Systemic Lupus Erythematosus:

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease of protean manifestations and variable behavior. Clinically, it is an unpredictable, remitting and relapsing disease of acute or insidious onset that may involve virtually any organ in the body; however, it affects principally the skin, kidneys, serosal membranes, joints, and heart. Immunologically, the disease is associated with an enormous array of autoantibodies, classically including antinuclear antibodies (ANAs).

SLE is a fairly common disease; its prevalence may be as high as 1 case per 2500 persons in certain populations. Like many autoimmune diseases, there is a strong (approximately 9 : 1) female preponderance, affecting 1 in 700 women of childbearing age. The disease is more common and severe in black Americans, affecting 1 in 245 women in that group. Its usual onset is in the second or third decade of life, but it may manifest at any age, including early childhood.

Etiology and Pathogenesis:
The fundamental defect in SLE is a failure to maintain self-tolerance. Consequently, a large number of autoantibodies is produced that can damage tissues either directly or in the form of immune complex deposits. Understanding the nature of these antibodies is important for diagnosis and for understanding the pathogenesis of the lesions.

Spectrum of Autoantibodies in SLE:

1. Antinuclear Antibodies: ANAs are directed against several nuclear antigens and can be grouped into four categories: (1) antibodies to DNA, (2) antibodies to histones, (3) antibodies to nonhistone proteins bound to RNA, and (4) antibodies to nucleolar antigens.

Several techniques are used to detect ANAs. Clinically, the most commonly used method is indirect immunofluorescence, The immunofluorescence test for ANAs is positive in virtually every patient with SLE, so that the test is quite sensitive.
However, it is not specific, because patients with other autoimmune diseases (and 5% to 15% of normal persons) also score positive.

2. Antibodies against blood cells, including red cells, platelets, and lymphocytes, are found in many patients.

3. Antiphospholipid antibodies are present in 40% to 50% of lupus patients and react with a wide variety of proteins in complex with phospholipids.

**Mechanisms of Tissue Injury:**

Regardless of the exact sequence by which autoantibodies are formed, they are clearly the mediators of tissue injury. Most of the systemic lesions are mediated by immune complexes (type III hypersensitivity). DNA/anti-DNA complexes can be detected in the glomeruli, and low serum levels of complement coupled with granular complement deposits in the glomeruli further support the role of immune complexes in the disease. In addition, autoantibodies against red cells, white cells, and platelets promote destruction and phagocytosis of these cells (type II hypersensitivity). There is no evidence that the ANAs involved in immune complex formation can permeate intact cells. However, if cell nuclei are exposed, the ANAs can bind to them. In tissues, nuclei of damaged cells react with ANAs, lose their chromatin pattern, and become homogeneous, to produce so-called LE bodies or hematoxylin bodies. An in vitro correlate of this is the LE cell, a neutrophil or macrophage that has engulfed the denatured nucleus of another injured cell. When blood is withdrawn and agitated, a number of leukocytes are sufficiently damaged to expose their nuclei to ANAs, with secondary complement activation; these antibody- and complement-opsonized nuclei are then readily phagocytosed. Although the LE cell test is positive in as many as 70% of patients with SLE, it is now largely of historical interest.

**Morphology:**

SLE is a systemic disease with protean manifestations. The morphologic changes in SLE are therefore extremely variable and depend on the nature of the autoantibodies, the tissue in which immune complexes deposit, and the course and duration of disease. The most characteristic morphologic changes result from the deposition of immune complexes in a variety of tissues:

1. **acute necrotizing vasculitis** affecting small arteries and arterioles may be present in any tissue. The arteritis is characterized by necrosis and by fibrinoid deposits within vessel walls containing antibody, In chronic stages, vessels show fibrous thickening with luminal narrowing.

2. **Kidney involvement is one of the most important clinical features of SLE,** with renal failure being the most common cause of death. The focus here is on
glomerular pathology, although interstitial and tubular lesions are also seen in SLE.

The pathogenesis of all forms of *glomerulonephritis* in SLE involves deposition of DNA/anti-DNA complexes within the glomeruli. These evoke an inflammatory response that may cause proliferation of the endothelial, mesangial, and/or epithelial cells and, in severe cases, necrosis of the glomeruli. Although the kidney appears normal by light microscopy in 25% to 30% of cases, almost all cases of SLE show some renal abnormality if examined by immunofluorescence and electron microscopy. According to the World Health Organization morphologic classification, there are five patterns of glomerular disease in SLE (none of which is specific to the disease): class I, normal by light, electron, and immunofluorescence microscopy (less than 5% of SLE patients); class II, mesangial lupus glomerulonephritis; class III, focal proliferative glomerulonephritis; class IV, diffuse proliferative glomerulonephritis; and class V, membranous glomerulonephritis.

3. **Joint involvement** is frequent but is usually not associated with striking anatomic changes nor with joint deformity. When present, it consists of swelling and a nonspecific mononuclear cell infiltration in the synovial membranes. Erosion of the membranes and destruction of articular cartilage, such as occurs with rheumatoid arthritis, is exceedingly rare.

4. **Central nervous system (CNS) involvement** is also very common, with focal neurologic deficits and/or neuropsychiatric symptoms

5. The **spleen** may be moderately enlarged. Capsular fibrous thickening is common, as is follicular hyperplasia with numerous plasma cells in the red pulp. Central penicillar arteries characteristically show thickening and perivascular fibrosis, producing **onion-skin lesions**.

6. **Involvement of the heart** is manifested primarily in the form of pericarditis. Myocarditis, in the form of a nonspecific mononuclear cell infiltrate, and valvular lesions, called **Libman-Sacks endocarditis**, also occur but are less common in the current era of aggressive corticosteroid therapy. The valvular **nonbacterial verrucous endocarditis** takes the form of irregular, 1- to 3-mm warty deposits, distinctively on either surface of the leaflets (i.e., on the surface exposed to the forward flow of the blood or on the underside of the leaflet).

**Rheumatoid Arthritis:**
Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease affecting many tissues but principally attacking the joints to produce a **nonsuppurative proliferative synovitis** that frequently progresses to destroy articular cartilage and underlying bone with resulting **disabling arthritis**. When extra-articular involvement develops—for example, of the skin, heart, blood vessels, muscles, and lungs—RA may resemble SLE or scleroderma.
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**Morphology:**

1. **Symmetric arthritis,** principally affecting the small joints of the hands and feet, ankles, knees, wrists, elbows, and shoulders. Typically, the proximal interphalangeal and metacarpophalangeal joints are affected, but distal interphalangeal joints are spared. Axial involvement, when it occurs, is limited to the upper cervical spine; similarly, hip joint involvement is extremely uncommon. Histologically, the affected joints show **chronic synovitis,** characterized by (1) synovial cell hyperplasia and proliferation; (2) dense perivascular inflammatory cell infiltrates (frequently forming lymphoid follicles) in the synovium composed of CD4+ T cells, plasma cells, and macrophages; (3) increased vascularity due to angiogenesis; (4) neutrophils and aggregates of organizing fibrin on the synovial surface and in the joint space; and increased osteoclast activity in the underlying bone, leading to synovial penetration and bone erosion. The classic appearance is that of a **pannus,** formed by proliferating synovial-lining cells admixed with inflammatory cells, granulation tissue, and fibrous connective tissue; the overgrowth of this tissue is so exuberant that the usually thin, smooth synovial membrane is transformed into lush, edematous, frondlike (villous) projections.

2. **Rheumatoid subcutaneous nodules** develop in about one-fourth of patients, occurring along the extensor surface of the forearm or other areas subjected to mechanical pressure; rarely they can form in the lungs, spleen, heart, aorta, and other viscera. Rheumatoid nodules are firm, nontender, oval or rounded masses as large as 2 cm in diameter. Microscopically, they are characterized by a central focus of fibrinoid necrosis surrounded by a palisade of macrophages, which in turn is rimmed by granulation tissue.

**Sjögren Syndrome:**

is a clinicopathologic entity characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), resulting from immune-mediated destruction of the lacrimal and salivary glands. It occurs as an isolated disorder (primary form), also known as the sicca syndrome, or more often in association with another autoimmune disease (secondary form). Among the associated disorders, RA is the most common, but some patients have SLE, polymyositis, systemic sclerosis, vasculitis, or thyroiditis.
Systemic sclerosis(scleroderma):
Although commonly called *scleroderma*, this disorder is better labeled systemic sclerosis (SS), because it is characterized by excessive fibrosis throughout the body and not just the skin. Cutaneous involvement is the usual presenting symptom and eventually appears in approximately 95% of cases, but it is the visceral involvement of the gastrointestinal tract, lungs, kidneys, heart, and skeletal muscles that produces the major morbidity and mortality.

SS can be classified into two groups based on its clinical course:
1. *Diffuse scleroderma*, characterized by initial widespread skin involvement, with rapid progression and early visceral involvement.
2. *Limited scleroderma*, with relatively mild skin involvement, often confined to the fingers and face. Involvement of the viscera occurs late, and hence the disease in these patients generally has a fairly benign course. This is also called the CREST syndrome because of its frequent features of calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia.