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# Introduction and Physiology of Lupus

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Additional information is available at the end of the chapter

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## Abstract

Lupus is an autoimmune disease, which means that the immune system erroneously acts against its own healthy tissues. It usually follows a chronic course and hence can also be termed as a chronic disease. It may involve only a single organ, but in its due course, it usually involves multiple organs of the body. There are various types of rashes in systemic lupus erythematosus (SLE), the butterfly-like rash being the most famous. Up to now, many classifications of lupus have been given, but the classification into the discoid lupus and the disseminated lupus is being most widely accepted. From the time of Hippocrates, it was assumed to be present, and after many research studies, it is still a dreaded disease. Females are more affected than males by this disease. In the past, the survival rate of SLE was very poor. Now the survival rate has increased, thanks to the newer drugs and other strategies taken against this disease. The main causes of death from SLE were renal disease, neoplasm, CVD, cerebrovascular disease, respiratory disease and infection. It has been found that various genes cause the disease. In a small fraction of patients, the disease may be attributed to a single gene. But majority of the patients with this disease have multiple genes.

**Keywords:** chronic disease, autoimmune, autoantibodies, immune system, multiple organs

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## 1. Introduction

### 1.1. Definition of lupus

Systemic lupus erythematosus (SLE), which is simply known as lupus, is an autoimmune disease in which the immune system of the body erroneously onslaughts tissues in various parts of the body which are healthy [1, 2]. It may show only single organ sign or multiple

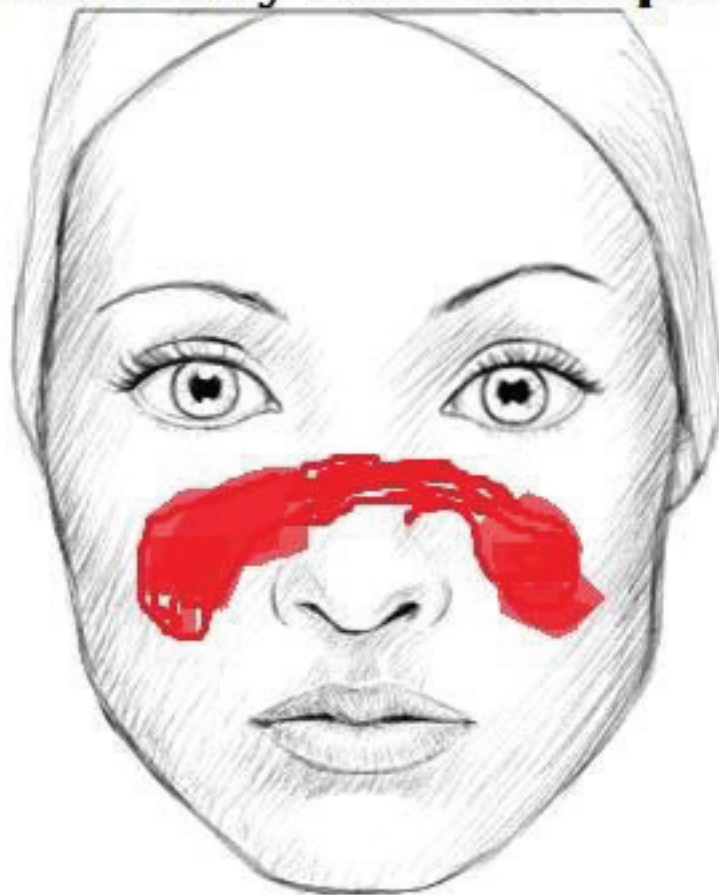
system sign at the onset. It can affect the brain, skin, joints and other parts of the body. It is an autoimmune problem that has a wide-ranging clinical presentation, encircling various parts of the body (**Figures 1 and 2**).

## 1.2. Varieties of lupus skin reactions

Varieties of lupus skin eruptions:

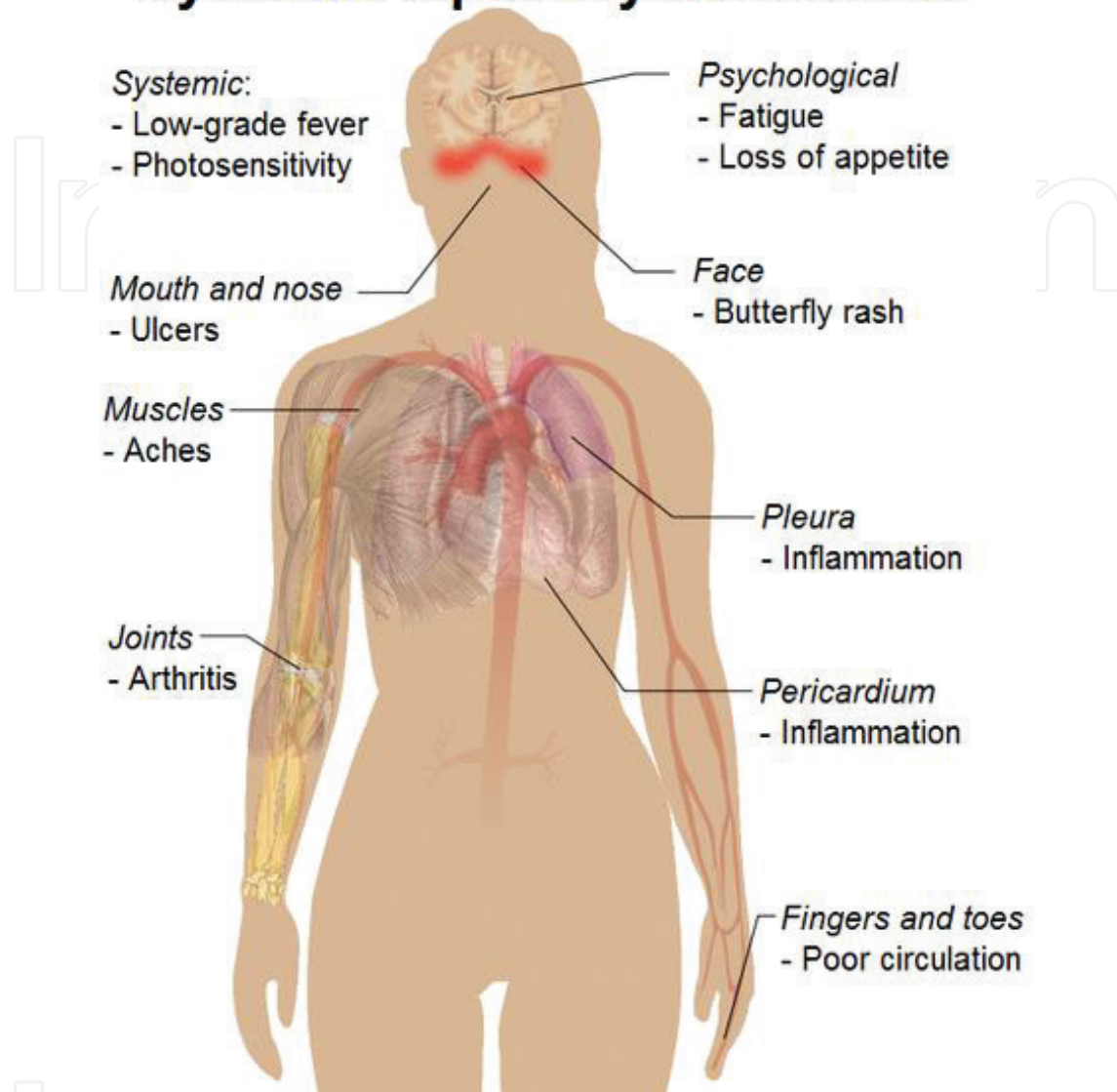
- (1) Acute cutaneous lupus (also called as the butterfly lupus rash or malar rash).
- (2) The subacute cutaneous lupus: There are two types: (a) the first one is very sensitive to exposure to the sun and depicts red coloured pimples as the skin eruptions development begins. (b) The second variety begins as flat lesions and get larger as they enlarge to the exterior.

### Butterfly rash of Lupus



**Figure 1.** The butterfly rash of lupus. It is a type of condition of the skin, which is denoted by the appearance of spots/skin eruptions over the cheekbones and also over the bridge of the nose.

## Most common symptoms of **Systemic lupus erythematosus**



**Figure 2.** The most usual systemic effects of systemic lupus erythematosus, which affects various organs as shown [131].

(3) Chronic cutaneous lupus (also called discoid lupus erythematosus—DLE): these skin eruptions are found in a very few of SLE patients.

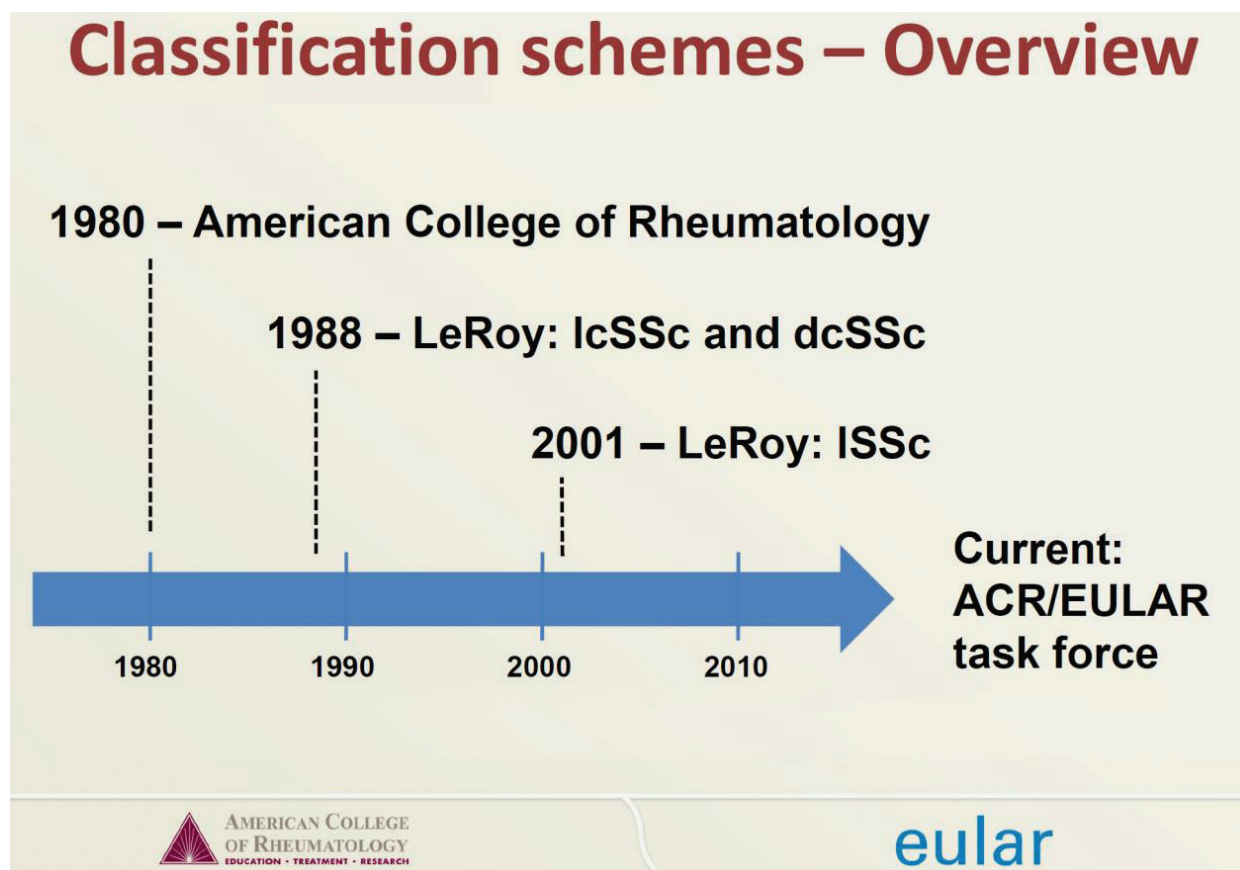
The disease SLE can attack people of all ages, races and both males and females, but it has been observed that more than 90% of new patients having SLE are women in their conceiving years. The prevalence of SLE, which has been reported recently, is 20–150 per 100,000. Data from metropolitan areas in the United States stipulated the prevalence to be 104–170 per 100,000 women [3]. The lowest incidence rates are observed in Caucasian populations [4].

### 1.3. Classification

Up to now, it has been divided into two parts: the discoid lupus and the disseminated lupus.

In 1971, classification criteria for SLE originated for the first time; they were subsequently revised in 1982 [5], and formally accepted by the American College of Rheumatology (ACR) in the year 1997 [6]. Whilst they have been accepted as ‘classification yardstick’, ACR (**Figure 3**) has been vastly used as diagnostic criteria for SLE. To diagnose a patient with SLE, the patient must have at least 4 of 11 ACR classification (**Table 1**) yardsticks. In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) foundation re-evaluated and made it valid [6, 7], and now according to them, the SLE patient must have at least 4 of 17 SLICC yardsticks, which should include at least one immunologic and one clinical criterion.

One of the most important scales to assess disease activity in SLE is the systemic lupus erythematosus disease activity index (SLEDAI) [8–10]. One of the famous modified indexes is known as the safety of estrogens in lupus erythematosus national assessment (SELENA) trial also called SELENA-SLEDAI system [11].



**Figure 3.** Classification schemes for lupus [ACR-endorsed Criteria for Rheumatic Diseases: <http://www.rheumatology.org/Practice-Quality/Clinical-Support/Criteria/ACR-Endorsed-Criteria>].

Criterion	Definition
1. Malar rash	Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds
2. Discoid rash	Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3. Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation
4. Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by physician
5. Nonerosive arthritis	Involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
6. Pleuritis or pericarditis	<p>1. Pleuritis—convincing history of pleuritic pain or rubbing heard by a physician or evidence of pleural effusion</p> <p>1. <i>OR</i></p> <p>2. Pericarditis—documented by electrocardiogram or rub or evidence of pericardial effusion</p>
7. Renal disorder	<p>1. Persistent proteinuria &gt; 0.5 g/d or &gt; than 3+ if quantitation not performed</p> <p>1. <i>OR</i></p> <p>2. Cellular casts—may be red cell, hemoglobin, granular, tubular, or mixed</p>
8. Neurologic disorder	<p>1. Seizures—in the absence of offending drugs or known metabolic derangements; e.g., uremia, ketoacidosis, or electrolyte imbalance</p> <p>1. <i>OR</i></p> <p>2. Psychosis—in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance</p>
9. Hematologic disorder	<p>1. Hemolytic anemia—with reticulocytosis</p> <p>1. <i>OR</i></p> <p>2. Leukopenia—&lt;4000/mm<sup>3</sup> on &gt; 2 occasions</p> <p>1. <i>OR</i></p> <p>3. Lymphopenia—&lt; 1500/mm<sup>3</sup> on &gt; 2 occasions</p> <p>1. <i>OR</i></p> <p>4. Thrombocytopenia—&lt;100,000/mm<sup>3</sup> in the absence of offending drugs</p>
10. Immunologic disorder	<p>1. Anti-DNA: antibody to native DNA in abnormal titer</p> <p>1. <i>OR</i></p> <p>2. Anti-Sm: presence of antibody to Sm nuclear antigen</p> <p>1. <i>OR</i></p> <p>3. Positive finding of antiphospholipid antibodies on:</p> <p>1. An abnormal serum level of IgG or IgM anticardiolipin antibodies,</p> <p>2. A positive test result for lupus anticoagulant using a standard method, or</p> <p>3. A false-positive test result for at least 6 months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test</p>

Criterion	Definition
11. Positive antinuclear antibody	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs

Reference: ACR-endorsed criteria for rheumatic diseases: <http://www.rheumatology.org/Practice-Quality/Clinical-Support/Criteria/ACR-Endorsed-Criteria>

**Table 1.** 1997 update of the 1982 American College of Rheumatology revised criteria for classification of systemic lupus Eeythematosus.

## 2. Historical perspective and physiology

Now, the origin of this disease is understandable clearly. It is conjectured that hormonal, environmental, genes, genetic variation and heredity play a significant role in its development [12]. It has been seen that if one member of a twin is affected the chances that the other twin may also be affected is 24%.

Documented proof of lupus can be tracked down to the time of the ancient Greek physician Hippocrates. In the year 400 BC, he wrote about herpes esthiomenos [13], which is conjectured to be lupus only. It has been seen that Hippocrates (**Figure 4**) mentioned about red, circumscribed inflammatory and often suppurating lesion on the skin or an internal mucous surface resulting in necrosis of tissue, which may depict present day lupus.

It has also been documented that there was a saint named Lupus, who lived in the sixth century A.D. [14].

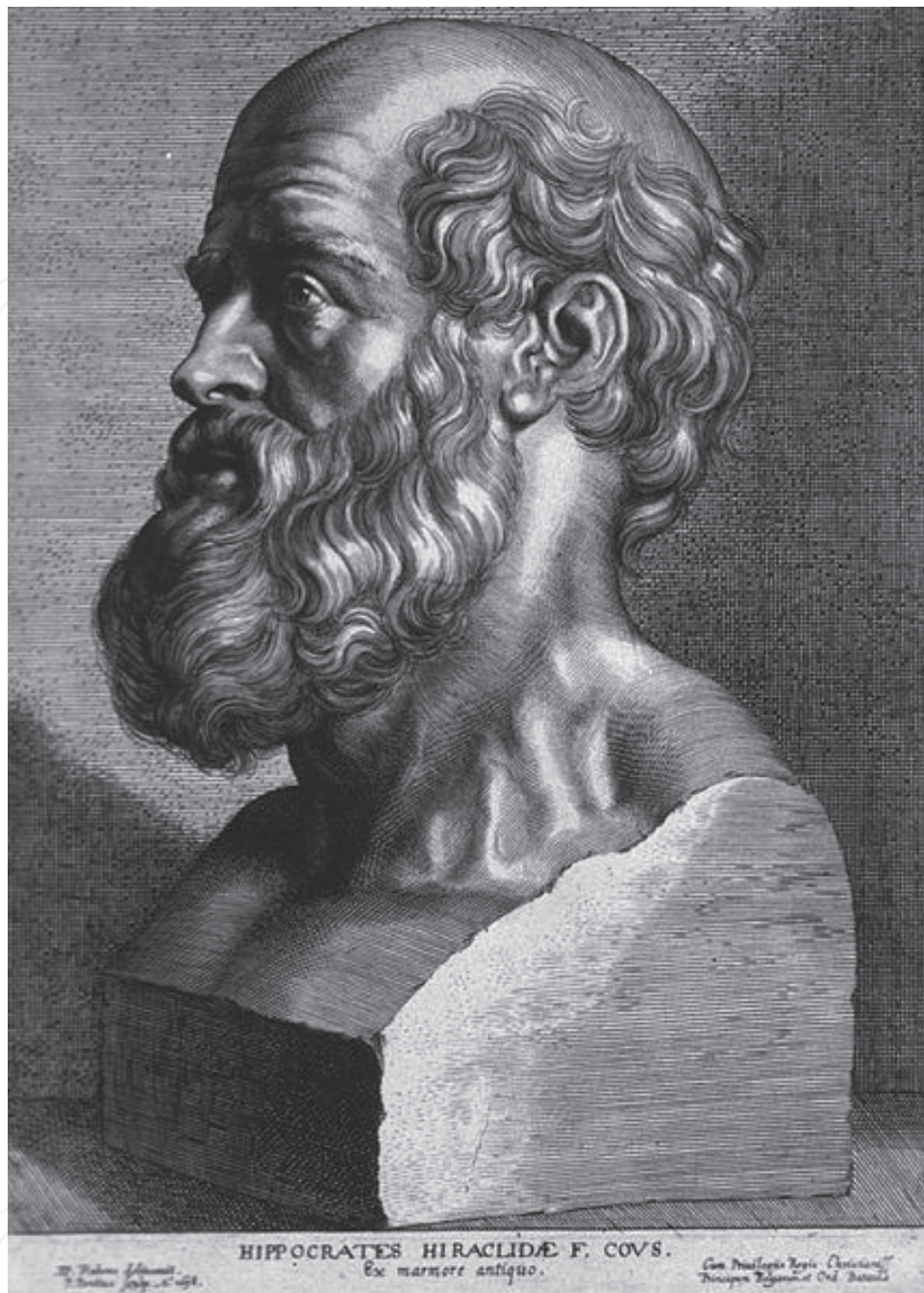
The history can be traced back into three parts as follows:

- (1) The traditional or classical phase during which the skin disarray was narrated.
- (2) The conventional period during which the entire body symptoms and signs of lupus were found out after careful searching unearthed and organised in a systematic way.
- (3) The contemporary period or modern phase which was portended by the unearthing of the LE cell in 1948 and is differentiated by other related discoveries in the field of science.

### 2.1. Traditional or classical phase

In the biography of St. Martin, for first time, we get an evidence of the word 'lupus' being used [15].

The word 'lupus' (which in Latin means 'wolf') is officially recognized to be coined by the Rogerius Grugardi, a physician who lived in the thirteenth century. He is accredited with coining 'noli me tangere', which means 'do not touch me'. He gave the term to the lesions and ulcers of the face associated with this disease. As time passed, the term underwent changes as the position of the disease changed. But the term 'lupus' remained. He used this term to



**Figure 4.** Hippocrates, engraving by Peter Paul Rubens, 1638 [Courtesy of the National Library of Medicine [<http://laphamsquarterly.org/contributors/hippocrates>].

delineate vicious lacerations of the face, which could be compared to the bite of a wolf. It was told that the characteristic butterfly rash analogous with lupus have a similarity with the teeth marks of a wolf's onslaught. The other hypothesis remarks that the terrifying impression on the face of a person resembled the impressions on the face of the wolf. The petrifying impression of people afflicted with lupus brings to the mind the terrifying tale of werewolves (**Figure 5**). These were mythologically described as humans who had magical power to meta-





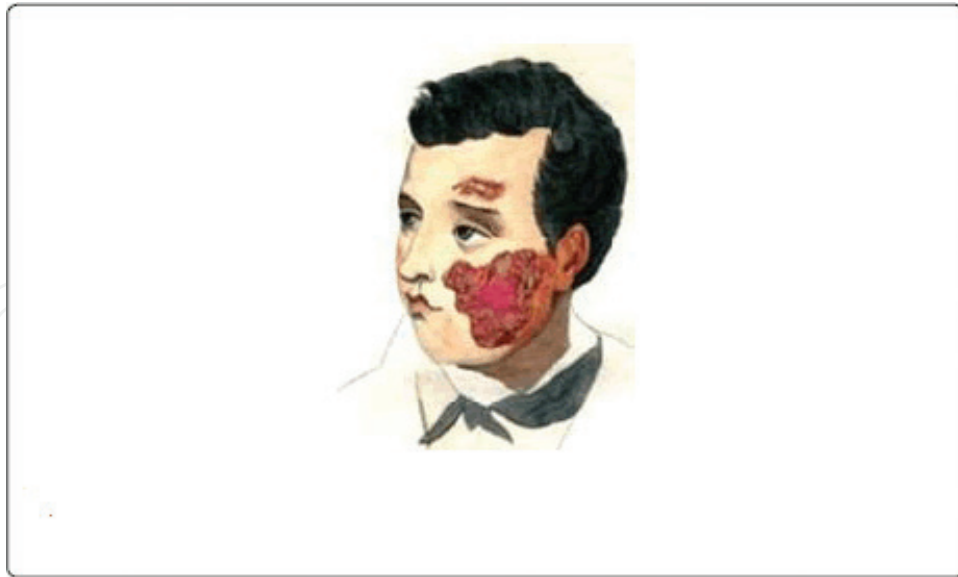
**Figure 5.** Werewolf attack—Woodcut of the sixteenth century by Lucas Cranach the Elder, 1512 [132].

morphose into animals. It was, therefore, the superstitious belief of the middle ages that the impressions on people faces afflicted with lupus resembled were wolves [16, 17].

## 2.2. Conventional or neoclassical phase

A student of Grugardi, Roland of Parma, wrote more about this disease. He also gave a detailed account of its different stages, which are not in use nowadays [18]. Erasmus Wilson (1809–1884) confused lupus with tuberculosis and syphilis [19] (**Figures 6 and 7**).

Robert Willan (1757–1812) was the one who first classified lupus based on clinical observations. Before him, the classification of lupus was mainly done according to symptomatology.



**Figure 6.** Lupus Vulgaris picture taken from Cazenave and Schedel's book [133].

Willan (**Figure 8**) segregated his findings into three parts: (i) lupus that extirpates the uppermost layer, (ii) lupus that extirpates the surface up to the bottom and (iii) lupus that is associated with overgrowth and dysplasia [20]. His student Thomas Bateman (1778–1821) helped him in publishing a book regarding lupus [21, 22].

Established and conventional elucidations of the variegated skin manifestations were made by Thomas Bateman.

It was in 1612 that the St. Louis Hospital was built by Biet (a pupil of Bateman) and Alibert. In the beginning, its main purpose was to help victims of plague. From 1800, it started treating skin disorders. Laurent Theodore Bielt (1781–1840) and Cazenave (1802–1877), who are renowned in the work of lupus, came from this school. Henri Schedel and Cazenave wrote book *Abrege Pratique Des Maladies De La Peau* in the year 1828.

Notable contributions were also made by Cazenave (**Figures 6 and 7**), who is credited with formulating the phrase *lupus érythémateux* (lupus erythematosus) in the mid-nineteenth century (**Figure 9**); creditable contributions were also made by Moriz Kaposi (1837–1902) in the late nineteenth century (**Figure 10**).

The contusions now alluded to as discoid lupus was described in 1833 by Cazenave who gave a characteristic account of the contusions; the typical distribution of the butterfly rash in the face was written by Ferdinand von Hebra in 1846.

The photosensitivity of the lesions of lupus was first described by Jonathon Hutchinson (1828–1913).

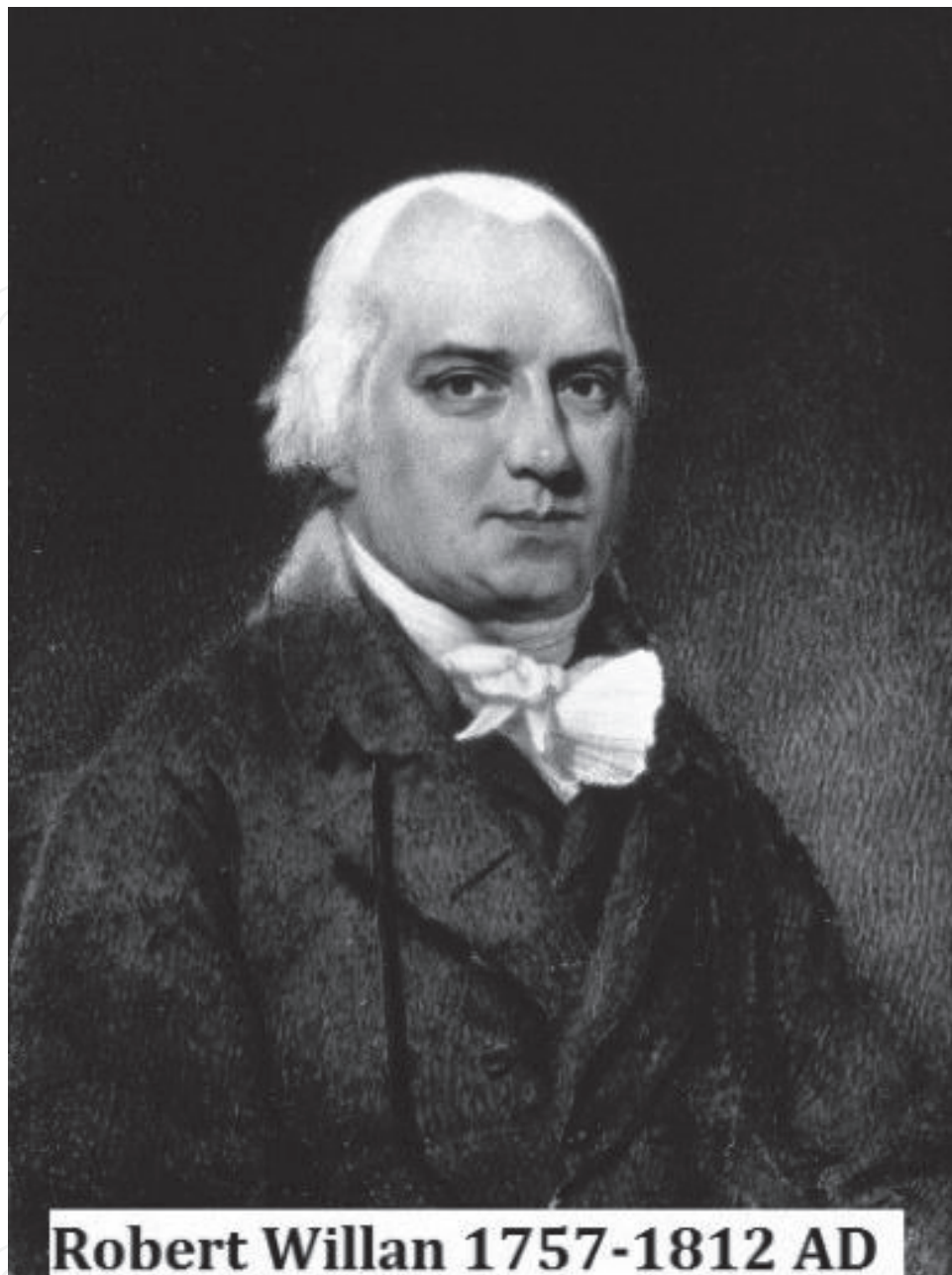
The beginning of the conventional period of lupus is accredited to the year 1872 in which Kaposi, a Viennese physician, at first delineated the whole body affecting character of lupus. It was first suggested by Kaposi about the two distinct varieties of lupus erythematosus: the



**Figure 7.** Drawing of lupus—1856 [Lupus erythematosus. Atlas der Hautkrankheiten. Farblithographie von Anton Elfinger. Heft I, Tafel 6, 59 × 45 cm (1856)].

discoid conformation and a disseminated conformation. In addition, he quantified the systemic manifestations of the disseminated form, which included lymphadenopathy, subcutaneous nodules, fever, arthritis with synovial hypertrophy of both small and large joints, anaemia, weight loss and involvement of the central nervous system [23]. Sir William Osler (**Figure 11**) also contributed much to the SLE concept. It was the works of this founding father of John Hopkins Hospital and Jadassohn (**Figure 12**) that the disseminated or systemic form of lupus was firmly confirmed [24, 25].

Over the following 30 years, disease studies registered the actuality of wire-loop lesions in individuals with glomerulonephritis and nonbacterial verrucous endocarditis (Libman-Sacks



**Figure 8.** A painting of Robert Willan (1757–1812) [Painting by unknown, Photographed by A. C. Cooper. <http://catalogue.wellcome.ac.uk/record=b1162089>].

disease), discovered and named by Emanuel Libman and Benjamin Sacks [26, 27]; it was these reviews at the autopsy table that led to the fabrication of collagen disease, which was suggested by Kemperer and colleagues in the 1940s [28]. Major advancements in the field of lupus occurred during 1920–1930 by the pathologists working at Mt. Sinai Hospital in New York.

The first use of sulphonamides for the treatment of lupus occurred in 1938. Although it was unable to cure the disease, it brought some relief to the patients from the symptoms [29]. For centuries, two principles were being accepted and they were not considered wrong. Giovanni



***Pierre Louis Alpheé Cazenave  
(1795-1877)***

**Figure 9.** Pierre Louis Alpheé Cazenave (1795–1877) [[https://upload.wikimedia.org/wikipedia/commons/5/5d/Cazenave%2C\\_P.-L.\\_Alph%C3%A9e.jpg](https://upload.wikimedia.org/wikipedia/commons/5/5d/Cazenave%2C_P.-L._Alph%C3%A9e.jpg)] | Author=unknown/anonymous | Date=before 1877|].

B. Morgagni (1682–1771) stated that a particular organ is affected by each different variety of lupus. Paul Ehrlich (1854–1915) stated the second principle in which he said that autoimmune destruction in lupus is false [30]. A German pathologist, Fritz Klinge (1892–1974), refused to accept the first principle. His study of rheumatic fever and rheumatoid arthritis showed that lupus affects connective tissue in addition to the heart [30].

Wilhelm Generich, a German dermatologist, studied extensively and proved that parts of our own body can attack its own [31].



**Figure 10.** Moritz Kaposi (23 October 1837–6 March 1902) [From the images from the History of Medicine (NLM), US National Library of Medicine (NLM). The NLM considers this item to be in public domain. [https://es.wikipedia.org/wiki/Moritz\\_Kaposi#/media/File:Moriz\\_Kaposi.jpg](https://es.wikipedia.org/wiki/Moritz_Kaposi#/media/File:Moriz_Kaposi.jpg)].

### **2.3. The modern phase**

In 1948, the unanticipated event in a healthcare in the mid-1900s which announced the modern era was the finding of the LE cell by Hargraves et al. [32]. These findings set the scene for the present period of the utilization of immunology for studying lupus erythematosus;



**Figure 11.** Sir William Osler (12 July 1849–29 December 1919) [This file is licensed under the Creative Commons Attribution 4.0 International license].

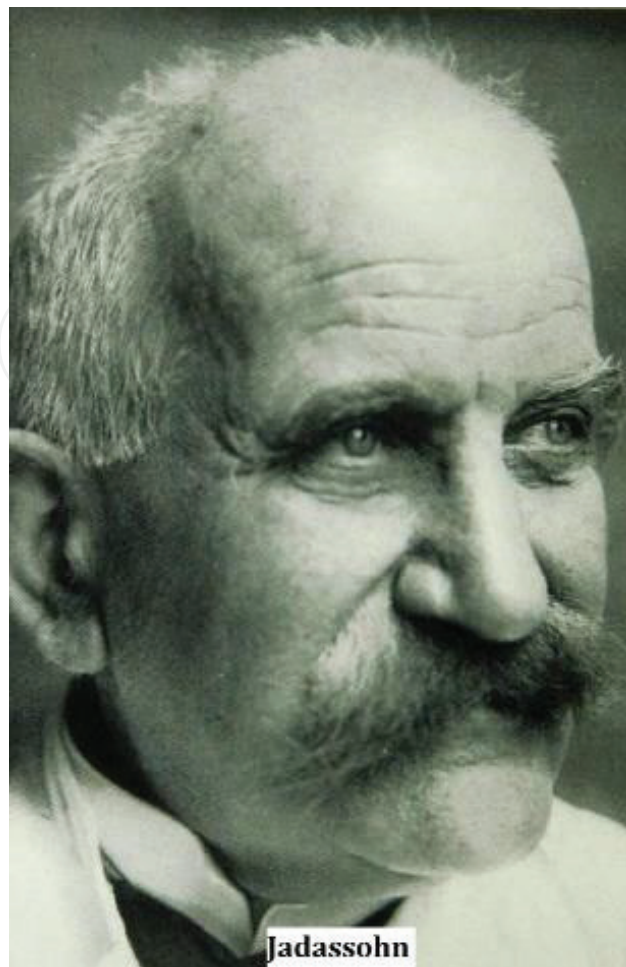
immunology also facilitated the recognition of people with much lighter forms of the disease. This, along with the use of cortisone for the treatment of this disease made life much easier for mankind [33].

In the 1950s, two new tests as being associated with lupus: the biologic false-positive test for syphilis [34] and the immunofluorescent test for antinuclear antibodies [35].

In 1957, Friou utilized the method of indirect immunofluorescence to show that antinuclear antibodies were present in the blood of people having systemic lupus [35]. After sometime, antibodies to deoxyribonucleic acid (DNA) [36] and antibodies to extractable nuclear antigens (nuclear ribonucleoprotein (nRNP), Sm, Ro, La), etc. were discovered.

Two notable advances in this age have been the invention of animal models of lupus and the discovery of the role of genetic predisposition with lupus occurrence.

The hereditary materialization of systemic lupus was first discovered by Leonhardt in 1954 and later confirmed by various observations by Arnett and Shulman [37]. Eventually, lupus having familial aggregation, the concurrence of lupus in monozygotic twin pairs and the relation of genetic markers with lupus have been delineated and reported over the last 20 years [38].



**Figure 12.** Joseph Jadassohn (10 September 1863–24 March 1936) [British Journal of Dermatology, vol. XLVIII (1937)].

### 3. Epidemiology of lupus

#### 3.1. Incidence and prevalence of SLE

It can be said with evidence from many studies that lupus mainly affects young women, having a peak during the ages of 15–40 years. However, the onset age can be taken from infancy and the last age will be the old age [39].

Most of the studies on SLE have reported incidence of 1–10 per 100,000 person-years.

It has been found that the incidence and prevalence of SLE in blacks almost twice or thrice the rate found in whites [40–63]. SLE has been found in all the six continents of the world ((North America, Europe, South America, Australia, Africa and Asia) [64–69]. According to a large study done in Michigan, it was seen that according to the American College of Rheumatology definition, incidence rates were five and a half per 1 lakh population-years, 95% confidence interval being 5–6.1. It was found that female populations had a comparatively higher incidence (the



95% confidence interval being almost nine) and the male population had a lesser 95% confidence limit (in between one and two). It was observed that blacks had a higher incidence rate than whites. Black females also had a higher incidence rate than white females. It was seen that the age-standardised prevalence was more almost six times more in blacks than in whites [70]. Another study, which was done in a predominantly white population in the United States, showed that the incidence rate was almost 3%. It was also seen that the incidence in women was much more (almost nine times more in women than in men) than that in men [71].

Many studies (epidemiological) have found that Caucasians have a twofold to threefold lower incidence and prevalence rates than Asians [72–79]. Moreover, it was found in many studies that Asians had more severe symptoms and signs of the disease, more aggressive kidney involvements, and the autoantibody positivity was also higher in Asians than in non-Asians [76, 79–83].

### 3.2. Progression of the disease

It has been seen that kidney involvement is more common in males than in females—males also had kidney damages earlier in the course of their disease than females, who got the disease late in their disease course [84].

Regardless of age/other factors involved, it has been found that American, Hispanic, Asian and African SLE patients tend to have more renal serosal, hematological and neurological manifestations [69, 85–90]. It may be possible that differences seen in the different ethnic groups may be due to genetic causes, or, possibly due to socio-economic conditions which have been prevalent from ages [91–93].

There is a lupus also known as pediatric lupus it usually presents before 16 years of age. In this disease, major organ systems are involved and the patient presents with neuropsychiatric complications [88, 94–99].

When lupus occurs late in life, it usually has a more gradual onset. They have less organ systems involved, and the disease is mild in them, but the progress and natural course, for some unknown reasons, is bad [100–108].

### 3.3. What is the mortality rate in these patients?

In the past, the survival rate of SLE was very poor. Now the survival rate has increased, thanks to the newer drugs and other strategies taken against this disease. Also, the detection of the milder forms of this disease or detection of the disease in the earlier stages has also made it possible to increase the survival rate. Improved survival rate has been noted in studies from patients in Sweden, Taiwan, Canada, Minnesota and California [41, 109–112].

Up to now, according to many surveys, the risk of death for SLE patients is still two times that of normal patients. The 95% CI is 2.3–3.8 approximately [113].

### 3.4. Causes of death in patients with SLE

In 2014, Thomas et al. reported that the main causes of death from SLE were renal disease, neoplasm, cardiovascular disease (CVD), cerebrovascular disease, respiratory disease and infection [114]. This data was also supported by a Canadian study [115].

It was seen in many other studies that treatment of infection with prednisone and other immunosuppressive agents was related to the death of SLE patients [116, 117]. In addition, acute confusional states, seizures were reported to cause a higher proportion of deaths in SLE [118–123].

## 4. Relationship of SLE with heredity and genes

SLE is a long-standing disease of variable stringency, sometimes becoming more severe and sometimes becoming less severe, with courses that can be fatal—if not treated early. The pre-clinical phase of the disease is denoted by autoantibodies which can be found in other systemic autoimmune diseases and results in a noticeable autoimmune phase.

The finding of SLE in identical twins, first-degree relatives having increased rate of SLE, and the sons and daughters of SLE patients having more risk of developing the disease contemplate an inheritance determined by polygenes. It has been found that various genes cause the disease. In a small fraction of patients (<5%), the disease may be attributed to a single gene. For instance, patients having homozygous deficiencies of some parts of complement have a danger of evolving SLE or a lupus-like disease [124]. But majority of the patients require multiple genes. Researches have proved that it is estimated that at least four sensitive genes are required for the formation of the disease [125, 126]. In addition, many other types of genes, especially polymorphic non-MHC genes have been reported to occur in SLE, especially genes that encode mannose-binding protein (MBP), tumour necrosis factor  $\alpha$ , the T cell receptor, interleukin 6 (IL-6), CR1, immunoglobulin Gm and Km allotypes, Fc $\gamma$ RIIA and Fc $\gamma$ RIIA (both IgG Fc receptors), and heat shock protein 70 [127, 128].

SLE patients have imperfect removal of immune complexes by phagocytic cells [129]. This is due to the decreased numbers of CR1 receptors for complement and defective receptors on cell surfaces [32, 33]. It has also been found from a recent study that non-inflammatory swallowing up of apoptotic cells is damaged in patients with SLE [130].

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