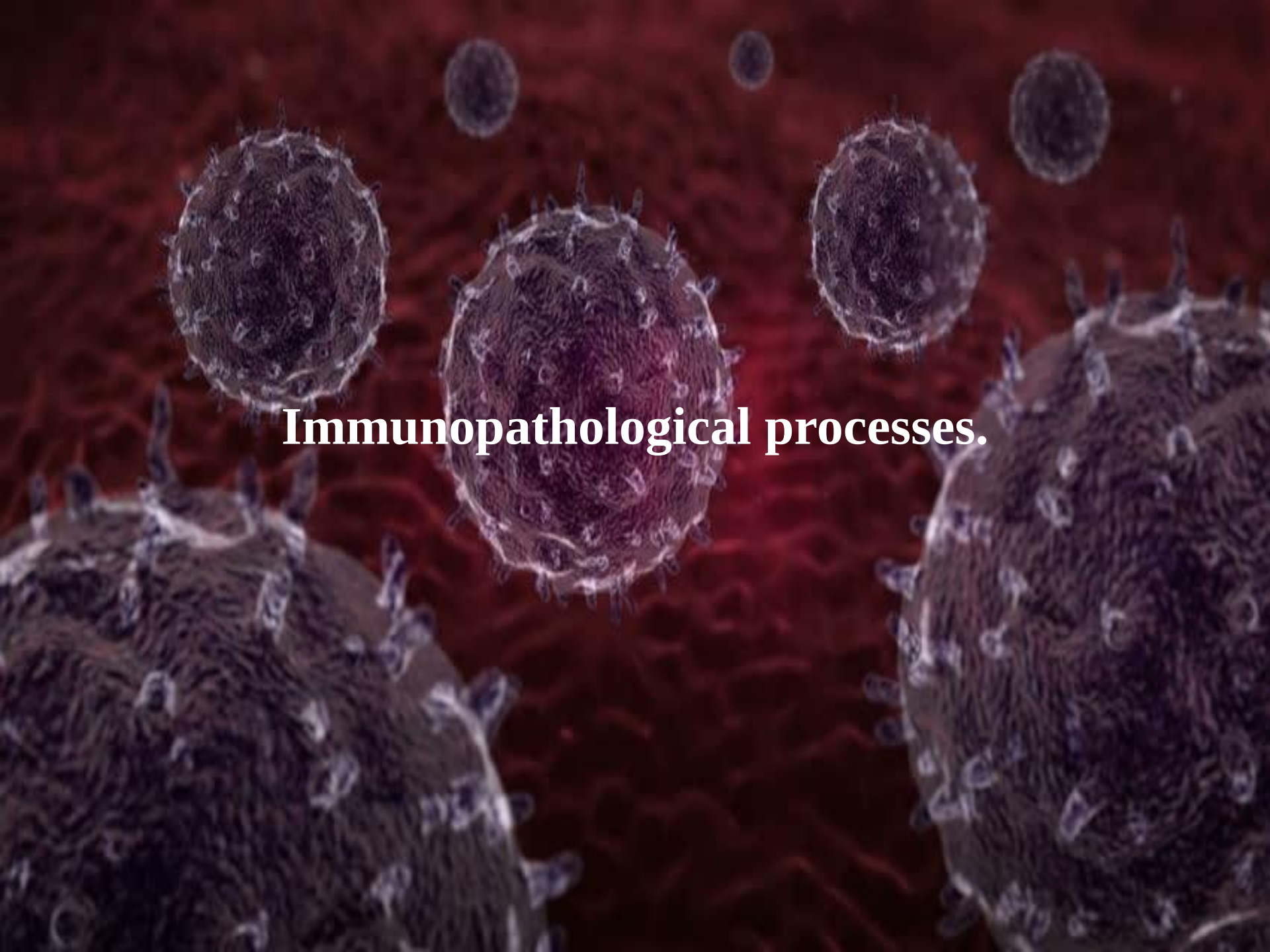


Immunopathological processes.

Immunopathological processes.

Microspecimens:

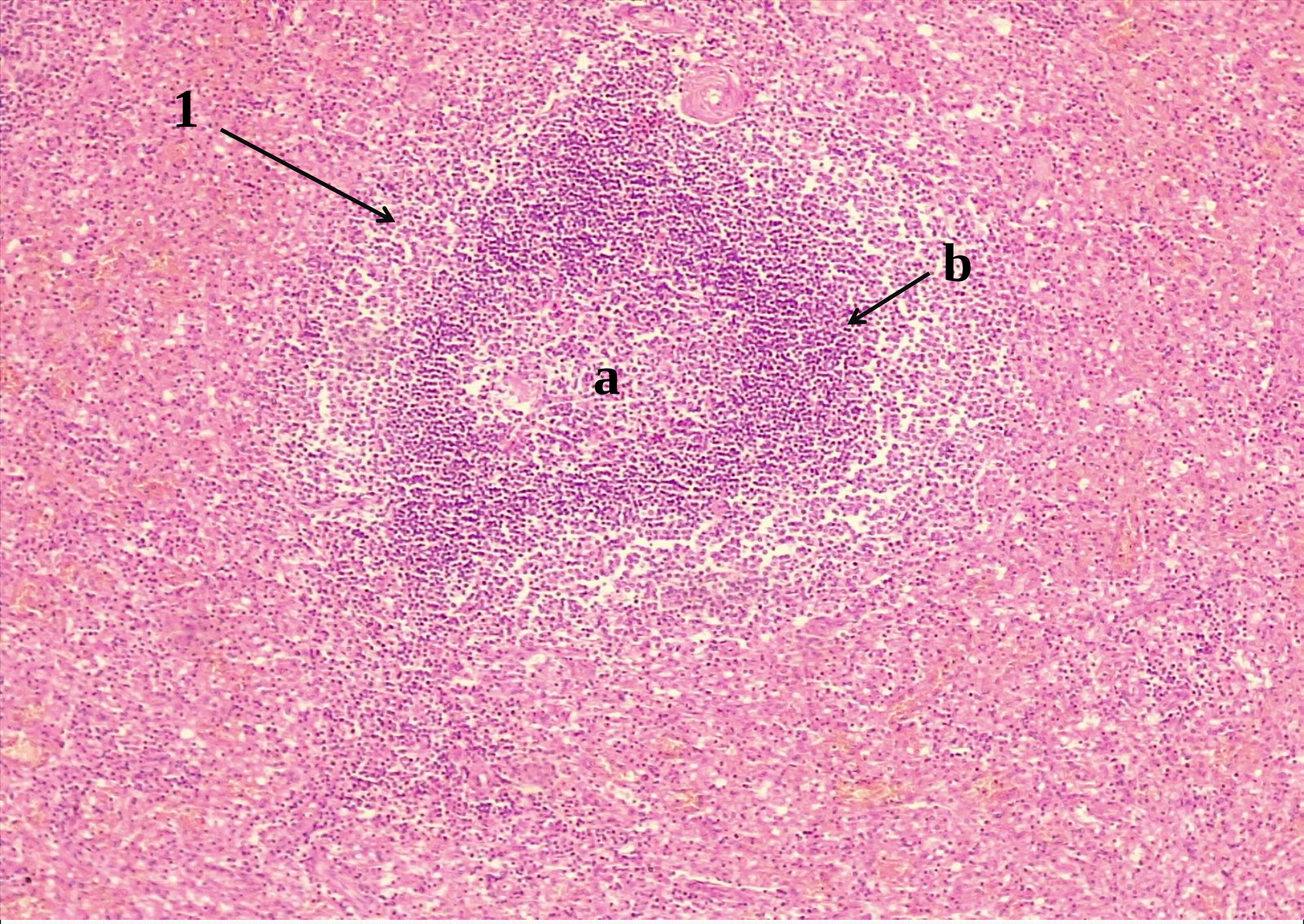
№ 200. Hyperplasia of lymphoid splenic follicles in antigenic stimulation. *(H-E. stain).*

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.

№ 201. Hypoplasia of lymphoid splenic follicles in primary combined immunodeficiency syndrome.

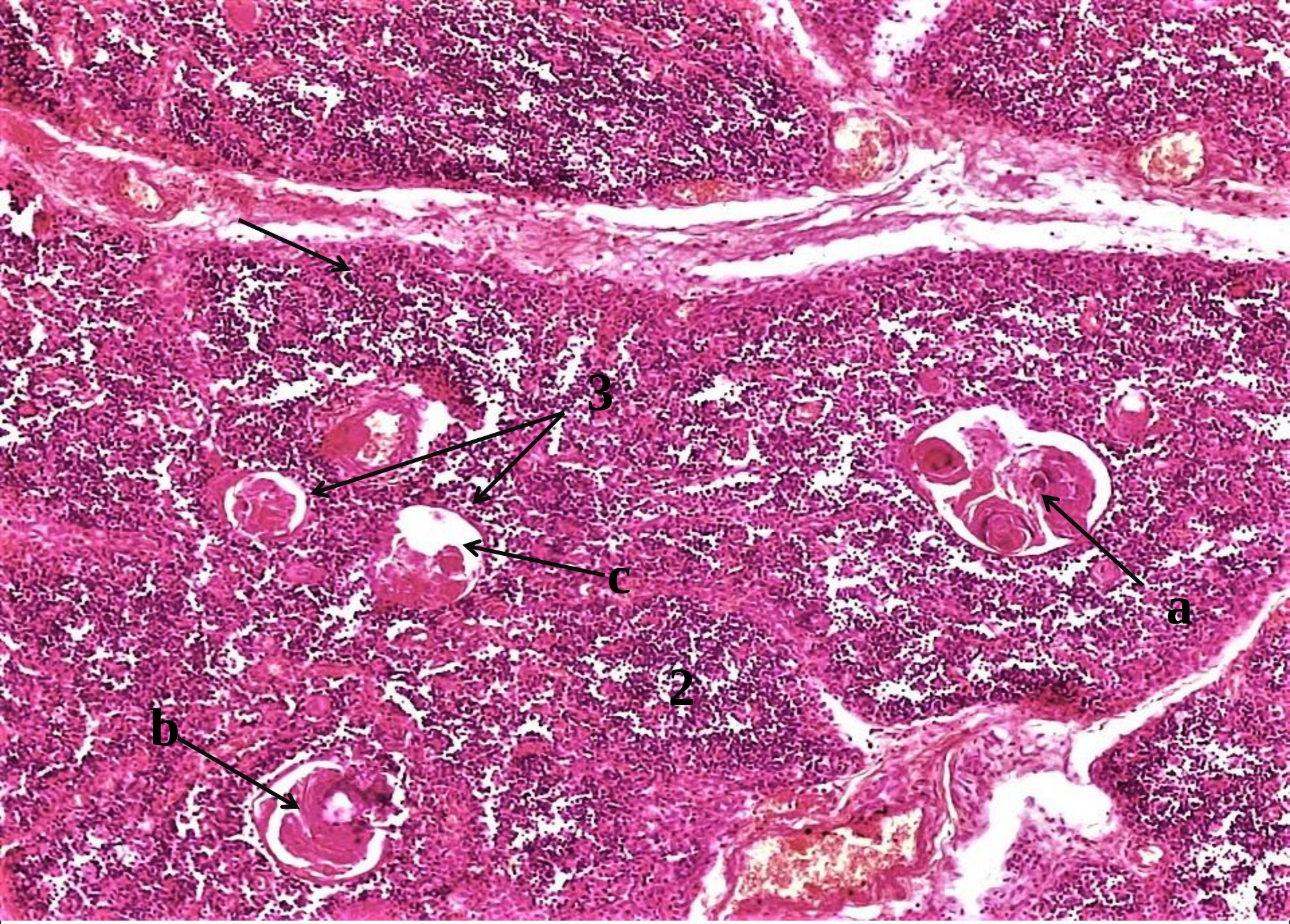
(H-E. stain).

Indications:

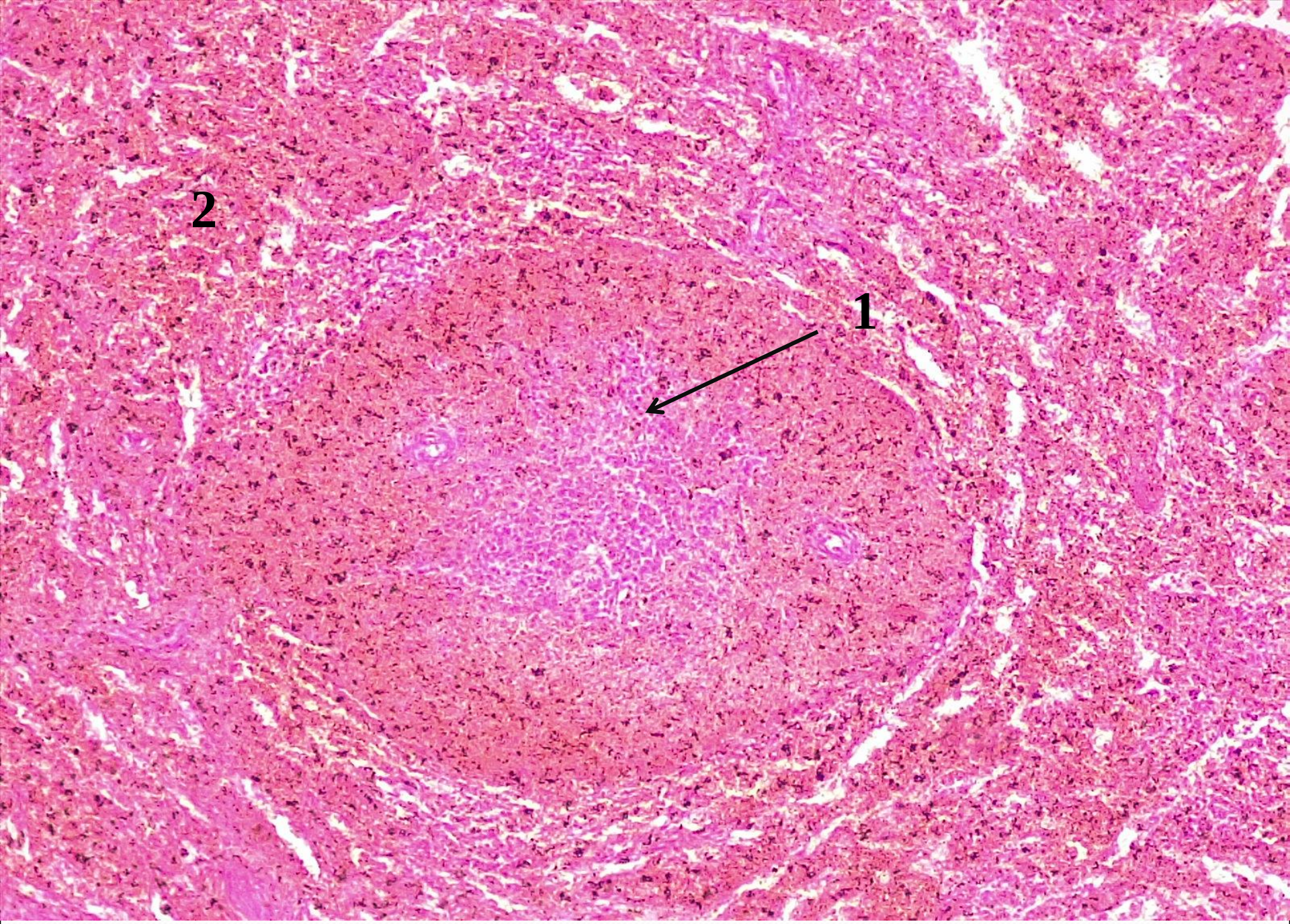
1. Hypoplasia of lymphoid follicles (reducing the number of lymphocytes).
2. Red pulp with hemosiderosis.

Microscopically, lymphoid follicles are diminished in size, weakly contoured, germinal centers are missing, number of lymphocytes is reduced, adjacent red pulp is hyperemic with diffuse hemosiderosis.

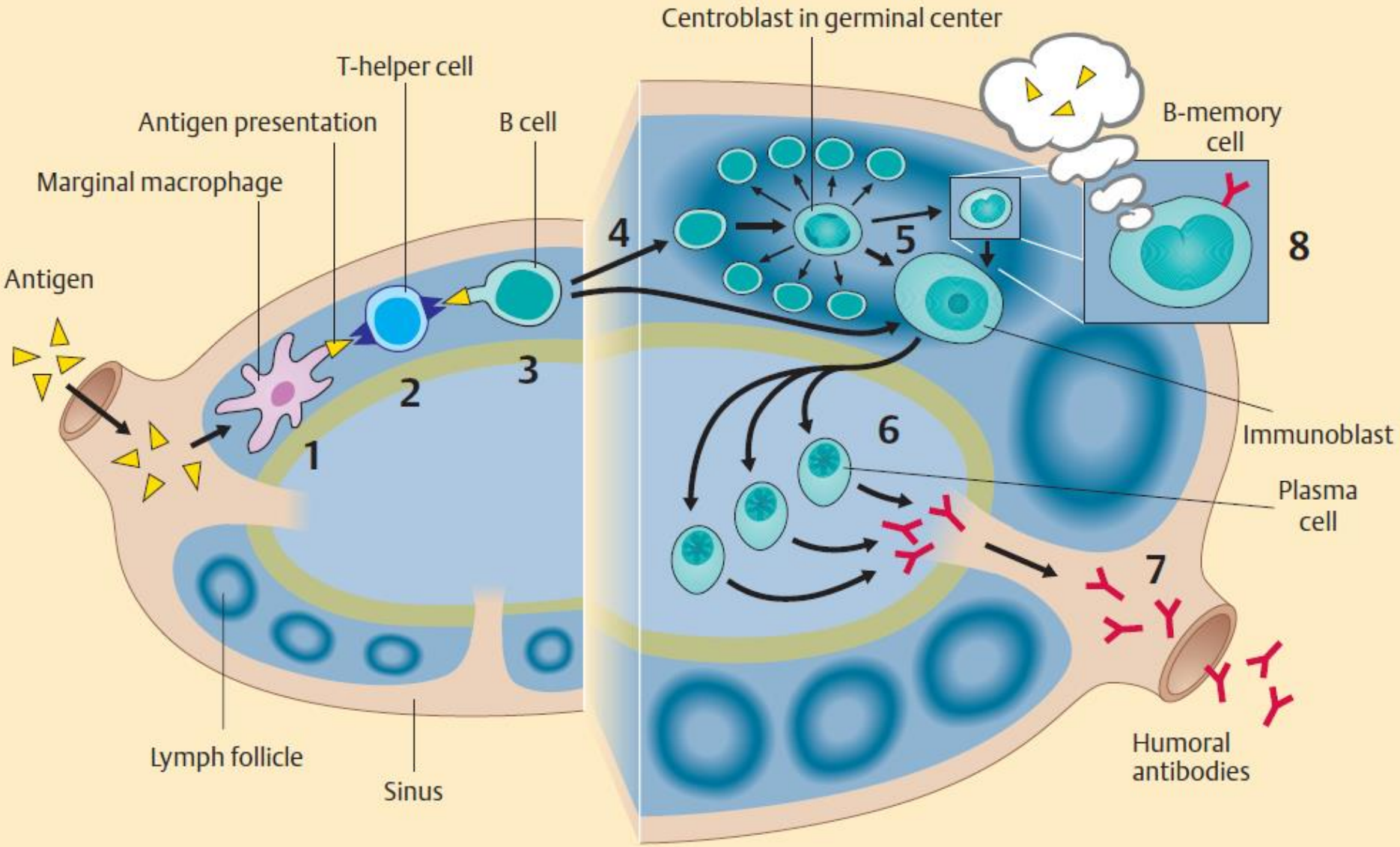
Hypoplasia of lymphoid splenic follicles is manifestation of peripheral lymphoid tissue hypoplasia, which is observed in primary immunodeficiency syndromes. These syndromes are congenital, genetically determined, with autosomal-dominant transmission. The hypoplasia process involves both the thymus-dependent areas of the splenic follicles (periarterial) and the bursa-dependent areas (the periphery of follicles). In these children the lymphocytes are dysfunctional or even absent, developing humoral and cellular immune deficiency with a high frequency of severe recurrent infections, caused by bacteria, viruses, fungi and protozoa.



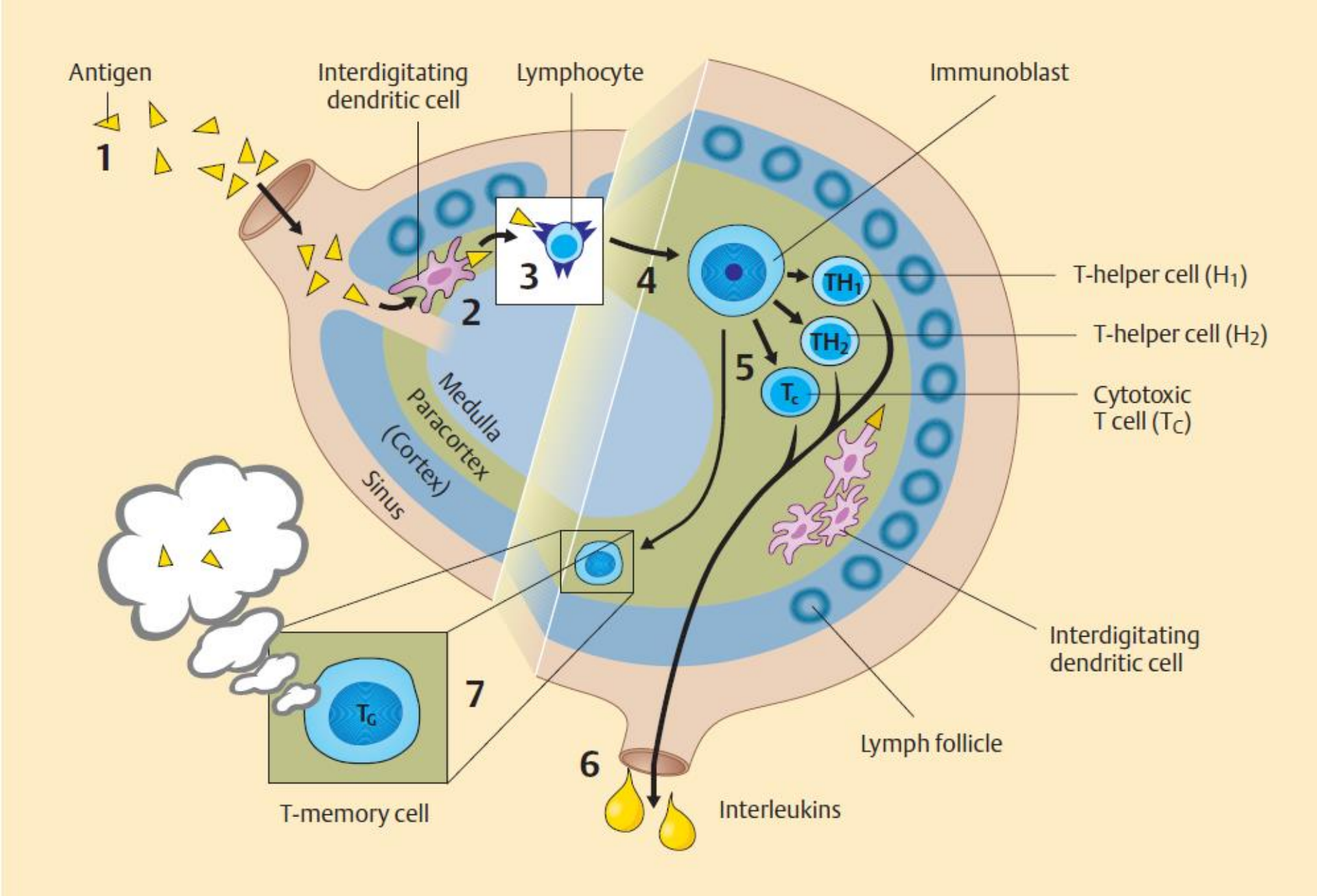
№ 173. Accidental thymus involution. *(H-E. stain).*



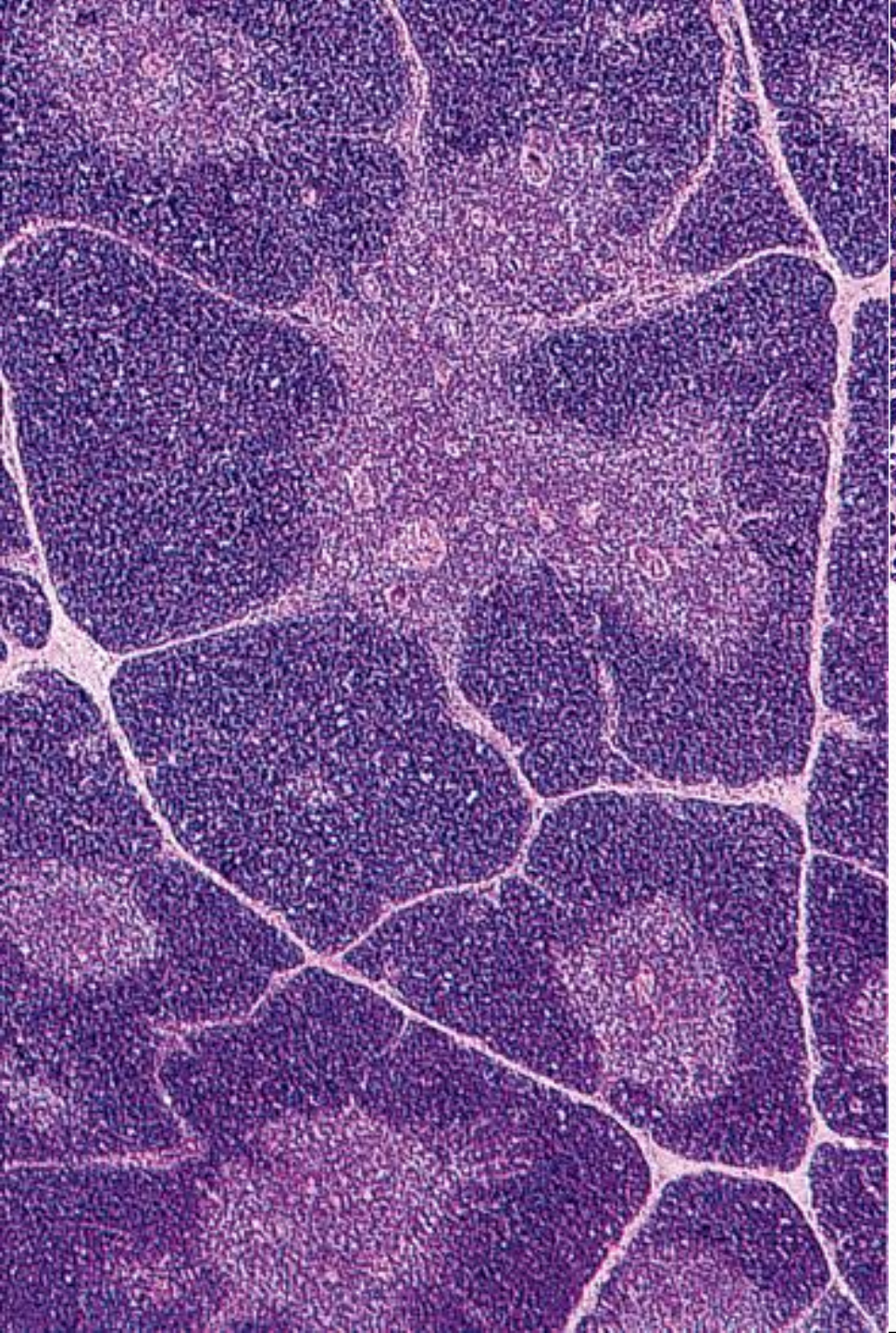
№ 201. Hypoplasia of lymphoid splenic follicles in primary combined immunodeficiency syndrome.

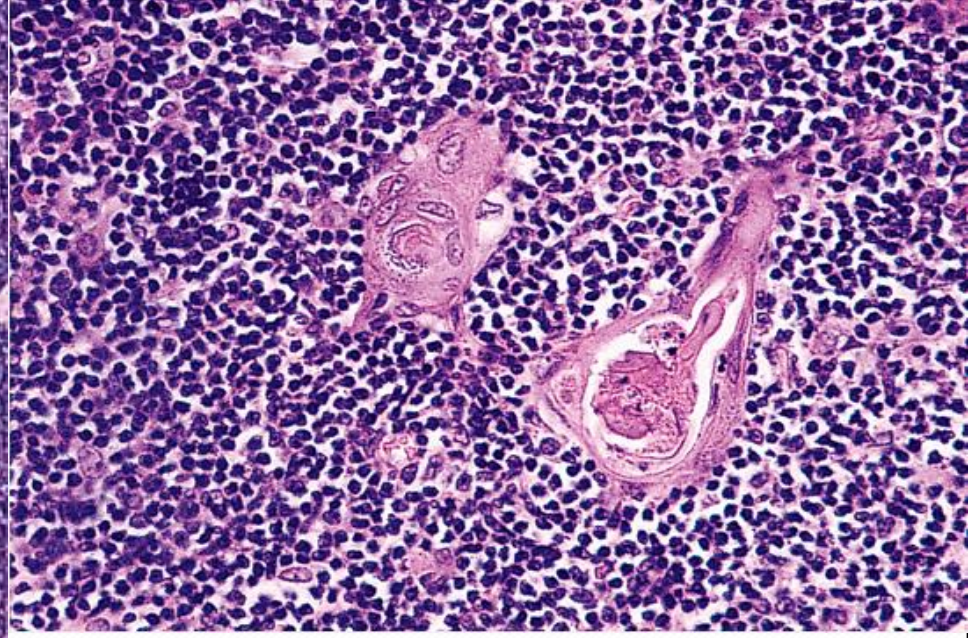


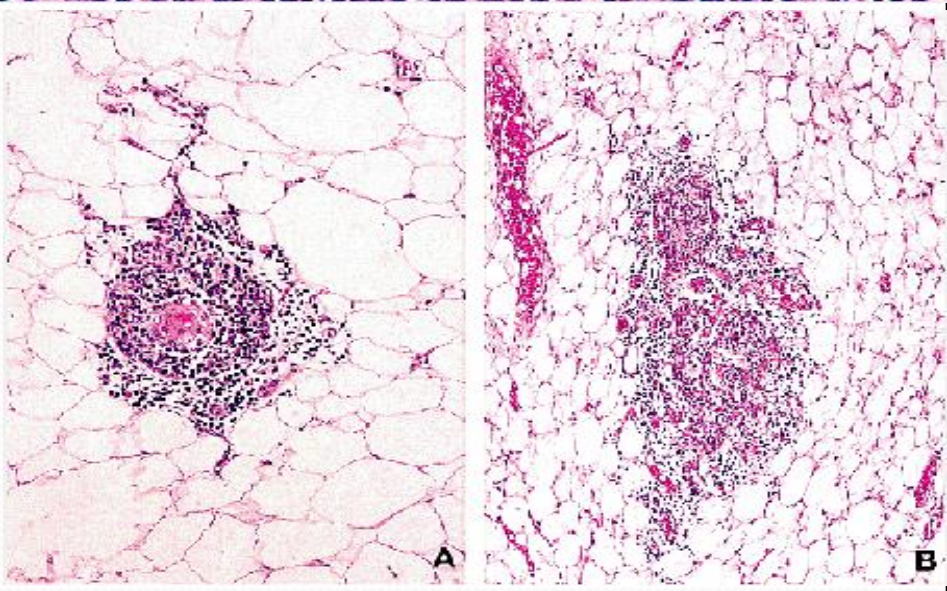
Humoral immune response.



Cellular immune response.

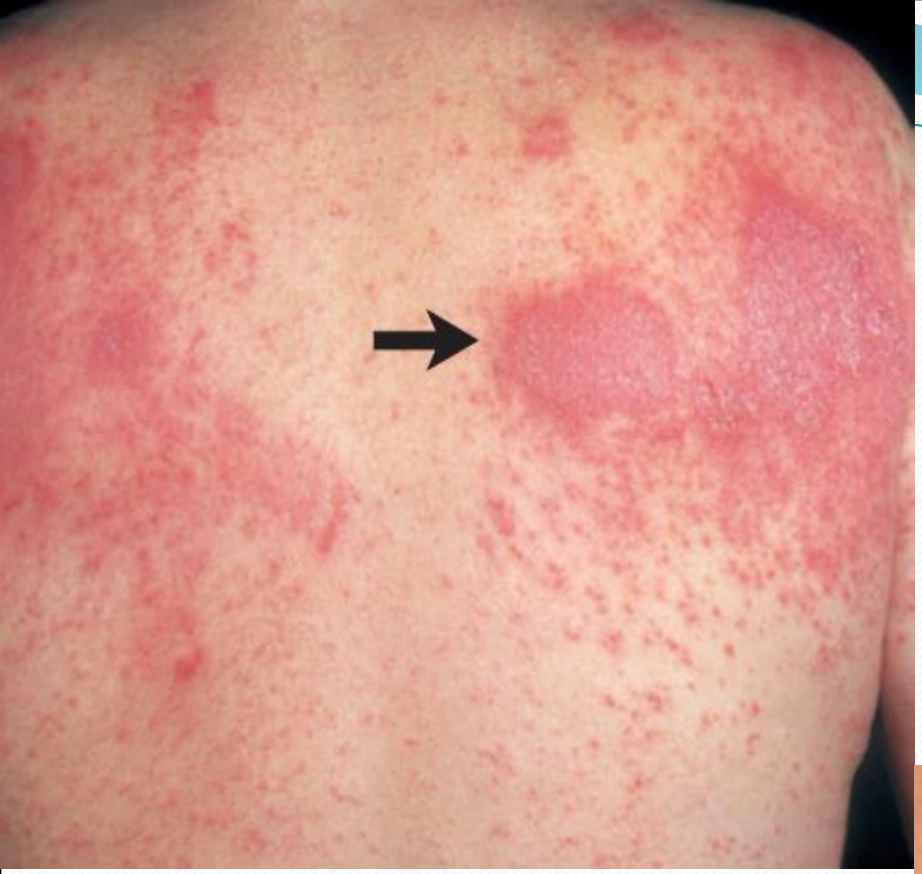






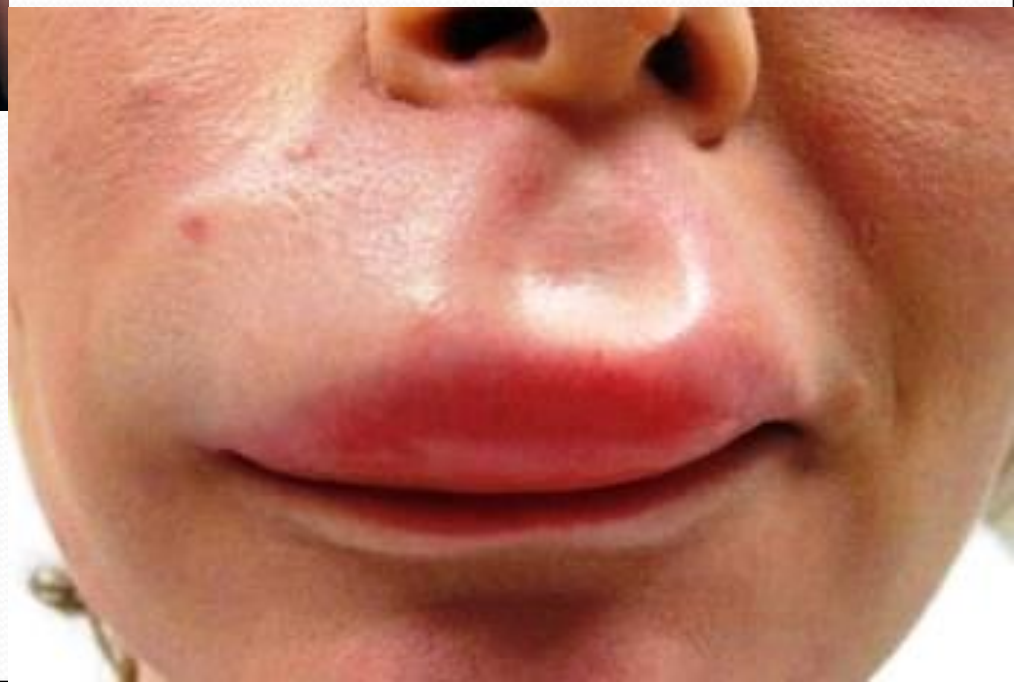
The normal structure of the thymus, A, B - physiological involution.

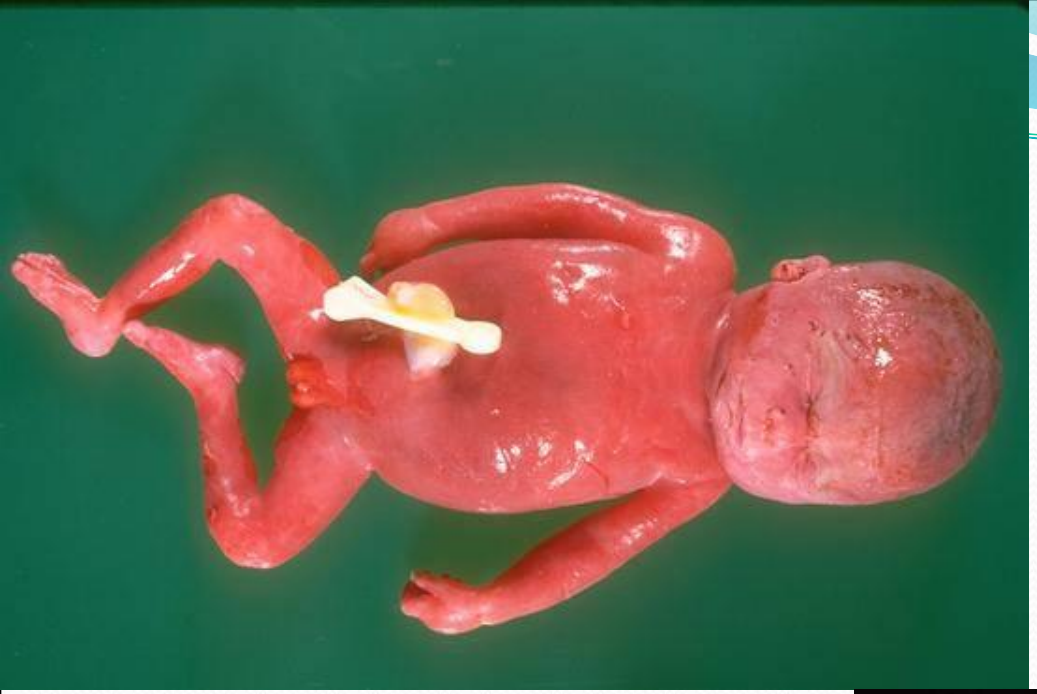
Immediate hypersensitivity reaction (type I).



Allergic (atopic) dermatitis.

Quincke's edema

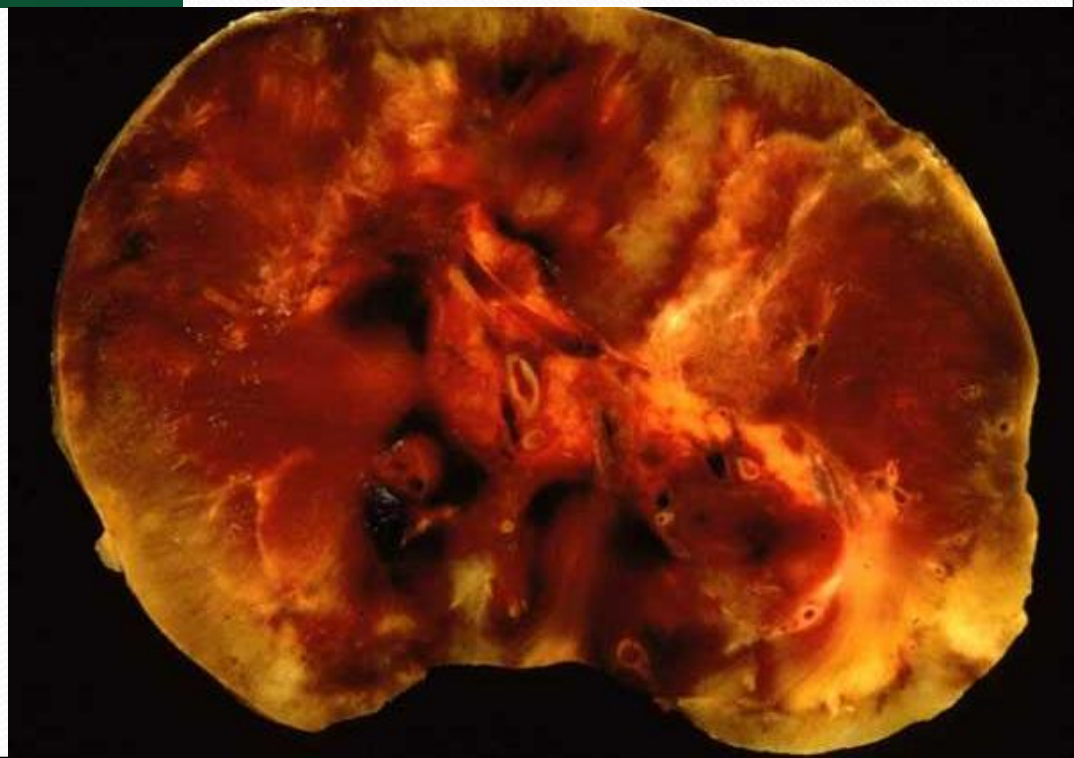


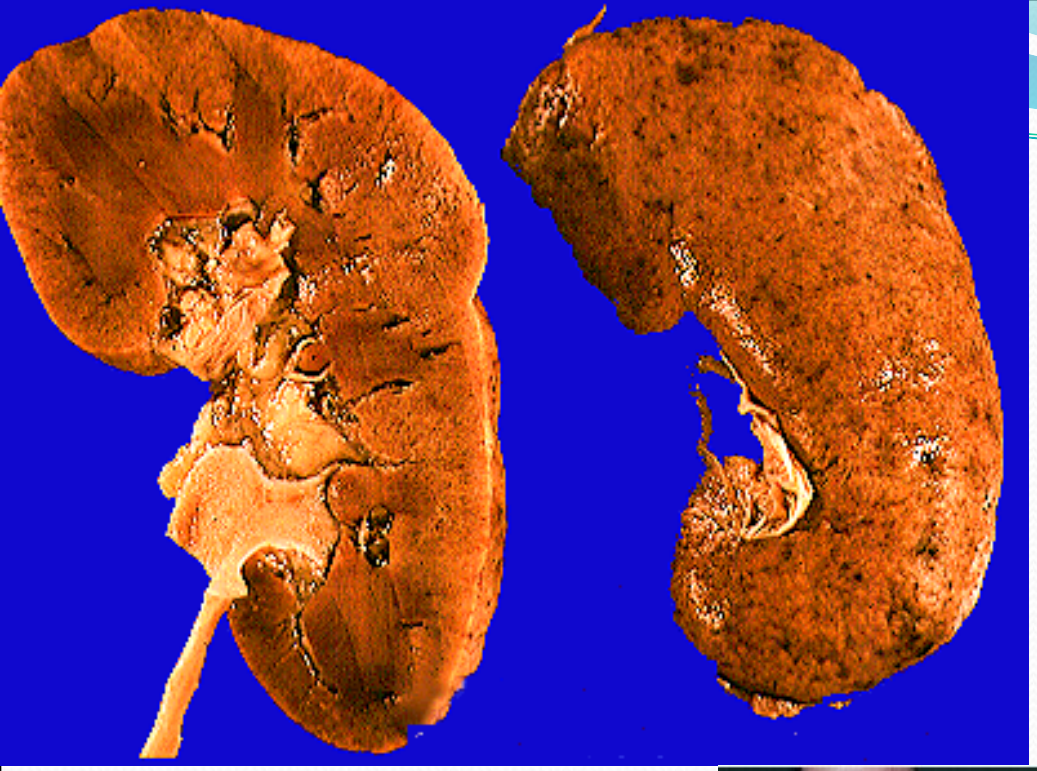


Antibody-mediated or cytotoxic hypersensitivity reaction (type II).

Acute renal graft rejection.

Fetal hydrops (hemolytic disease of the newborn).

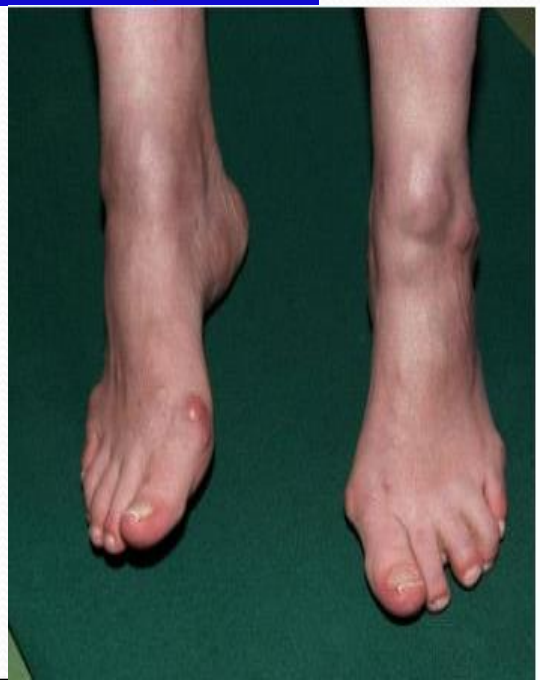


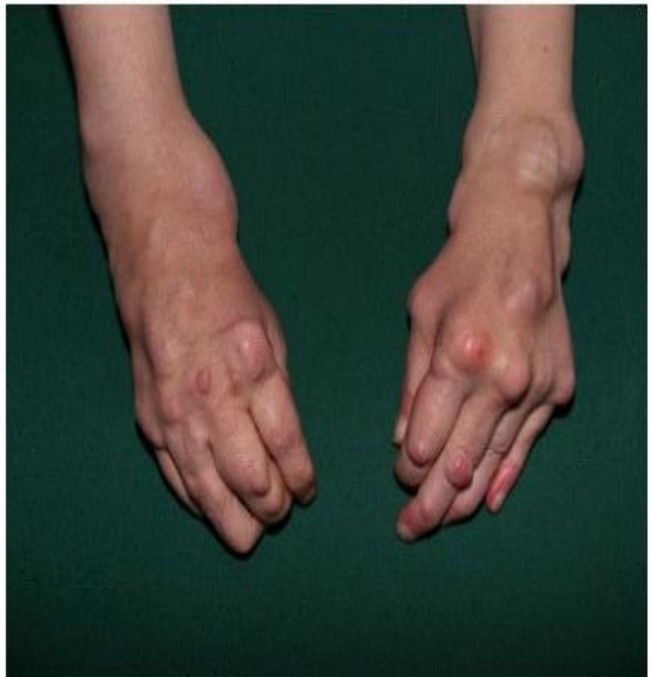


Hypersensitivity reaction mediated by toxic immune complexes (type III)

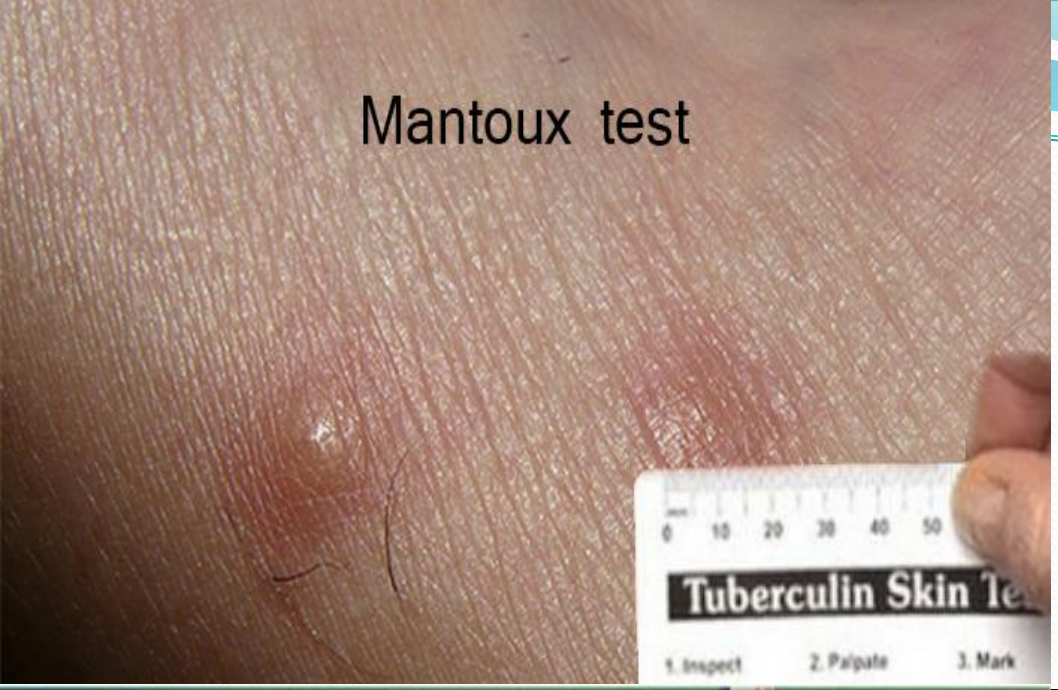
Rheumatoid arthritis.

Lupus glomerulonephritis.

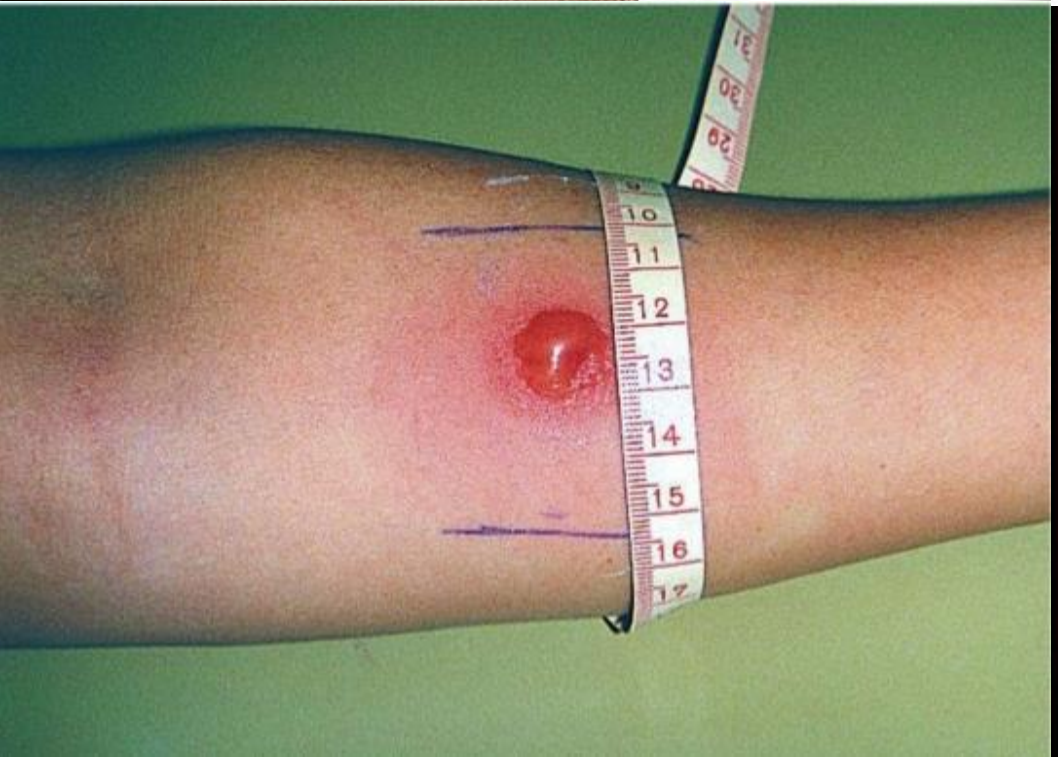


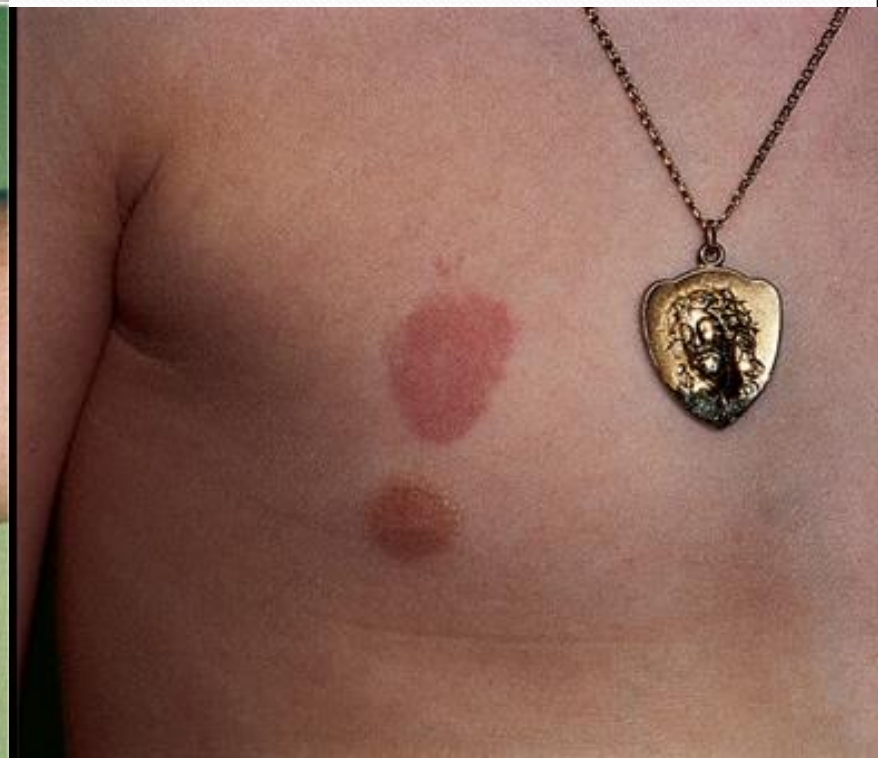


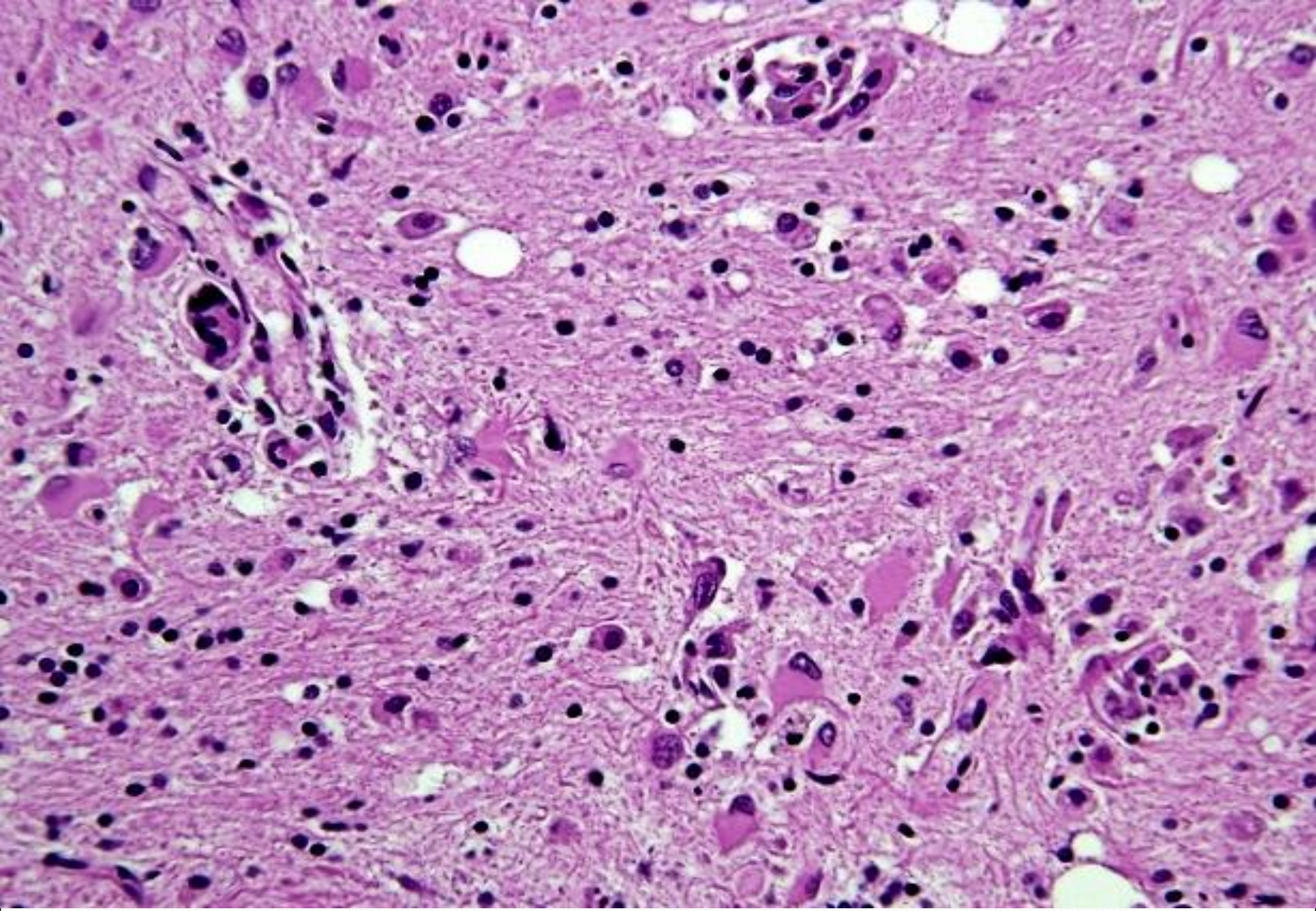
T cell-mediated hypersensitivity reaction (type IV).



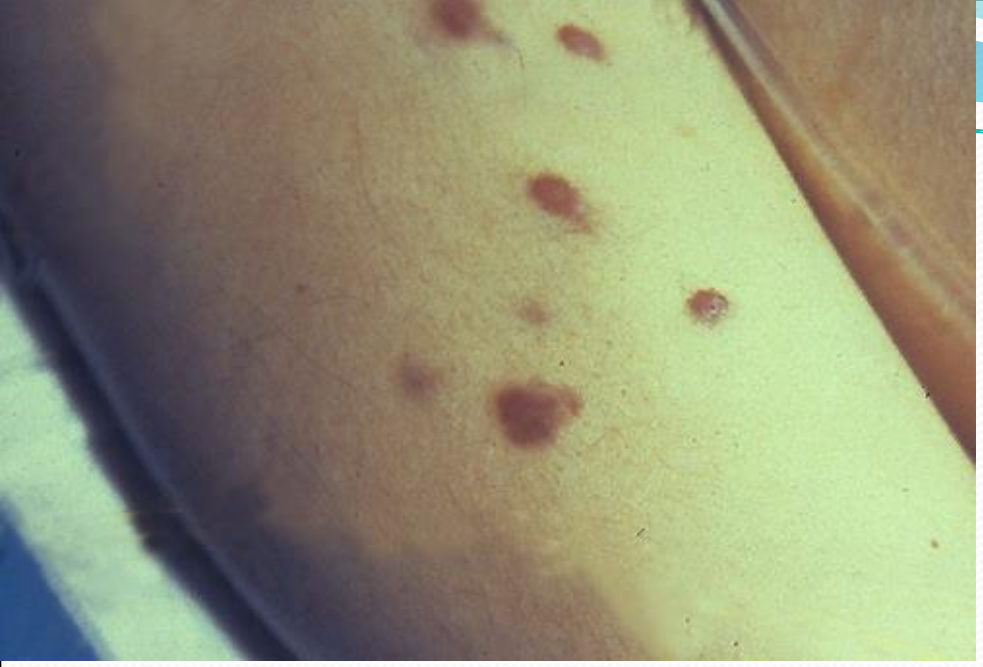
Dermatită de contact.

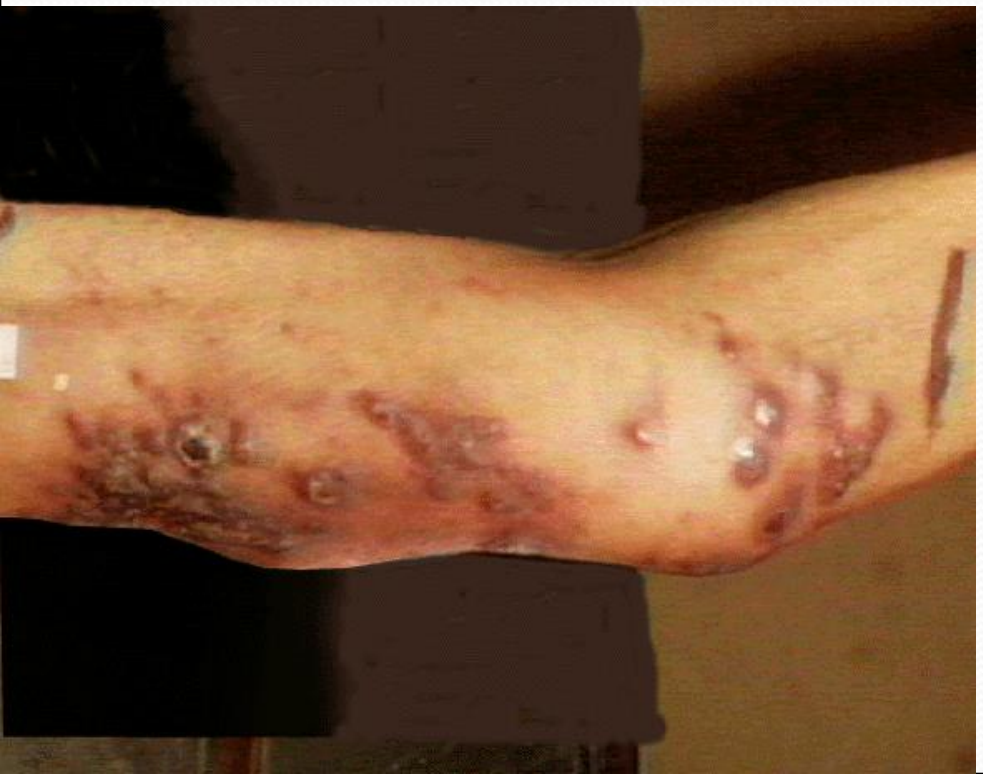


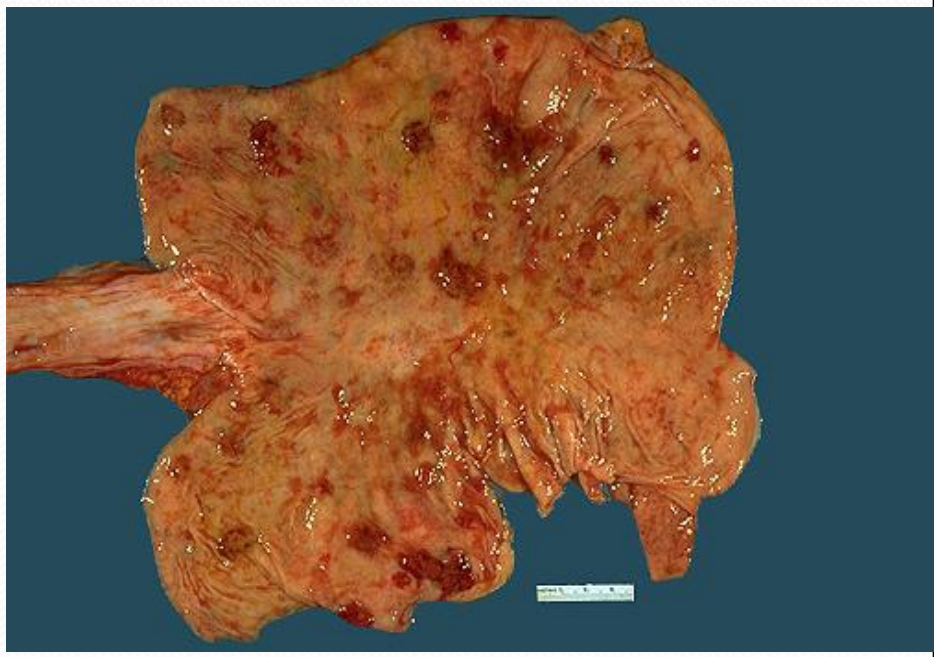




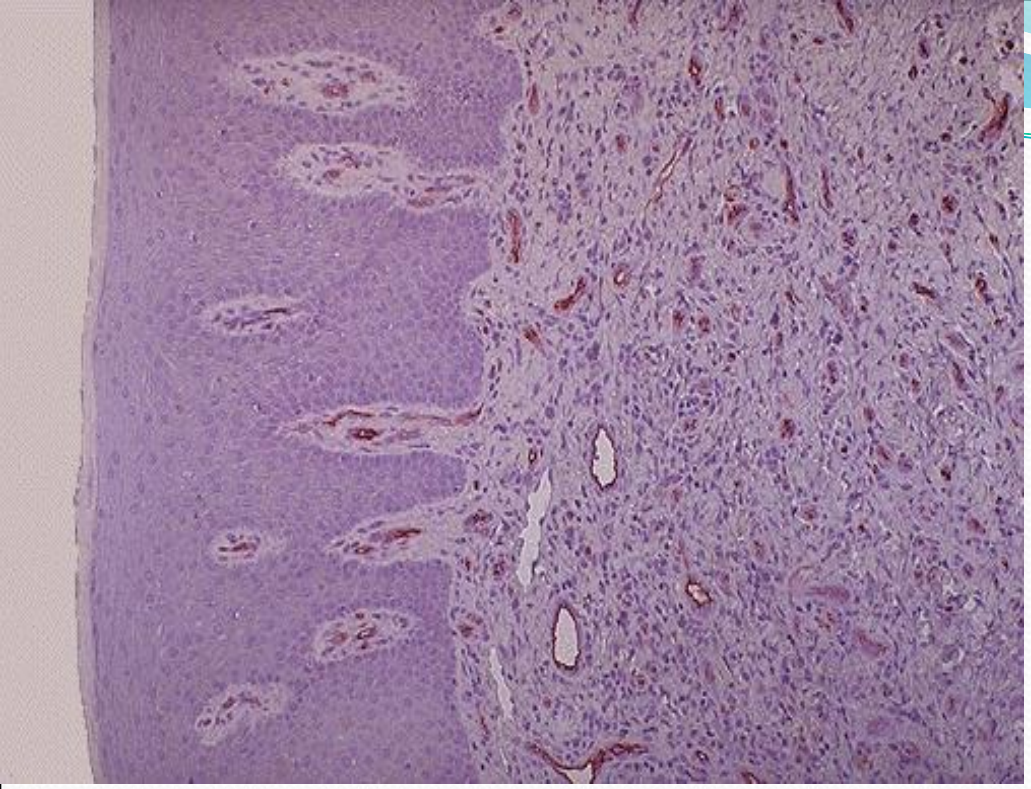
HIV encephalopathy with giant cells, resulting from fusion of HIV-infected macrophages.

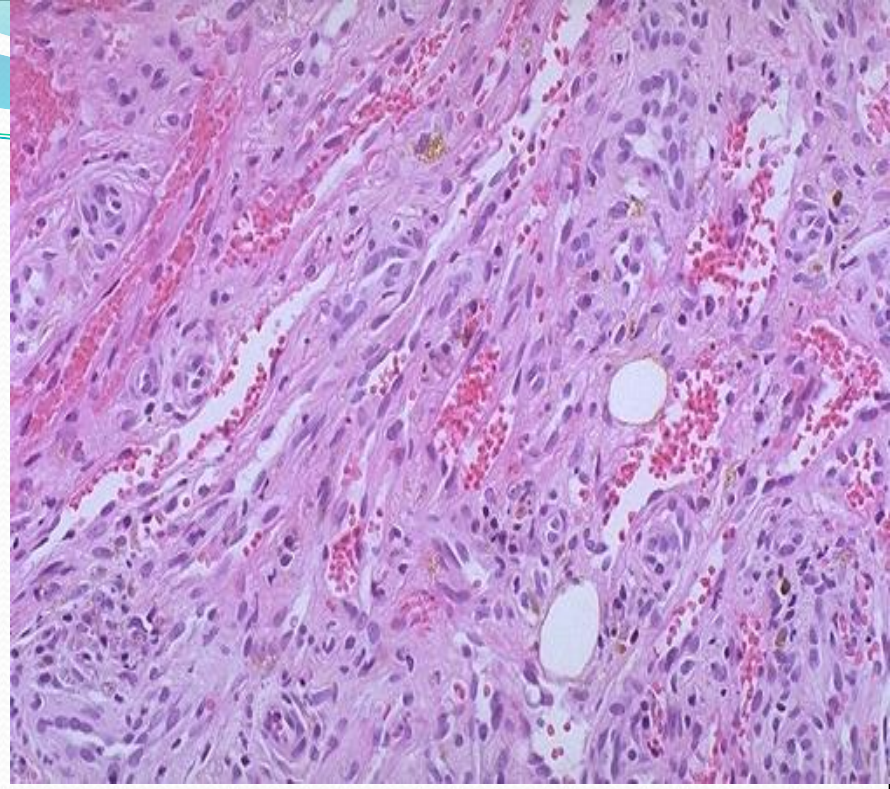


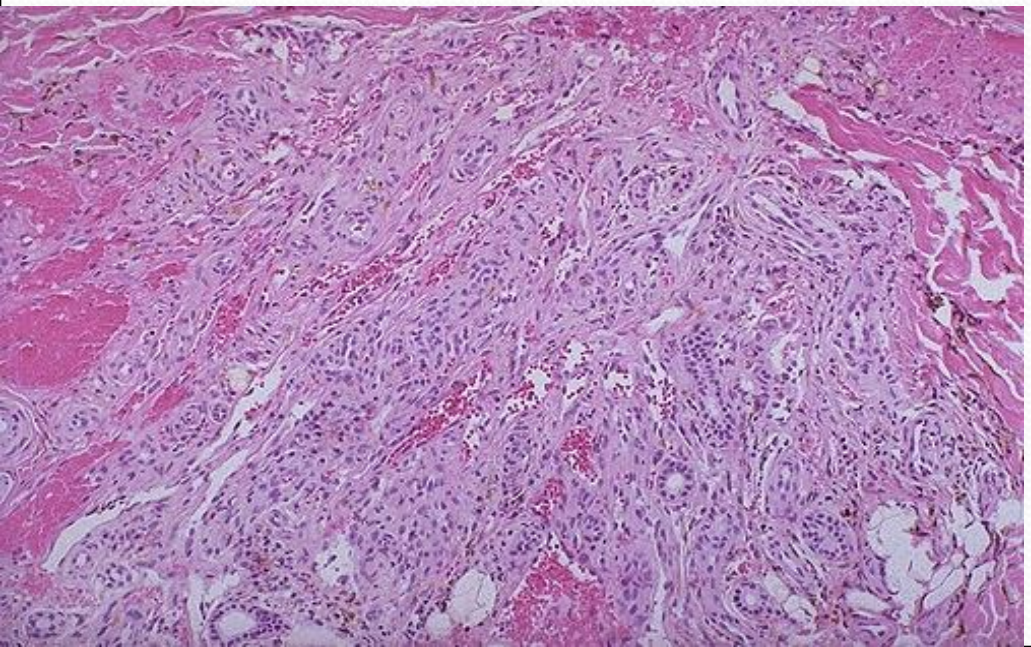




Kaposi sarcoma *(skin, liver, stomach)*.

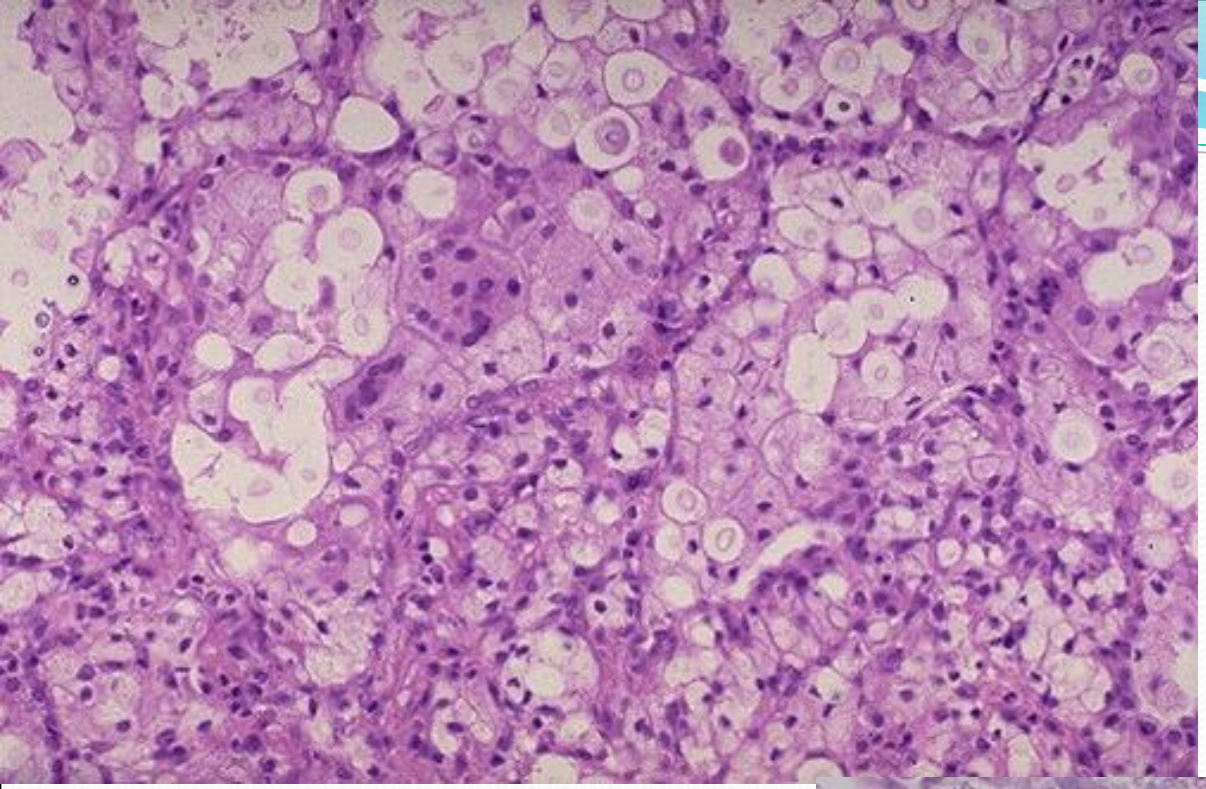






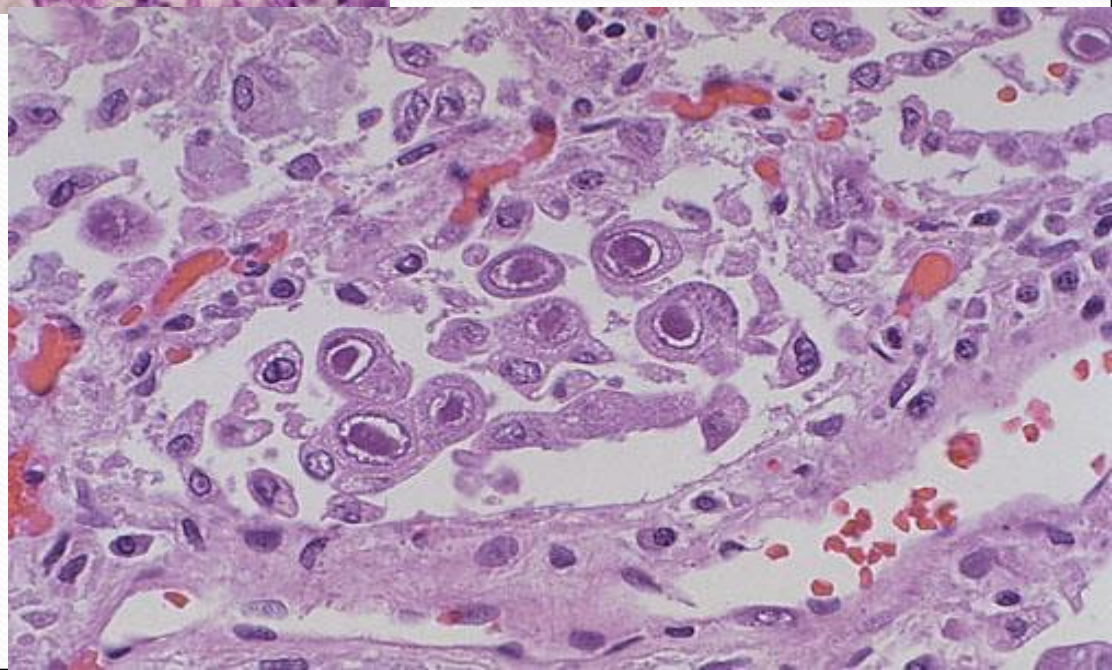
Kaposi sarcoma

(vascular structures, hemorrhages, spindle-shaped stromal cells)



Pulmonary cytomegaloviral infection.

Pulmonary cryptococcosis.



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

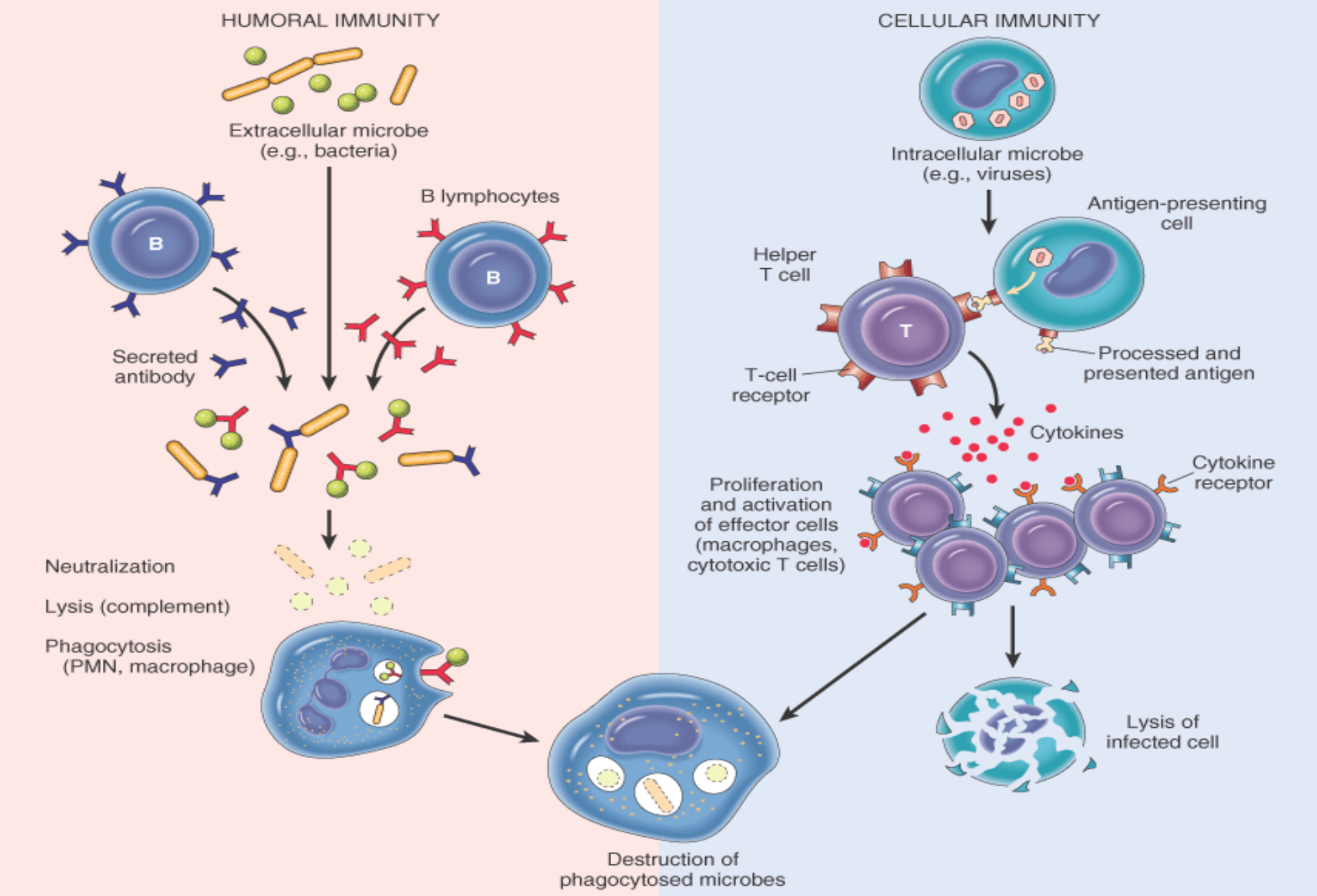
- **BARRIERS**
- **CELLS: LYMPHOCYTES, MACROPHAGES, PLASMA CELLS, NK CELLS**
- **CYTOKINES/CHEMOKINES**
- **PLASMA PROTEINS: Complement, Coagulation Factors**
- **Toll-Like Receptors, TLR's**

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.



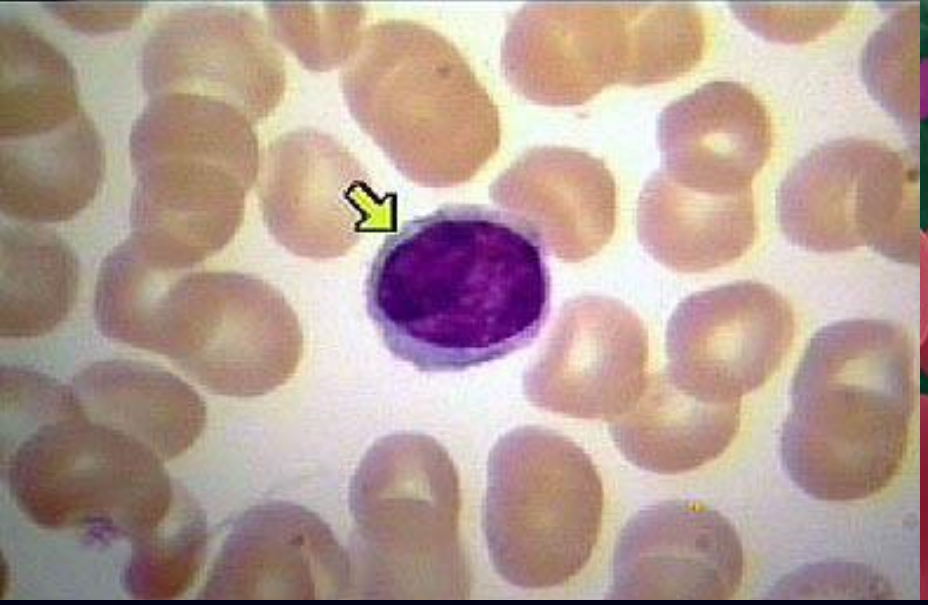
The classic types of adaptive immunity are:
1)Humoral, 2) Cellular

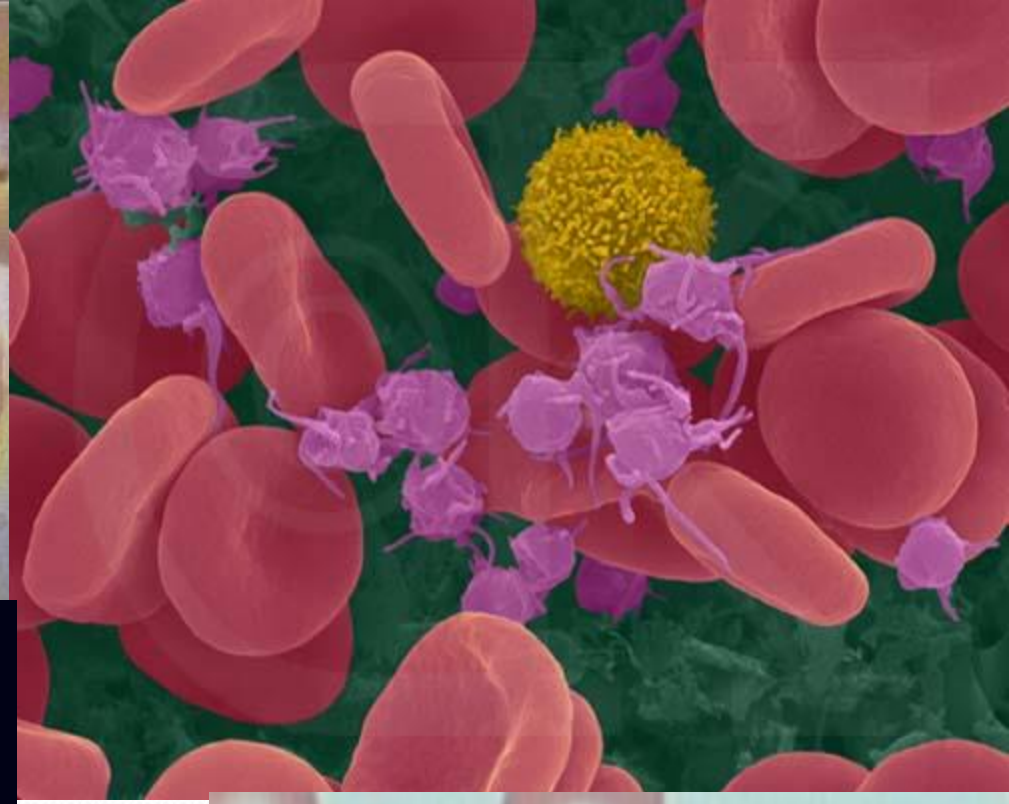
CELLS of the IMMUNE SYSTEM

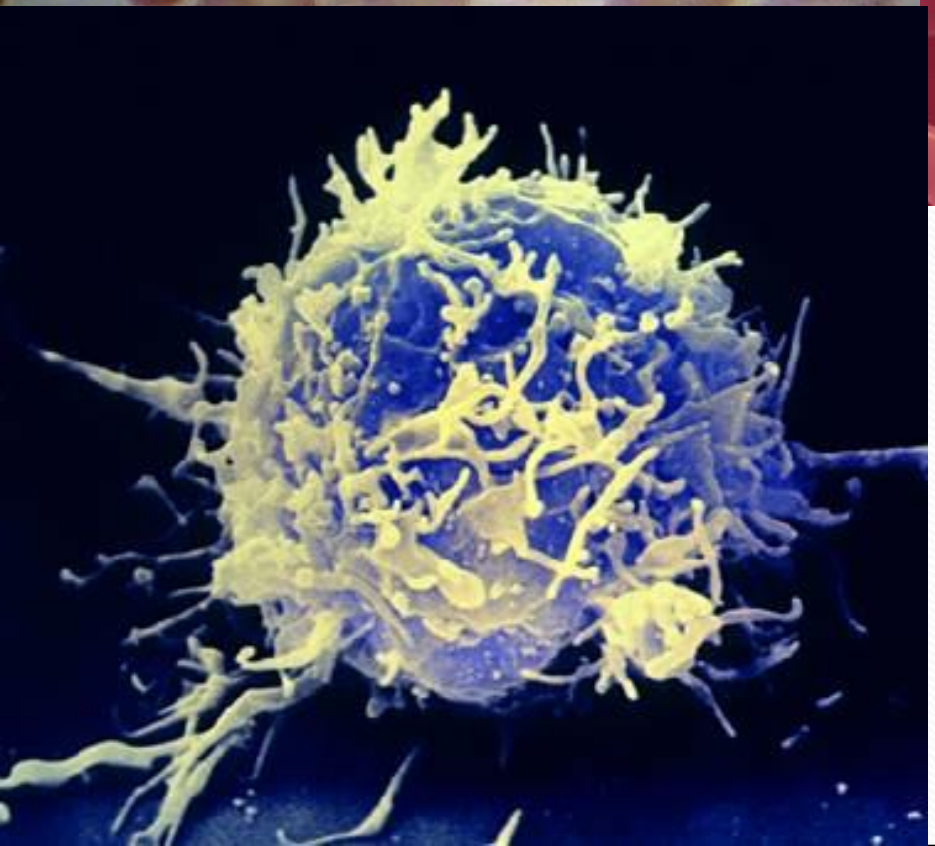
- **LYMPHOCYTES, T**
- **LYMPHOCYTES, B**
- **PLASMA CELLS (MODIFIED B CELLS)**
- **MACROPHAGES, aka "HISTIOCYTES", (APCs, i.e., Antigen Presenting Cells)**
- **"DENDRITIC" CELLS (APCs, i.e., Antigen Presenting Cells)**
- **NK (NATURAL KILLER) CELLS**

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.







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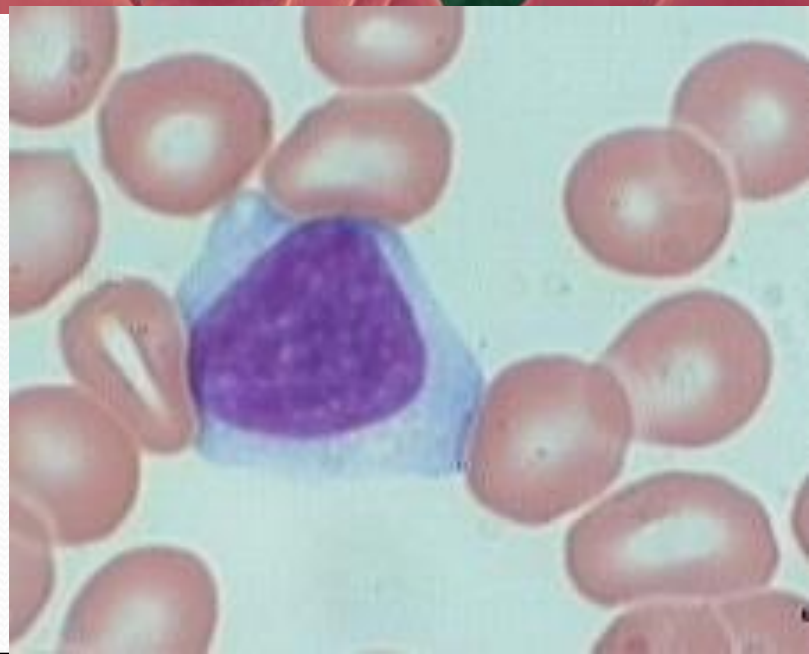
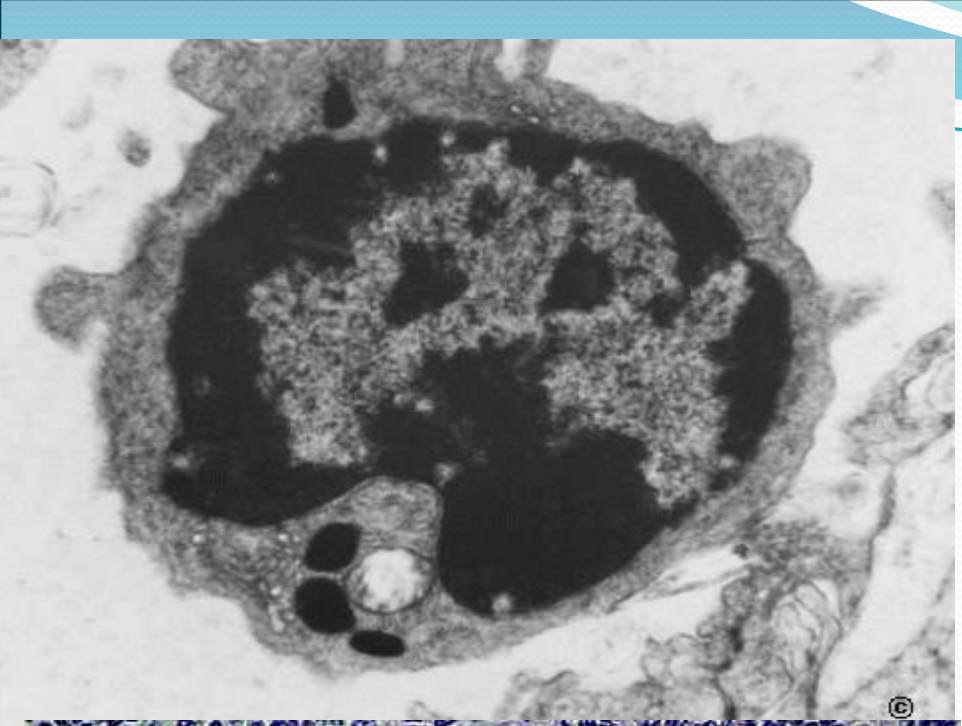
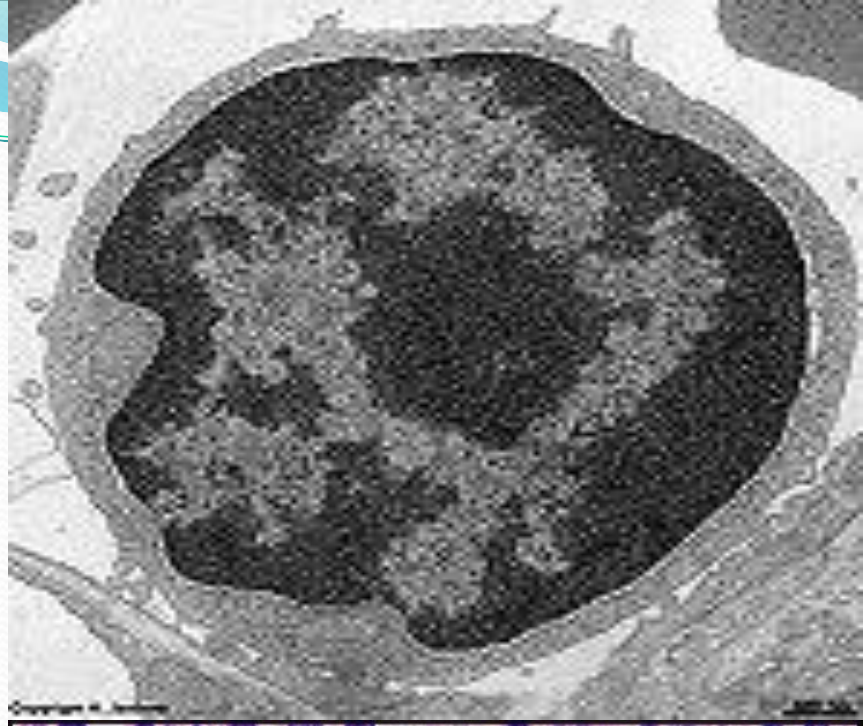
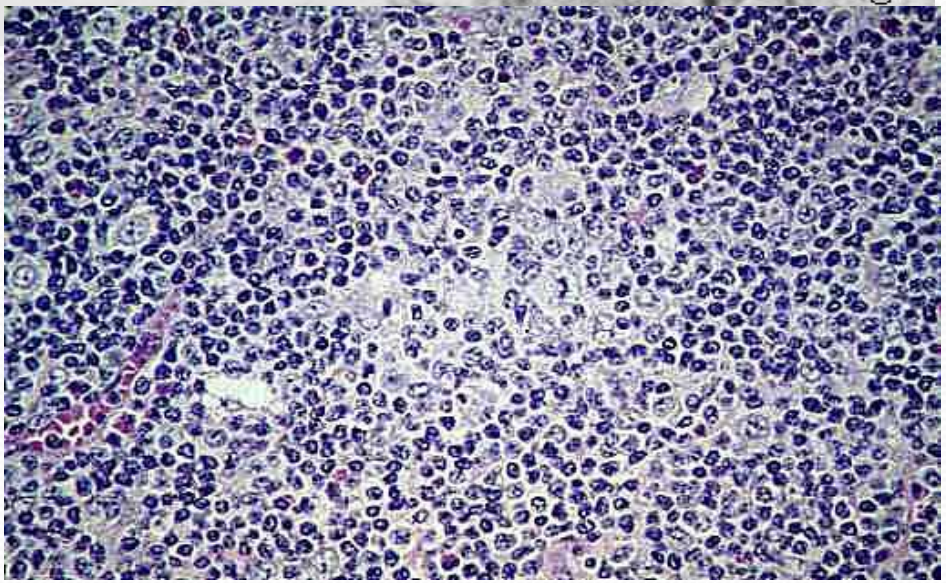
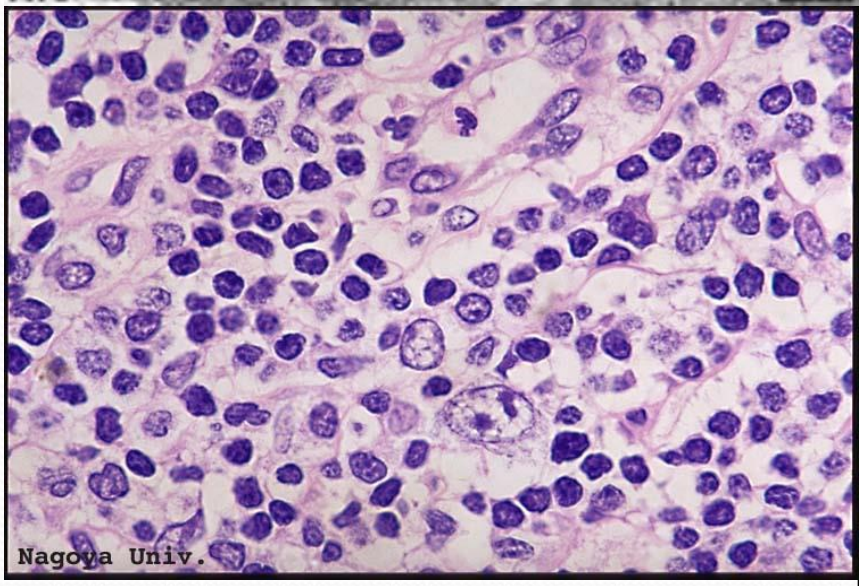










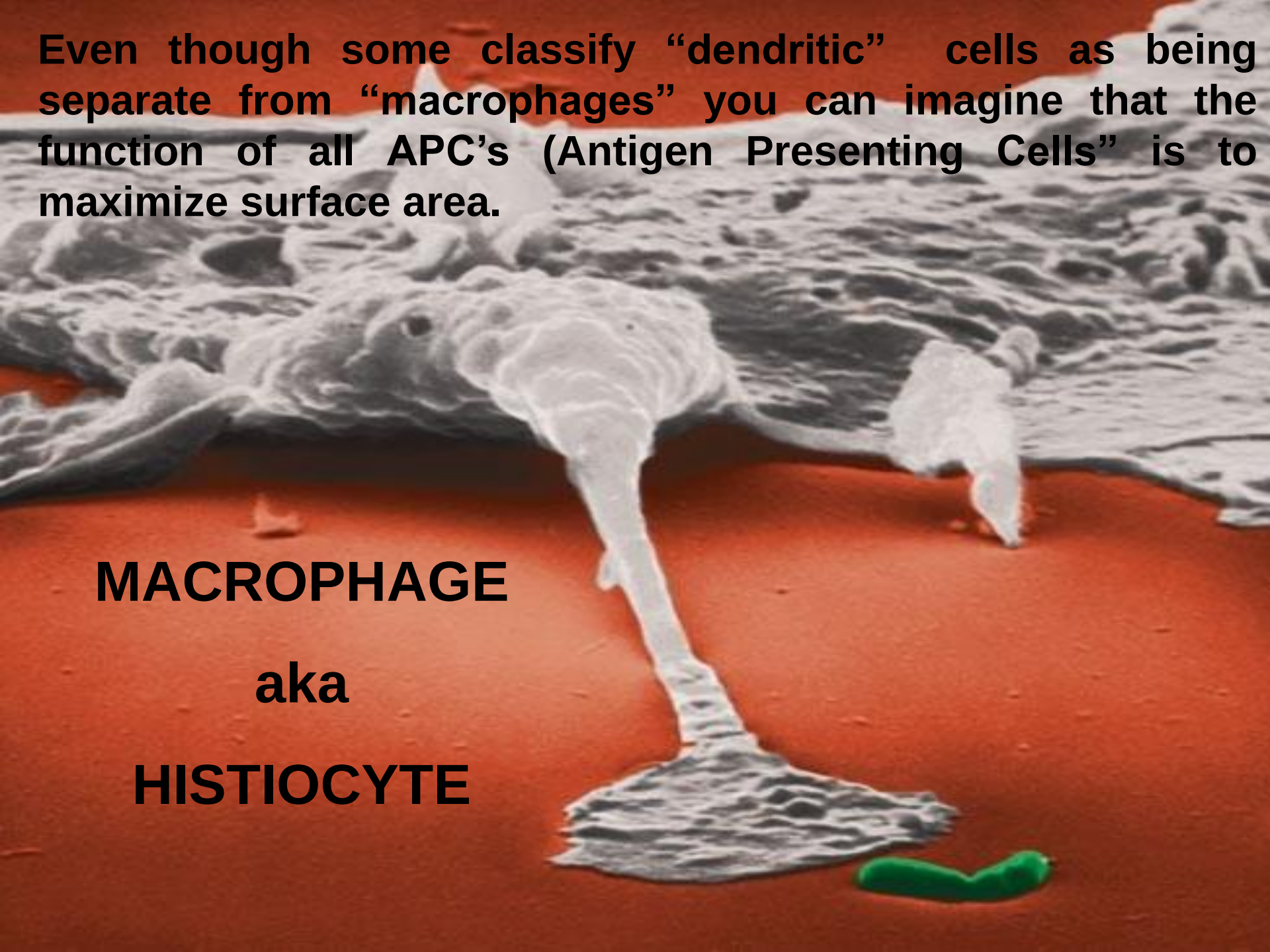
Note even a normal lymph has “cartwheeling” like a plasma cell.

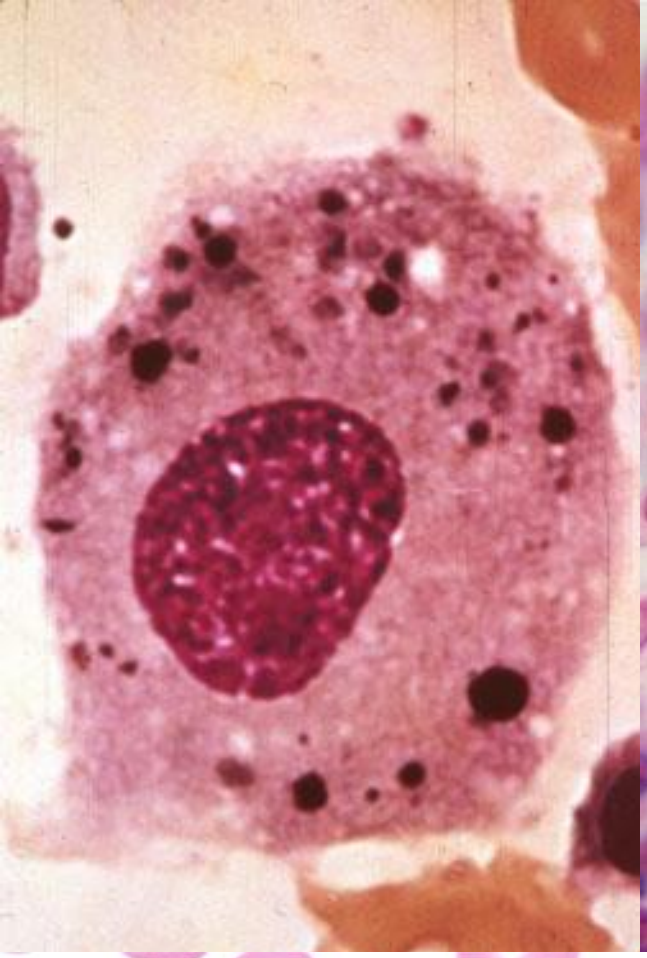
ANY ROUND CELL WITH RATHER DENSE STAINING NUCLEUS AND MINIMAL CYTOPLASM IN CONNECTIVE TISSUE, A BIT BIGGER THAN AN RBC, IS A

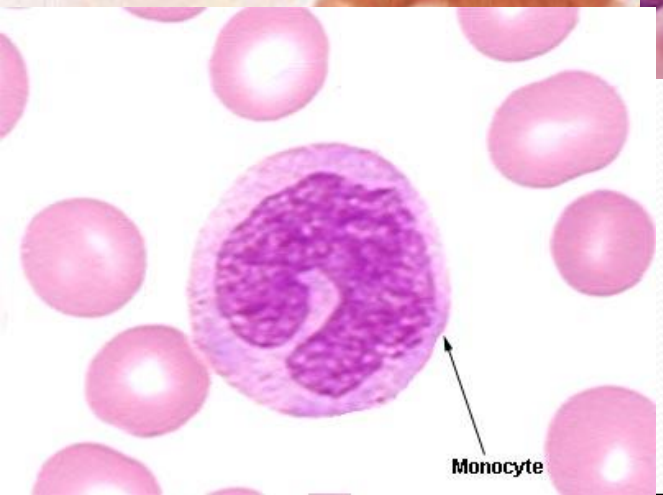
LYMPHOCYTE

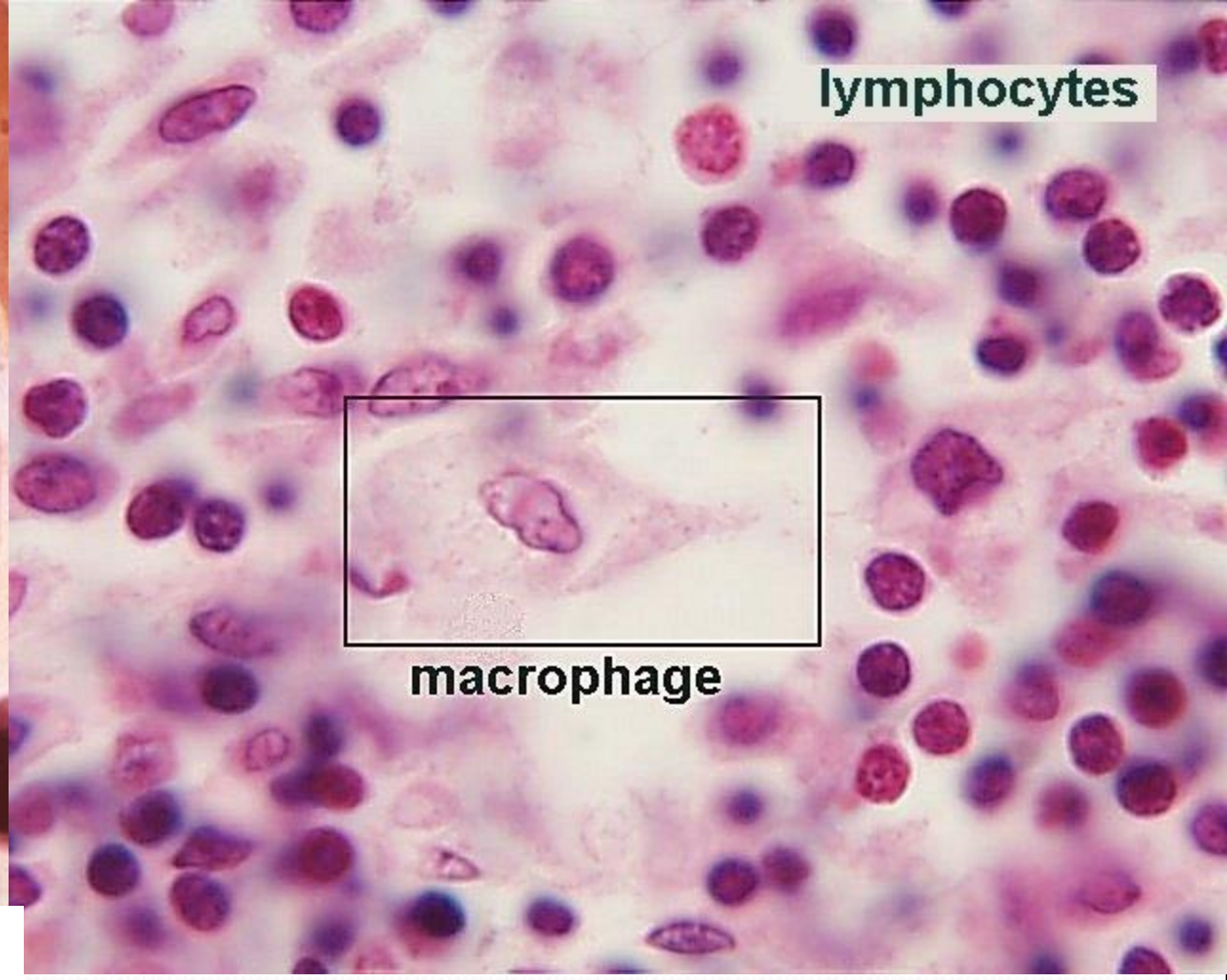
…UNTIL PROVEN OTHERWISE

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

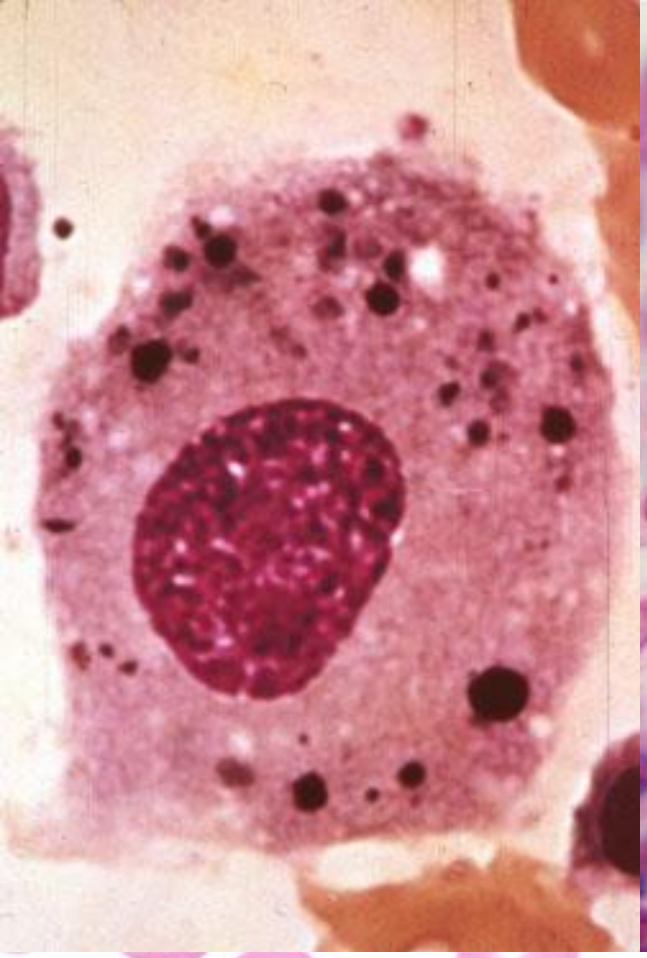

Even though some classify “dendritic” cells as being separate from “macrophages” you can imagine that the function of all APC’s (Antigen Presenting Cells” is to maximize surface area.
MACROPHAGE
aka
HISTIOCYTE

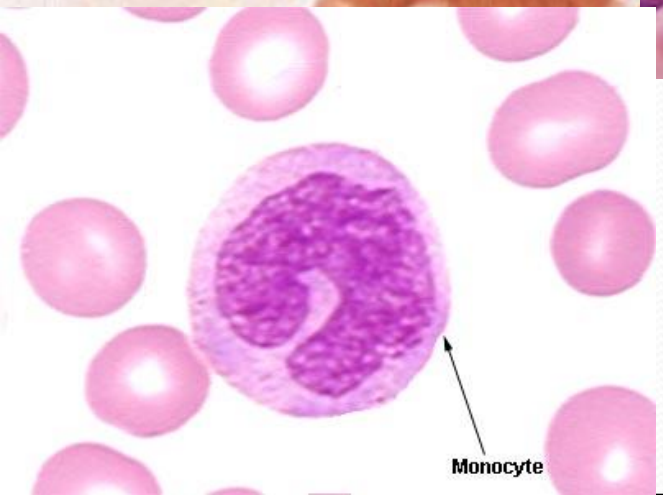


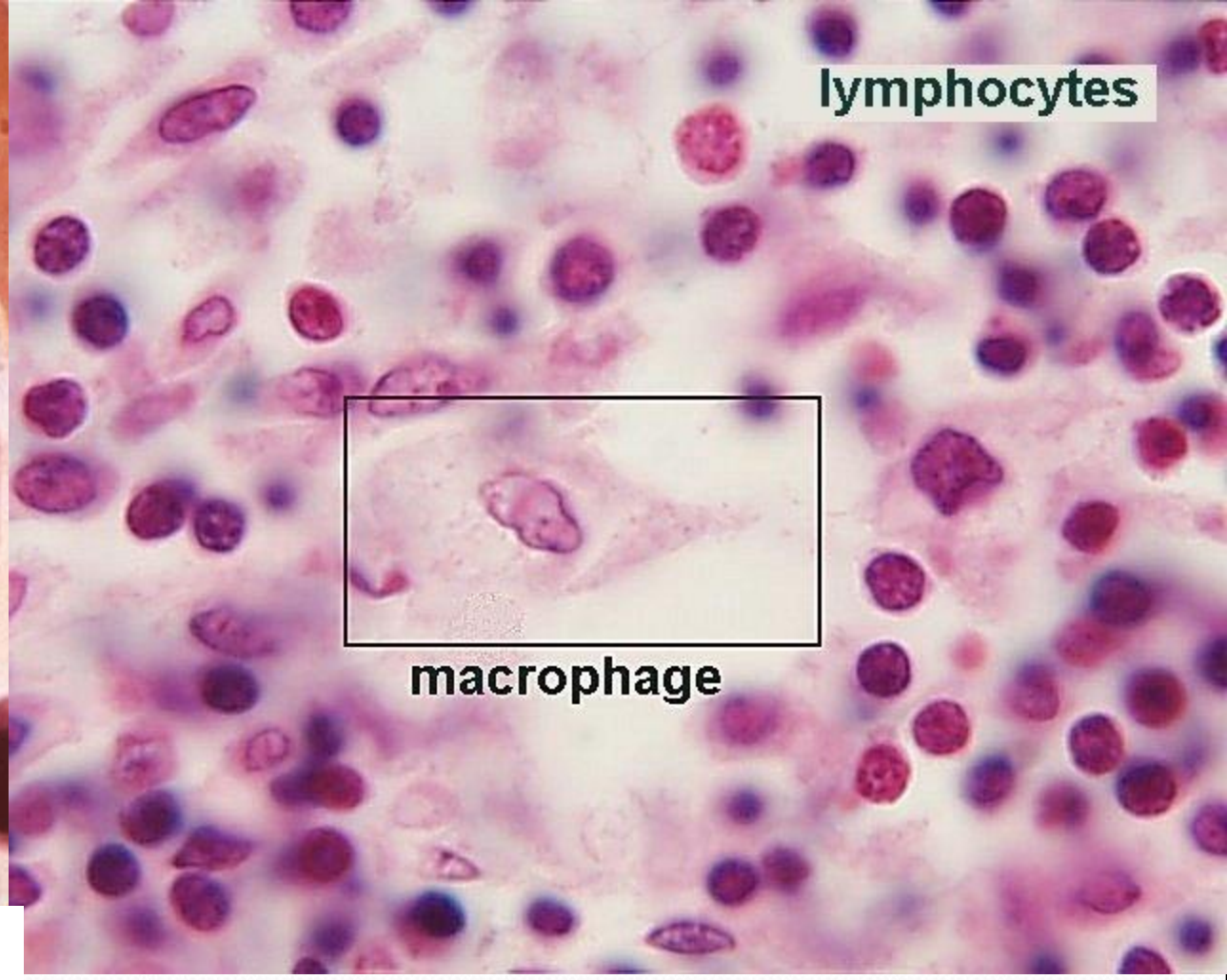




MACROPHAGES are MONOCYTES that have come out of circulation and have gone into tissue

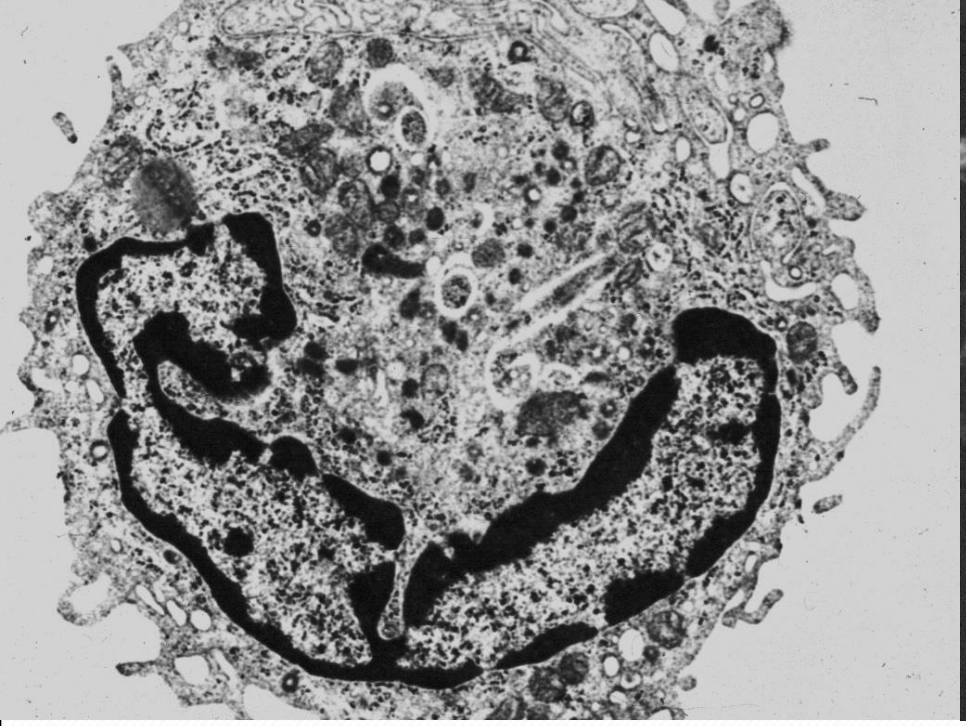


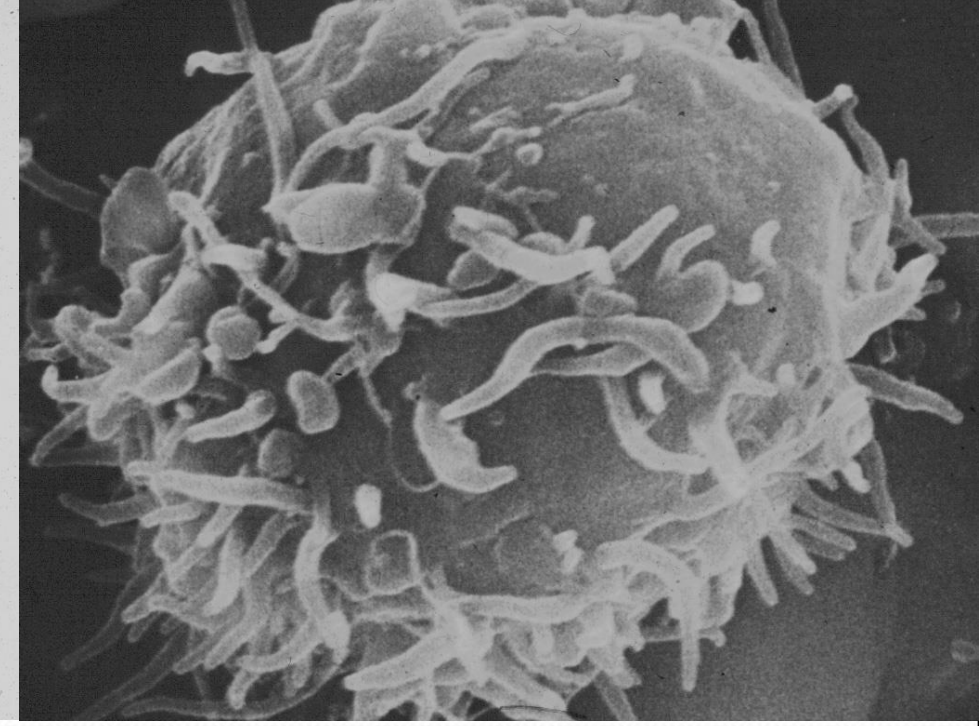




Even though we call a macropahge a “mono”-cyte, conventionally, it’s nucleus can be as convoluted or “cerebrated” as a neutrophil.

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.

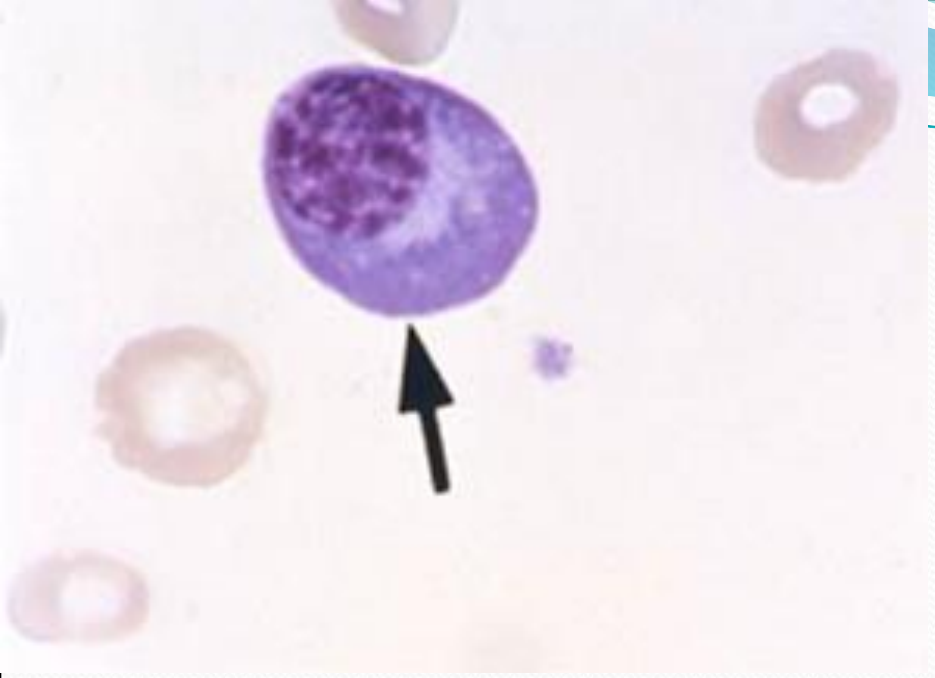
ANY CELL MIXED IN WITH LYMPHOCYTES BUT HAS A LARGER MORE "OPEN", LESS DENSE, LESS CIRCULAR NUCLEUS WITH MORE CYTOPLASM IS A

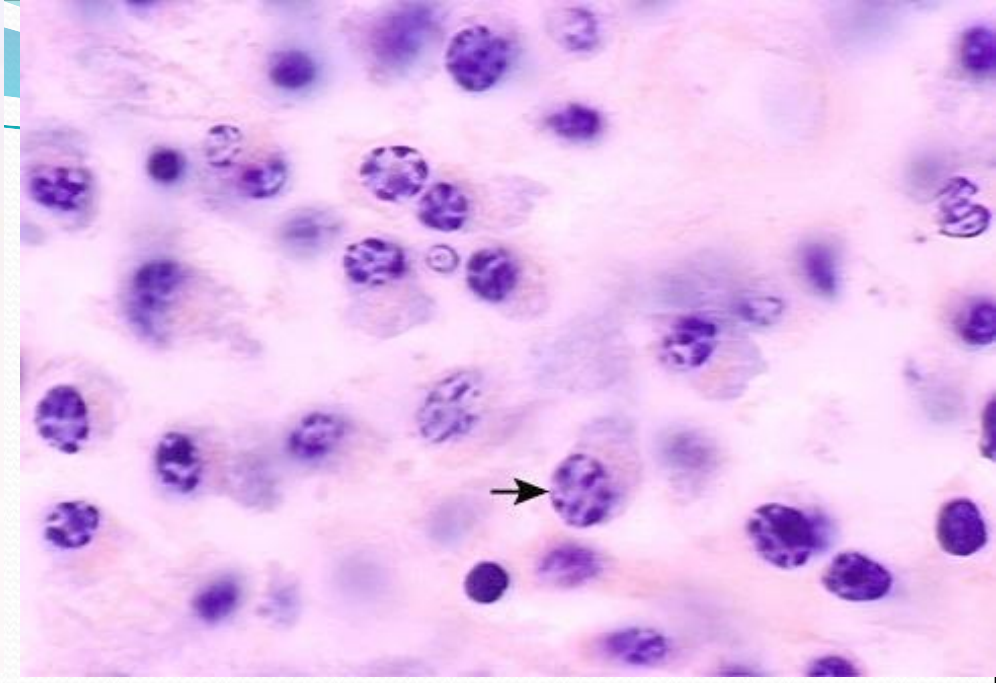
MACROPHAGE

…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

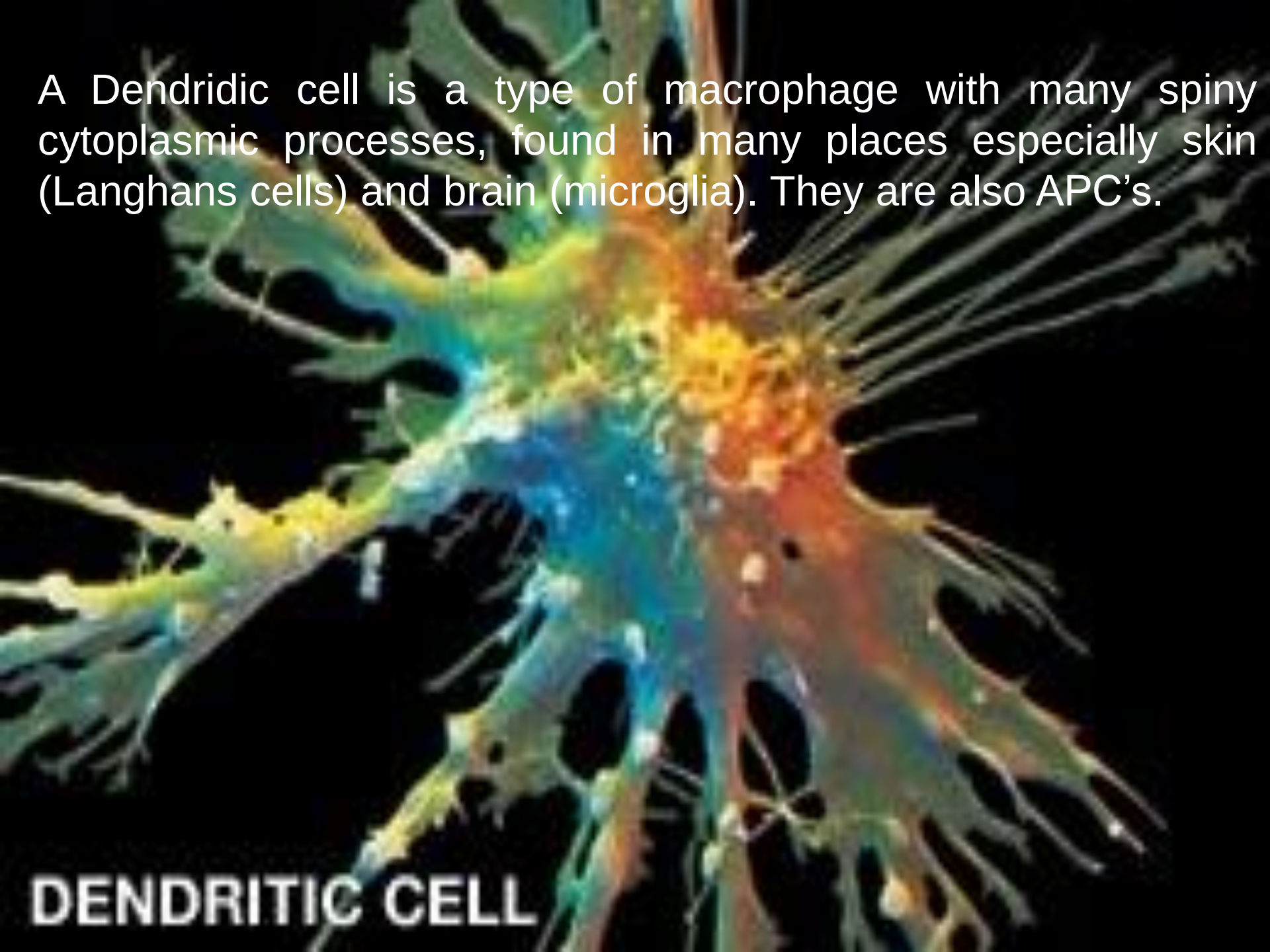
3) PERIPHERAL CHROMATIN

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

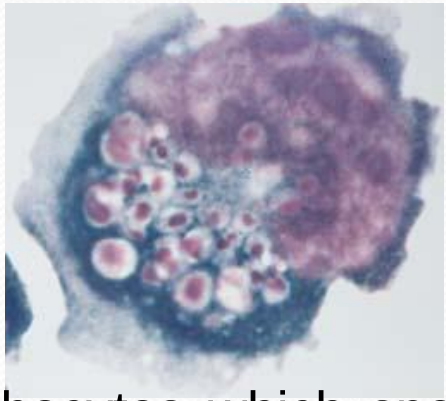
4) “CLEAR ZONE” BETWEEN NUCLEUS AND WIDER LIP OF CYTOPLASM

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.

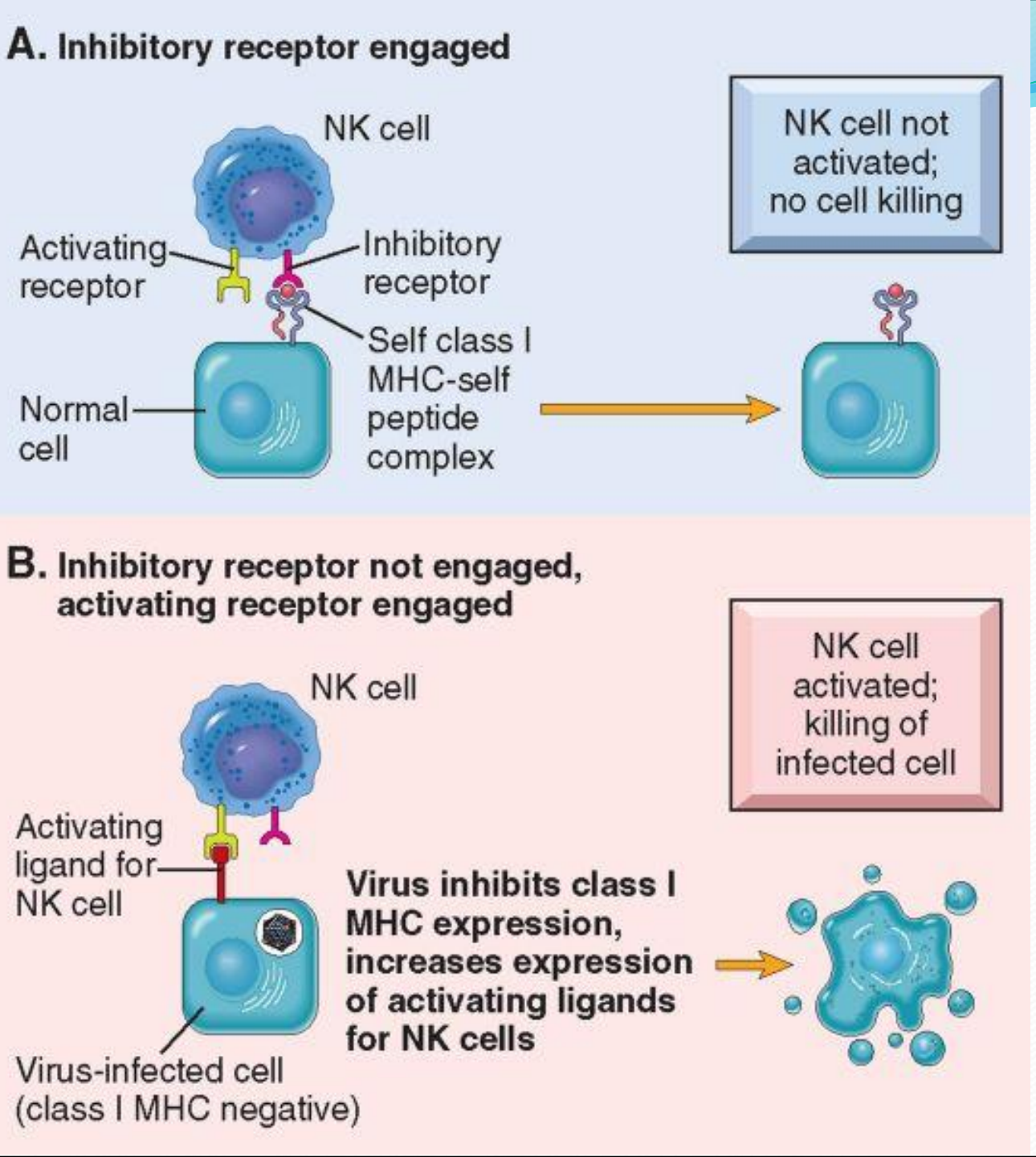


NK CELLS



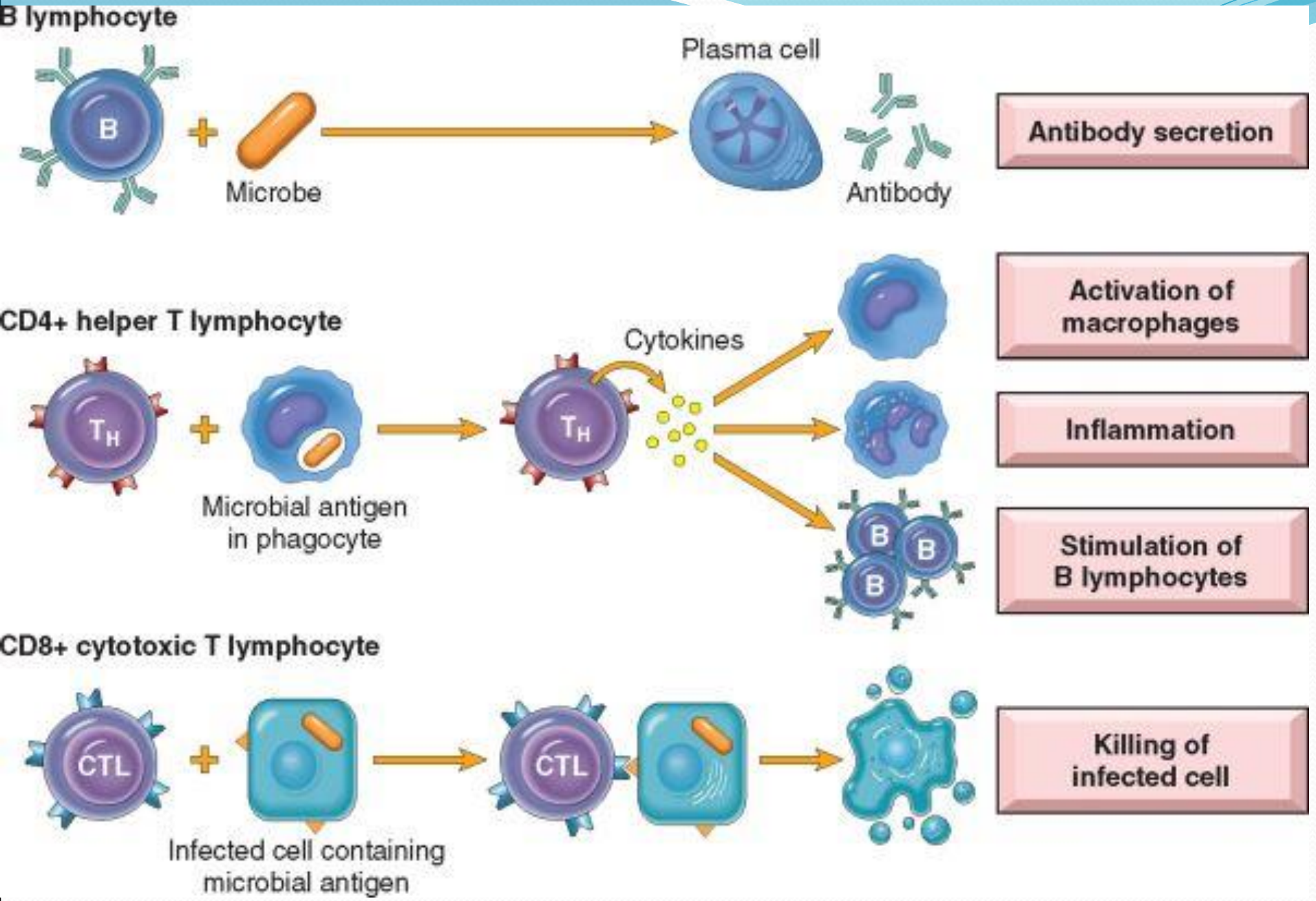
NK cells are types of lymphocytes which specialize in direct killing of cells which the come in contact with, hence the term NK, **N**atural **K**iller.

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-infected cell (class I MHC negative)
Virus inhibits class I MHC expression, increases expression of activating ligands for NK cells
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

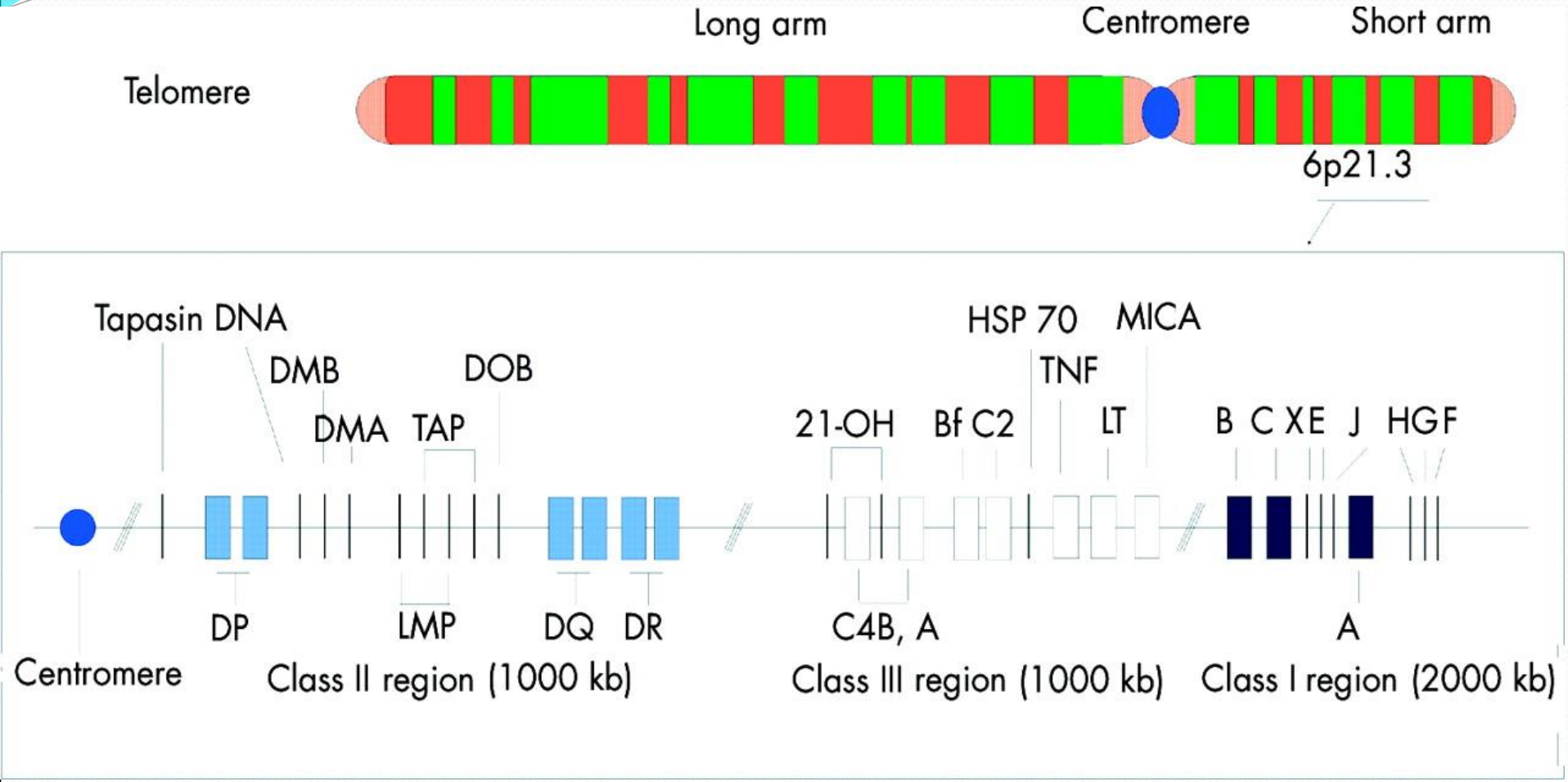
- **CYTOKINES are PROTEINS produced by MANY cells, but usually LYMPHOCYTES and MACROPHAGES, numerous roles in acute and chronic inflammation, AND immunity**
  - **TNF, IL-1, by macrophages**
- **CHEMOKINES are small proteins which are attractants for PMNs**

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

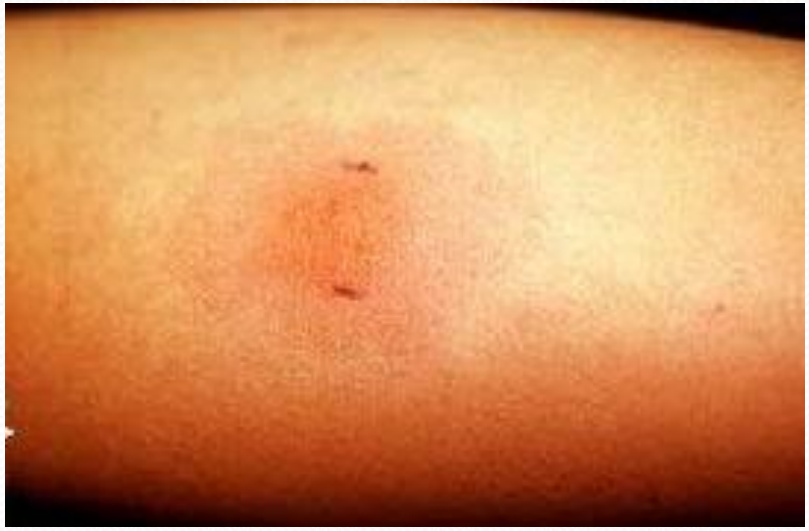
- Antigen/Antibody "Complexes"
- Where do they go?
  - Kidney (Glomerular Basement Membrane)
  - Blood Vessels
  - Skin
  - Joints
- Common Type III Diseases- SLE (Lupus), Poly(Peri)arteritis Nodosa, Poststreptococcal Glomerulonephritis, Arthus reaction (hrs), Serum sickness (days)

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.

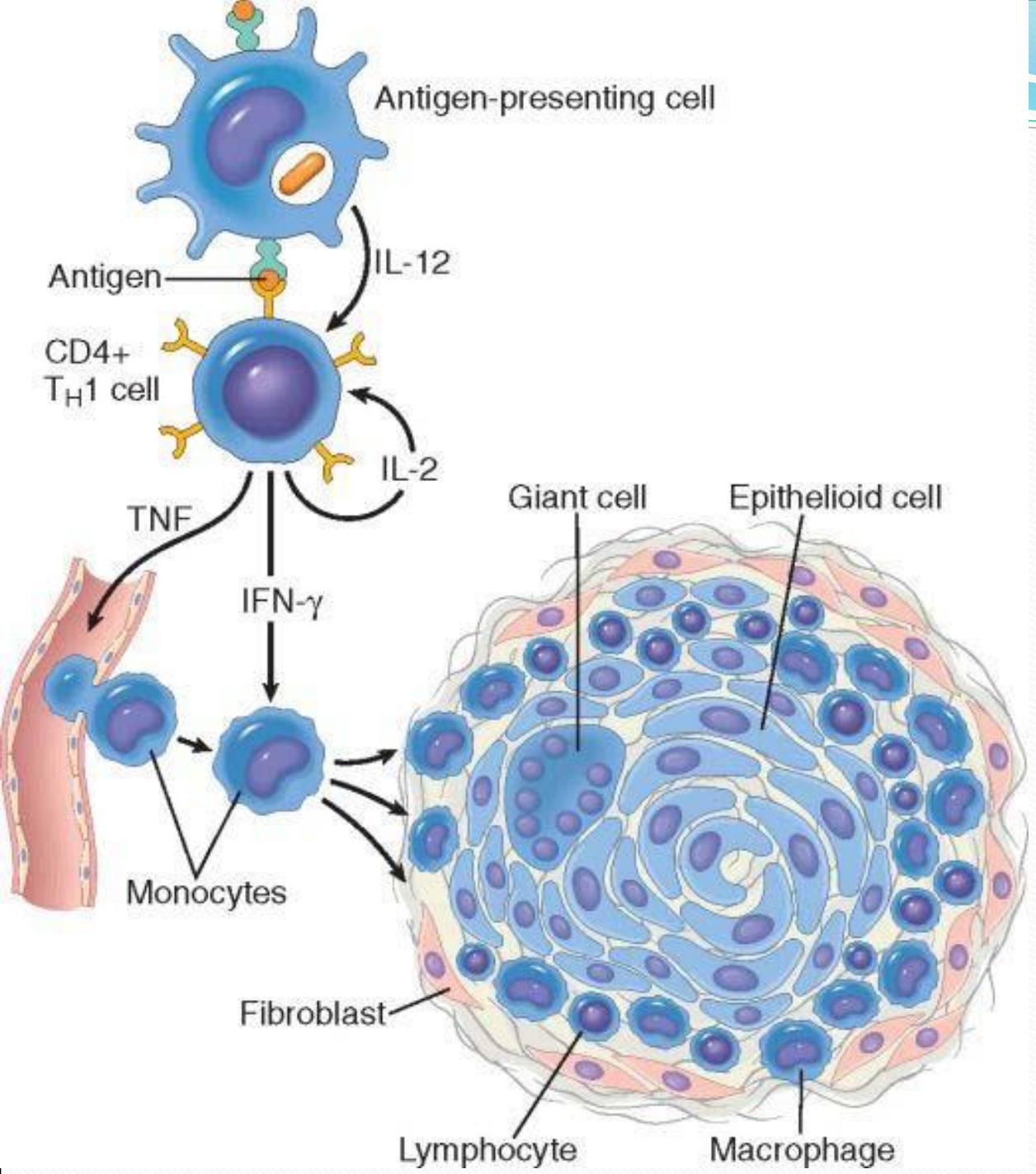
Symptoms can take as long as fourteen days after exposure to appear, and may include signs and symptoms commonly associated with allergic reactions or infections, such asrashes, itching, joint pain (arthralgia), fever, and swollen lymph nodes (lymphadenopathy), and malaise. Historically, it was a result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

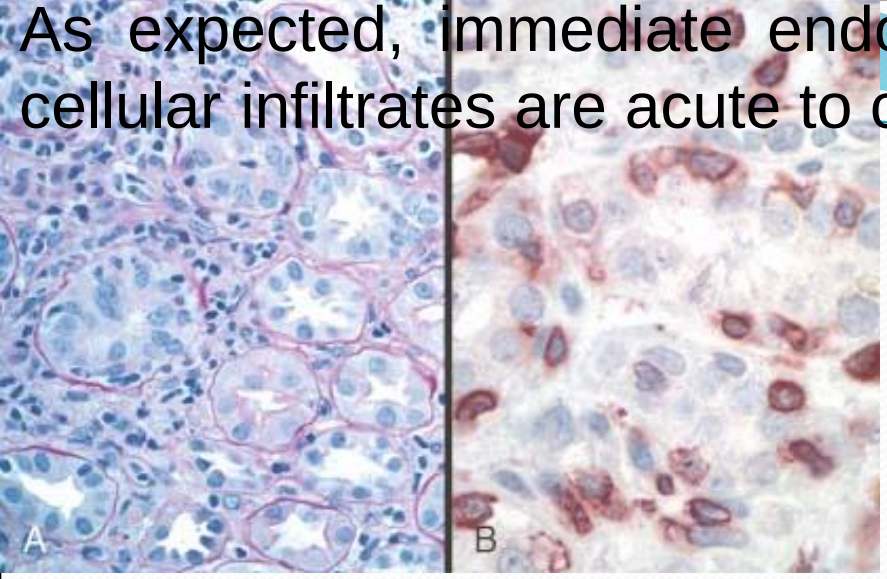
SUMMARY

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

RENAL TRANSPLANT REJECTION

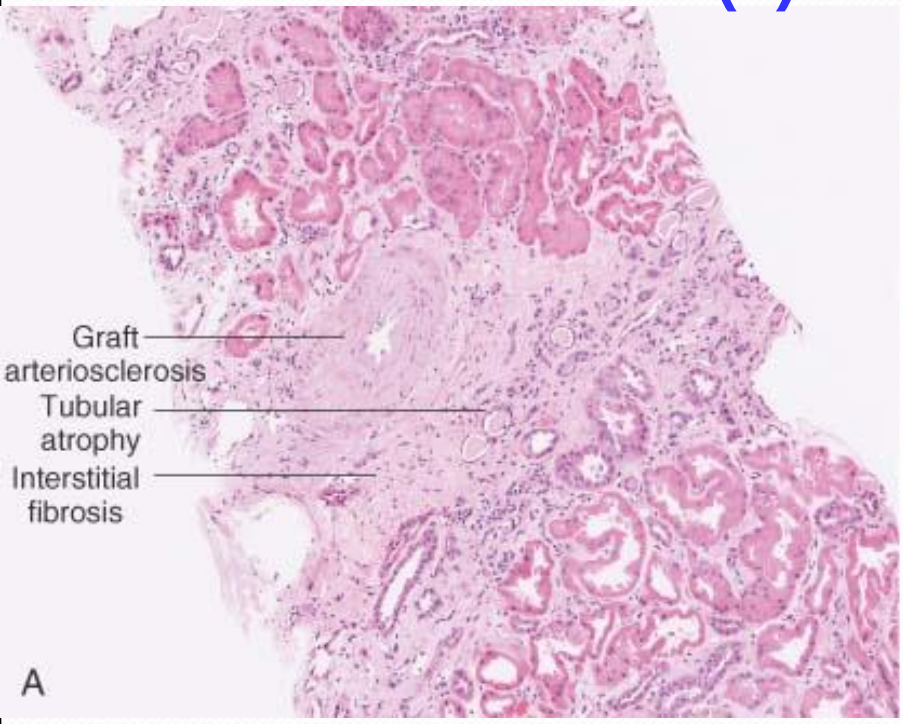
- **HYPERACUTE (minutes) : AG/AB reaction of vascular endothelium**
- **ACUTE (days→ months): cellular (INTERSTITIAL infiltrate) and humoral (VASCULITIS)**
- **CHRONIC (months): slow vascular fibrosis**

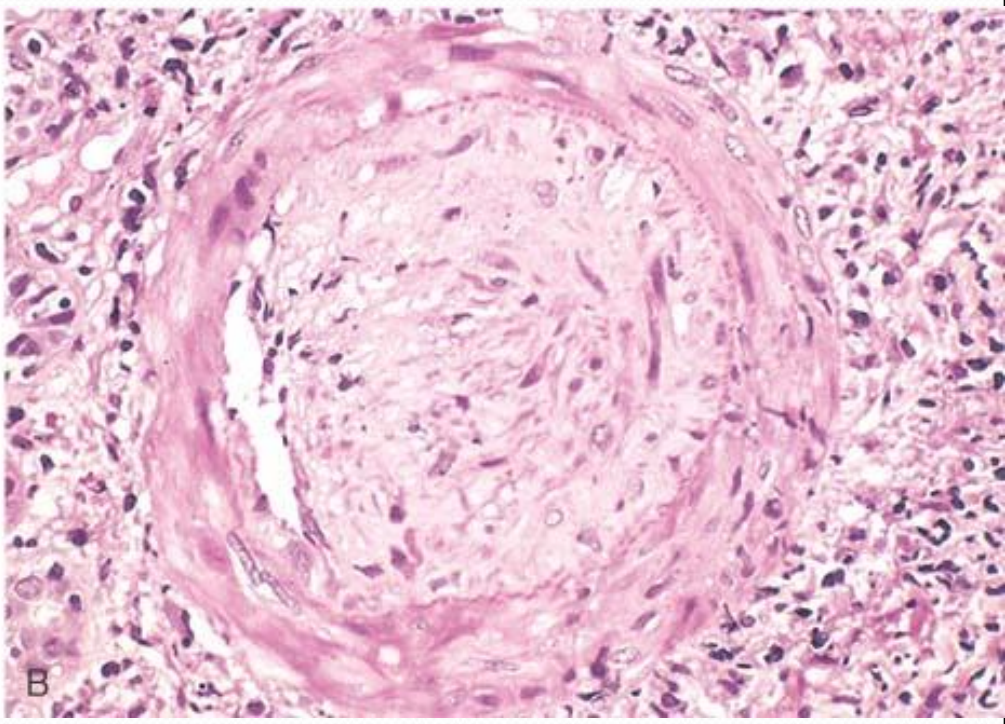
As expected, immediate endothelial responses are hyperacute, cellular infiltrates are acute to chronic, and fibrosis is chronic.



ACUTE CELLULAR (T)

ACUTE HUMORAL





CHRONIC