia, oedema, 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 the mucous surfaces, Recurrence is a special feature of the 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 alone may be present, and to the outward view the patient may have no indication whatever of erythema exudativum" [32].

This definition was made entirely on clinical observations. In his 1895 paper entitled "On the Visceral Complications of Erythema Exudativum Multiforme" he documented 11 different cases. The second paper was written about 7 patients and the third paper he wrote about 11 patients [33]. The name of the second and third papers was "On the Visceral Manifestations of the Erythema Group of Skin Diseases." The actual skin diseases included Henoch-Schonlein papura, Erythema multiforme, angioedema, and Gonococcal septicemia. Out of the 29 patients, only 2 definitely had lupus erythematosus [34]. The first case was case XIX, a 15 year old female who presented with a photosensitive malar rash, pleuritic chest pain, fever, and an enlarged spleen. Later on a rash had developed on her hands. Patient XIX also developed arthritis and edema; the edema was reported to be so severe that it got to the point of anasarca. Patient XIX died seven months later as a result of albuminuria and falling urinary secretion. Osler would conclude that she died of uremia. The 1982 Revised ACR criteria for the classification of systemic lupus erythematosus shows that patient XIX had lupus erythematosus because she exhibited a photosensitive malar rash, pleurisy, and renal disease [34]. The second case was case XXVI, a 24 year old female, who had developed a rash on her face, mainly on the cheek and nose. She met with Dr. George Fox, a professor of dermatology at Columbia University gave his diagnosis because this patient presented a malar rash, fever, lymphadenopathy, and pleurisy, although that could have been attributed to pneumonia [34].

"Case XXVI. Onset in September, 1901, with erythema of the nose and cheeks; extension to the elbows and arms, usually in the form of wheals, but some spots purpuric; chill, followed by consolidation of the lower lobe of left lung; protracted fever; enlargement of the lymphatic glands; delayed resolution of the pneumonia; urine clear in the attack; gradual recovery; in May, 1902, onset of acute nephritis; uremia; death in a convulsion - L.E" [34].

Patient XXVI developed femoral vein thrombosis, weight loss, and renal disease. Osler described her rashes as red, raised patches. She went through bouts of fever and by the time Osler met with her, she was very thin and very pale [34].

"In case XXVI there was a protracted pneumonia following directly upon a severe outbreak of exudative erythema. It is likely that the recurring skin lesions, the pleuropneumonia, the phlebitis, the general glandular enlargement, and the fatal nephritis were due to one and the same poison" [34]. Osler suggested these symptoms were from the same disease. Although not all the major criteria for systemic lupus erythematosus for patient XXVI were met, this patient most likely suffered from the disease [34]. Case XXVI died shortly after nephritis set in.

"In May she went to Atlantic City, where she improved rapidly. Toward the end of the month an acute nephritis came on, without any special exposure; the urine was scanty, high colored, contained blood and tube case and much albumin. There was fever, 101°F-102°F no skin rash. I saw here with Dr. Marvel shortly after she had a uraemic convulsion. She died within a week of the onset of nephritis" [34].

A 125 page review of lupus erythematosus was written by Jadassohn in 1904. In it he described many of the symptoms of lupus erythematosus [35]. There were various modifications of the use of

"lupus erythematosus" rather than "erythema exudativum" that was used by Osler. Kraus and Bohac, in 1908, introduced a few terms to the study of lupus. "Acute LE" was used to describe lupus when the cutaneous and visceral forms of the disease were present. The discoid form of lupus was given the term "chronic LE" and "Acute disseminated LE" was used to describe lupus that started acutely (systemic symptoms) and then assumed a disseminated (cutaneous) form [36]. In case reports in 1936, and later again in 1942, it was shown that lesions were not required to diagnose systemic lupus erythematosus. "Disseminated lupus erythematosus" was introduced by Brunsting [37] and "systemic lupus erythematosus" was finally made popular by Harvey, et al. [38]. If it was shown that visceral symptoms were shown to be associated with cutaneous LE, the next step was to substantiate if they were related or just a coincidence that had to be determined. If no skin lesions were present, could the clinician safely assume a diagnosis of systemic lupus?

Emanuel Libman (1876-1946) and Benjamin Sacks (1896-1971) reported on four patients in 1923, all of whom had non-infectious endocarditis. Two of these patients presented the characteristic malar rash of lupus erythematosus. Libman and Sacks noted that these patients seemed similar to the erythema patients in Osler's papers. More patients were believed to have systemic lupus erythematosus, but since no rash was shown, these patients were diagnosed with polyserositis with polyarthritis and glomerulonephritis [39,40].

Libman, in 1911, had hospitalized a girl who had shown a 10-week history of polyarthralgia, precordial pain, dyspnea, and oliguria. He went on to observe "an erythematous eruption of butterfly pattern, which resembled acute lupus erythematosus disseminatus." He collected sterile blood samples and during a five week course, hematuria and a precordial rub developed. Autopsy of this patient revealed "endocarditis of a peculiar type, particularly because of the unusual manner of spread of the endocardial lesions along the posterior wall of the left ventricle and also glomerulonephritis" [39]. This was not reported until 1924 and was part of a study of nonbacterial valvular and mural endocarditis in which the patients were treated by Libman and autopsies were performed by Benjamin Sacks. The above case was the 4th in this study. Case 1 and case 2 were first reported in 1923. Two of the four cases presented the common butterfly facial rash, and three of the cases presented with nephritis. Libman and Sacks went on to say "the similarity of certain of the symptoms to those observed in the erythema group of Osler" but they did not diagnose these patients with SLE, rather they classified this as "Libman-Sacks Syndrome" [40]. The photosensitive nature of LE was first brought to attention. In 1921, a Viennese dermatologist documented a case of a woman who developed discoid LE after she had intense sun exposure. After a few months the lesions went away and she was given ultraviolet radiation to her back. By the next day lesions had appeared and this further solidified the dermatologist's finding [41]. This goes back even further to Rasch in which he noted that the lesions were typically on the areas of uncovered skin. In 1907 Rasch stated that LE was aggravated by sunlight, and sunlight itself caused this condition [42].

In 1936, Belote and Ratner came to the realization that Libman-Sacks Syndrome was just a subclass of Osler's erythema group, but likely not of LE. It was later shown in 1940 that the form of endocarditis are in these cases were a manifestation of SLE, regardless of the appearance of the skin lesions [43].

In 1938, sulfonamides were first used to treat, at first discoid LE, and then SLE a few years after that. It did not cure the disease, but it did help the symptoms [44]. However, it was later shown that these

drugs can aggravate the disease once the body gains a tolerance to the drug. This was first described in 1945 in which a young soldier was given sulfadiazine [45]. He was being treated for pyelonephritis but developed SLE. LE was so unresponsive to other treatments that it seemed a necessary evil to use this treatment [46].

Gold compounds were reported to be used for lupus but also aggravated the disease. It was said:

“The general opinion that this method of treatment (gold) is contraindicated for acute and subacute disseminated lupus erythematosus is well founded on sad experience. The capillaries seem unduly sensitive not only to gold therapy but also to a wide variety of therapeutic agents. . This is understandable in the case of therapy with gold preparations, since it affects the structures (capillaries) attacked by lupus erythematosus itself” [46].

While it was shown that gold aggravates the symptoms of LE, it was later shown that other drugs can actually induce LE. The first such drug was hydralazine followed by hydantoin, and then procainamide; in 1954, 1953, and 1962 respectively [47-49]. Hydralazine was used to treat hypertension, but in large doses it was shown to cause symptoms of LE [47]. At first arthritis developed, and the symptoms would continue to evolve if hydralazine usage was not stopped. Comens and Schroder even showed that LE cells were present in people that did not have any symptoms of SLE but that did use hydralazine [50].

Anticonvulsants were also shown to induce SLE. Diphenylhydantoin and mesantoin were the two first notable drugs that were shown to have this characteristic. Seizures may be an early predictor of SLE, so it was hypothesized that these drugs actually “uncover” SLE [51]. Procainamide, an antiarrhythmic drug, has been the most indisputable drug that induces SLE. In 1969, Dubois compared 520 cases of idiopathic SLE against 33 cases of drug induced SLE. He showed that while the drugs did induce SLE, the symptoms were usually less severe and fewer in number. In particular the drug-induced SLE lacked the gastrointestinal, neurological, and renal symptoms of the disease [52]. Blomgren, et al. showed that within 6 months of a patient being placed on procainamide, half of the patients developed antinuclear antibodies (ANAs). They concluded that this drug uncovered the patient's predisposition to idiopathic LE [53].

Doherty and Siegel have stated that Libman-Sacks endocarditis has become less prevalent in fatal cases of SLE due to the increased usage of corticosteroids in the treatment of SLE. From 1924 to 1951, Libman-Sacks endocarditis was prevalent in 59% of SLE cases as compared to only 36% of the cases reported from 1953 to 1976 [54]. Libman and Sacks also noted abnormalities of the spleen in their patients. They went on to describe it as:

“The greater part of each malpighian body [lymph follicle] was occupied by a number of arterioles, each of which was surrounded by a broad zone of hyaline-like connective tissue. The arteriolar lumen in each instance was diminished in calibre” [40].

Kaiser studied this condition and found it to be associated with 83% of cases of SLE while only associated with 3% in other diseases [55]. Kaiser went on to say:

“Its discovery post mortem should at least raise the suspicion of that diagnosis ... [and] its coincidence with the other well recognized lesions of the connective tissue such as verrucous endocarditis and the “wire loop” glomerular changes can serve to strengthen the post mortem diagnosis of disseminated lupus erythematosus” [55].

Baerh, in 1935, added onto the idea of disseminated lupus erythematosus. Baerh wrote a report of 23 patients. He also differentiated a type of nephritis in 13 of his 23 patients that were irregular to LE [27]. He stated:

“The commonest and most characteristic glomerular alteration was a peculiar hyaline thickening of the capillary walls The thickened wall appears rigid, as if made of heavy wire. We have; therefore, called it the “wire loop lesion” ... It is quite different from the hyaline degeneration seen in glomeruli of arteriosclerotic kidneys or of chronic glomerulonephritis. It is apparently represents a toxic degenerative process” [27].

It was shown that renal failure was not usually the main cause of death of patients with LE, but most likely because infection caused early death. Harvey, et al. found in two-thirds of autopsied patients with SLE that SLE was the main cause of renal damage [37]. Two old principles had been accepted for hundreds of years and they were not proven false until 1942. The first principle was made by Giovanni B. Morgagni (1682-1771), in 1761, in which he concluded that each disease of lupus affects a certain organ. The second principle was made by Paul Ehrlich (1854-1915) in 1901, where he stated that an organism cannot react against itself [56]. Fritz Klinge (1892-1974), a German pathologist, refuted the first principle. He studied rheumatic fever and found that this disease not only affects the synovium and heart but that it also affects connective tissue. Klinge also found this to be true in Rheumatoid Arthritis [56]. Klemperer, et al. studied SLE and discovered that:

“The apparent heterogeneous involvement of various organs in this disease had no logic until it became apparent that the widespread lesions were identical in that they were mere local expressions of a morbid process affecting the entire collagenous tissue system. The most prominent of these alterations is fibrinoid degeneration—a descriptive morphologic term indicating certain well defined optical and tinctorial alterations in the collagenous fibres and ground substance” [56].

These findings made by Klemperer, et al. ushered in the term “collagen disease” [57].

German dermatologist Wilhelm Generich set out to prove the second principle false. In 1921 he believed that the body could attack itself and he went on to say:

“Lymphocytic (leukocytic) ferments are liberated by the disintegration of lymph nodes. They act on the organism as denatured protein and in sufficient quantity cause anaphylaxis. Furthermore, the liberated ferments exert their biologic effect, which seemingly consists of sensitizing the vascular endothelium and destroying certain components of connective tissue cells, especially, predisposed components of the skin and eventually also of all parenchymatous organs, if an abundant accumulation (acute LE) of the ferments develops in the blood” [58].

Arnold Rich (1893-1968) advanced this hypothesis. Rich believed that the collagen and endothelium of patients were affected by the primary lesions of SLE because of anaphylaxis, but how this happened was not known [59]. Granular hematoxylin stained bodies were found in the heart of Libman-Sacks cases by Gross, and later on in 1950, Klemperer, et al. detected these bodies in 32 out of 35 cases of Libman-Sacks sufferers [57].

The Wassermann test for syphilis was invented in 1906 and quickly gained popularity. It was shown that some diseases gave false positive results [60]. In 1909 and 1910, cases of SLE were reported in Germany

that had given false positives for syphilis [61]. The false positives ranged from less than 3% all the way up to 44%. Cases of discoid LE rarely give false positive results whereas SLE gives false positive results for syphilis, accounting for the variation in the findings [25,62]. The etiology of the false positive test comes from data by Coburn and Moore. They showed that hyperglobulinemia in SLE patients led to the biologically false positive results [63]. The rise of the TPI (treponema pallidum immobilization) test in 1949 led to the declined use of the Wassermann test. In fact, the Wasserman test could diagnose SLE years before any clinical manifestations of SLE existed. The Wassermann test was used until the discovery of the LE cell [64].

It was shown by Pangborn, in 1941, that phospholipids were the substance used in the fixation test for syphilis. The actual mechanism for the false positive tests was not discovered until 1983, when a test for anticardiolipin antibodies was developed [65]. Conley, et al. in 1948, discovered cases of an anticoagulant in patients with a bleeding problem but who are not hemophiliacs were. In 1952, two cases of SLE with such bleeding problems were documented [66]. It was later shown by Lee and Sanders that this anticoagulant was not too uncommon for patients with SLE, but it was uncommon for it to cause bleeding [67]. In 1963, this substance was also shown to cause thrombosis [68]. Later on in 1975 this substance was shown to cause spontaneous miscarriages in SLE patients [69]. This syndrome was given the name antiphospholipid syndrome [70].

Modern Period

The modern period was ushered in by Hargraves and his colleagues with the discovery of the LE cell. Hargraves discovered the LE cells in patients suffering from acute disseminated lupus erythematosus and hypothesized that the LE cell was a result of the phagocytosis of free nuclear material, and as a result contains a vacuole with contents of partially lysed and digested nuclear material. Hargraves noted that in the marrow aspirate of a young child with an unknown disease, "peculiar rather structureless globular bodies taking purple stain." Two more patients presented this until SLE was finally diagnosed in them [71].

This discovery was made by collecting the serum from patients suffering from lupus erythematosus and then adding it to the bone marrow of healthy patients. Polymorphonuclear leukocyte clumps formed around the nuclear material of these preparations, and this was clearly noticeable when compared to control studies [72] Hargrave went on to say: "The 'LE cell' is the end result either of phagocytosis of free nuclear material or an actual autolysis of one or more lobes of the nucleus. The 'LE' cell is practically always a mature neutrophilic polymorphonuclear leukocyte in contradistinction to the 'tart cell' which is most often a histiocyte" [72]. The most important feature of the LE cell was that this could be present when no other symptoms were shown. John R Haserick, a dermatologist at the Cleveland Clinic, continued research on the LE cell. In his findings he showed that by incubating non-LE marrow with LE serum, LE cells could be produced. This was produced because there was a factor in the blood of LE patients that form the LE cells [73], and it was later shown, in 1950, that this is a gamma factor globulin. Klemperer, et al. showed "hematoxylin bodies" that seemed to be identical to the material that was phagocytosed in the LE cell [74]. This strengthened the idea that the LE cell is related to the pathogenesis of LE. Though many methods to collect LE cells were introduced, the method proposed by Hargraves and Zimmer seemed to be the most popular.

Kievits, et al. showed that the LE cell was present in 16% of patients with rheumatoid arthritis and this raised doubt that the LE cell could be used for definite diagnosis of SLE [75]. Further raising doubt about using the LE cell to diagnose SLE was made by Rothfield, et al. when they showed that the LE cell could not be detected in about one-quarter of the cases of SLE [76].

Part of the reason why the LE cell could not be detected in SLE patients was found by investigators in Switzerland in 1954. They showed that isolated cell nuclei can actually absorb the serum factor that caused LE cell formation and they hypothesized that this factor was actually an antibody that was an antagonist to components of the nucleus [77].

Immunofluorescent microscopy was used by Friou, et al. in 1957, to show the presence of this antibody [78]. It was later shown in 1959 that this antibody was a DNA-histone nucleoprotein, and Beck later showed that three different fluorescent stain patterns could be identified [79]. Techniques advanced within the next decade and by the end of the decade, numerous antibodies were discovered that were associated with SLE. These discoveries brought along the idea that immunology was involved in the manifestation of this disease.

The year 1954 marked the first time where there was a documented case of placental transfer of the LE factor, the above mentioned anti-DNA antibody [80]. Later that year, discoid LE developed in an infant whose mother developed SLE shortly after that [81]. This was a transient form of discoid LE. This neonatal form of discoid LE usually cleared within the first year, but there are cases of infant death. For instance in 1957, a mother delivered a baby who died the next day of heart blockage. The infant was shown to have myocardial hematoxylin bodies present in its heart [82]. More cases like this arose, and in 1977, heart blockage became the main symptom of neonatal LE. About half of the cases of neonatal LE present with this symptom [83]. The anti-Ro antibody seems to be the likely cause of neonatal discoid LE and SLE [84].

It was shown in 1957 that there was a factor in serum of some cases of SLE that reacted with DNA. Three laboratories came to these findings almost at the same time [85,86]. In 1960 it was shown that this antibody could react both with normal DNA and denatured DNA. Double stranded DNA antibody detection is more specific for cases of SLE, but not quite as sensitive as single stranded DNA antibody detection [87]. Sm was a cytoplasmic antigen in SLE serum and was discovered by Tan and Kunkel. Though highly specific for cases of SLE, it was only present in about one-third of the SLE cases [88].

Later on, techniques were developed that allowed uncomplexed histones to be extracted from nuclei and then recombine the histones with DNA. These extracted histones can be used to find antigens, depending on the histone structure, and the result would be antihistone antibodies [89]. Antihistone antibodies are found more with drug-induced lupus [90]. This led to even more discoveries of antibodies and their roles in SLE. The antinuclear antibodies (ANAs) only account for about 5% of SLE cases. (Figure 3) Most of the ANAs react to the cytoplasmic RNA antigen known as Ro [91].

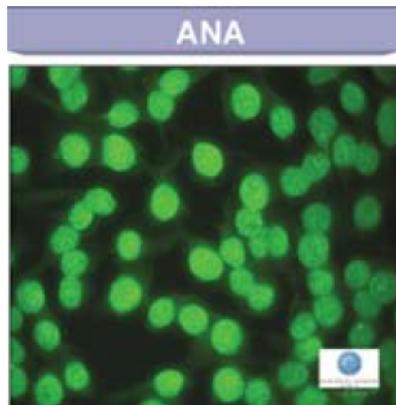


Figure 3: Antinuclear Antibodies. Professor Georg Wick, Medical University of Innsbruck.

The “lupus band test” was developed in 1963 to test for lupus. In this test, a skin biopsy is performed and then examined by using immunofluorescent microscopy to detect if immunoglobulins are deposited at the dermoepidermal junction [92]. With discoid LE, the test is positive in lesioned skin but negative in normal skin. Around 50% of SLE cases are positive for the “lupus band test” with their normal skin [93]. However, like most other lupus tests, this isn’t highly specific because it was shown that at least 15% of rheumatoid arthritis cases and various other bullous dermatoses will show a positive result for the “lupus band test”[94]. Stephania Jablonska, a professor of Dermatology at the University of Warsaw and a research dermatologist concerned most of her career with cause and nature of epidermodysplasia verruciformis. In 1975, immunofluorescent technologies were being perfected and were moving from the laboratory into the clinical field. Joblanska led the team that used these techniques to diagnose lupus erythematosus and bullous diseases [95].

An intermediate form of LE was discovered in 1979 that was called subacute cutaneous LE. This appeared to be an intermediate of SLE and discoid LE. In about 20% of these cases, discoid LE may precede the lesions of SLE, or even occur at the same time. These lesions differ from those seen in discoid LE because they appear more like psoriasis and they lack follicular plugging. These lesions do not scar as easily when they are healing. Patients with subacute cutaneous LE are more photosensitive than discoid LE or SLE patients and about half of the patients fulfill the requirements to be diagnosed with SLE. The majority of subacute cutaneous LE is ANA positive, but they are anti-Ro positive, which would usually represent ANA-negative SLE [96]. Hydrochlorothiazide was shown to induce subacute cutaneous LE in 1985[97]. The modern area is also characterized by the development of an animal model for testing and showing there is a genetic predisposition associated with lupus. The first animal model was the familial 1 hybrid of the New Zealand Black and New Zealand White mouse. This murine model has given much insight into lupus such as autoantibody formation, mechanisms of immunological tolerance, the development of glomerulonephritis, the role of sex hormones and the course of the disease, and new treatments to the disease [98]. Leonhardt was the first to describe the genetic predisposition of Lupus and more studies done by Arnett and Shulman at Johns Hopkins showed there was a definite familial occurrence associated with lupus [99]. In the last twenty years there is evidence that has arisen to show

the familial occurrence of lupus, the concordance of lupus in monozygotic twins, and different genetic markers that are associated with lupus [99]. Currently studies of human lymphocyte antigen genes are being done to determine the amino acid structure of the cell surface molecules of the T-helper cells in patients with LE. There has been some progress made with these studies. Scientists have connected some of the genetic-serological subsets with the clinico-serological subsets in patients with LE, and researchers hope this will lead to the discovery of etiological factors in SLE [99].

Today, immunomodulation is an important therapy for managing and treating this disease. Three examples to this approach are cyclophosphamide, mycophenolate mofetil, and azathioprine. Cyclophosphamide is an alkylating agent that prevents DNA synthesis by cross linking the DNA strands and therefore prevents cell division. Mycophenolate mofetil inhibits inosine monophosphate dehydrogenase, which is an enzyme used in the rate limiting step of de-novo purine synthesis. Azathioprine is an imidazolyl derivative of mercaptopurine that antagonizes the metabolism of purine. Another area of treatment is with biological agents such as rituximab and lymphostat B. Rituximab is a monoclonal antibody that is directed against the CD20 antigen on B-lymphocytes. Lymphostat B is another monoclonal antibody of B lymphocyte stimulator [100]. The growth of new knowledge will hopefully allow an improved understanding of the immunopathogenesis of LE and the development of more effective treatments.

Summary

The history of lupus erythematosus dates back all the way to 400 BC with the works of Hippocrates. Hippocrates was the first to describe the possible ulcers of lupus erythematosus as herpes esthiomenos. Later on in the 12th century, surgeon Rogerius Grugardi and his student Rolando of Parma, used the term *noli me tangere* (touch me not) to the facial lesions and ulcers of lupus. Erasmus Wilson studied lupus, and like many at the time, confused lupus and tuberculosis as manifestations of the same disease. Robert Willan brought order to the naming of skin disorders. Using the works of Mercurialis, Turner, and Von Planke, Willan published this in his *Manual on Skin Diseases* and in it lupus, herpes, *noli me tangere*, among others, were all differentiated. Thomas Bateman, a student of Willan, continued the work of Willan after his death. Laurent Biett’s work contributed to arguably one of the most important books of the 19th century, *Abrege Pratique Des Maladies De La Peau*, though Biett’s pupils Cazenave and Schedel wrote the textbook. Ferdinand Hebra was the first to describe the facial rashes associated with LE and he was the first to describe it as a butterfly rash. Hebra was also the first to publish illustrations of LE. Jonathon Hutchison noted the photosensitive nature of LE and later described Hebra’s butterfly rash as a batwing rash. Hutchinson also noted that tubercule bacteria were not always present in cases of LE. Mariz Kaposi first described the two forms of LE; discoid and disseminated. Physician Payne first used Quinine to treat LE and physician Philip S Hency used ACTH and cortisone to treat LE. Later Sulzberger and Witten used hydrocortisone for LE treatment. Sir William Osler wrote three papers on 29 different patients he studied and in which 2 suffered from LE. Emmanuel Libman and Benjamin Sacks are credited with discovering “Libman-Sacks Syndrome” that is associated with LE. Sulfonamides were used in 1938 to treat LE, but it was later shown these drugs can induce LE. It was later shown that several drug classes can induce LE by “uncovering” a predisposition to the disease. Diagnosis of the disease proved difficult. The Wasserman

test for syphilis showed that for some cases of LE, a biological false positive result was given. This test was used for diagnosis until Hargraves discovered the LE cell. Later on immunofluorescence was used to show the presence of antinuclear antibodies. Immunofluorescent microscopy was later used for "lupus band tests" that were performed on skin biopsies. Murine models were developed in New Zealand that helped out extensively with the research of LE. Leonhardt first described the genetic predisposition of lupus erythematosus and Arnett and Shulman of Johns Hopkins showed there was a familial occurrence that was associated with LE. Lupus used to be a death sentence with patients living no longer than 5 years after diagnosis. Today patients may live normal lives thanks to the efforts of the above mentioned men and women that devoted their lives to the research of LE and DLE.

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References

1. Blotzer JW (1983) Systemic lupus erythematosus I: historical aspects. *Md State Med J* 32: 439-441.
2. Holubar K (1980) Terminology and iconography of lupus erythematosus. A historical vignette. *Am J Dermatopathol* 2: 239-242.
3. Smith CD, Cyr M (1988) The history of lupus erythematosus. From Hippocrates to Osler. *Rheum Dis Clin North Am* 14: 1-14.
4. Adams F (1939) The genuine works of Hippocrates. Williams & Wilkins CD, Baltimore, USA, pp. 300-301.
5. Neuburger M (1911) *Geschichte der Medizin*, Stuttgart, F. Enke 2: 307.
6. Bateman T (1818) A practical synopsis of cutaneous diseases (4th edn.) Philadelphia: Collins & Croft, London, pp. 305.
7. Paracelsus T Bucher, Schriften J Huser (eds.) (1639) (Reprint: Hildesheim: G Olms. Von dem Buch wie die Artzney kompt (1971) 1:235.
8. Wilson E (1863) On diseases of the skin (5th edn.) Philadelphia: Blanchard & Lea, London, pp. 315.
9. Bateman T (1936) A Practical Synopsis of Cutaneous Diseases, According to the Arrangements of Dr. Willan (8th edn.) London: Longman, Rees, Orme, Brown, Green and Longman.
10. Wallace D, Dubois HB (1997) *Lupus Erythematosus* (5th edn.) Williams & Wilkins, USA, pp. 3-16.
11. Holubar K (1980) Terminology and iconography of lupus erythematosus. A historical vignette. *Am J Dermatopathol* 2: 239-242.
12. Cazenave A, Schedel HE (1852) *Manual of Diseases of the Skin* (2nd edn.) S.S. & Wood, USA, pp. 35-36.
13. Hebra, F Kaposi M (eds.) *On Diseases of the Skin including the Exanthemata*, Tay W (trans). London, The New Sydenham Society, 4: 1875.
14. Hebra F, Effinger K *Atlas derhautlo-ankheiten. Felt von Ferdinand Hebra. Bilder on Anton Effinger*, pp. 1856-1876.
15. Hutchinson J (1879) *Lupus erythematosus*. *Med Times Gaz* 1: 1-3.
16. Hutchinson J (1880) *On Lupus & its Treatment*. *Br Med J* 1: 650-652.
17. Hutchinson J (1888) *Harveian lectures on lupus*. *Br. Med J* 1:6-10; 58-63; 113-118.
18. Hartzell MB (1917) *Diseases of the skin. Their pathology and treatment*. Philadelphia: Lippencott, pp. 362.
19. Goeckerman WH (1921) Is lupus erythematosus discoides chronicus due to tuberculosis? *Arch Derm Syph* 3: 788-801.
20. Keil H (1933) Relationship between lupus erythematosus and tuberculosis. *Arch Derm Syph* 28: 765-779.
21. Kaposi KM (1869) *Zum Wesen und zue Therapie des Lupus erythematosus*. *Arch fDermat u Syph* 1: 18-41.
22. Kaposi M (1872) *Neue Beitrage zur Kenntnis des Lupus erythematosus*. *Arch f Dermat u Syph* 4: 36-78
23. Kaposi M (1893) *Pathologie und Therapie der Hautkrankheiten*. Wein: Urban & Schwarzenberg, pp. 714.
24. MacLeod JM (1913) Discussion on the nature, varieties, causes, and treatment of lupus erythematosus. *Br Med J* 2: 313-319.
25. Montgomery H, McCreight WG (1949) Disseminate lupus erythematosus. *Arch Derm Syphilol* 60: 356-372.
26. Burch PR, Rowell NR (1968) The sex- and age-distributions of chronic discoid lupus erythematosus in four countries. Possible aetiological and pathogenetic significance. *Acta Derm Venereol* 48: 33-46.
27. Baehr G (1951) Disseminated lupus erythematosus. In: Cecil RL, Loeb RF (eds.) *A textbook of medicine*. (8th edn.) Philadelphia: WB Sanders, pp. 483-488.
28. Arnold HLJR (1956) *Lupus erythematosus profundus; commentary and report of four more cases*. *AMA Arch Derm* 73: 15-33.
29. Payne JF (1894) A post-graduate lecture on lupus erythematosus. *Clin J* 4: 223.
30. Hench PS (1952) The reversibility of certain rheumatic and nonrheumatic conditions by the use of cortisone or of the pituitary adrenocotropic hormone. *Ann Intern Med* 36: 1-38.
31. Osler W (1895) On the visceral complications of erythema exudativum multiforme. *Am J Med Sci* 110: 629-646.
32. Osler W (1900) The visceral lesions of the erythema group. *Br J Dermatol* 12: 227-245.
33. Osler W (1904) On the visceral manifestations of erythema group of skin diseases. *Am J Med Sci* 127: 1-23.
34. Jadassohn J (1904) *Lupus erythematosus*. In: Mracek F, editor. *Handbuch der Hautkrankheiten*. Wein, Alfred Holder, pp. 298-404.
35. Kraus A, Bohac C (1908) Bericht uber act Falle von Luupus erythematosus acutus. *Arch f Dermat u Syph* 43: 117-156.
36. Brunsting LA (1952) Disseminated (systemic) lupus erythematosus. *Proc Staff Meet Mayo Clin* 27: 410-412.
37. Harvey AM, Shulman LE, Tumulty PA, Conley CL, Schoenrich EH (1954) Systemic lupus erythematosus: review of the literature and clinical analysis of 138 cases. *Medicine (Baltimore)* 33: 291-437.
38. Libman E, Sacks B (1923) A hitherto undescribed form of valvular and mural endocarditis. *Trans Assoc Amer Phys* 38: 46-61.
39. Libman E, Sacks B (1924) A hitherto undescribed form of valvular and mural endocarditis. *Arch Intern Med* 33: 701-737.
40. Pulay E (1921) *Stoffwechselfathologie und Hautkrankheiten* (17th edn.) *Dermat Wchnschr* 73: 1217-1234.
41. Rasch C (1926) Some Historical and Clinical Remarks on the Effect of Light on the Skin and Skin Diseases. *Proc R Soc Med* 20: 11-30.
42. Belote GH, Rather HS (1936) The so-called Libman-Sacks syndrome. Its relation to dermatology. *Arch Derm & Syph* 33: 642-664.
43. Ingels AE (1938) *Lupus erythematosus treated with sulfanilamide*. *Arch Derm & Syph* 37: 879-884.
44. Hoffman BJ (1945) Sensitivity to sulfadiazine resembling acute disseminated lupus erythematosus. *Arch Derm & Syph* 51: 190-192.
45. Gold S (1951) Role of sulphonamides and penicillin in the pathogenesis of systemic lupus erythematosus. *Lancet* 1: 268-272.
46. Dustan HP, Taylor RD, Corcoran AC (1954) Rheumatic and febrile syndrome during prolonged hydralazine treatment. *J Am Med Assoc* 154: 23-29.
47. Ruppli H, Vossen R (1957) [Side-effect of hydantion; therapy in the framework of visceral lupus erythematosus]. *Schweiz Med Wochenschr* 87: 1555-1558.
48. Ladd AT (1962) Procainamide-induced lupus erythematosus. *N Engl J Med* 267: 1357-1358.
49. COMENS P, SCHROEDER HA (1956) The L. E. cell as a manifestation of delayed hydralazine intoxication. *J Am Med Assoc* 160: 1134-1136.

50. Lindqvist T (1957) Lupus erythematosus disseminatus after administration of mesantoin; report of two cases. *Acta Med Scand* 158: 131-138.
51. Dubois EL (1969) Procainamide induction of a systemic lupus erythematosus-like syndrome. Presentation of six cases, review of the literature, and analysis and followup of reported cases. *Medicine (Baltimore)* 48: 217-228.
52. Blomgren SE, Condemi JJ, Bignall MC, Vaughan JH (1969) Antinuclear antibody induced by procainamide. A prospective study. *N Engl J Med* 281: 64-66.
53. Doherty NE, Siegel RJ (1985) Cardiovascular manifestations of systemic lupus erythematosus. *Am Heart J* 110: 1257-1265.
54. Kaiser IH (1942) The specificity of pariarterial fibrosis of the spleen in disseminated lupus erythematosus. *Bull J Hopkins Hosp* 71: 31-42.
55. Klinge F (1933) Der Rheumatismus; pathologisch-anatomische und experimentell-pathologische Tatsachen. *Ergeb d allg Path u path Anat* 27: 1-355.
56. Klemperer P, Pollack AD, Baehr G (1984) Landmark article May 23, 1942: Diffuse collagen disease. Acute disseminated lupus erythematosus and diffuse scleroderma. By Paul Klemperer, Abou D. Pollack and George Baehr. *JAMA* 251: 1593-1594.
57. Gennerich W (1921) Uber die Aetiologie des Lupus erythematoes. *Arch f Derm u Syph* 135: 184-207.
58. Rich AR (1947) Hypersensitivity in disease, with special reference to periarteritis nodosa, rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis. *Harvey Lect* 42: 106-147.
59. Wasserman A, Neisser A, Bruck C (1906) Eine serodiagnostische reaktion bei syphilis. *Dtsch Med Wochenschr* 32: 745-746.
60. Rein CR, Kostant GH (1950) Lupus erythematosus; serologic and chemical aspects. *Arch Derm Syphilol* 61: 898-903.
61. Coburn AF, Moore DH (1943) The plasma proteins in disseminate lupus erythematosus. *Bull J Hopkins Hosp* 73: 196-204
62. Moore JE, Lutz WB (1955) The natural history of systemic lupus erythematosus: an approach to its study through chronic biologic false positive reactors. *J Chronic Dis* 1: 297-316.
63. Haserick JR, Long R (1952) [Systemic lupus erythematosus preceded by false-positive serologic tests for syphilis: presentation of five cases]. *Ann Intern Med* 37: 559-565.
64. Pangborn MC (1941) A new serologically active phospholipid from beef heart. *Proc Soc Exp Biol Med* 48: 484-486.
65. Conley CL, Rathbun HK, et al. (1948) Circulating anticoagulant as a cause of hemorrhagic diathesis in man. *Bull Johns Hopkins Hosp* 83: 288-296.
66. Lee SL, Sanders M (1955) A disorder of blood coagulation in systemic lupus erythematosus. *J Clin Invest* 34: 1814-1822.
67. Bowie EJ, Thompson JH, Pascuzzi CA, Owen CA (1963) Thrombosis In Systemic Lupus Erythematosus Despite Circulating Anticoagulants. *J Lab Clin Med* 62: 416-430.
68. Nilsson IM, Astedt B, Hedner U, Berezin D (1975) Intrauterine death and circulating anticoagulant ("antithromboplastin"). *Acta Med Scand* 197: 153-159.
69. Harris EN, Gharavi AE, Wasley GD, Hughes GR (1988) Use of an enzyme-linked immunosorbent assay and of inhibition studies to distinguish between antibodies to cardiolipin from patients with syphilis or autoimmune disorders. *J Infect Dis* 157: 23-31.
70. Hargraves MM (1969) Discovery of the LE cell and its morphology. *Mayo Clin Proc* 44: 579-599.
71. Hargraves MM (1949) Production in vitro of the L.E. cell phenomenon; use of normal bone marrow elements and blood plasma from patients with acute disseminated lupus erythematosus. *Proc Staff Meet Mayo Clin* 24: 234-237.
72. Haserick JR, Bortz DW (1949) A new diagnostic test for acute disseminated lupus erythematosus. *Cleve Clin Q* 16: 158-161.
73. Haserick JR, Lewis LA (1950) Blood factor in acute disseminated lupus erythematosus; induction of specific antibodies against L. E. factor. *Blood* 5: 718-722.
74. Goslings J, Hijmans W, Kievits JH, Schutt HR (1956) Rheumatoid arthritis and the positive L.E.-cell phenomenon. *Ann Rheum Dis* 15: 211-216.
75. Rothfield NF, Phythyon JM, McEwen C, Miescher P (1961) The role of antinuclear reactions in the diagnosis of systemic lupus erythematosus: a study of 53 cases. *Arthritis Rheum* 4: 223-239.
76. Miescher P, Fauconnet M (1954) [Absorption of L. E. factor by isolated cell nuclei]. *Experientia* 10: 252-253.
77. Friou GJ (1967) Antinuclear antibodies: diagnostic significance and methods. *Arthritis Rheum* 10: 151-159.
78. Beck JS (1969) Antinuclear antibodies: methods of detecton and significance. *Mayo Clin Proc* 44: 600-629.
79. Reed BR, Huff JC, Jones SK, Orton PW, Lee LA, et al. (1985) Subacute cutaneous lupus erythematosus associated with hydrochlorothiazide therapy. *Ann Intern Med* 103: 49-51.
80. Bridge RG, Foley FE (1954) Placental Transmission Of The Lupus Erythematosus Factor. *Am J Med Sci* 227: 1-8.
81. Mccuistion CH, Schoch Ep JR (1954) Possible Discoid Lupus Erythematosus In Newborn Infant; Report Of A Case With Subsequent Development Of Acute Systemic Lupus Erythematosus In Mother. *Ama Arch Derm Syphilol* 70: 782-785.
82. Hogg GR (1957) Congenital, Acute Lupus Erythematosus Associated With Subendocardial Fibroelastosis; Report Of A Case. *Am J Clin Pathol* 28: 648-654.
83. McCune AB, Weston WL, Lee LA (1987) Maternal and fetal outcome in neonatal lupus erythematosus. *Ann Intern Med* 106: 518-523.
84. Cappelini R, Polli E, Celada F (1957) A Dna-Reacting Factor In Serum Of A Patient With Lupus Erythematosus Diffusus. *Proc Soc Exp Biol Med* 96: 572-574.
85. Robbins WC, Holman HR, Deicher H, Kunkel HG (1957) Complement fixation with cell nuclei and DNA in lupus erythematosus. *Proc Soc Exp Biol Med* 96: 575-579.
86. Schur PH, Stollar BD, Steinberg AD, Talal N (1971) Incidence of antibodies to double-stranded RNA in systemic lupus erythematosus and related diseases. *Arthritis Rheum* 14: 342-347.
87. Tan EM, Kunkel HG (1966) Characteristics of a soluble nuclearantigen precipitating with sera of patients with systemic lupus erythematosus. *J Immunol* 96: 464-471.
88. Fritzler MJ, Tan EM (1978) Antibodies to histones in drug-induced and idiopathic lupus erythematosus. *J Clin Invest* 62: 560-567.
89. Tan EM, Robinson J, Robitaille P (1976) Studies on antibodies to histones by immunofluorescence. *Scand J Immunol* 5: 811-818.
90. Maddison PJ, Provost TT, Reichlin M (1981) Serological findings in patients with "ANA-negative" systemic lupus erythematosus. *Medicine (Baltimore)* 60: 87-94.
91. Burnham TK, Neblett TR, Fine G (1963) The Application Of The Fluorescent Antibody Technic To The Investigation Of Lupus Erythematosus And Various Dermatoses. *J Invest Dermatol* 41: 451-456.
92. Burnham TK, Fine G (1971) The immunofluorescent "band" test for lupus erythematosus. 3. Employing clinically normal skin. *Arch Dermatol* 103: 24-32.
93. Ma AS, Soltani K, Bristol LA, Bernstein JE, Sorensen LB (1984) Cutaneous immunofluorescence studies in adult rheumatoid arthritis in sun-exposed and non-sun-exposed areas. *Int J Dermatol* 23: 269-272.
94. Jablonska S, Beutner EH, Michel B, Cormane RH, Holubar K, et al. (1975) Uses for immunofluorescent tests of skin and sera. *Arch Dermatol* 111: 371-381.
95. Sontheimer RD, Thomas JR, Gilliam JN (1979) Subacute cutaneous lupus erythematosus: a cutaneous marker for a distinct lupus erythematosus subset. *Arch Dermatol* 115: 1409-1415.
96. Sontheimer RD (1989) Subacute cutaneous lupus erythematosus: a decade's perspective. *Med Clin North Am* 73: 1073-1090.

97. Bielschowsky M, Helyer BJ, Howie JB (1959) Spontaneous hemolytic anemia in mice of the NZB/BL strain. *Proc Univ Otago Med School* 37: 9.
98. Arnett FC, Shulman LE (1976) Studies in familial systemic lupus erythematosus. *Medicine (Baltimore)* 55: 313-322.
99. Hochberg MC (1987) The application of genetic epidemiology to systemic lupus erythematosus. *J Rheumatol* 14: 867-869.
100. Ginzler EM, Dvorkina O (2005) Newer therapeutic approaches for systemic lupus erythematosus. *Rheum Dis Clin North Am* 31: 315-328.