

1

What is systemic lupus erythematosus?

→ Key points

- ◆ Systemic lupus erythematosus, though first ‘named’ in 1851, has existed long before that.
- ◆ It involves the internal organs, as well as the skin.
- ◆ It is usually classified or diagnosed on the basis of criteria established by the American College of Rheumatology.
- ◆ As well as ‘classical’ clinical features, e.g. photosensitive skin rash, it is also linked to characteristic blood-test abnormalities (e.g. anti-dsDNA antibodies).

The word lupus comes from the Latin meaning wolf and, although rather fanciful, the red and occasionally very unpleasant rashes that may occur on the faces of patients with lupus were said to be reminiscent of a wolf devouring the flesh. Opinions differ as to how long the term has been used, but one suggestion proposes that a monk, Herbernus of Tours, was the first to use it approximately a thousand years ago. Initially, the term seems to have been used in a rather random way but in the last five hundred years it has largely been reserved for skin rashes affecting the face.

The first really clear-cut description of ‘discoid’ (literally in the round shape of a disc) lupus was that of Laurent Biott in Paris in 1833 (see Table 1.1) and it was his compatriot Pierre Cazenave who first coined the term lupus erythematosus in 1851. For some time thereafter, confusion persisted with the use of the term lupus vulgaris, which is actually a skin rash due to tuberculosis.

Table 1.1 The history of lupus

460–370 BC	Herpes esthiomentoas of Hippocrates. Probably a synonym for SLE – according to Lusitanus (AD 1510–68).
AD 916	Herbernus of Tours in his 'Miracles of St Martin' used the term lupus in a description of the healing of Eraclius.
1230–1611	Rogerius (c.1230), Paracelsus (1493–1541), Manardi (c.1500), Sennert (1611) all credited with mentioning lupus in their writings.
1845	Hebra first likened the facial rash to a butterfly shape.
1851	Cazenave used the term 'lupus érythémateux', distinguishing it from three other types of lupus.
1872	Kaposi recognizes lupus as a systemic disease.
1904	Jadassohn in Vienna published a 125-page review clearly distinguishing discoid (skin only) and systemic lupus.
1924	Libman and Sacks described an endocarditis now recognized as a form of SLE.
1935	Baehr, Klemperer, and Shirfrin reported structural changes in the glomerulus of lupus patients.
1941	Klemperer, Pollack, and Baehr coined the term 'diffuse connective tissue disorder'.
1948	Discovery of the LE cell test by Hargreaves, Richmond, and Marks.
1949	Thorn and colleagues used cortisone therapy.
1951	Page employed quinacrine (mepacrine), an antimalarial drug, to control lupus with dermal lesions.
1954	Dustan, Taylor, Corcoran, and Page observed that hydralazine could induce LE cells: probably the first report of drug-induced lupus.
1957–58	Friou and colleagues described anti-nuclear antibodies in SLE sera.
1959	Bielschowsky, Helyer, and Howie derived the NZB mouse, the first mouse model of lupus.
1969	Koffler and colleagues correlated immunofluorescent staining patterns of the glomeruli with degree of proteinuria.
1971	American Rheumatism Association published criteria for classification of SLE (revised in 1982 and in 1997).
1976	The first suggestion of Urowitz and colleagues of a link between SLE and atherosclerosis.

(continued)

Table 1.1 The history of lupus (*continued*)

1980–83	Schwartz, Stollar, and colleagues dissected the spectrum of autoantibody-producing cells in both autoimmune mice and humans with SLE.
1980–90	Physicians at the National Institutes of Health, including Klippel, Plotz, and Steinberg, demonstrated the use of combinations of prednisolone and intravenous cyclophosphamide given as boluses for the treatment of severe, especially renal, disease. Hughes, Harris, and colleague identified the important clinical associations of anti-phospholipid antibodies.
1987–93	Combined international efforts undertaken to compare and validate disease activity indices, e.g. BILAG, SLAM, SLEDAI.
1996	Systemic Lupus International Collaborating Clinics (SLICC) agree a validated damage index for SLE.
2000	The first use of a biological agent (rituximab) in the treatment of a lupus patient at University College London.

It was an English physician, Hutchison, in 1873 who first drew attention to the photosensitive nature of the lupus rash. By the early twentieth century, lupus was clearly distinguished as a disease in its own right, occurring in two major forms of discoid, in which only the skin is involved, and systemic, in which the internal organs as well as the skin are affected. The original link between skin and internal-organ disease was made in Vienna in 1872 by Moritz Kaposi.

Fact

The immune system consists of an army of white blood cells and other cells found in the bloodstream and the body's tissues. Its principal function is to protect the body against invading pathogens, such as viruses and bacteria.

Fact

Moritz Kaposi is the same Kaposi after whom a form of skin cancer, once rare but now more frequently seen in association with patients who have AIDS, was named.

This historical description does not, however, define the nature of the disease that we now recognize. Systemic lupus erythematosus (SLE) is the consequence of inflammation resulting from an attack by the immune system on the patient's own body, including, ironically, against the immune system itself! There is a simple analogy that helps to explain this. Under normal circumstances whenever we eat, breathe or drink, millions of these pathogens enter our body and, rather like a radar system, the immune system is able to 'scan' and spot these invaders, distinguish them as foreign, i.e. not part of the body, surround and destroy them. The ability to distinguish the body's own tissues (i.e. self), from these invaders (i.e. non-self), is critical to the body's survival. By analogy, during the two Gulf Wars, the American troops at night, on several occasions, shot and killed some of their own forces because in the darkness the troops could not easily distinguish their side ('self') from the enemy ('non-self'). The popular press dubbed this phenomenon 'friendly fire'. This is a good way to look at autoimmune (self-destructive) diseases in general. If the autoimmune attack is directed against the pancreas, the consequence is diabetes; if the attack is directed against parts of the nervous system, the result is multiple sclerosis, and if it is against the adrenal gland, Addison's disease results (Fig. 1.1). The attack against the body's own immune system that occurs in SLE, results in a wide variety of clinical problems ranging from rashes to convulsions, from arthritis to mouth ulcers. No organ or system within the body is entirely safe, although some, notably the skin and joints, are much more frequently affected than others such as the liver or eye.

The vast majority of patients who develop lupus are women (around 90%) and most do so after the onset of periods and before the menopause (thus between 15 and 50 years). However, children and those over 50 may, less frequently, also develop the disease. In these categories, the ratio of females to males is lower – approximately 4:1. The numbers of patients in different ethnic groups also varies. A study in England reported around 40 cases in 100 000 of the Caucasian population; close to 100 per 100 000 in the Asian population (from India, Pakistan and Bangladesh) and just over 200 per 100 000 in the Black population. The figures for Chinese and Hispanic populations are around that of the UK Asian group. Many 'lupus doctors' believe that the disease is more severe in the Black and Chinese populations.

The American College of Rheumatology have produced a set of classification criteria, which are set out in Table 1.2. In order to make a diagnosis of lupus, it is generally accepted that four of these classification criteria should be present. The four (or more) features do not have to be present simultaneously. For example, a patient aged 19 may present with joint pain and swelling (arthritis), have a low white-cell count and a positive antinuclear antibody

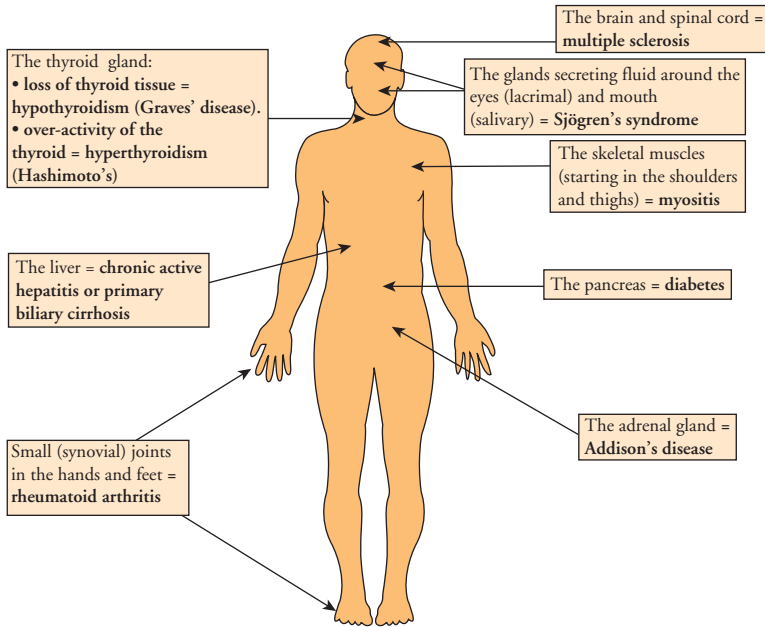


Figure 1.1 Some examples of autoimmune disease – ‘sites of attack’.

test (all features suggestive of lupus), but the formal diagnosis must await the development of a fourth feature, say crops of mouth ulcers, which might not appear for another year.

The frequency with which the different clinical features listed as classification criteria, and other commonly observed problems, varies between ethnic groups. For example, white lupus patients are more likely to be sensitive to the light (photosensitive) and thus to develop lupus rashes on a hot summer's day, whereas Black lupus patients have a greater risk of developing kidney involvement.

These criteria also include a number of possible blood-test abnormalities. These include some relatively simple problems, such as a reduction in the number of total white blood cells (leucopenia) and, in particular, a fall in the number of lymphocytes (lymphopenia). In addition, some antibodies (a type of protein described in more detail in Chapter 4), generally known as autoantibodies as they attack the body's own tissues, are key features of SLE.

Table 1.2 Autoimmune rheumatic disease

Criteria of the American Rheumatism Association for the Classification of SLE
1. Malar rash.
2. Discoid rash.
3. Photosensitivity.
4. Oral ulcers.
5. Arthritis.
6. Serositis. Pleuritis. Pericarditis.
7. Renal disorder. Proteinuria >0.5 g/24 h or 3+, persistently. Cellular casts.
8. Neurological disorder. Seizures. Psychosis (having excluded other causes, e.g. drugs).
9. Haemolytic disorder. Haemolytic anaemia. Leucopenia or $<4.0 \times 10^9/l$ on two or more occasions. Lymphopenia or $<1.5 \times 10^9/l$ on two or more occasions. Thrombocytopenia $<100 \times 10^9/l$.
10. Immunological disorders. Positive LE cell. Raised anti-native DNA antibody binding. Anti-Sm antibody. False-positive serological test for syphilis, present for at least six months.
11. Antinuclear antibody in raised titre.

'... a person shall be said to have SLE if four or more of the 11 criteria are present, serially or simultaneously, during any interval of observation.'

Antinuclear antibodies are present in virtually all patients with SLE, although they may be found in the blood of patients with a variety of other diseases, as well as some healthy individuals. More specific for SLE are anti-double-stranded (ds) DNA antibodies and antibodies to a structure known as the Smith antigen,

the anti-Sm antibodies. Antiphospholipid antibodies are another criterion and are also commonly present in patients with SLE. However, they too are found in other conditions especially the primary antiphospholipid antibody syndrome (which is characterized by a combination of recurrent spontaneous abortion and a tendency to blood clots).

 **Fact**

The Smith antigen is a complex combination of RNA and other material derived from the nucleus of cells.

In the next few chapters of this book we will look in more detail at these clinical features and blood test abnormalities identifying those seen early in the disease and will contrast them to others which appear to be late complications.

