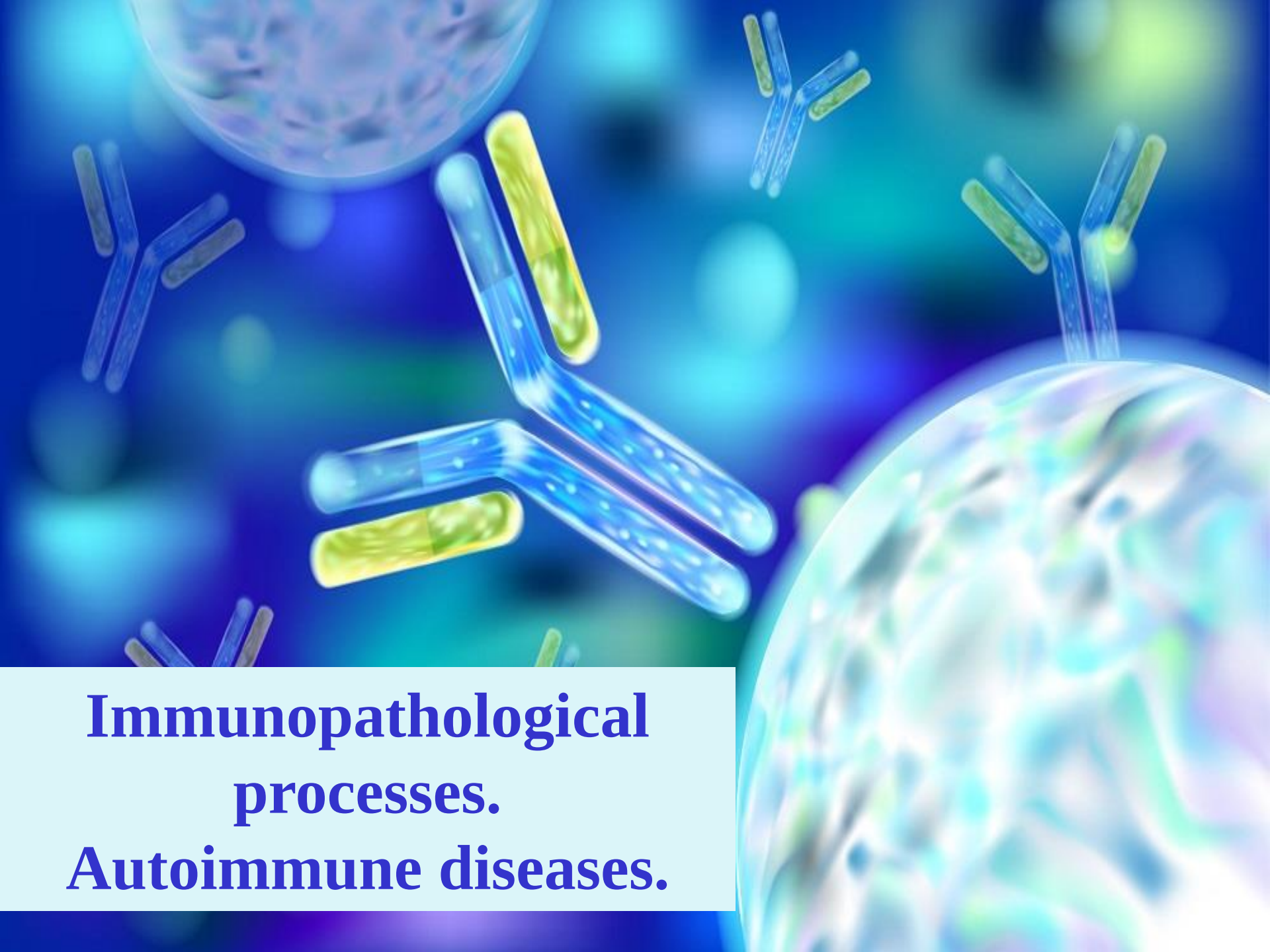


Immunopathological processes. Autoimmune diseases.

Immunopathological processes. Autoimmune diseases.

Microspecimens:

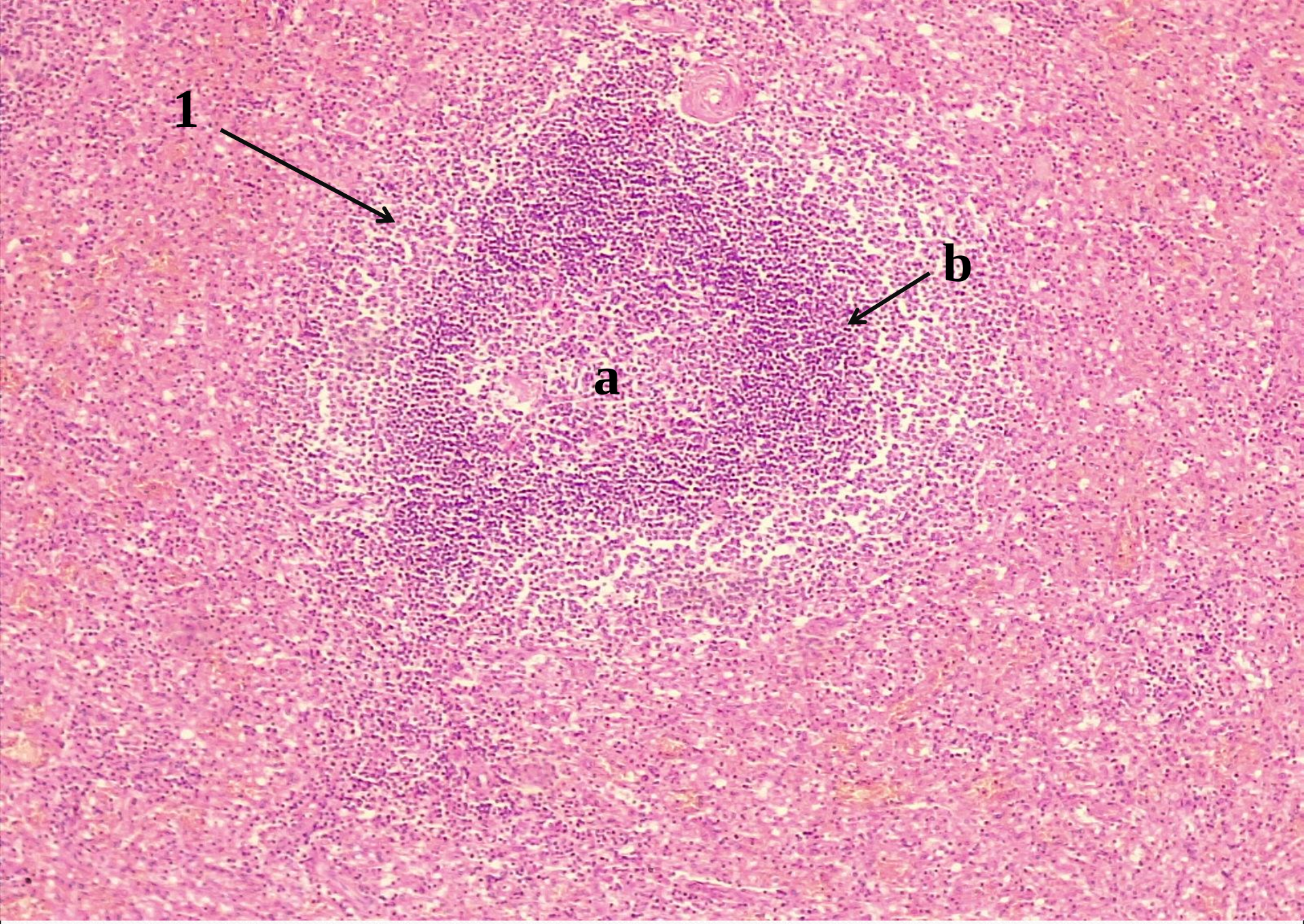
№ 200. Hyperplasia of lymphoid splenic follicles in antigenic stimulation. *(H-E. stain).*

Indications:

1. Lymphoid follicle:
   a. germinal center enlarged in size;
   b. the peripheral part of the follicle.

Microscopically, in spleen there is hyperplasia of the secondary lymph follicles, they are enlarged in size, with clear, well-defined germinal centers, rich in lymphoblasts and macrophages, at the periphery of the follicles, the proliferation of plasmablasts and plasmacytes is observed.

Macroscopically, the spleen is enlarged, has a mottled appearance, with multiple whitish foci, representing hyperplasia of lymphatic follicles with germinal centers on the background of hyperemic juicy red pulp. The appearance of secondary follicles and the extent of their development, as well as the plasmatization of peripheral, burso-dependent follicle areas, reflect the degree of intensity of the humoral immune reaction and increased level of antibody produced by plasma cells. The humoral immune reaction develops in response to the penetration into the body of various soluble (dissolved) antigenic substances, e.g., microbial toxins, extracellular pathogens (bacteria). Destruction of the antigen by the specific antibody produced by the plasma cells takes place, the precursor of which is the lymphocyte B. The antigen-antibody complex is phagocyted by macrophages and eliminated from the body (immune phagocytosis).



№ 200. Hyperplasia of lymphoid splenic follicles in antigenic stimulation. *(H-E. stain).*

№ 173. Accidental thymus involution. *(H-E. stain).*

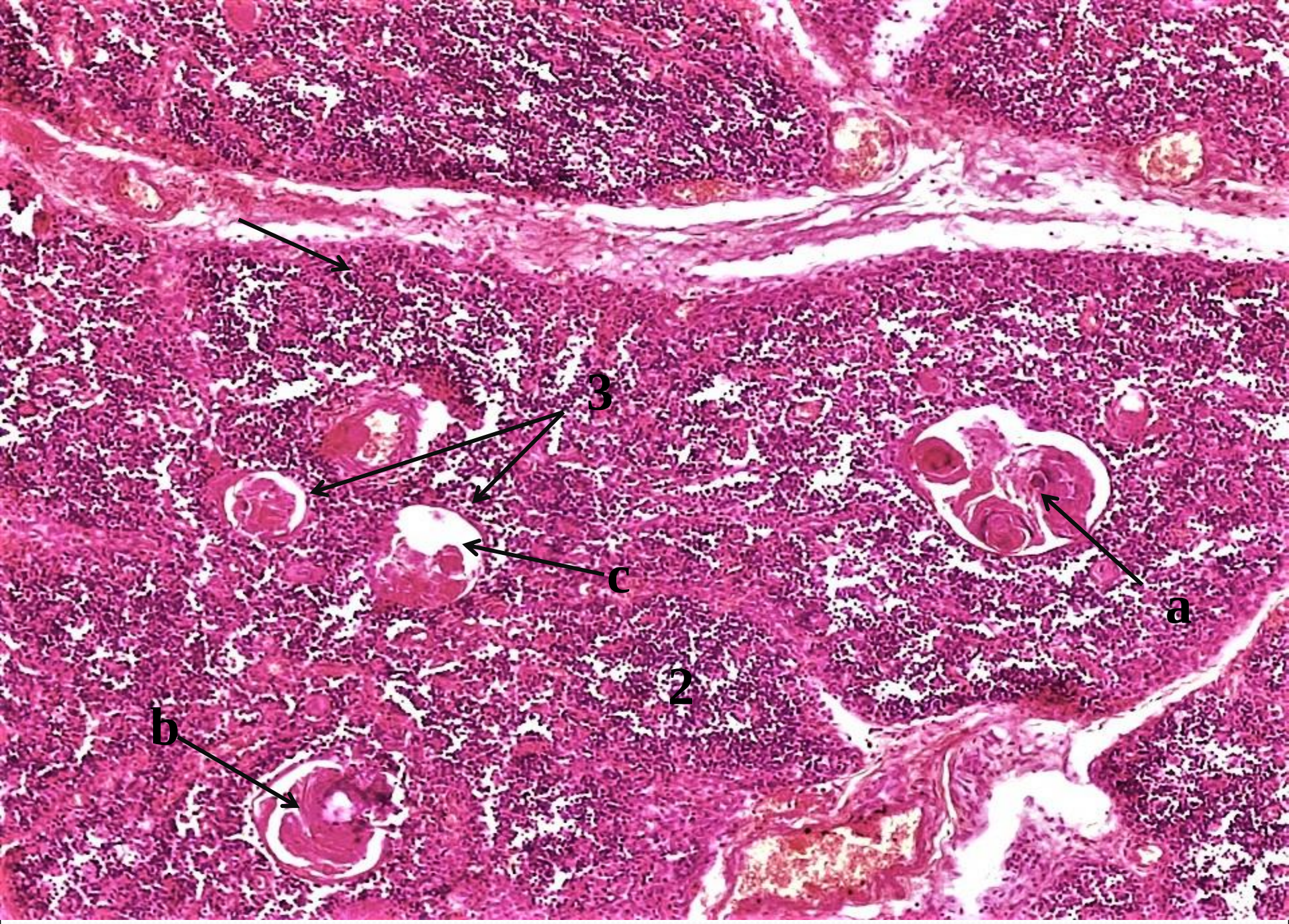
Indications:

1. Reducing the number of lymphocytes in the cortex of thymic lobule.
2. Lymphocytes of the medulla of the thymic lobule.
3. Hassall's corpuscles with dystrophic and necrotic lesions:
   a. calcium deposits;
   b. homogeneous eosinophilic foci;
   c. cystic cavities.

Microscopically, thymic lobes are reduced in size, the cortical layer is thin and poor in lymphocytes, the medullary layer has lymphocyte content equal or even richer than in the cortical layer. The normal feature for the thymic lobes (lymphocyte-rich cortex, of basophilic color, and clear, lymphocyte-poor medulla) is poorly pronounced or absent. The Hassall corpuscles are decreased in size, represent homogeneous eosinophilic masses, some of them are with cystic cavities and foci of calcinosis. The reticular epithelium is collapsed, the interlobular connective tissue bundles are thickened.

In accidental or stress involution of the thymus, take place massive destruction of lymphocytes from cortical layer, characterized by, lymphocytes karyorrhexis, their active phagocytosis by the macrophages, collapse of the reticular epithelium, degenerative calcinosis and appearance of cystic cavities in Hassall corpuscles. Macroscopically the thymus decreases rapidly in size and mass (about 8-10 times in a few days). Characteristic histological sign - equalization or even inversion of the layers of the thymic lobes by lymphocytes content, cortico-medullary distinction disappears due to depletion of the cortical T lymphocytes, lymphocytes content in medullary layer becoming equal or greater.

It is encountered in children with severe infectious diseases, malignant tumors with metastases, leukemias, traumas, different states of shock and severe stress, when the rapid release of adrenal corticosteroids occurs and massive antigenic stimulation of the immune system. Glucocorticoid hormones have the ability to induce thymocytes apoptosis. The degree of thymus involution is more pronounced the longer and more severe is basic disease. The pathological process may be reversible, thymus has a remarkable regenerative potential, but in severe states acquired atrophy of thymus may occur. In such cases, the thymus turns into a fibro-adipose mass with remaining islands of reticular epithelium and a small number of lymphocytes. The importance of stress involution of thymus, is decreased cellular and humoral immunity.



№ 173. Accidental thymus involution. *(H-E. stain).*

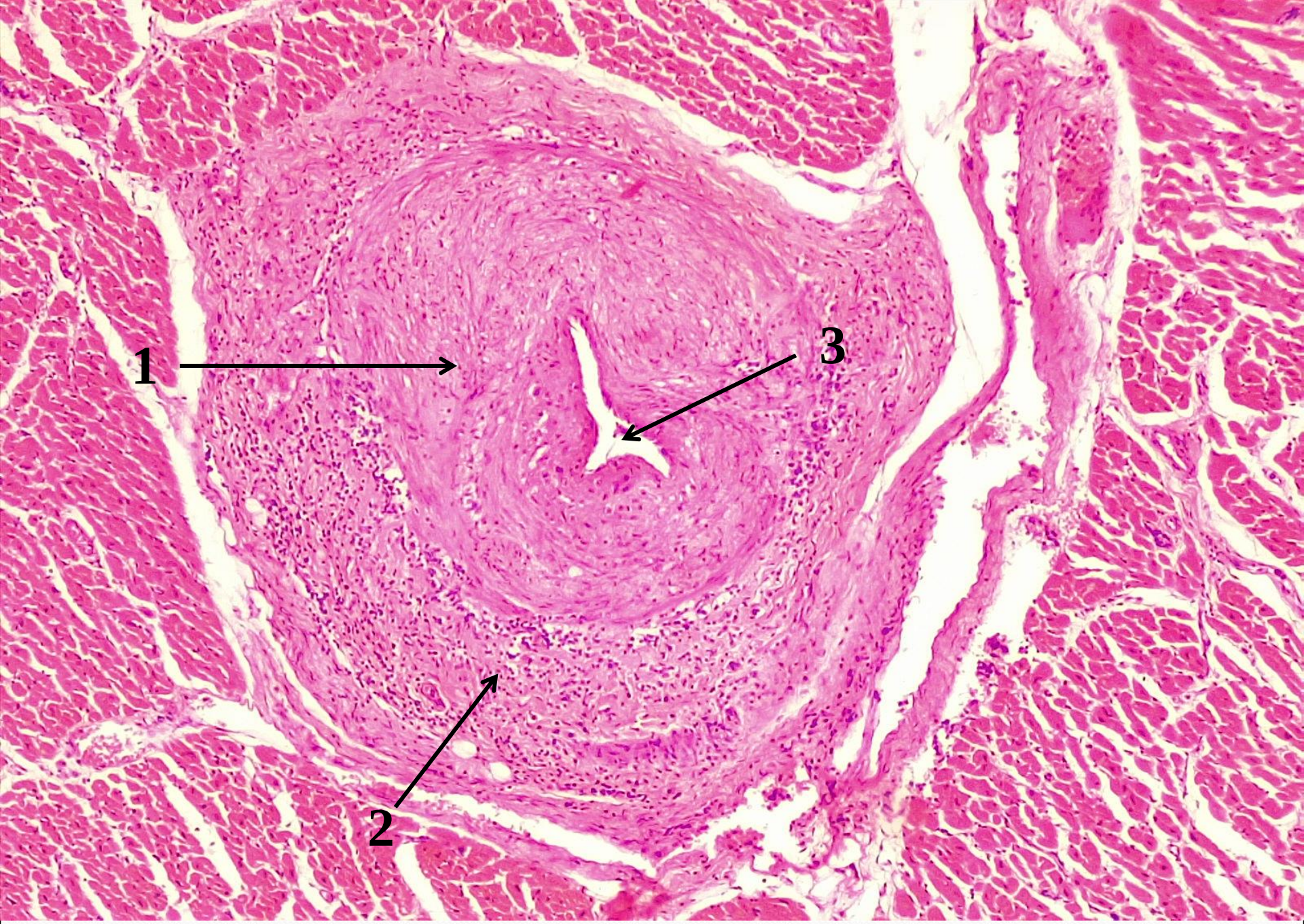
№ 125. Polyarteritis nodosa. *(H-E. stain).*

Indications:

1. Thickened arterial wall.
2. Diffuse lymphocytic and macrophage infiltration located predominantly in adventitia.
3. Narrowed artery lumen.

In the microspecimen, there are branches of the coronary arteries with thickened walls, lumen stenosis. The arterial walls are edematous, infiltrated with lymphocytes, plasmacytes and macrophages. The inflammatory process has a focal, nodular character and is more pronounced in the adventitia. In adjacent cardiomyocytes – granular and hyaline degeneration.

Nodular polyteritis is a systemic vasculitis, generalized, affecting the small and medium caliber arteries, being involved more frequently the renal (90-100%), coronary (88-90%), mesenteric (57-60%), cerebral (45%) arteries, and others. Morphologically it is manifested by predominantly exudative changes in the media of the vessels and predominantly proliferative - in adventitia. It can be acute, subacute and chronic. During periods of acute exacerbation there may be fibrinoid necrosis of the walls of the arteries, thrombosis and infarction. It results in nodular sclerosis and non-uniform stenosis of the arteries with chronic ischemia of the respective areas, parenchyma atrophy and sclerosis. It is an immune disease, mediated by circulating immune complexes or formed in situ. In 1/3 of the patients cases, have hepatitis B, and in the arteries there are immune complexes, consisting of the surface antigen of the hepatitis B virus - HBsAg and the anti-HBsAg antibody.



№ 125. Polyarteritis nodosa. *(H-E. stain).*

№ 148 Hashimoto's thyroiditis. *(H-E. stain).*

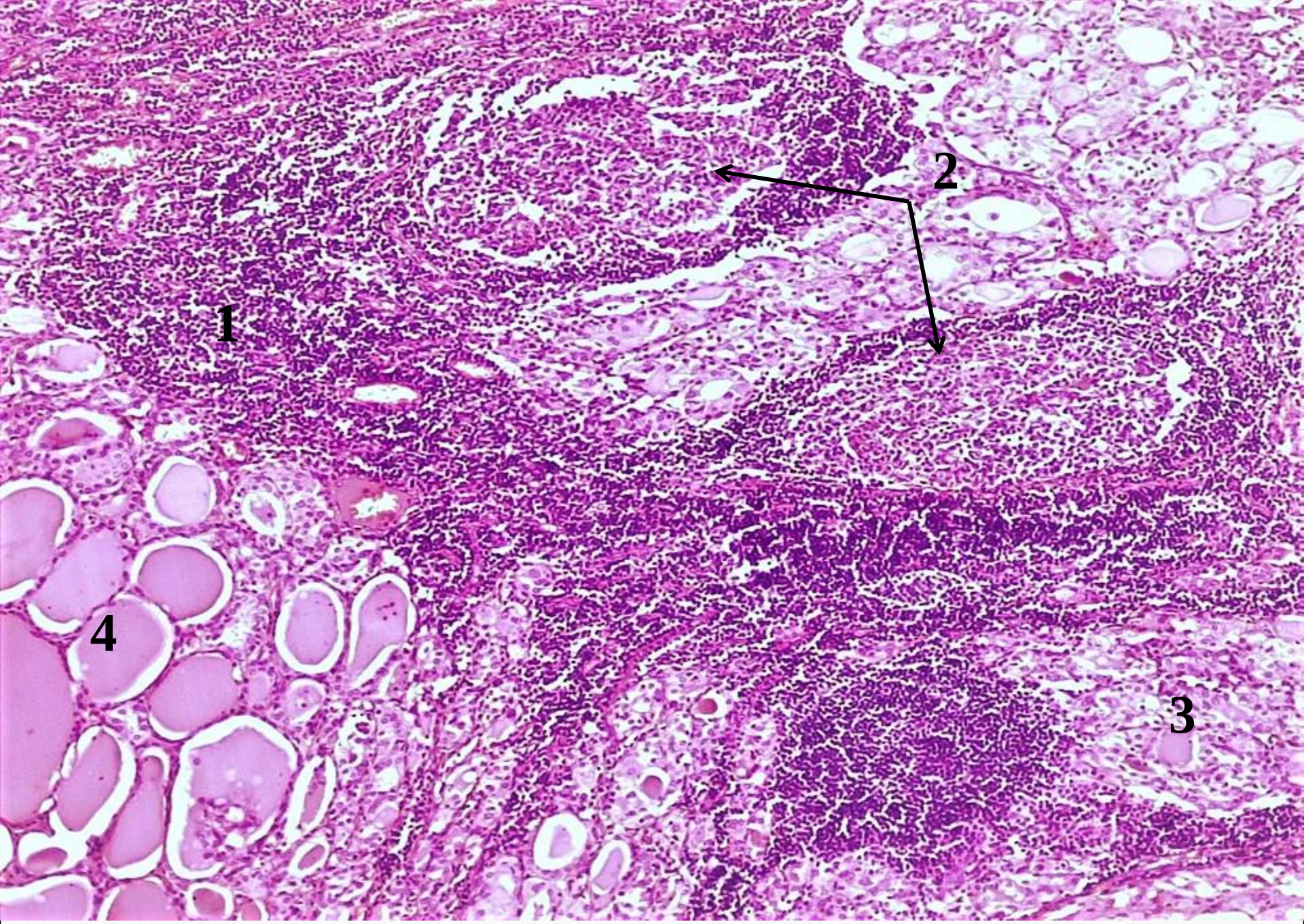
Indications:

1. Lymphocyte infiltration of the thyroid gland.
2. Lymphatic follicles.
3. Atrophied thyroid follicles with pale colloid.
4. Unchanged thyroid follicles.

In the thyroid gland there is diffuse infiltration of the stroma with lymphocytes and plasmocytes, sometimes with the formation of lymphoid follicles with clear germinal centers. These infiltrates replace the glandular parenchyma, the thyroid follicles are atrophied, contain weakly colored or vacuolized colloid, some of them without lumen, also are present foci of fibrosis. In some follicles the epithelial cells become intensely eosinophilic, with granular cytoplasm, transforming into Hurthle or oncocyte cells, which is a reactive oncocytal metaplasia of the follicular epithelium.

Macroscopically at the initial stage the thyroid gland is enlarged diffused in size, and over time it progressively atrophies, densifies, the parenchyma being replaced by connective tissue. Clinically, it is manifested by hypothyroidism and developes mixedem. It is found almost exclusively in women between 40 and 50 years of age.

Hashimoto's autoimmune thyroiditis or chronic lymphocytic thyroiditis is a true organ-specific autoimmune disease (with organ specificity). It is the first autoimmune disease described by the Japanese physician Hashimoto in 1912. It is the most common cause of hypothyroidism in non-endemic regions, where iodine content is sufficient. The pathogenetic mechanism consists in the disturbance of immunological tolerance to thyroid antigens. In the body appear autoantibodies against to thyoglobulin, thyroid peroxidase, anti-TSH (thyroid stimulating hormone) receptors, which react with the autoantigenic components of thyroid follicles, cause autoimmune inflammation, gradual destruction of thyroid cells by apoptosis, replacement of the glandular parenchyma, with lymphoid infiltrate and fibrous conectiv tissue. The main etiopathogenetic factors are viral infection, radiation and genetic predisposition (certain subtypes of histocompatibility antigens - HLA-DR3 and HLA-DR5).



№ 148 Hashimoto's thyroiditis. *(H-E. stain).*

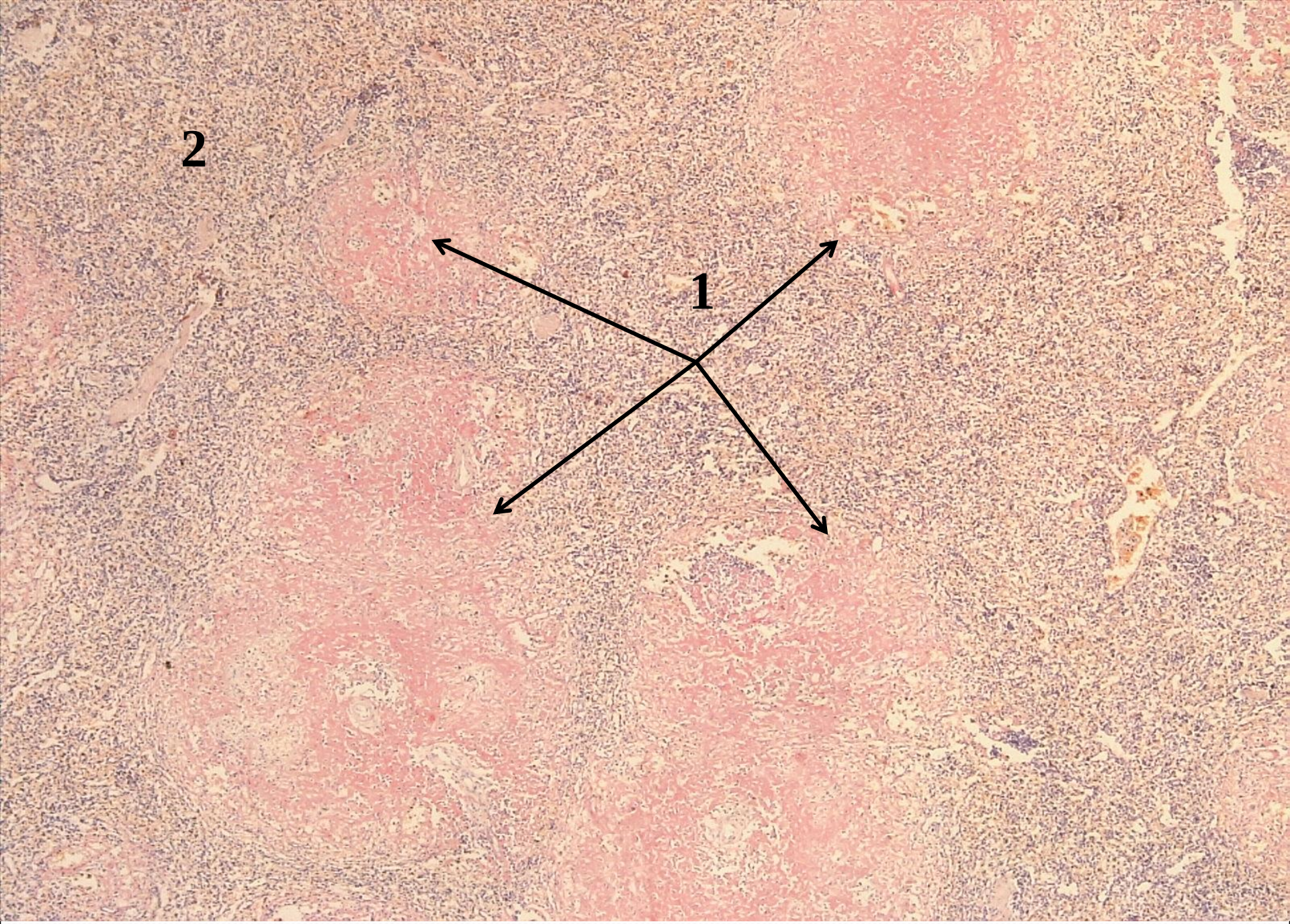
№ 21. Focal spleen amyloidosis *(sago spleen).* *(Congo-red and hematoxylin stain.).*

Indications:

1. Focal deposits of amyloid in the center of lymphoid follicles.
2. Unchanged red pulp.

In the spleen we can see focal deposits of amyloid, uniformly colored in red with Congo red, located in the center of the lymph follicles; deposition of the amyloid masses begins in the walls of the centrofollicular arteries, and then extends throughout the follicle, which gives the macroscopic spleen appearance of a "sago spleen" (amyloid inclusions remember sago grains).

Spleen amyloidosis is a manifestation of generalized amyloidosis, being most commonly found in secondary, reactive amyloidosis (biochemical variant -AA). It is found in tuberculosis, bronchiectasis, chronic osteomyelitis, rheumatoid arthritis, systemic lupus erythematosus. In this form of amyloidosis besides the spleen, other organs of the abdominal cavity are affected, e.g., the kidneys, liver, adrenals, intestine. In some cases in the spleen, the amyloid deposits may be diffuse, spreading all over the red pulp, and macroscopically it becomes greasy. The consequences of spleen amyloidosis may be progressive in amyloid deposits and irreversible atrophy of an organ parenchyma with functional impairment.



№ 21. Focal spleen amyloidosis *(sago spleen).* *(Congo-red and hematoxylin stain.).*

№ 19. Renal amyloidosis. *(Congo-red and hematoxylin stain.)*

Indications:

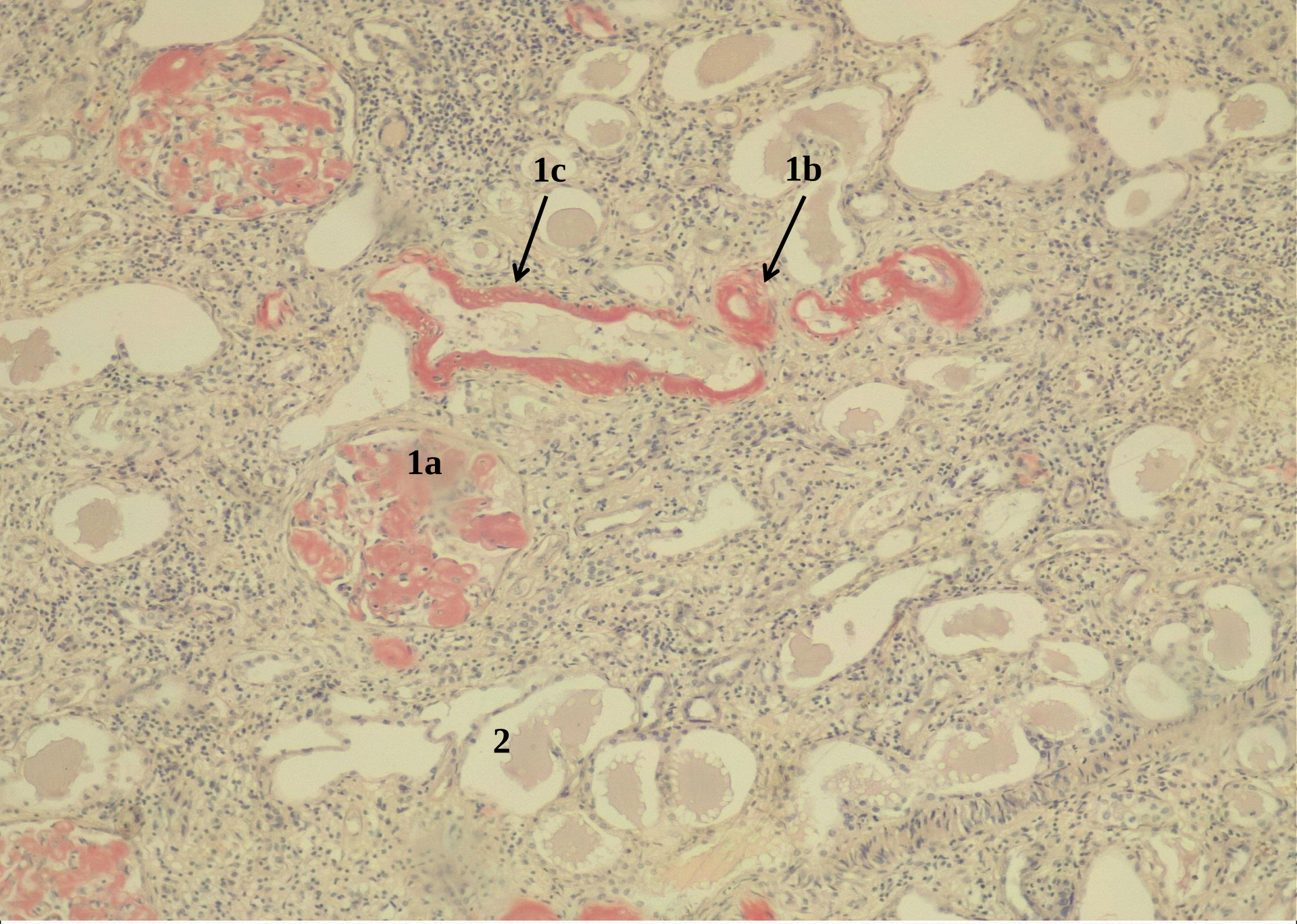
1. Amyloid deposits:
   a. in glomerular capillaries;
   b. in the artery wall;
   c. on the basement membrane of the renal tubules.
2. Protein cylinders in tubule lumen.

In the kidneys it is observed the selective deposition of a homogeneous mass, colored in red, in the glomerular capillaries, under the endothelium, as well as in the walls of the arterioles and small arteries, in tubes containing the basement membrane, under the epithelium and on the path of the reticulum fibers of the stroma. In the epithelial cells of the tubes they contain granular dystrophy, in the lumen of some tubes - hyaline cylinders.

Kidney amyloidosis is a manifestation of generalized amyloidosis. *The macroscopic picture– macrospecimen № 82. Regardless of the organ, the amyloid deposits are detected histologically in: a) the walls of the blood and lymphatic vessels (in the intima or adventitia), b) in the glandular structures (tubes, collecting ducts) and c) in the stroma, along the reticular fibers and collagenic (perireticular and pericolagenic amyloidosis).*

The main methods of identification of the amyloid substance in the histological slides are Congo red (it is colored in red) and polarizing microscopy (it is colored in yellow-green). Macroscopically the amyloid can be identified with the help of the specific Virchow reaction: amyloid deposits are colored with iodine (Lugol solution) in red-brown, which turns after treating the section with a 10% solution of sulfuric acid from blue-violet to dark green.

Amyloidosis is an irreversible process, in the kidneys progressively evolving towards complete replacement of glomeruli and pyramids with amyloid masses, and subsequently diffuse proliferation of connective tissue and amyloid shrunken of the kidneys with the development of renal failure and azotemic uremia.



№ 19. Renal amyloidosis. *(Congo-red and hematoxylin stain.)*

II. Macrospecimens:

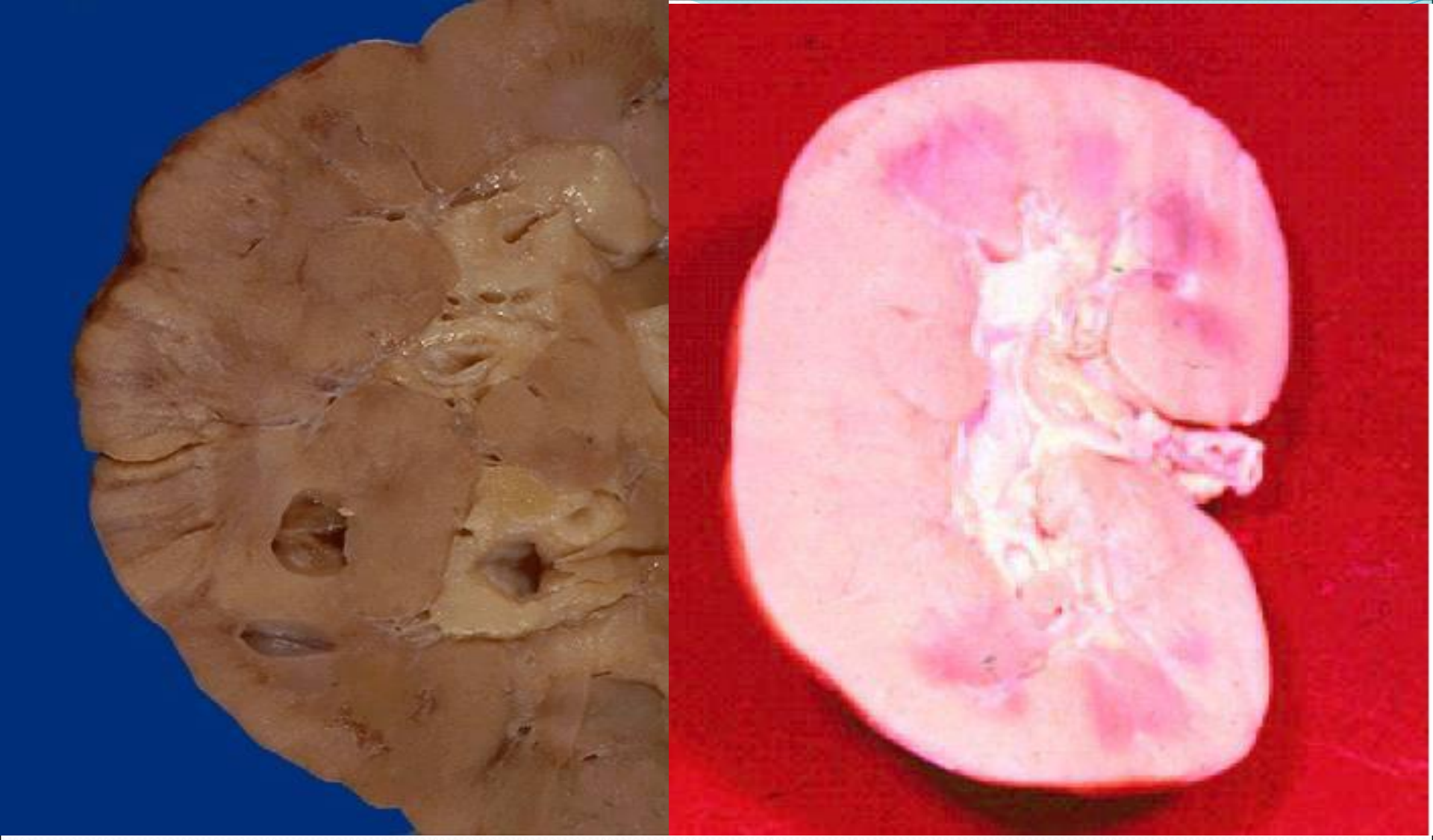
№ 82. Renal amyloidosis.

The kidney is enlarged in size of dense consistency, gray yellowish color and lardy or waxy appearance, the surface is slightly wavy, on section layers are poorly delimited - "big white amyloidic kidney".

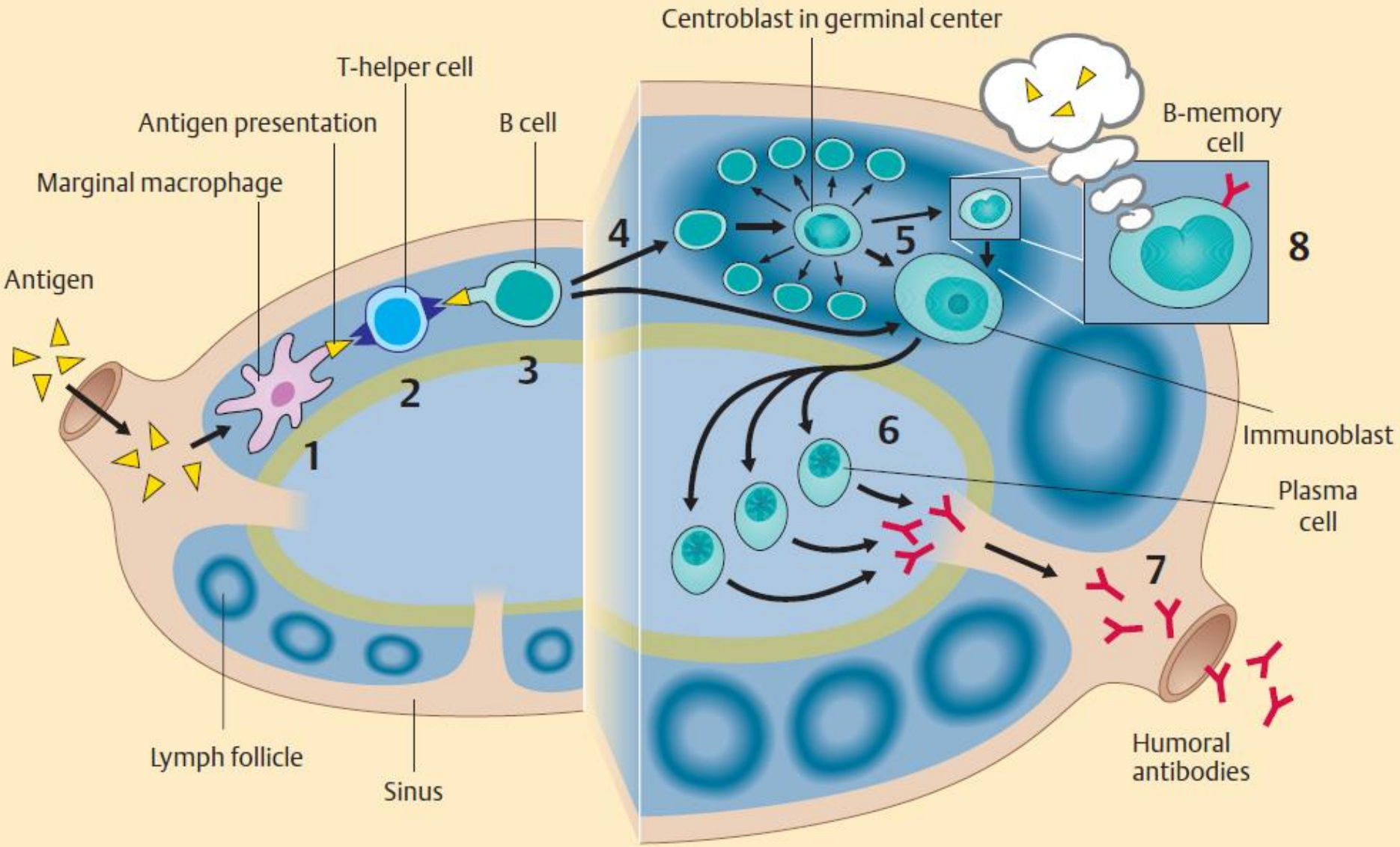
Renal amyloidosis (amyloid nephropathy) is found in both primary amyloidosis, e.g., multiple myeloma (AL amyloidosis) and secondary amyloidosis, eg, purulent osteomyelitis, tuberculosis, bronchiectasis, rheumatoid arthritis (AA amyloidosis).

Clinically manifested by nephrotic syndrome: massive proteinuria (more than 3.5 g in 24 hours, hypoalbuminemia, generalized edema, hyperlipidemia and lipiduria, azotemia, hypertension (in 50% of cases).

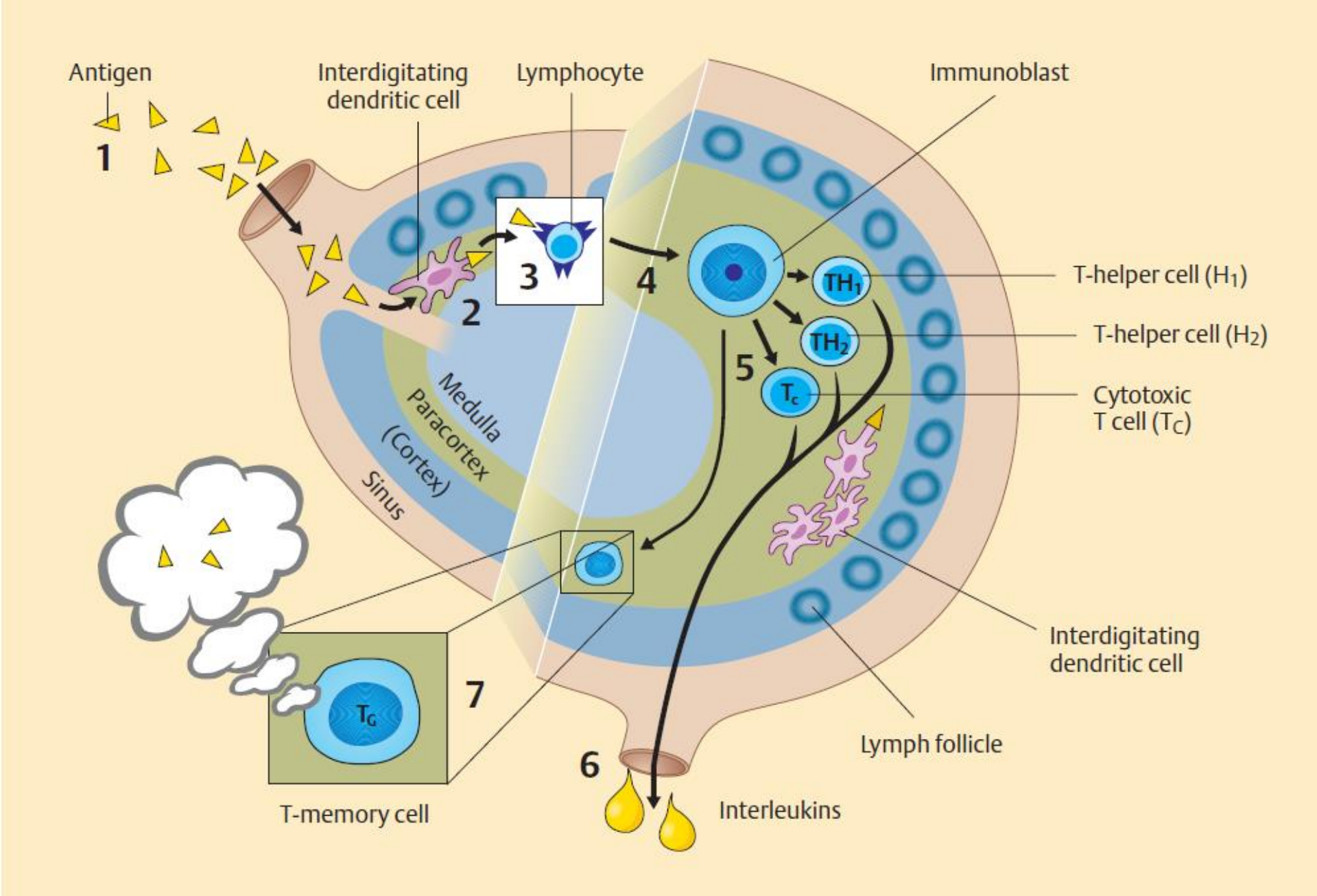
Complications: renal failure, association of infections due to decreased immunity, cardiovascular insufficiency, predisposition to thrombosis of vessels due to loss with urine of immunoglobulins and anticoagulant system proteins.



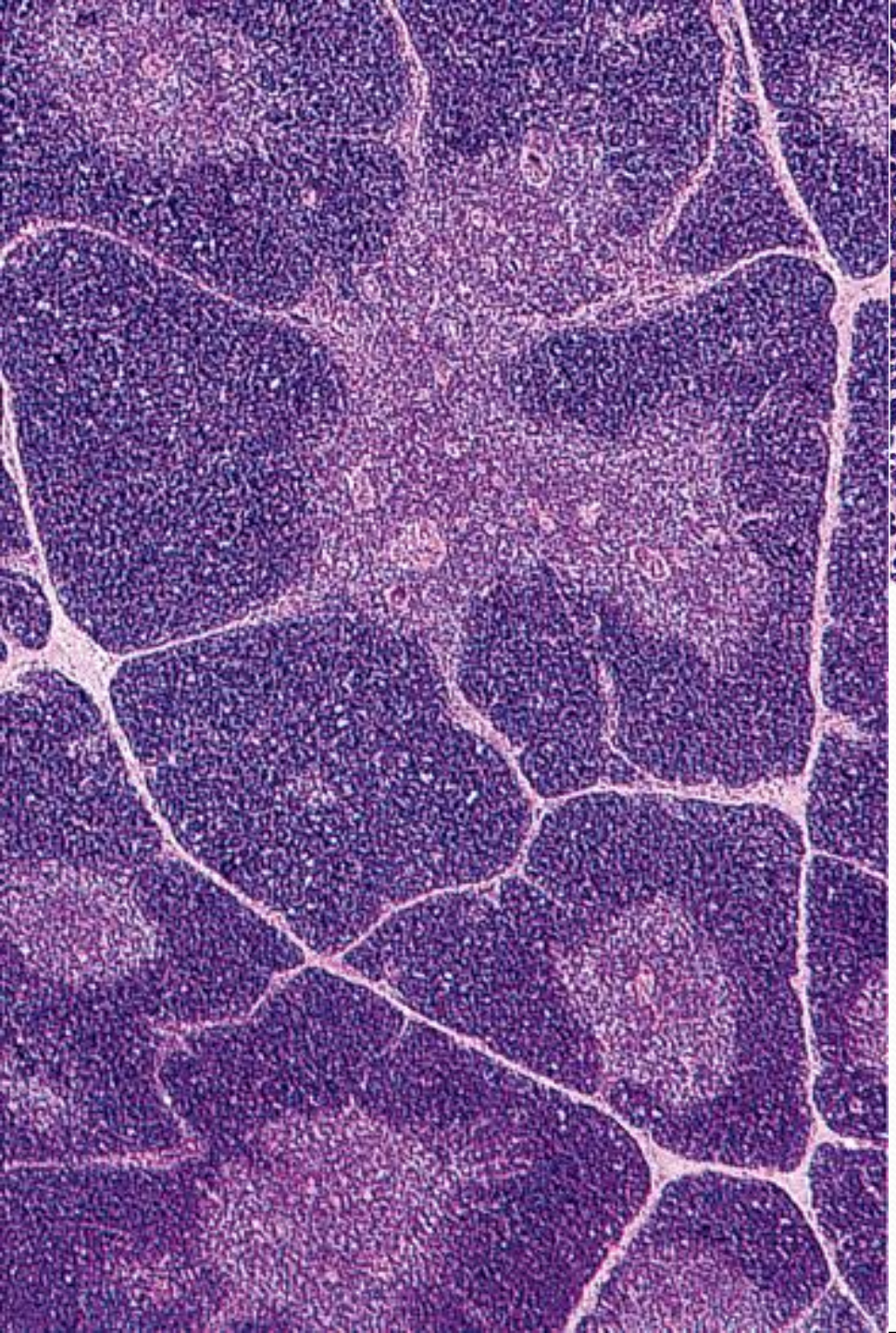
№ 82. Renal amyloidosis.

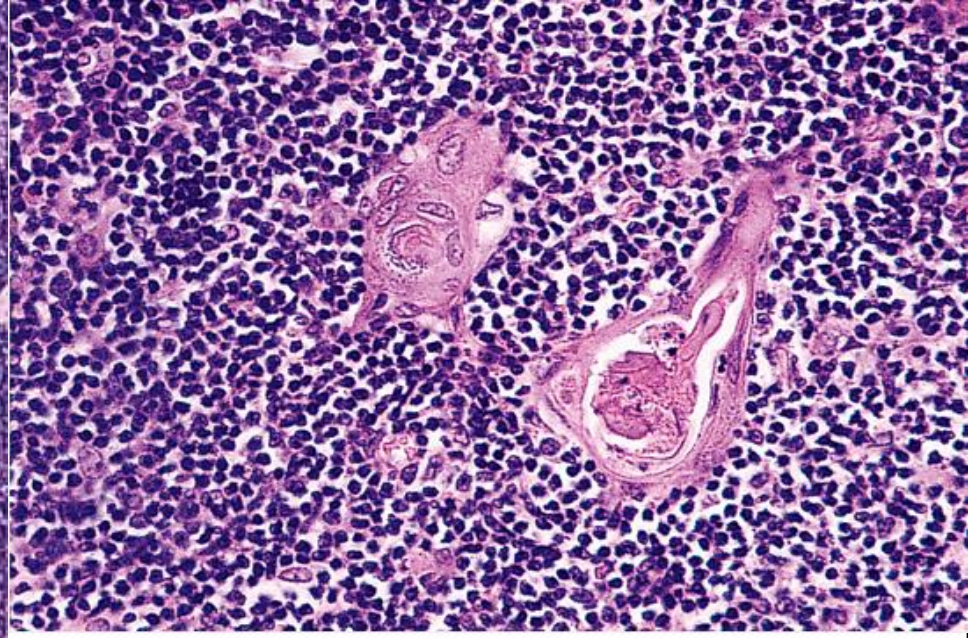


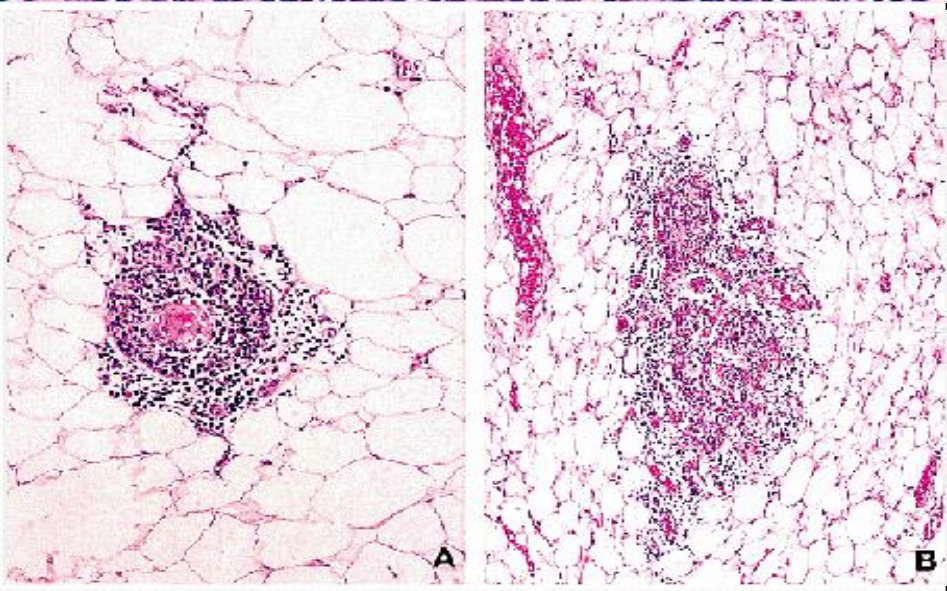
Humoral immune response.



Cellular immune response.

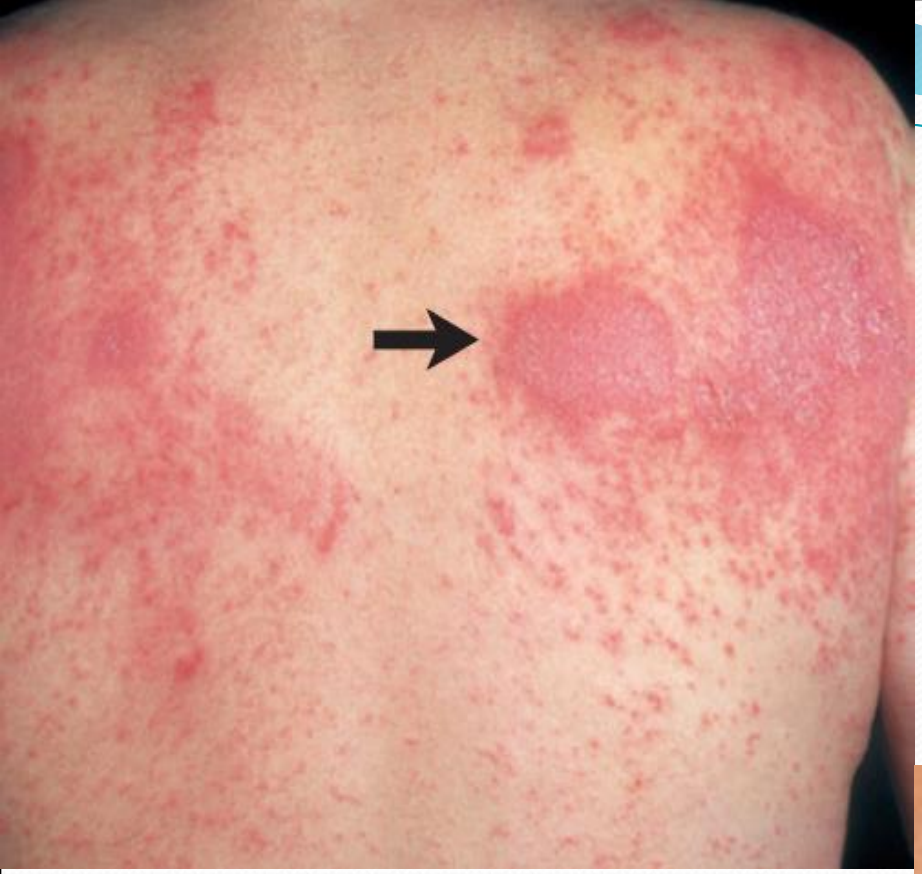






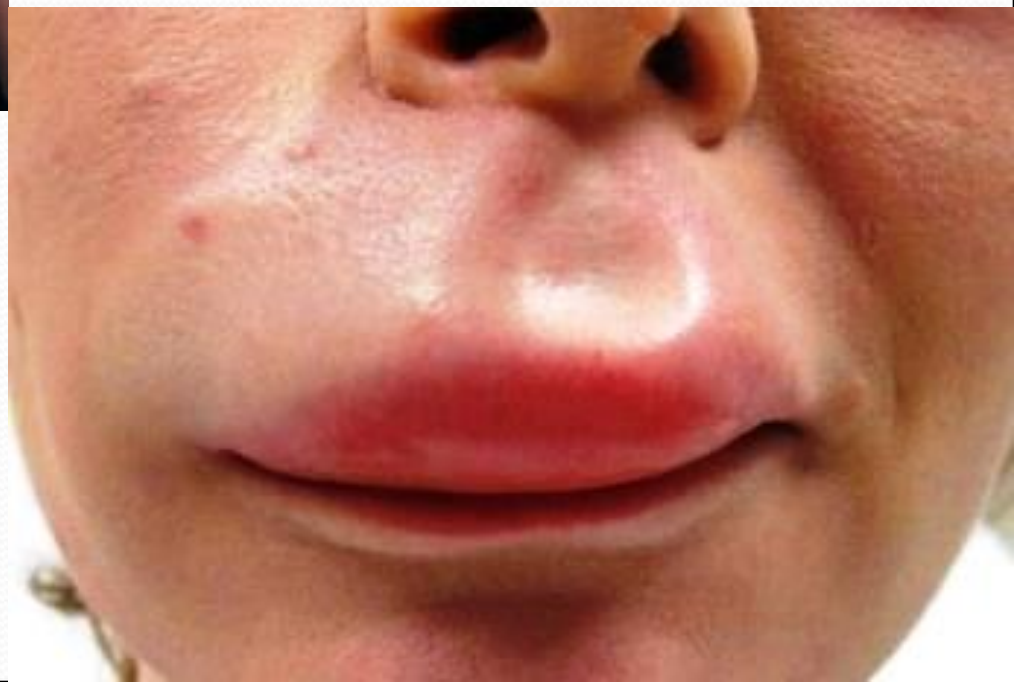
The normal structure of the thymus, A, B - physiological involution.

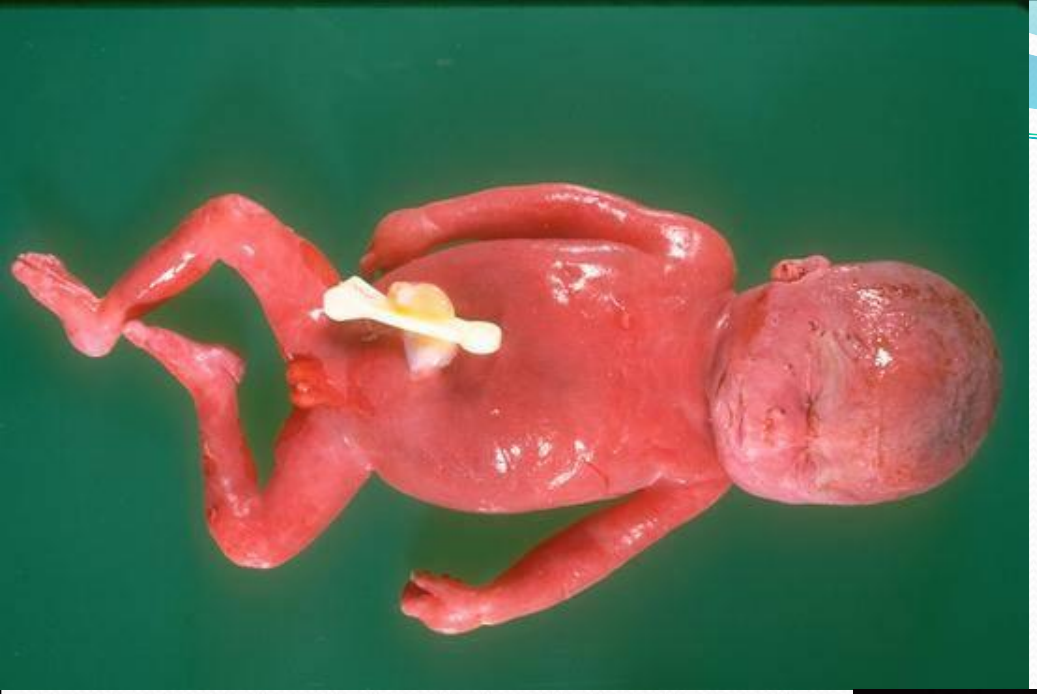
Immediate hypersensitivity reaction (type I).



Allergic (atopic) dermatitis.

Quincke's edema

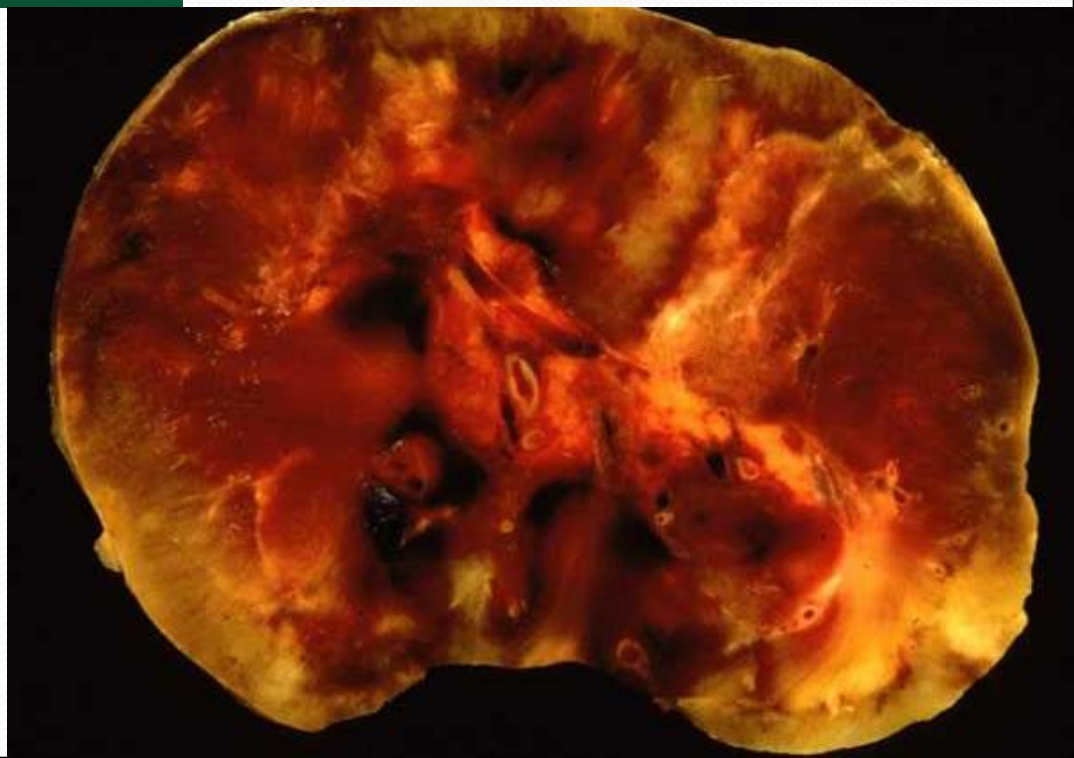


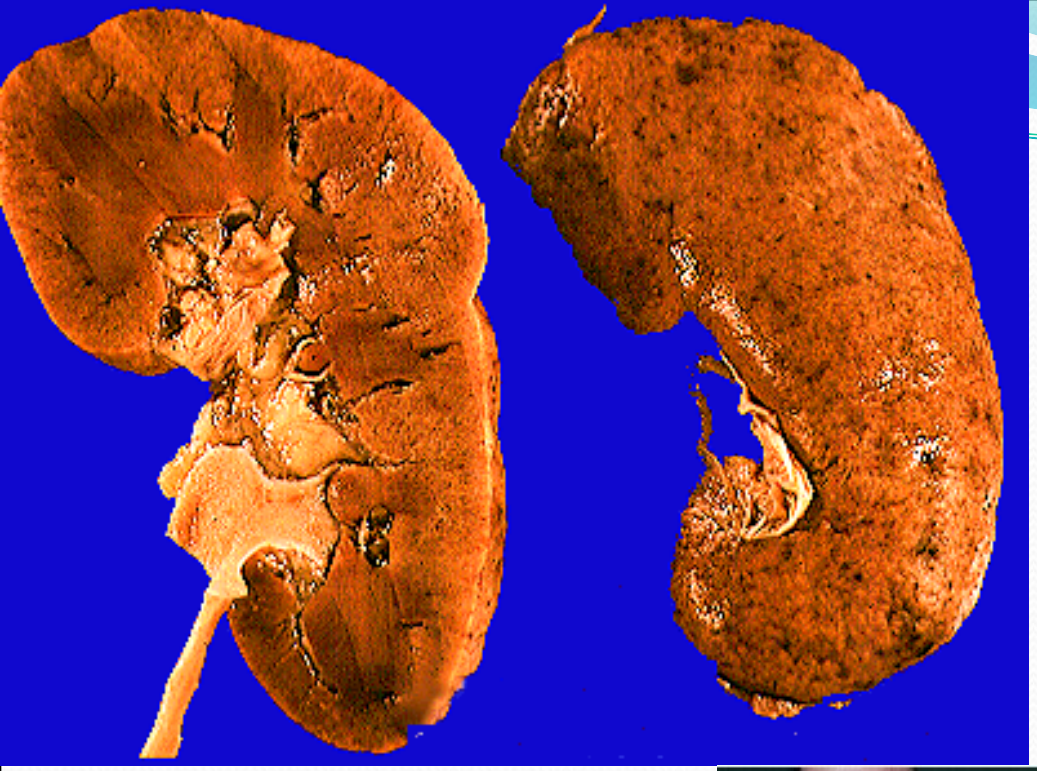


Antibody-mediated or cytotoxic hypersensitivity reaction (type II).

Acute renal graft rejection.

Fetal hydrops (hemolytic disease of the newborn).

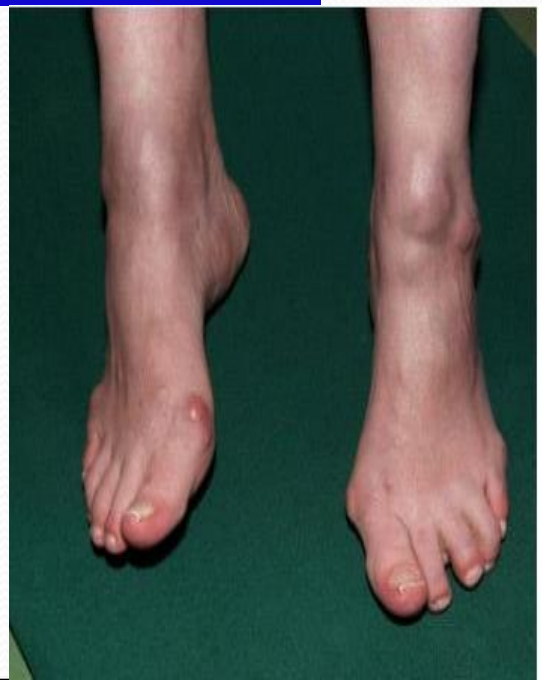


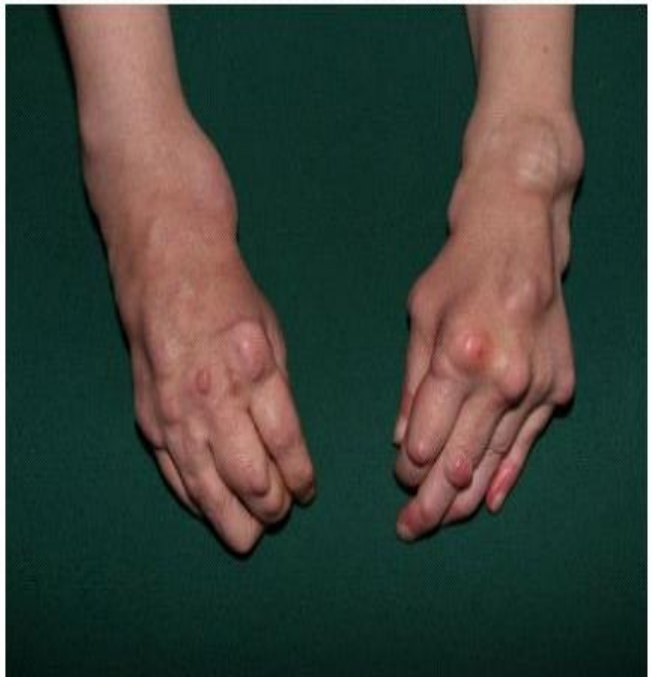


Hypersensitivity reaction mediated by toxic immune complexes (type III)

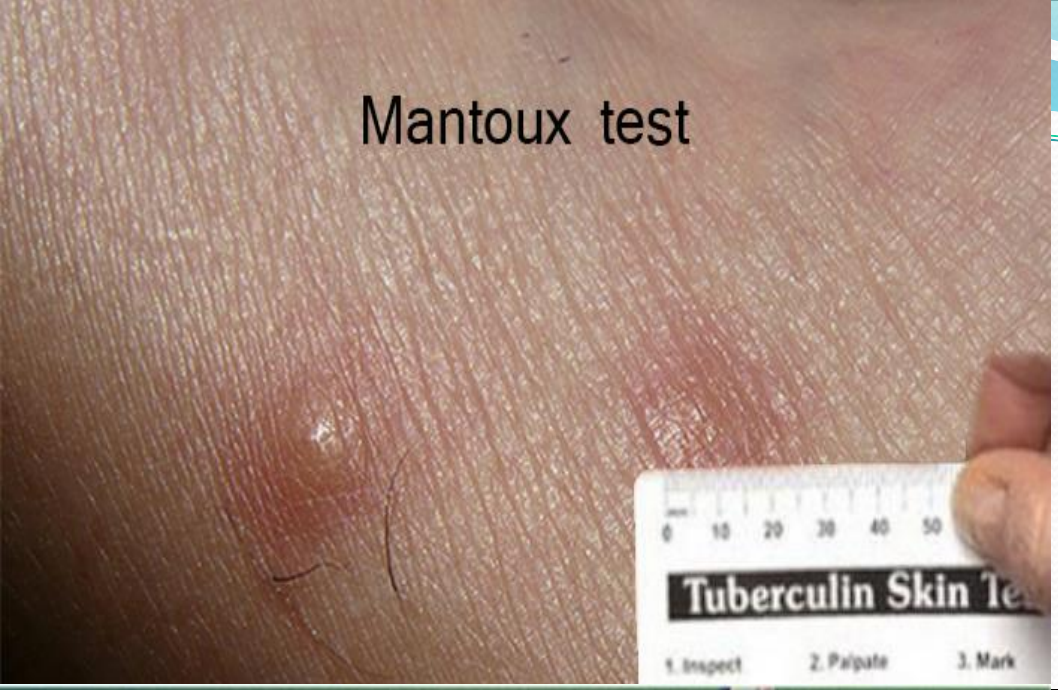
Rheumatoid arthritis.

Lupus glomerulonephritis.

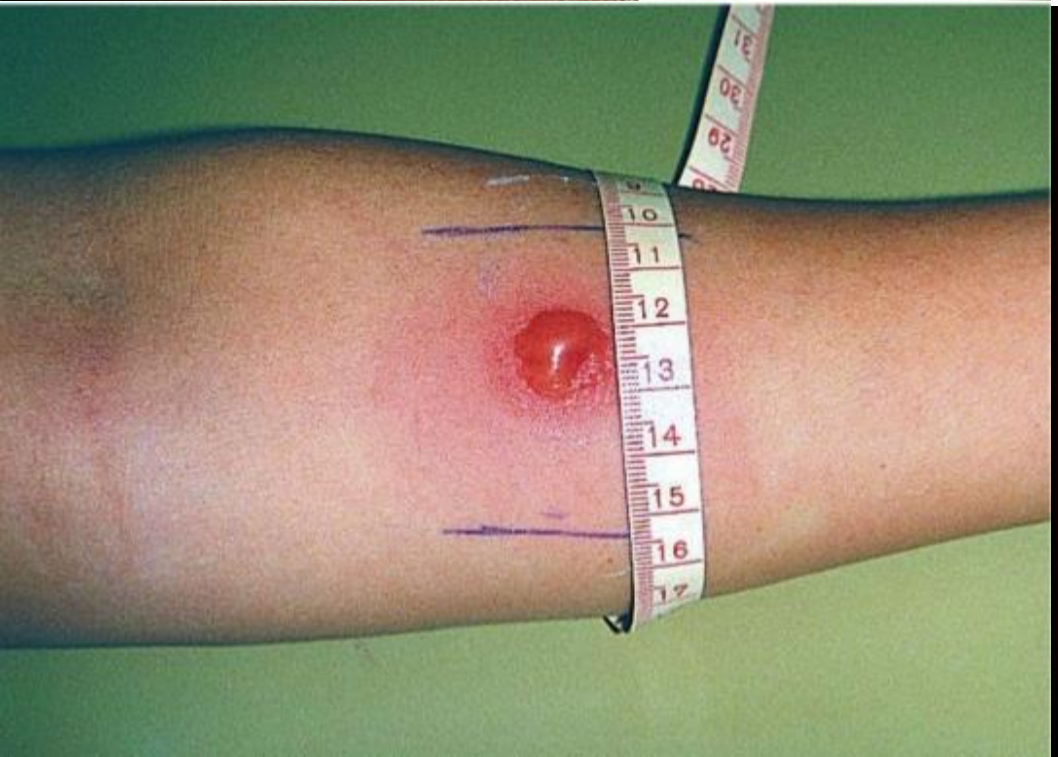


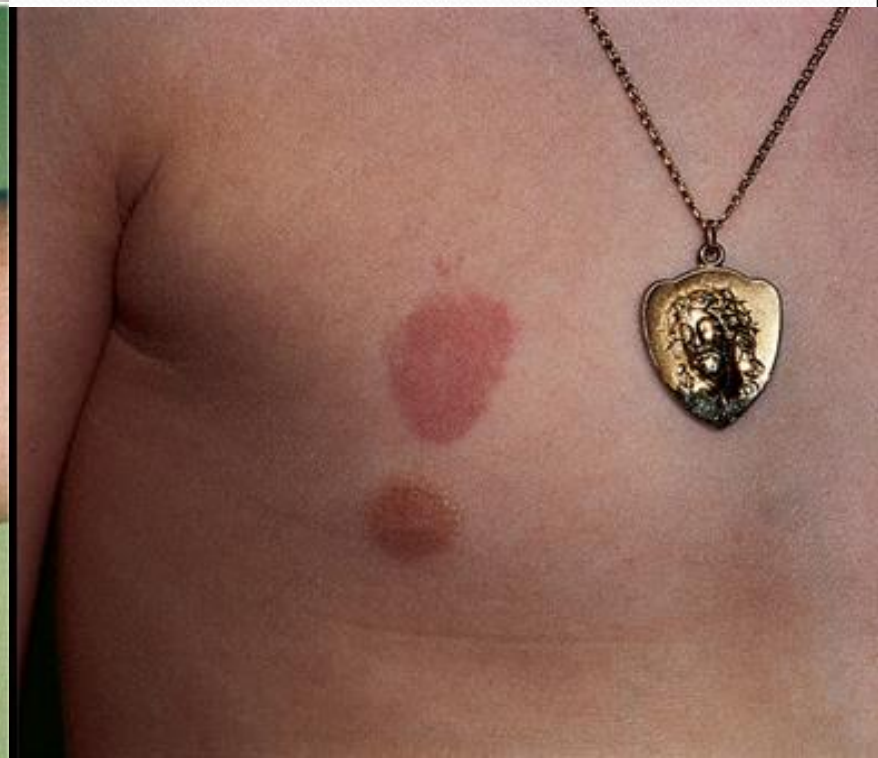


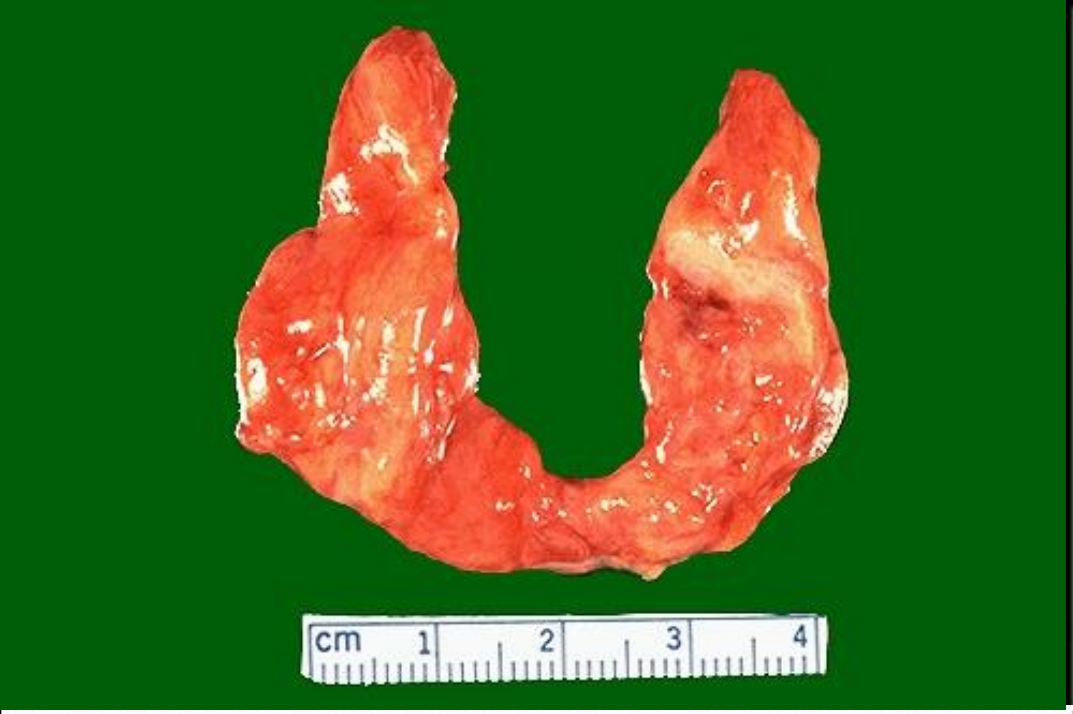
T cell-mediated hypersensitivity reaction (type IV).



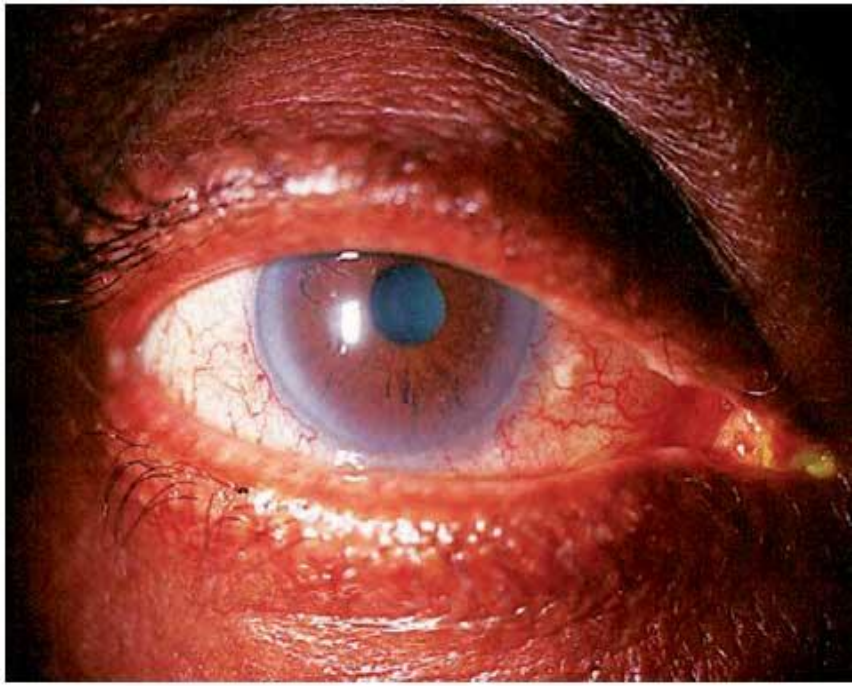
Dermatită de contact.



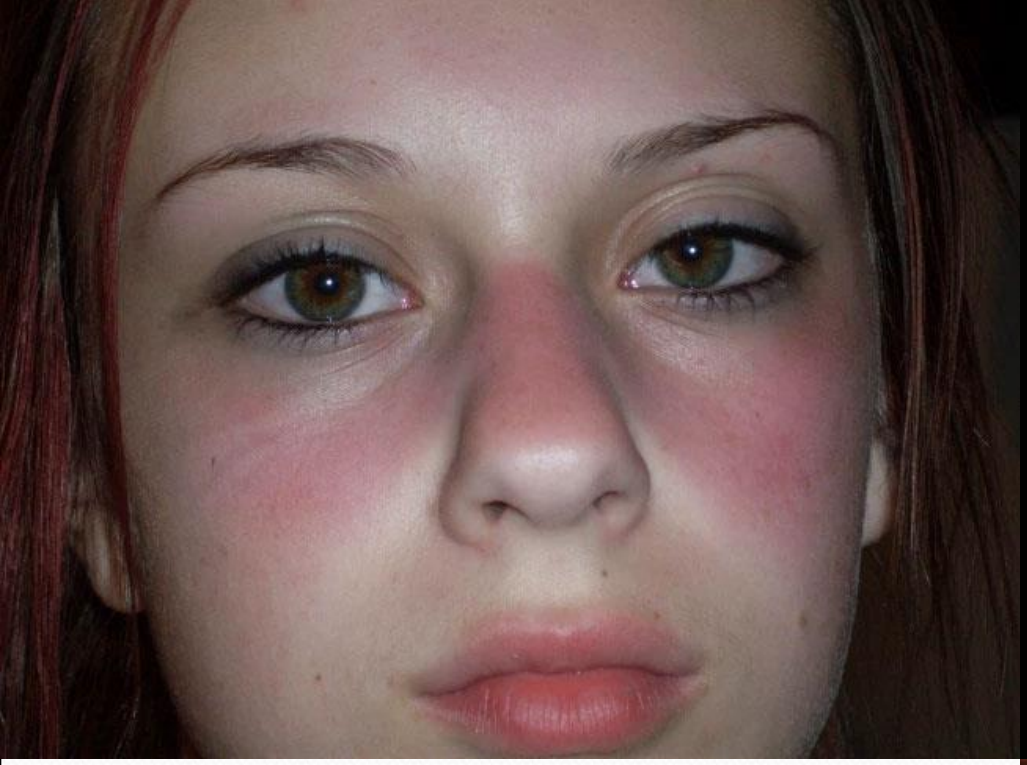


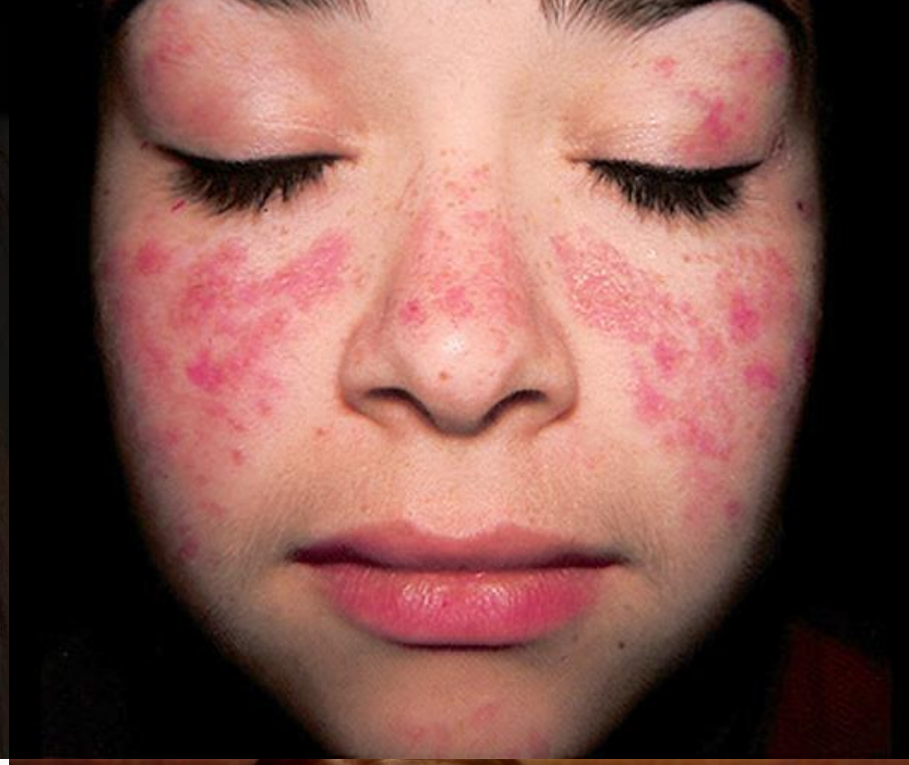


Hashimoto's thyroiditis.

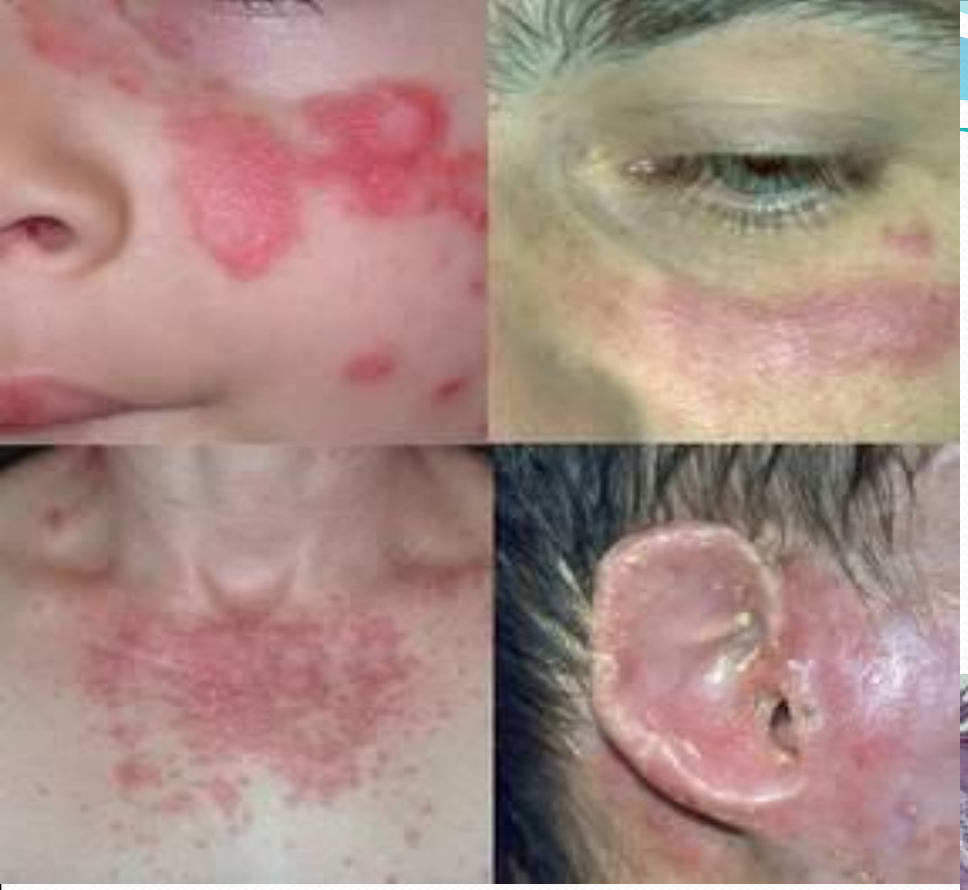


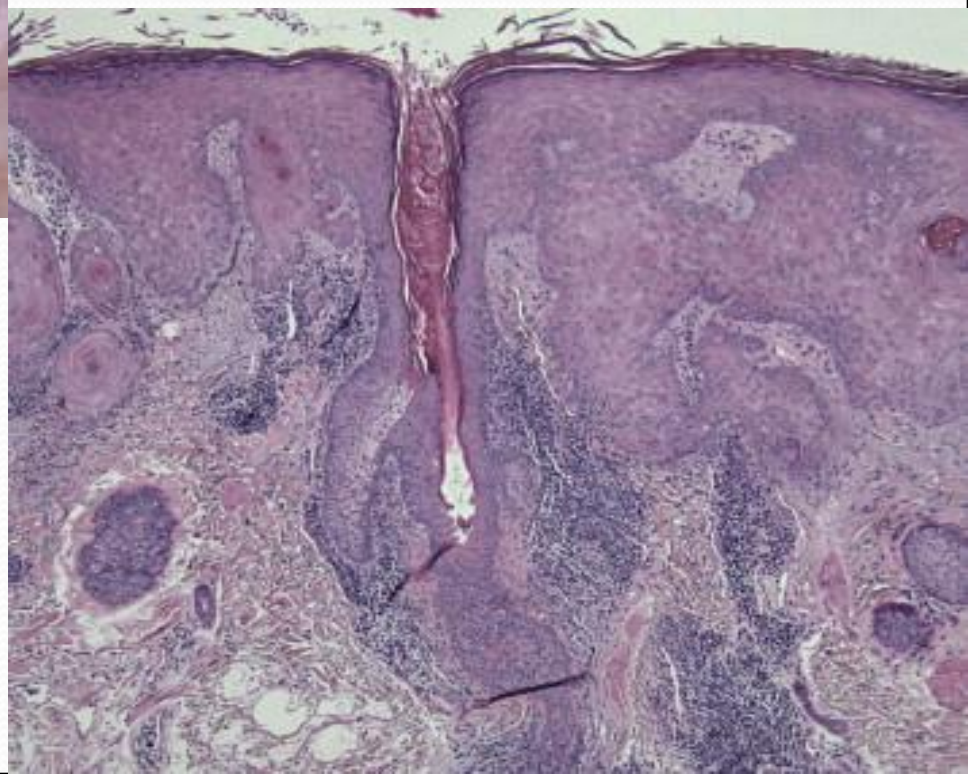
Patients with Sjögren's syndrome often exhibit inflammatory dry eye, as seen here.



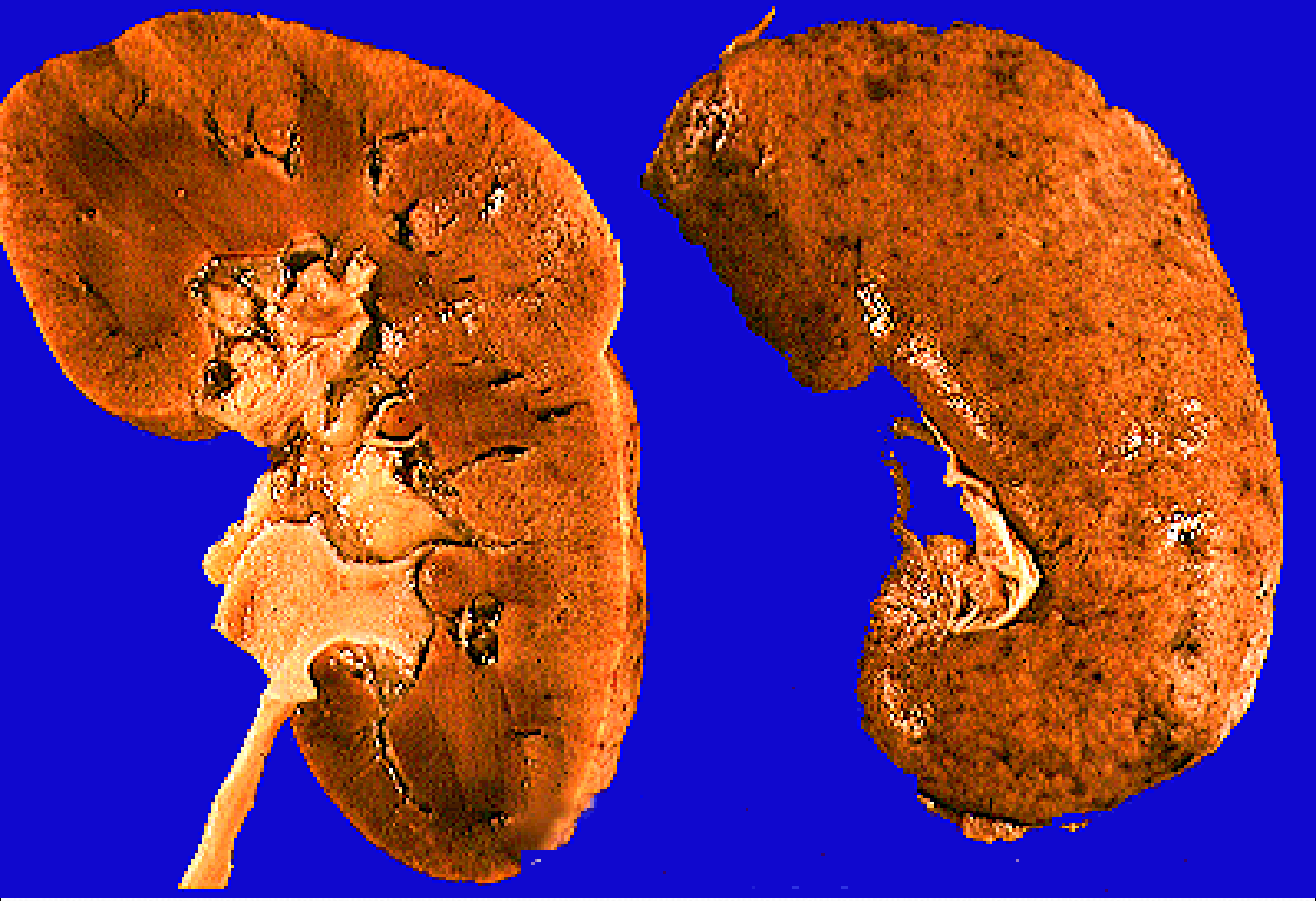


Systemic lupus erythematosus
("butterfly rash")

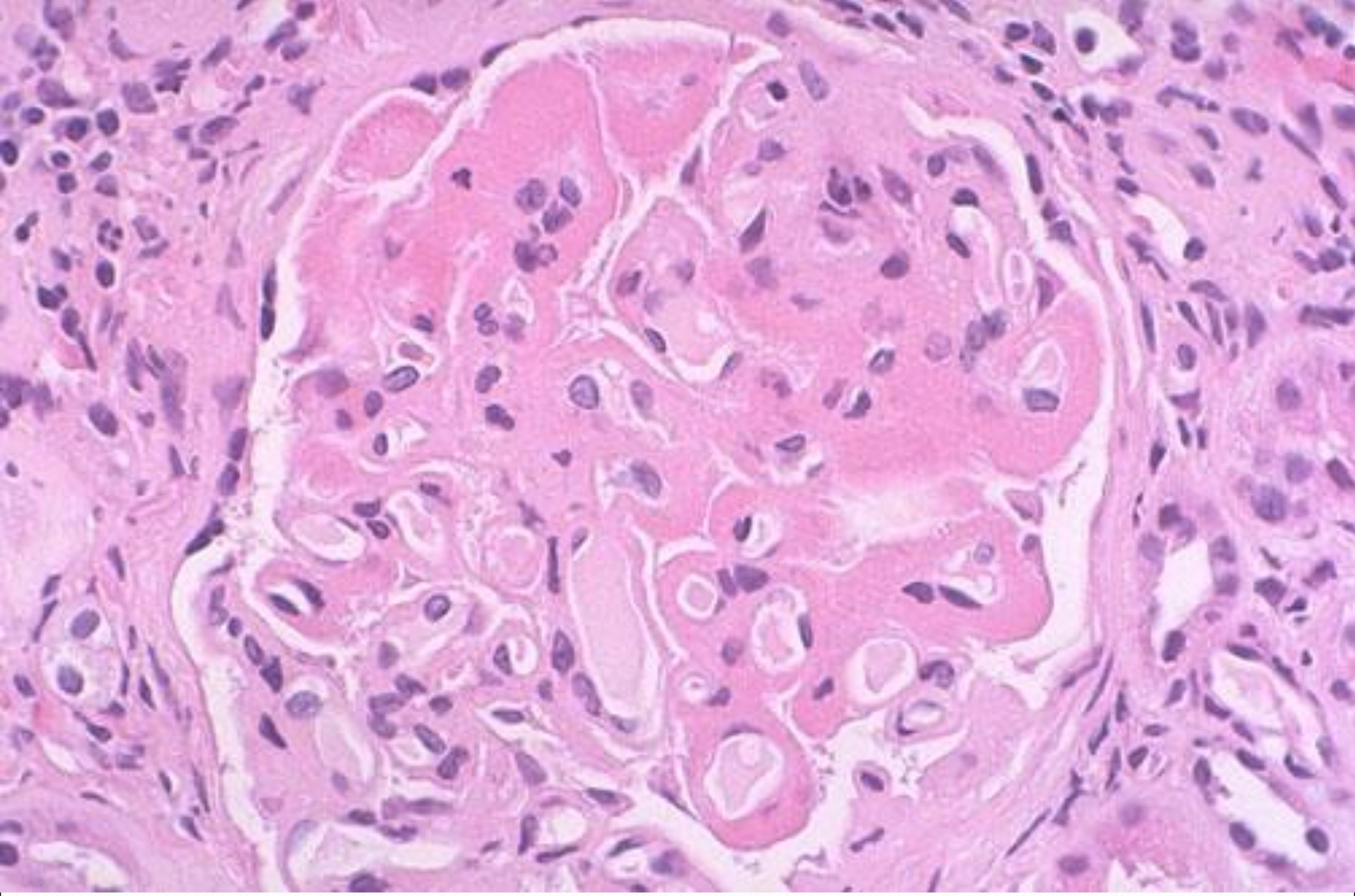




Discoid lupus erythematosus

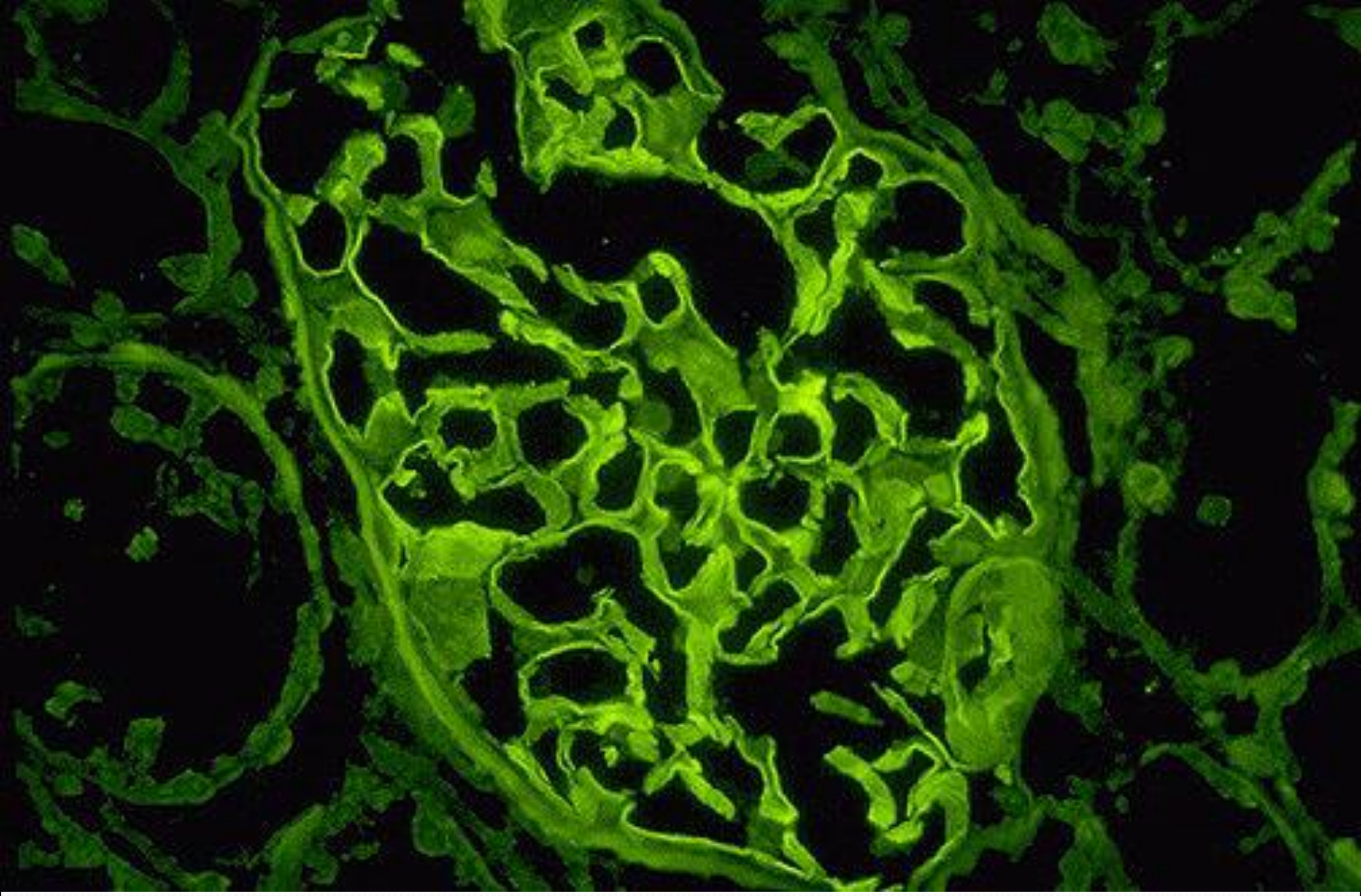


Lupus glomerulonephritis.

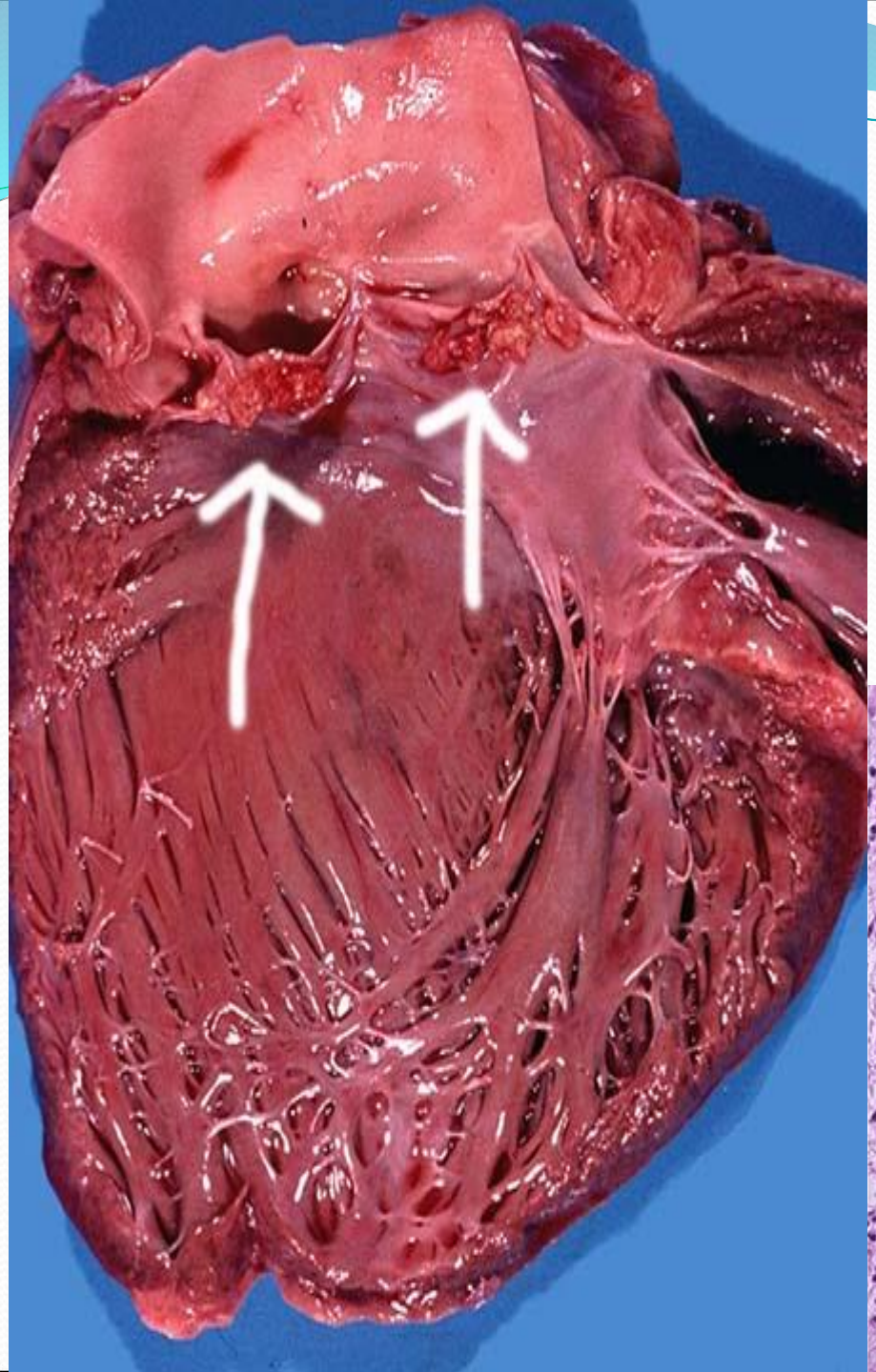


Lupus glomerulonephritis.

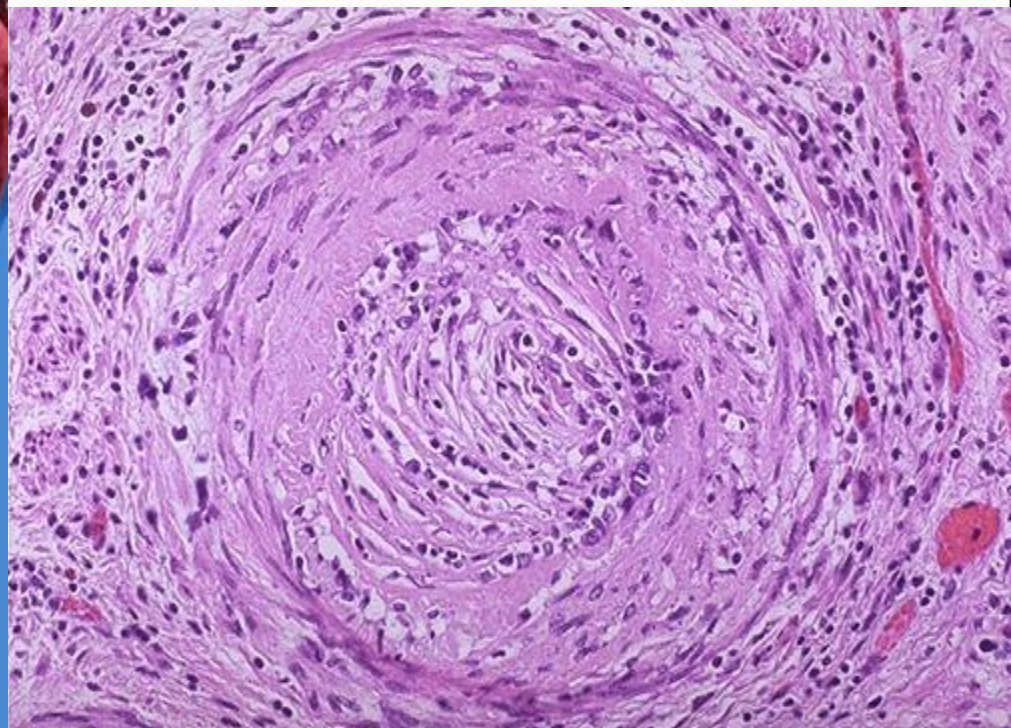
(glomerular capillaries with wire loop appearance).

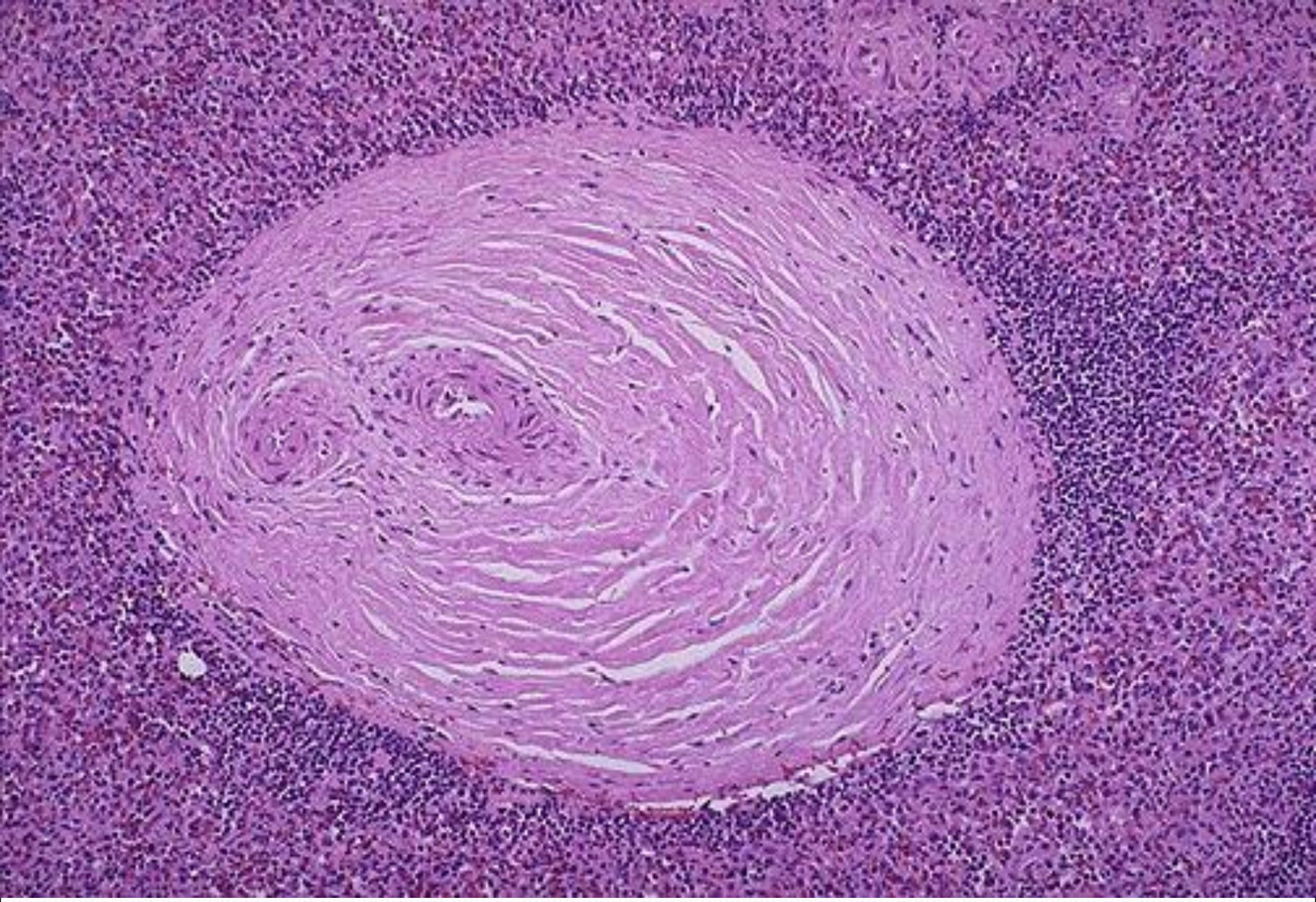


Lupus glomerulonephritis, fluorescent microscopy with antibodies against IgG (*linear aspect of the deposits of immune complexes*).

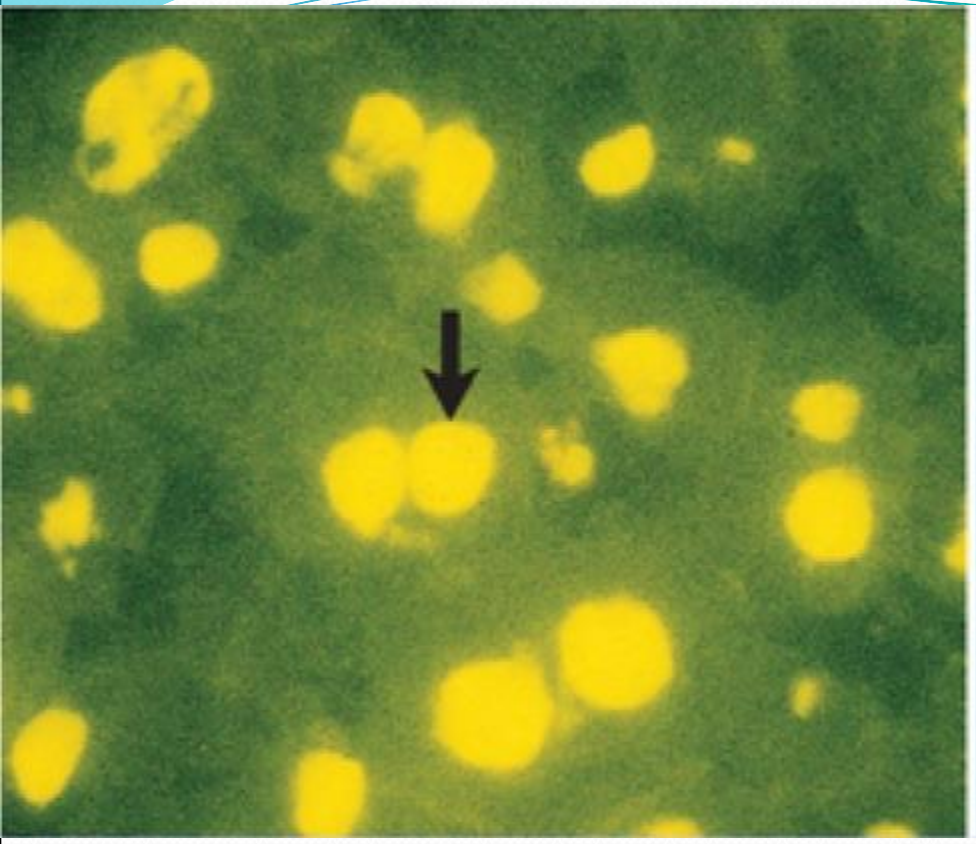


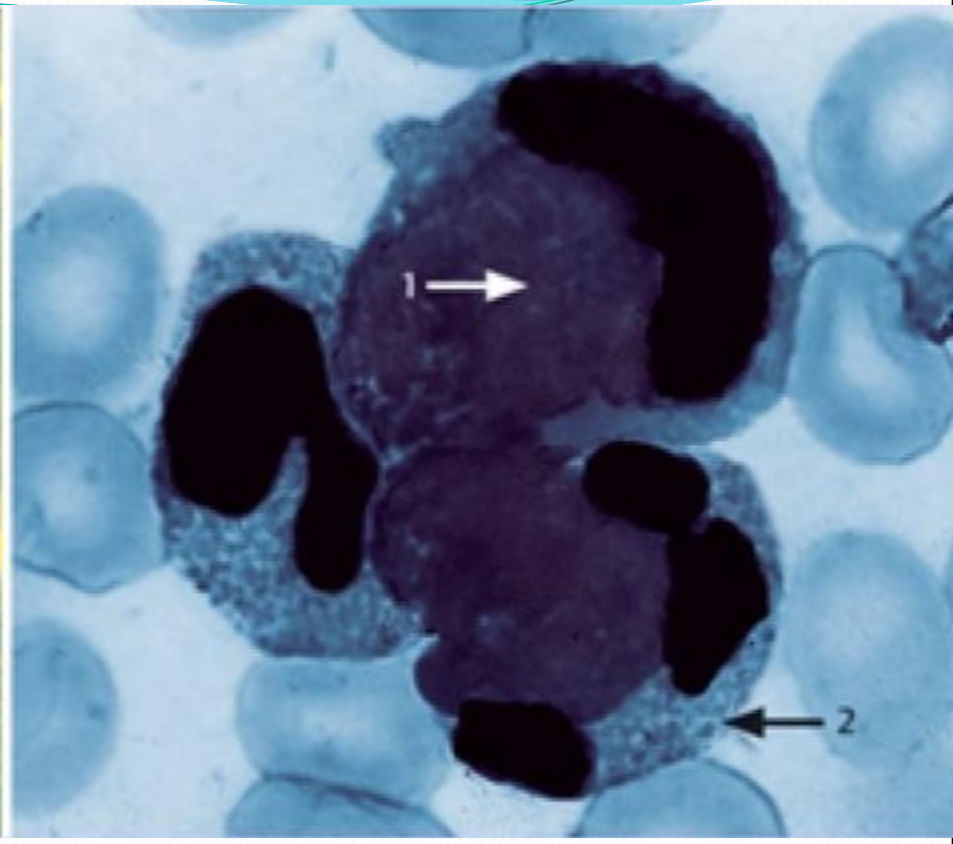
SLE: Libman-Sacks endocarditis, vasculitis.



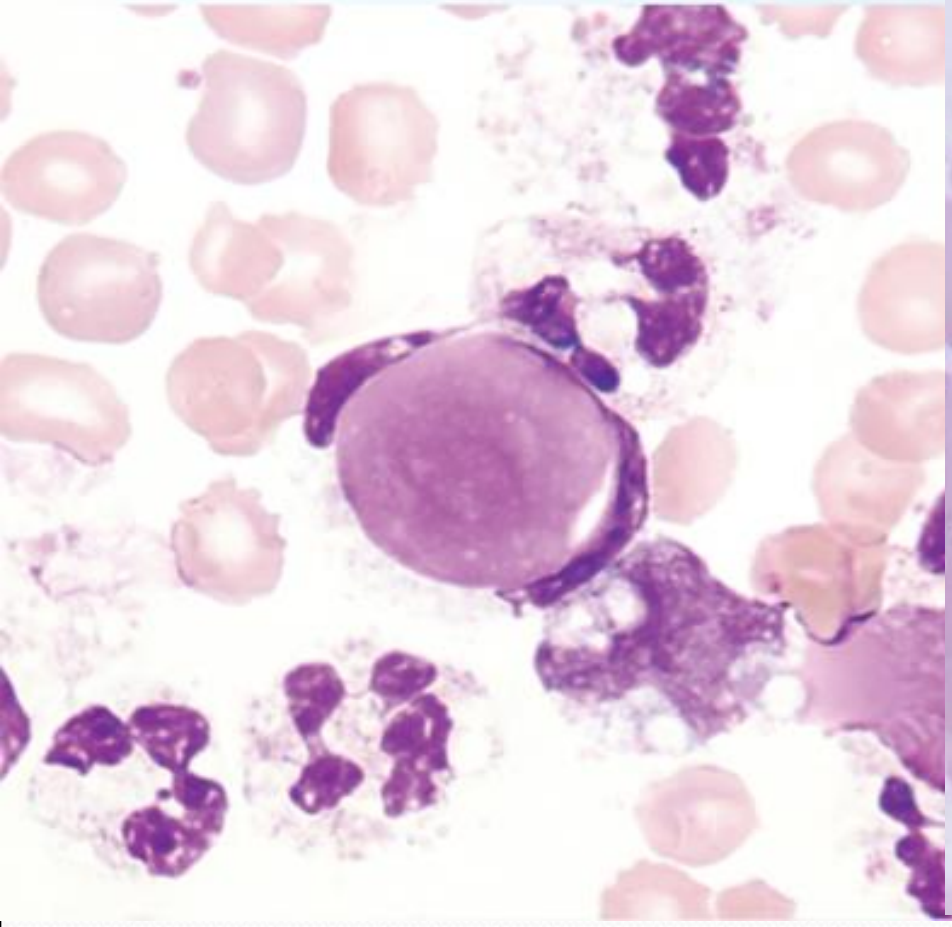


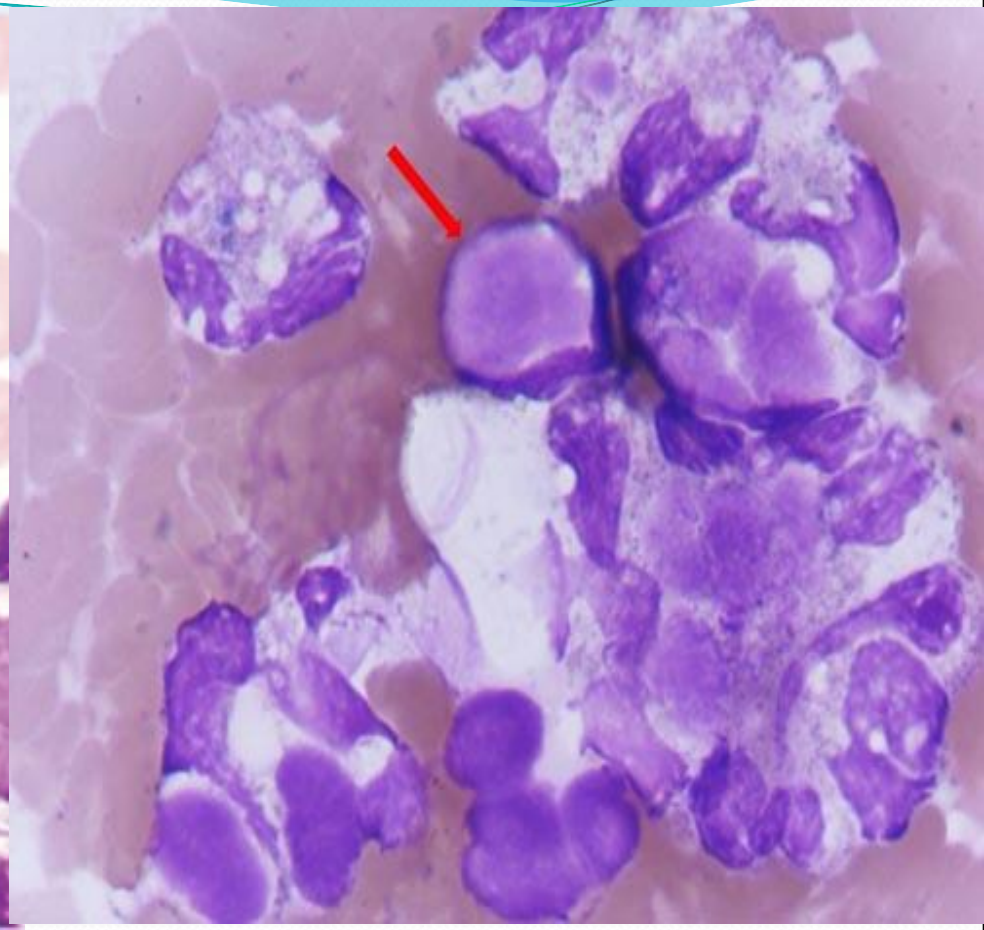
Periarterial sclerosis “onion-skin lesion” in spleen in SLE.





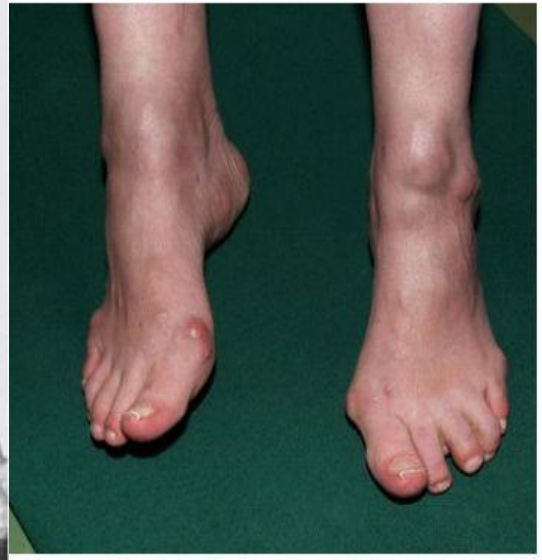
Antinuclear autoantibodies and hematoxylin bodies.

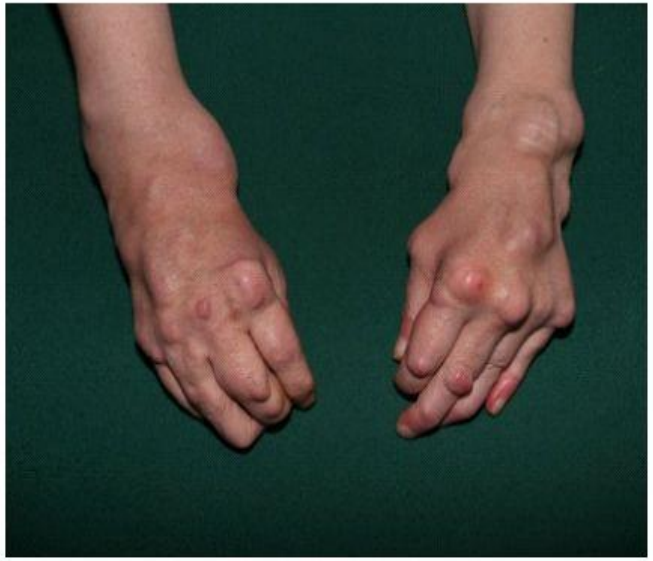


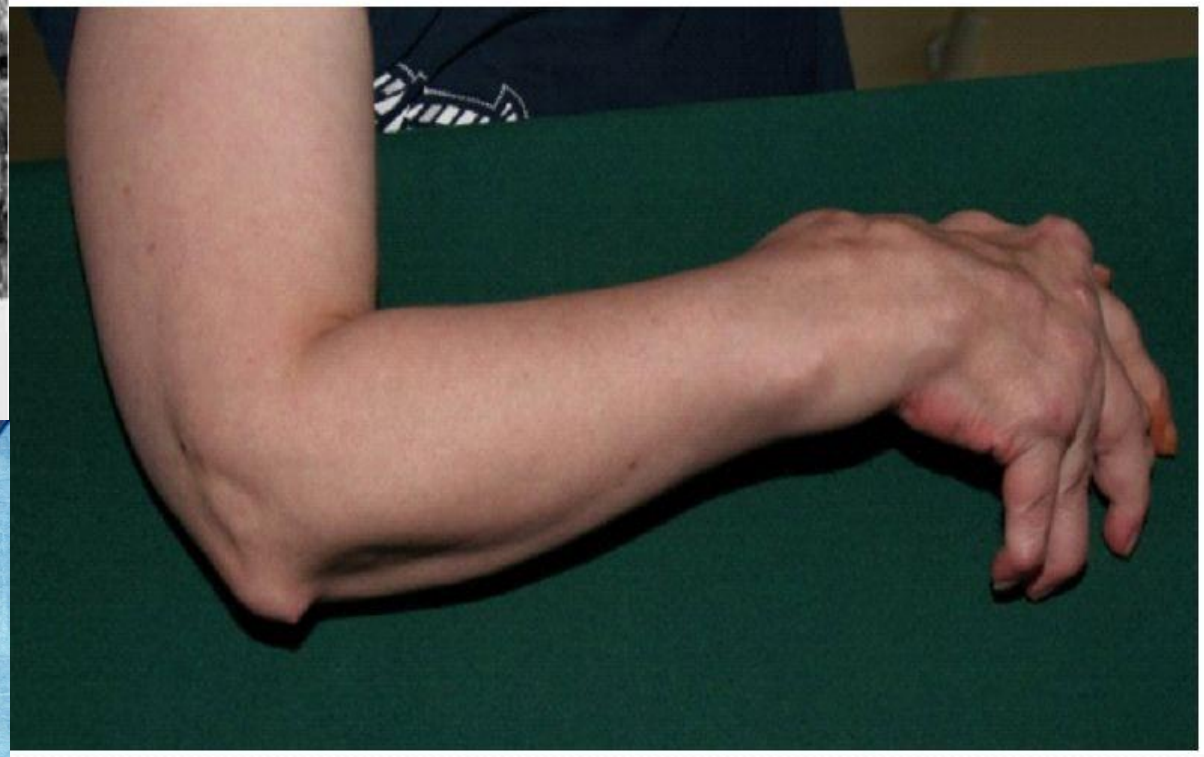


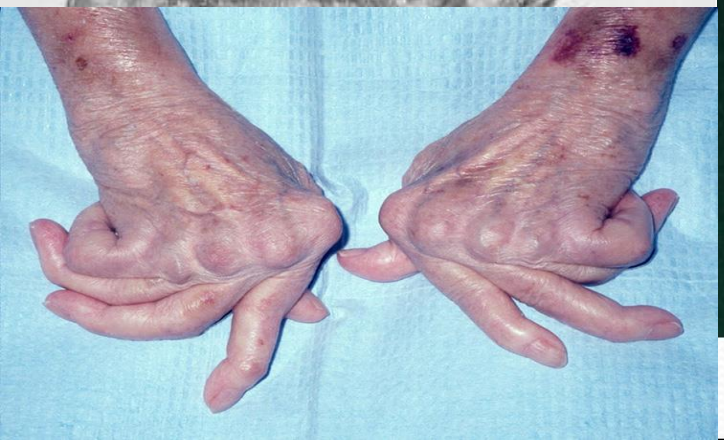
Lupus erythematosus (LE) cell

(neutrophil leukocyte, which phagocytosed a denatured nucleus).

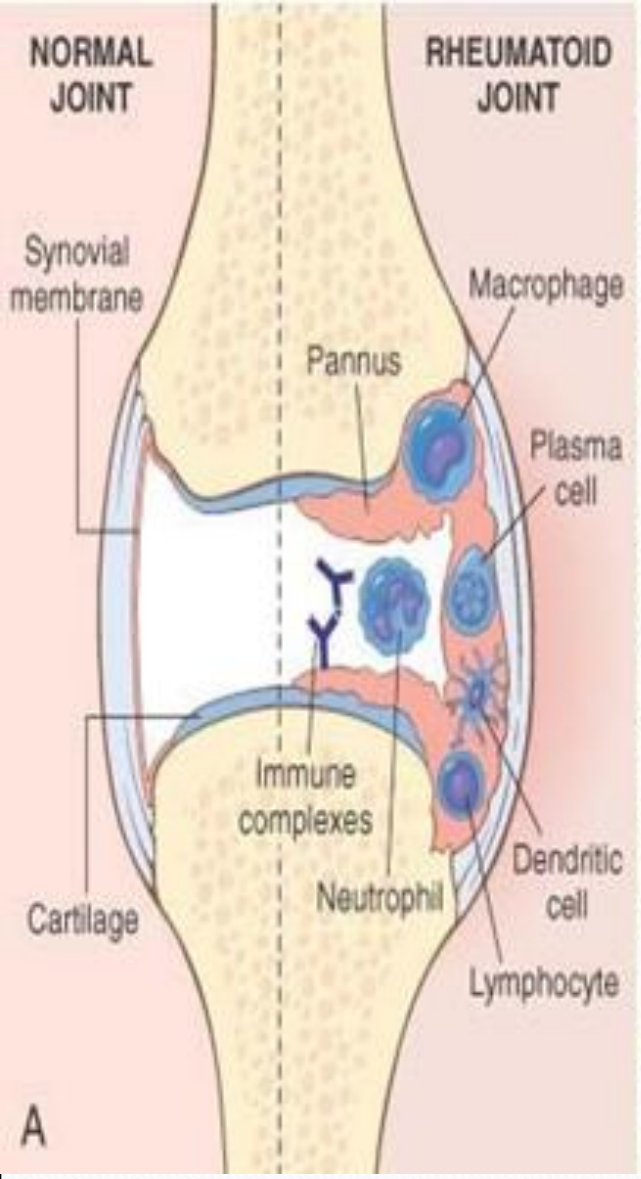


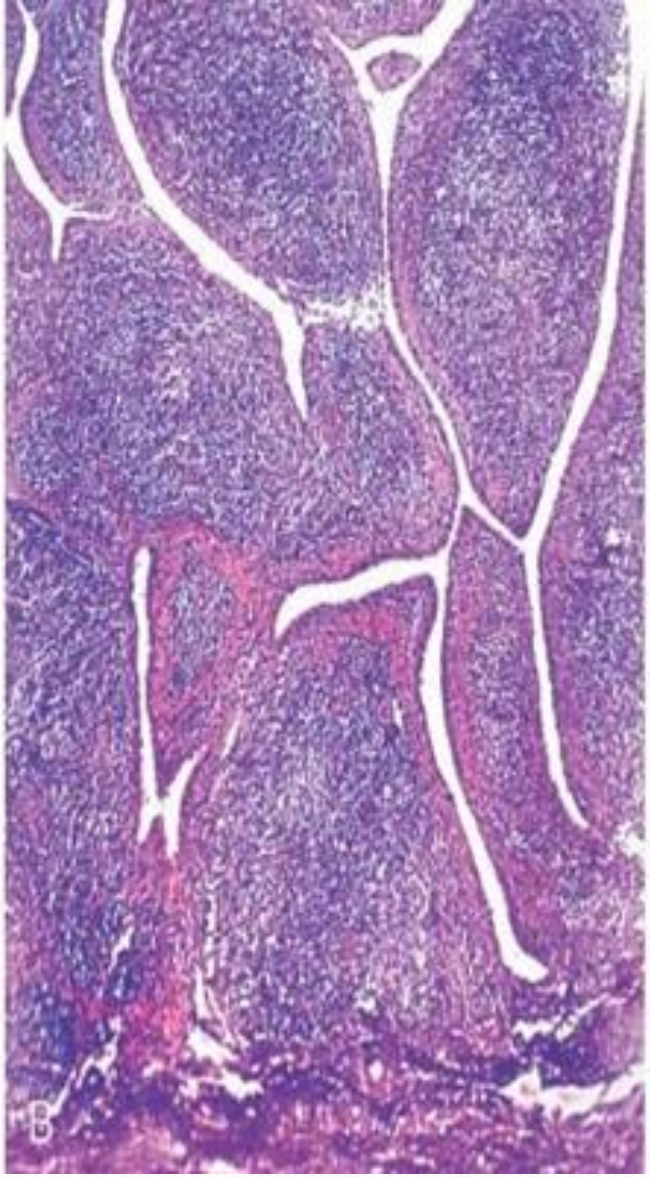


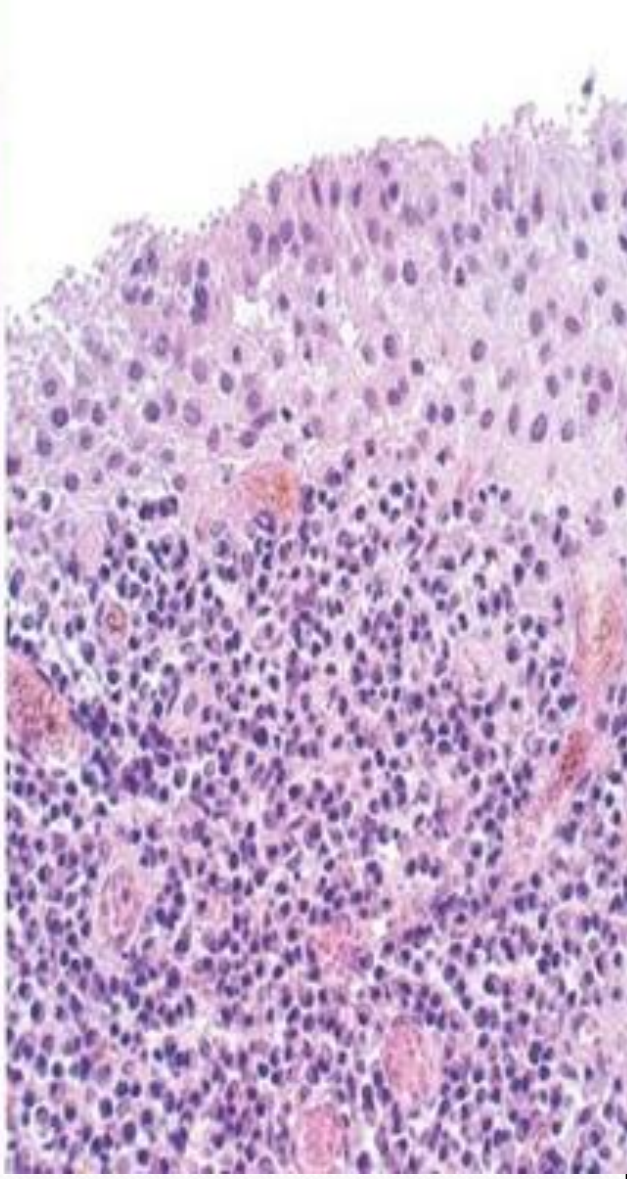




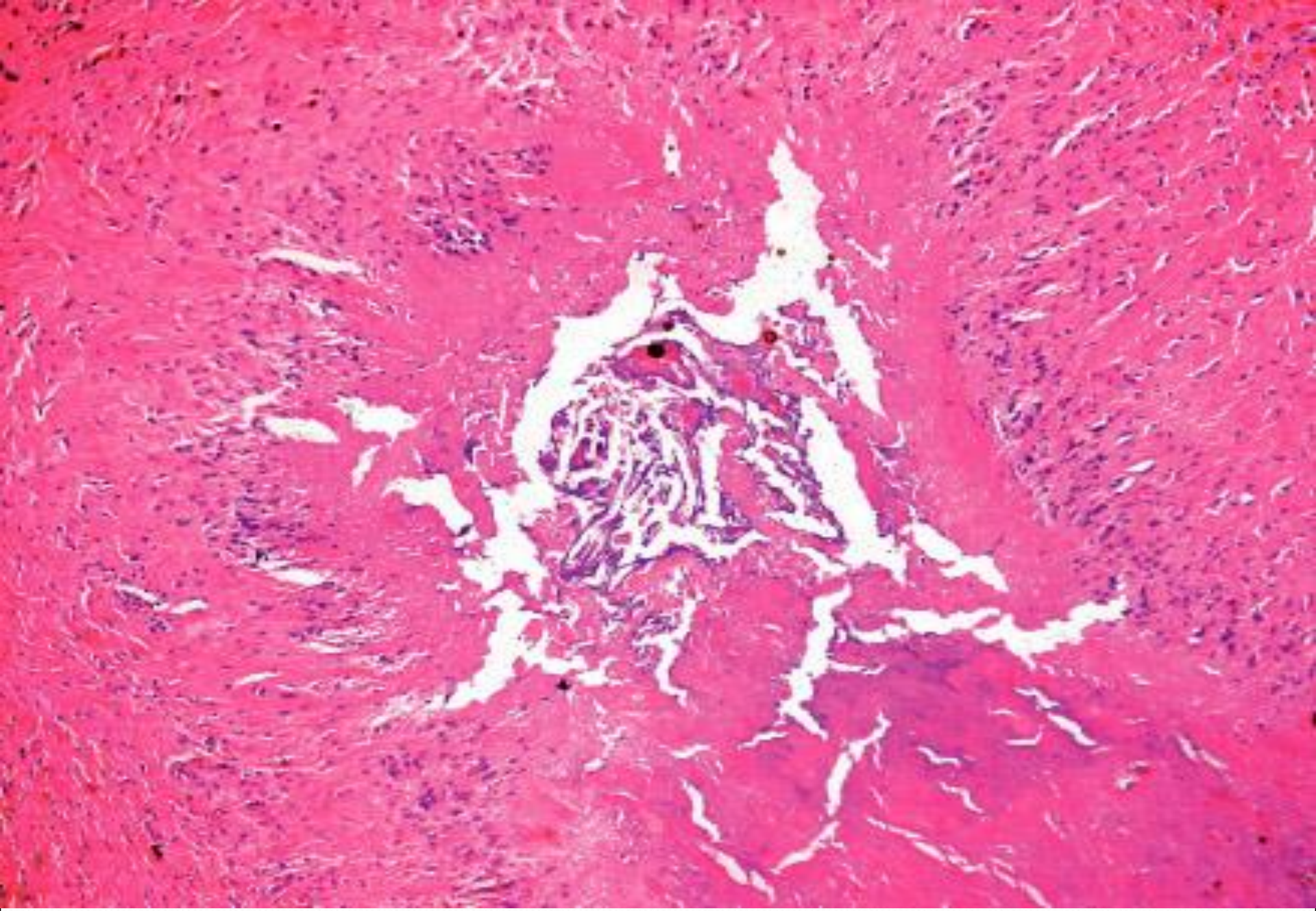
Rheumatoid arthritis



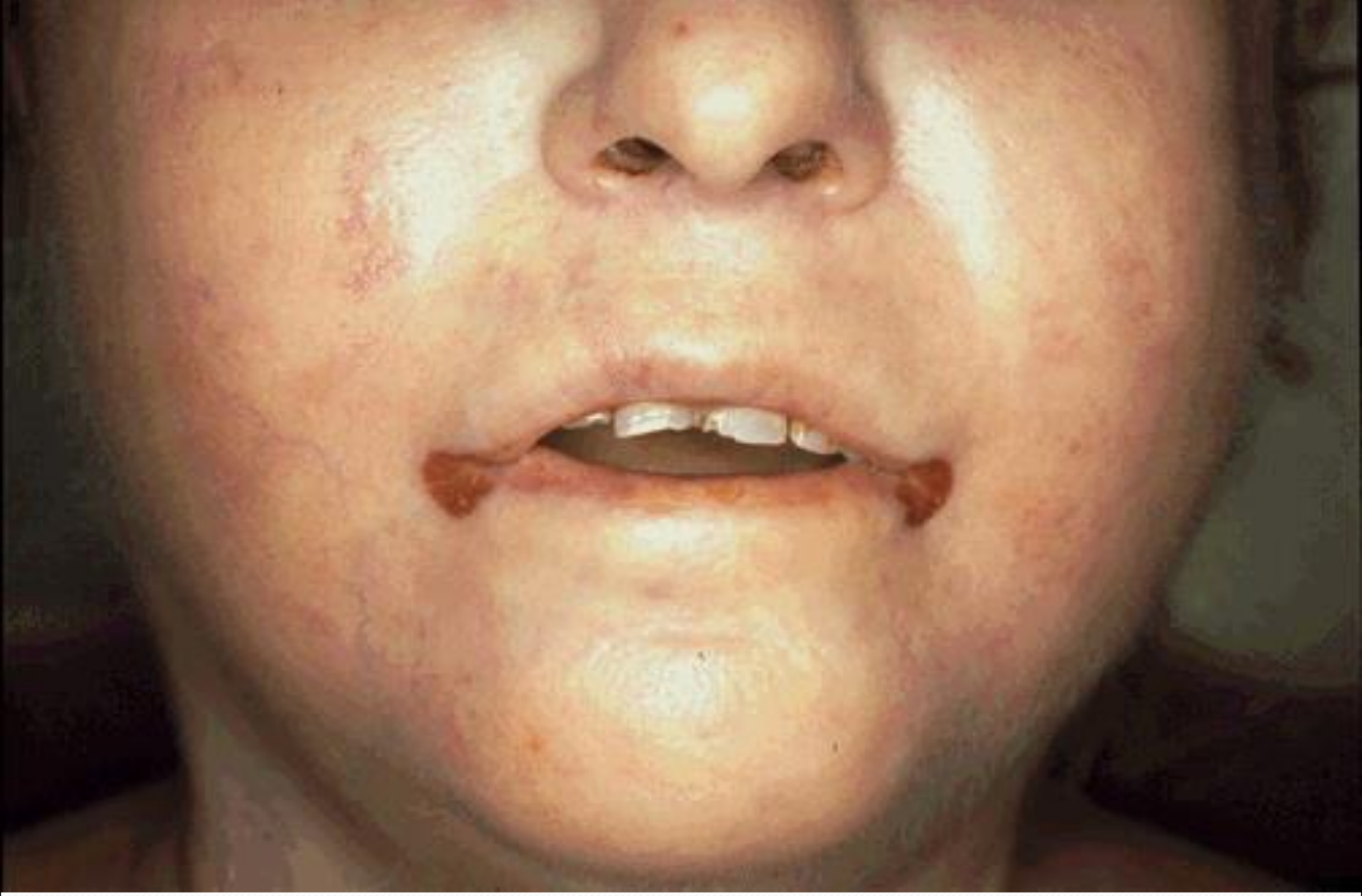




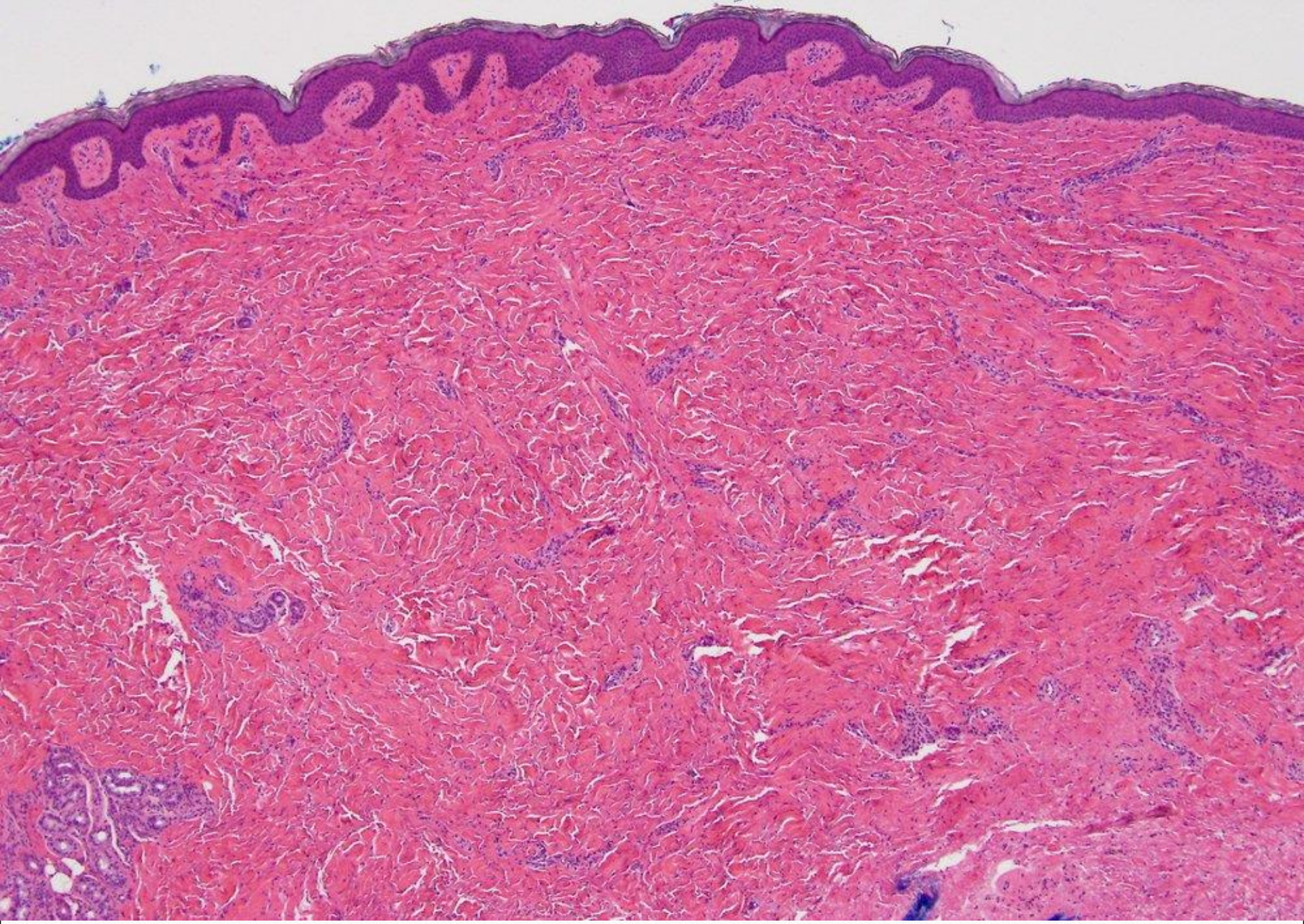
Rheumatoid arthritis.
The mechanism of the pannus appearance (granulation tissue) on the synovial membrane.



Rheumatoid nodule. (*H-E stain*).



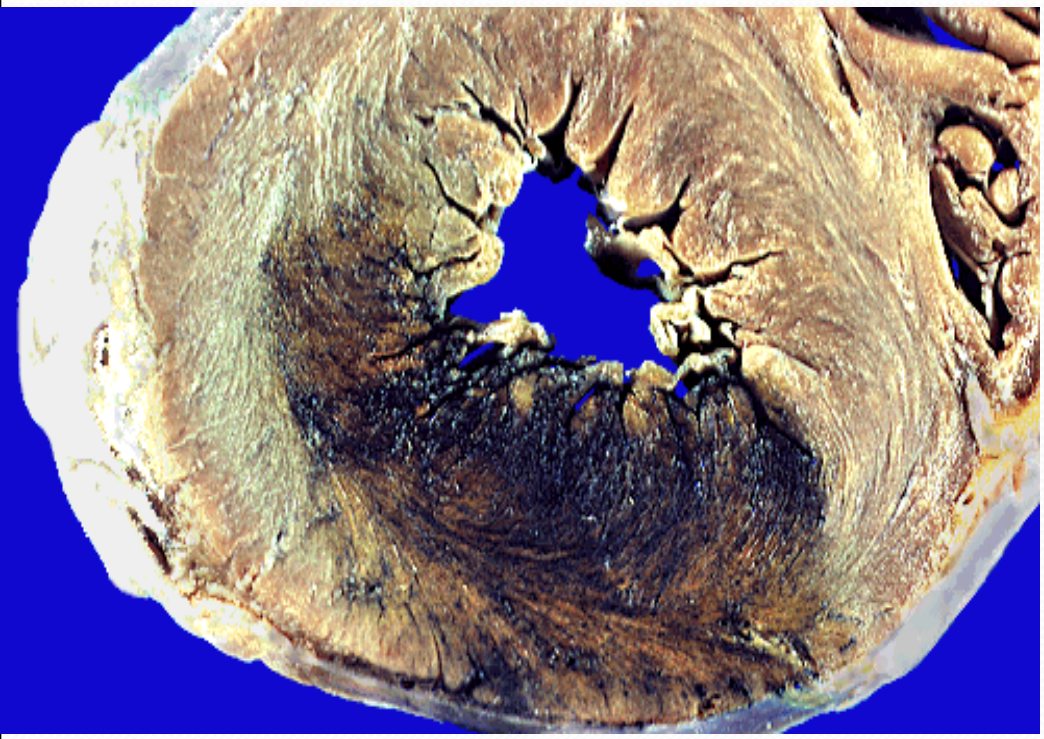
Systemic sclerosis ***(thickening of the skin, reduction of elasticity and mobility, amimic face).***



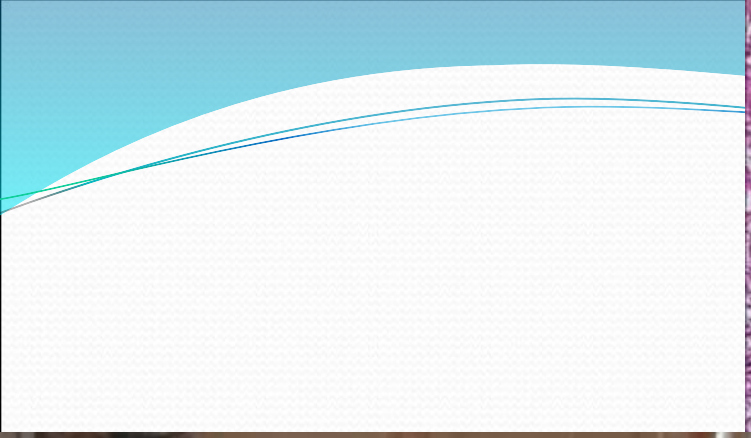
Systemic sclerosis *(hyalinosis of the connective tissue of the dermis). (H-E stain).*

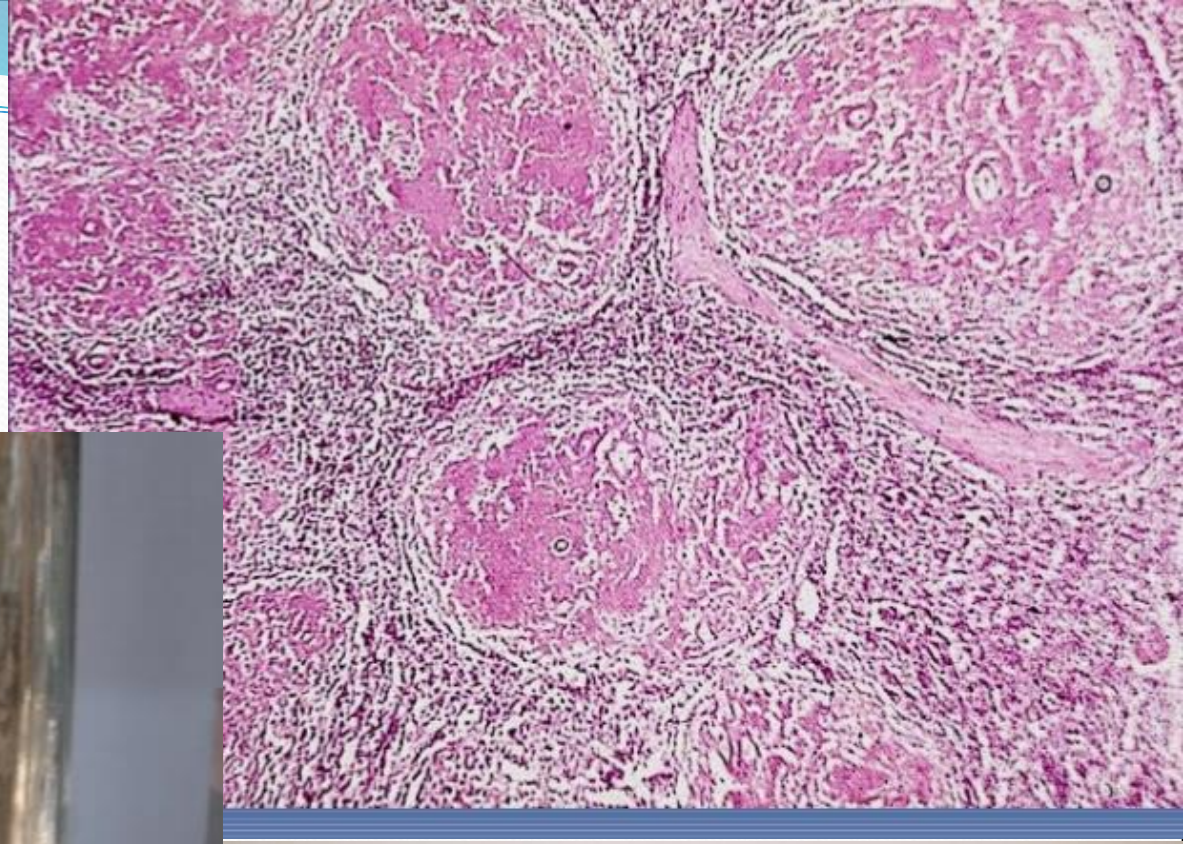
Myocardial amyloidosis

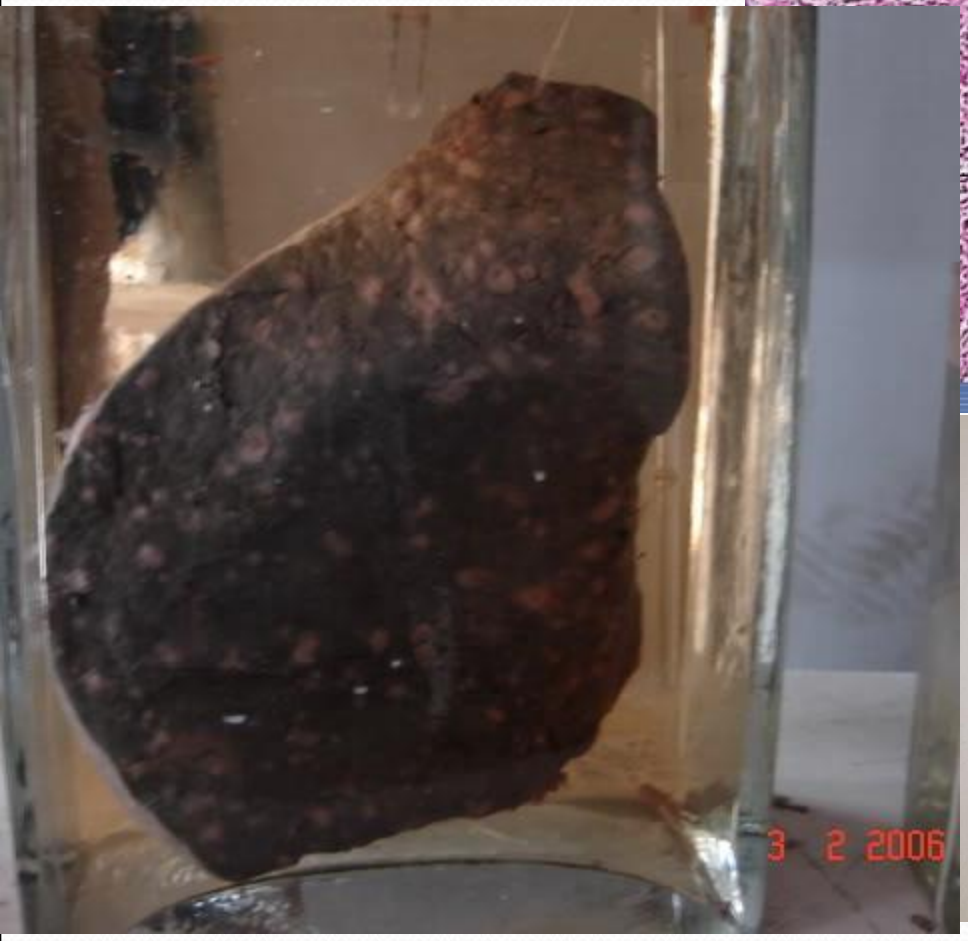
Macroscopic identification.



Virchow macroscopic reaction: on successive application to the section surface of iodine or Lugol's solution and sulfuric acid (10%) the amyloid stains in blue-violet or dark green.







Focal spleen amyloidosis (*sago spleen*).

Diffuse spleen amyloidosis.

Image beneath - norm.

OBJECTIVES

- Differentiate between the concepts of “Innate” and “Adaptive” immunity
- Visually recognize and understand the basic roles of lymphocytes, macrophages, dendritic cells, NK cells
- Understand the roles of the major cytokines in immunity
- Differentiate and give examples of the four (4) different types of hypersensitivity reactions

OBJECTIVES

- Know the common features of autoimmune diseases, and the usual four (4) main features (Etiology, Pathogenesis, Morphology, and Clinical Expression) of **S**ystemic **L**upus **E**rythematosus, **R**heumatoid **A**rthritis, Sjögrens, Systemic Sclerosis (Scleroderma), **M**ixed **C**onnective Tissue **D**isease, and "Poly-" (aka, "Peri-") -arteritis Nodosa
- Differentiate between Primary (Genetic) and Secondary (Acquired) Immunodeficiencies

OBJECTIVES

- Understand the usual four (4) main features of AIDS, i.e., etiology, pathogenesis, morphology, clinical expression
- Understand the usual four (4) main features of Amyloidosis

IMMUNITY

- **INNATE** (present before birth, "NATURAL")
- **ADAPTIVE** (developed by exposure to pathogens, or in a broader sense, antigens)

MHC

Major Histocompatibility Complex

- A genetic "LOCUS" on Chromosome 6, which codes for cell surface compatibility
- Also called HLA (Human Leukocyte Antigens) in humans and H-2 in mice
- It's major job is to make sure all self cell antigens are recognized and "tolerated", because the general rule of the immune system is that all UN-recognized cells will NOT be tolerated

INNATE IMMUNITY

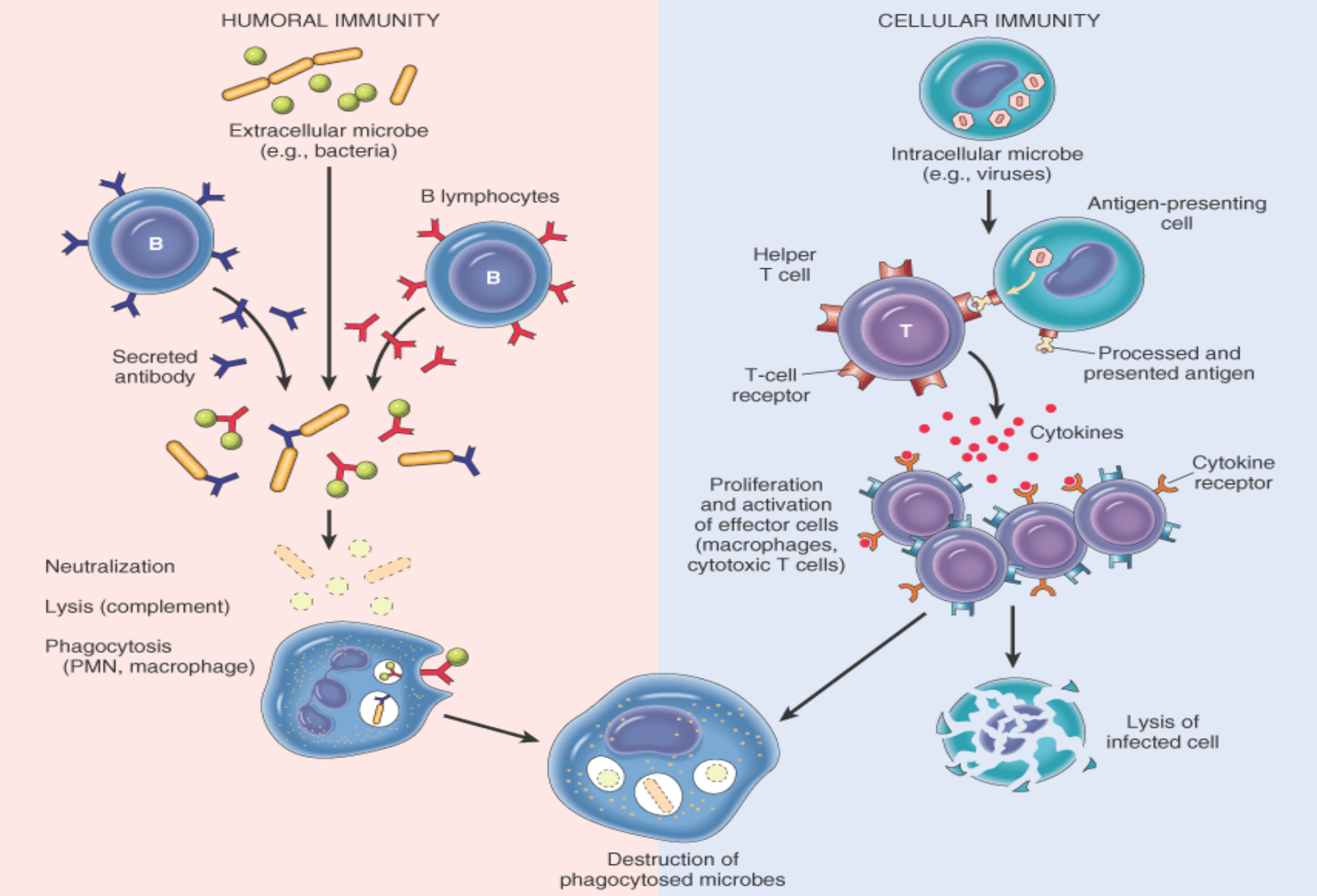
- **BARRIERS**
- **CELLS: LYMPHOCYTES, MACROPHAGES, PLASMA CELLS, NK CELLS**
- **CYTOKINES/CHEMOKINES**
- **PLASMA PROTEINS: Complement, Coagulation Factors**
- **Toll-Like Receptors, TLR's**

Toll-like receptors (**TLRs**) are a class of single membrane-spanning non-catalytic receptors on macrophages and other APCs that recognize structurally conserved molecules derived from microbes once they have breached physical barriers such as the skin or intestinal tract mucosa, and activate immune cell responses.

ADAPTIVE IMMUNITY

- **CELLULAR, i.e., direct cellular reactions to antigens**
- **HUMORAL, i.e., antibodies**

Adaptive immunity is “learned”. It relies on PREVIOUS EXPOSURE to the pathogen or foreign antigen.



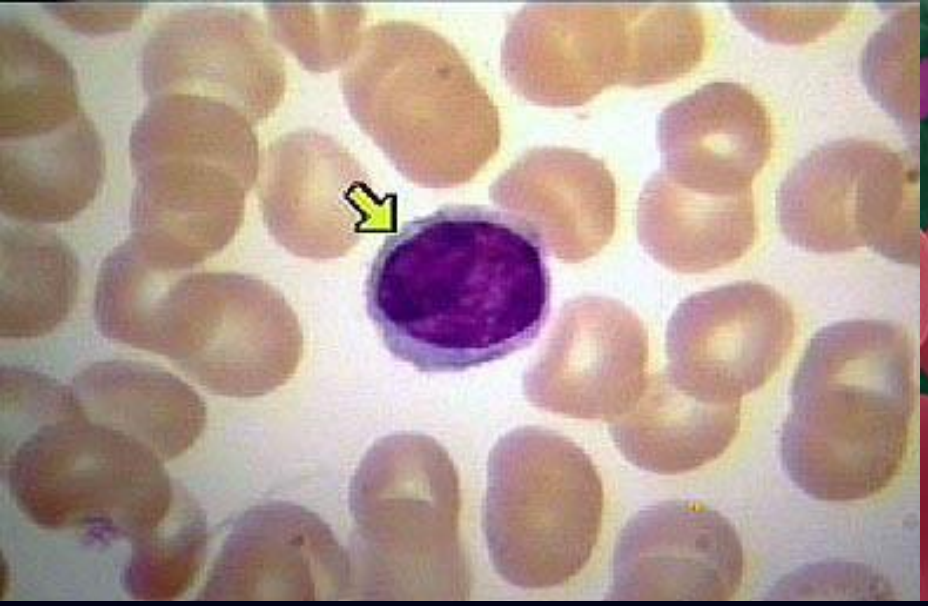
The classic types of adaptive immunity are:
1)Humoral, 2) Cellular

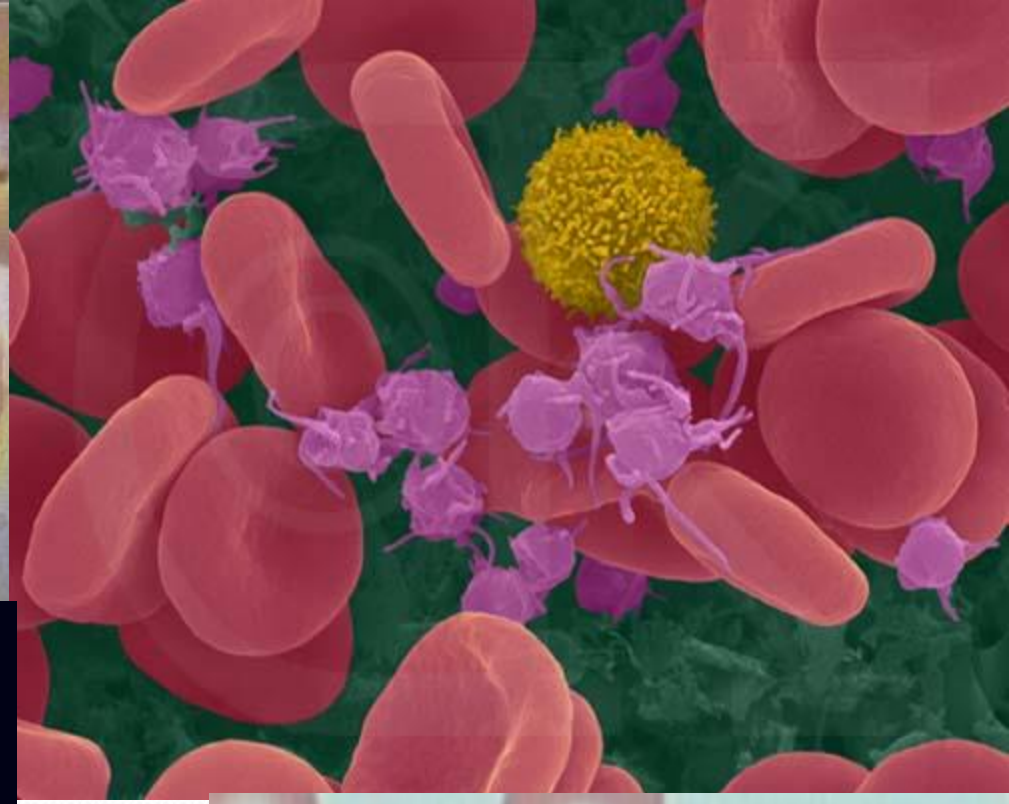
CELLS of the IMMUNE SYSTEM

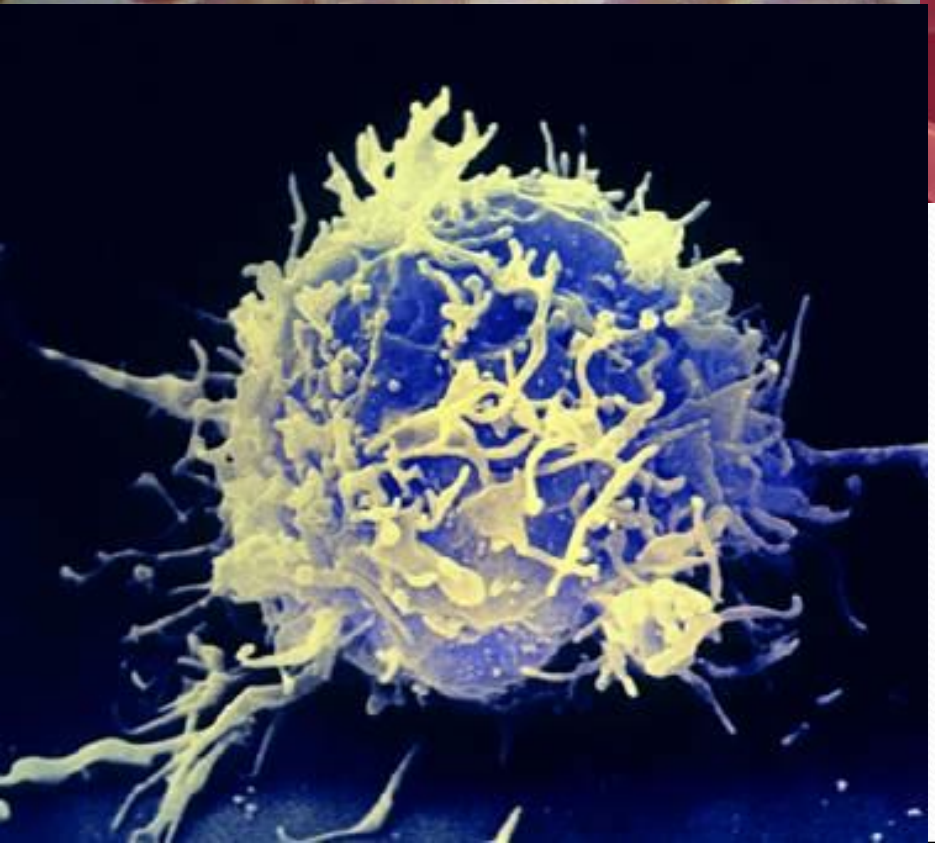
- **LYMPHOCYTES, T**
- **LYMPHOCYTES, B**
- **PLASMA CELLS (MODIFIED B CELLS)**
- **MACROPHAGES, aka "HISTIOCYTES", (APCs, i.e., Antigen Presenting Cells)**
- **"DENDRITIC" CELLS (APCs, i.e., Antigen Presenting Cells)**
- **NK (NATURAL KILLER) CELLS**

If you wanted to make this simple you can say there are 3 types of cells, T-lymphocytes, B-lymphocytes, and Macrophages or APC's.

If you wanted to make it incredibly simple then just say lymphocytes and macrophages.







L

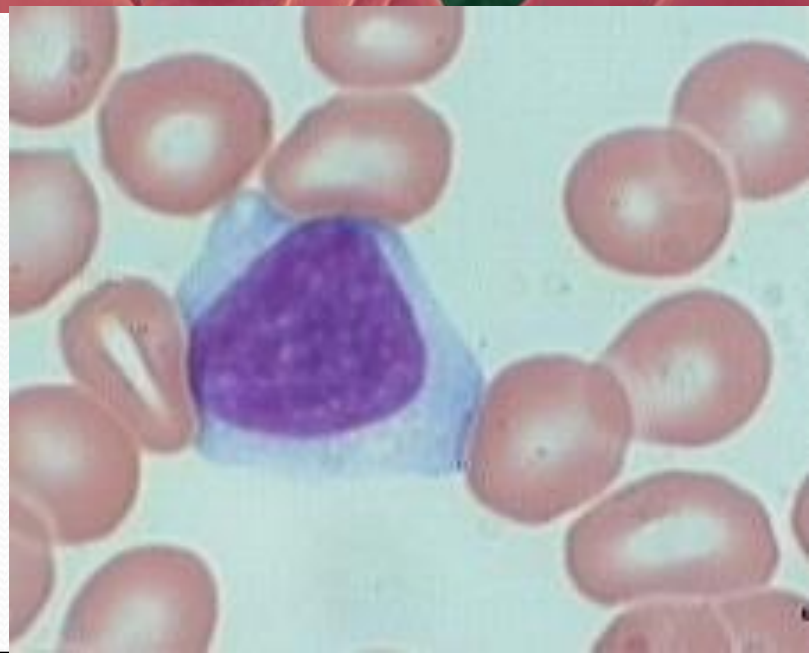
Y

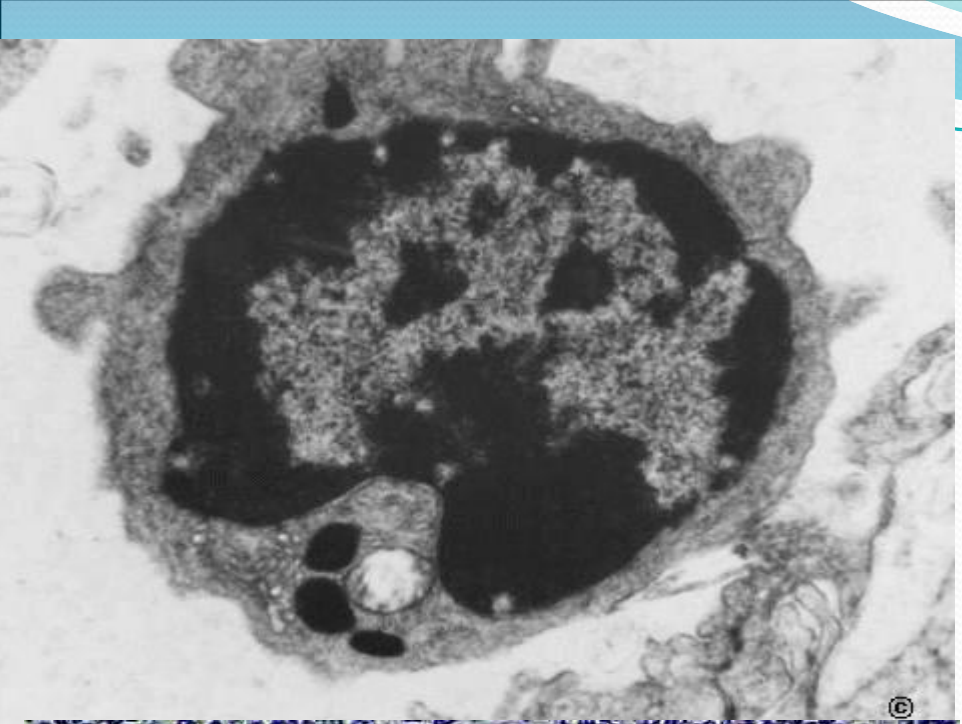
M

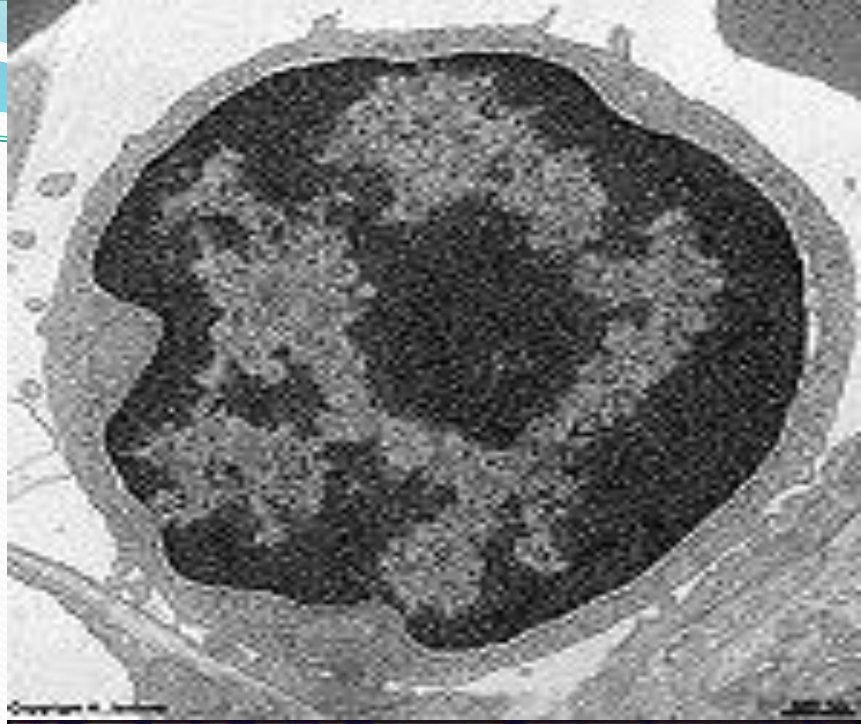
P

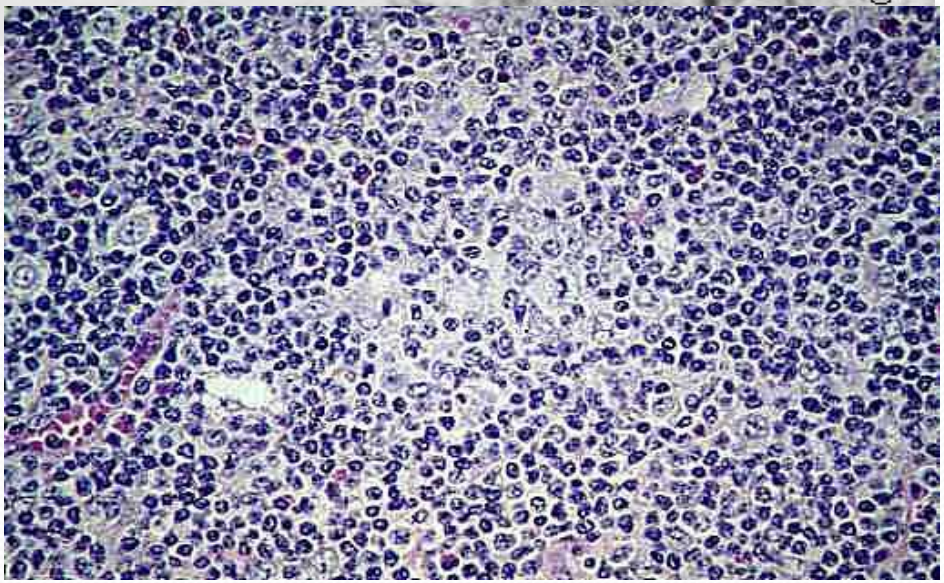
H

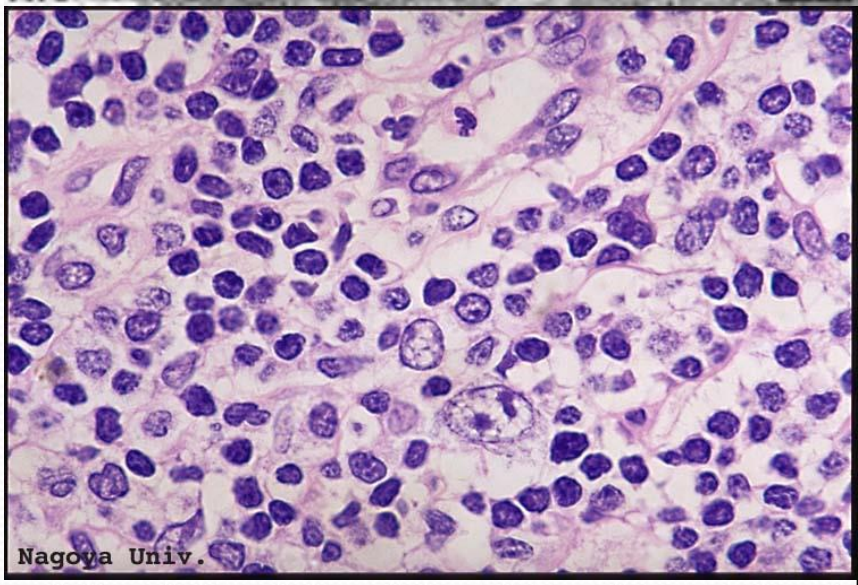
S











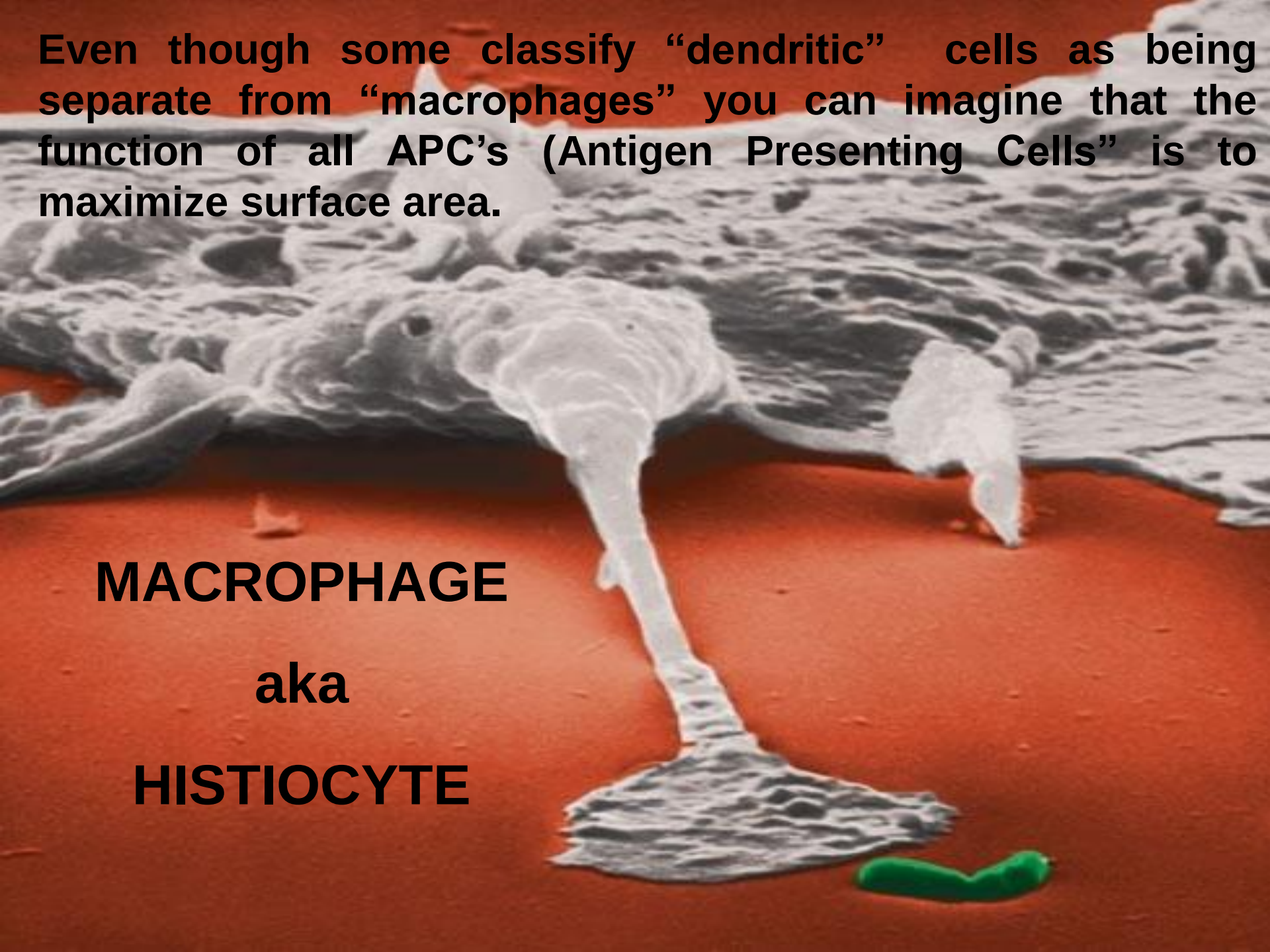
Note even a normal lymph has “cartwheeling” like a plasma cell.

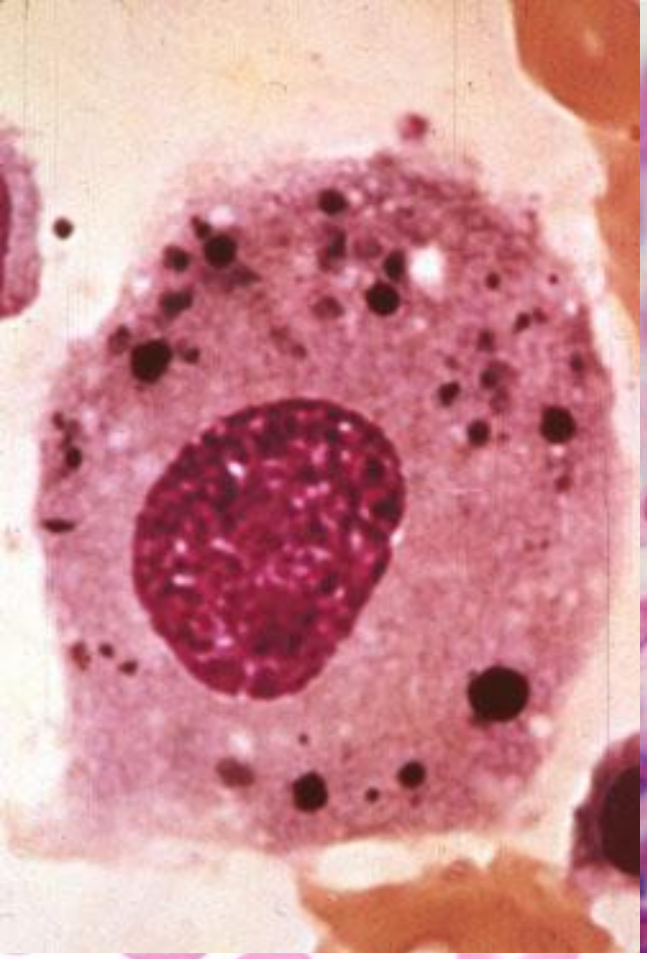
ANY ROUND CELL WITH RATHER DENSE STAINING NUCLEUS AND MINIMAL CYTOPLASM IN CONNECTIVE TISSUE, A BIT BIGGER THAN AN RBC, IS A

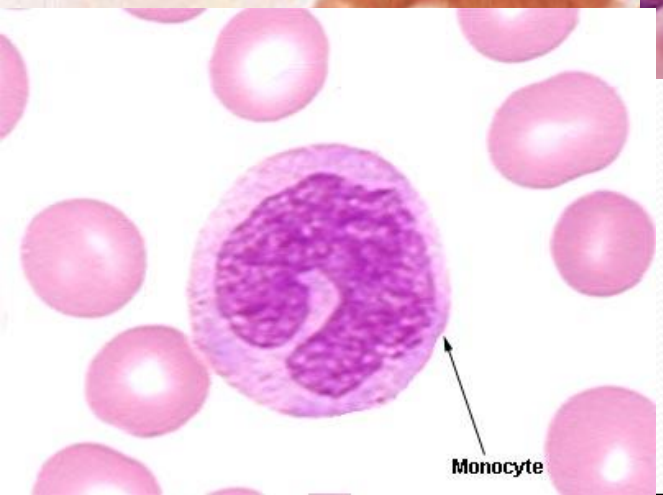
LYMPHOCYTE

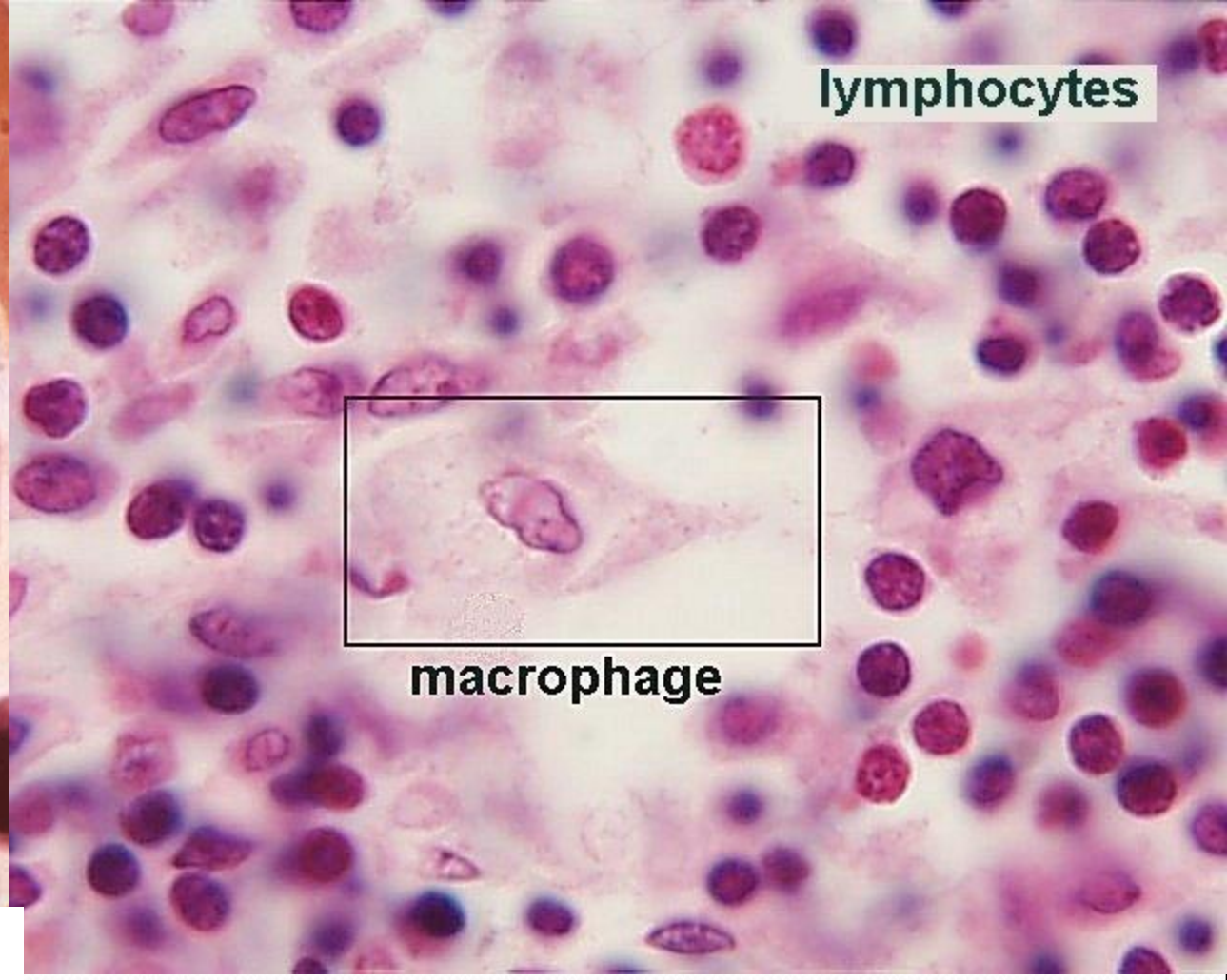
…UNTIL PROVEN OTHERWISE

About ½ trillion lymphocytes in the human body, or 1% of all cells.

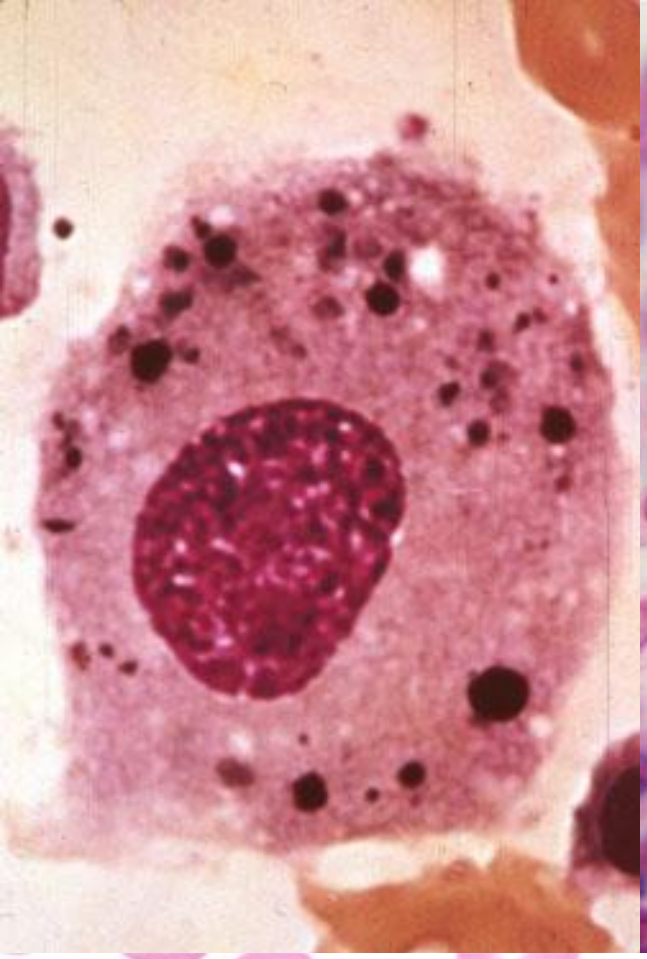

Even though some classify “dendritic” cells as being separate from “macrophages” you can imagine that the function of all APC’s (Antigen Presenting Cells” is to maximize surface area.
MACROPHAGE
aka
HISTIOCYTE

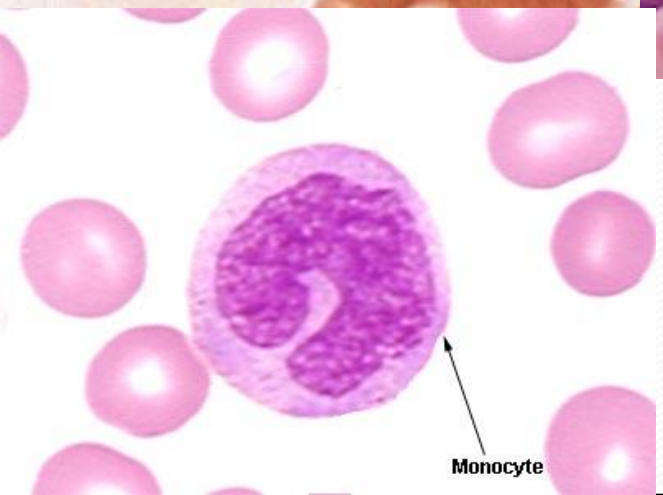


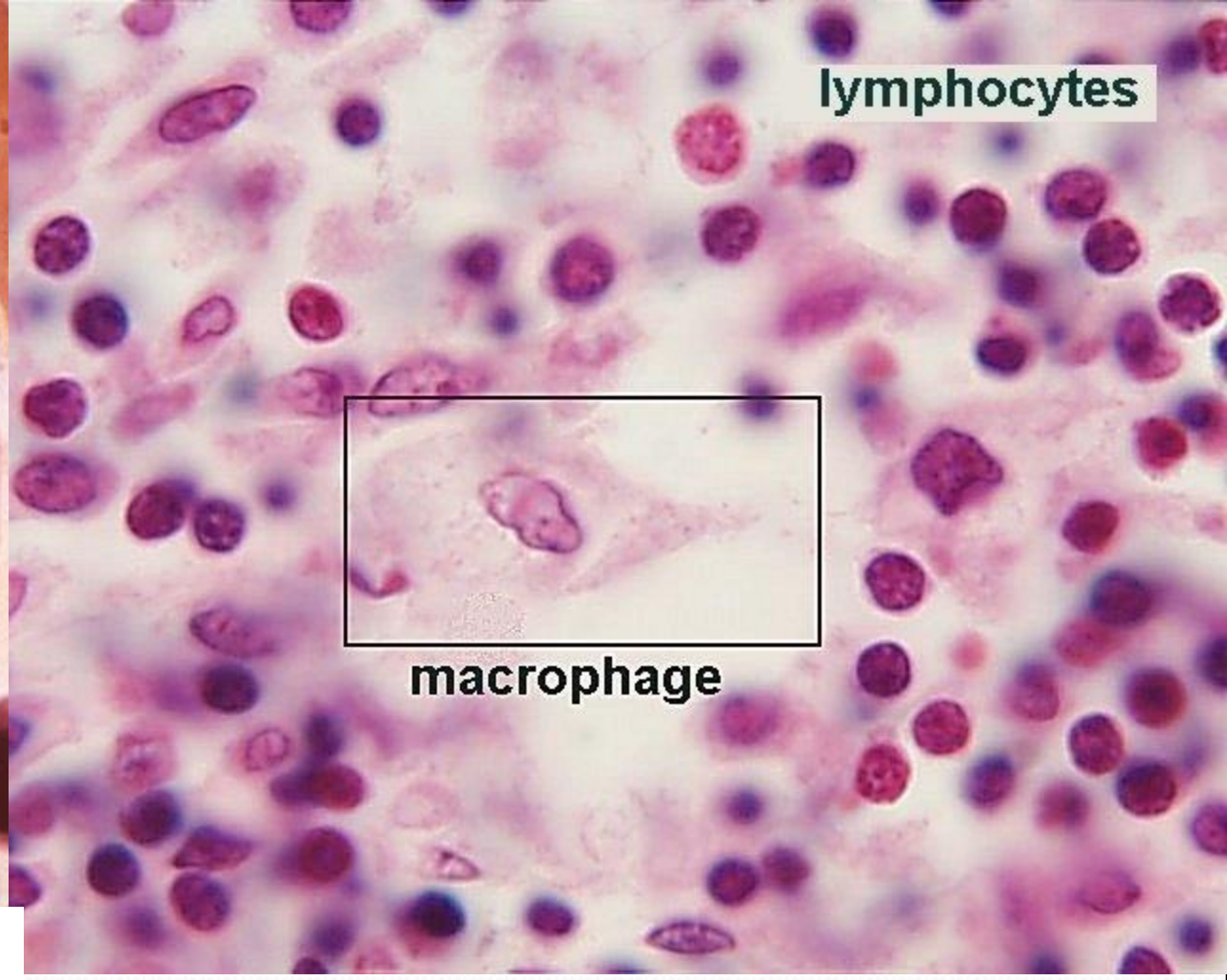




MACROPHAGES are MONOCYTES that have come out of circulation and have gone into tissue

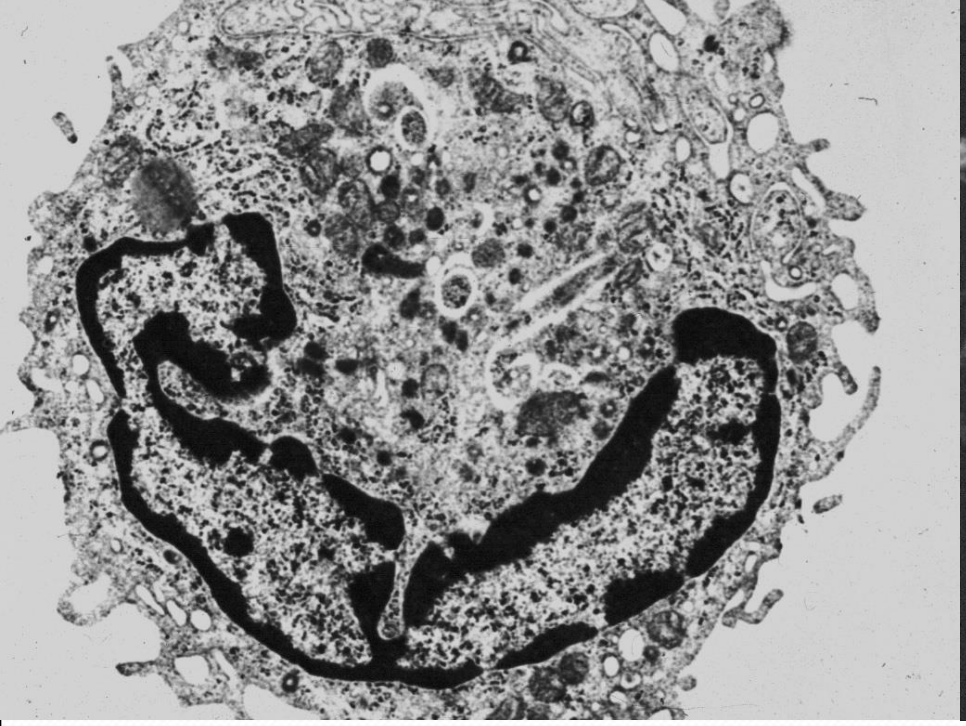


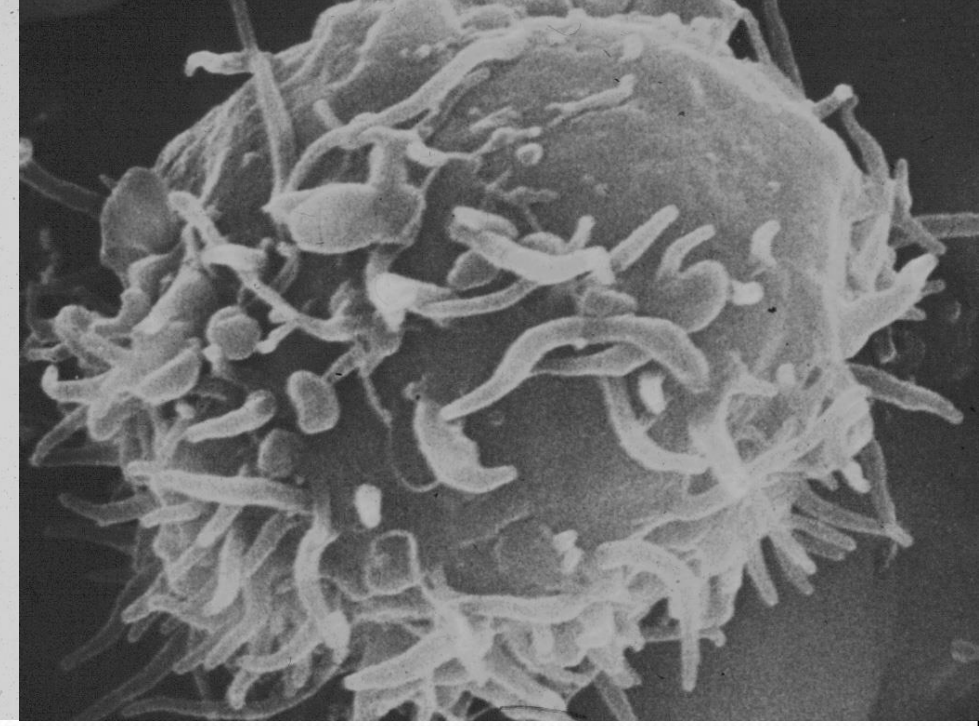




Even though we call a macropahge a “mono”-cyte, conventionally, it’s nucleus can be as convoluted or “cerebrated” as a neutrophil.

Are almost all “pigmented” cells in the body, intrinsic or extrinsic, macrophages? Yes!





MACROPHAGES, TEM, SEM

It is very important to understand the “misnomer”.

We called neutrophils “polys” because of “poly” or “multi” lobes in its nucleus.

And we called lymphs and macrophages “monos” because we said the nuclei were “mono”nucleaded.

But in reality, the nucleus of a macrophage (aka, tissue monocyte) can be VERY comvoluted.

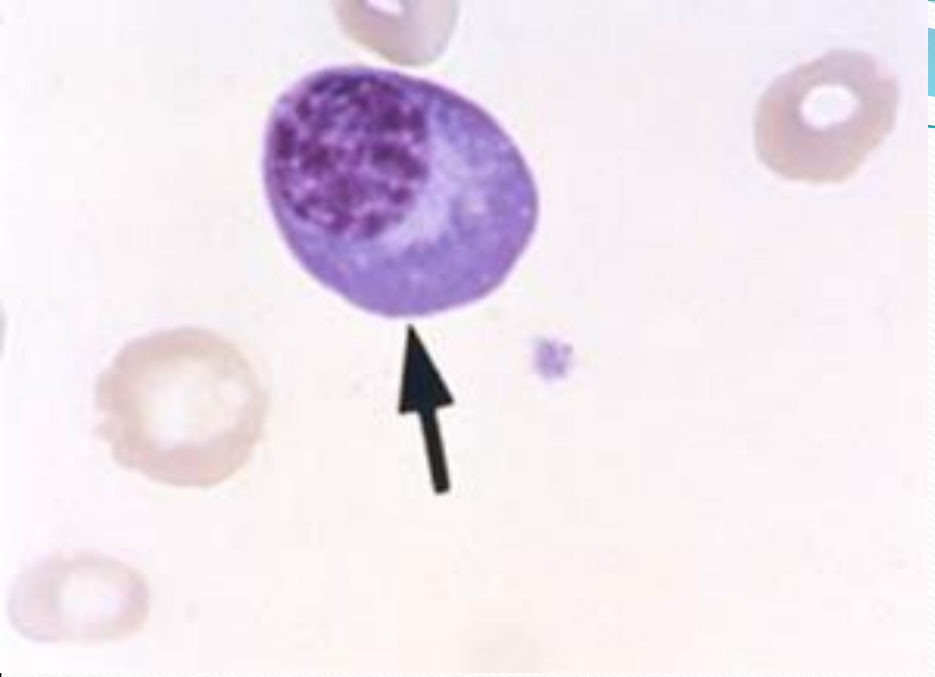
ANY CELL MIXED IN WITH LYMPHOCYTES BUT HAS A LARGER MORE "OPEN", LESS DENSE, LESS CIRCULAR NUCLEUS WITH MORE CYTOPLASM IS A

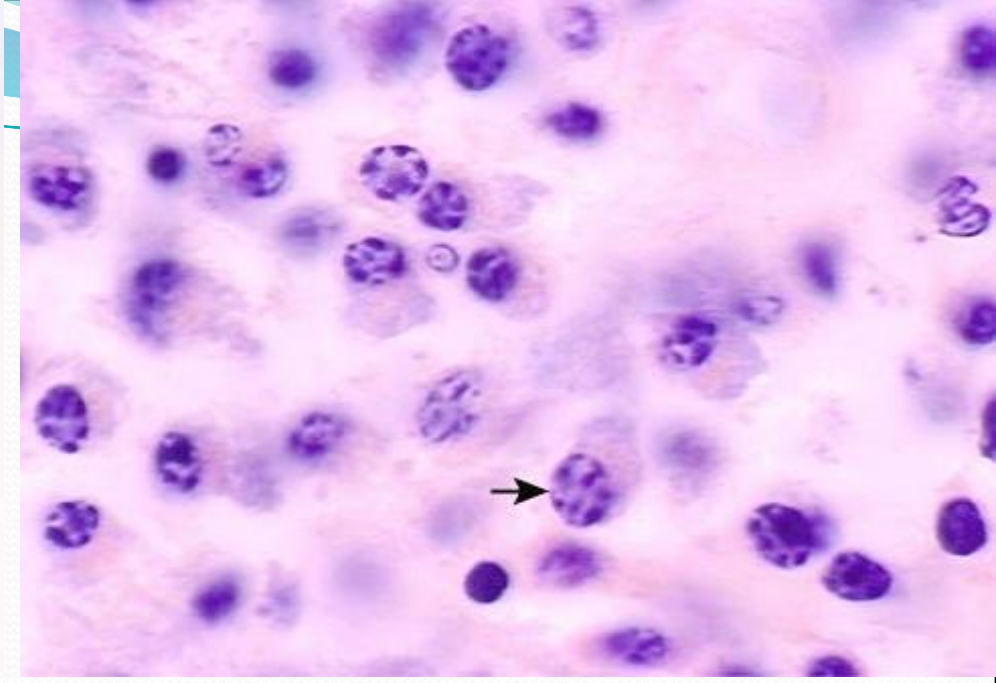
MACROPHAGE

…UNTIL PROVEN OTHERWISE

ALMOST ALL "GRANULAR" or "PIGMENTED" CELLS IN CONNECTIVE TISSUE ARE MACROPHAGES. GRANULOMAS, GIANT CELLS, ARE CHIEFLY MACROPHAGES ALSO.

It might also be allowed to call a macrophage a "APC", i.e., an **A**ntigen **P**resenting **C**ell, of cellular immunity.





1) ROUND NUCLEUS

2) OVOID CYTOPLASM

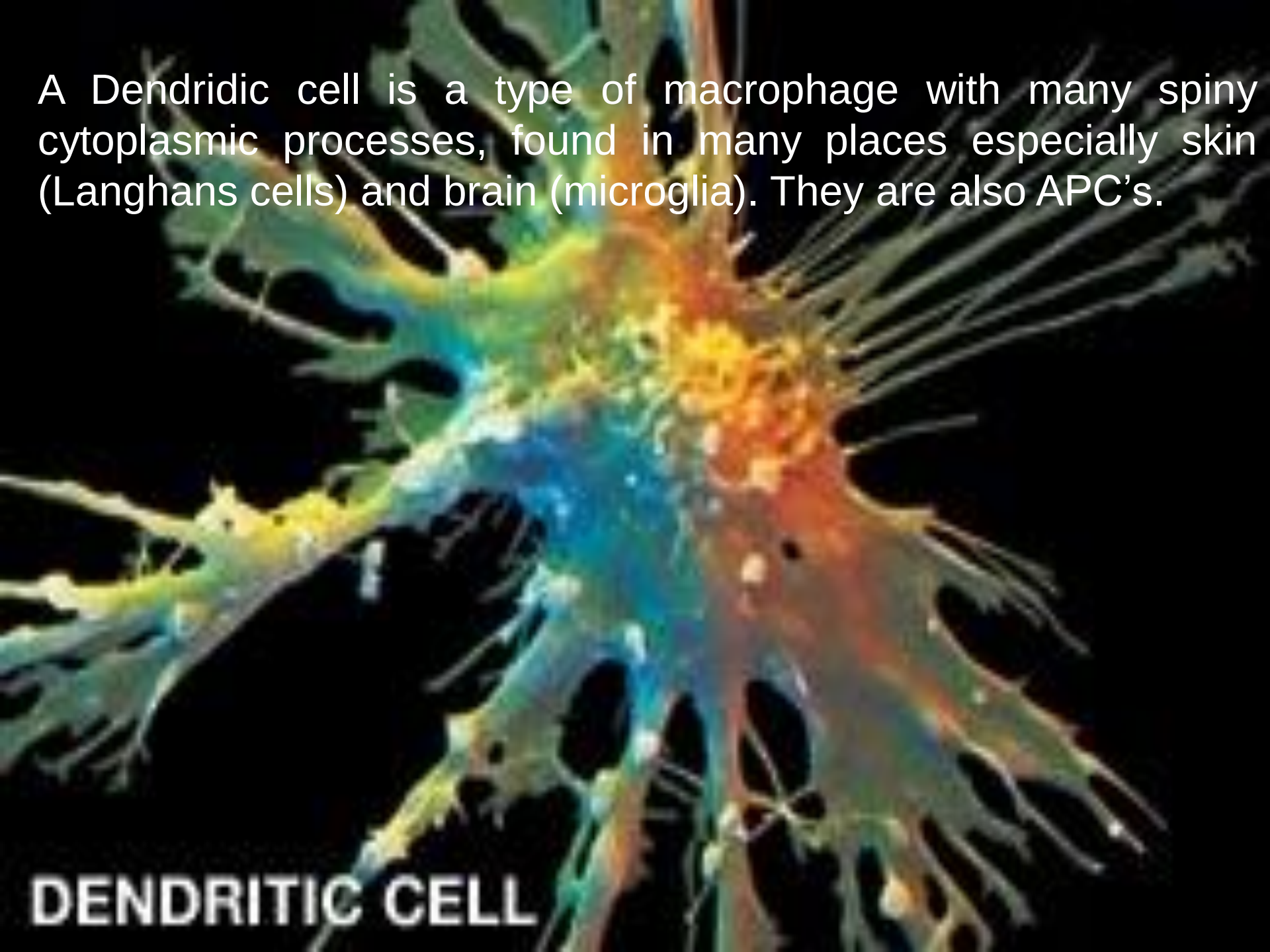
3) PERIPHERAL CHROMATIN

Plasma cells are B-lymphocytes that have dedicated themselves to be antibody factories.

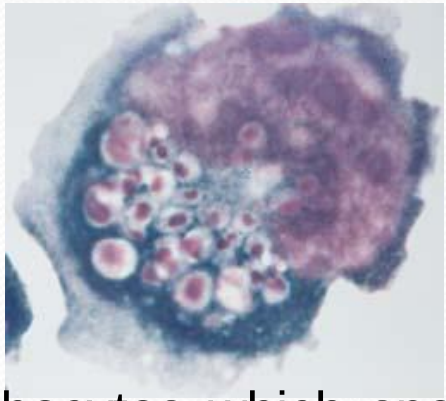
4) “CLEAR ZONE” BETWEEN NUCLEUS AND WIDER LIP OF CYTOPLASM

PLASMA CELLS

A Dendridic cell is a type of macrophage with many spiny cytoplasmic processes, found in many places especially skin (Langhans cells) and brain (microglia). They are also APC's.

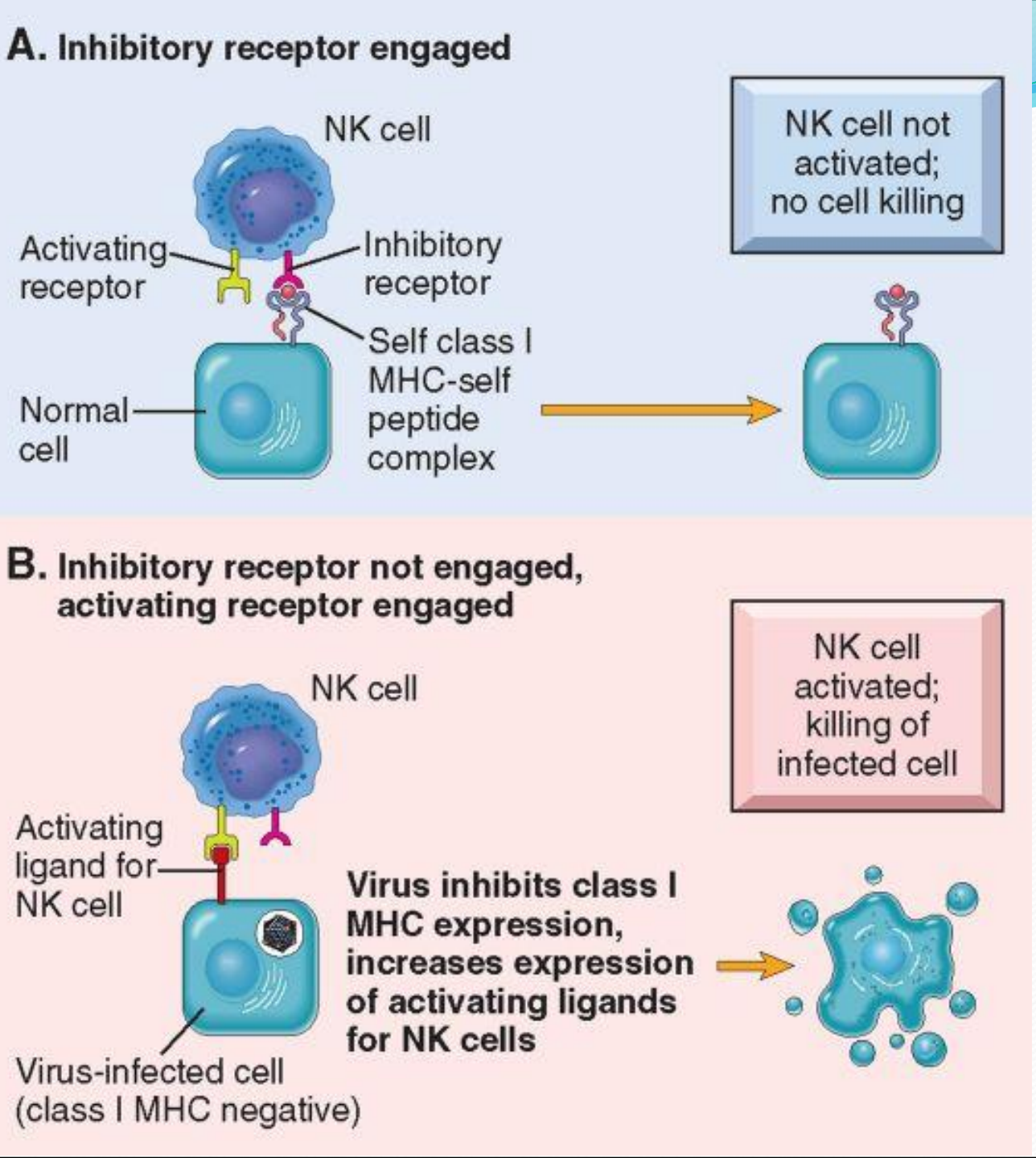


NK CELLS



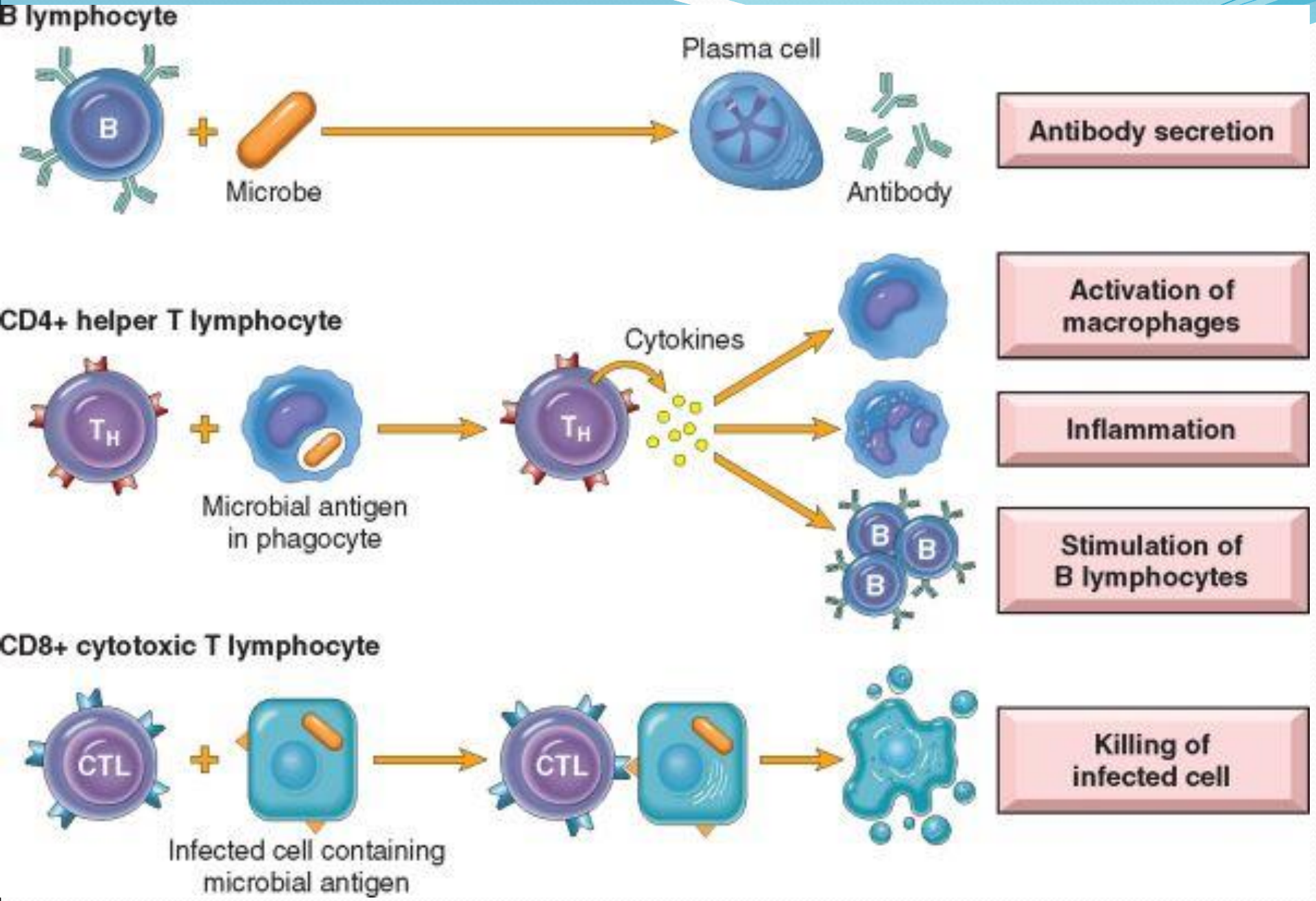
NK cells are types of lymphocytes which specialize in direct killing of cells which the come in contact with, hence the term NK, **N**atural **K**iller.

Natural killer cells (or **NK cells**) are a type of cytotoxic lymphocyte that constitute a major component of the innate immune system. NK cells play a major role in the rejection of tumors and cells infected by viruses. The cells kill by releasing small cytoplasmic granules of proteins called perforin and granzyme that cause the target cell to die by apoptosis. The cell reminds me of the Rodney Dangerfield's joke where he says his footbal team was so tough, after they sacked the quarterback, they then went after his family.


A. Inhibitory receptor engaged
NK cell
Activating receptor
Inhibitory receptor
Self class I MHC-self peptide complex
Normal cell
NK cell not activated; no cell killing
B. Inhibitory receptor not engaged, activating receptor engaged
NK cell
Activating ligand for NK cell
Virus inhibits class I MHC expression, increases expression of activating ligands for NK cells
Virus-infected cell (class I MHC negative)
NK cell activated; killing of infected cell

GENERAL SCHEME of CELLULAR EVENTS

- **APCs** (Macrophages, Dendritic Cells)→
- **T-Cells**→ (Control Everything)
  - **CD_4**→ "REGULATORS" (Helper)
  - **CD8**→ "EFFECTORS"
- **B-Cells**→ Plasma Cells→ AB's
- **NK Cells**→


B lymphocyte
B
Microbe
Plasma cell
Antibody
Antibody secretion
CD4+ helper T lymphocyte
TH
Microbial antigen in phagocyte
Cytokines
TH
Activation of macrophages
Inflammation
B
B
B
Stimulation of B lymphocytes
CD8+ cytotoxic T lymphocyte
CTL
Infected cell containing microbial antigen
CTL
Killing of infected cell

CYTOKINES

- **MEDIATE** INNATE (NATURAL) IMMUNITY, IL-1, TNF, INTERFERONS
- **REGULATE** LYMPHOCYTE GROWTH (many interleukins, ILs)
- **ACTIVATE** INFLAMMATORY CELLS
- **STIMULATE** HEMATOPOESIS, (CSFs, or **C**olony **S**timulating **F**actors)

CYTOKINES/CHEMOKINES

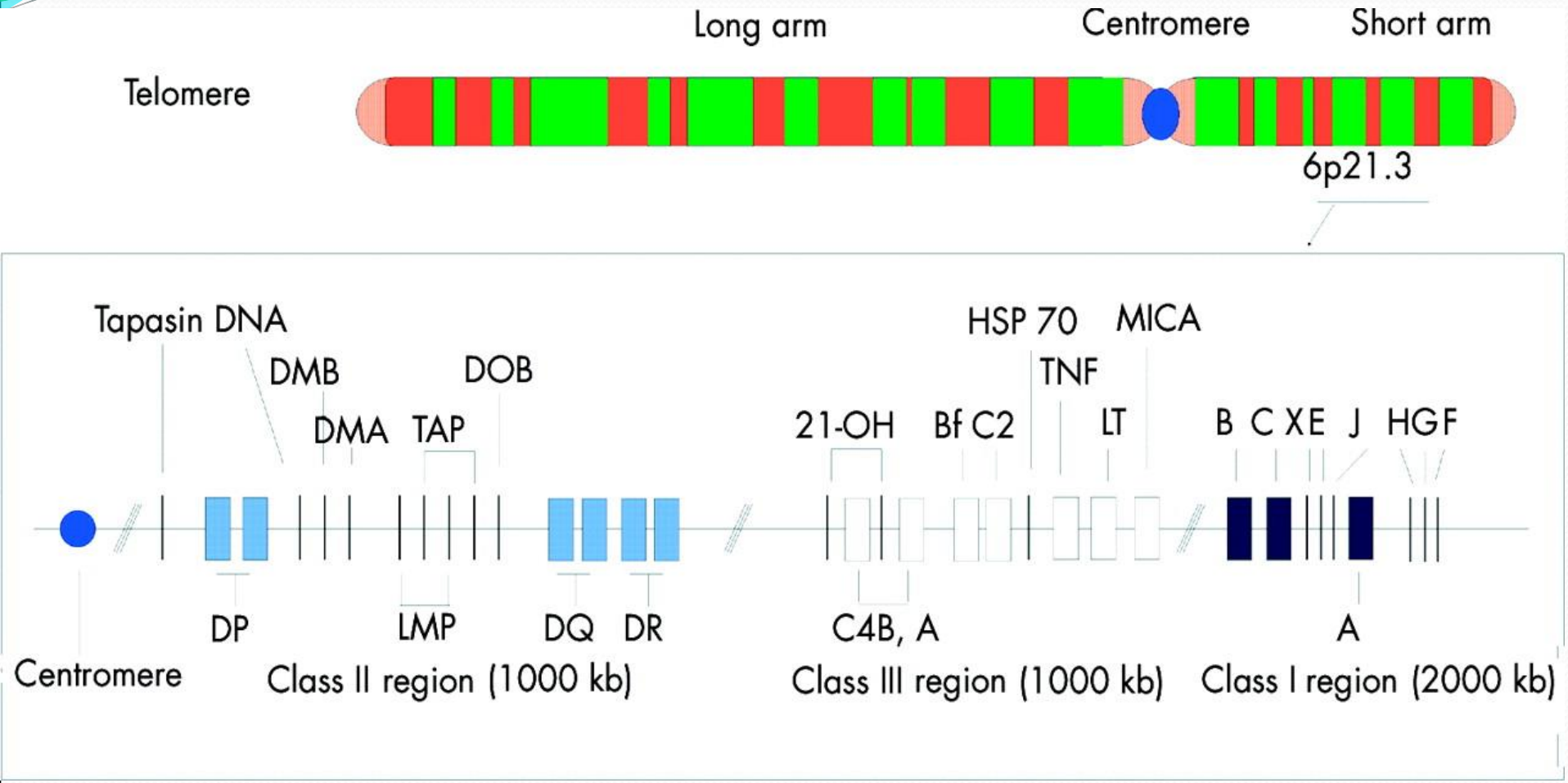
- **CYTOKINES are PROTEINS produced by MANY cells, but usually LYMPHOCYTES and MACROPHAGES, numerous roles in acute and chronic inflammation, AND immunity**
  - **TNF, IL-1, by macrophages**
- **CHEMOKINES are small proteins which are attractants for PMNs**

This is the same EXACT slide from our discussion of acute inflammation.

MHC

Major Histocompatibility Complex

- A genetic "LOCUS" on Chromosome 6, which codes for cell surface compatibility
- Also called HLA (Human Leukocyte Antigens) in humans and H-2 in mice
- It's major job is to make sure all self cell antigens are recognized and "tolerated", because the general rule of the immune system is that all UN-recognized cells will NOT be tolerated


Long arm
Centromere
Short arm
Telomere
6p21.3
Tapasin DNA
DMB
DOB
DMA
TAP
HSP 70
MICA
TNF
21-OH
Bf C2
LT
B C XE J HGF
DP
LMP
DQ
DR
C4B, A
A
Centromere
Class II region (1000 kb)
Class III region (1000 kb)
Class I region (2000 kb)

MHC MOLECULES (Gene Products)

- **I** (All nucleated cells and platelets), cell surface glycoproteins, ANTIGENS

- **II** (APC's, i.e., macs and dendritics, lymphs), cell surface glycoproteins, ANTIGENS

- **III** Complement System Proteins

IMMUNE SYSTEM DISORDERS

WHAT CAN GO WRONG?

- **HYPERSENSITIVITY REACTIONS, I-IV**
- **"AUTO"-IMMUNE DISEASES, aka "COLLAGEN" DISEASES (BAD TERM)**
- **IMMUNE DEFICIENCY SYNDROMES, IDS:**
  - **PRIMARY (GENETIC)**
  - **SECONDARY (ACQUIRED)**

HYPERSENSITIVITY REACTIONS (4)

- **I (Immediate Hypersensitivity)**
- **II (Antibody Mediated Hypersensitivity)**
- **III (Immune-Complex Mediated Hypersensitivity)**
- **IV (Cell-Mediated Hypersensitivity)**

A good understanding of the 4 different types of classical "hypersensitivity" reactions, should be obtained. These are always taught as the general FOUR types of hypersensitivity, but are by no means complete or mutually exclusive.

Type I

IMMEDIATE HYPERSENSITIVITY

- "Immediate" means seconds to minutes
- "Immediate Allergic Reactions", which may lead to anaphylaxis, shock, edema, dyspnea death
  - 1) **Allergen exposure**
  - 2) **IMMEDIATE** phase: MAST cell DEgranulation, vasodilatation, vascular leakage, smooth muscle (broncho)-spasm
  - 3) **LATE** phase (hours, days): Eosinophils, PMNs, T-Cells

TYPE II HYPERSENSITIVITY
ANTIBODY MEDIATED IMMUNITY

- ABs attach to cell surfaces
  - OPSONIZATION (basting the turkey)
  - PHAGOCYTOSIS
  - COMPLEMENT FIXATION (cascade of C1q, C1r, C1s, C2, **C3**, C4, C5.....)
  - LYSIS (destruction of cells by rupturing or breaking of the cell membrane)

TYPE II DISEASES

- **Autoimmune Hemolytic Anemia, AHA**
- **Idiopathic Thrombocytopenic Purpura, ITP**
- **Goodpasture Syndrome (Nephritis and Lung hemorrhage)**
- **Rheumatic Fever**
- **Myasthenia Gravis**
- **Graves Disease**
- **Pernicious Anemia, PA**

Understandably, these are all “AUTO”-immune diseases, or FAILURES of the MHC. Note most are organ-specific (i.e., “local”) rather than systemic.

TYPE III HYPERSENSITIVITY

IMMUNE COMPLEX MEDIATED

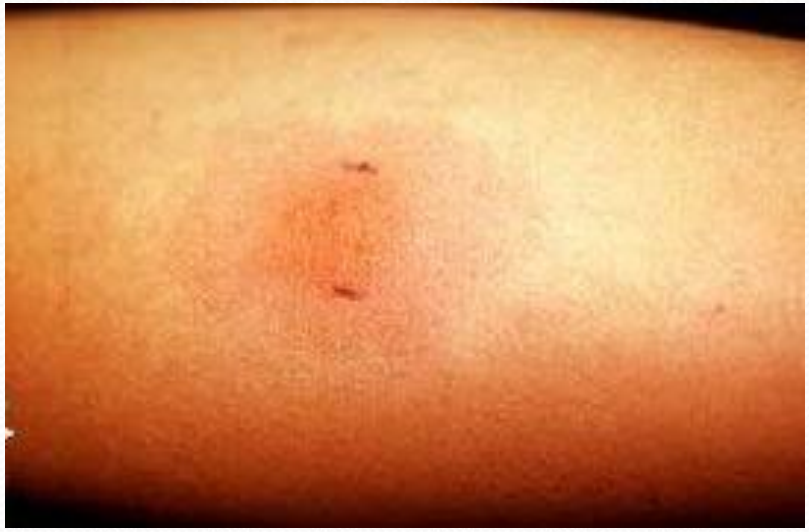
- **Antigen/Antibody "Complexes"**
- **Where do they go?**
  - **Kidney (Glomerular Basement Membrane)**
  - **Blood Vessels**
  - **Skin**
  - **Joints**
- **Common Type III Diseases- SLE (Lupus), Poly(Peri)arteritis Nodosa, Poststreptococcal Glomerulonephritis, Arthus reaction (hrs), Serum sickness (days)**

An Arthus reaction is a local vasculitis associated with deposition of immune complexes and activation of complement. Immune complexes form in the setting of high local concentration of vaccine antigens and high circulating antibody concentration. Arthus reactions are characterized by severe pain, swelling, induration, edema, hemorrhage, and occasionally by necrosis. These symptoms and signs usually occur 4–12 hours after vaccination.

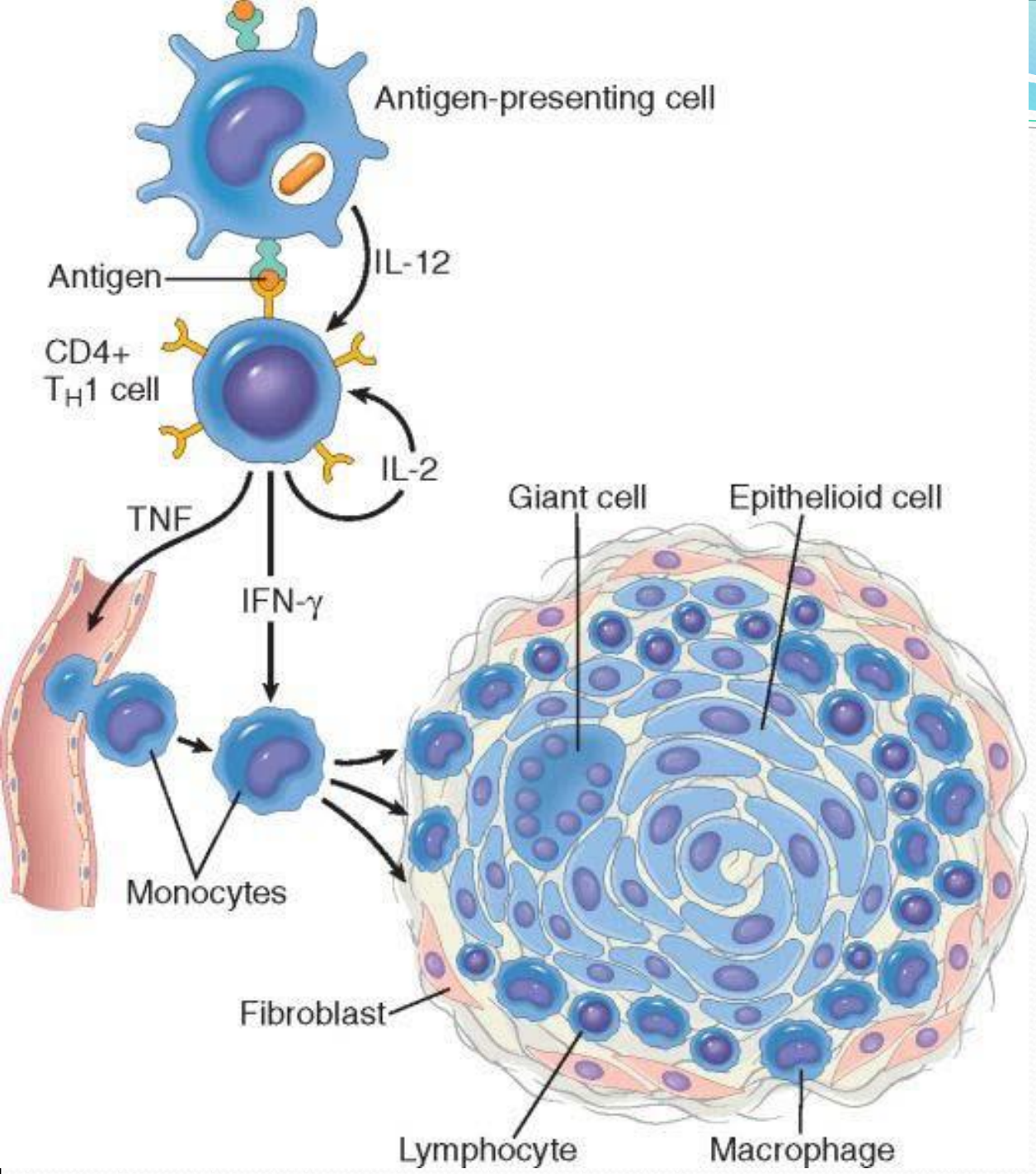
Symptoms can take as long as fourteen days after exposure to appear, and may include signs and symptoms commonly associated with allergic reactions or infections, such asrashes, itching, joint pain (arthralgia), fever, and swollen lymph nodes (lymphadenopathy), and malaise. Historically, it was a result of animal serum injections.

TYPE IV HYPERSENSITIVITY
CELL-MEDIATED (T-CELL) DELAYED HYPERSENSITIVITY

- Tuberculin Skin Reaction



- DIRECT ANTIGEN→CELL CONTACT
  - GRANULOMA FORMATION
  - CONTACT DERMATITIS



Schematic for granuloma formation in Type IV Hypersensitivity

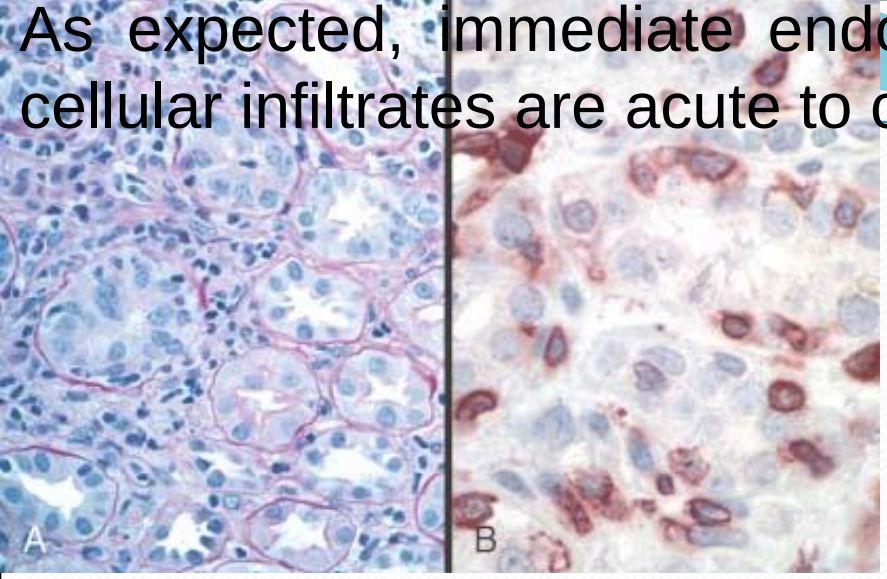
SUMMARY

- I Acute allergic reaction
- II Antibodies directed against cell surfaces
- III Immune complexes
- IV Delayed Hypersensitivity, e.g., Tb skin test

RENAL TRANSPLANT REJECTION

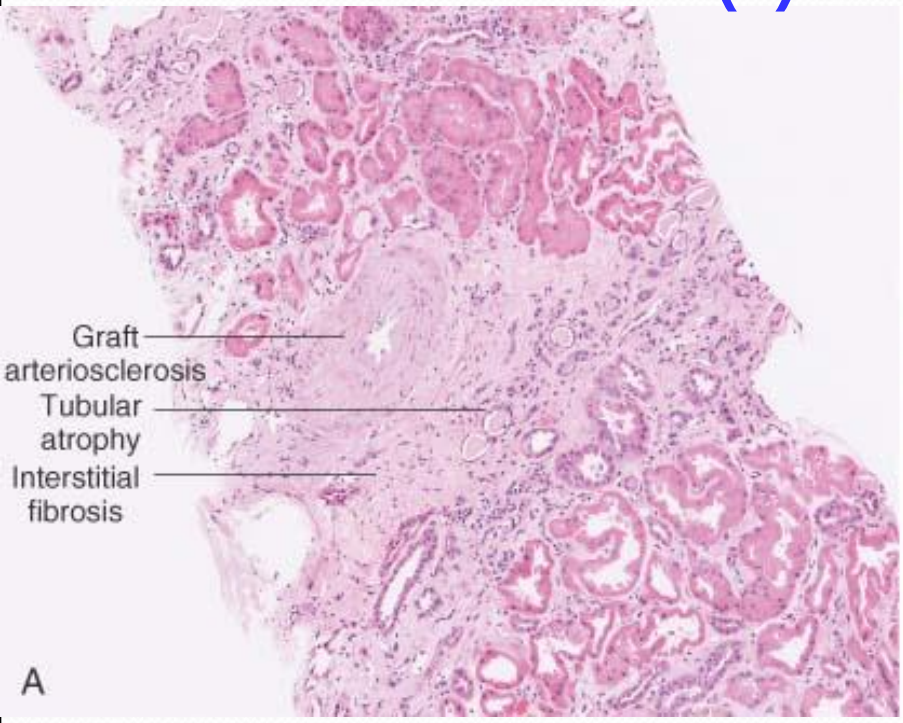
- **HYPERACUTE (minutes) : AG/AB reaction of vascular endothelium**
- **ACUTE (days→ months): cellular (INTERSTITIAL infiltrate) and humoral (VASCULITIS)**
- **CHRONIC (months): slow vascular fibrosis**

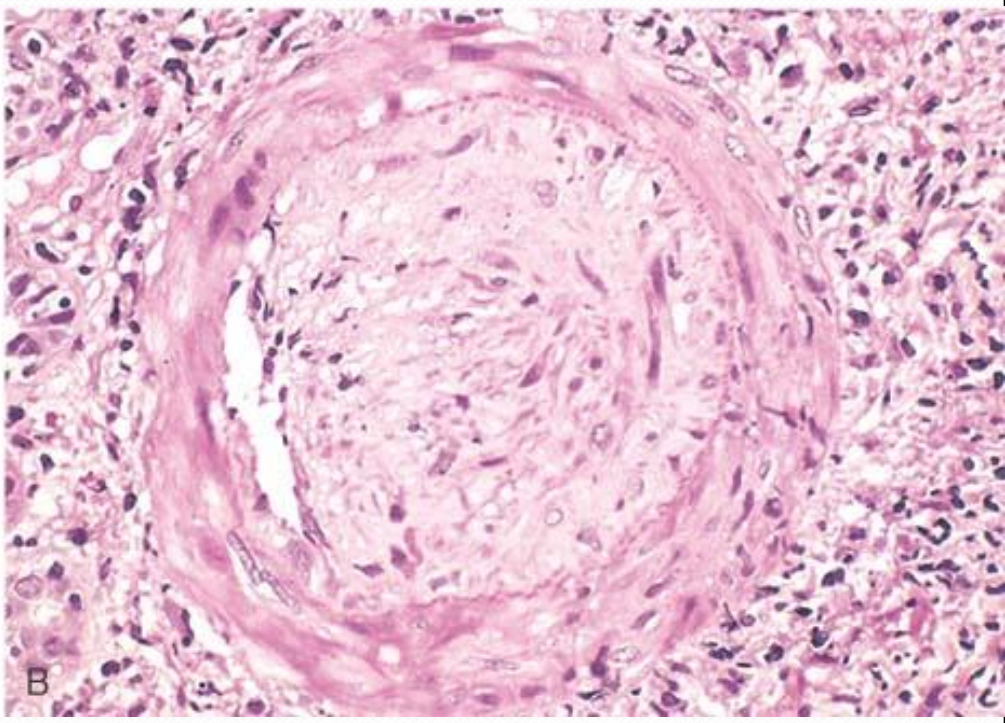
As expected, immediate endothelial responses are hyperacute, cellular infiltrates are acute to chronic, and fibrosis is chronic.



ACUTE CELLULAR (T)

ACUTE HUMORAL





CHRONIC

AUTO-IMMUNE DISEASES

- Failure of SELF RECOGNITION
- **Failure of SELF TOLERANCE**
- **TOLERANCE**
  - **CENTRAL** (Death of self reactive lymphocytes)
  - **PERIPHERAL** (anergy, suppression by T-cells, deletion by apoptosis, sequestration (Ag masking))
- STRONG **GENETIC PREDISPOSITION**
- OFTEN **RELATED TO OTHER** AUTOIMMUNE DISEASES
- OFTEN TRIGGERED BY **INFECTIONS**

AUTO-IMMUNE DISEASES

- Central tolerance occurs during lymphocyte development and operates in the thymus and bone marrow. Here, T and B lymphocytes that recognize self antigens are deleted before they develop into fully immunocompetent cells, preventing autoimmunity.
- Peripheral tolerance is immunological tolerance developed after T and B cells mature and enter the periphery.

Acquired or induced tolerance refers to the immune system's adaptation to external antigens characterized by a specific non-reactivity of the lymphoid tissues to a given antigen that in other circumstances would likely induce cell-mediated or humoral immunity. One of the most important natural kinds of acquired tolerance is immune tolerance in pregnancy, where thefetus and the placenta must be tolerated by the maternal immune system.

CLASSIC AUTOIMMUNE DISEASES (SYSTEMIC)

- **LUPUS (SLE) Systemic Lupus Erythematosus**
- **RHEUMATOID ARTHRITIS**
- **SJÖGREN SYNDROME**
- **SYSTEMIC SCLEROSIS (scleroderma)**
- **"collagen" diseases (term no longer used)**

Do not think that because the names of some of these SYSTEMIC auto-immune diseases seem to localize to certain areas, like joints, salivary glands, or skin, that they are NOT SYSTEMIC diseases.

CLASSIC AUTOIMMUNE DISEASES (LOCAL)

- HASHIMOTO THYROIDITIS
- AUTOIMMUNE HEMOLYTIC ANEMIA
- MULTIPLE SCLEROSIS
- AUTOIMMUNE ORCHITIS
- GOODPASTURE SYNDROME
- AUTOIMMUNE THROMBOCYTOPENIA
- "PERNICIOUS" ANEMIA
- INSULIN DEPENDENT DIABETES MELLITUS
- MYASTHENIA GRAVIS
- GRAVES DISEASE

It is always dangerous to call a disease "local" because the more we study it, the more we realize it isn't.

Nevertheless, this is the classic list of "local" autoimmune diseases.

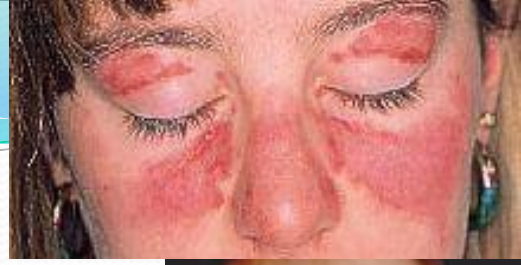
N.B.

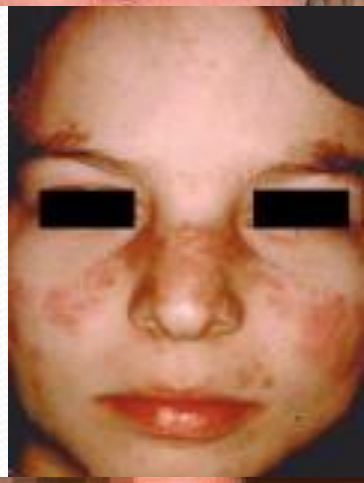
- **The list of diseases proven to be "autoimmune" grows by leaps and bounds every year!!!**

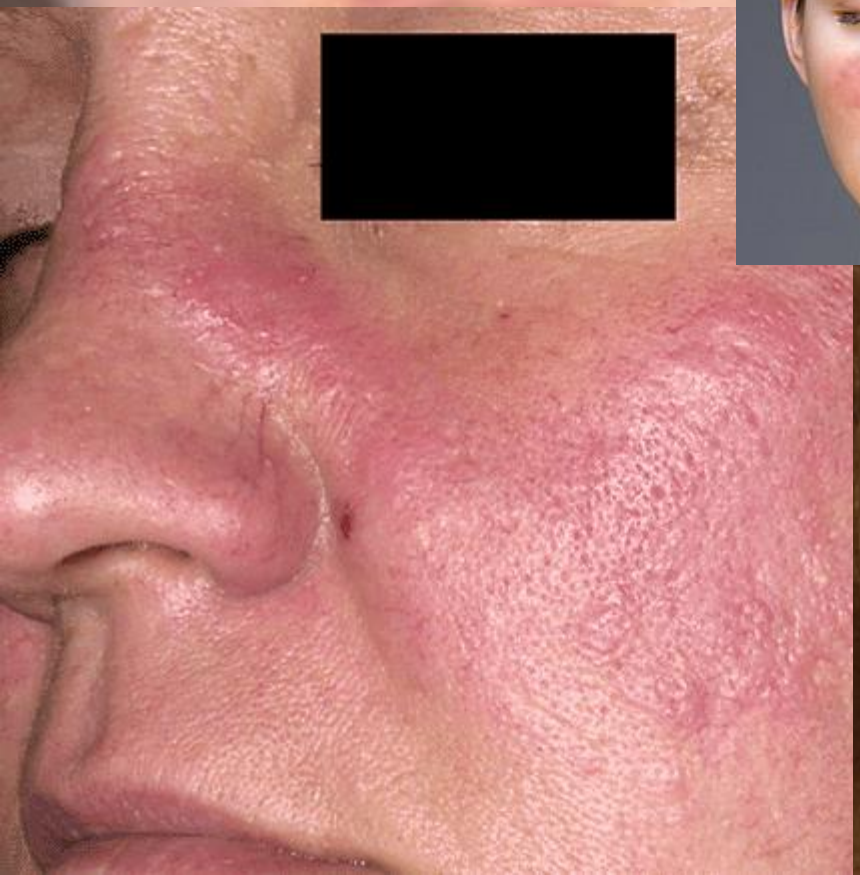
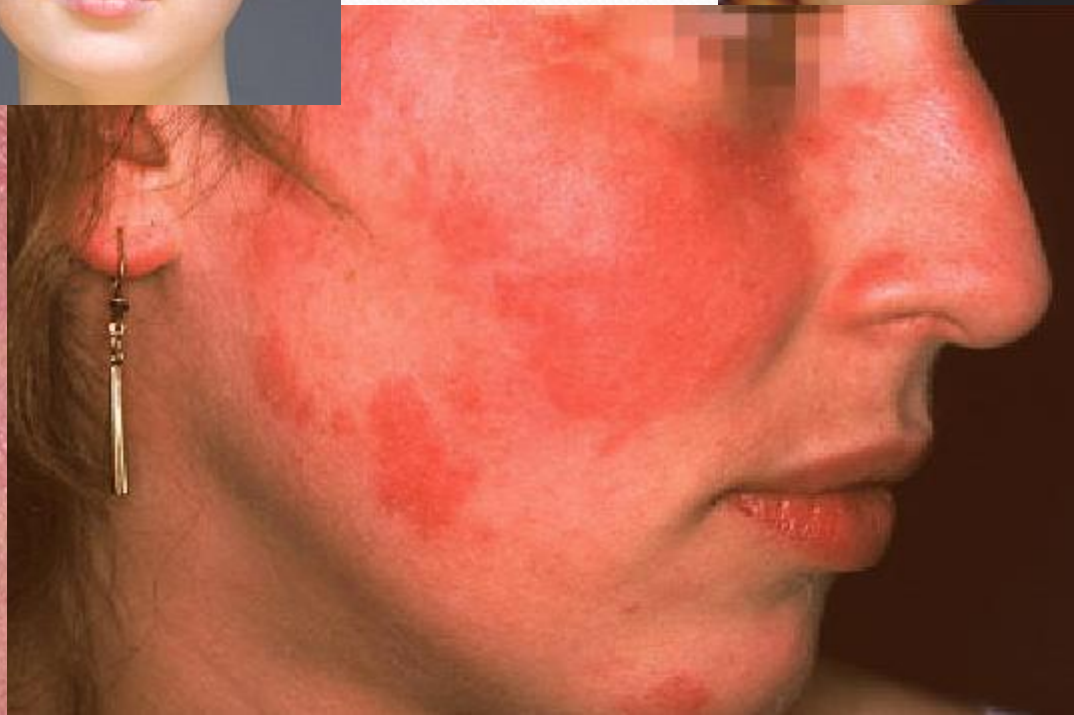
Would it be fair to say EVERY disease is autoimmune? Probably NOT!
Would it be fair to say almost every disease can result as a failure of some immune process? Probably!

LUPUS (SLE)

- **Etiology:** Antibodies (ABs) directed against the patient's own DNA, HISTONES, NON-histone RNA, and NUCLEOLUS
- **Pathogenesis:** Progressive DEPOSITION and INFLAMMATION to immune deposits, in skin, joints, kidneys, vessels, heart, CNS
- **Morphology:** "Butterfly" rash, skin deposits, glomerolunephritis (NOT discoid)
- **Clinical expression:** Progressive renal and vascular disease, POSITIVE A.N.A.



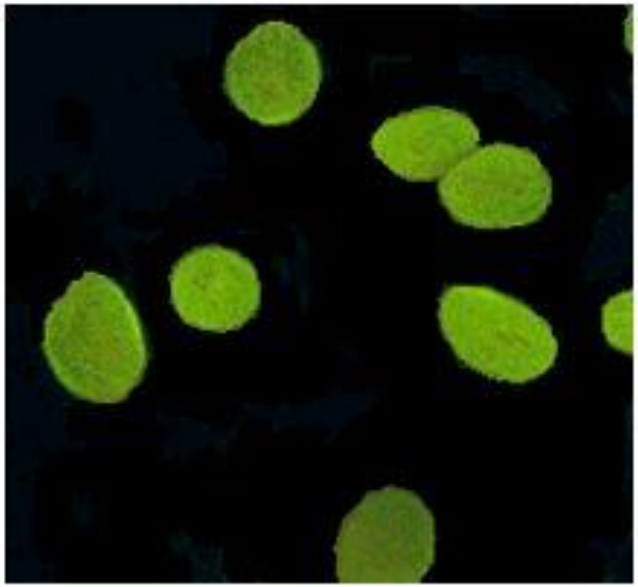



HOMO

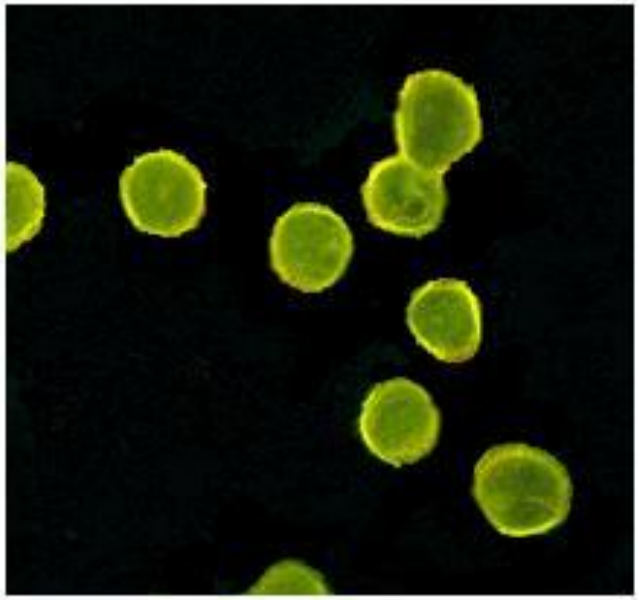
SPECK

RIM

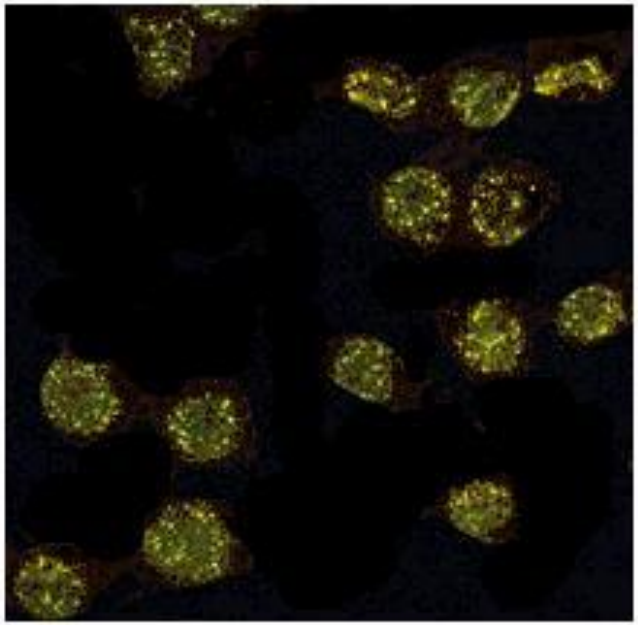
NUCLEOLAR



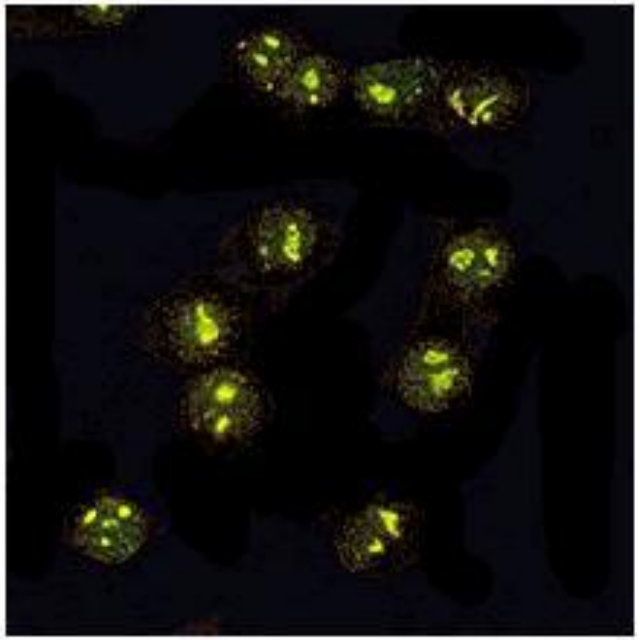
Homogenous pattern



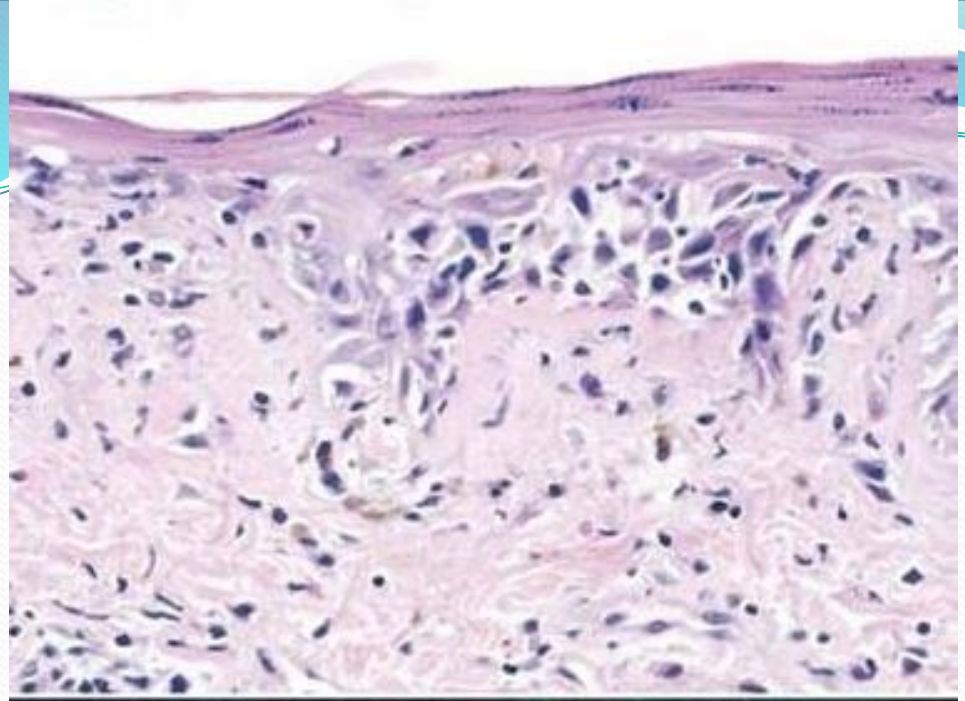
Rim pattern

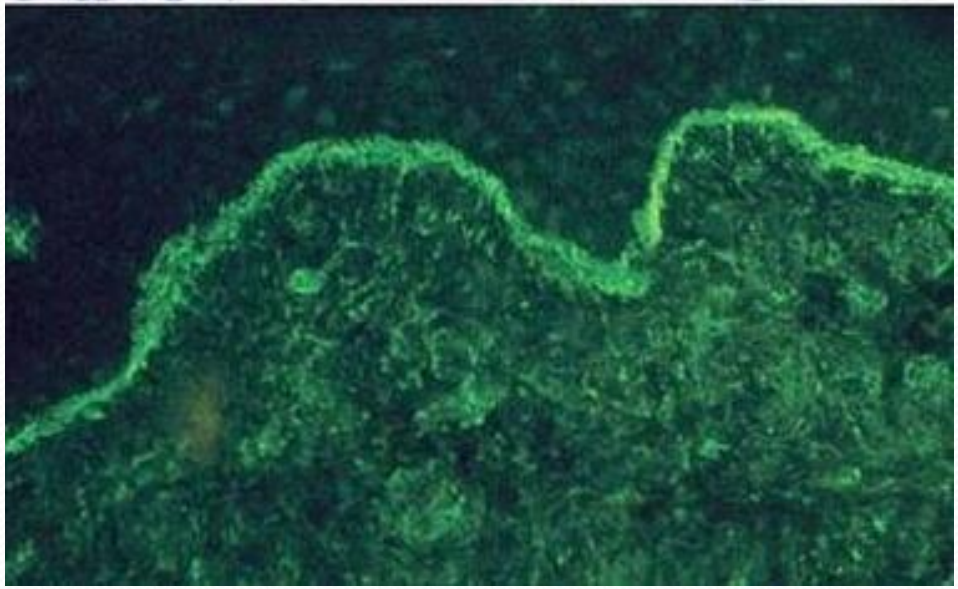


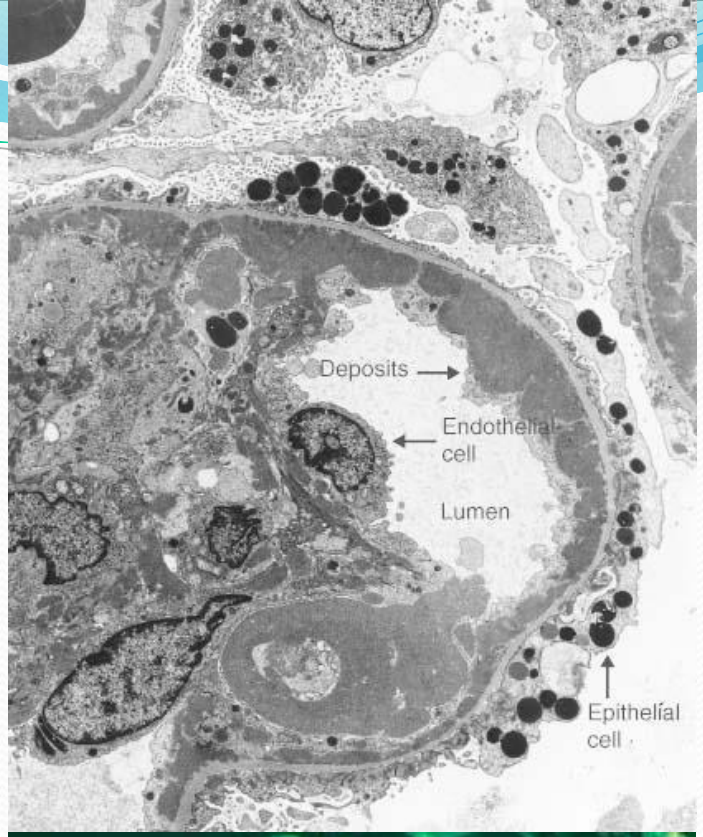
Speckled pattern

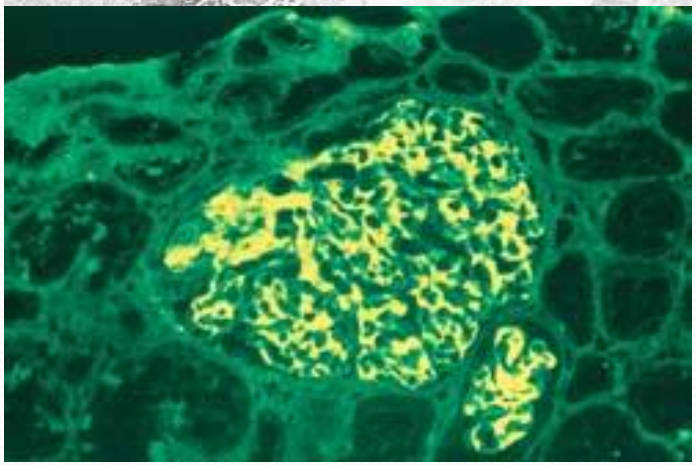


Nucleolar pattern



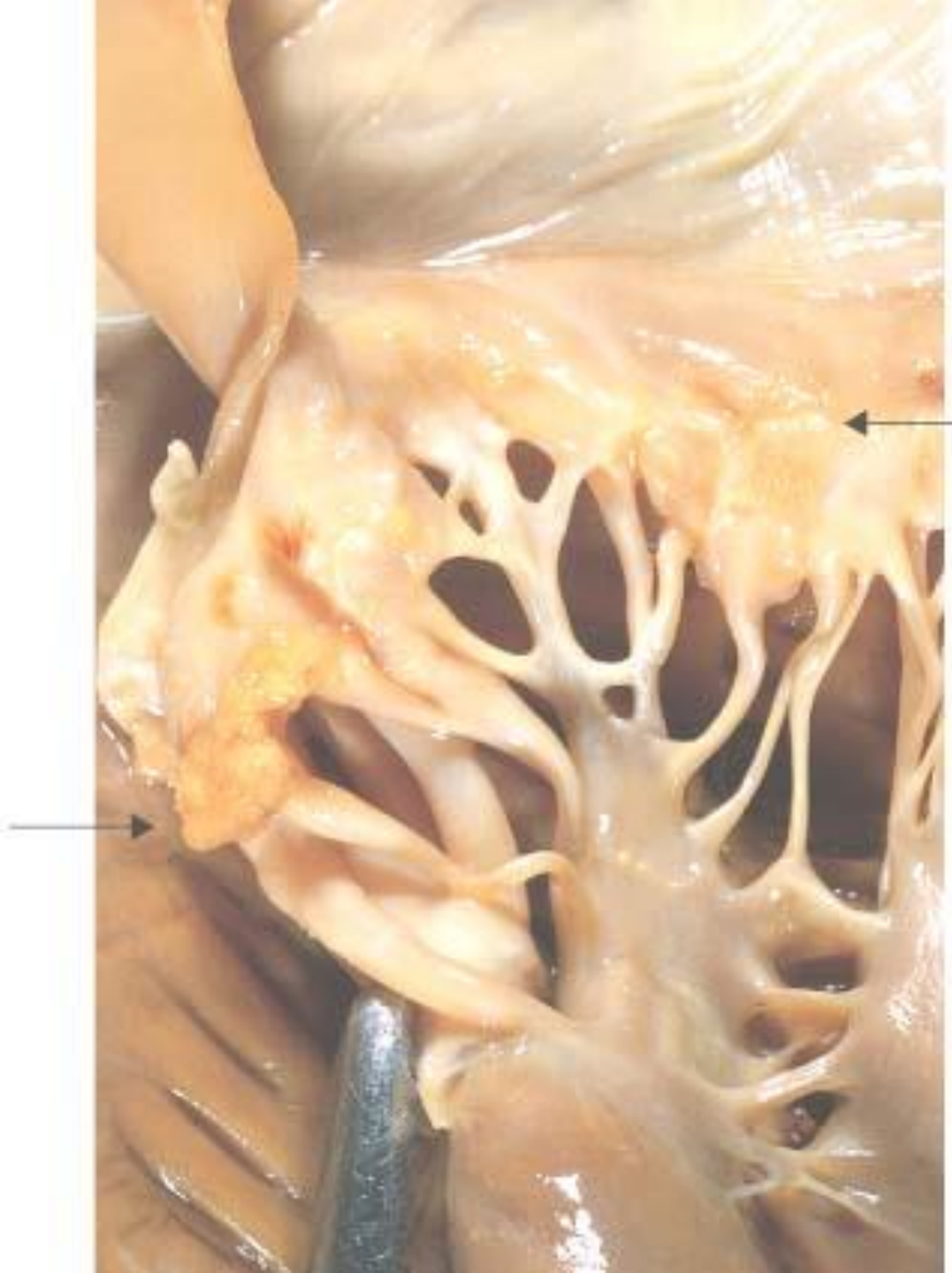






SLE, SKIN

SLE, GLOMERULUS



Libman-Sacks vegetations, also called Libman-Sacks endocarditis, are on BOTH sides of the leaflet.

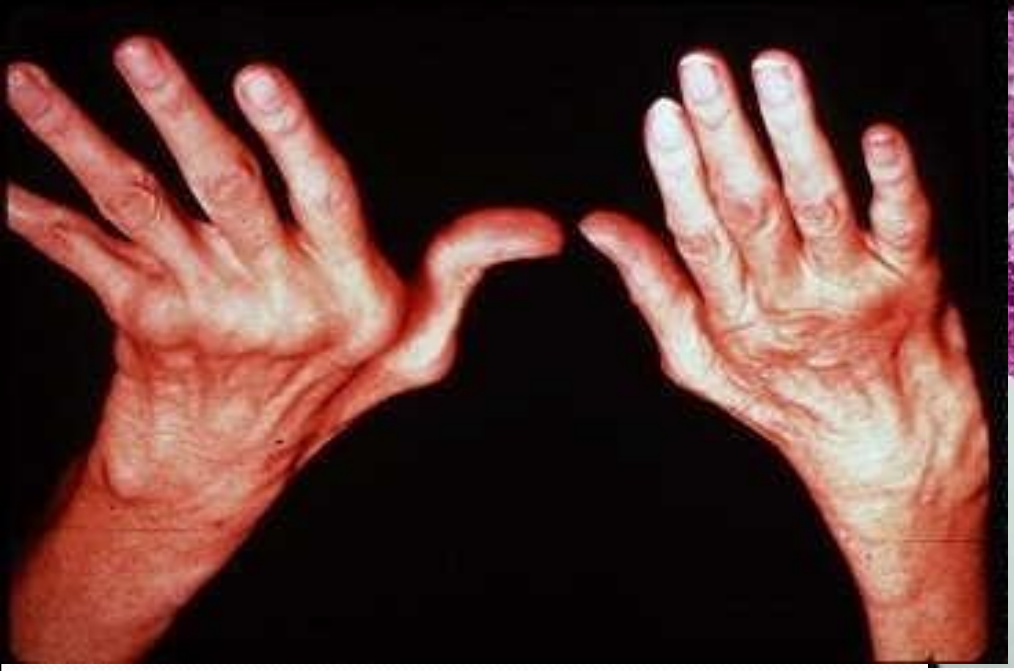
TABLE 6-10 -- Clinical and Pathologic Manifestations of Systemic Lupus Erythematosus

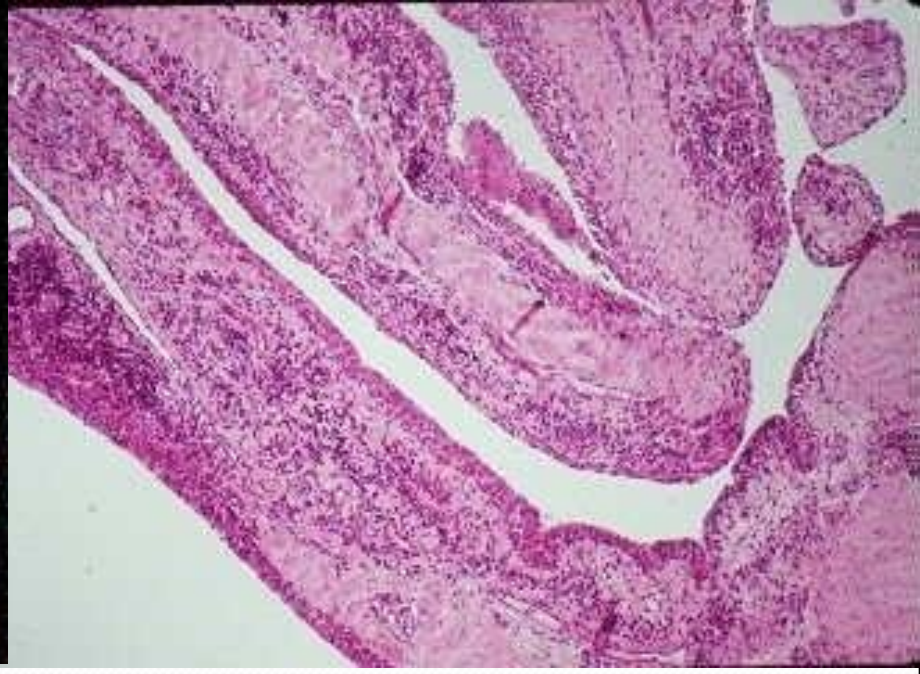
Clinical Manifestation	Prevalence in Patients, %
Hematologic	100
Arthritis	90
Skin	85
Fever	83
Fatigue	81
Weight loss	63
Renal	50
Central nervous system	50
Pleuritis	46
Myalgia	33
Pericarditis	25
Gastrointestinal	21
Raynaud phenomenon	20
Ocular	15
Peripheral neuropathy	14

Renal failure in a young woman is always highly suspect of lupus.

MORE SYSTEMIC AUTOIMMUNE DISEASES

- RHEUMATOID ARTHRITIS
- SJÖGREN SYNDROME
- SCLERODERMA (SYSTEMIC SCLEROSIS)



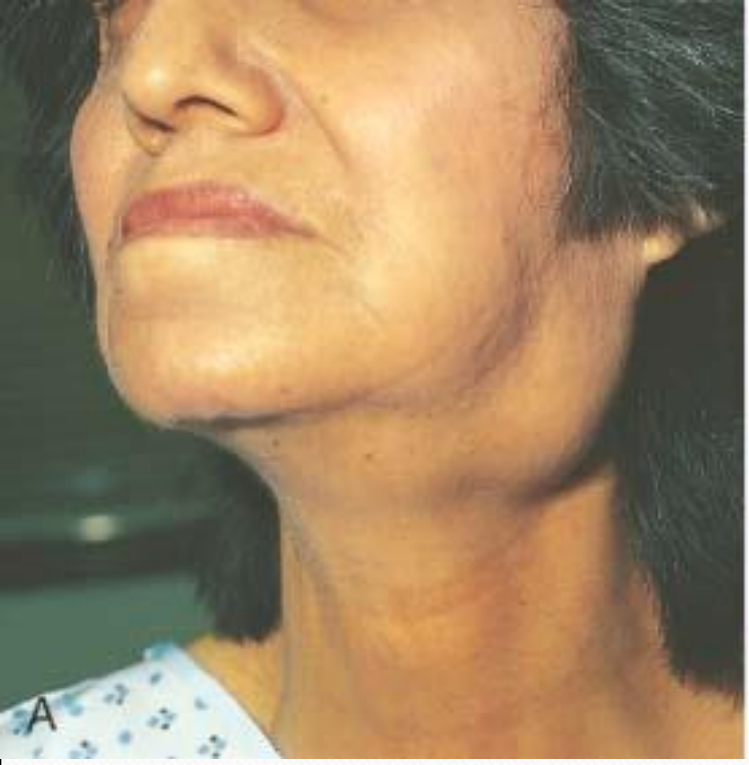


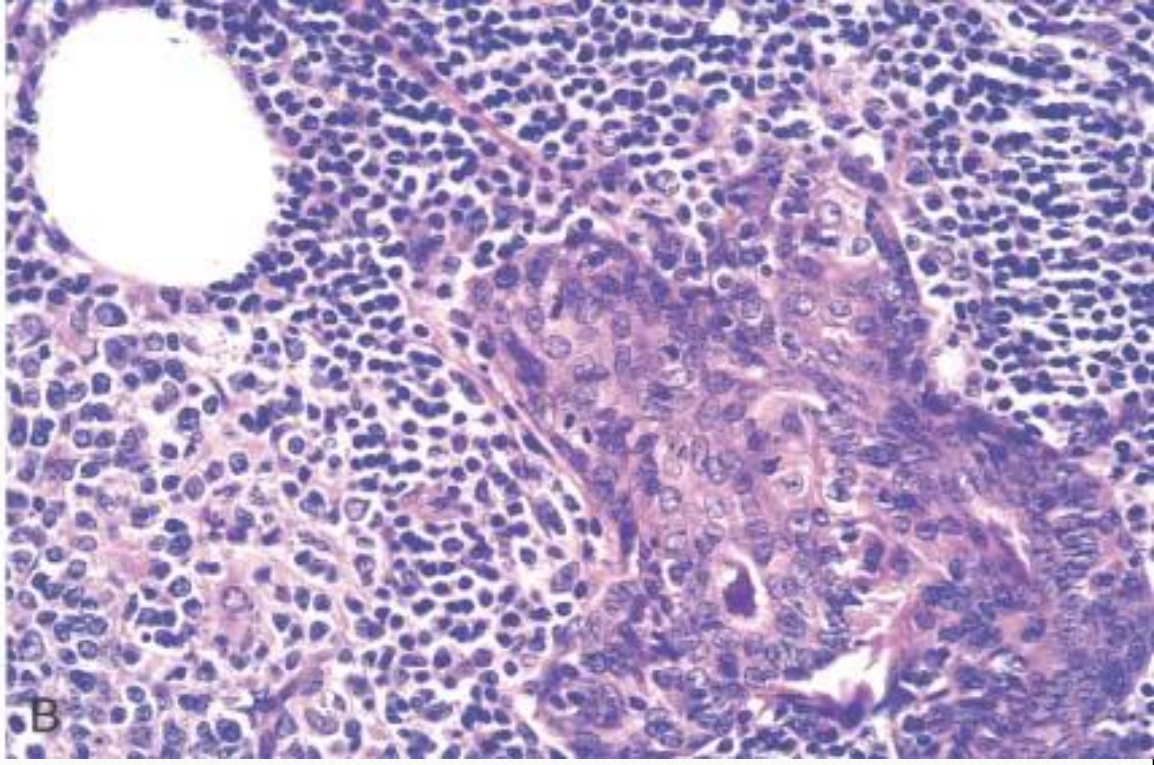
Rheumatoid factor (RF or RhF) is an autoantibody (antibody directed against an organism's own tissues) most relevant in rheumatoid arthritis. It is an antibody against the Fc portion of IgG, which is itself an antibody.
In rheumatoid arthritis the primary areas of the body ravaged by autoimmune destruction are synovium and blood vessels.

↑

Destructive Rheumatoid Synovitis

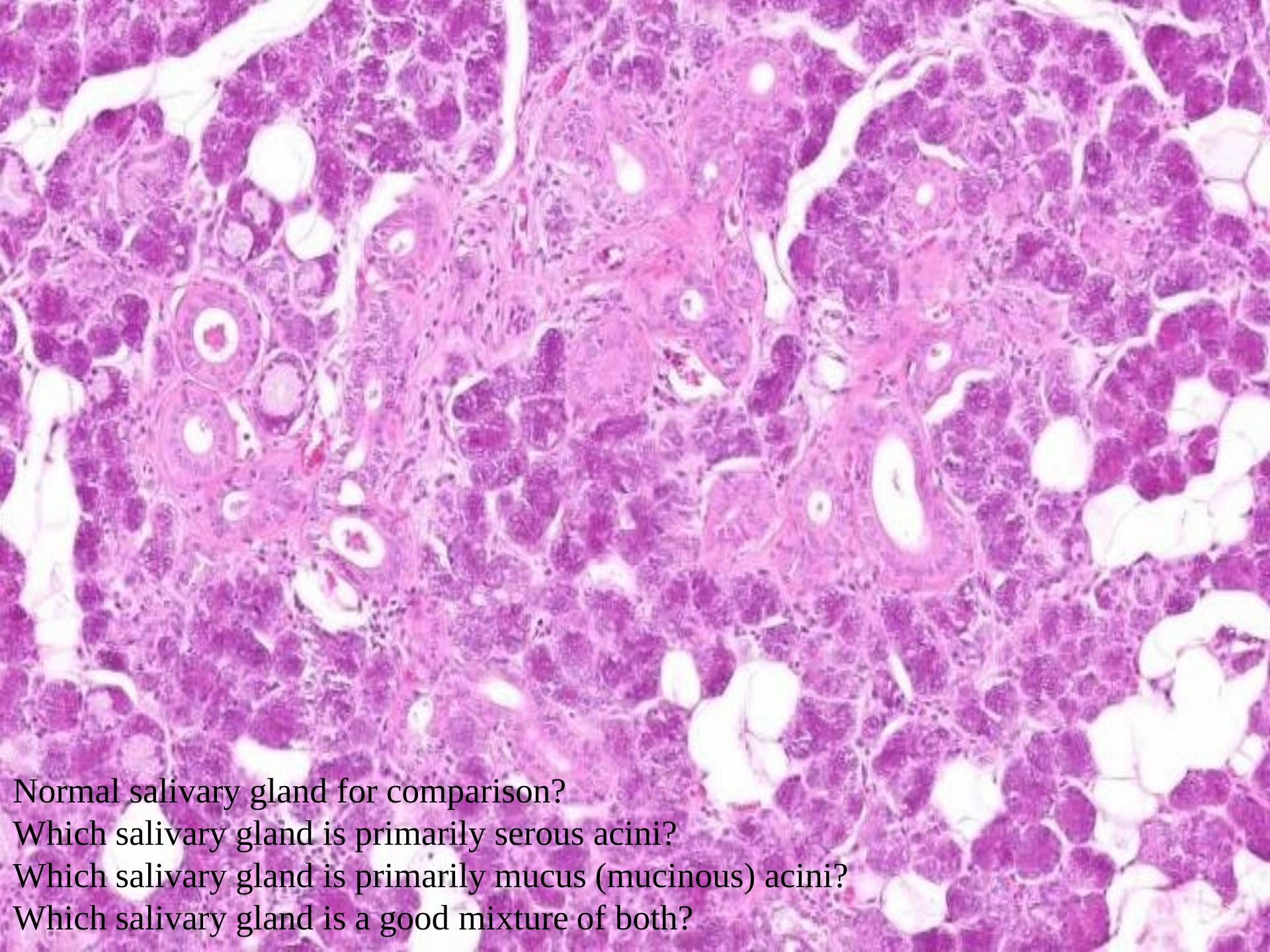
←**NORMAL** Bi-Layered Synovium



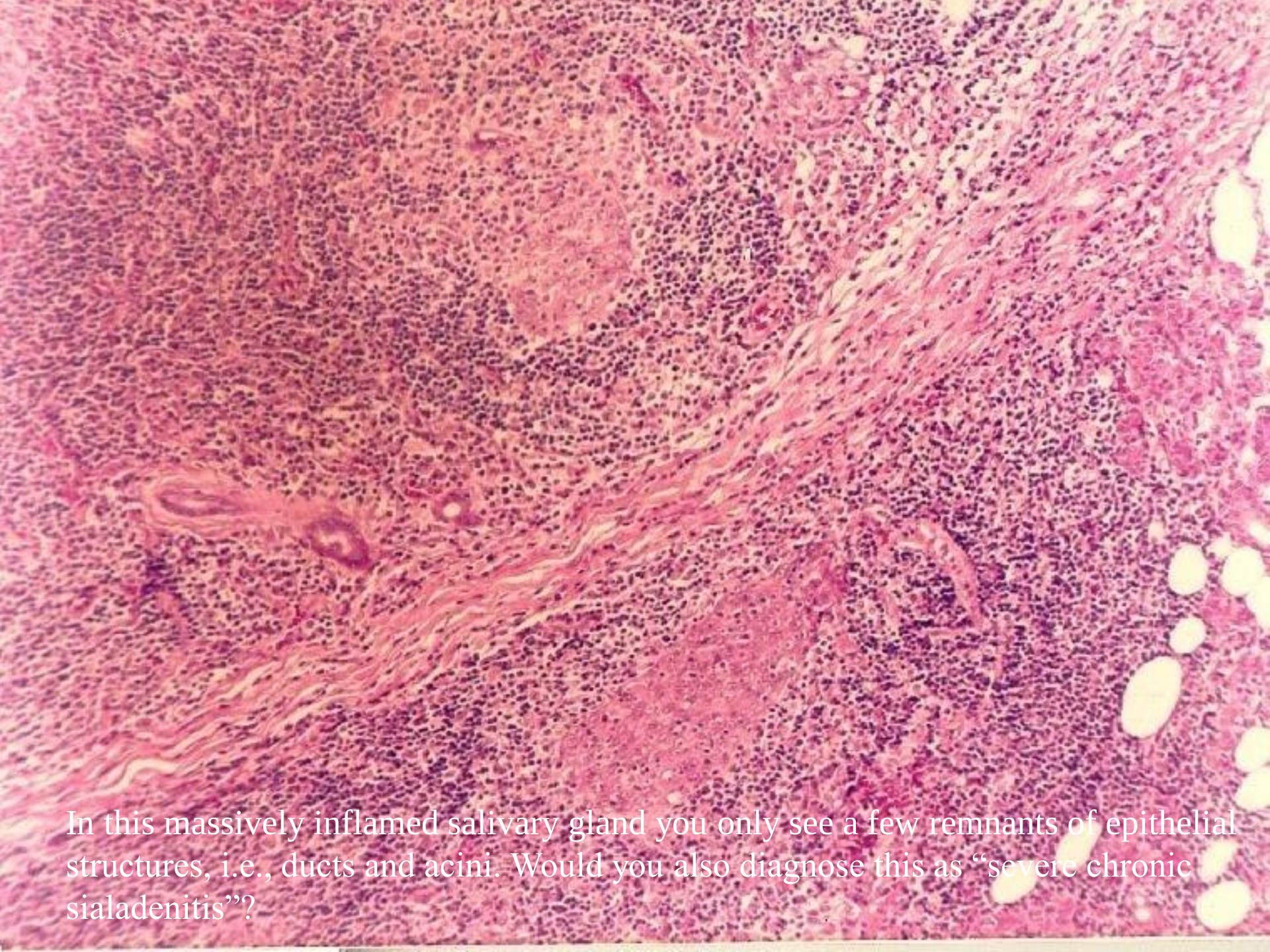


SJÖGREN SYNDROME

Keratoconjunctivitis “sicca” (i.e., “dry” is another name for Sjögren Syndrome, another SYSTEMIC auto-immune disease.

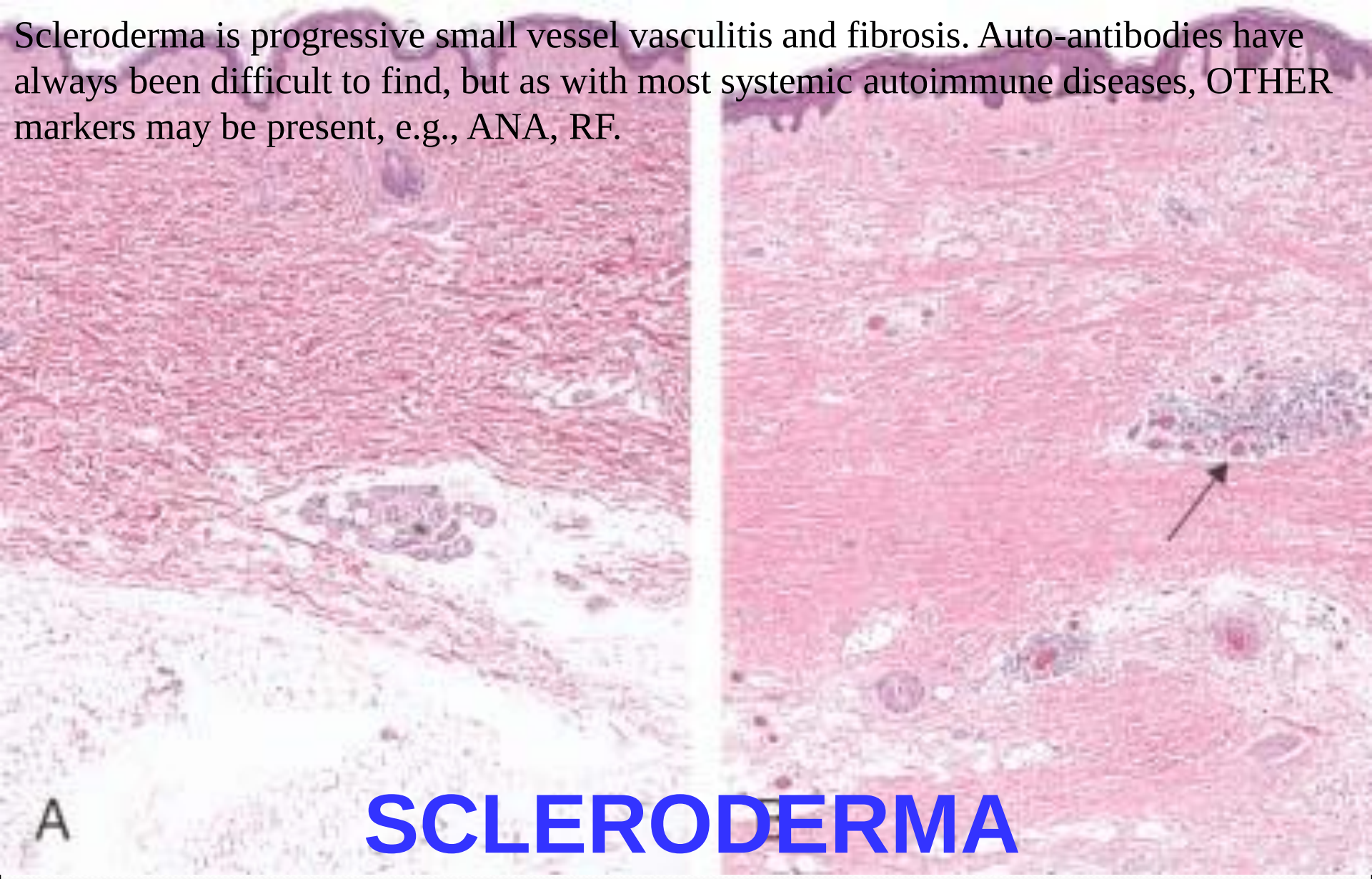


Normal salivary gland for comparison?
Which salivary gland is primarily serous acini?
Which salivary gland is primarily mucus (mucinous) acini?
Which salivary gland is a good mixture of both?



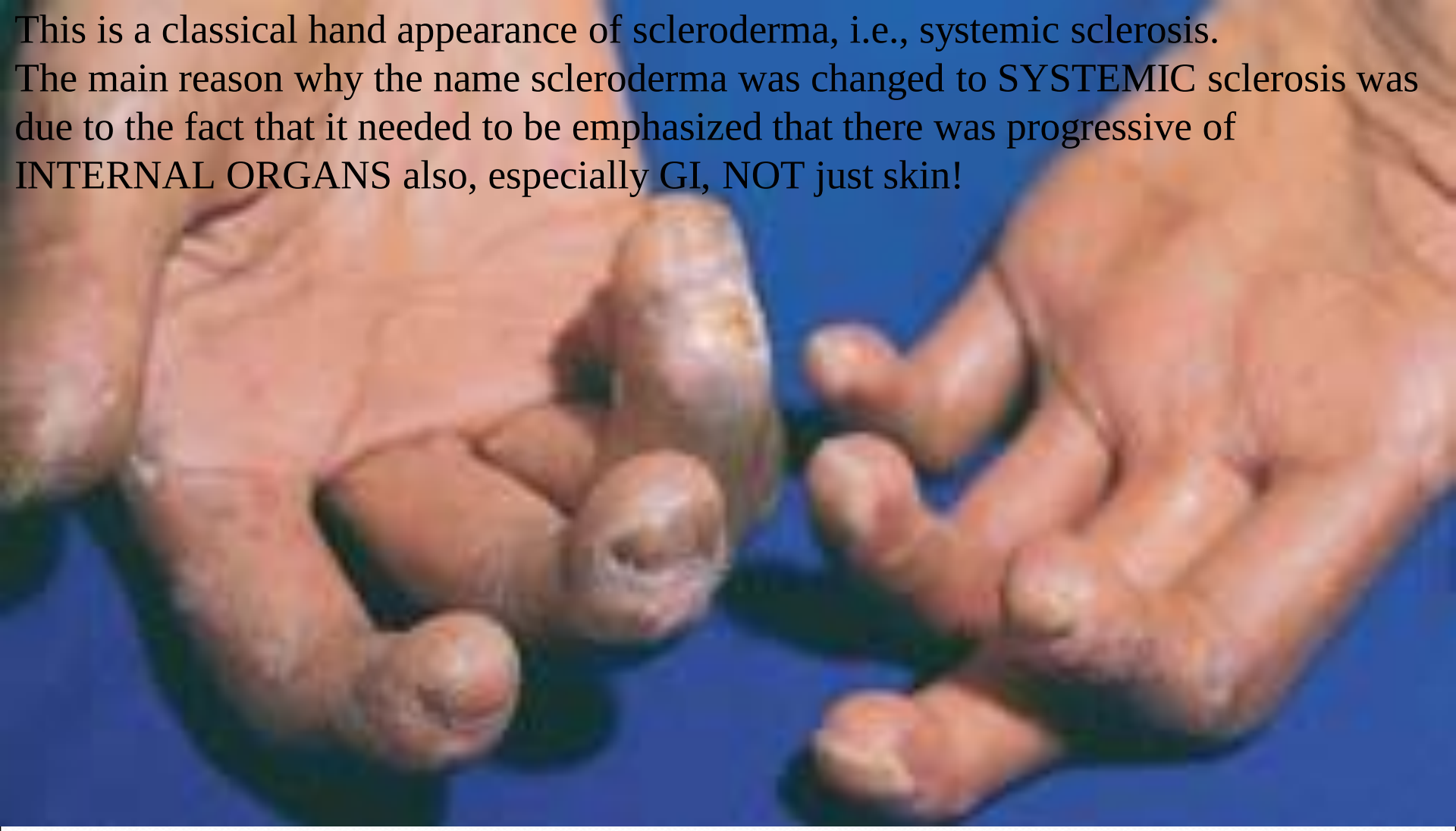
In this massively inflamed salivary gland you only see a few remnants of epithelial structures, i.e., ducts and acini. Would you also diagnose this as “severe chronic sialadenitis”?

Scleroderma is progressive small vessel vasculitis and fibrosis. Auto-antibodies have always been difficult to find, but as with most systemic autoimmune diseases, OTHER markers may be present, e.g., ANA, RF.



SCLERODERMA

(SYSTEMIC SCLEROSIS)



SYSTEMIC SCLEROSIS

(SCLERODERMA)

MORE AUTOIMMUNE DISEASES (LOCAL)

- HASHIMOTO THYROIDITIS
- AUTOIMMUNE HEMOLYTIC ANEMIA
- MULTIPLE SCLEROSIS
- AUTOIMMUNE ORCHITIS
- GOODPASTURE SYNDROME
- AUTOIMMUNE THROMBOCYTOPENIA (ITP)
- “PERNICIOUS” ANEMIA
- INSULIN DEPENDENT DIABETES MELLITUS (I)
- MYASTHENIA GRAVIS
- GRAVES DISEASE

ImmunoDefiency Syndromes (-IDS)

- PRIMARY (GENETIC) (P-IDS?)
- SECONDARY (ACQUIRED) (A-IDS)

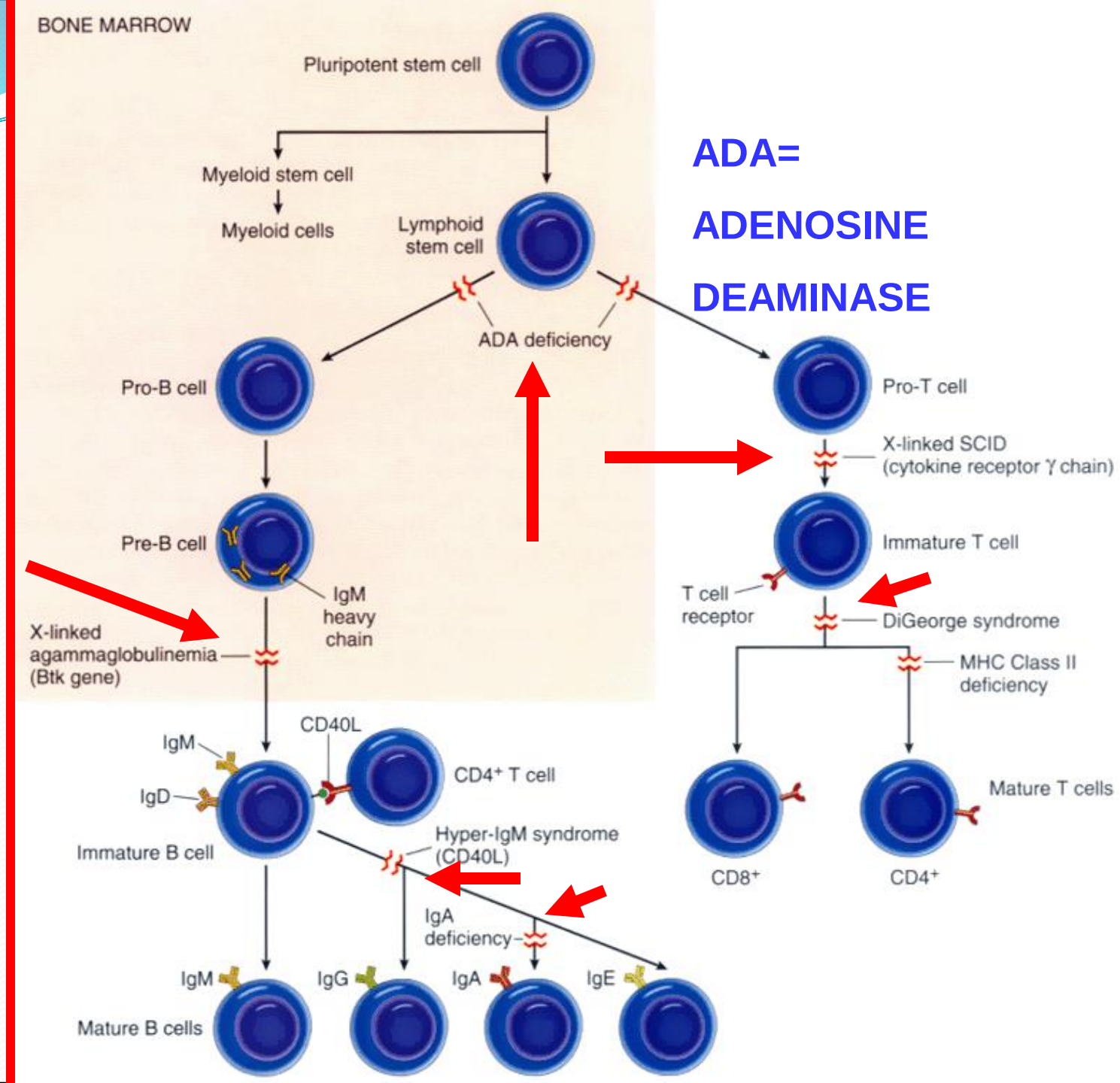
PRIMARY

- CHILDREN with repeated, often severe infections, cellular AND/OR humoral immunity problems, autoimmune defects
- BRUTON (X-linked agammaglobulinemia)
- COMMON VARIABLE
- IgA deficiency
- Hyper -IgM
- DI GEORGE (THYMIC HYPOPLASIA) 22q11.2
- SCID (Severe Combined Immuno Deficiency)
- ....with thrombocytopenia and eczema (WISKOTT-ALDRICH)
- COMPLEMENT DEFICIENCIES

PRIMARY

- **22q11.2 deletion syndrome**, also known as Velocardiofacial Syndrome, DiGeorge Syndrome and Strong Syndrome is a disorder caused by the deletion of a small piece of chromosome 22. The deletion occurs near the middle of the chromosome at a location designated q11.2. It has a prevalence estimated at 1:4000. Do you remember what CATCH is the mnemonic for? Hint: the "T" stands for "T"hymic aplasia.
- SCID: Chronic diarrhea, ear infections, recurrent *Pneumocystis jirovecii* pneumonia, and profuse oral candidiasis commonly occur. These babies, if untreated, usually die within 1 year due to severe, recurrent infections. However, treatment options are much improved since David Vetter, "the Boy in the Bubble".
- **Wiskott-Aldrich syndrome** (WAS) is a rare X-linked recessive disease characterized by eczema, thrombocytopenia (low platelet count), immune deficiency, and bloody diarrhea (secondary to the thrombocytopenia). It is also sometimes called the *eczema-thrombocytopenia-immunodeficiency syndrome* in keeping with Aldrich's original description in 1954.

- You should probably know the clinical presentation "profiles" of these patients with PIDS (PRIMARY Immune Deficiency Syndromes)
- Bruton's: Males (of course) with infections, especially enteroviral, after a few months of life, after maternal antibodies are gone.
- COMMON VARIABLE: Most patients in 20's, UTIs, LTIs
- IgA Deficiency: Usually NO symptoms
- Hyper IgM: Recurrent pyogenic infections, pneumonia, PCP, neutropenia, thrombocytopenia.
- DiGeorge: Birth defects, learning disabilities, infections, thymus problems. C-A-T-C-H
- SCID: Candidiasis, diaper rash, failure to thrive, "The Boy in the Bubble"



ADA=

ADENOSINE

DEAMINASE

Previous slide is important for understanding the UNIFYING concepts between ALL the PRIMARY immunodeficiencies.
Bruton's x-linked agammaglobulemia: NO tyrosine kinase (BTK gene)
COMMON VARIABLE: Various genetic defects, both B and T cells involved.
IgA deficiency: Unknown
Hyper IgM: CD40-L gene defect
DiGeorge: 22q11 deletion, failure of development of 3^{rd} and 4^{th} pharyngeal pouch.
SCID: Early T-Cell failure. Would you think the "C" in combined stands for T, B, or T4,T8?

Would you imagine an ADA deficiency would be the worst of all possible defects?
Ans: YES
If there were no red arrows in this diagram, would it be a good diagram to explain lymphocyte "differentiation"? Ans: YES

Examples of Infections in Immunodeficiencies

Pathogen Type	T-Cell-Defect	B-Cell Defect	Granulocyte Defect	Complement Defect
Bacteria	Bacterial sepsis	Streptococci, staphylococci, *Haemophilus*	Staphylococci, *Pseudomonas*	**Neisserial** infections, other pyogenic bacterial infections
Viruses	Cytomegalovirus, Epstein-Barr virus, severe varicella, chronic infections with respiratory and intestinal viruses	Enteroviral encephalitis		
Fungi and parasites	*Candida, Pneumocystis carinii*	Severe intestinal giardiasis	*Candida, Nocardia, Aspergillus*	
Special features	Aggressive disease with opportunistic pathogens, failure to clear infections	Recurrent sinopulmonary infections, sepsis, chronic meningitis		

This is a useful slide for understanding, VERY GENERALLY, which kinds of infections result from which kinds of deficiencies. As you can see, there is considerable overlap. Note that the RED pathogens are fairly typical for defects in the class of defects ABOVE them

GENERAL IMMUNE ABNORMALITIES

- LYMPHOPENIA
- DECREASED T-CELL FUNCTION
- B-CELL ACTIVATION, POLYCLONAL
- ALTERED MONOCYTE/MACROPHAGE FUNCTION

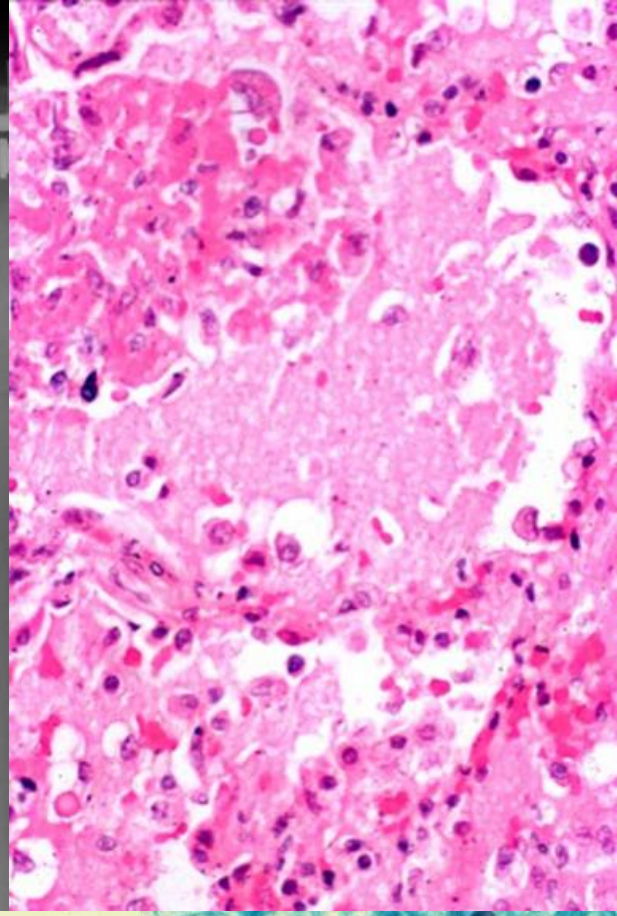
INFECTIONS

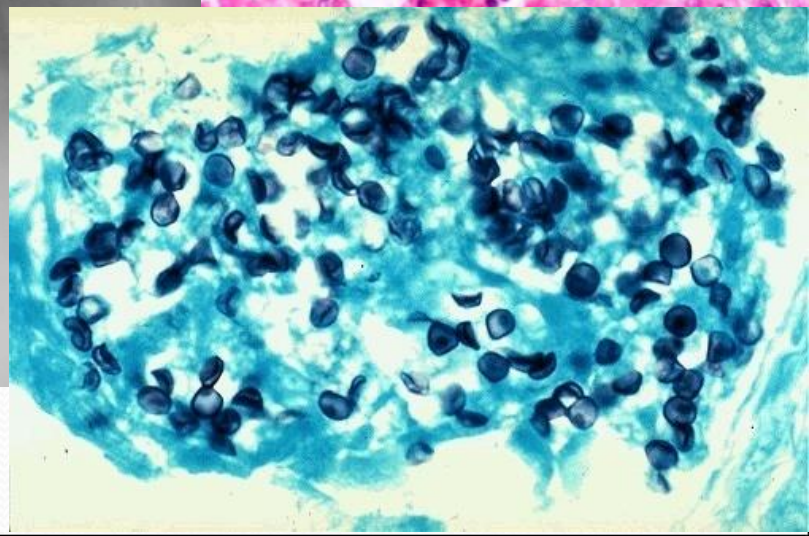
- **Protozoal/Helminthic: Cryptosporidium, PCP (Pneumocystis Carinii Pneumonia), Toxoplasmosis**
- **Fungal: Candida, and the usual 3**
- **Bacterial: TB, Nocardia, Salmonella**
- **Viral: CMV, HSV, VZ (Herpes Family)**

Cryptosporidium is a protozoan pathogen of the Phylum Apicomplexa and causes a diarrheal illness called cryptosporidiosis

Note BOTH the radiologists AND the pathologists use the word “WOOLY”. Why?

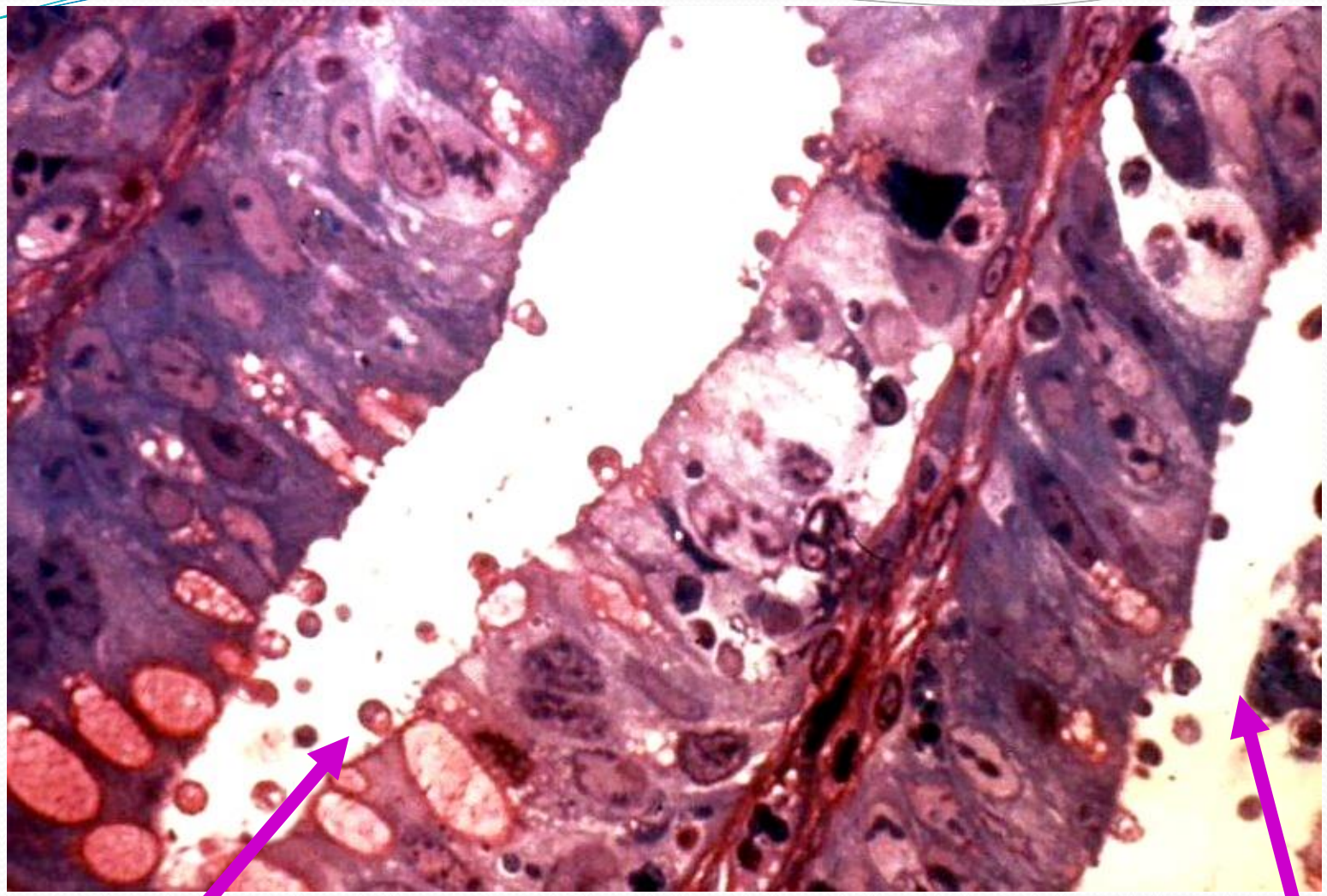
1) “Wooly” infiltrates on the chest x-ray, radiologically
2) Cotton “wooly” exudates in the alveoli, microscopically



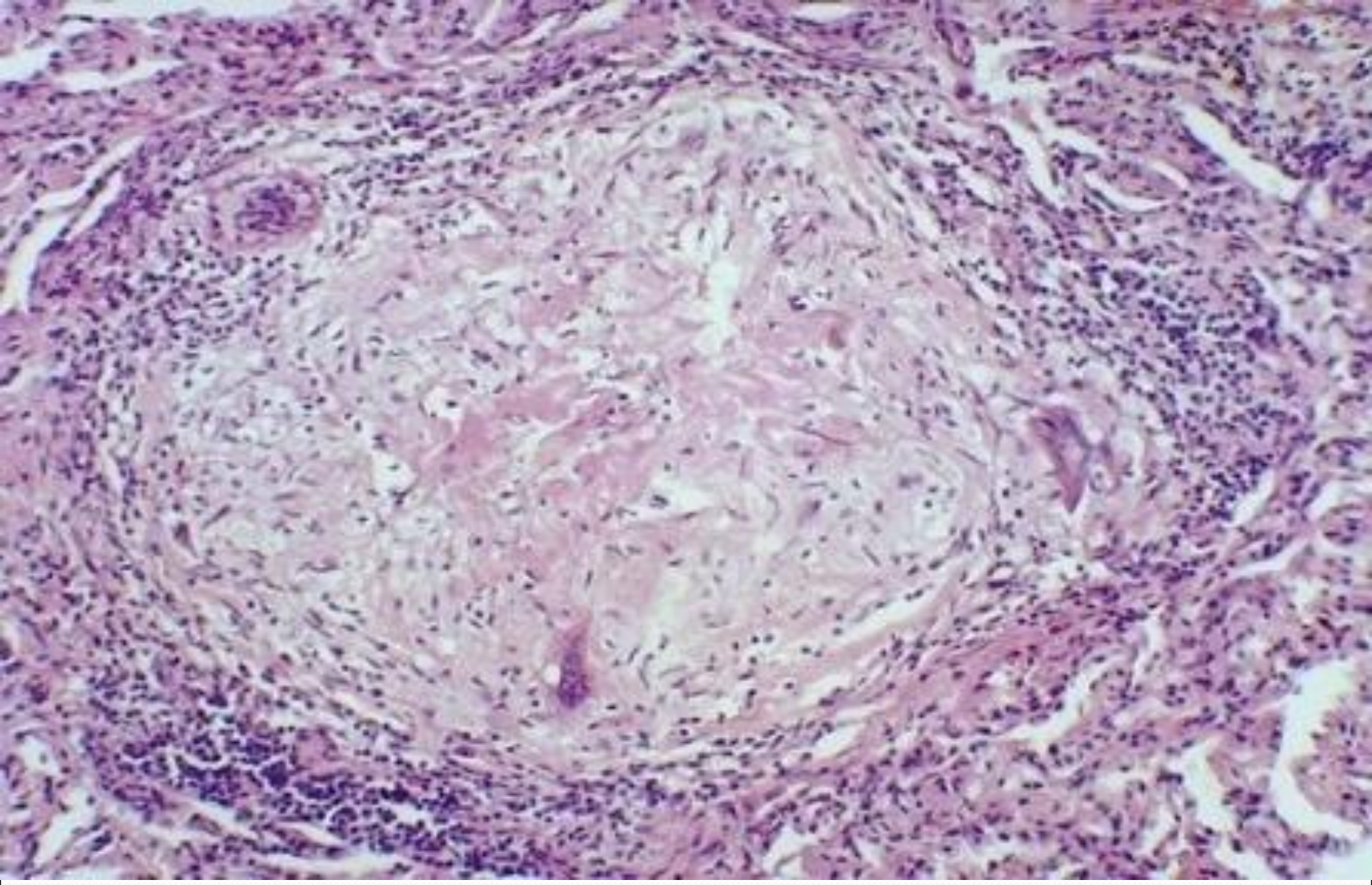


PCP

We are all exposed to the protozoan, and can tolerate it. AIDS patients have a much harder time.



CRYPTOSPORIDIUM



CASEATING GRANULOMA

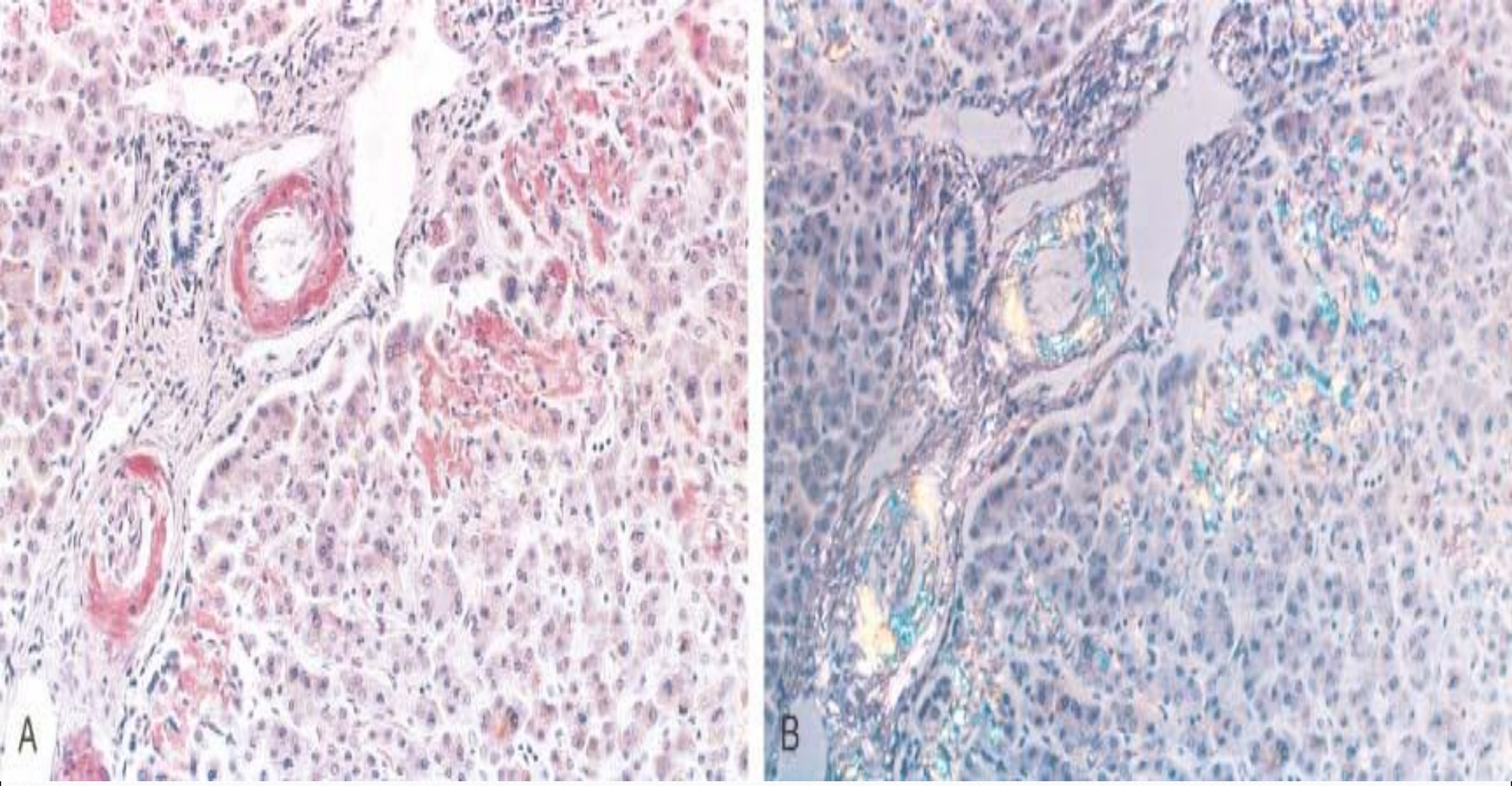
CANCERS of AIDS

- KAPOSI SARCOMA
- B-CELL LYMPHOMAS
- CNS LYMPHOMAS
- CERVIX CANCER, SQUAMOUS CELL

AMYLOIDOSIS

- **BUILDUP OF AMYLOID "PROTEIN"**
  - **AL (Amyloid Light Chain)**
  - **AA (NON-immunoglobulin protein)**
  - **Aß (Alzheimer's)**
- **WHERE? BLOOD VESSEL WALLS, at first**
  - **KIDNEY**
  - **SPLEEN**
  - **LIVER**
  - **HEART**

Why is amyloid called amyloid? Because in the early days, it took up STARCH stains applied to GROSS specimens, e.g., IODINE stains.
But of course now we know it's a PROTEIN, chiefly immunoglobulin protein chronic buildup.
It is therefore not surprising that diseases which have chronic immunoglobulin buildup over many years are associated with amyloidosis, i.e., multiple myeloma (also called plasma cell "dyscrasias"), granulomatous diseases, classically.



CONGO RED STAIN, WITHOUT, and WITH, POLARIZATION

AMYLOID ASSOCIATIONS

- **PLASMA CELL "DYSCRASIAS", i.e., MULTIPLE MYELOMA**
- **CHRONIC GRANULOMATOUS DISEASE, e.g., TB**
- **HEMODIALYSIS**
- **HEREDOFAMILIAL**
- **LOCALIZED**
- **ENDOCRINE MEAs (Multiple Endocrine Adenomas)**
- **AGING**

Diseases in which there is a cumulative buildup of immunoglobulin would be a setting for amyloidosis, so myelomas and chronic granulomatous diseases are at the top of the list.