Immunopathology 2025’

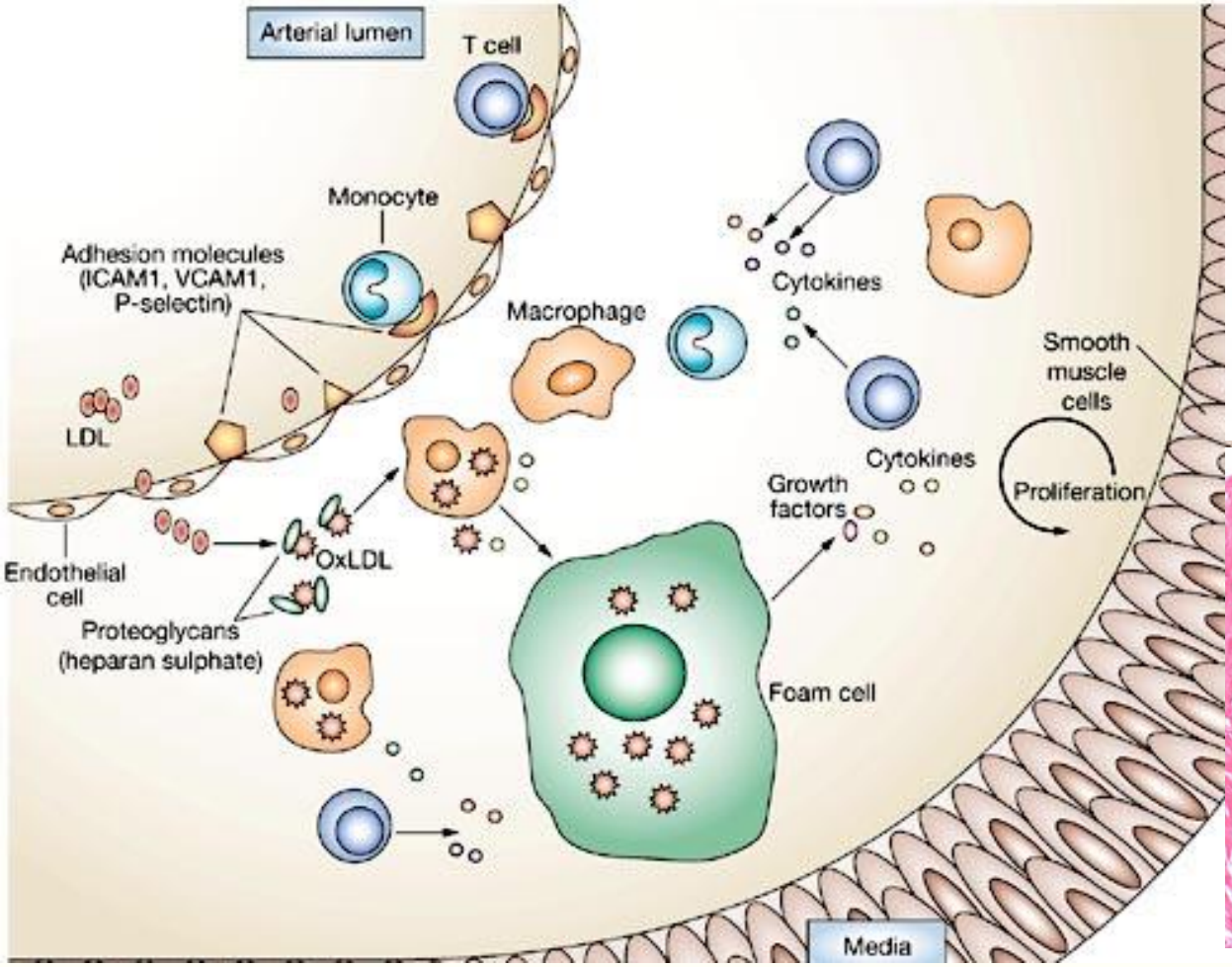
Autoimmunity II.

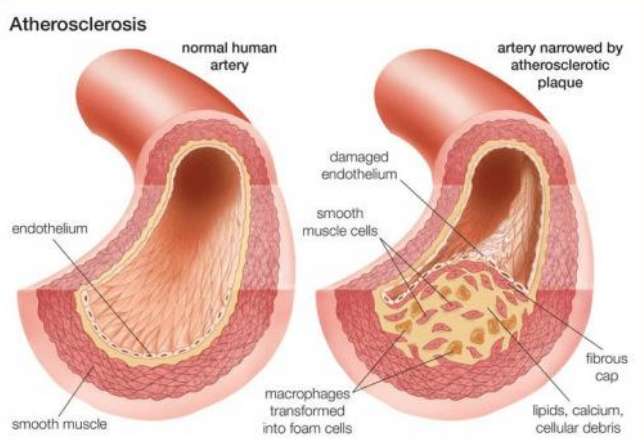
Autoimmune diseases

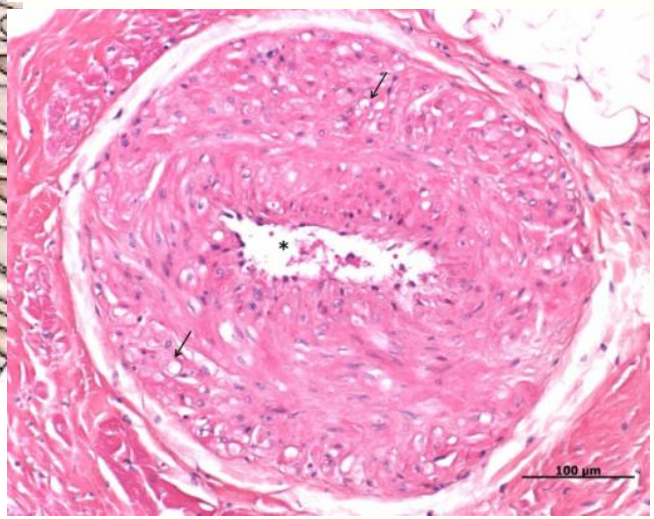
Characteristics of autoimmune diseases

- **Pathological autoimmunity:**

  autoimmune diseases caused by self-reacting inflammatory immune responses resulting **permanent tissue/organ injury**



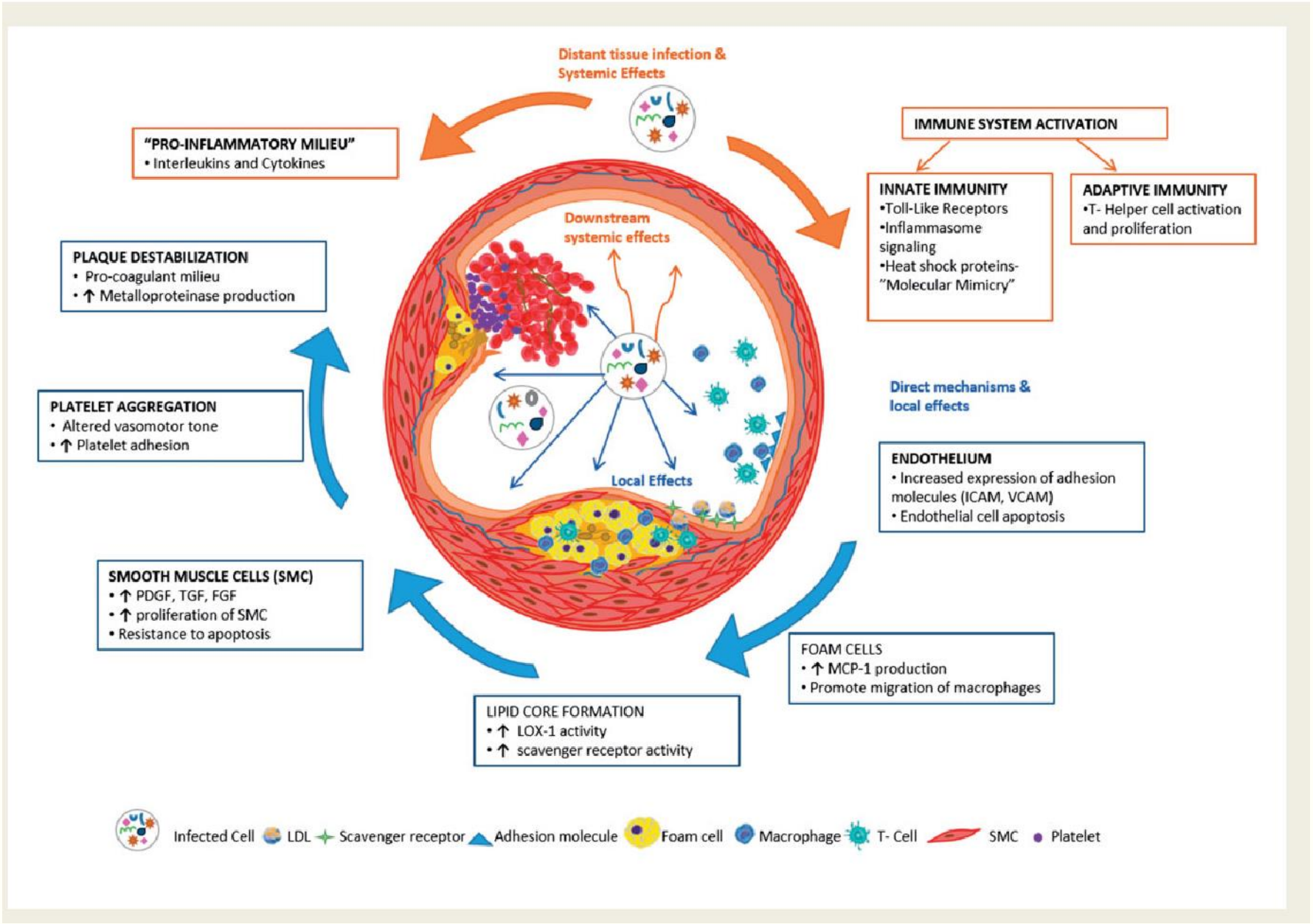


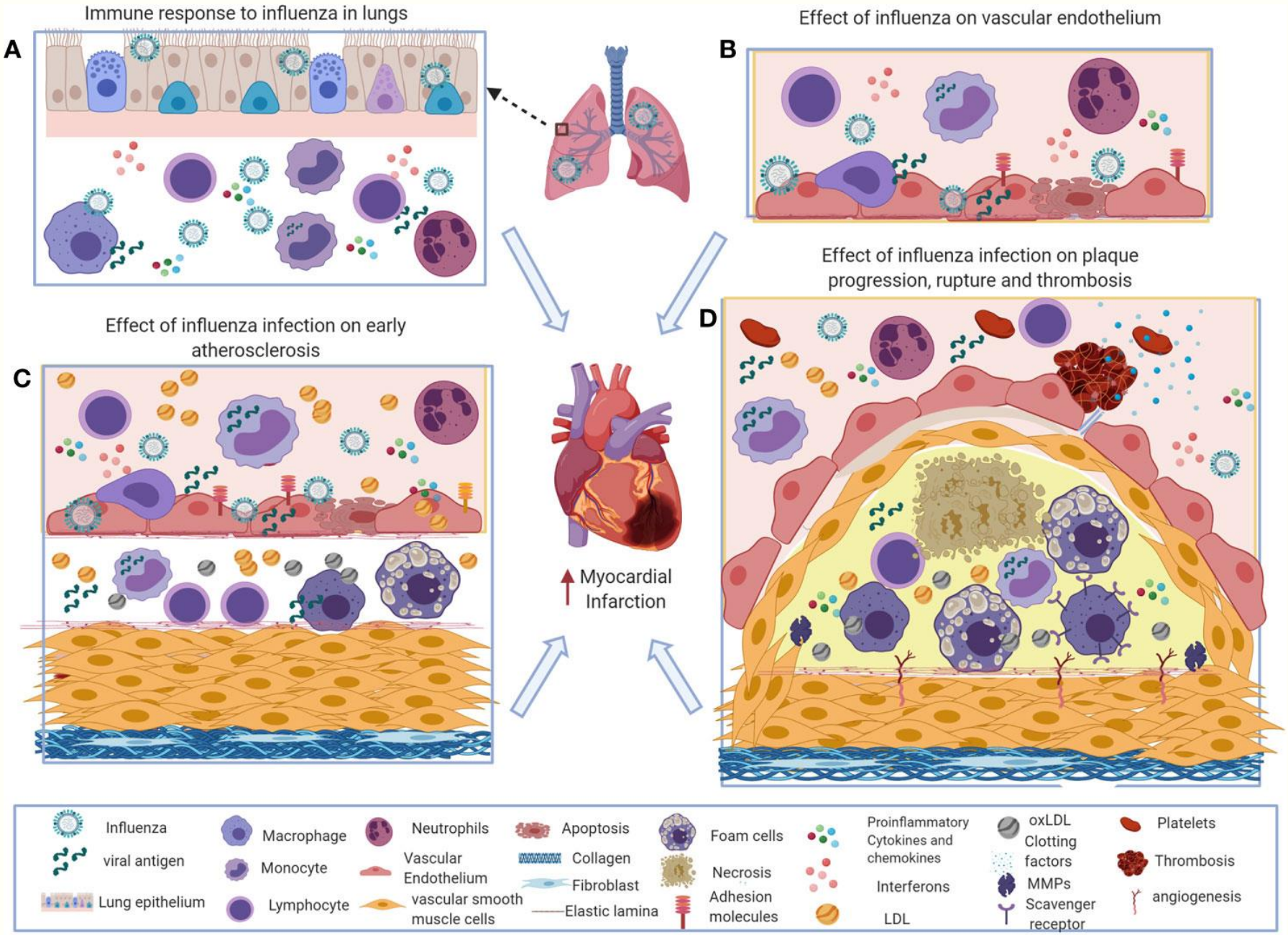


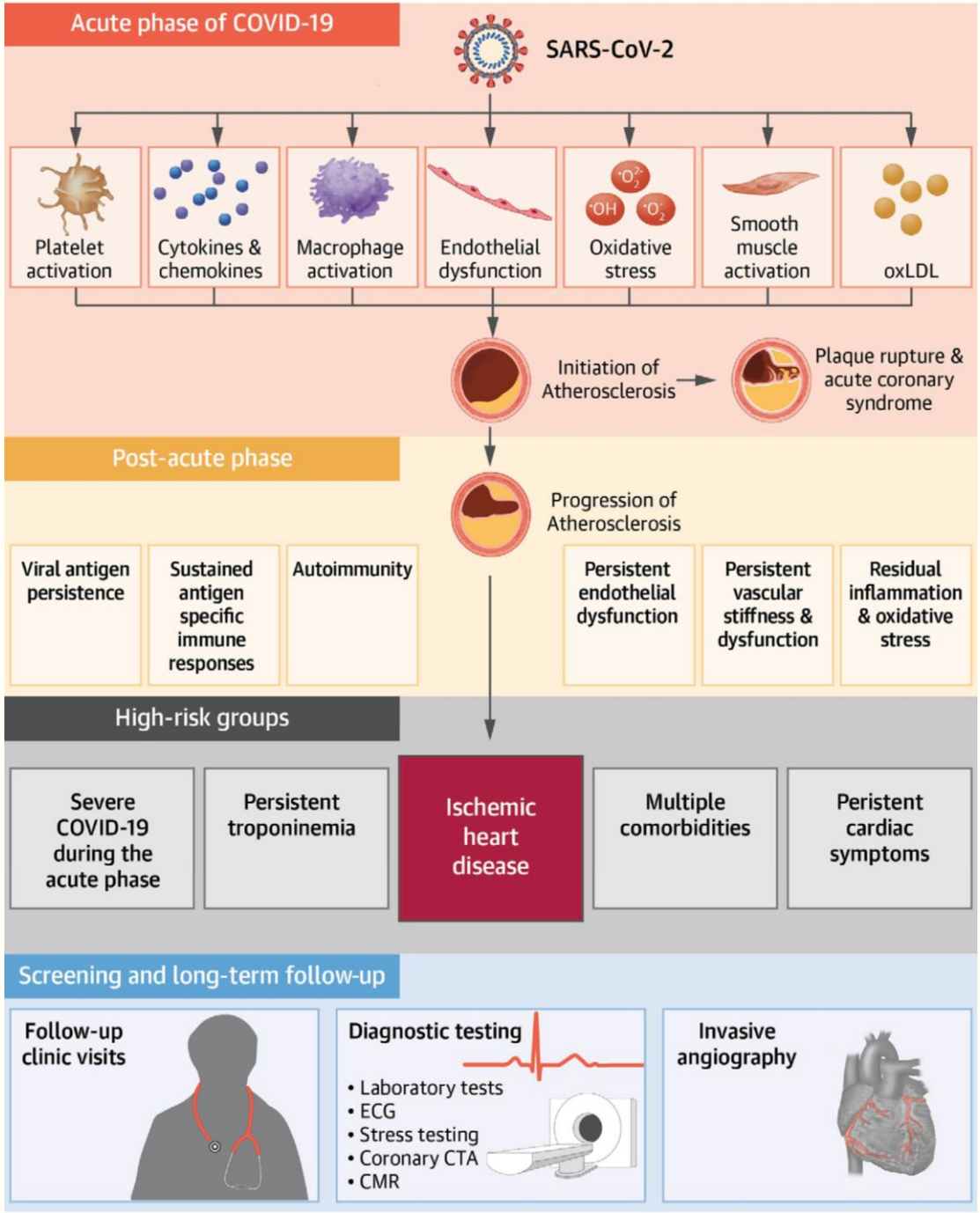
Early in the development of atherosclerosis, low-density-lipoprotein cholesterol becomes oxidized, which results in endothelial cell dysfunction and the expression of vascular cell adhesion molecules and chemokines

In response to these adhesion molecules, monocytes are recruited; these differentiate into macrophages and endocytose (through interactions with scavenger receptors) into the vessel wall. These **macrophages** then take up oxidized low-density-lipoprotein cholesterol and become foam cells, which subsequently produce **growth factors and cytokines that lead to the proliferation of vascular-smooth-muscle cells and the development of plaques**. T cells, predominantly Th1 cells, are also recruited to the subendothelial space where they produce cytokines that can promote a systemic inflammatory response.

Role of infections in development of arteriosclerosis



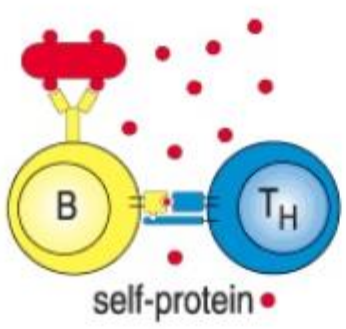

Immune response to influenza in lungs
A
Effect of influenza on vascular endothelium
B
Effect of influenza infection on plaque progression, rupture and thrombosis
D
Effect of influenza infection on early atherosclerosis
C
Myocardial Infarction
Influenza
viral antigen
Lung epithelium
Macrophage
Monocyte
Lymphocyte
Neutrophils
Vascular Endothelium
vascular smooth muscle cells
Apoptosis
Collagen
Fibroblast
Elastic lamina
Foam cells
Necrosis
Adhesion molecules
Proinflammatory Cytokines and chemokines
Interferons
LDL
oxLDL
Clotting factors
MMPs
Scavenger receptor
Platelets
Thrombosis
angiogenesis

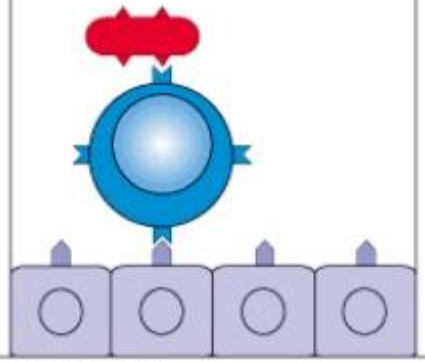

Acute phase of COVID-19
SARS-CoV-2
Platelet activation
Cytokines & chemokines
Macrophage activation
Endothelial dysfunction
Oxidative stress
Smooth muscle activation
oxLDL
Initiation of Atherosclerosis
Plaque rupture & acute coronary syndrome
Post-acute phase
Progression of Atherosclerosis
Viral antigen persistence
Sustained antigen specific immune responses
Autoimmunity
Persistent endothelial dysfunction
Persistent vascular stiffness & dysfunction
Residual inflammation & oxidative stress
High-risk groups
Severe COVID-19 during the acute phase
Persistent troponinemia
Ischemic heart disease
Multiple comorbidities
Peristent cardiac symptoms
Screening and long-term follow-up
Follow-up clinic visits
Diagnostic testing
• Laboratory tests
• ECG
• Stress testing
• Coronary CTA
• CMR
Invasive angiography

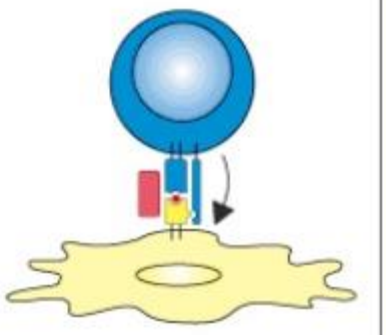
Association of autoimmunity and infections

Infectious organism	*Autoimmune disease*	*HLA-antigen*
Group A Streptococcus	Rheumatic carditis	
Shigella flexneri, Salmonella typhimurium, Yersinia enterocolitica, Campylobacter jejuni	Reactive arthritis	HLA-B27
Borrelia burgdorferi	Chronic arthritis in Lyme disease	HLA-DR2, -DR4
Chlamydia trochomatis	Reiter's syndrome (arthritis)	HLA-B27
Mycoplasma pneumoniae	Autoimmune hemolytic anemia	

Mechanism	Binding of pathogen to self protein	Molecular mimicry	Superantigen
Effect	Pathogen acts as carrier to allow anti-self response	Production of cross-reactive antibodies or T cells	Polyclonal activation of autoreactive T cells
Example	? Interstitial nephritis	Rheumatic fever ? Diabetes ? Multiple sclerosis	? Rheumatoid arthritis







ORGAN-SPECIFIC AUTOIMMUNE DISEASES

Gastrointestinal tract

- pernicious anemia (Biermer anemia)
- autoimmune liver diseases (autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis)

Muscle, nerves and brain

- myasthenia gravis
- polyneuropathies
- Guillain-Barré syndrome
- multiple sclerosis

Eyes

- autoimmune uveitis
- autoimmune retinopathy
- sympathetic ophthalmia

Skin

- vitiligo
- autoimmune bullous diseases
- alopecia areata

Autoimmune cytopenia

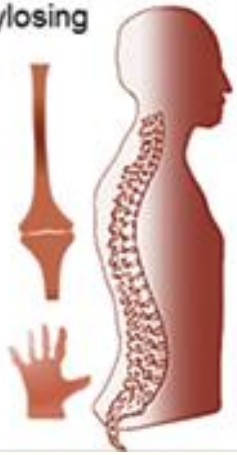
- autoimmune haemolytic anaemia
- autoimmune neutropenia
- autoimmune thrombocytopenia

Endocrine glands

- type 1 diabetes
- autoimmune thyroiditis (Hashimoto's thyroiditis and Graves's disease)
- Addison's disease
- autoimmune polyendocrinopathies

SYSTEMIC OR NON ORGAN-SPECIFIC AUTOIMMUNE DISEASES

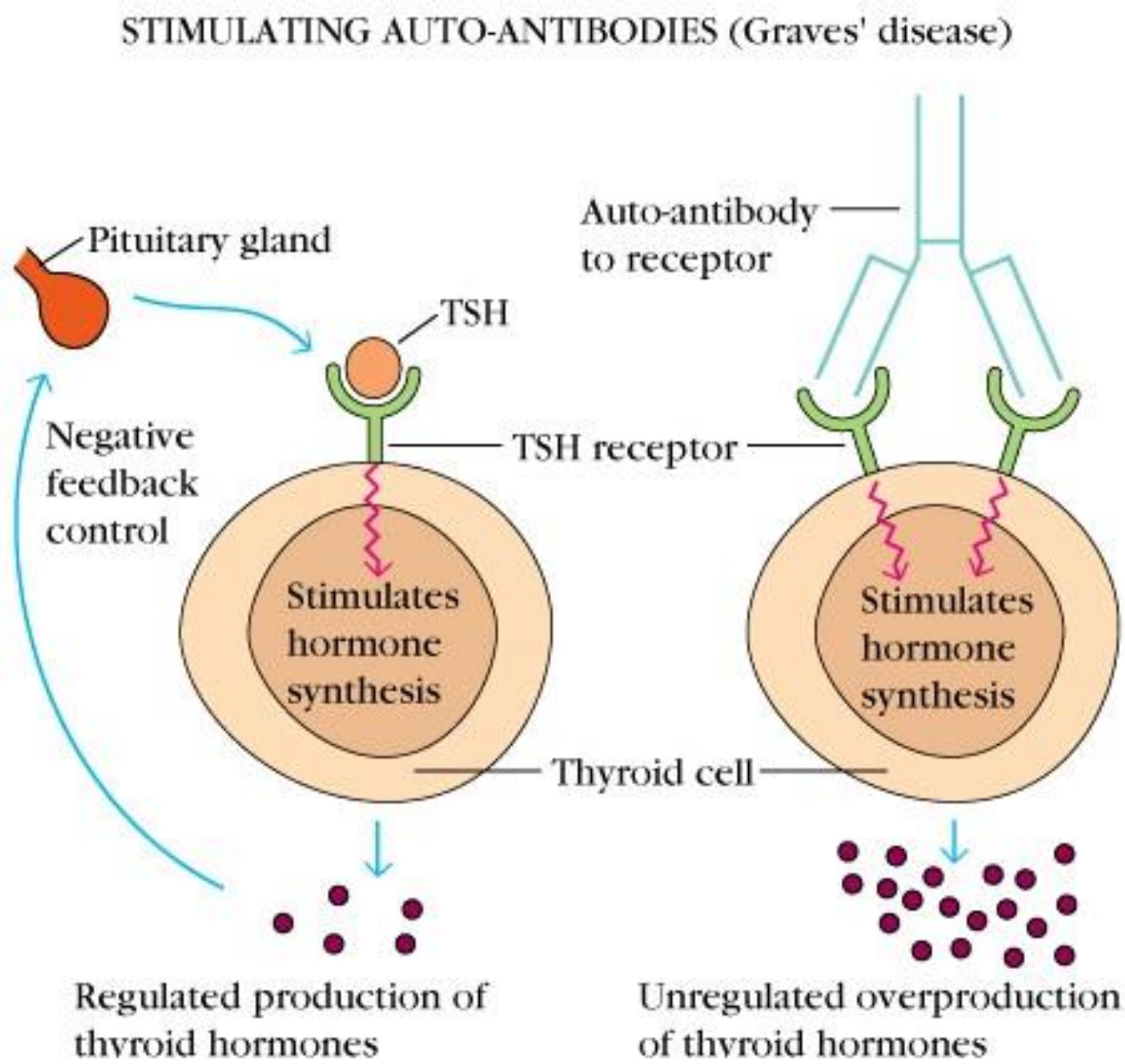
- systemic lupus erythematosus
- Gougerot-Sjögren syndrome
- systemic autoimmune rheumatic diseases (rheumatoid arthritis, ankylosing spondylitis, rheumatic fever, rheumatic heart disease, etc.)
- scleroderma
- polymyositis
- dermatopolymyositis
- mixed connectivity
- primitive vasculitis
- atrophic polychondritis
- antiphospholipid syndrome
- celiac dise ase
- myocarditis



CLINICAL CONTEXT

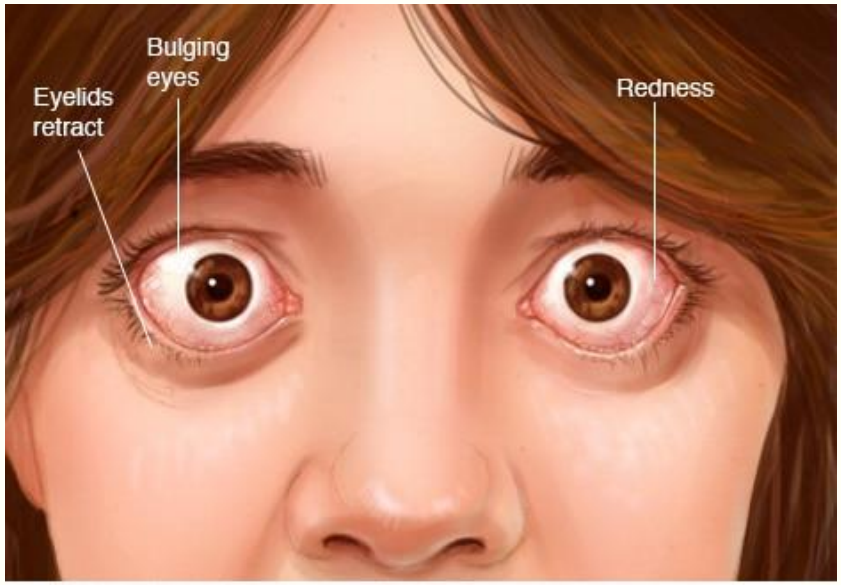
- central neurological/ neuropsychiatric involvement
- peripheral neuropathies
- eye involvement
- lung involvment
- cardiac/muscular involvement
- valvulopathy
- cutaneous vascular involvement
- renal involvement
- joint involvement

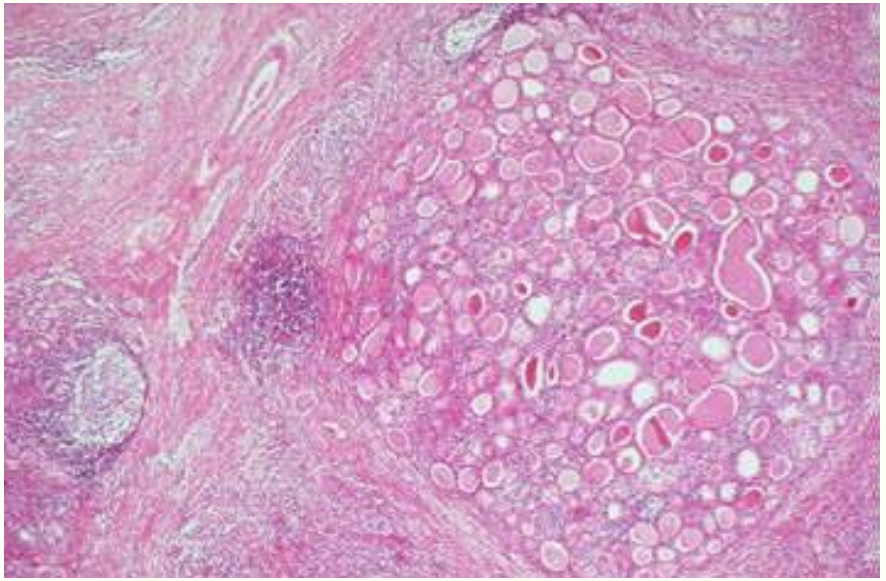
Grave's disease

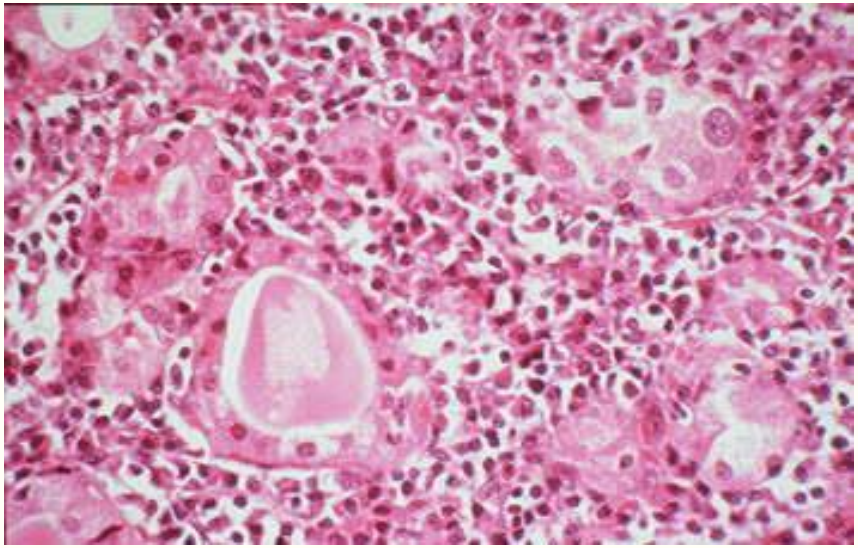


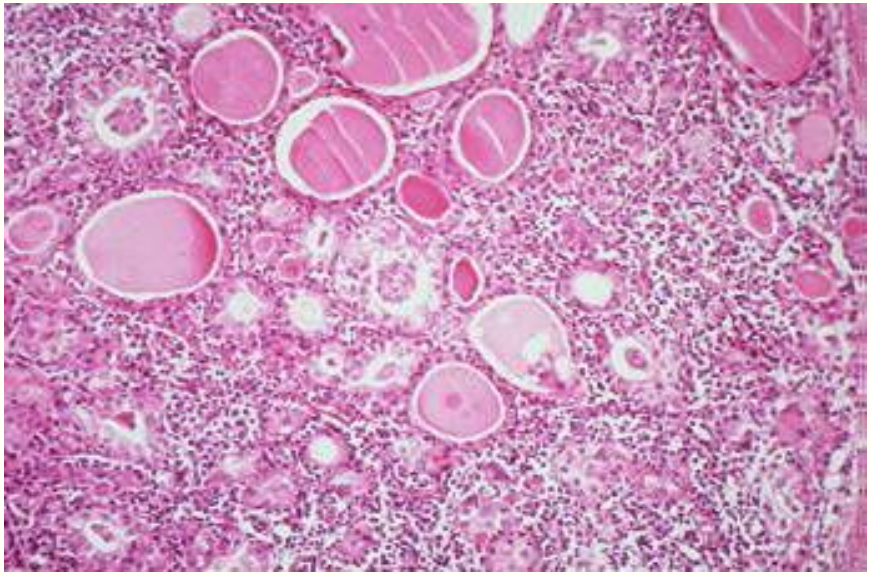
In **Graves' Disease** a patient produces autoantibodies that bind to the receptors for thyroid-stimulating hormone (TSH). TSH is produced by the pituitary gland and the receptors for TSH are present on thyroid cells. Binding of these autoantibodies mimics the normal action of TSH which is to stimulate the production of two thyroid hormones, thyroxine and triiodothyronine. However, the autoantibodies are not under a negative feedback control system and therefore lead to overproduction of the thyroid hormones. For this reason these autoantibodies have been termed **long-acting thyroid-stimulating (LATS) antibodies**. Overproduction of thyroid hormones leads to many metabolic problems.

Grave's disease

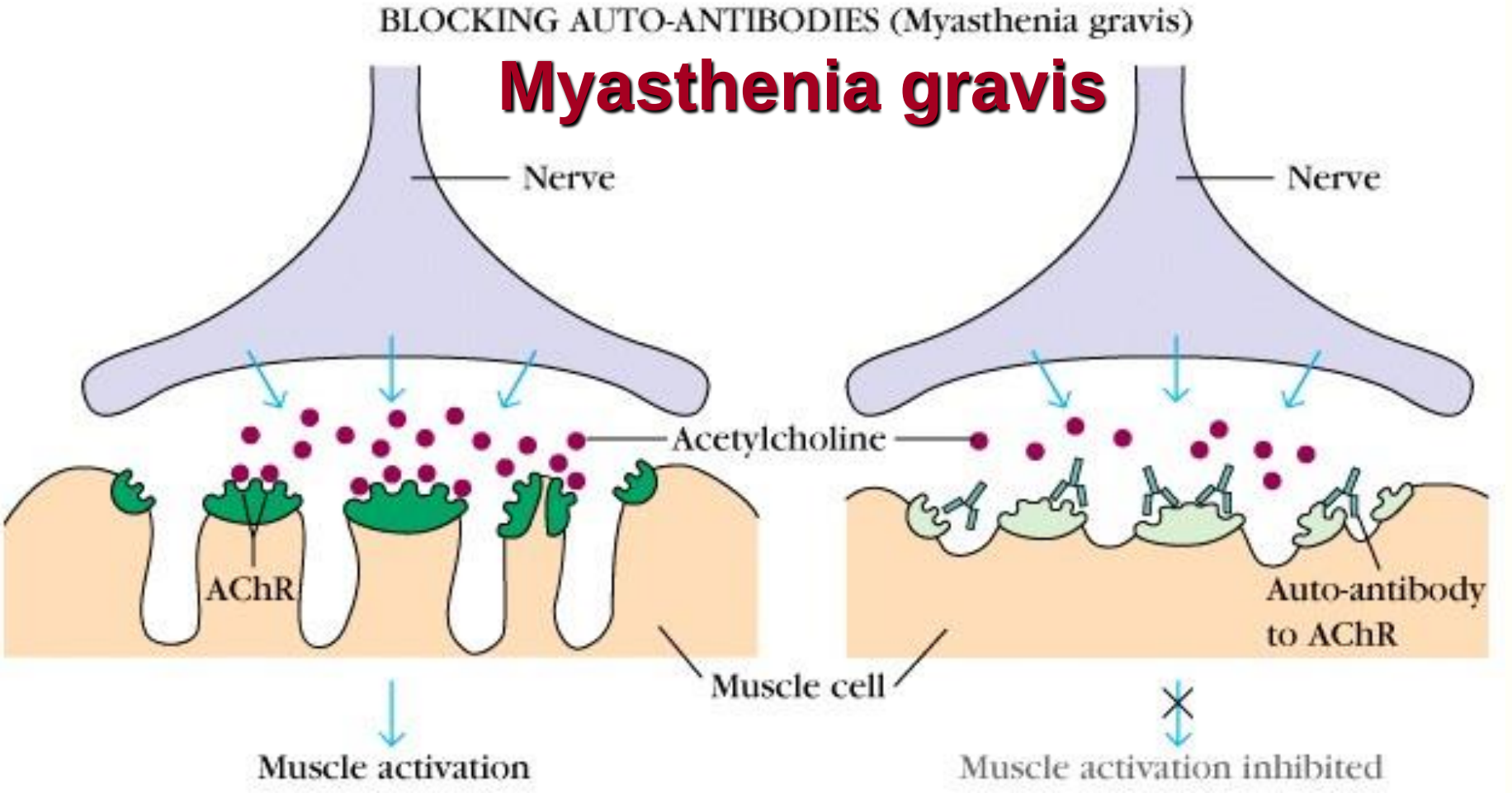






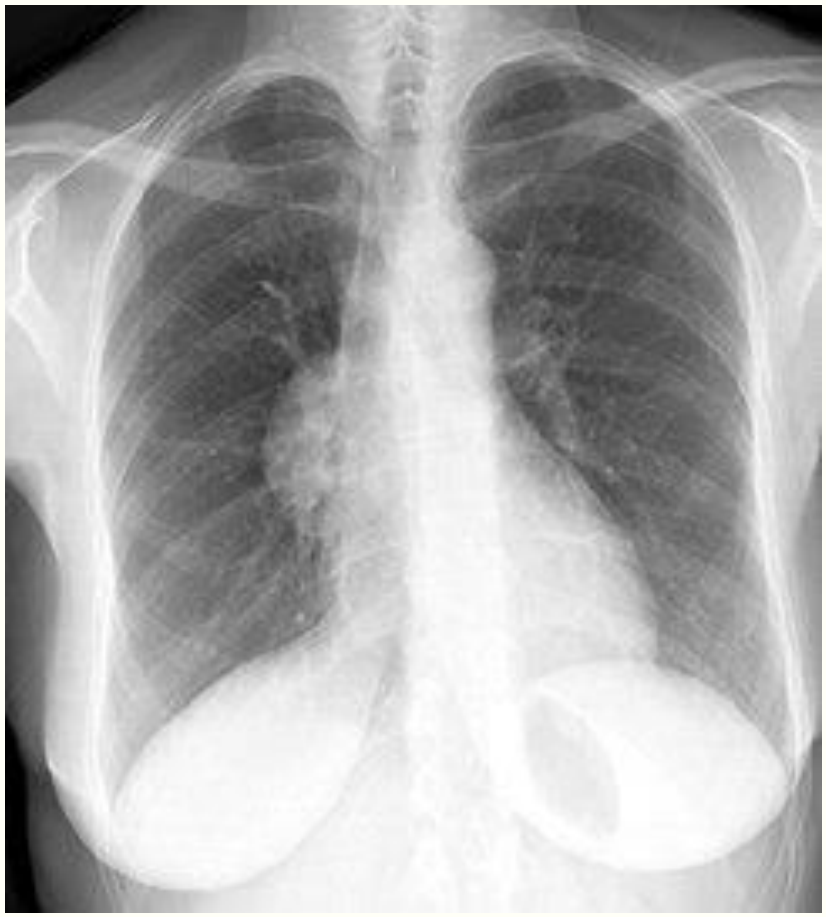


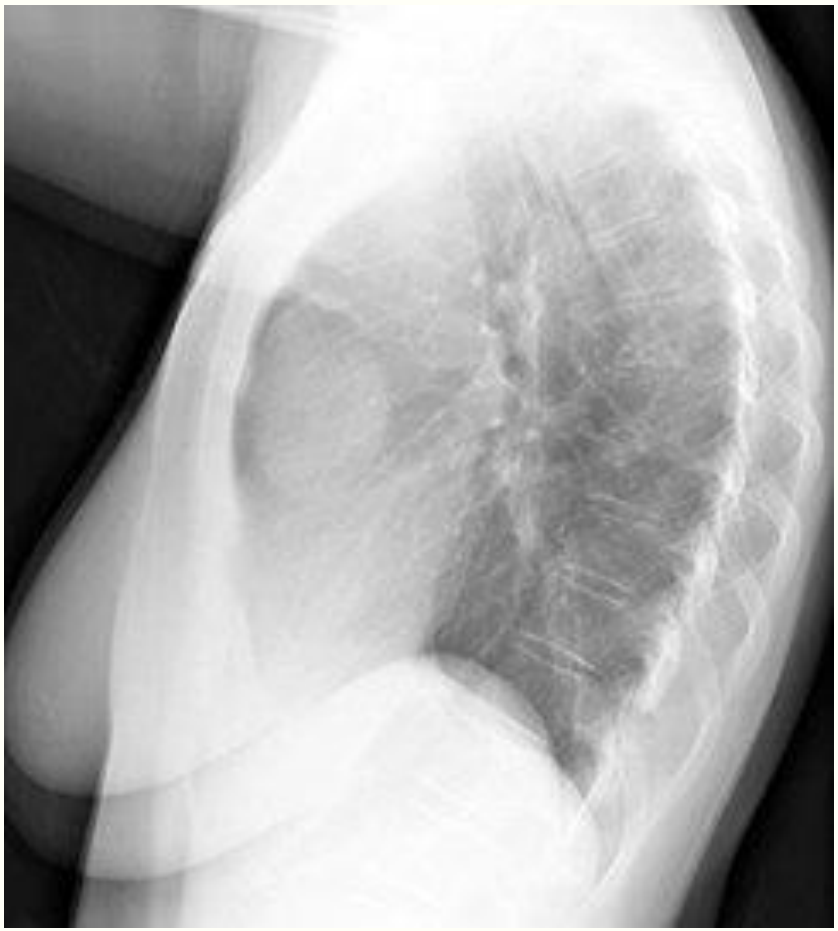
Myasthenia gravis



A patient with this disease produces autoantibodies to the acetylcholine receptors on the motor end-plates of muscles. Binding of acetylcholine in therefore blocked and muscle activation is inhibited. The autoantibodies also induce complement-mediated degradation of the acetylcholine receptors, resulting in progressive weakening of the skeletal muscles.

Myasthenia Gravis

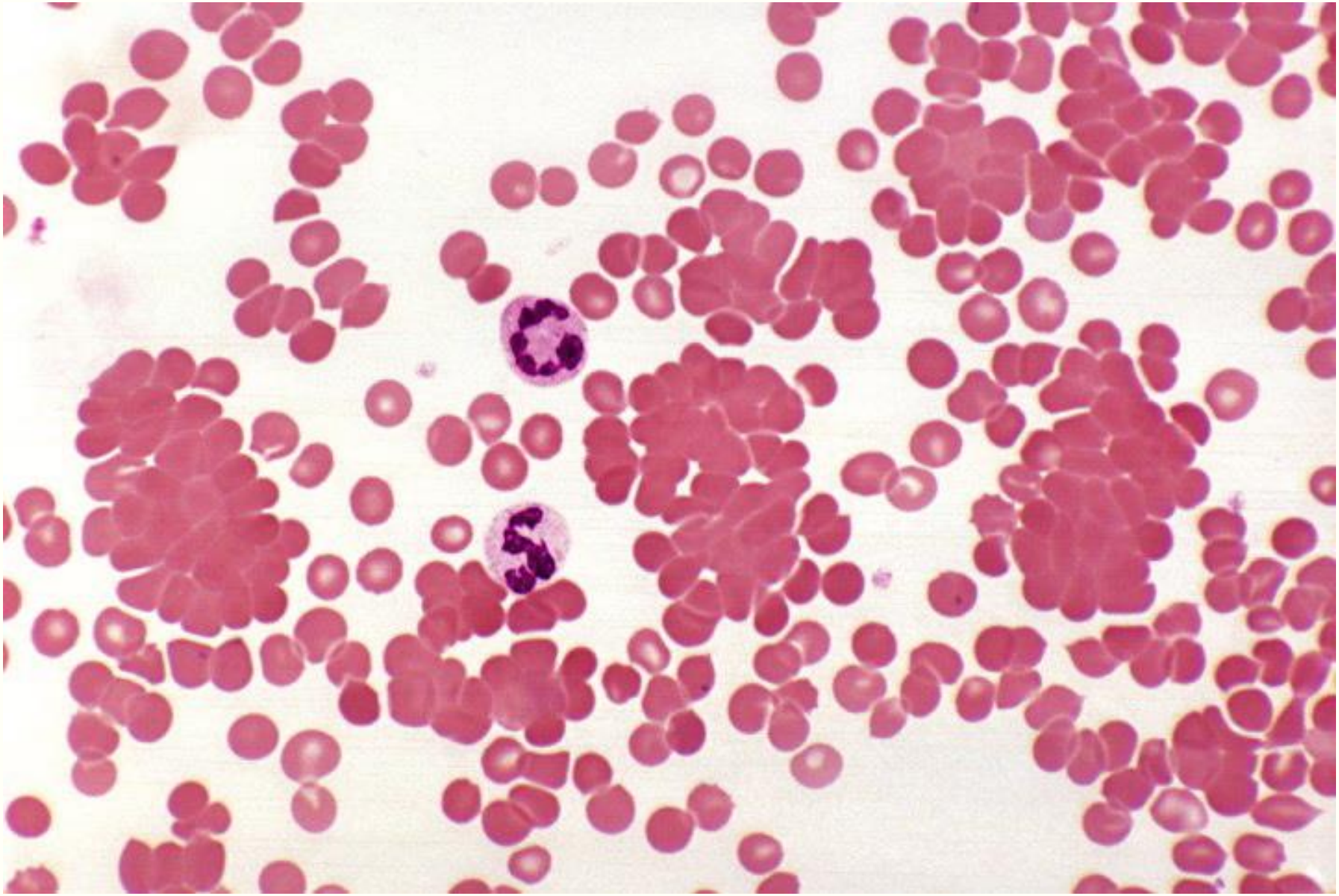




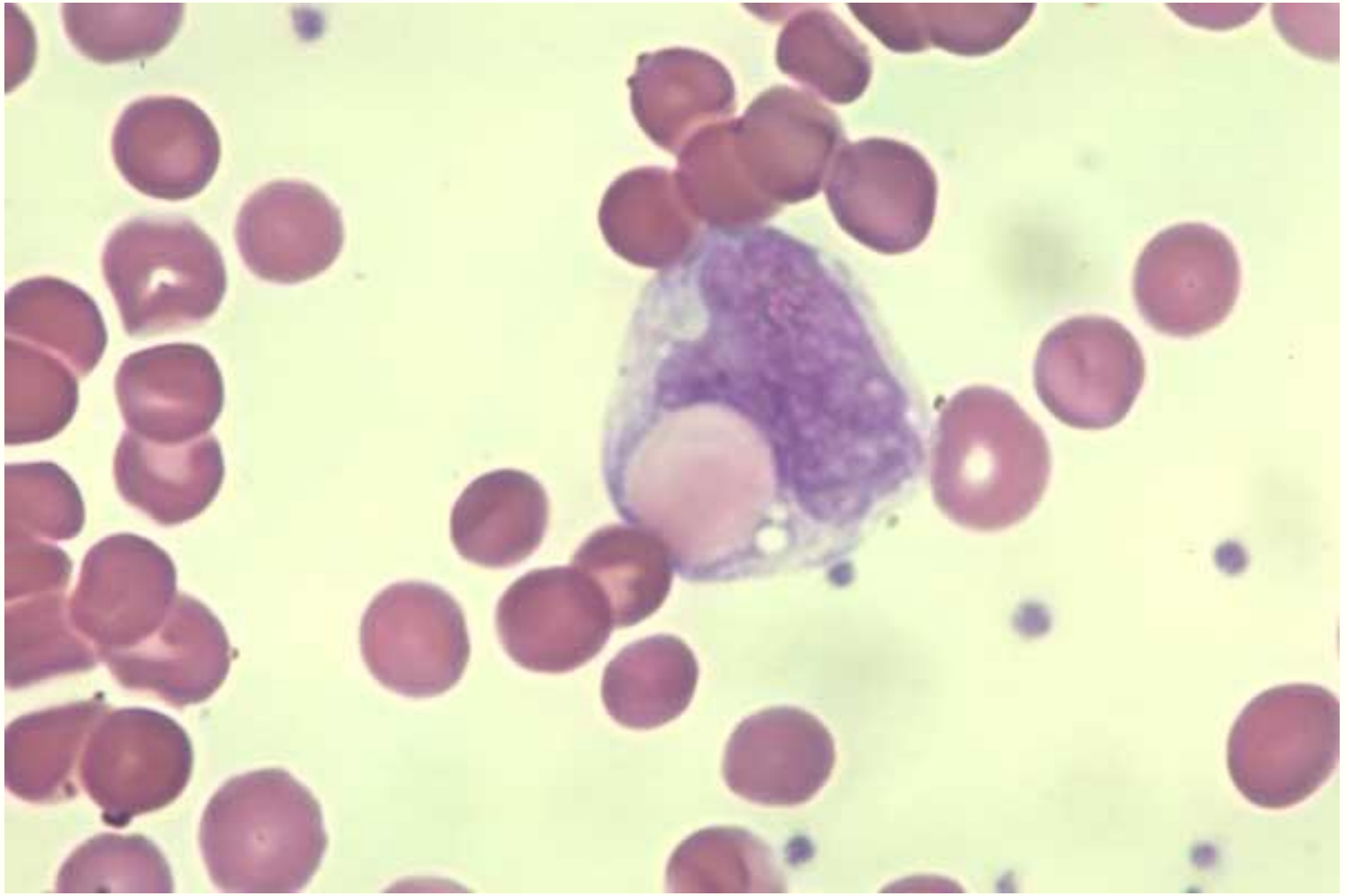
Thymoma in patient with Myasthenia Gravis

Chest X-ray: Right anterior mediastinal mass

Autoimmune hemolytic anemia

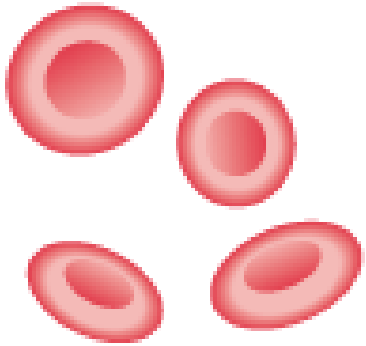


Monocyte with RBC; erythrophagocytosis; many spherocytes; **Autoimmune hemolytic disease** - 100X

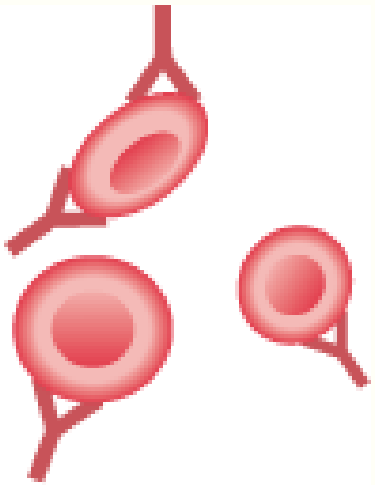


Coombs' test

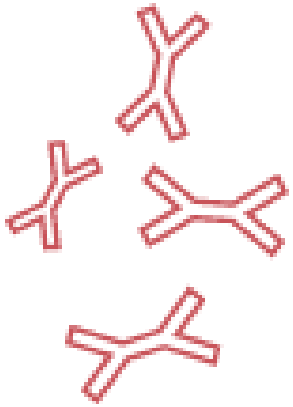
Patient's serum with IgG (Y)



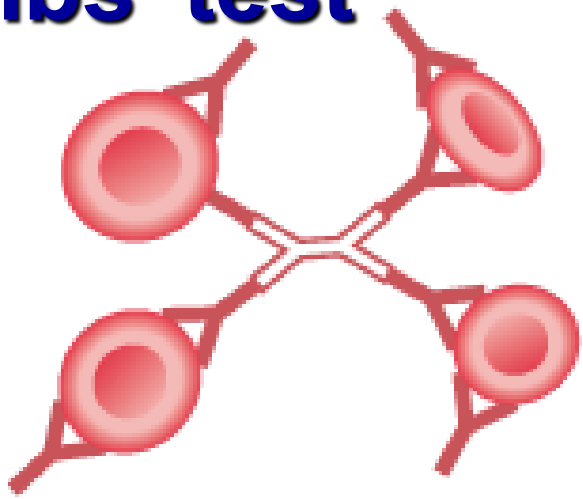
Incubation with reagent RBCs



Binding of any IgG to reagent RBCs

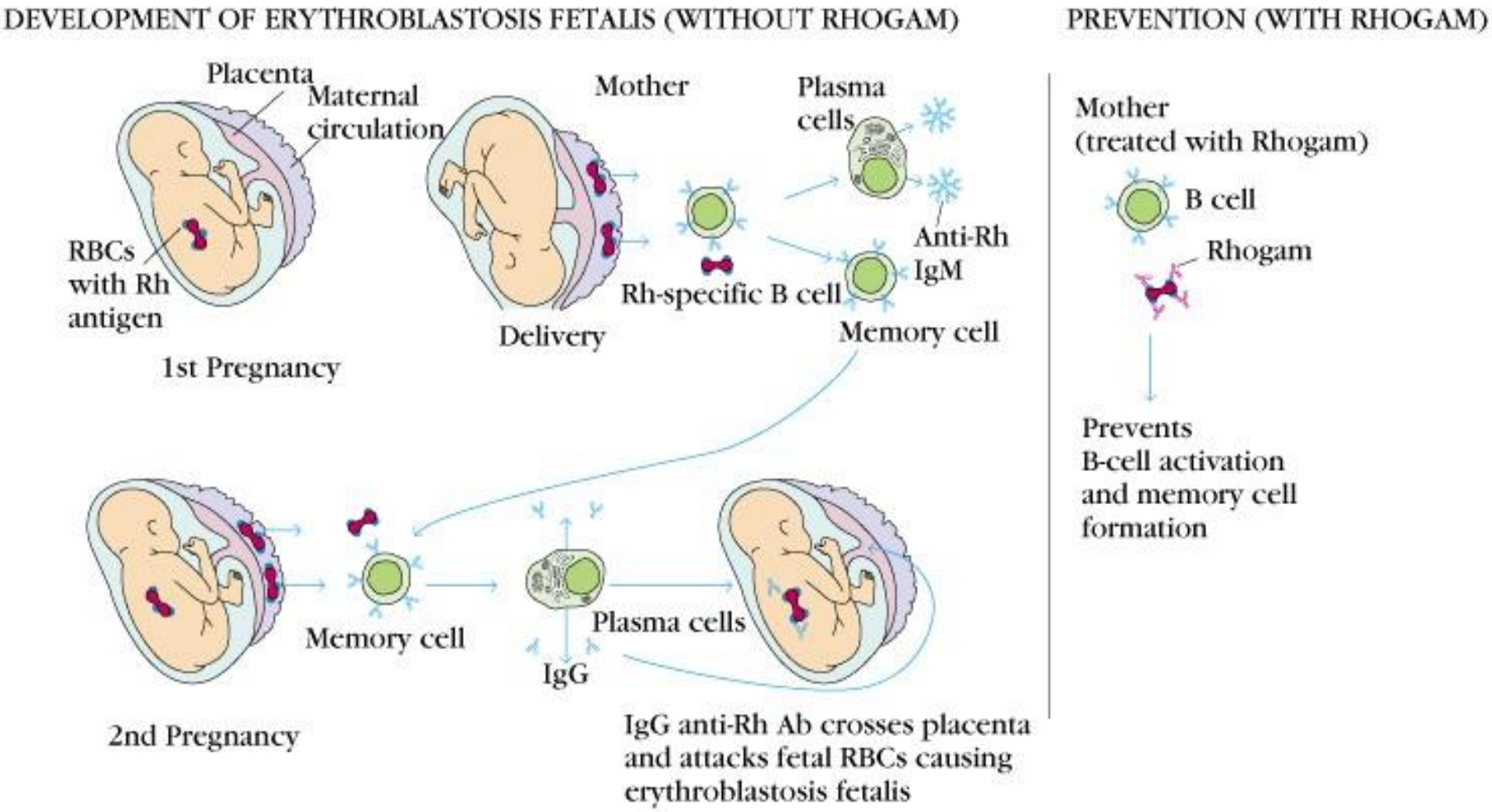


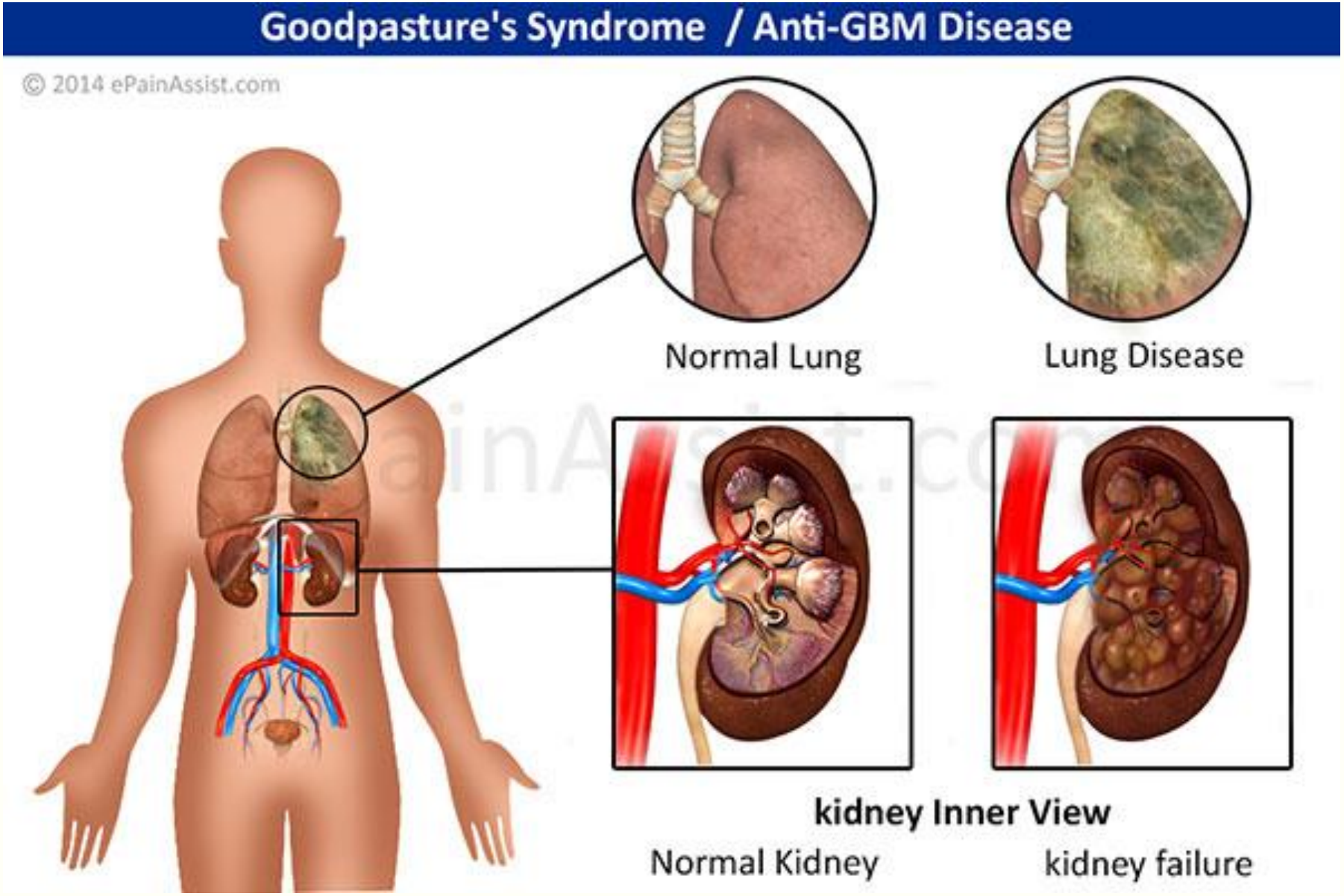
Incubation with antibodies to human Ig (Y)



Agglutination (positive indirect Coombs' test)

Autoimmune hemolytic disease

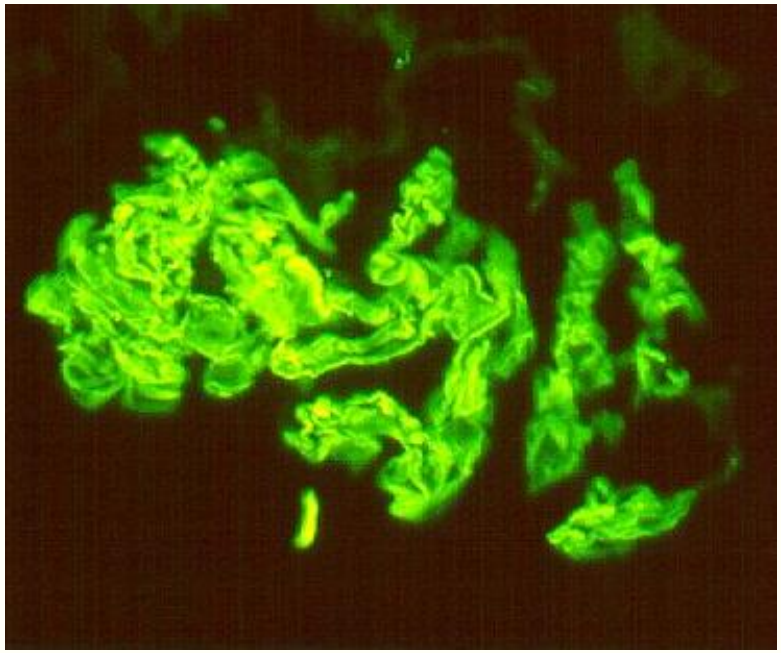


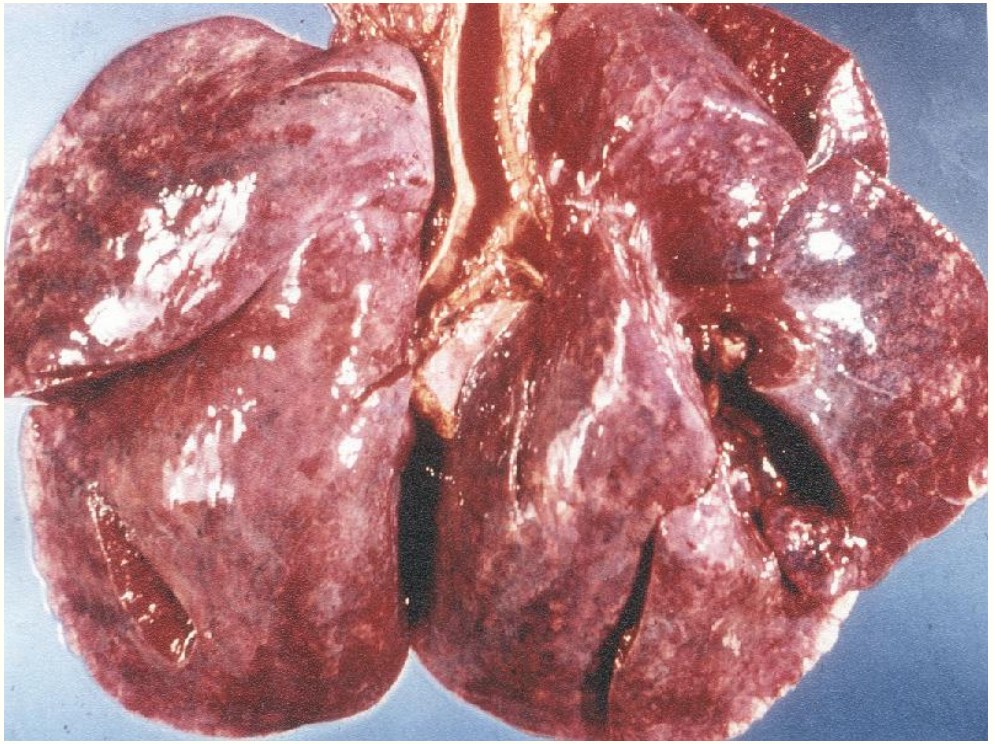


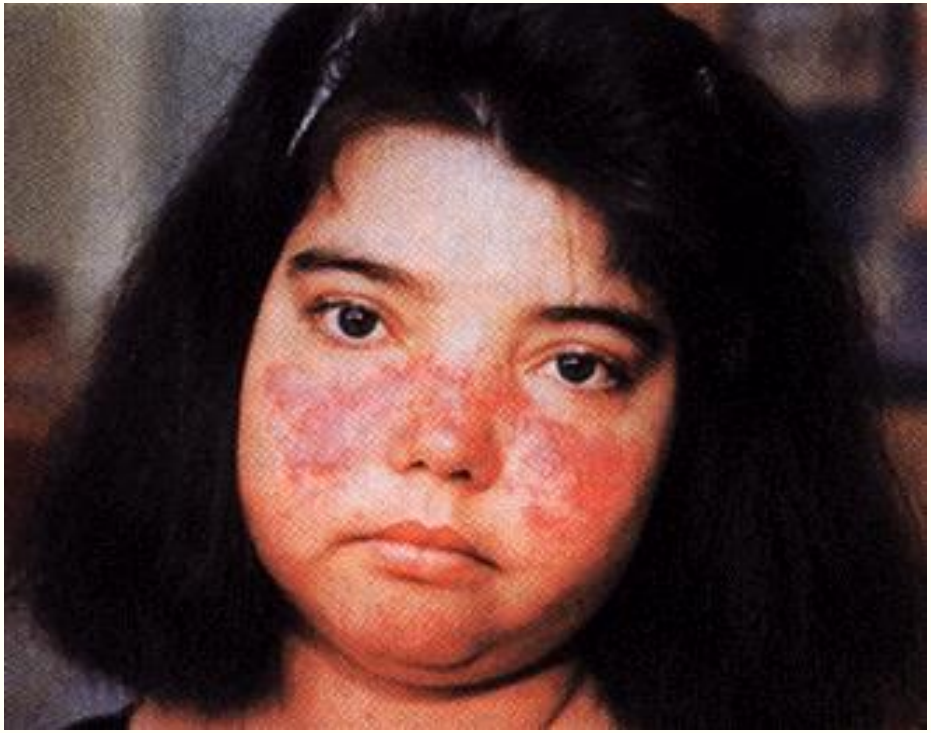
Autoantibodies attack the alpha-3 subunit of type IV collagen in basement membranes of glomeruli and lung alveoli.

Goodpasture syndrom

Goodpasture syndrom

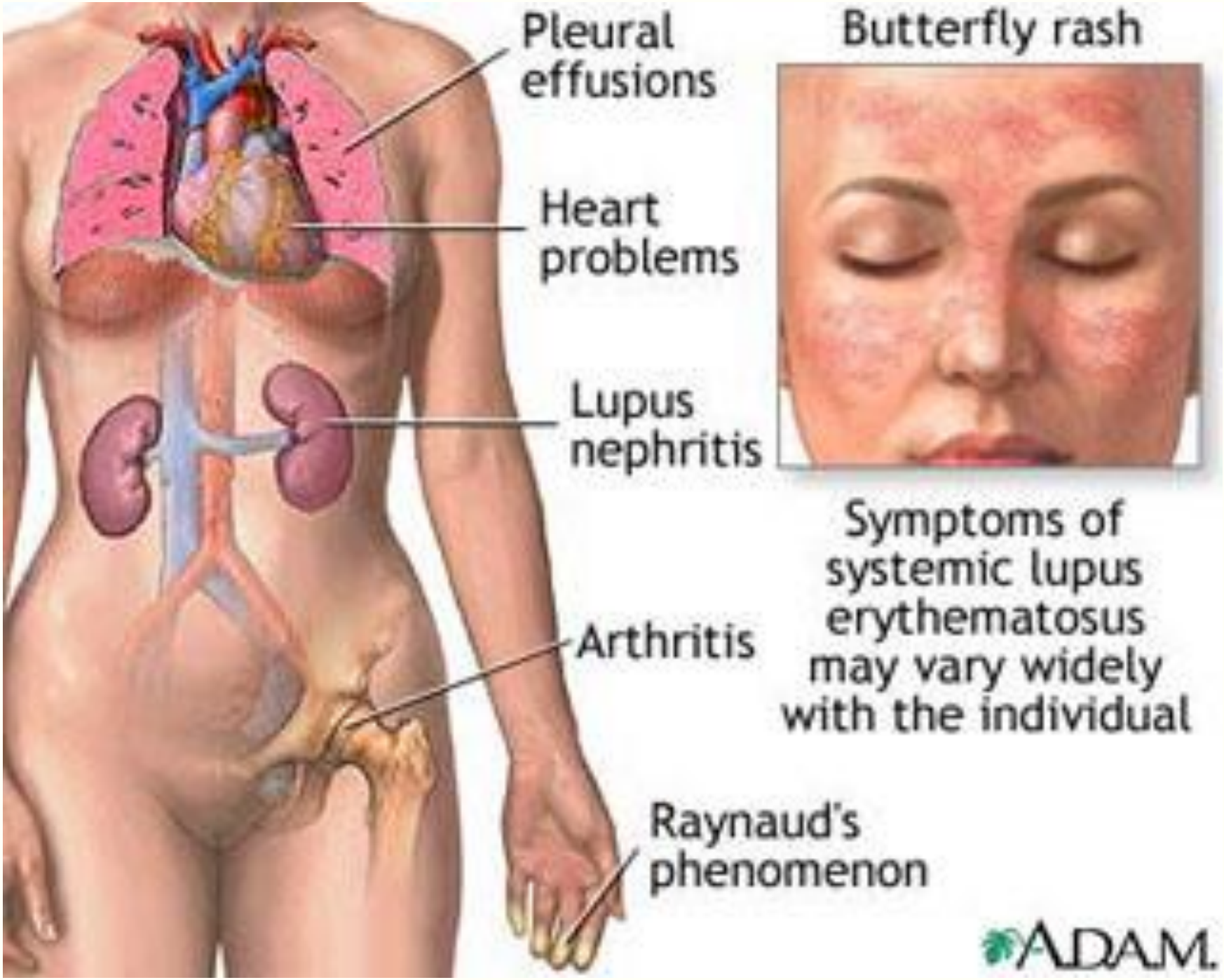




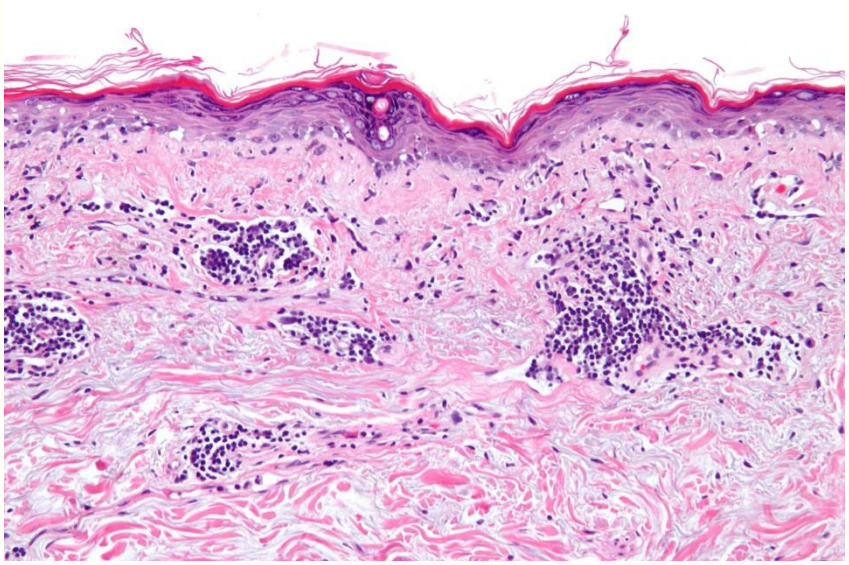


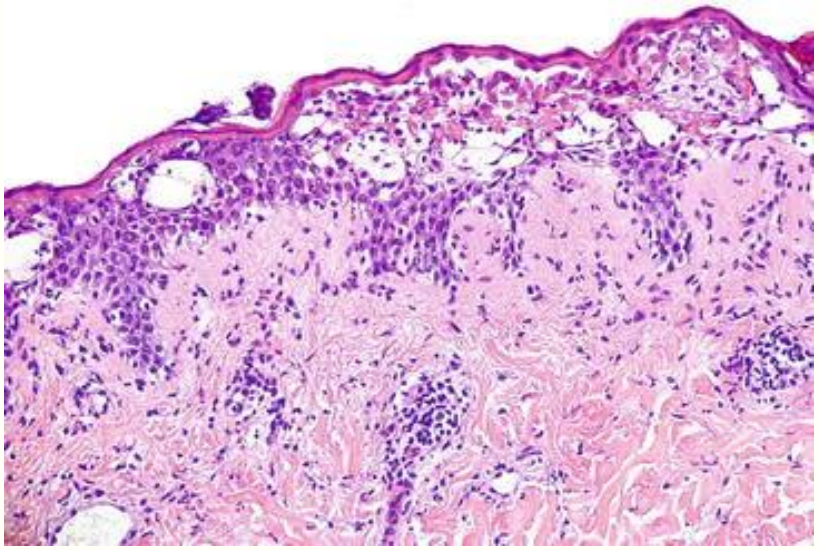
Characteristic "butterfly" rash over the cheeks of a young girl with SLE.

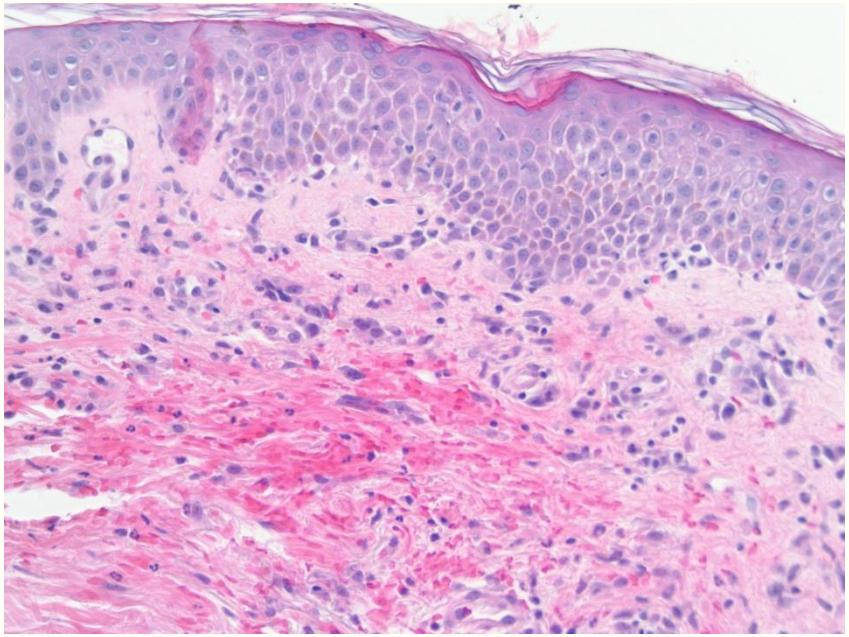
Systemic Lupus Erythematosus (**SLE**) is characterized by fever, weakness, arthritis, skin rashes, pleurisy, and kidney dysfunction. Affected individuals may produce **autoantibodies** to a range of tissue antigens such as DNA, histones, RBCs, platelets, leukocytes, and clotting factors. SLE typically appears in women between 20 and 40 years of age with a female:male ratio of 10:1. An example of complications arising from SLE is when **immune complexes** are deposited along the walls of small blood vessels. This deposition activates complement system, resulting in glomerulonephritis and damage to the blood-vessel wall (**vasculitis**) causing widespread tissue damage.

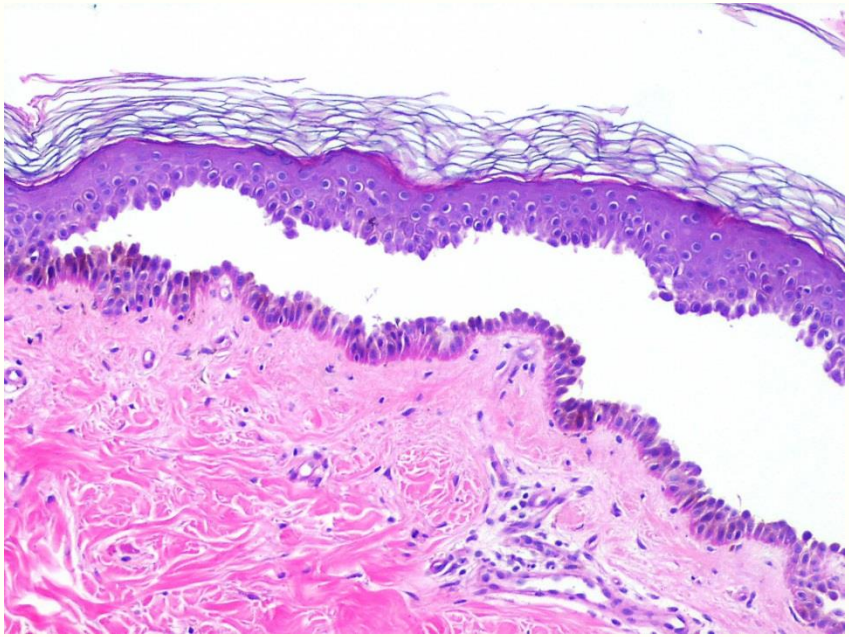

Pleural effusions
Heart problems
Lupus nephritis
Arthritis
Raynaud's phenomenon
Butterfly rash
Symptoms of systemic lupus erythematosus may vary widely with the individual
A.D.A.M.

Skin laesions in SLE

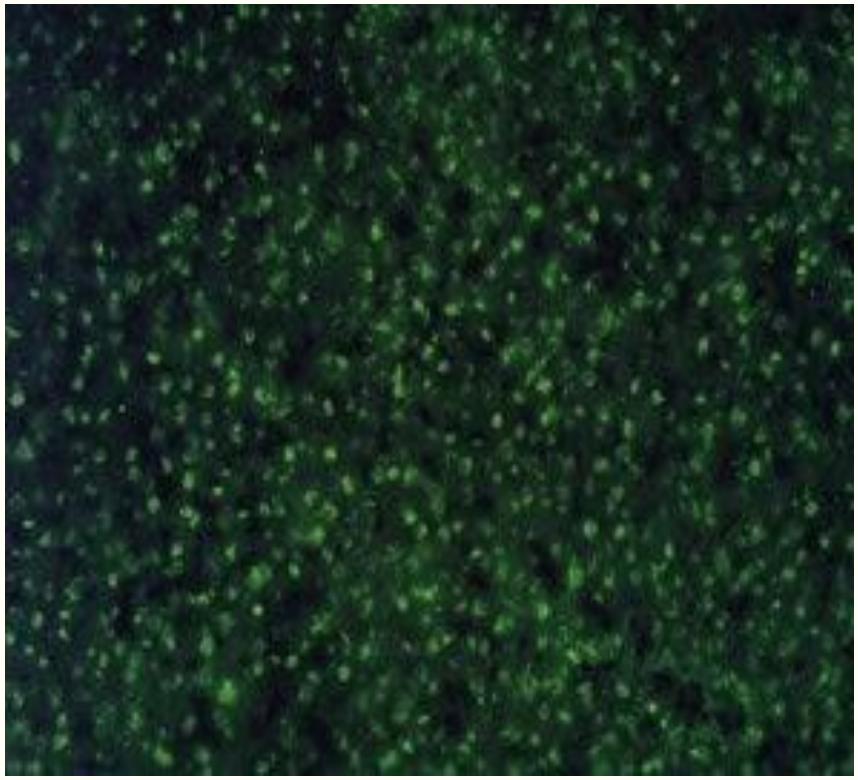




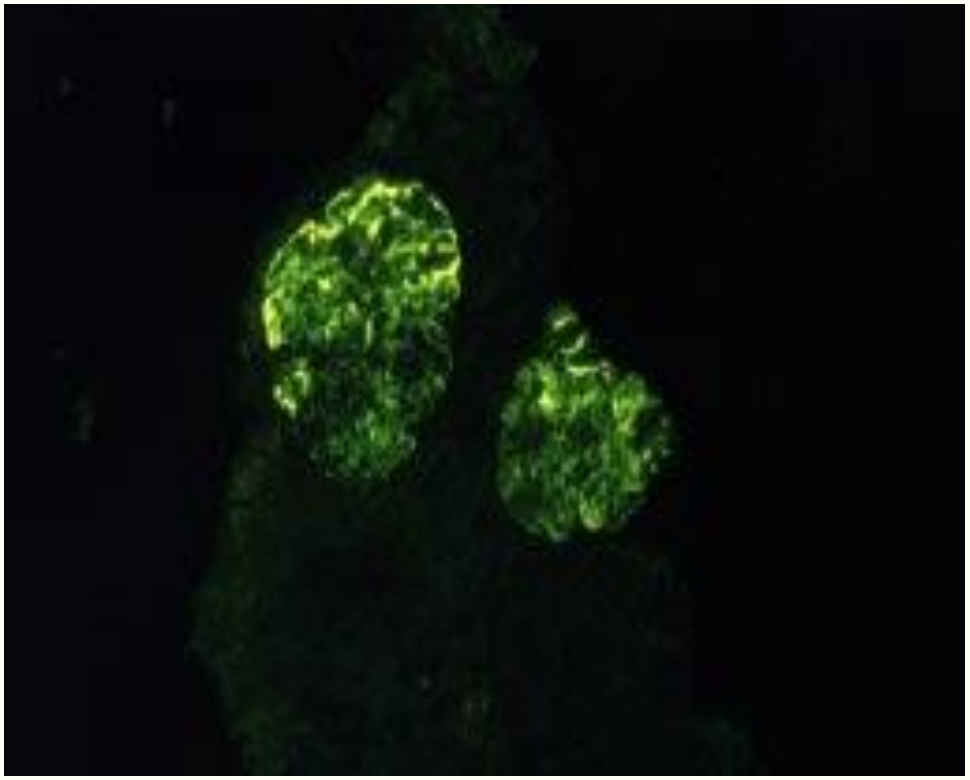




SLE

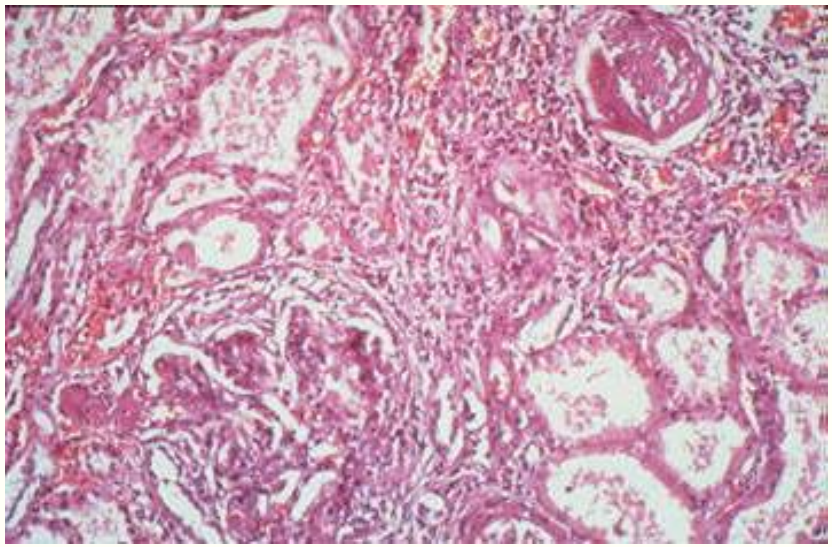


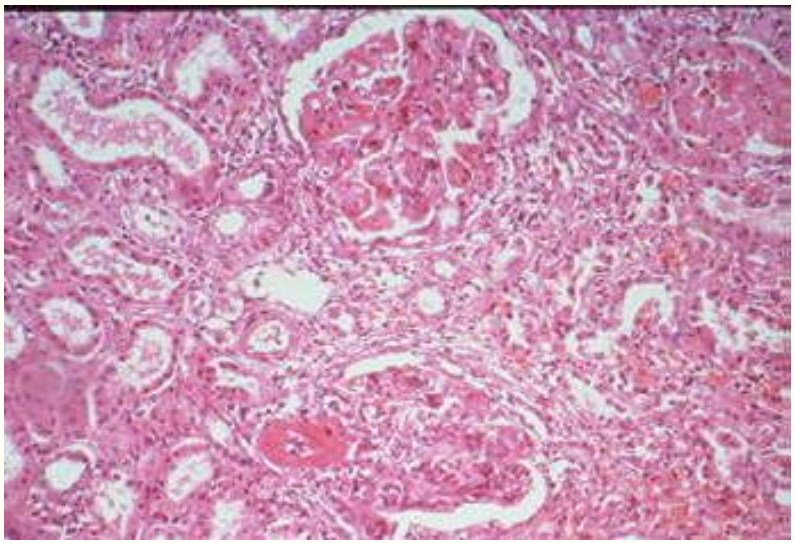
ANA positivity

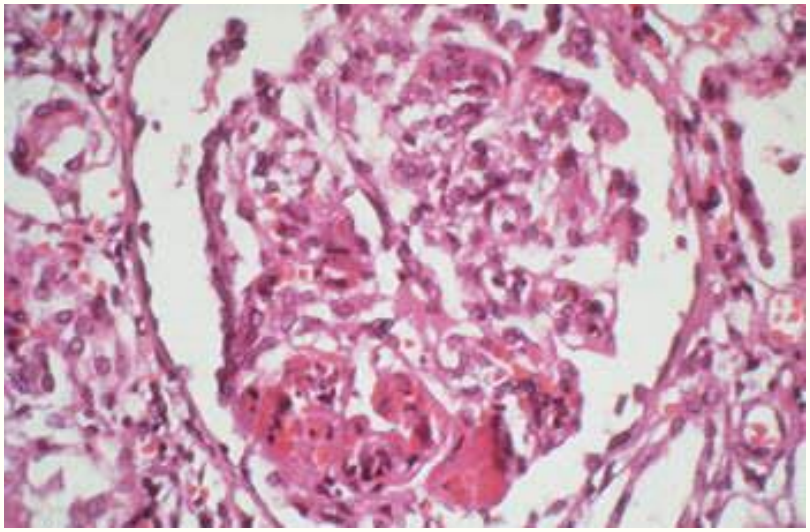


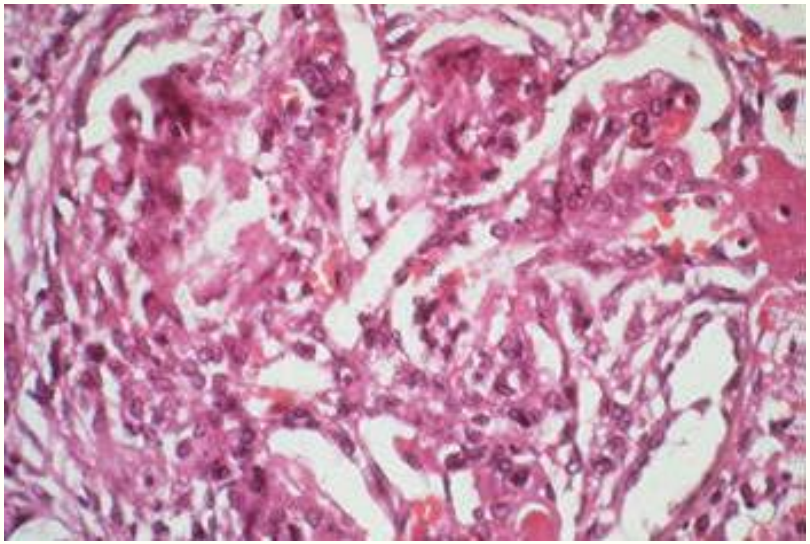
Glomerular basal membrane positivity

SLE

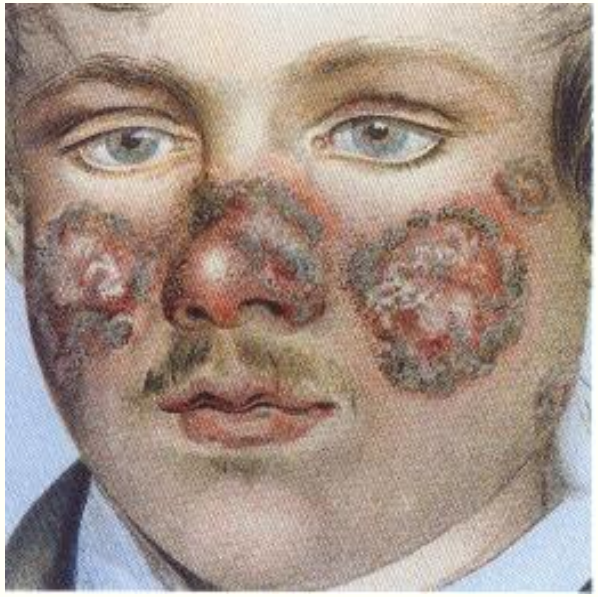


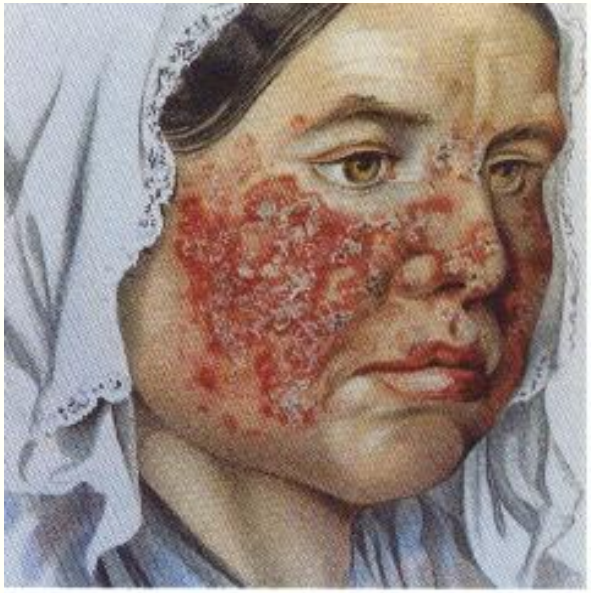


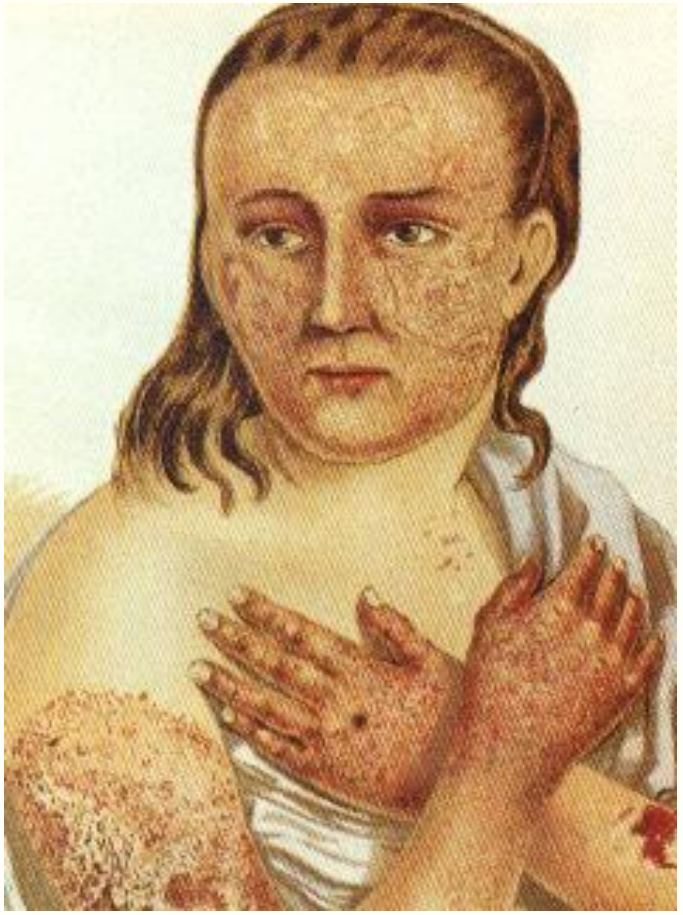




SLE



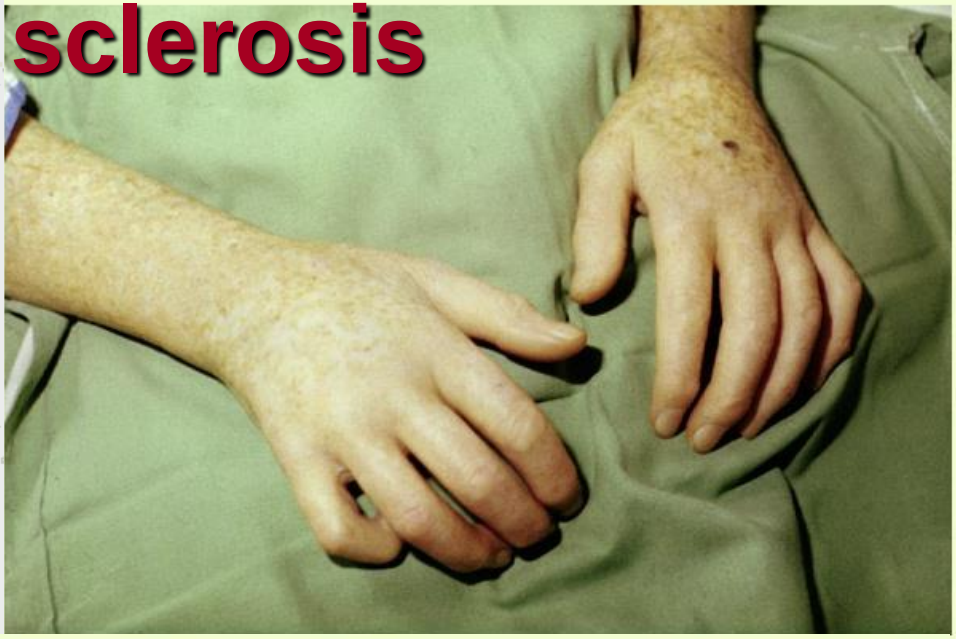


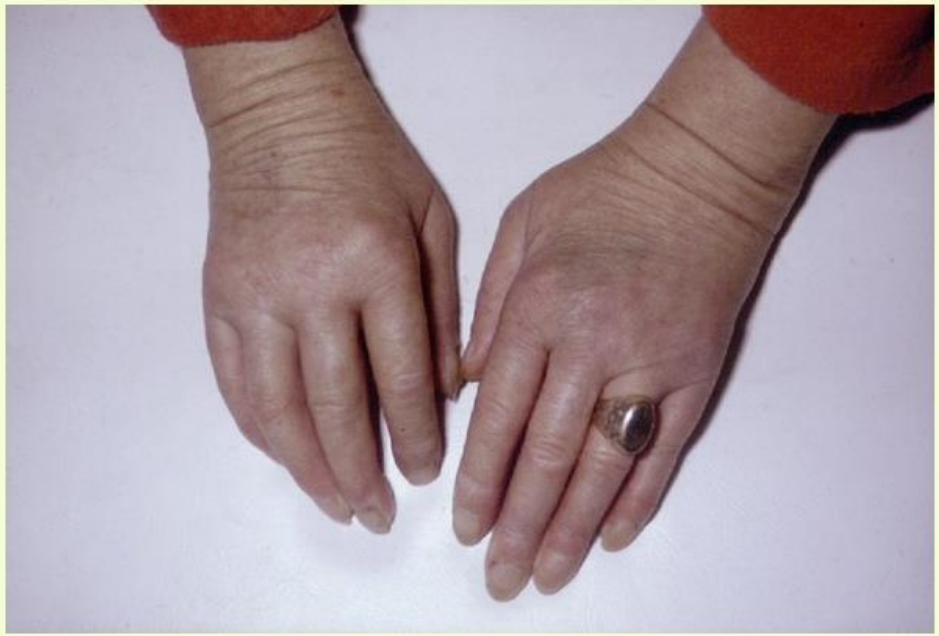


Kaposi M. ***Arch Dermat u Syph*** **1869; 1: 18-41.**

Systemic sclerosis

Paul Kee's drawing from own hand





Sclerodermás kézelváltozások

The limited symptoms of scleroderma are referred to as CREST

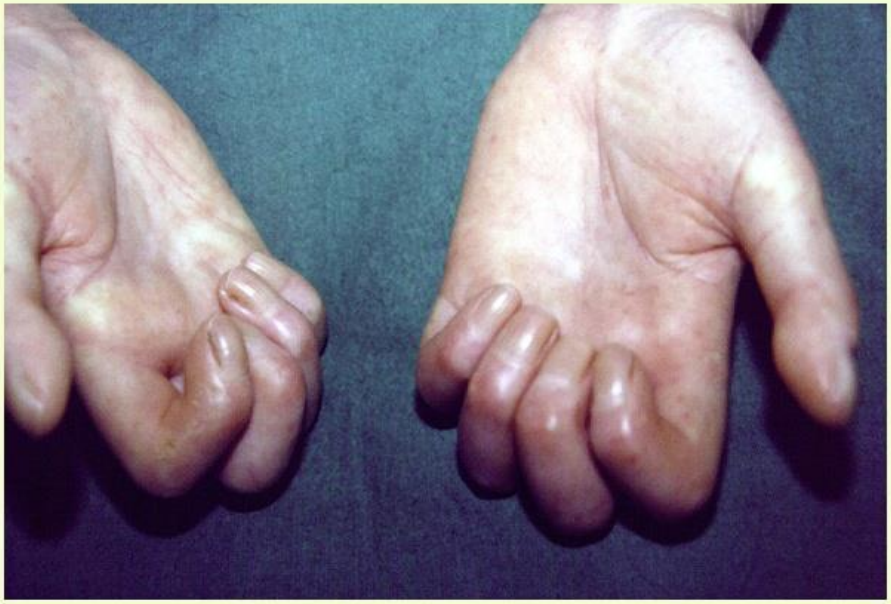
Calcinosis- calcium deposits in the skin

Raynaud's phenomenon- spasm of blood vessels in response to cold or stress

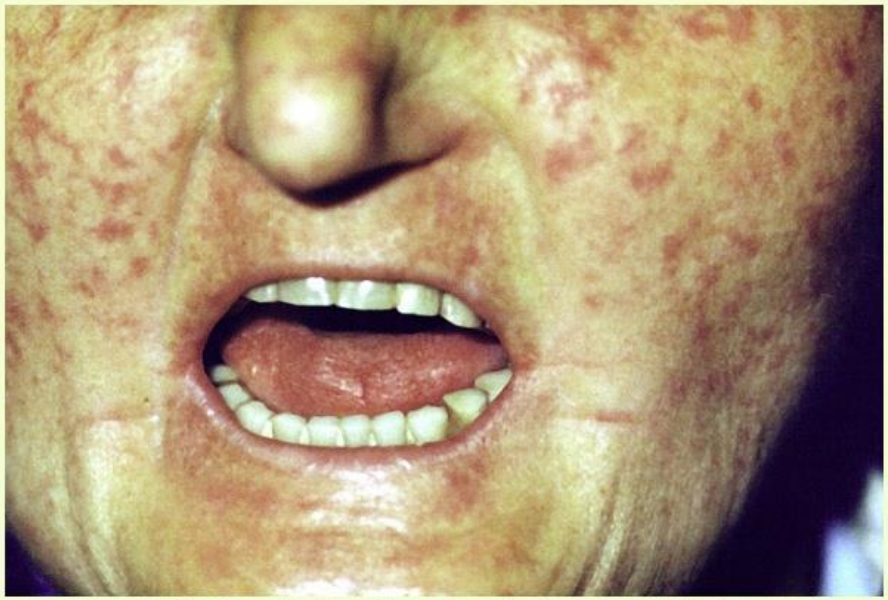
Esophageal dysfunction- acid reflux and decrease in motility of esophagus

Sclerodactyly- thickening and tightening of the skin on the fingers and hands

Telangiectasias- dilation of capillaries causing red marks on surface of skin



Késôi, súlyos sclerodermás kézelváltozások



Csökkent maximalis oralis apertura ill. teleangiectasia SSc-ben

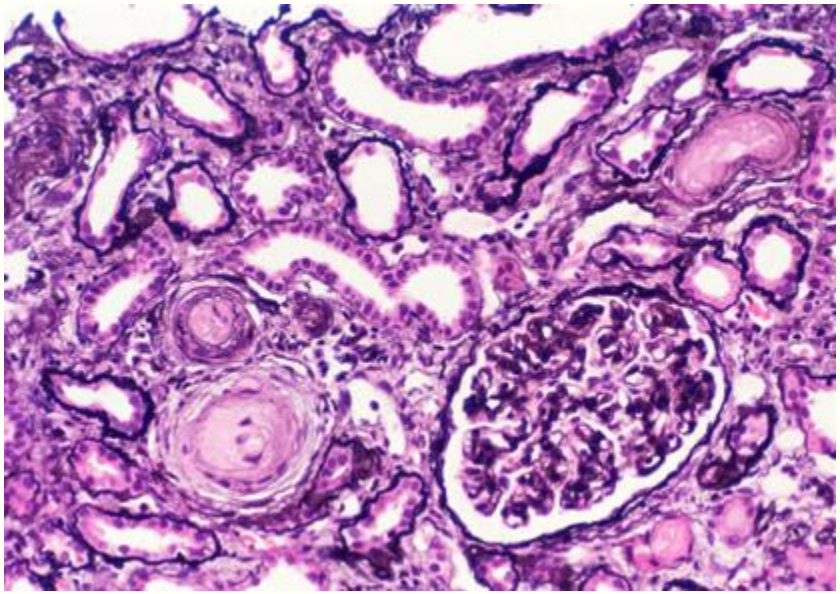
Diffuse cutaneous SSc **(dcSSc):** skin manifestation both on the extremities and on the trunk, severe internal organ involvement, **poor prognosis**

Limited cutaneous SSc **(lcSSc):** skin involvement only on the face and distal part of extremities, no internal organ involvement, **good prognosis**

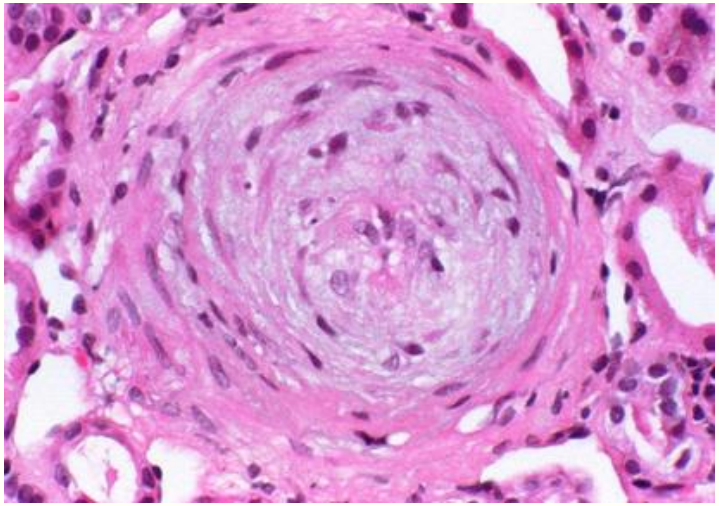
The major autoantibody in SSc targets DNA topoisomerase I (Topo I or Scl-70)

Anti-Topo I autoantibodies are detected **mainly, but not exclusively** in dcSSc

Progressive Systemic Sclerosis

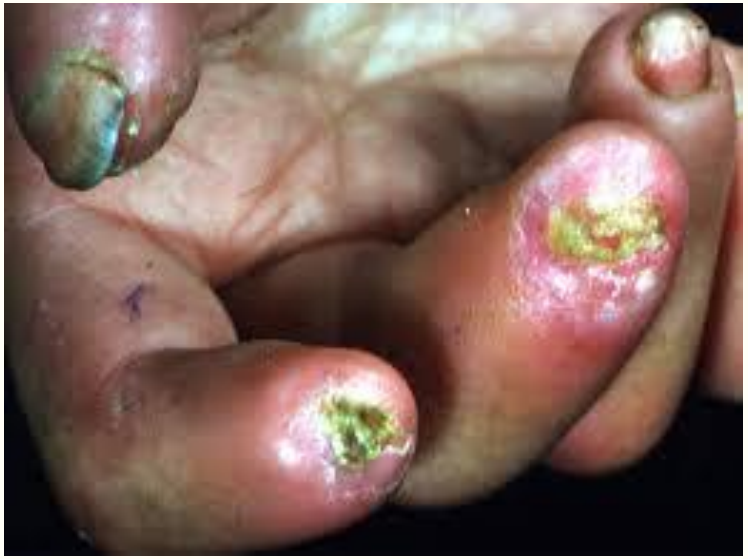


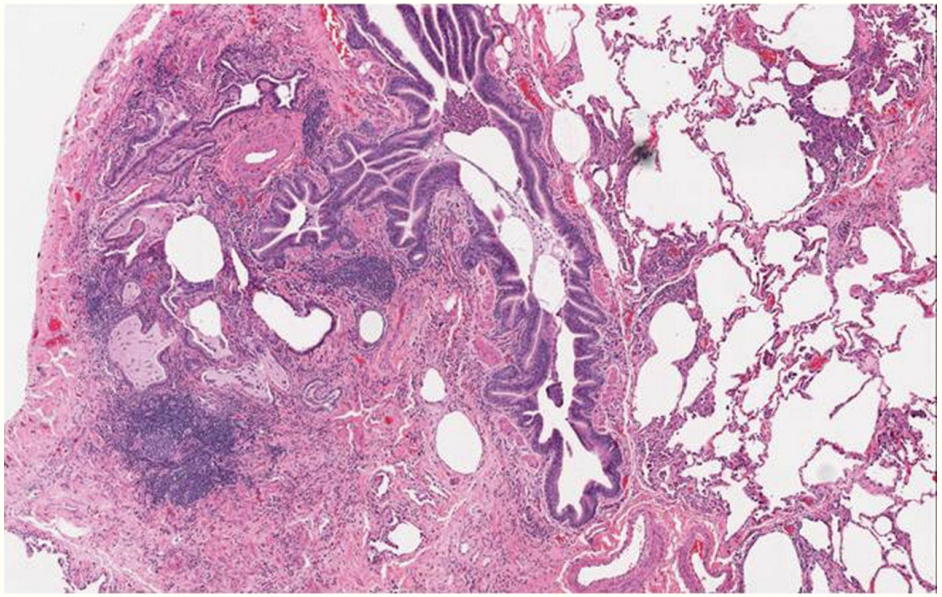
The artery shows early organization with "onion skin" change caused by lamellation and mucoid change with swelling of the intimal layer, with corrugation of the glomerular basement membrane. (Jones' silver stain, magnification X200).

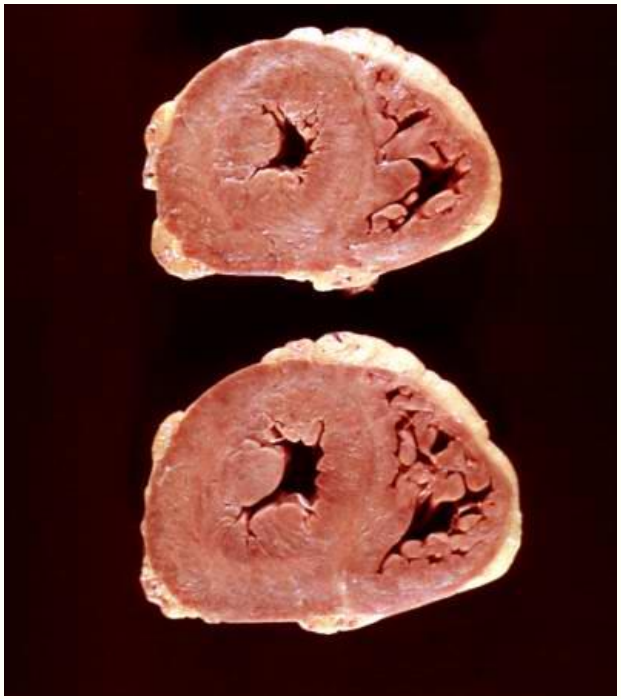


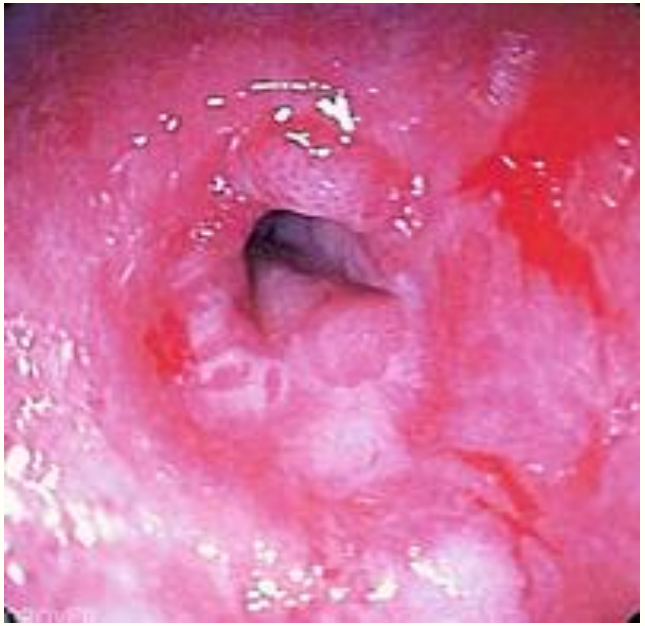
Fibrous organization of the intimal injury of arteries in a more chronic stage of progressive systemic sclerosis . (Periodic acid Schiff reaction, magnification X400).

Progressive Systemic Sclerosis

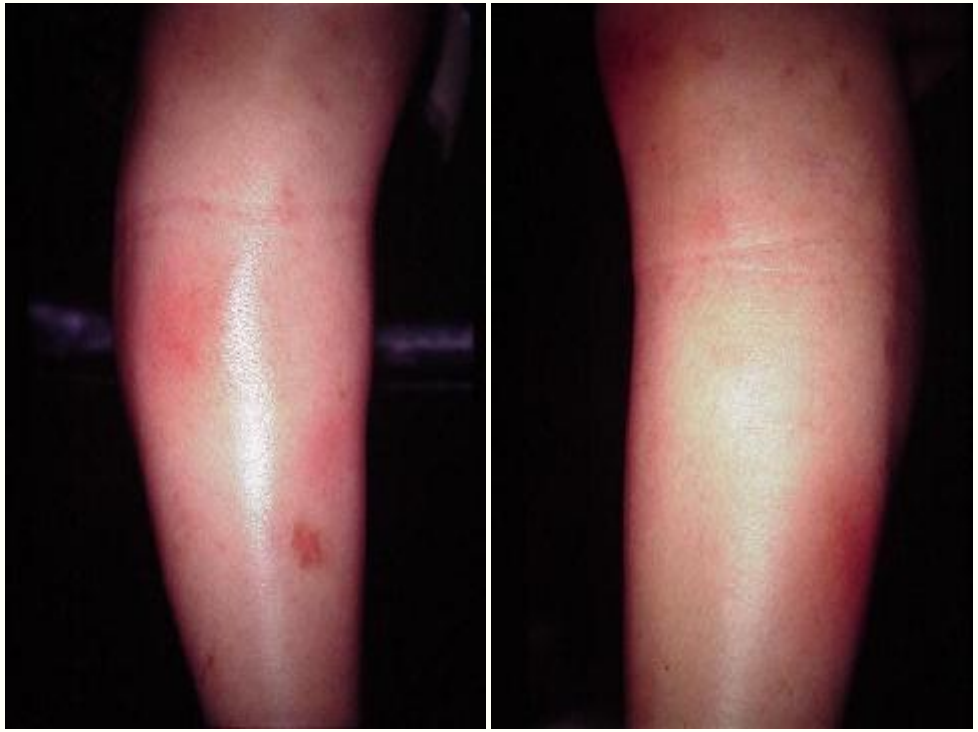


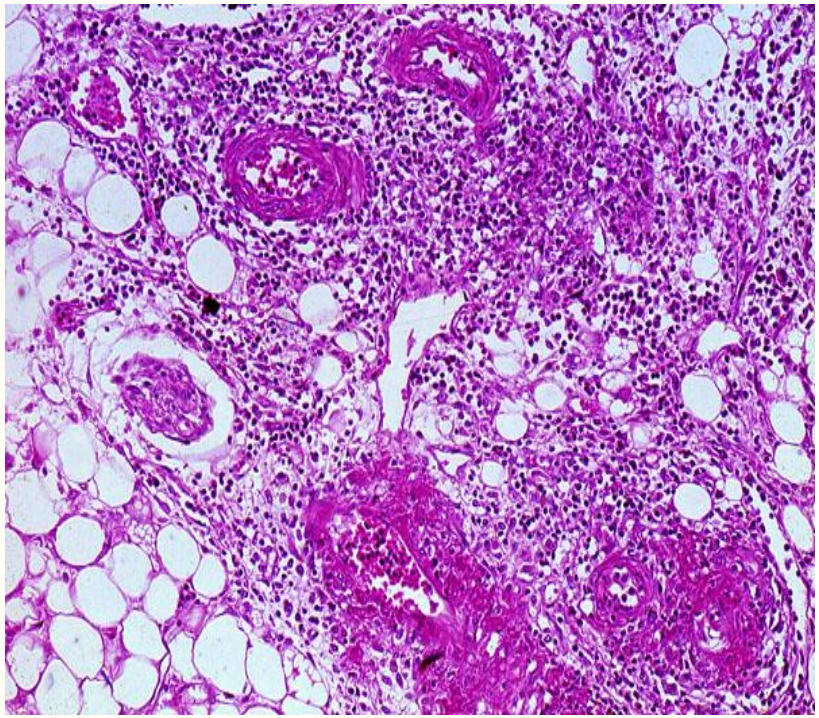






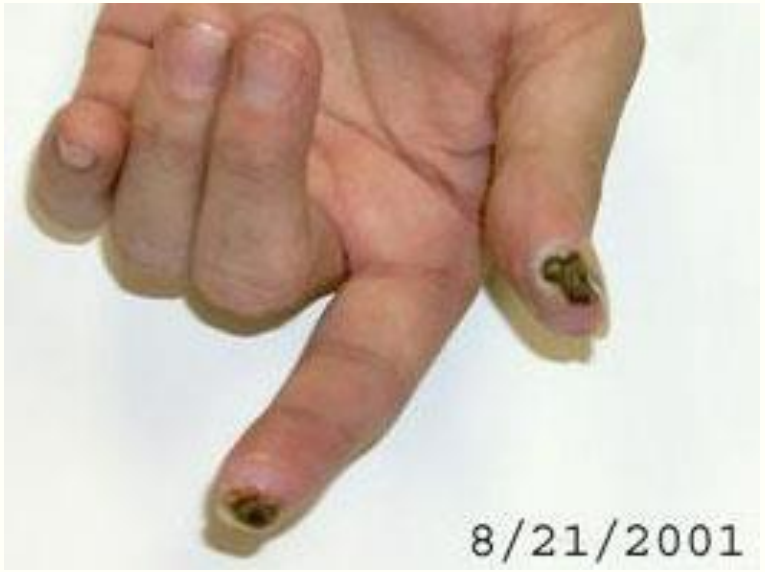
Periarteritis nodosa

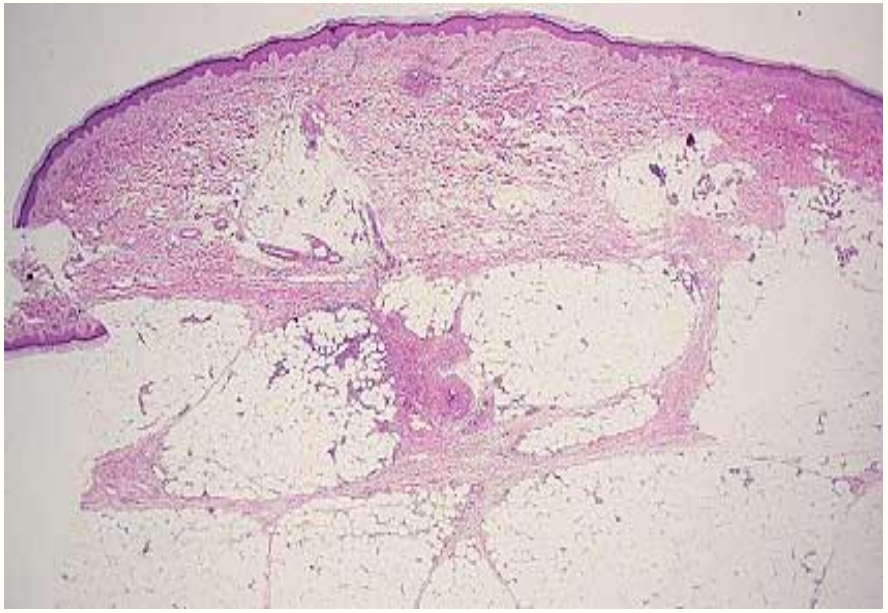


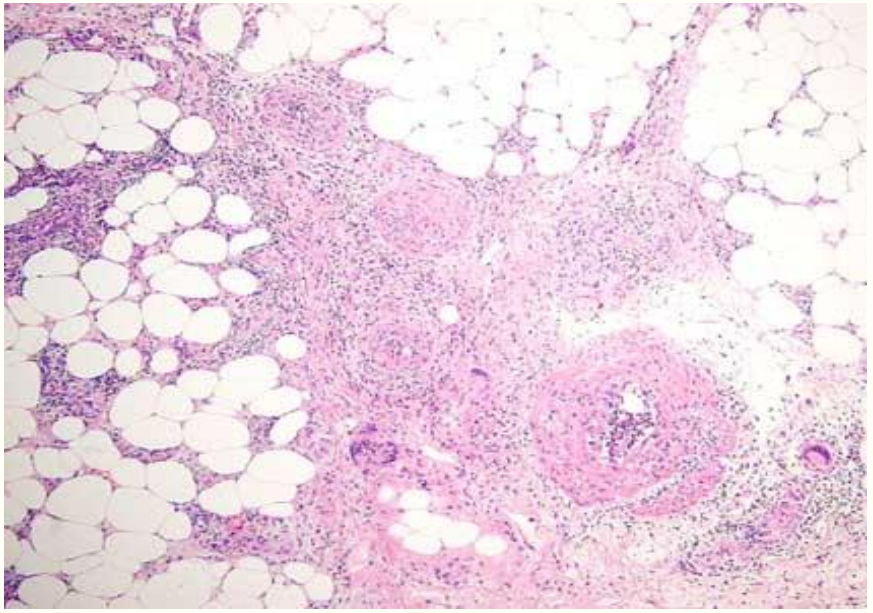


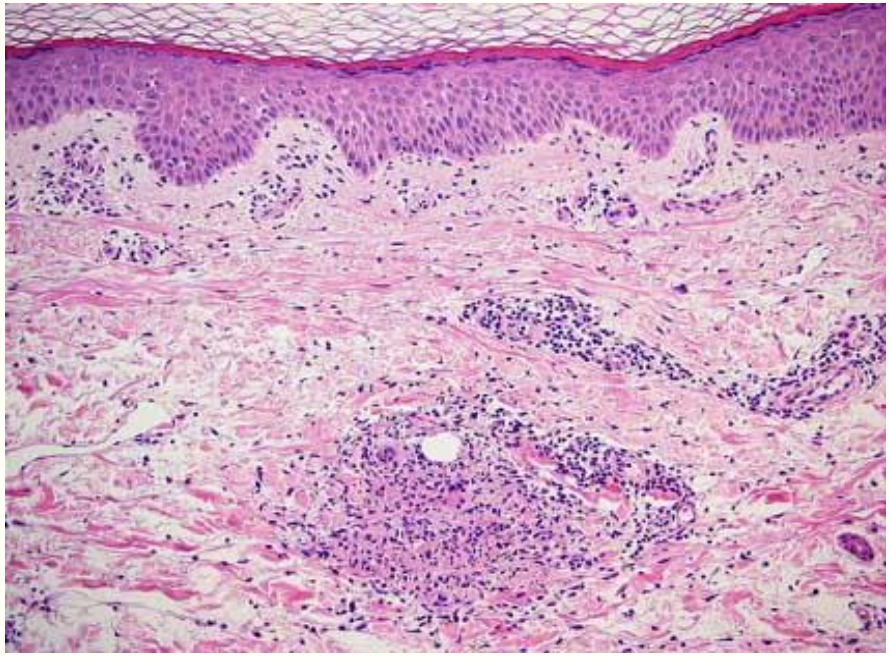
The medium sized arteries in the fat tissue appear magenta red because their wall is impregnated with fibrin (fibrinoid necrosis). There is also marked inflammation in the wall of these blood vessels extending into the perivascular connective tissue (arteritis and periarteritis).

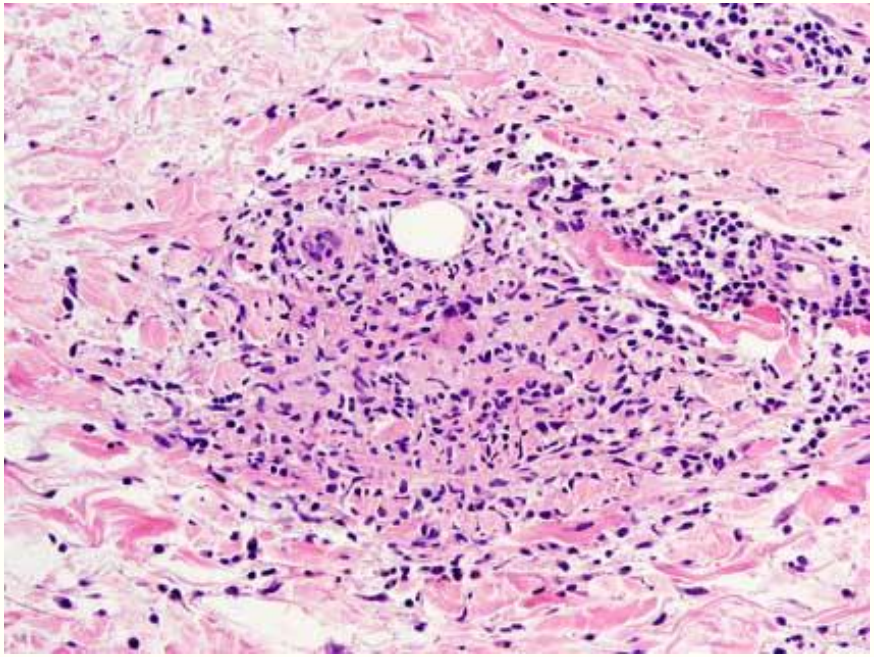
Periarteritis nodosa

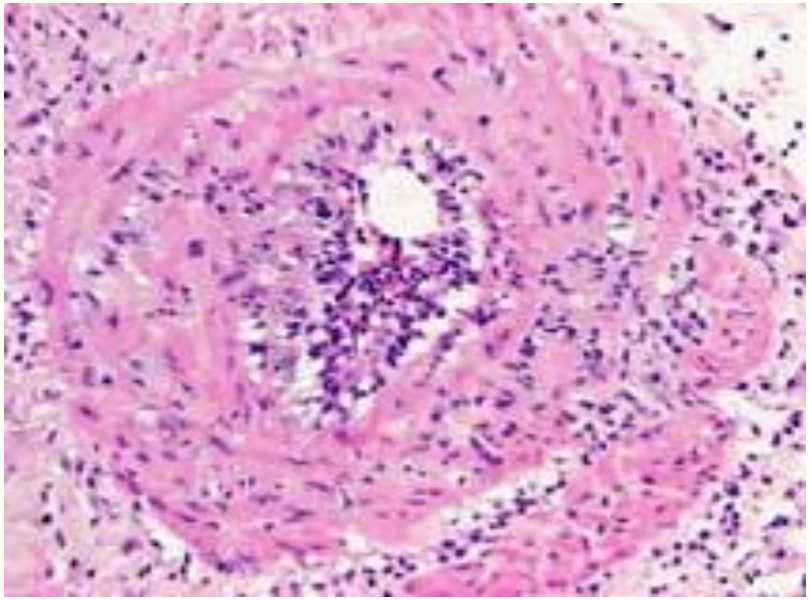


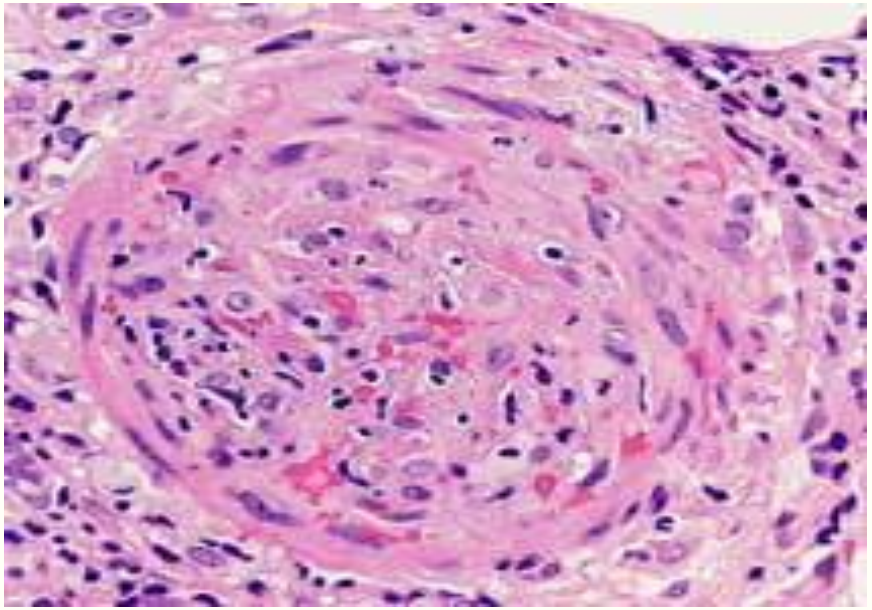


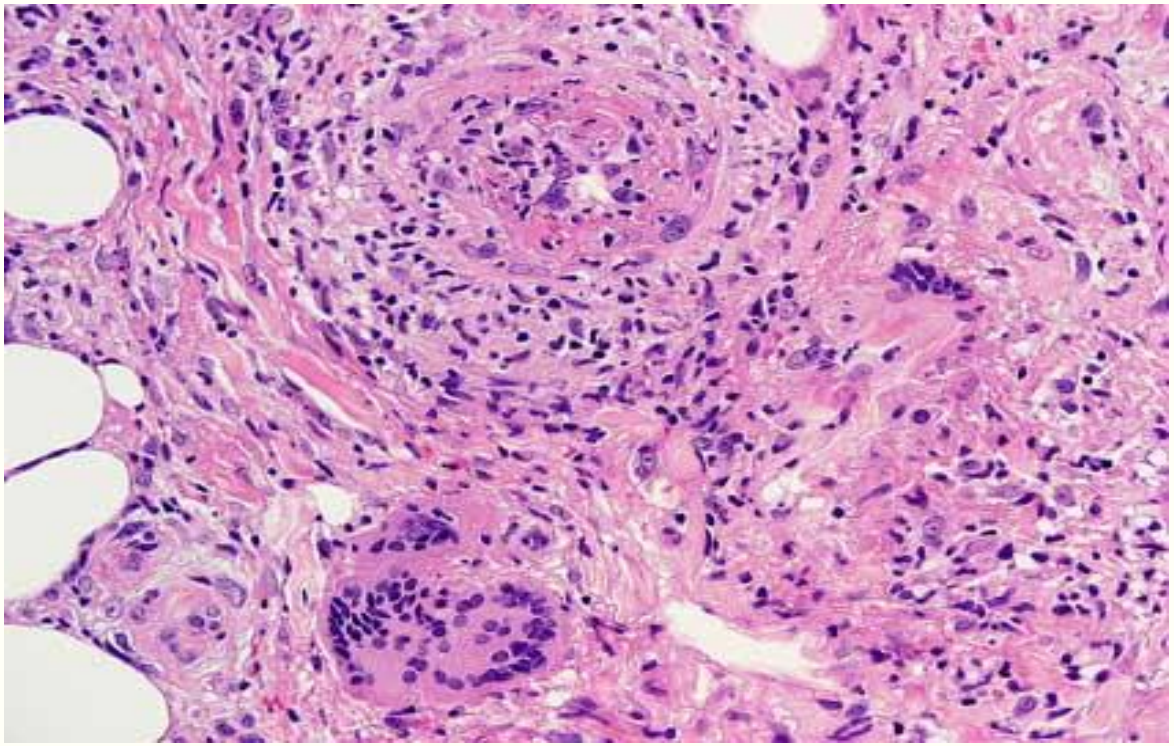






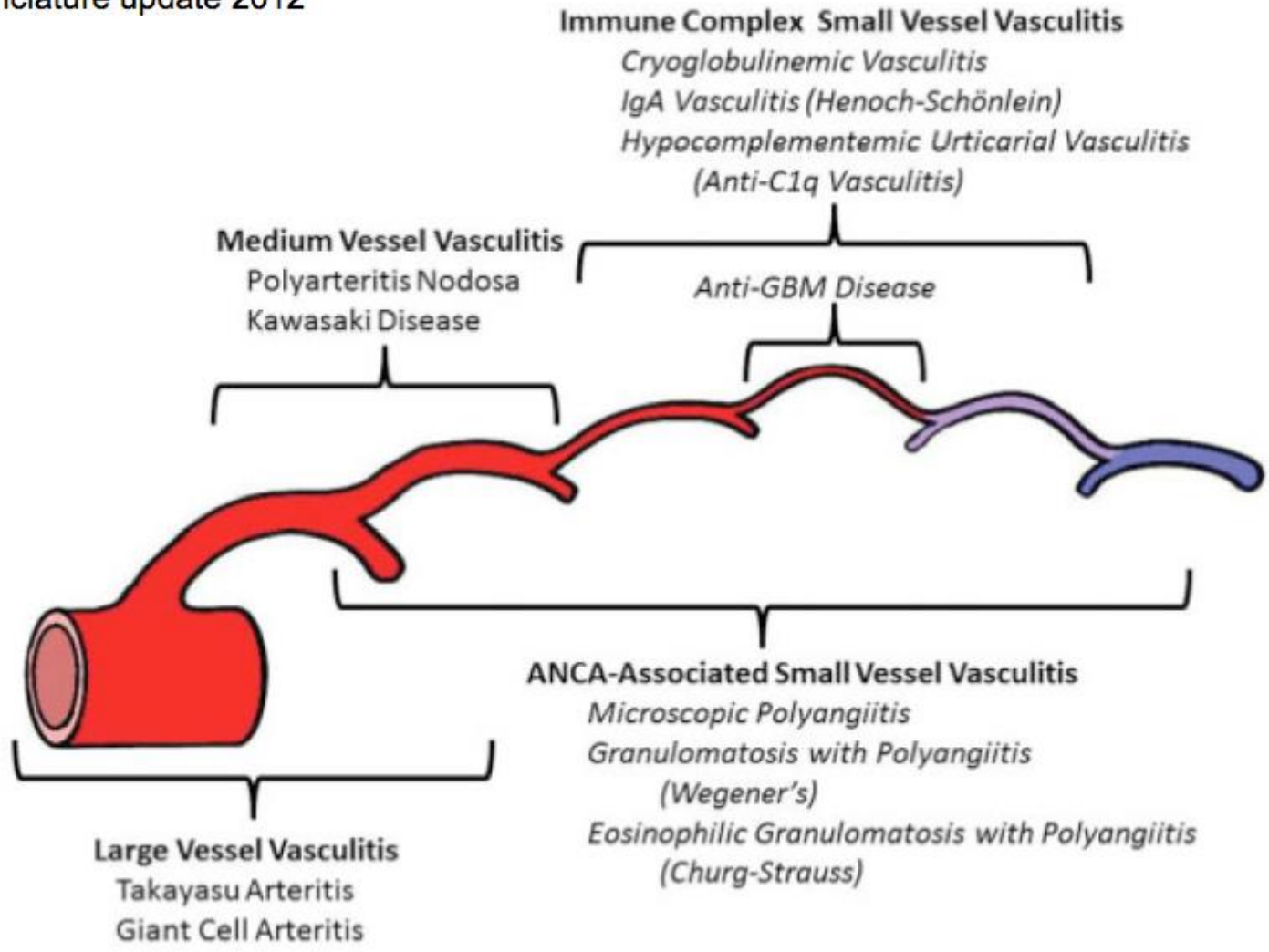




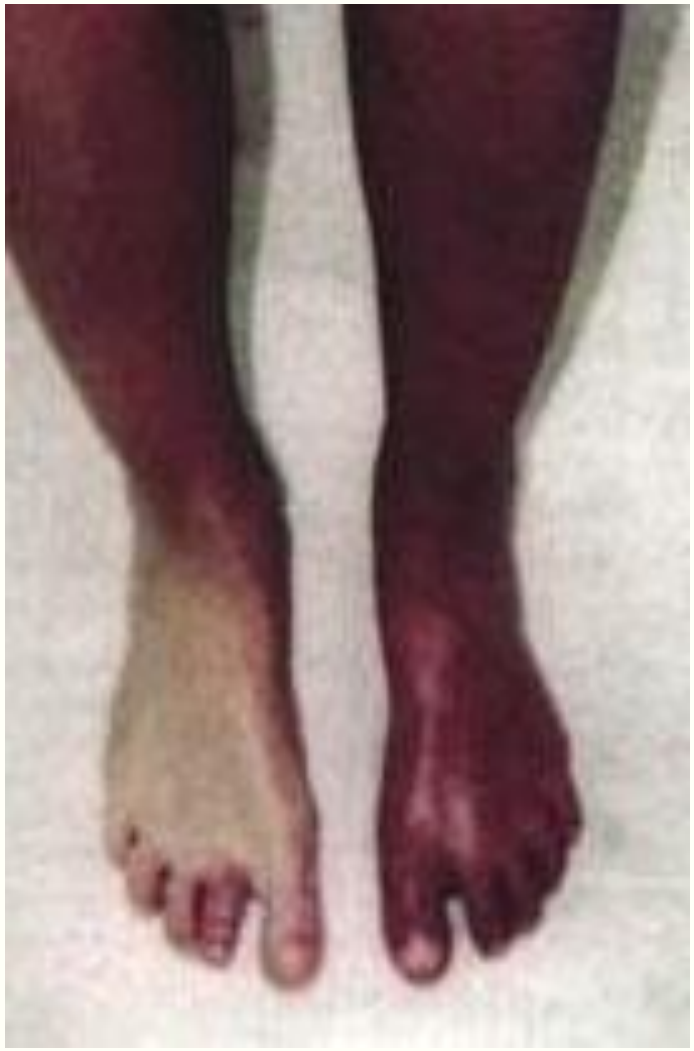


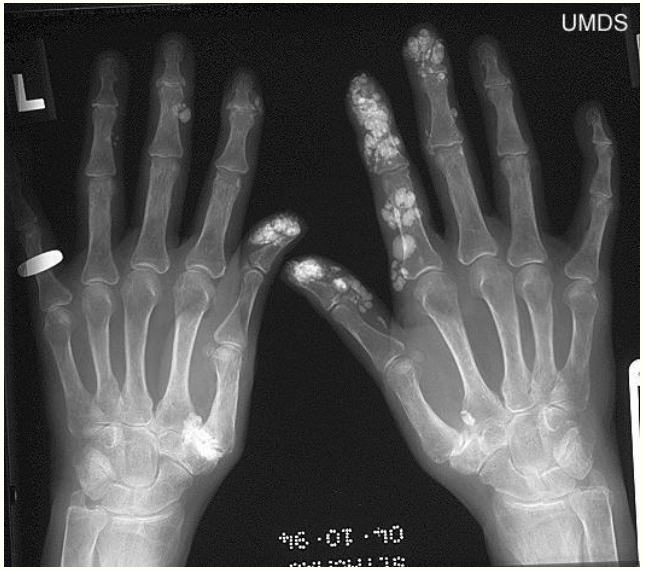
Classification of Vasculitis

Chapel Hill Consensus Criteria
Nomenclature update 2012

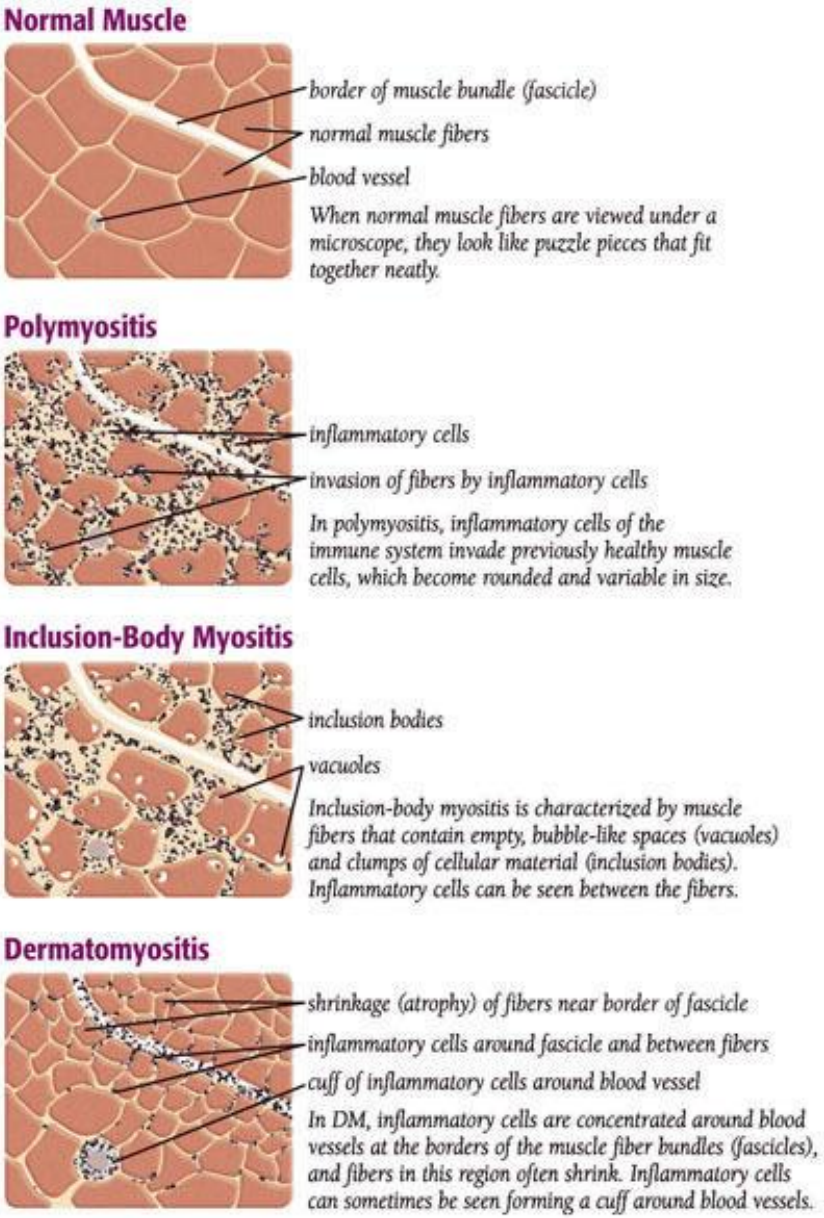


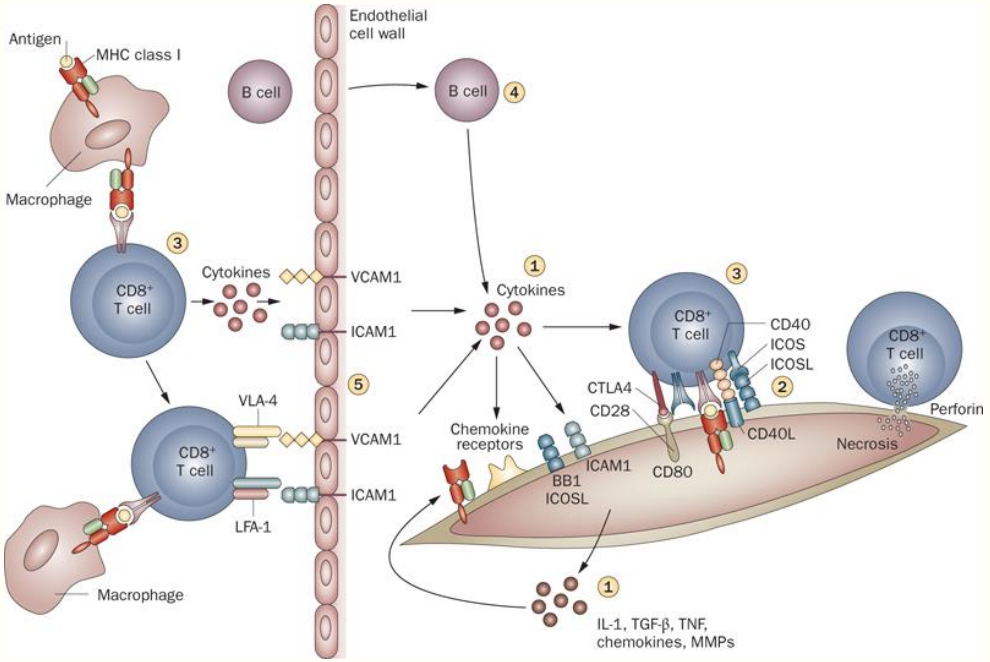
Raynaud's Syndrome





Autoimmune myositis





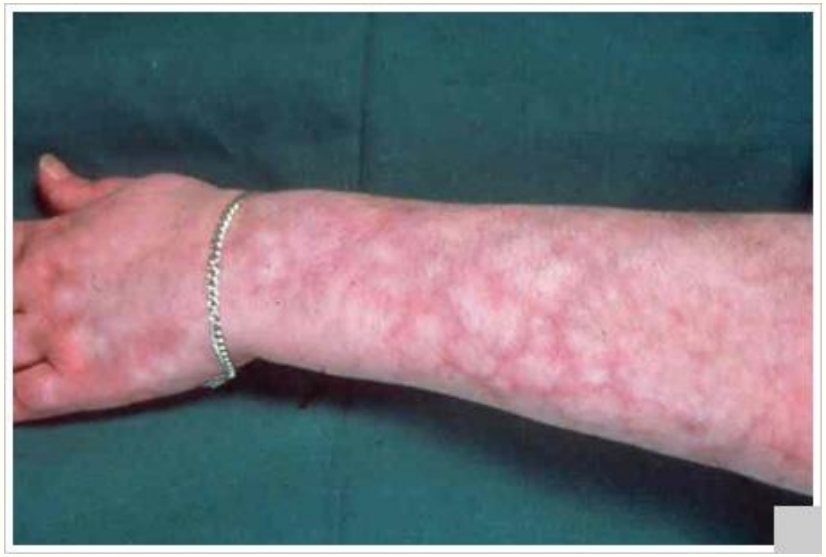
Symptoms:

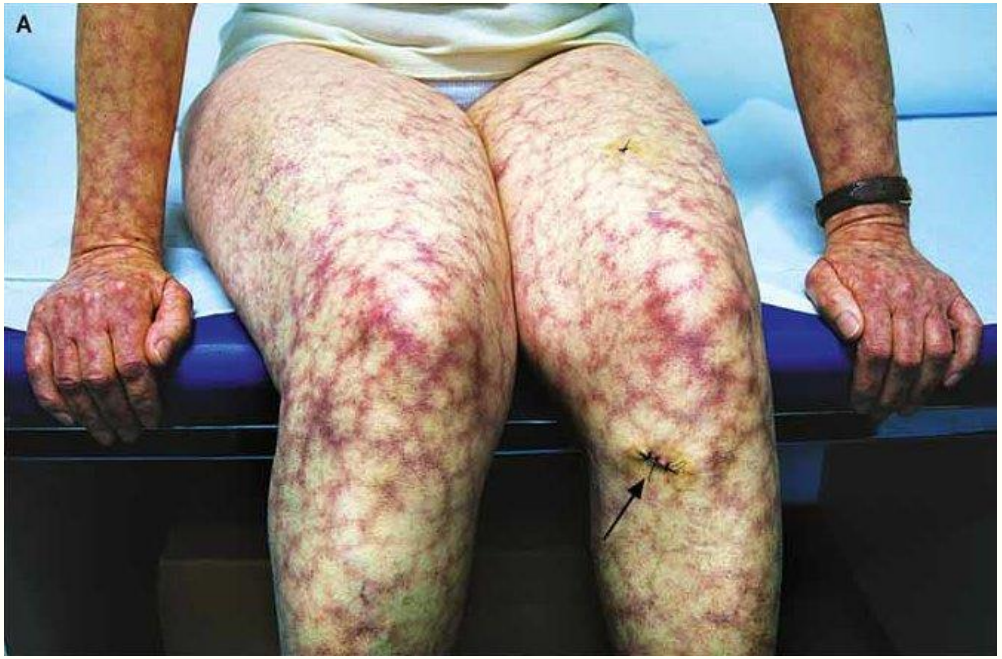
- Muscle weakness and pain
- Dysphagia
- Inflammatory skin reactions
- Laboratory alterations (autoantibodies)
- Overlapping with other autoimmune or other diseases (infections, malignant tumors etc.)

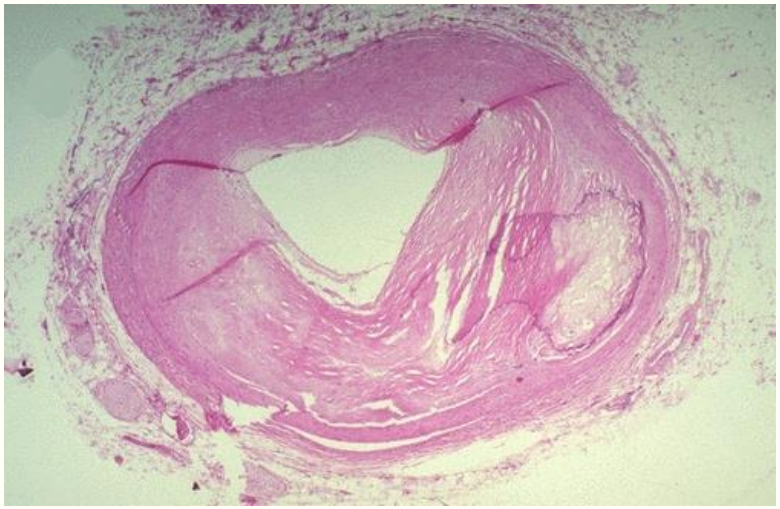
Anti-Phospholipid Antibody Syndrome

- **The APAS (or APS) is an autoimmune disorder comprising such clinical symptoms like arterial or venous thrombosis, thrombocytopenia and recurrent fetal loss. Primary APAS is characterized by the appearance of autoantibodies to negatively charged phospholipids including cardiolipin antibodies.**
- Autoimmune patients exhibit cardiolipin antibodies that seem to recognise cardiolipin in association with a plasma protein cofactor. This cofactor has been identified as ß2 glycoprotein-I (ß2 GP-I) (apolipoprotein H). ß2 GP-I affects platelet aggregation and coagulation.
- The positively charged fifth domain of ß2 GP-I interacts with negatively charged phospholipids such as cardiolipin. This interaction results in conformational changes of the protein and the exposure of cryptic epitopes apparently recognised by autoimmune cardiolipin autoantibodies.

anti-Phopholipid syndrome



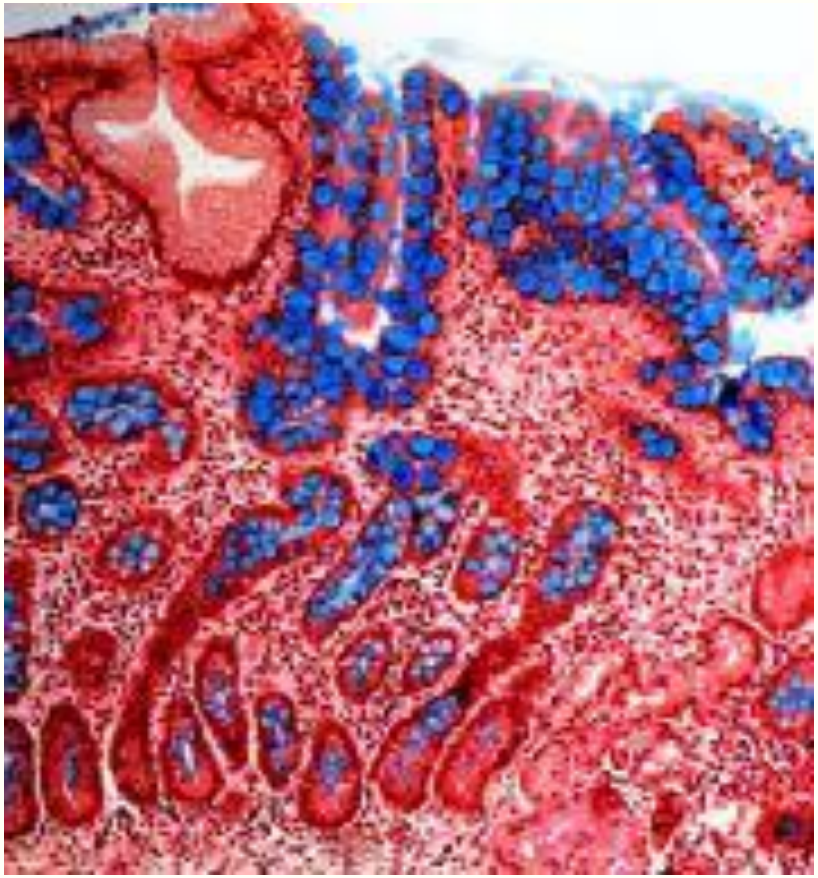


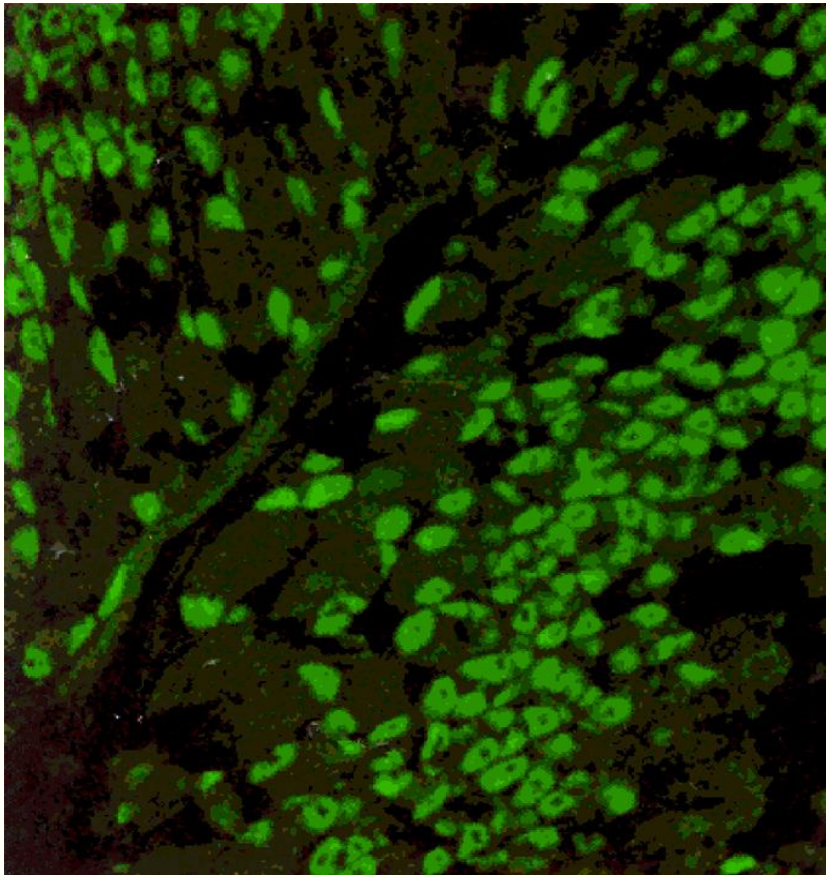


Livedo reticularis

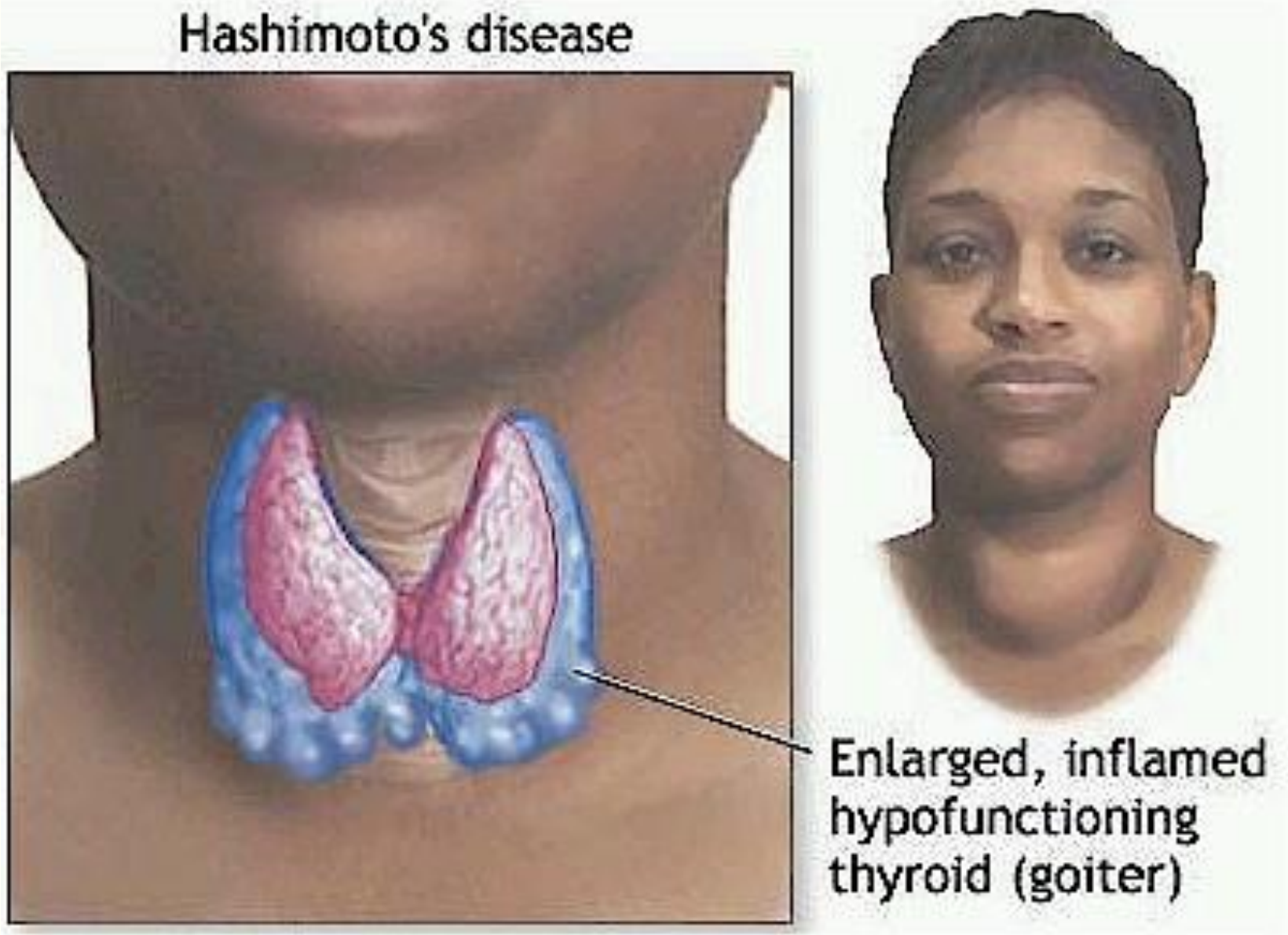
Antiphospholipid Syndrome (APS, APLS, Hughes Syndrome, or Sticky Blood): abnormal antibodies linked to abnormal blood clots within veins and arteries.

Autoimmune atrophic gastritis

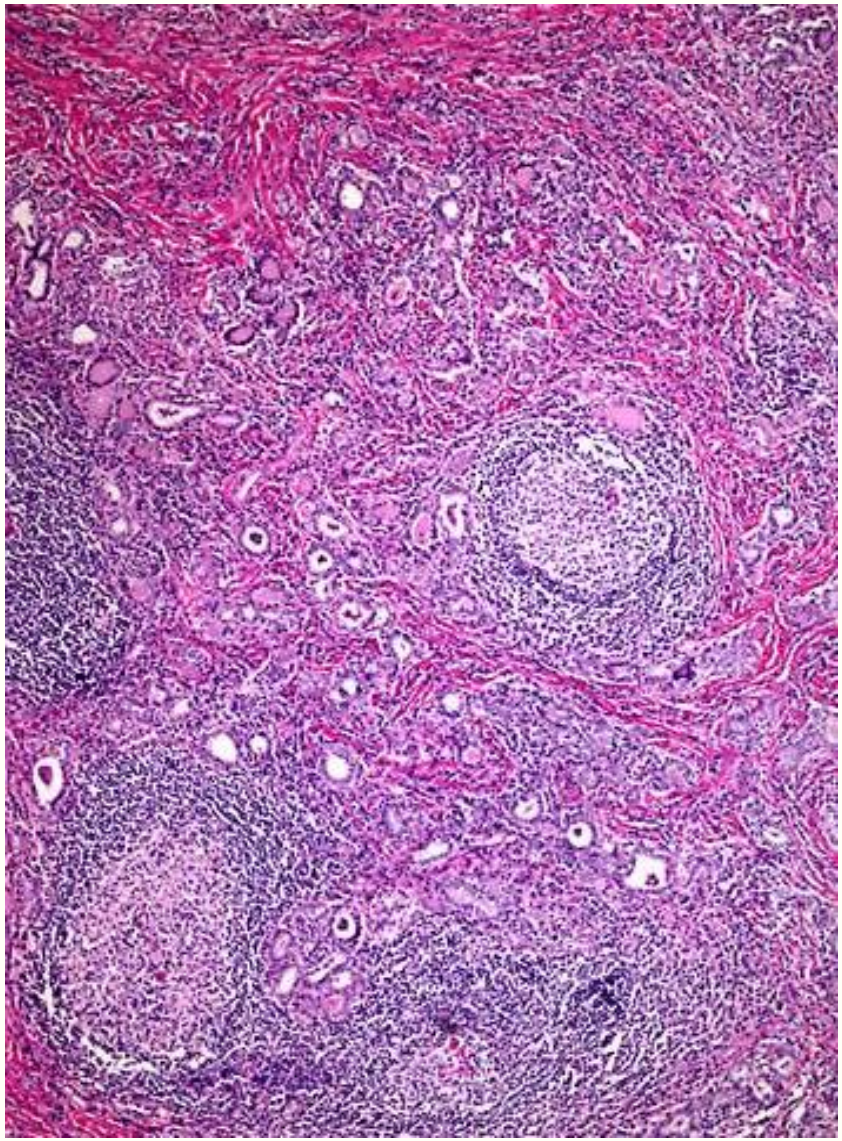


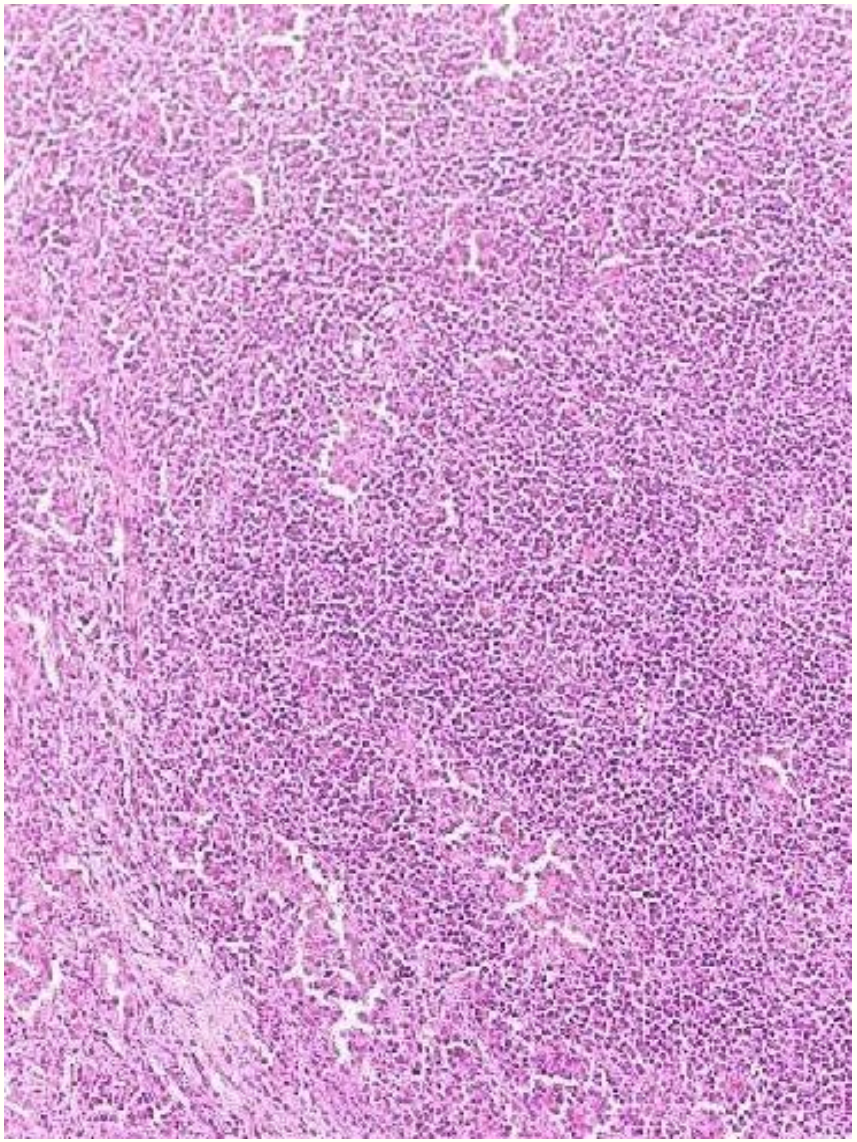


Chronic inflammation of the stomach mucosa, leading to loss of gastric glandular cells. The stomach's secretion of hydrochloric acid, pepsin, and intrinsic factor is impaired. Digestive problems, vitamin B12 deficiency, megaloblastic anaemia or malabsorption of iron can occurre. In autoimmune atrophic gastritis are statistically more likely to develop gastric carcinoma, Hashimoto's thyroiditis, and achlorhydria.

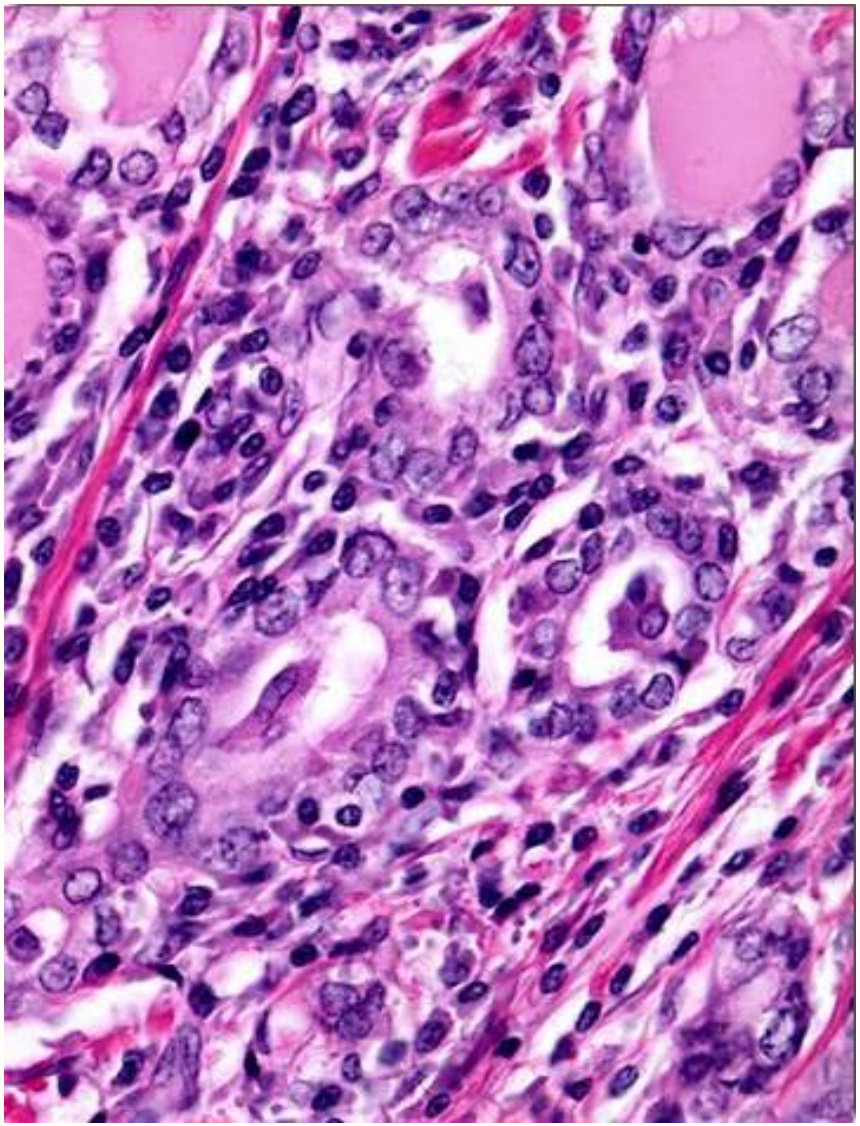

Hashimoto's disease
Enlarged, inflamed hypofunctioning thyroid (goiter)

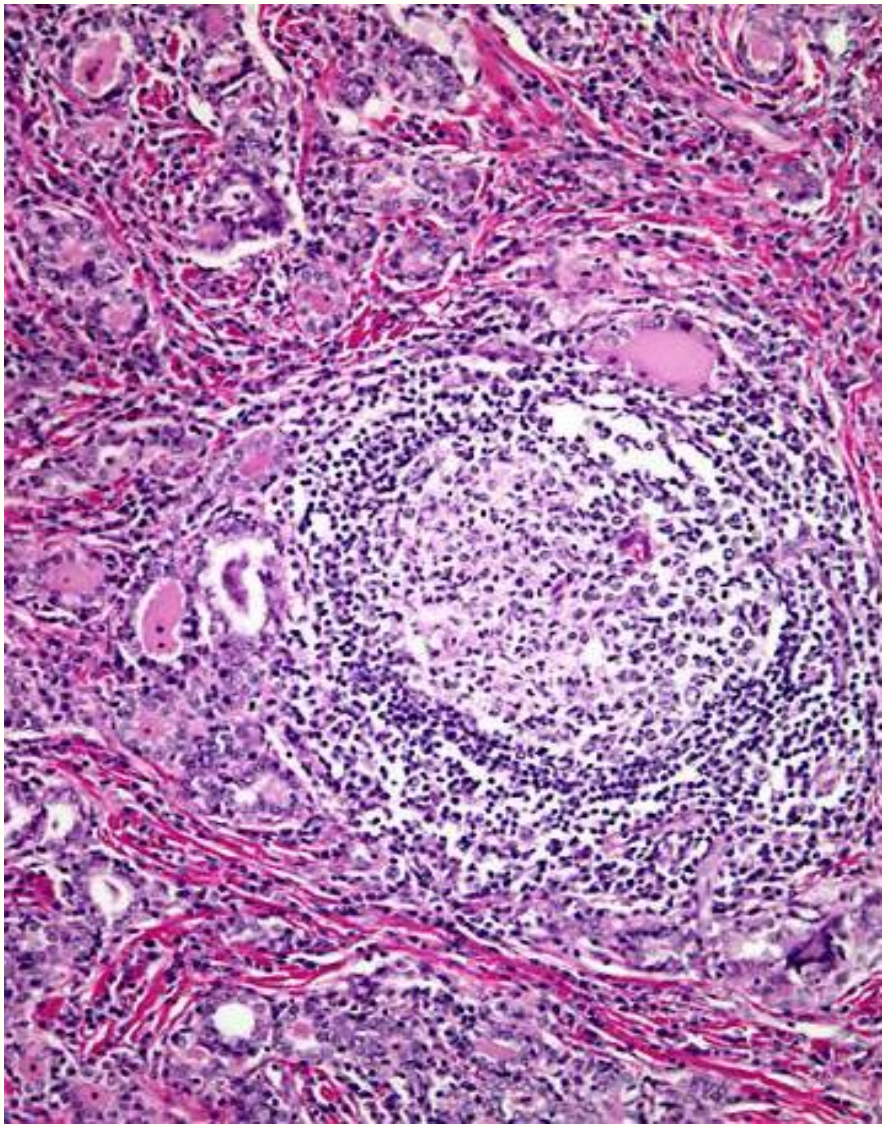
Hashimoto's disease





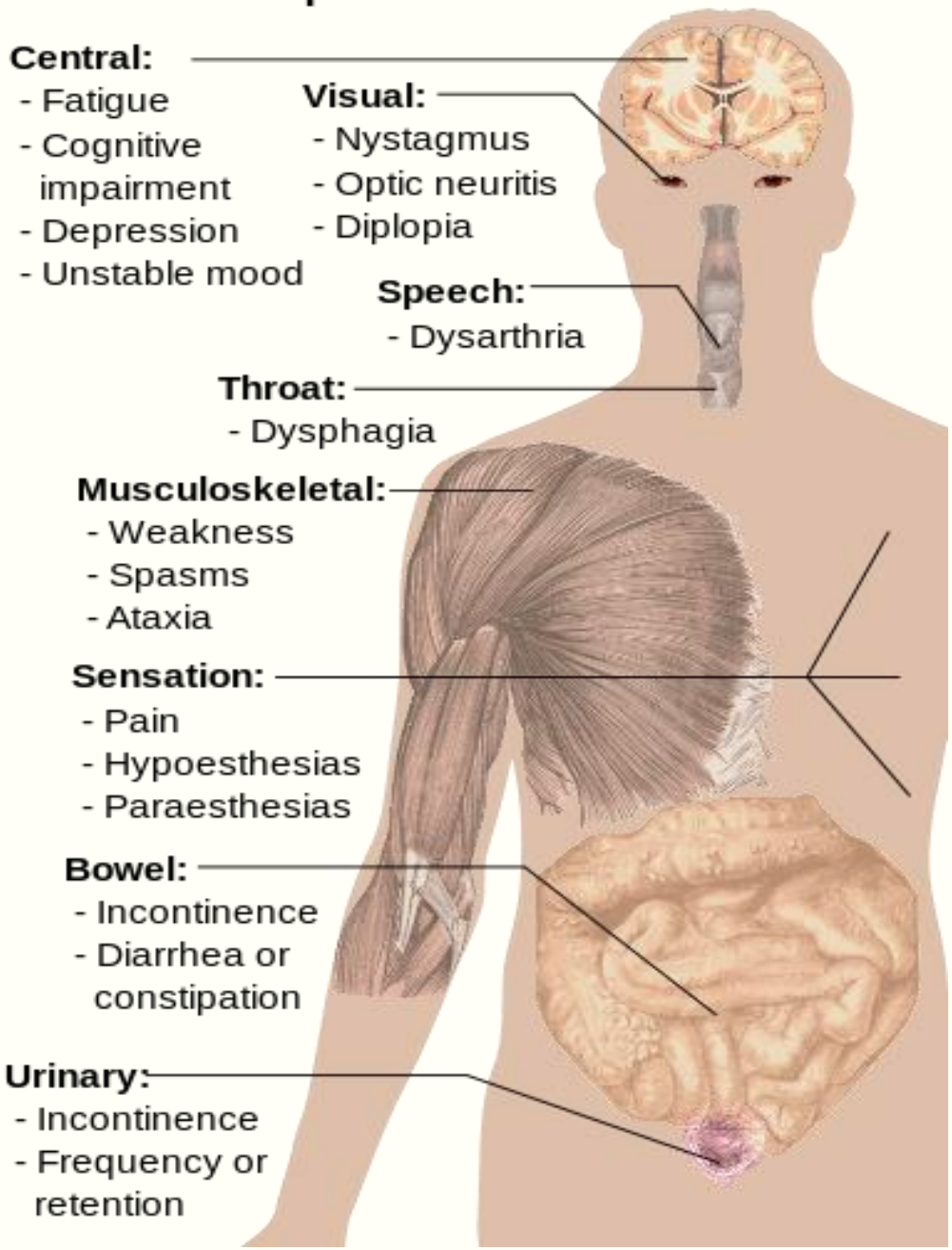
Hashimoto's disease



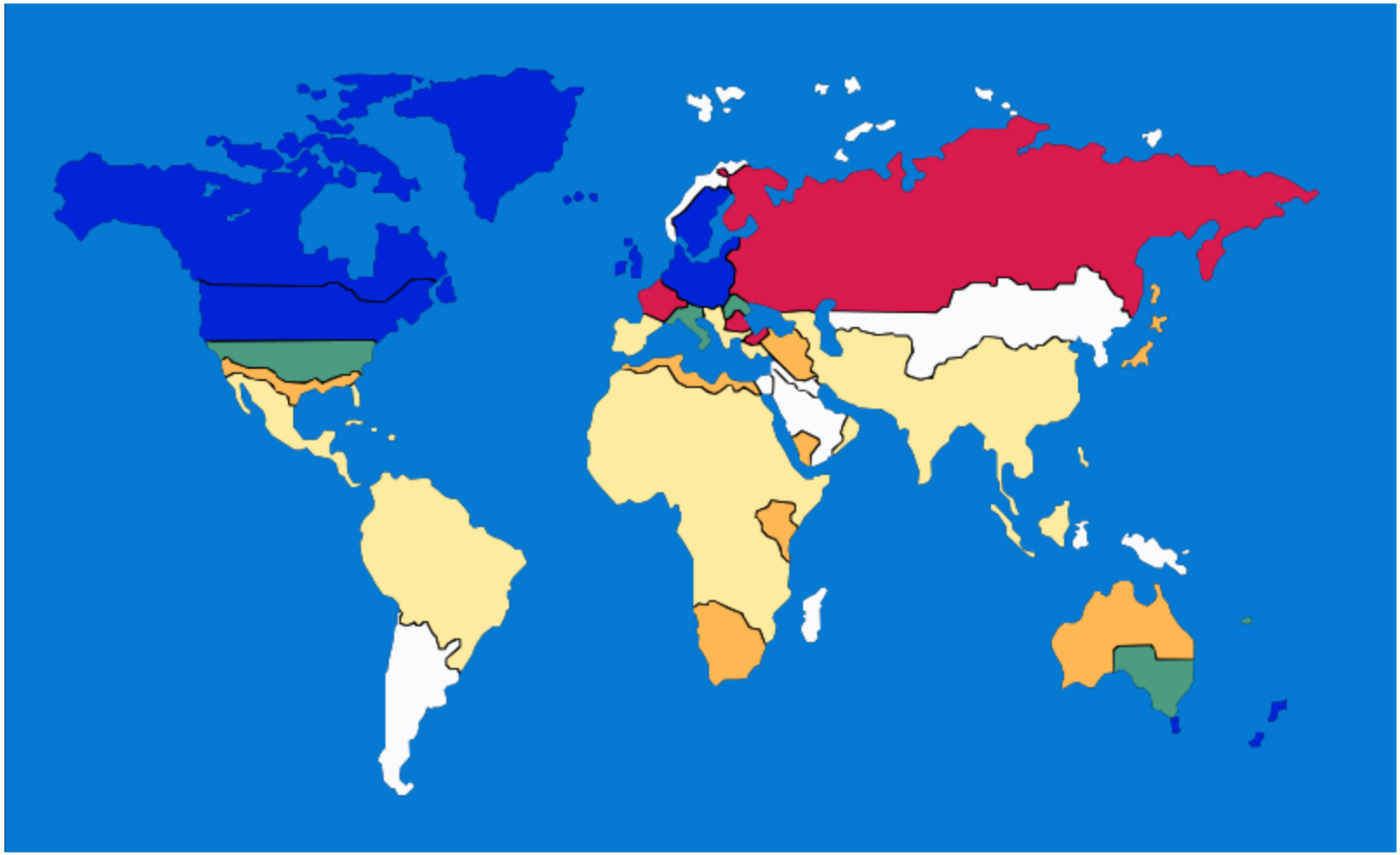


Main symptoms of

Multiple sclerosis

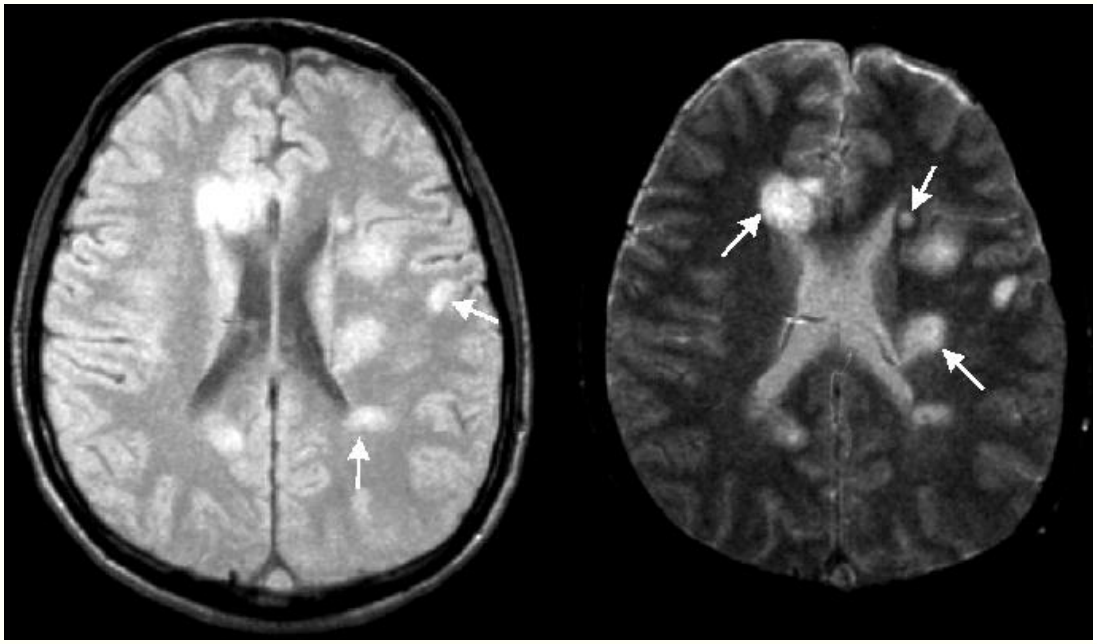


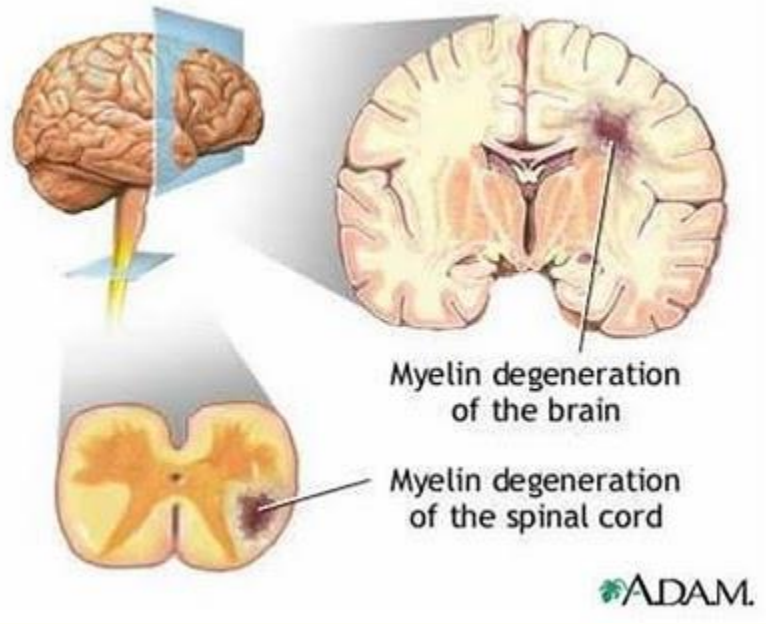
Geogpahical incidence of multiple sclerosis

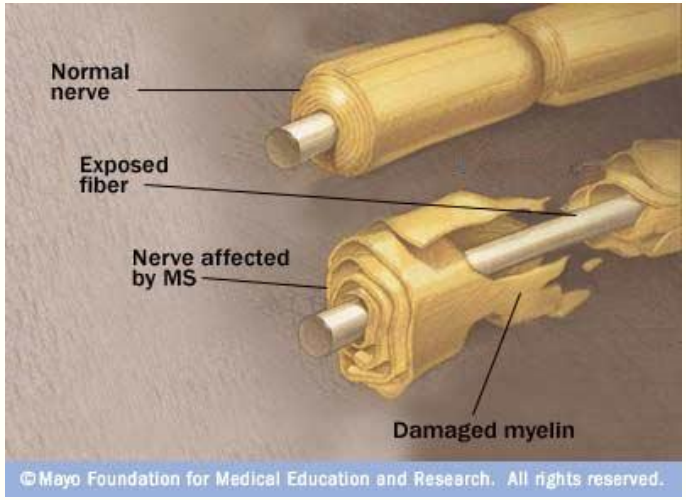


high risk probable high risk low risk probable low risk North South gradient risk

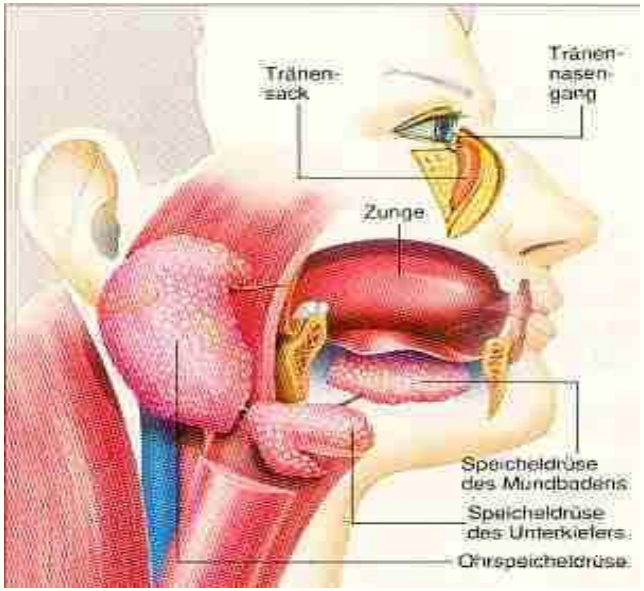
Demyelinisation in multiple sclerosis

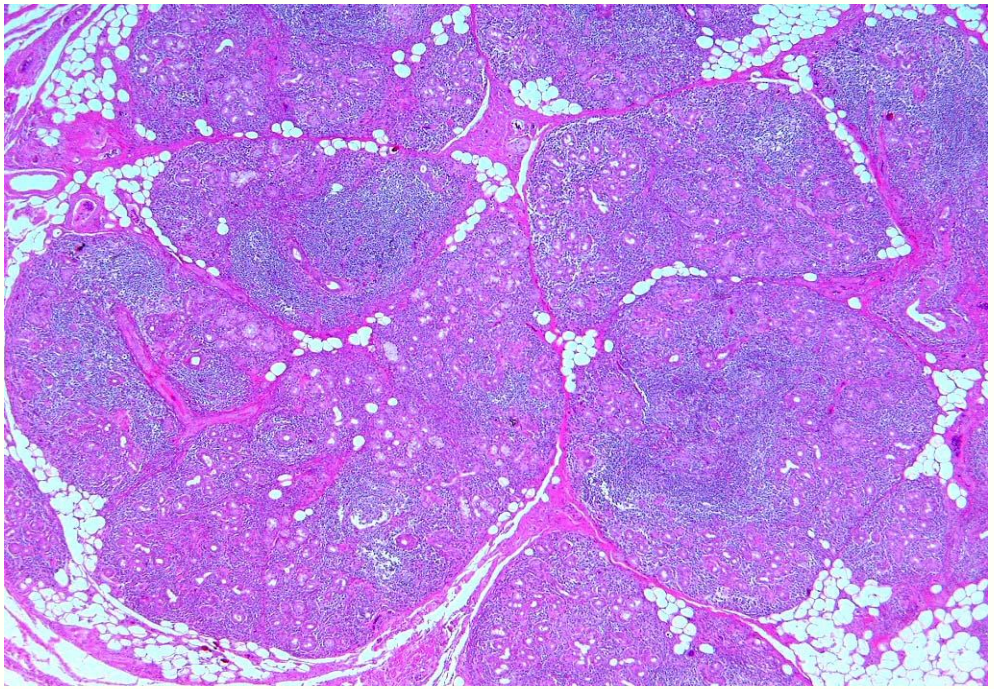


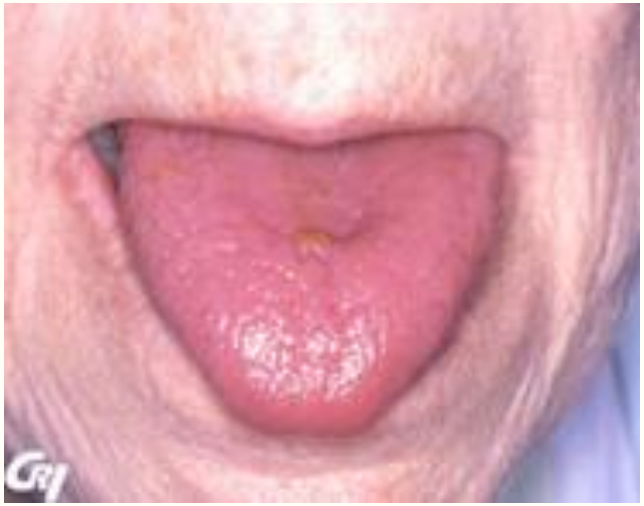


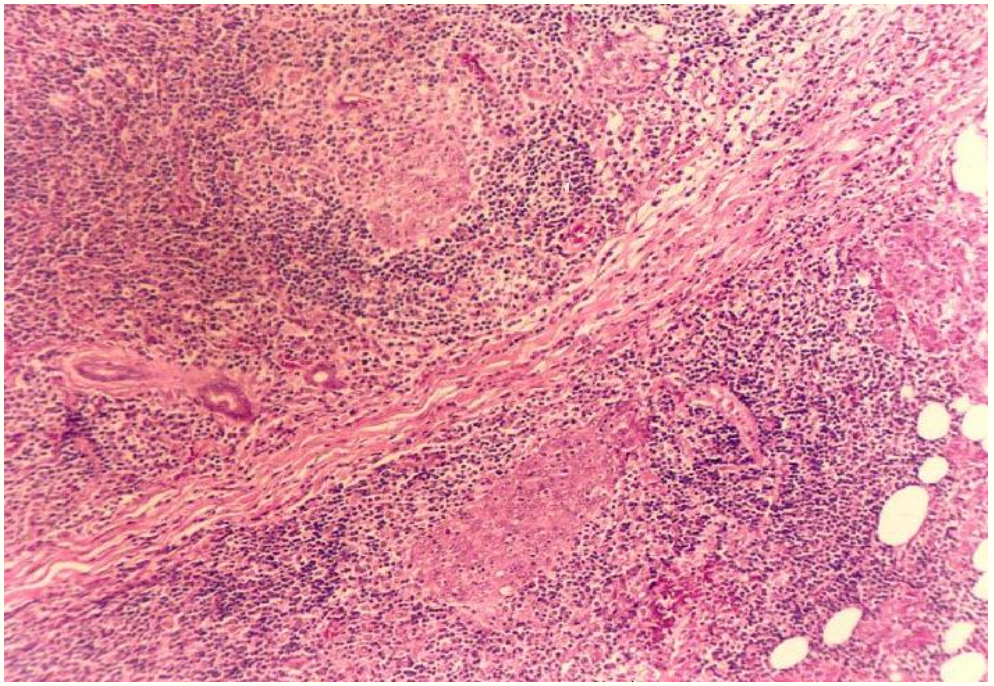


Sjögren syndrome

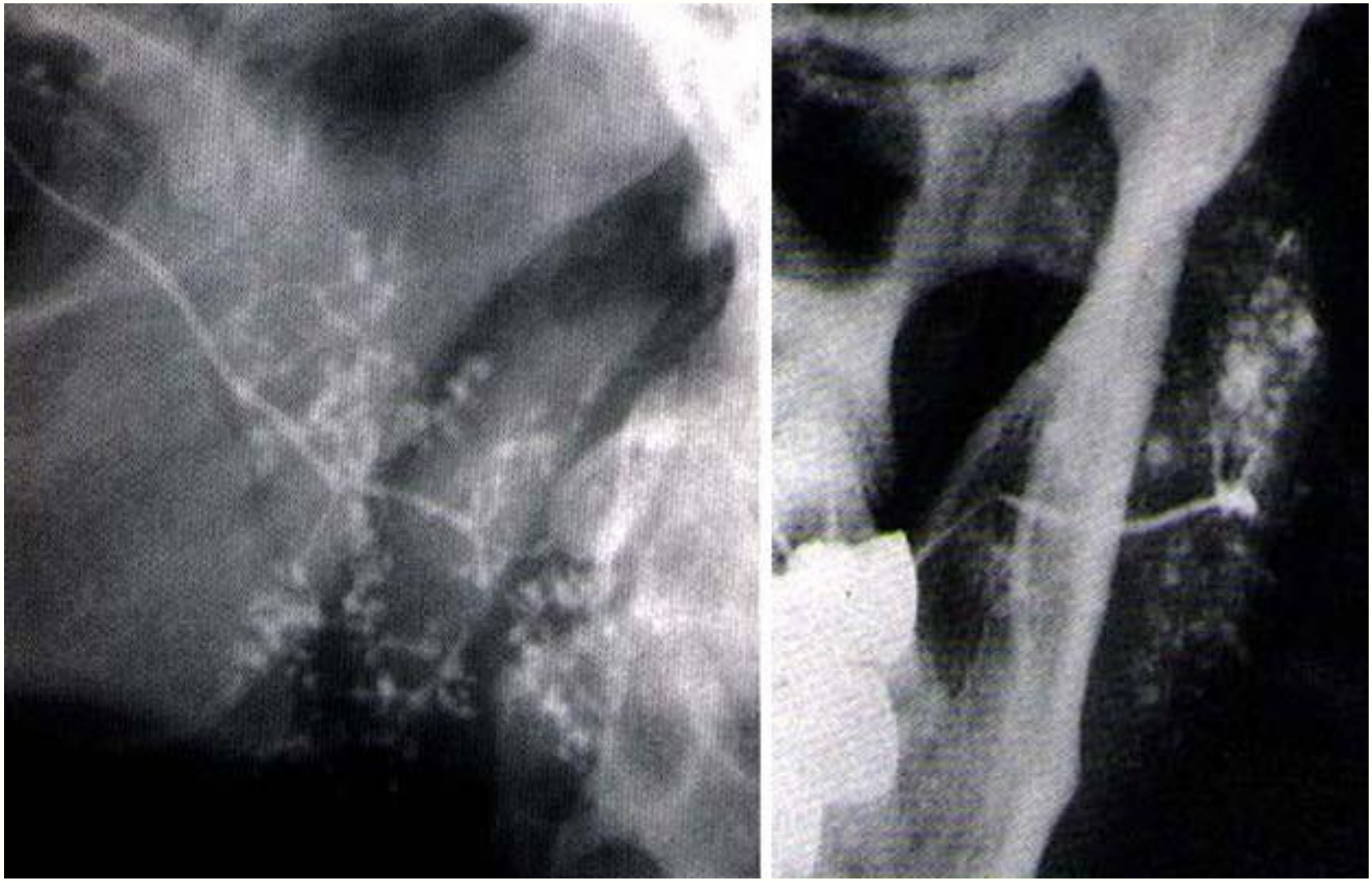








Sjögren syndrome



Sjögren's syndrome is a chronic disorder that causes insufficient moisture production in certain glands of the body.

Sjögren's syndrome is named after the Swedish eye doctor, *Henrik Sjogren*, who first described the condition:

- Extremely dry eyes
- Extremely dry mouth and throat
- Enlarged parotid glands and sometimes infection of the parotid glands
- Excessive fatigue
- Aches, pains in muscles and joints

Sjögren's syndrome occurs in two basic forms:

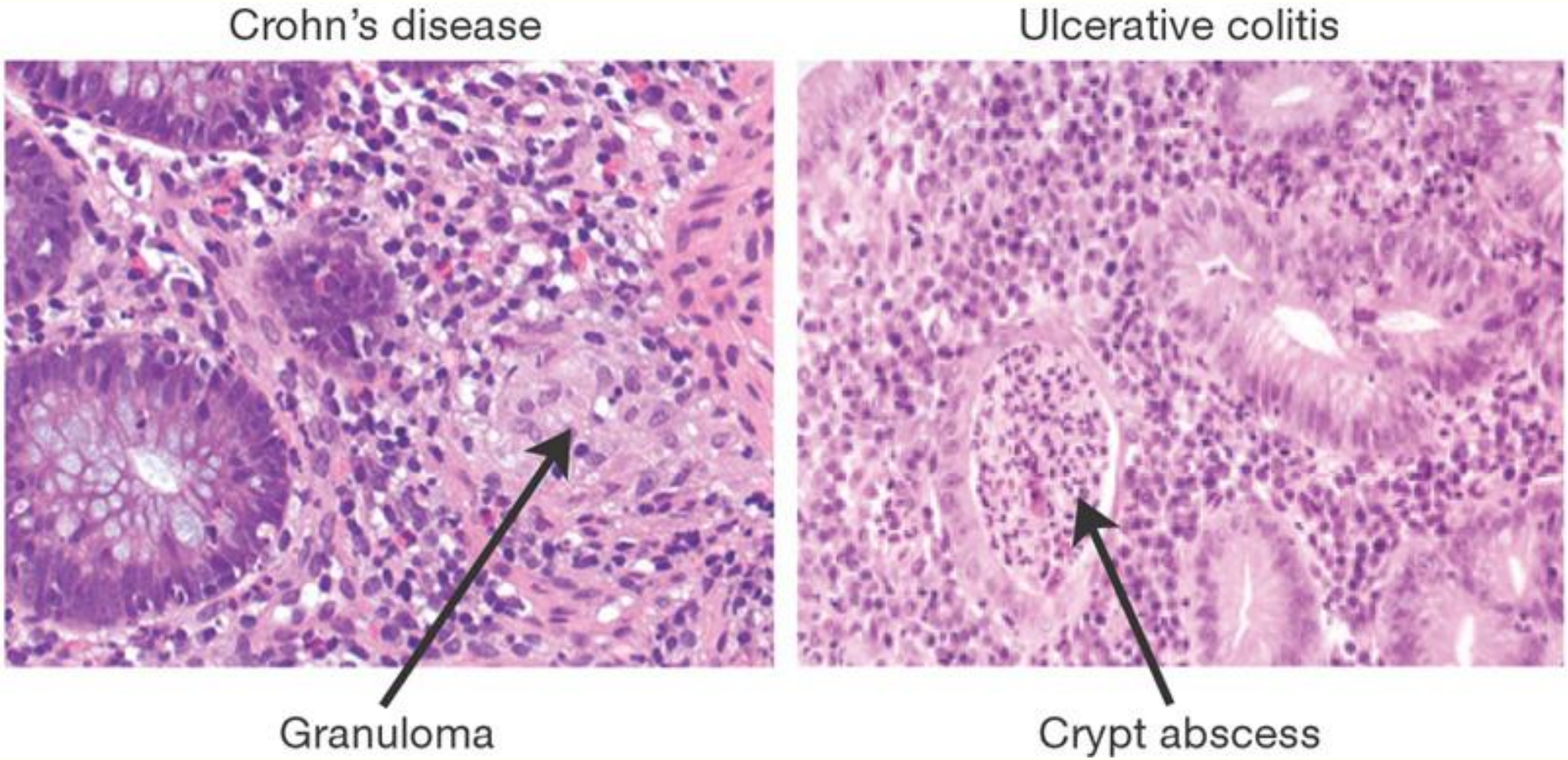
- Primary Sjögren's syndrome – the disease by itself, not associated with any other illness

- Secondary Sjögren's syndrome – disease that develops in the presence of another autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus or vasculitis

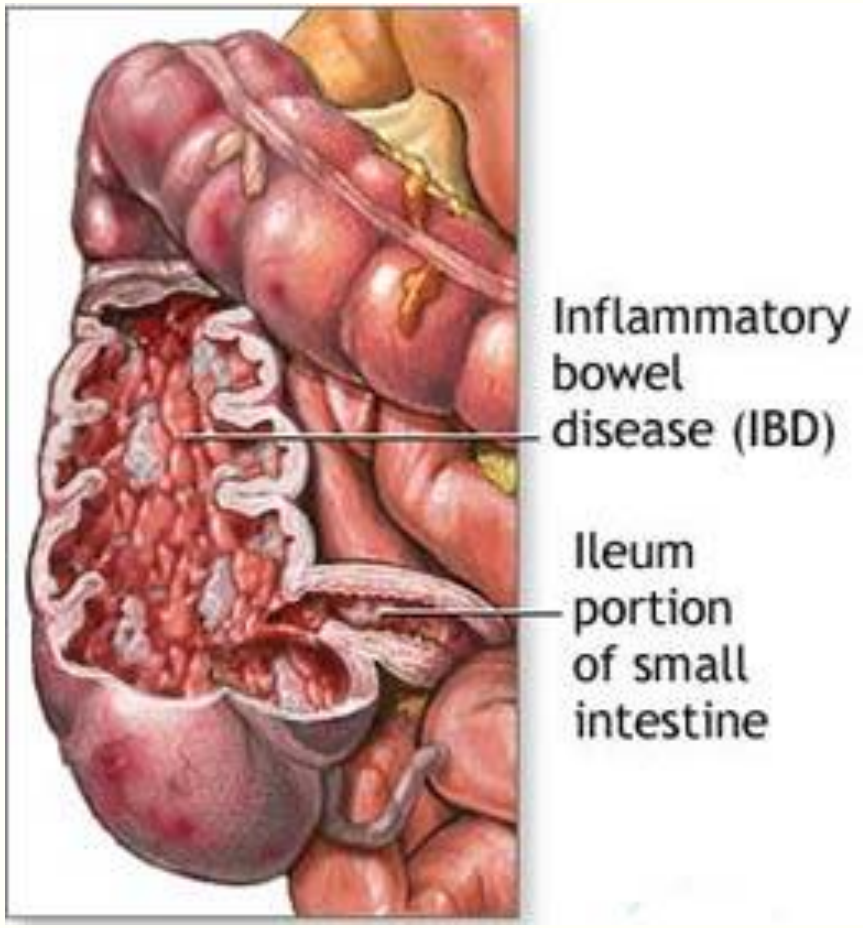
Inflammatory Bowel Diseases

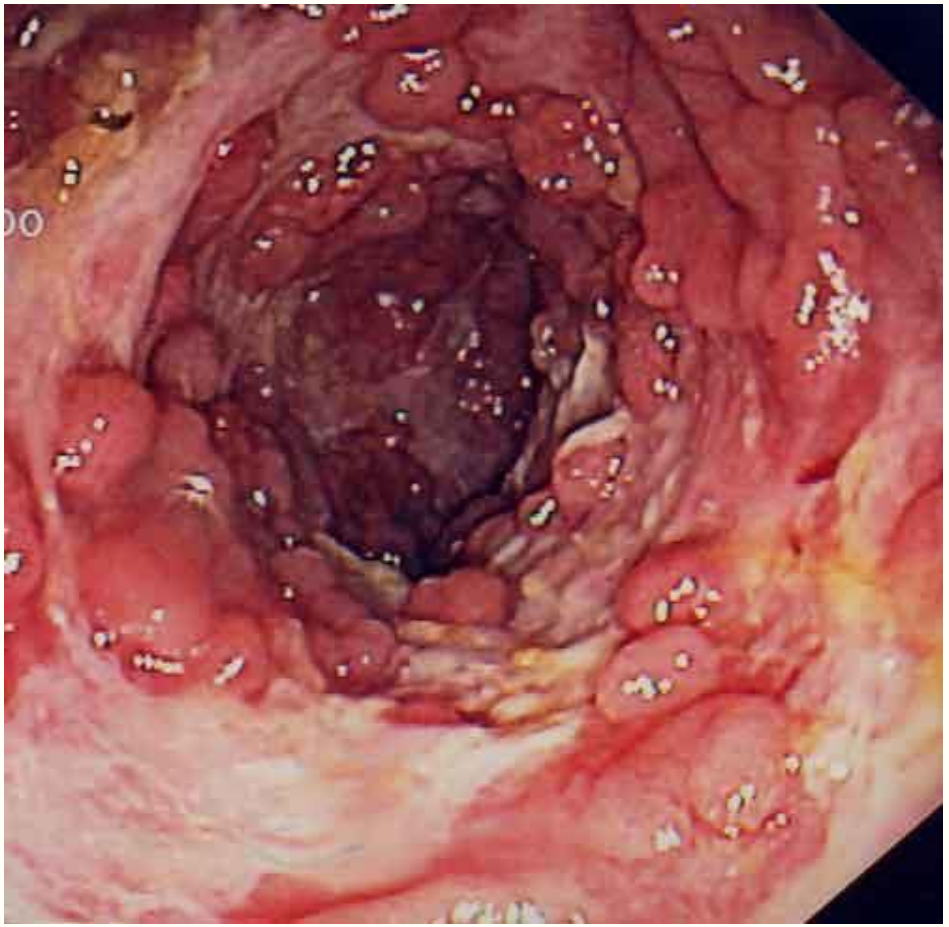
- Chron's disease,
- Ulcerative colitis
- Celiac disease
- Collagenous colitis
- Lymphocitic colitis
- Ischaemic colitis
- Diversion colitis
- Behcet's disease
- Indeterminate colitis

Inflammatory Bowel Diseases

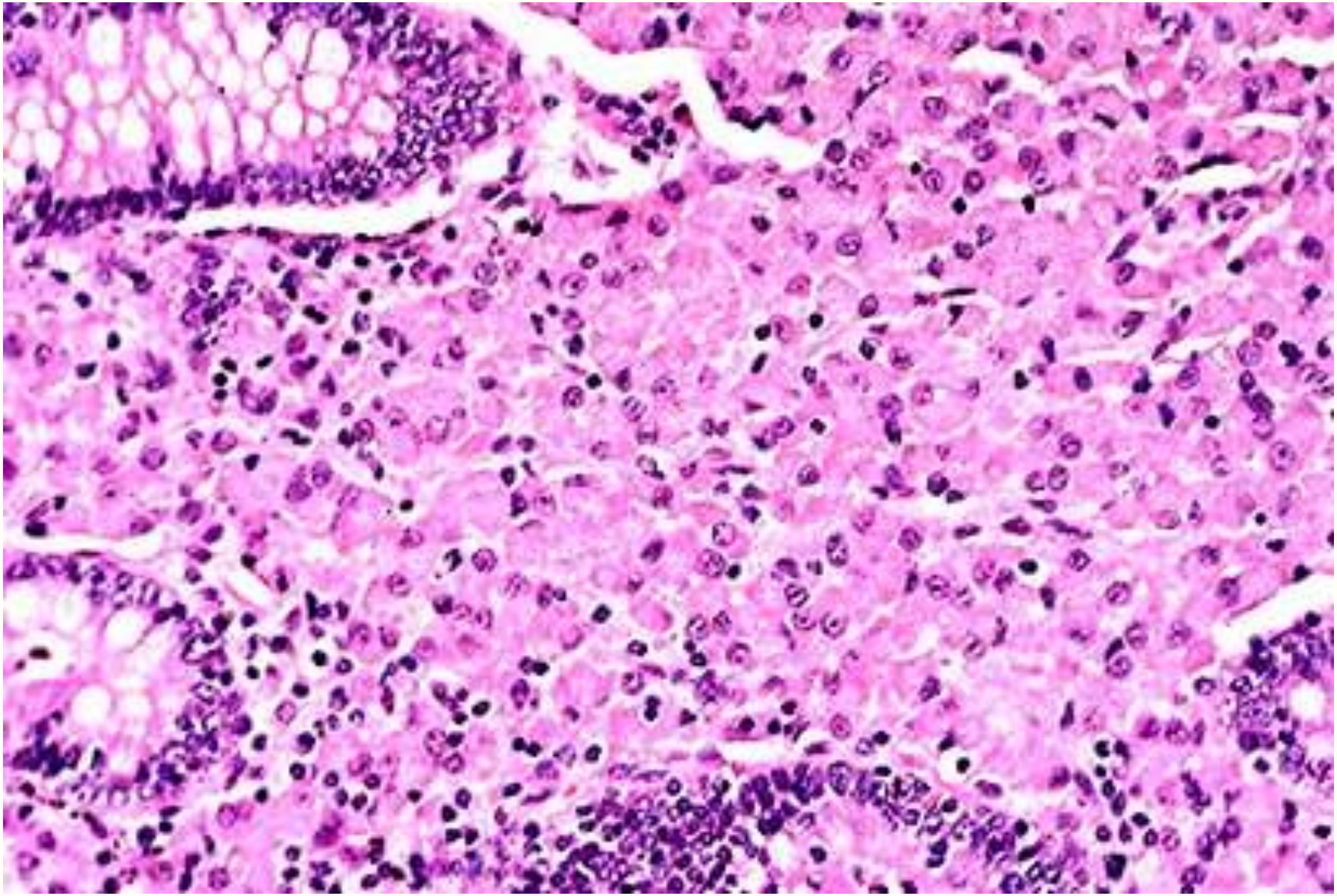


Crohn's disease

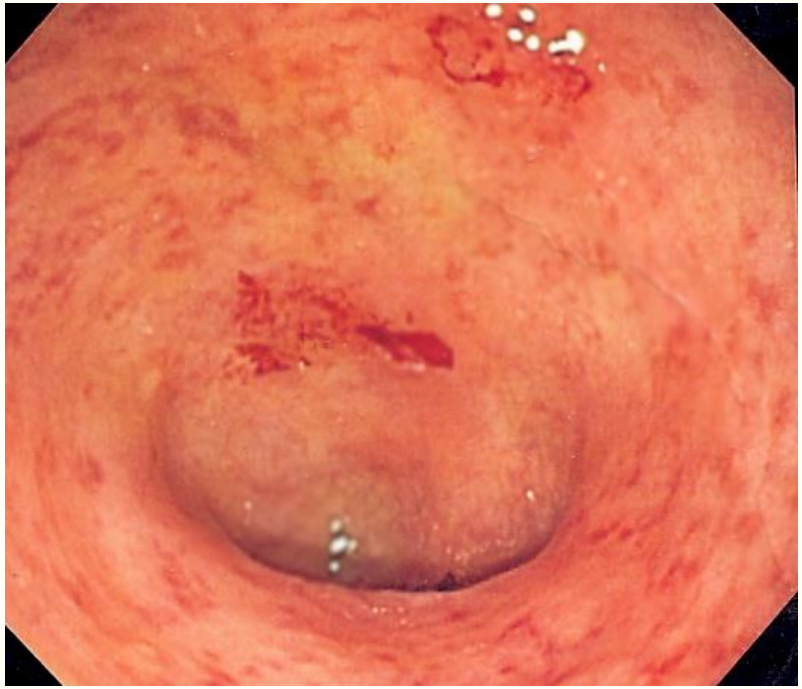


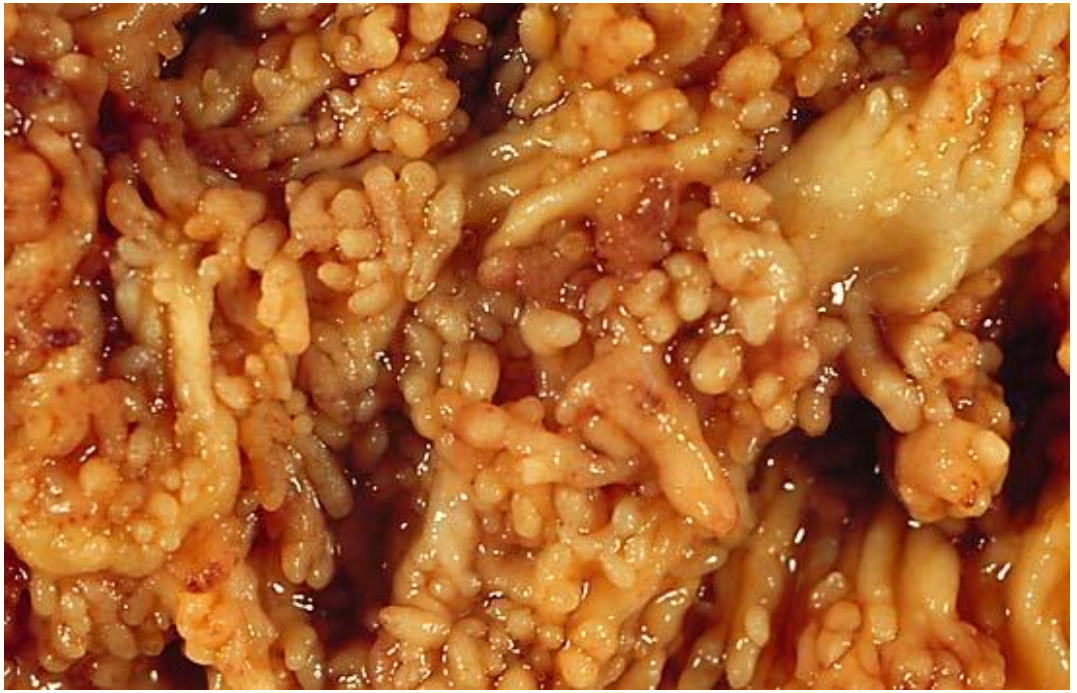


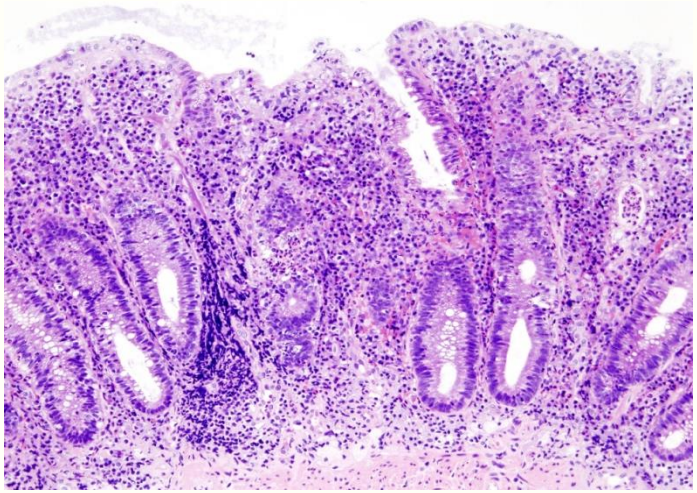
Crohn's disease

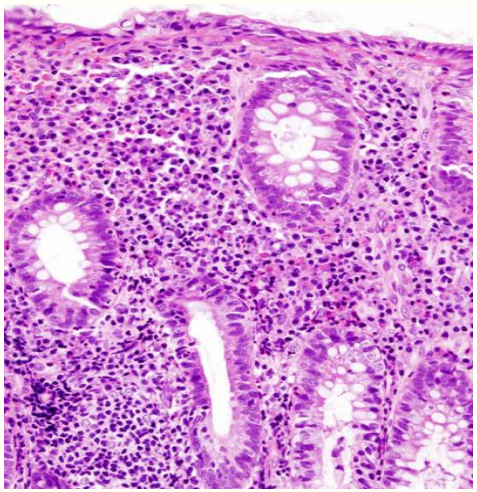


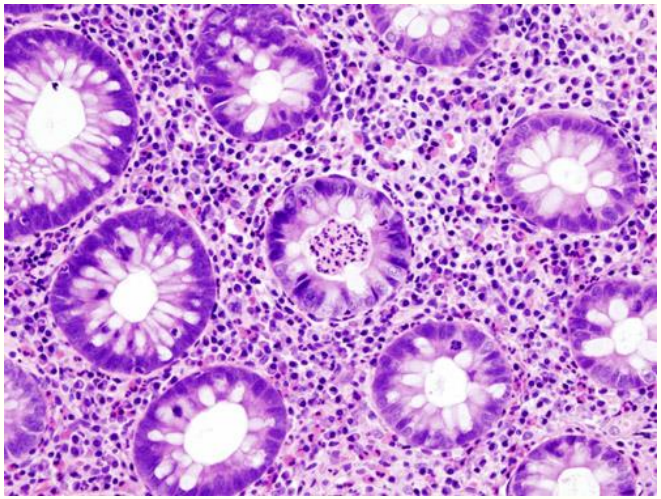
Ulcerative colitis



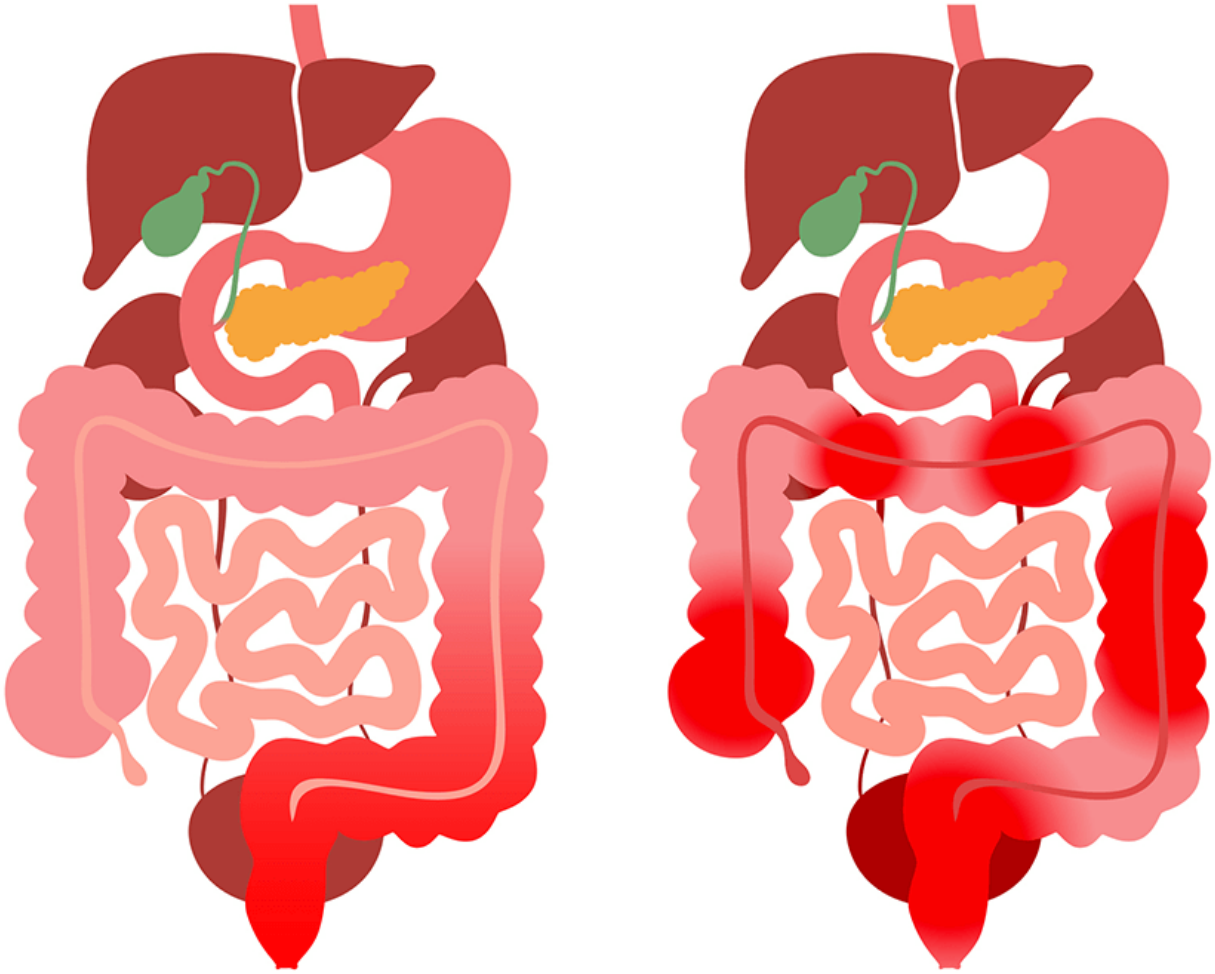








INFLAMMATORY BOWEL DISEASE (IBD)



Ulcerative colitis

Crohn's disease

Inflammatory Bowel Disease