Krasnoyarsk State Medical University Named After Professor V.F. Voino-Yasenetsky
Department of Pathological Anatomy Named After Professor P.G.Podzolkov

# Lecture 4.
# IMMUNE SYSTEM PATHOLOGY
# ADAPTATION PROCESSES

Contents:



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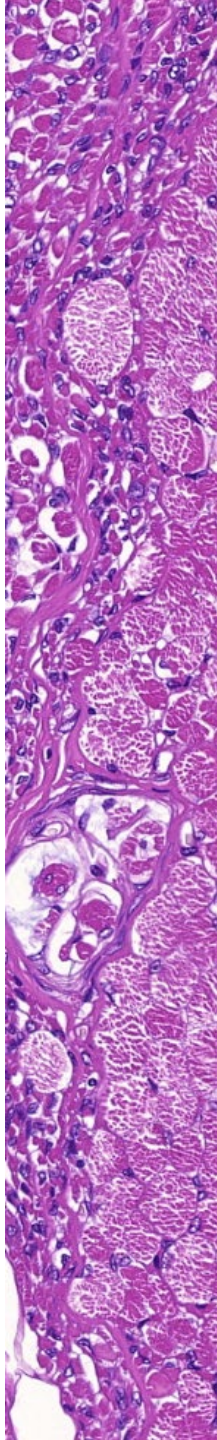

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# Ilya Ilyich Mechnikov

(3 May 1845 – 15 July 1916)


**Karl Ernst von Baer prize in 1867**

**Nobel Prize in Physiology or Medicine in 1908**

**awarded honorary degree from the University of Cambridge in Cambridge, UK, and the Copley Medal of the Royal Society in 1906**

**honorary memberships in the Academy of Medicine in Paris and the Academy of Sciences and Medicine in St. Petersburg**

**Honored as the "father of innate immunity“**

Mechnikov was the first to discover a process of immunity called phagocytosis and the cell responsible for it, called phagocyte, specifically macrophage, in 1882.

# Immune system

(definition)

The organ system that is involved in protecting the organism from infection, infestation, and other potential harm from the presence of foreign (non-self) bodies

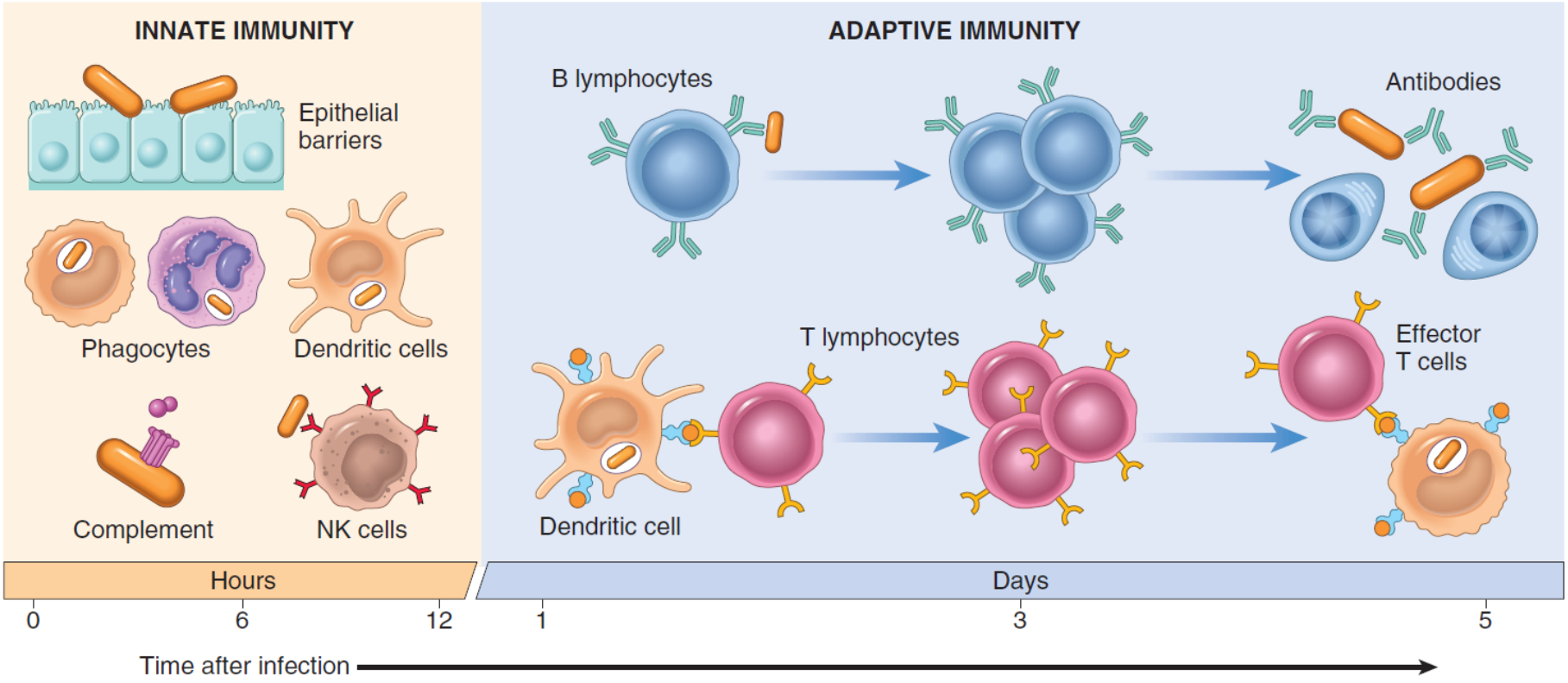
https://www.biologyonline.com/dictionary/immune-system

A complex network of cells, tissues, organs, and the substances they make that helps the body fight infections and other diseases. The immune system includes white blood cells and organs and tissues of the lymph system, such as the thymus, spleen, tonsils, lymph nodes, lymph vessels, and bone marrow.

https://www.cancer.gov/

**The immune system** is a complex of organs, tissues and cells that protect the body from infectious agents and objects foreign in their antigenic properties.

# THE NORMAL IMMUNE RESPONSE



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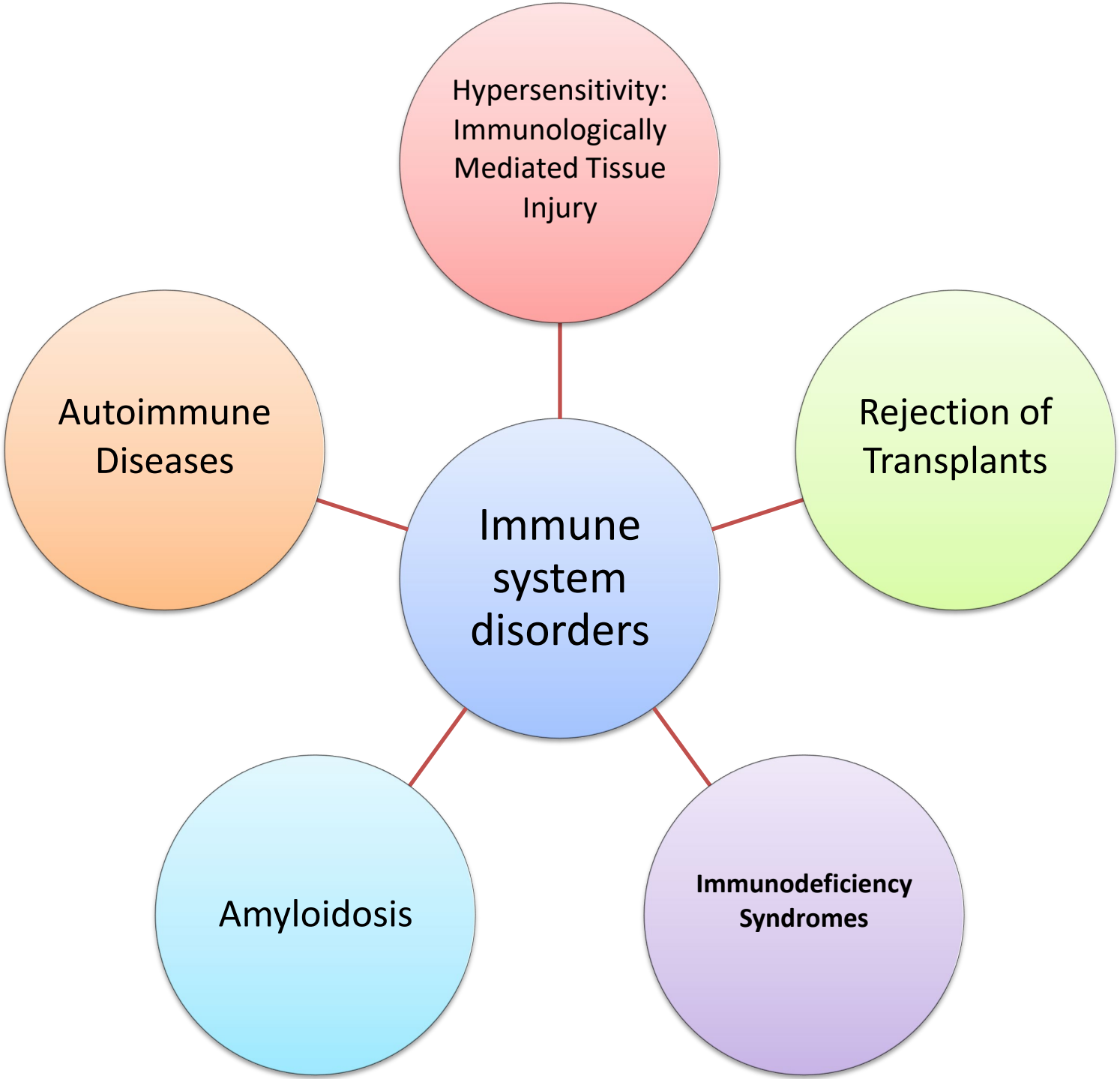
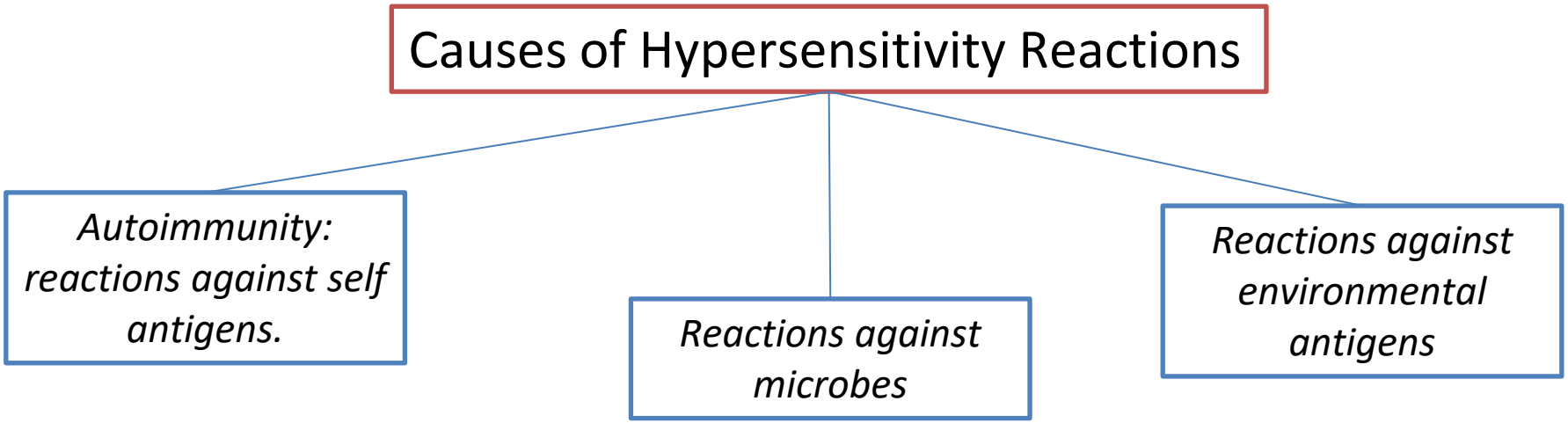

Hypersensitivity: Immunologically Mediated Tissue Injury
Autoimmune Diseases
Immune system disorders
Rejection of Transplants
Amyloidosis
Immunodeficiency Syndromes

# Hypersensitivity: Immunologically Mediated Tissue Injury

Immune responses that normally are protective also are capable of causing tissue injury. Injurious immune reactions are grouped under *hypersensitivity, and the resulting* diseases are called *hypersensitivity diseases.*



# Classification of Hypersensitivity Reactions

| Type | Immune Mechanisms | Histopathologic Lesions | Prototypical Disorders |
|---|---|---|---|
| Immediate (type I) hypersensitivity | Production of IgE antibody → immediate release of vasoactive amines and other mediators from mast cells; later recruitment of inflammatory cells | Vascular dilation, edema, smooth muscle contraction, mucus production, tissue injury, inflammation | Anaphylaxis; allergies; bronchial asthma (atopic forms) |
| Antibody-mediated (type II) hypersensitivity | Production of IgG, IgM → binds to antigen on target cell or tissue → phagocytosis or lysis of target cell by activated complement or Fc receptors; recruitment of leukocytes | Phagocytosis and lysis of cells; inflammation; in some diseases, functional derangements without cell or tissue injury | Autoimmune hemolytic anemia; Goodpasture syndrome |
| Immune complex–mediated (type III) hypersensitivity | Deposition of antigen-antibody complexes → complement activation → recruitment of leukocytes by complement products and Fc receptors → release of enzymes and other toxic molecules | Inflammation, necrotizing vasculitis (fibrinoid necrosis) | Systemic lupus erythematosus; some forms of glomerulonephritis; serum sickness; Arthus reaction |
| Cell-mediated (type IV) hypersensitivity | Activated T lymphocytes → (1) release of cytokines, inflammation and macrophage activation; (2) T cell–mediated cytotoxicity | Perivascular cellular infiltrates; edema; granuloma formation; cell destruction | Contact dermatitis; multiple sclerosis; type I diabetes; tuberculosis |

*Ig*, Immunoglobulin.



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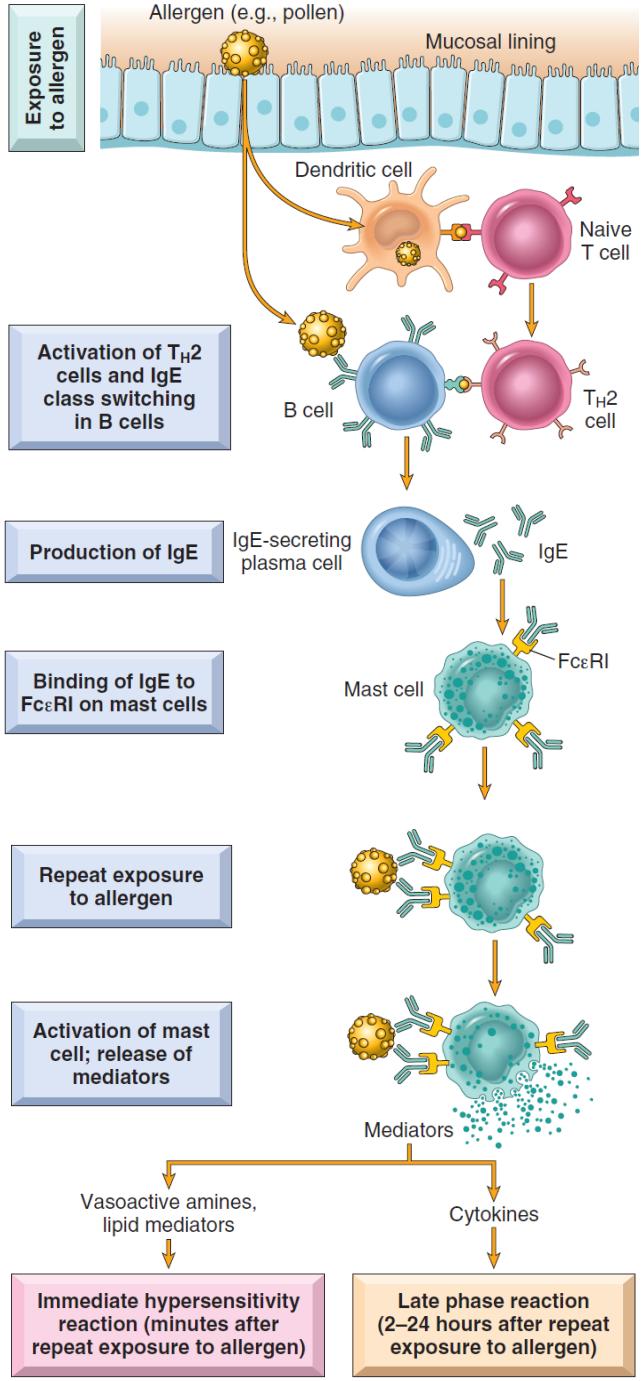
# Immediate (Type I) Hypersensitivity




Immediate hypersensitivity is a tissue reaction that occurs rapidly after the interaction of antigen with IgE antibody bound to the surface of mast cells.

**Key points:**

- Immediate (type I) sensitivity is also called an *allergic reaction.*
- induced by environmental antigens that stimulate strong TH2 responses and IgE production in genetically susceptible individuals.
- IgE coats mast cells by binding to the FcεRI receptor; reexposure to the allergen leads to cross-linking of the IgE and FcεRI, activation of mast cells.
- Principal mediators are histamine, proteases, and other granule contents; prostaglandins, leukotrienes; and cytokines.
- Mediators are responsible for the immediate vascular and smooth muscle reactions and the late-phase reaction (inflammation).
- The clinical manifestations may be local or systemic, and range from mildly annoying rhinitis to fatal anaphylaxis.



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# Antibody-Mediated Diseases (Type II Hypersensitivity)

Antibody-mediated (type II) hypersensitivity disorders are caused by antibodies directed against target antigens on the surface of cells or other tissue components.

| Disease | Target Antigen | Mechanisms of Disease | Clinicopathologic Manifestations |
|---|---|---|---|
| Autoimmune hemolytic anemia | Red blood cell membrane proteins | Opsonization and phagocytosis of red blood cells | Hemolysis, anemia |
| Autoimmune thrombocytopenic purpura | Platelet membrane proteins (GpIIb:IIIa integrin) | Opsonization and phagocytosis of platelets | Bleeding |
| Pemphigus vulgaris | Proteins in intercellular junctions of epidermal cells (desmogleins) | Antibody-mediated activation of proteases, disruption of intercellular adhesions | Skin vesicles (bullae) |
| Vasculitis caused by ANCA | Neutrophil granule proteins, presumably released from activated neutrophils | Neutrophil degranulation and inflammation | Vasculitis |
| Goodpasture syndrome | Protein in basement membranes of kidney glomeruli and lung alveoli | Complement- and Fc receptor–mediated inflammation | Nephritis, lung hemorrhage |
| Acute rheumatic fever | Streptococcal cell wall antigen; antibody cross-reacts with myocardial antigen | Inflammation, macrophage activation | Myocarditis, arthritis |
| Myasthenia gravis | Acetylcholine receptor | Antibody inhibits acetylcholine binding, down-modulates receptors | Muscle weakness, paralysis |
| Graves disease (hyperthyroidism) | TSH receptor | Antibody-mediated stimulation of TSH receptors | Hyperthyroidism |
| Pernicious anemia | Intrinsic factor of gastric parietal cells | Neutralization of intrinsic factor, decreased absorption of vitamin $B_{12}$ | Abnormal erythropoiesis, anemia |

*ANCA*, Anti-neutrophil cytoplasmic antibodies; *TSH*, thyroid-stimulating hormone.



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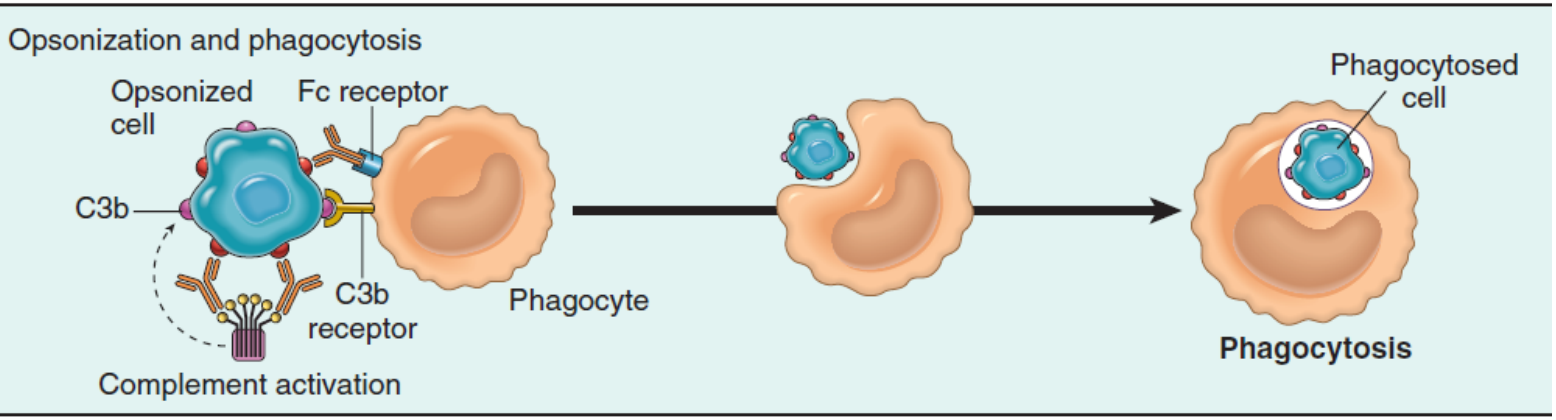
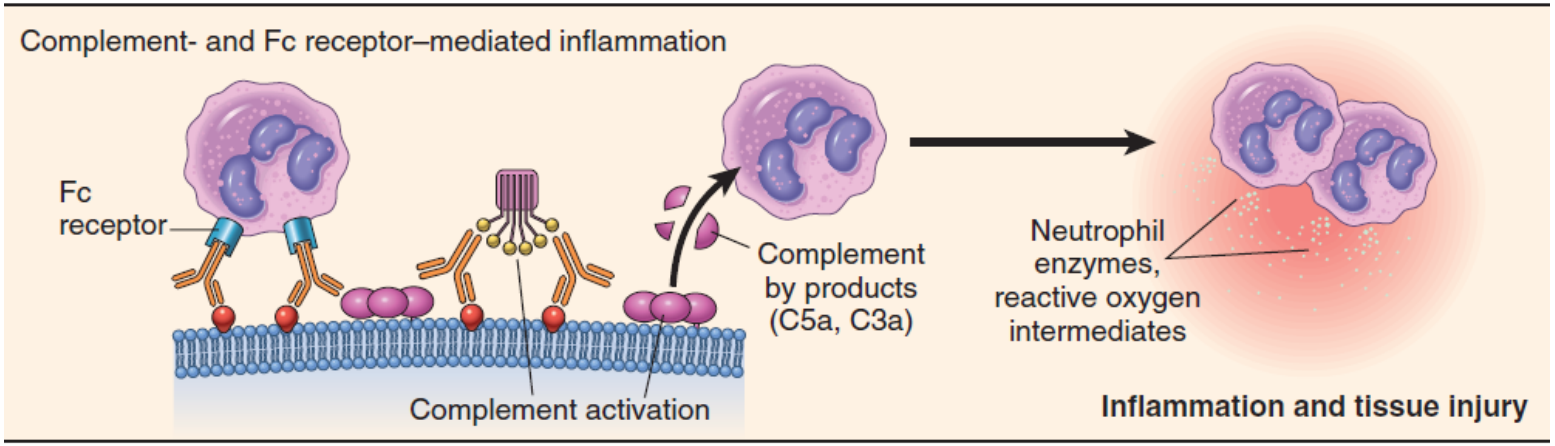
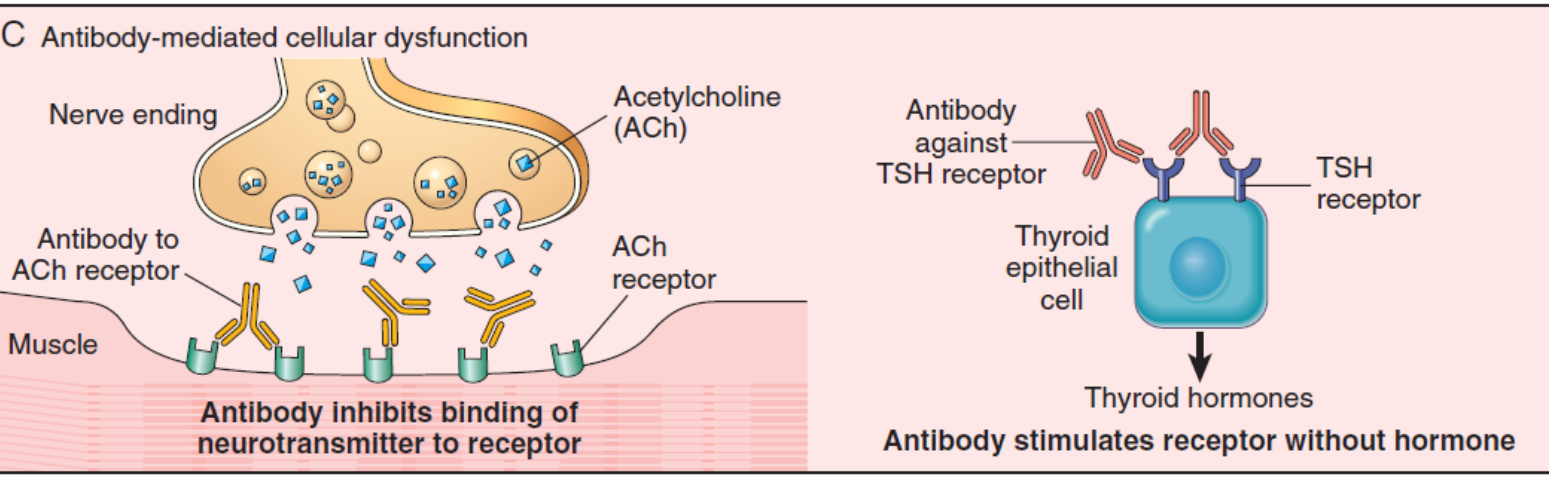



Opsonization and phagocytosis




Inflammation




Antibody-mediated cellular dysfunction



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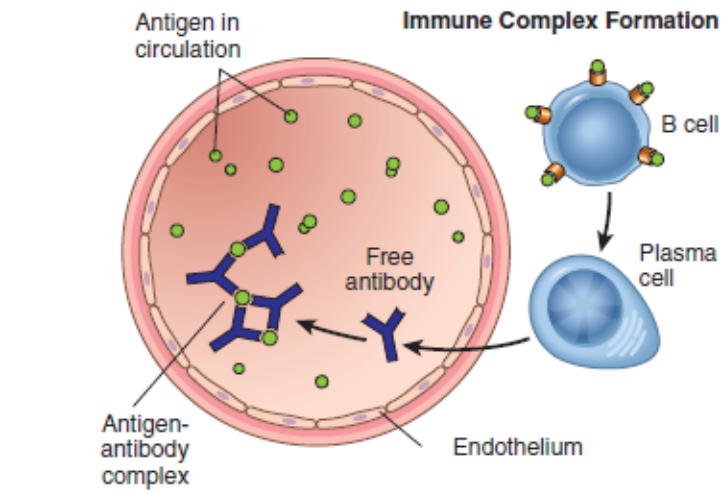
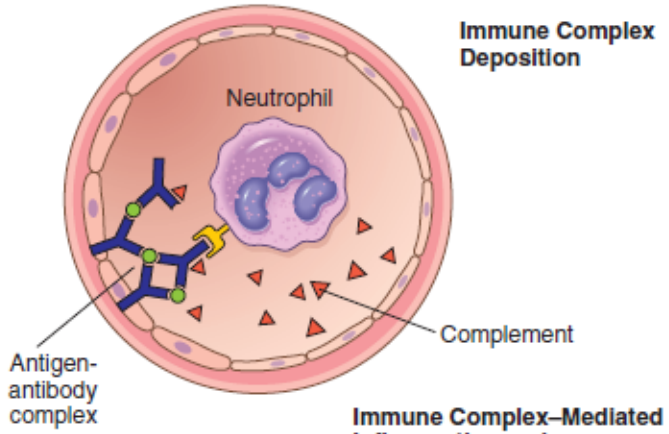
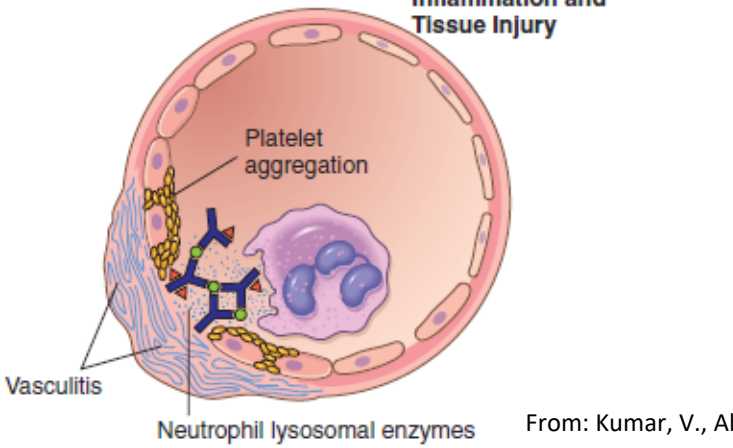
# Immune Complex–Mediated Diseases (Type III Hypersensitivity)

Antigen–antibody (immune) complexes that are formed in the circulation may deposit in blood vessels, leading to complement activation and acute inflammation.



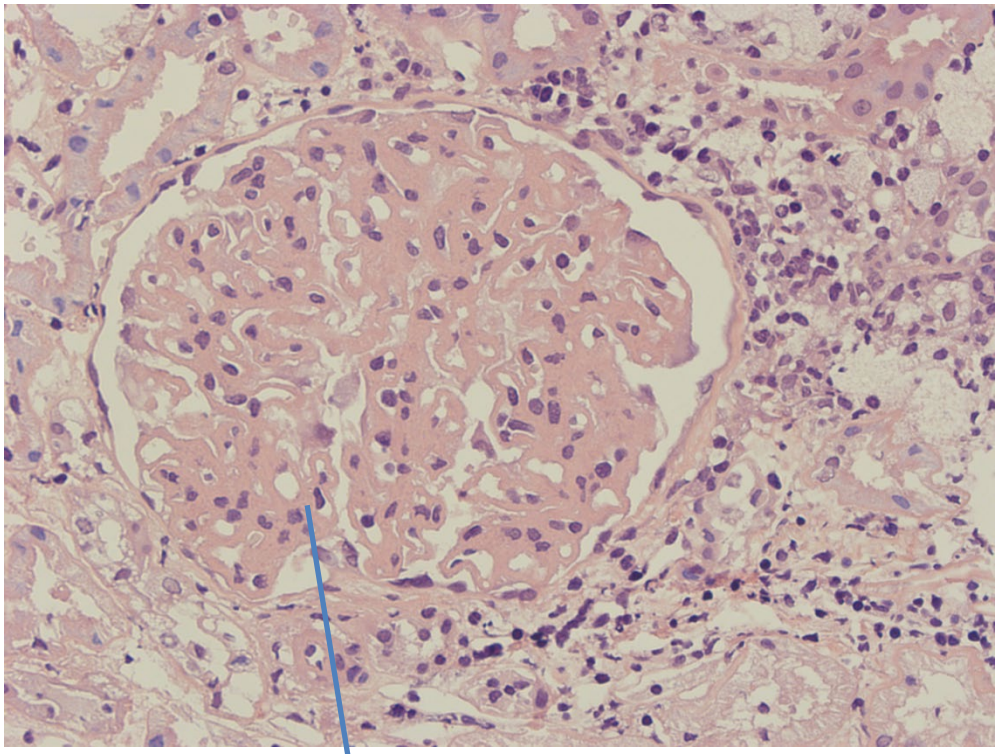




| Disease |
| --- |
| Systemic lupus erythematosus |
| Poststreptococcal glomerulonephritis |
| Polyarteritis nodosa |
| Reactive arthritis |
| Serum sickness |
| Arthus reaction (experimental) |

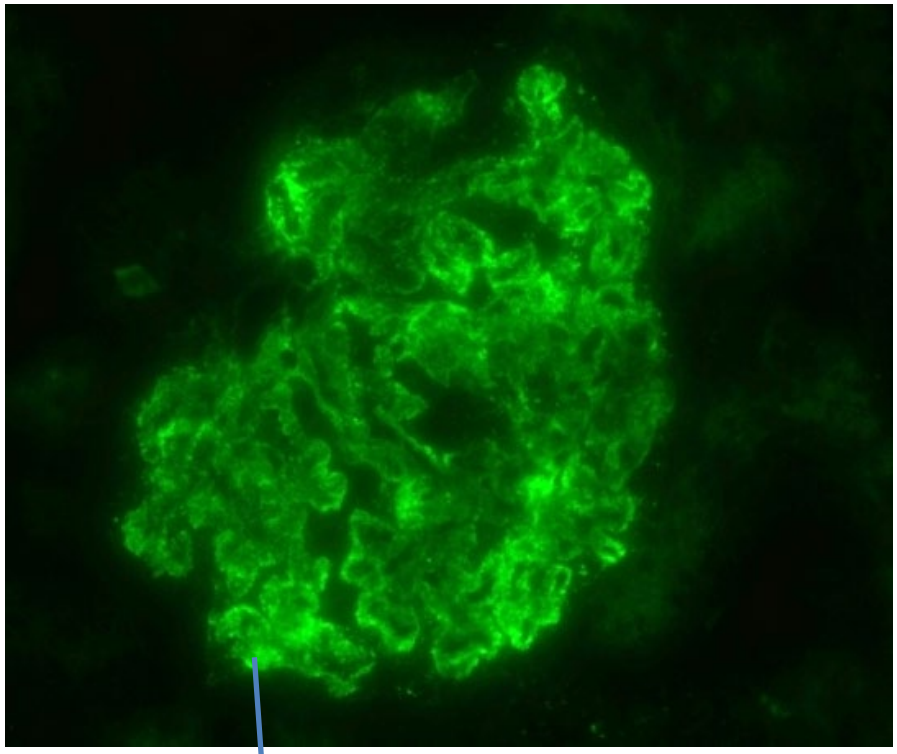


From: Kumar, V., Abbas, A. K., & Aster, J. C. (2017). Robbins Basic Pathology (10th ed.). Elsevier - Health Sciences Division.

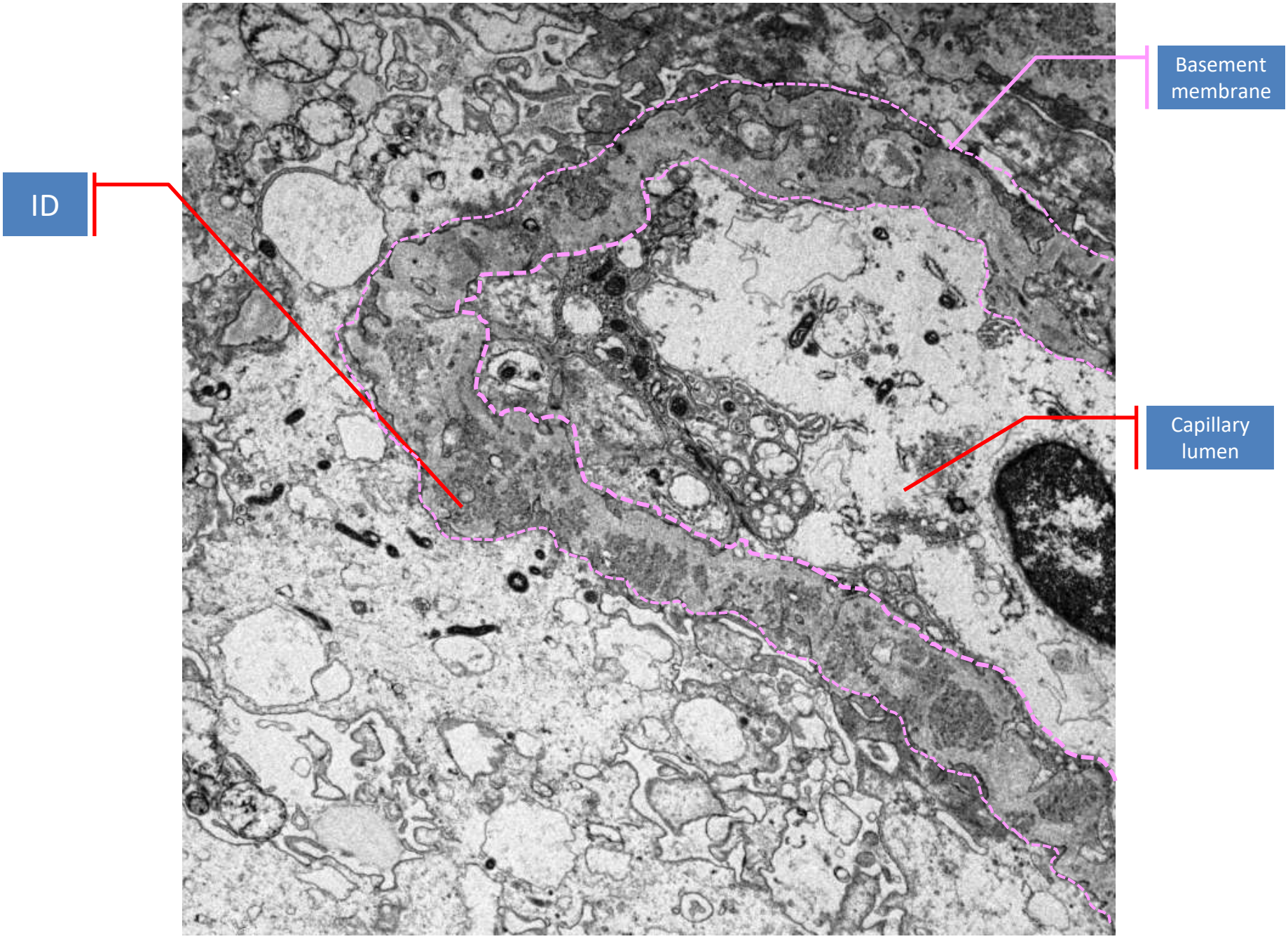
# Membranous nephropathy



thinning of the basement membranes of the glomerular capillaries



deposition of immunoglobulin G




**Electron microscopy:** in the basement membrane of the glomerular capillaries, electron-dense deposits of immunoglobulins are determined. In Xthe picture, they look like dark areas of irregular shape (denoted - ID). Magnification – x 2500.

# T Cell–Mediated Diseases (Type IV Hypersensitivity)

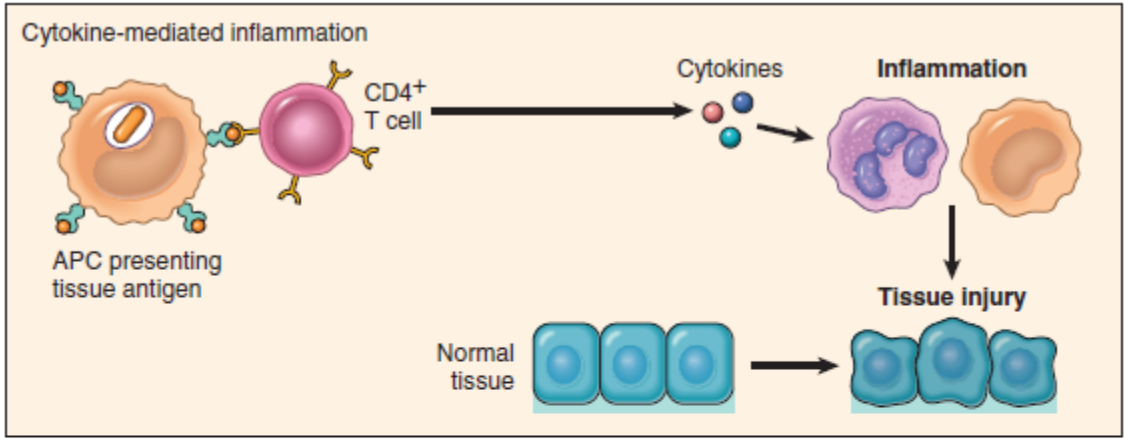
**Several autoimmune disorders, as well as pathologic reactions to environmental chemicals and persistent microbes, are now known to be caused by T cells.**

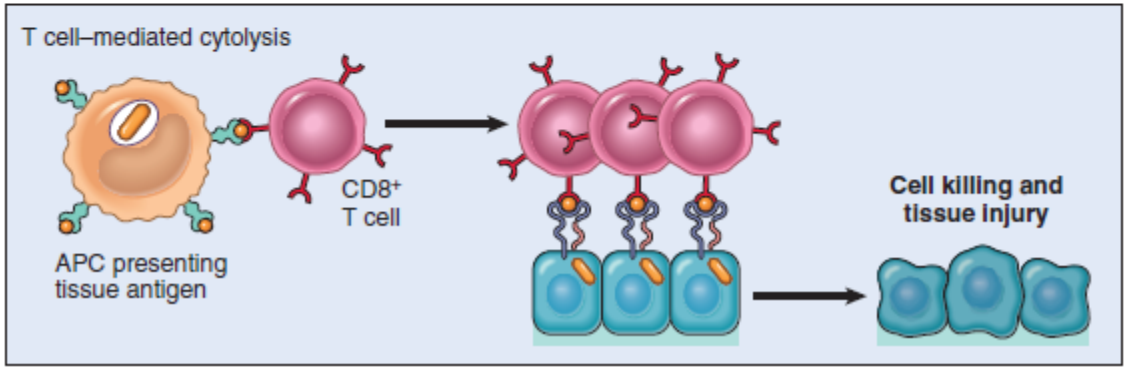
**Two types of T cell reactions:**

**(1) Cytokine-mediated** inflammation, cytokines are produced mainly by CD4+ T cells,

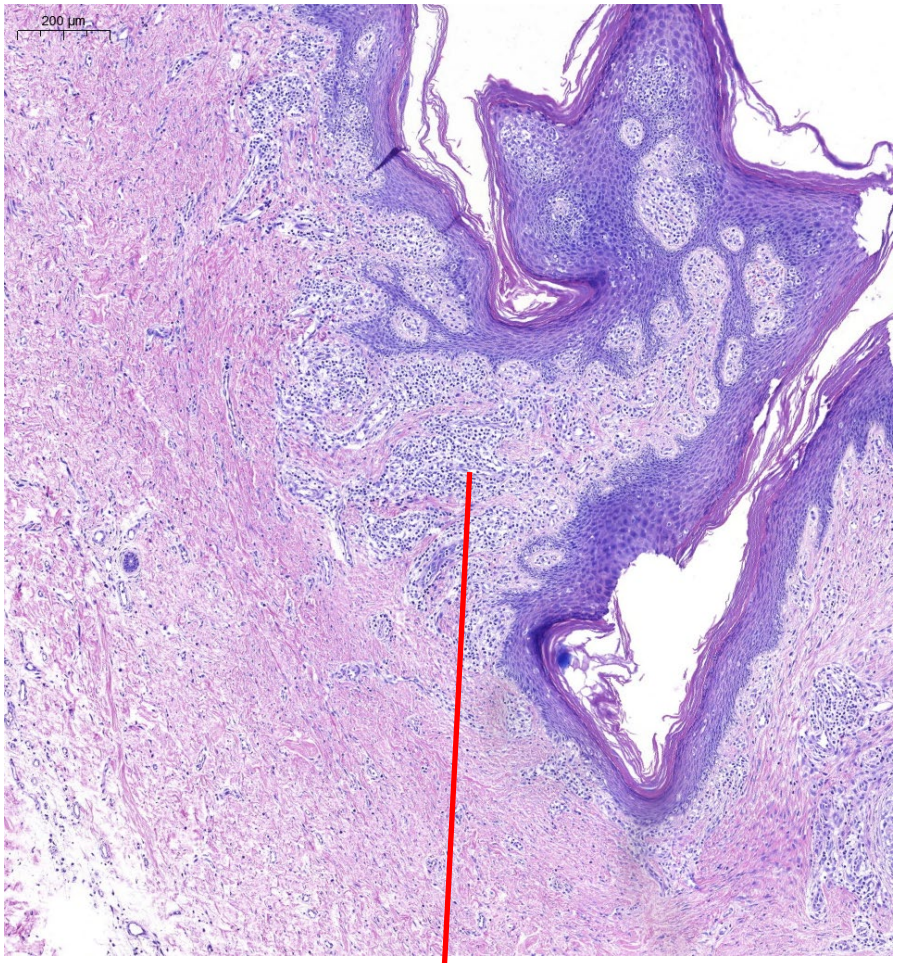
**(2) Direct cell cytotoxicity**, mediated by CD8+ T cells.

Rheumatoid arthritis
Multiple sclerosis
Type 1 diabetes mellitus
Inflammatory bowel disease
Psoriasis
Contact sensitivity

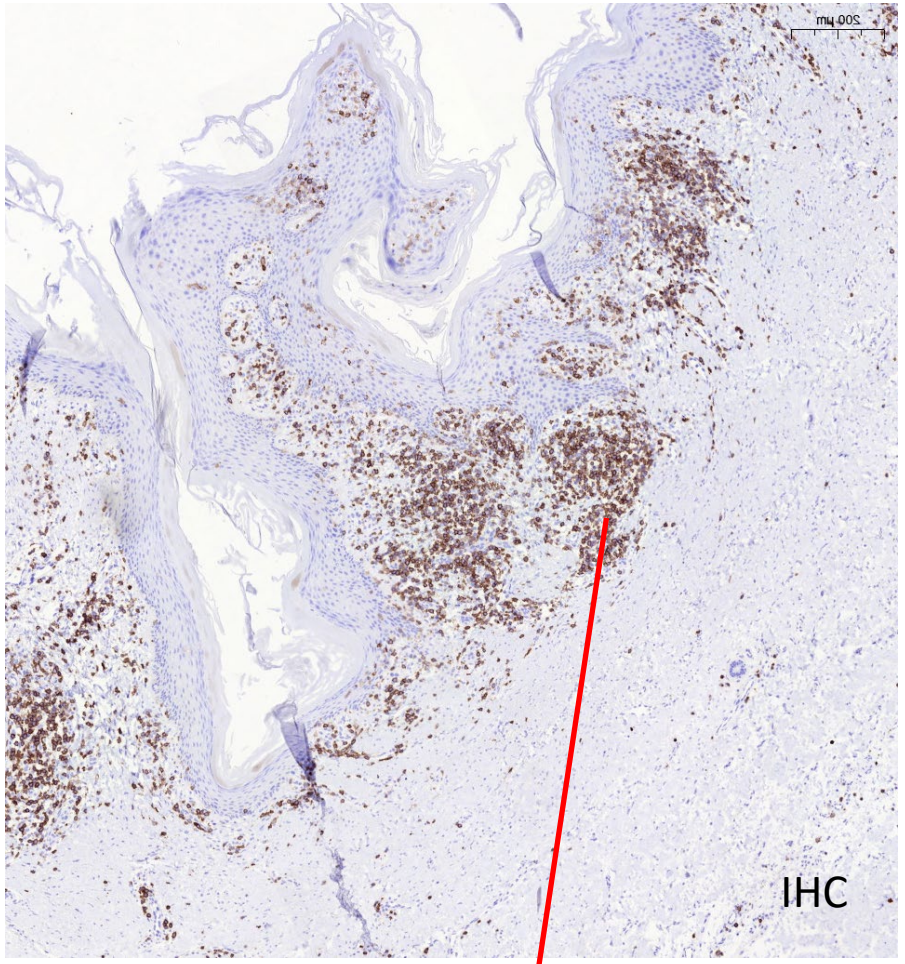


Example of delayed hypersensitivity reaction in the skin with accumulation of mononuclear inflammatory cells (lymphocytes and macrophages), with associated dermal edema and fibrin deposition. Immunoperoxidase staining (IHC) reveals a predominantly perivascular cellular infiltrate that marks positively with anti-CD4 antibodies




Lymphocytes



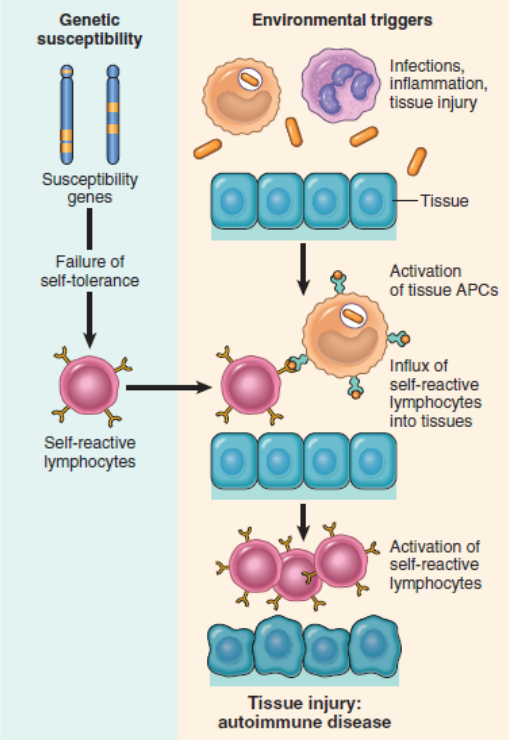

CD4+ T-cells

# AUTOIMMUNE DISEASES

- *Autoimmunity refers to immune reactions against self* ("auto") antigens.

Autoimmune diseases may be ***organ-specific****, in which* the immune responses are directed against one particular organ or cell type and result in localized tissue damage, or ***systemic****, characterized by lesions in many organs*

| Organ-Specific | Systemic |
|---|---|
| **Diseases Mediated by Antibodies** | |
| Autoimmune hemolytic anemia | Systemic lupus erythematosus |
| Autoimmune thrombocytopenia | |
| Autoimmune atrophic gastritis of pernicious anemia | |
| Myasthenia gravis | |
| Graves disease | |
| Goodpasture syndrome | |
| **Diseases Mediated by T Cells*** | |
| Type I diabetes mellitus | Rheumatoid arthritis |
| Multiple sclerosis | Systemic sclerosis (scleroderma)† Sjögren syndrome† |
| **Diseases Postulated to Be Autoimmune** | |
| Inflammatory bowel diseases (Crohn disease, ulcerative colitis)‡ | |
| Primary biliary cirrhosis† | Polyarteritis nodosa† |
| Autoimmune (chronic active) hepatitis | Inflammatory myopathies† |




Autoimmunity results from multiple factors, including susceptibility genes that may interfere with self-tolerance and environmental triggers (such as infections, tissue injury, and inflammation) that promote lymphocyte entry into tissues, activation of self-reactive lymphocytes, and tissue damage.

# IMMUNODEFICIENCY SYNDROMES

Immune deficiencies can be divided into ***primary*** *(or congenital) immunodeficiency disorders, which are genetically* determined, and ***secondary*** *(or acquired) immunodeficiencies,* which may arise as complications of cancers, infections, malnutrition, or side effects of immunosupression, irradiation, or chemotherapy for cancer and other diseases.

**Immunodeficiencies are manifested clinically by increased infections, which may be newly acquired or reactivation of latent infections.**

# Primary (Inherited) Immunodeficiencies

**Primary immunodeficiency diseases are inherited genetic disorders that impair mechanisms of innate immunity or the humoral and/or cellular arms of adaptive immunity.**

| Disease | Defect |
|---|---|
| **Defects in Leukocyte Function** | |
| Leukocyte adhesion deficiency I | Defective leukocyte adhesion because of mutations in the β chain of CD11/CD18 integrins |
| Leukocyte adhesion deficiency 2 | Defective leukocyte adhesion because of mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectins) |
| Chédiak-Higashi syndrome | Decreased leukocyte functions because of mutations affecting protein involved in lysosomal membrane traffic |
| Chronic granulomatous disease | Decreased oxidative burst |
| X-linked | Phagocyte oxidase (membrane component) |
| Autosomal recessive | Phagocyte oxidase (cytoplasmic components) |
| Myeloperoxidase deficiency | Decreased microbial killing because of defective MPO-$H_2O_2$ system |
| **Defects in the Complement System** | |
| C2, C4 deficiency | Defective classical pathway activation; results in reduced resistance to infection and reduced clearance of immune complexes |
| C3 deficiency | Defects in all complement functions |
| Deficiency of complement regulatory proteins | Excessive complement activation; clinical syndromes include angioedema, paroxysmal hemoglobinuria, and others |

Modified in part from Gallin JI: Disorders of phagocytic cells. In Gallin JI, et al, editors: *Inflammation: basic principles and clinical correlates*, ed 2, New York, 1992, Raven Press, pp 860–861.

There is no specific morphological picture in these diseases.

Confirmation of the diagnosis requires genetic testing.

# Secondary (Acquired) Immunodeficiencies

- **Secondary (acquired) immune deficiencies may be encountered in individuals with cancer, diabetes and other metabolic diseases, malnutrition, chronic infection, and in patients receiving chemotherapy or radiation therapy for cancer, or immunosuppressive drugs to prevent graft rejection or to treat autoimmune diseases.**

| Cause | Mechanism |
|---|---|
| Human immunodeficiency virus infection | Depletion of CD4+ helper T cells |
| Irradiation and chemotherapy treatments for cancer | Decreased bone marrow precursors for all leukocytes |
| Involvement of bone marrow by cancers (metastases, leukemias) | Reduced leukocyte development due to displacement of progenitors |
| Protein-calorie malnutrition | Metabolic derangements inhibit lymphocyte maturation and function |
| Removal of spleen | Decreased phagocytosis of microbes |

# AIDS 

**Definition:** AIDS is a disease caused by the retrovirus human immunodeficiency virus (HIV) and is characterized by profound immunosuppression that leads to opportunistic infections, secondary neoplasms, and neurologic manifestations.

Every day there are 4000 new HIV infections (adults and children) **2020**

- **60% are in sub-Saharan Africa**
- **10% are among children under 15 years of age**
- **90% are among adults aged 15 years and older, of whom:**
  - **51% are among women**
  - **31% are among young people (15–24)**
  - **20% are among young women (15–24)**

Source: UNAIDS 2021 epidemiological estimates.

# Regional HIV and AIDS statistics and features | 2020

| | Adults and children living with HIV | Adults and children newly infected with HIV | Adult and child deaths due to AIDS |
|---|---|---|---|
| **Eastern and southern Africa** | 20.6 million [16.8 million–24.4 million] | 670 000 [470 000–930 000] | 310 000 [220 000–470 000] |
| **Western and central Africa** | 4.7 million [3.9 million–5.8 million] | 200 000 [130 000–330 000] | 150 000 [100 000–210 000] |
| **Middle East and North Africa** | 230 000 [190 000–310 000] | 16 000 [12 000–28 000] | 7900 [6000–13 000] |
| **Asia and the Pacific** | 5.8 million [4.3 million–7.0 million] | 240 000 [170 000–310 000] | 130 000 [87 000–200 000] |
| **Latin America** | 2.1 million [1.4 million–2.7 million] | 100 000 [66 000–150 000] | 31 000 [20 000–46 000] |
| **Caribbean** | 330 000 [280 000–390 000] | 13 000 [8700–18 000] | 6000 [4300–8500] |
| **Eastern Europe and central Asia** | 1.6 million [1.5 million–1.8 million] | 140 000 [120 000–160 000] | 35 000 [28 000–43 000] |
| **Western and central Europe and North America** | 2.2 million [1.9 million–2.6 million] | 67 000 [53 000–81 000] | 13 000 [9200–17 000] |
| **GLOBAL** | 37.7 million [30.2 million–45.1 million] | 1.5 million [1.0 million–2.0 million] | 680 000 [480 000–1.0 million] |

The ranges around the estimates in this table define the boundaries within which the actual numbers lie, based on the best available information.

Source: UNAIDS 2021 epidemiological estimates.

**Transmission of HIV occurs under conditions that facilitate exchange of blood or body fluids containing the virus or virus-infected cells**

***Sexual transmission*** *is the dominant mode of infection* worldwide, accounting for more than 75% of all cases of HIV transmission. Most infected individuals are men who have sex with men.

**Viral spread occurs in two ways:**

(1) direct inoculation into the blood vessels breached by trauma and
(2) infection of DCs or CD4+ cells within the mucosa. Sexual transmission of HIV is enhanced by coexisting sexually transmitted diseases, especially those associated with genital ulceration.

***Parenteral transmission*** *of HIV has occurred in intravenous* drug abusers.

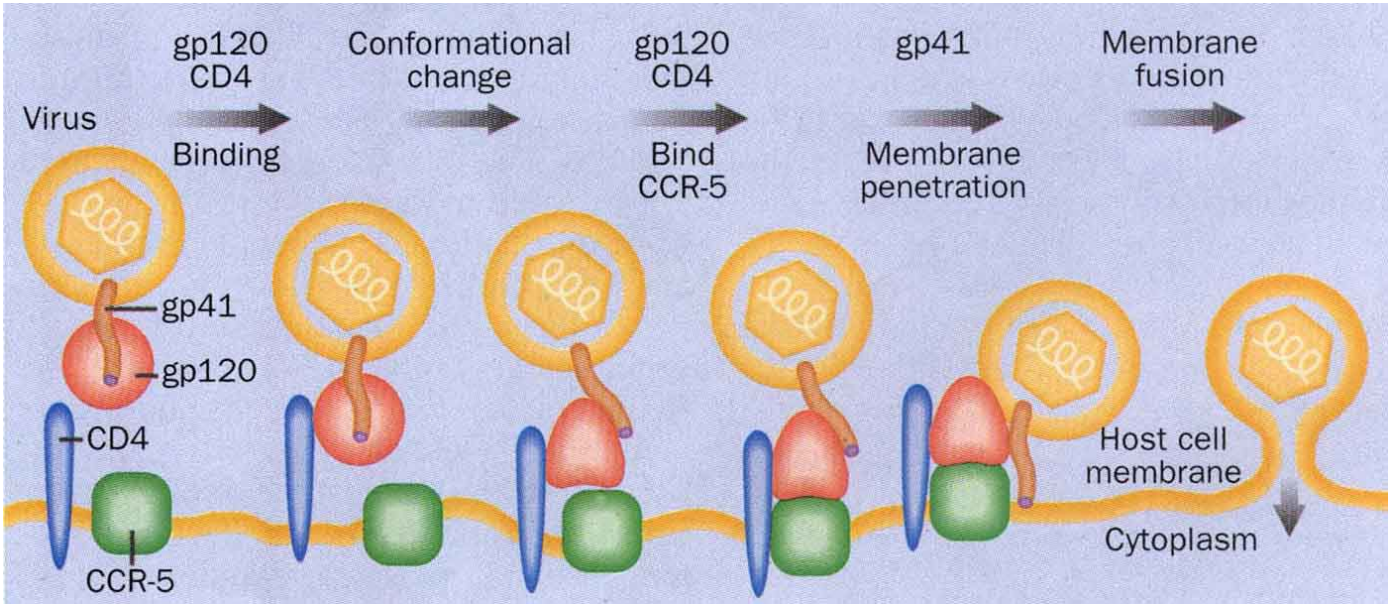
Transmission of HIV by transfusion of blood or blood products, such as lyophilized factor VIII and factor IX concentrates, has been virtually eliminated by public health measures, including screening of donated blood and plasma for antibody to HIV

***Mother-to-infant transmission*** *is the* major cause of pediatric AIDS. Infected mothers can transmit the infection to their offspring by three routes:

(1) in utero by transplacental spread;
(2) during delivery through an infected birth canal;
(3) after birth by ingestion of breast milk.

Fortunately, anti-retroviral therapy given to infected pregnant women has virtually eliminated mother-to-child transmission

**The life cycle of HIV consists of infection of cells, integration of the provirus into the host cell genome, activation of viral replication, and production and release of infectious virus.**




Wain-Hobson S. HIV. One on one meets two. Nature. 1996 Nov 14;384(6605):117-8. doi: 10.1038/384117a0. PMID: 8906782.

HIV infects cells by using the CD4 molecule as a receptor and various chemokine receptors as coreceptors.

Once internalized, the RNA genome of the virus undergoes reverse transcription, leading to the synthesis of doublestranded complementary DNA.

Completion of the viral life cycle in latently infected cells occurs only after cell activation, and in the case of most CD4+ T cells, virus activation results in death of the infected cells.

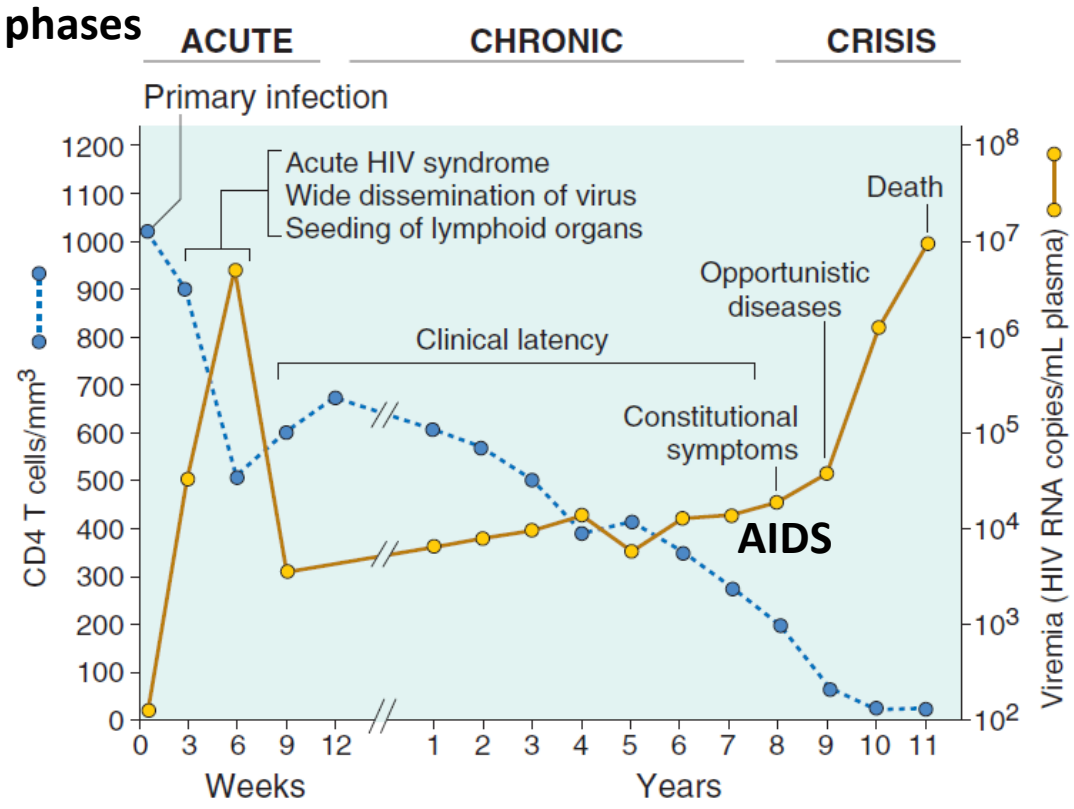
Loss of CD4+ T cells is mainly caused by the direct cytopathic effects of the replicating virus.

**Low-level chronic or latent infection of T cells is an important feature of HIV infection.**

# *Pathogenesis of Central Nervous System Involvement*

- **Macrophages and microglia, cells in the** CNS that belong to the macrophage lineage, are the predominant cell types in the brain that are infected with HIV.
- HIV is carried into the brain by infected monocytes
- neurologic deficit is caused indirectly by viral products and by soluble factors produced by infected microglia, such as the cytokines IL-1, TNF, and IL-6

# Clinical course of HIV infection




During the early period after primary infection, there is dissemination of virus, development of an immune response to HIV, and often an acute viral syndrome. During the period of clinical latency, viral replication continues and the CD4+ T-cell count gradually decreases, until it reaches a critical level below which there is a substantial risk for AIDS-associated diseases.

# Opportunistic Infections

- **Opportunistic infections account for the majority of deaths in untreated patients with AIDS.**

***Pneumocystic pneumonia - 15-30%***

***Candidiasis*** -
-*is the most common fungal infection in* patients with AIDS, and infection of the oral cavity, vagina, and esophagus are its most common clinical manifestations.

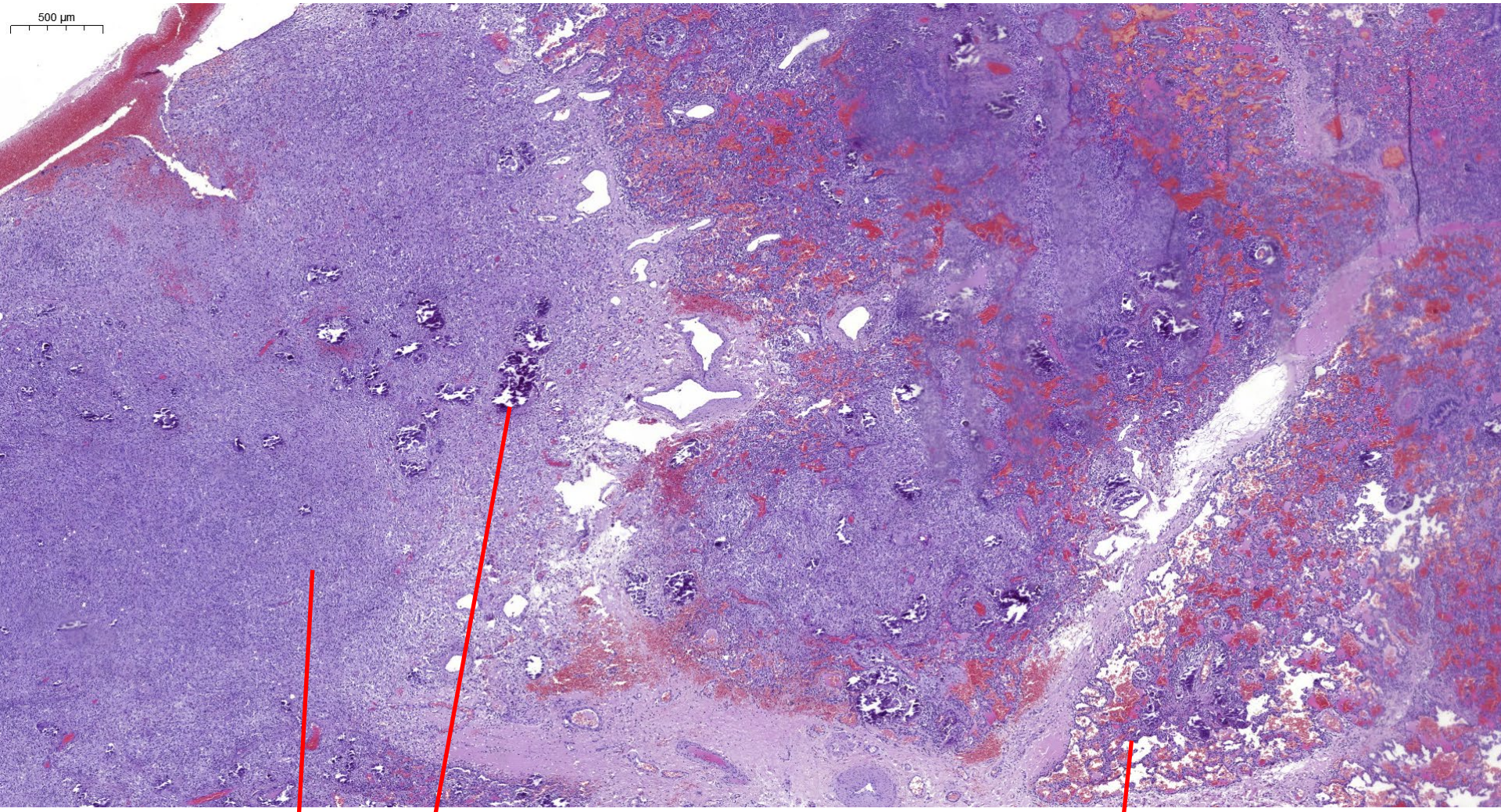
***Cytomegalovirus*** *(CMV) may cause disseminated disease,* but more commonly affects the eye and gastrointestinal tract. Chorioretinitis - 25%

Disseminated bacterial infection with ***nontuberculous, or atypical, mycobacteria*** *(mainly Mycobacterium avium, intracellulare)* also occurs late, in the setting of severe immunosuppression.

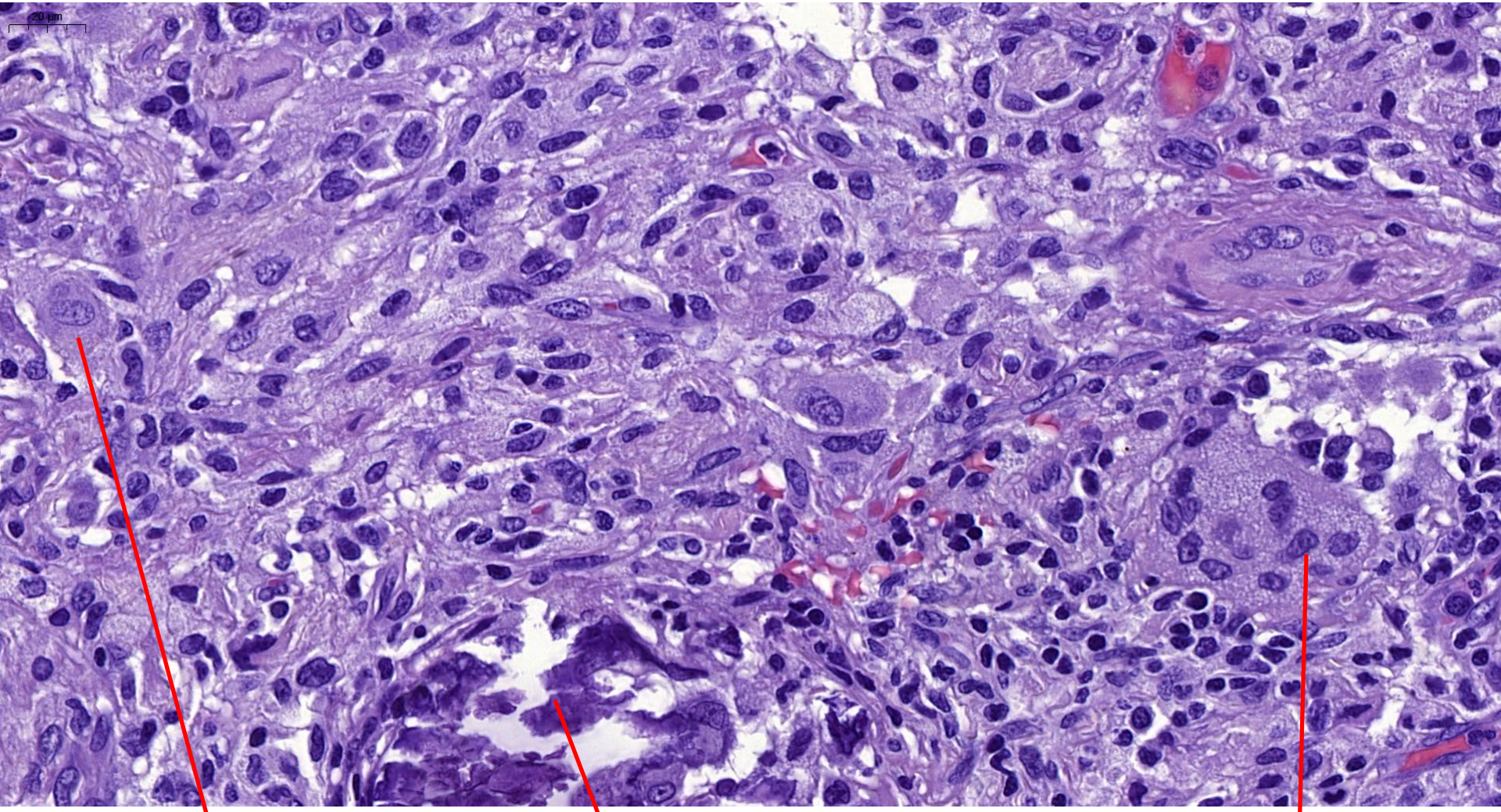
***Cryptococcosis*** *occurs in about 10% of AIDS patients. As* in other settings with immunosuppression, meningitis is the major clinical manifestation of cryptococcosis.

***Toxoplasma gondii****, another frequent invader of the CNS* in AIDS, causes encephalitis and is responsible for 50% of all mass lesions in the CNS.

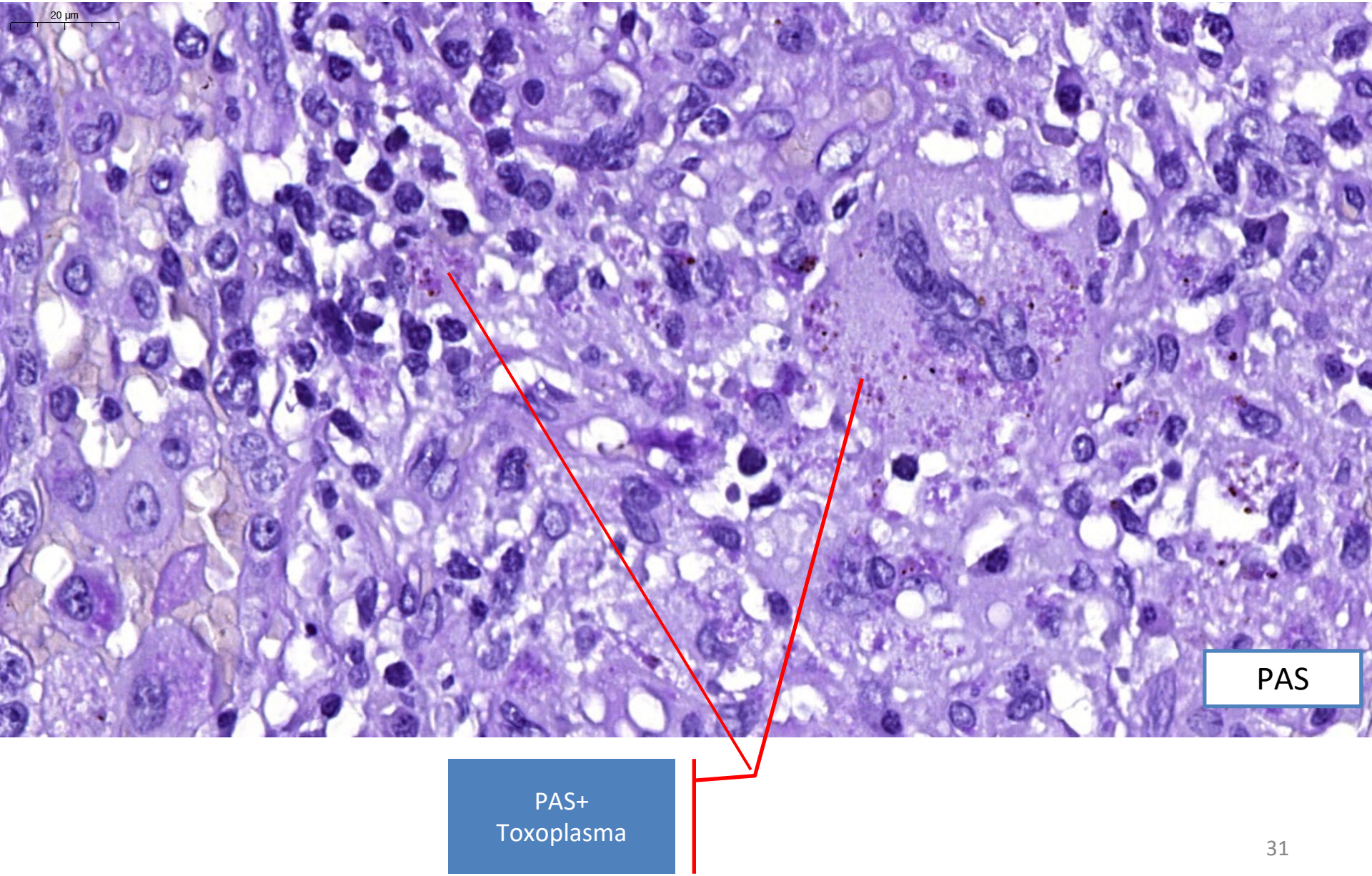
# Lung toxoplasmosis in AIDS



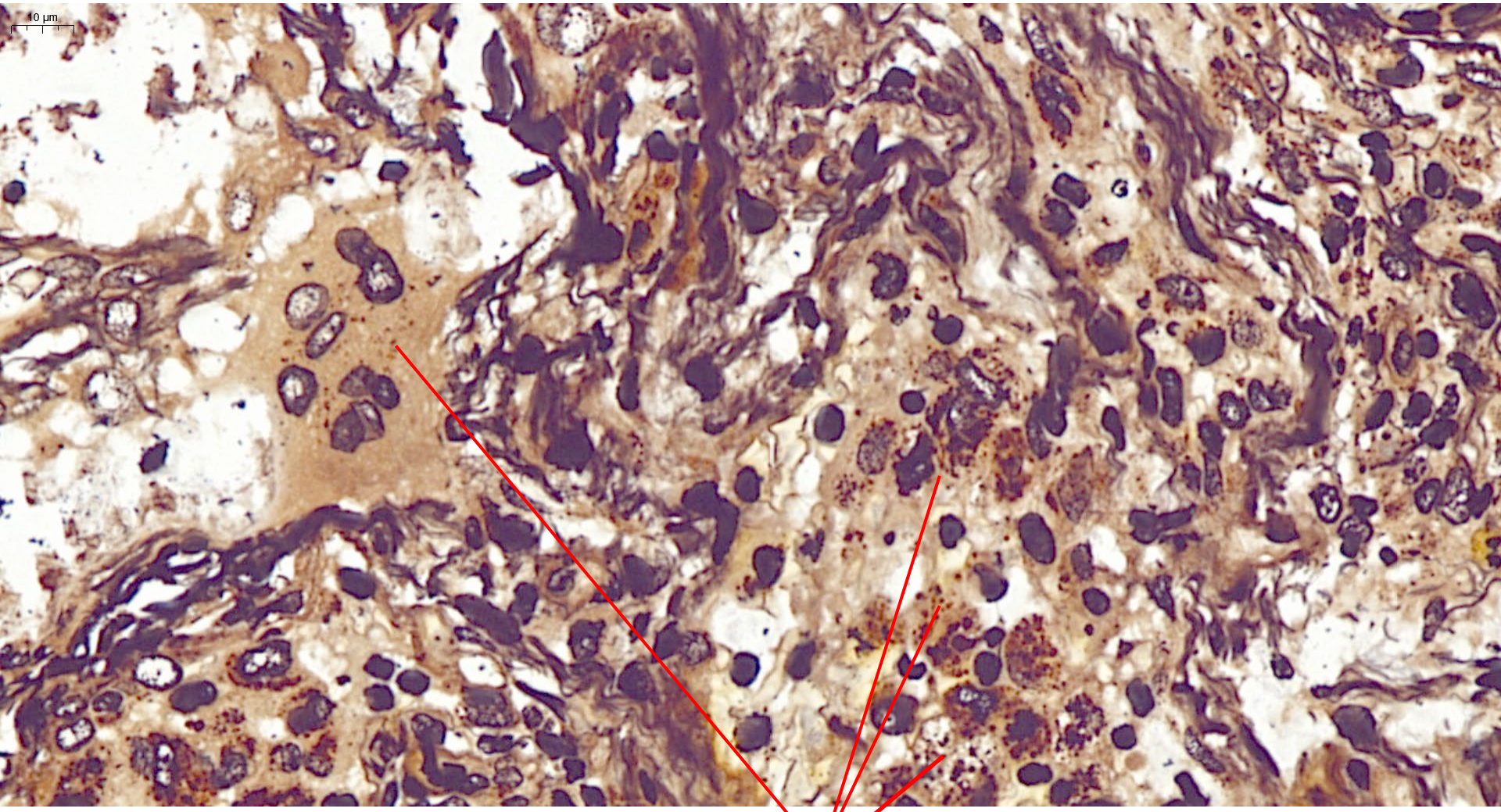
# Lung toxoplasmosis in AIDS



# Lung toxoplasmosis in AIDS



# Lung toxoplasmosis in AIDS



# Tumors and AIDS

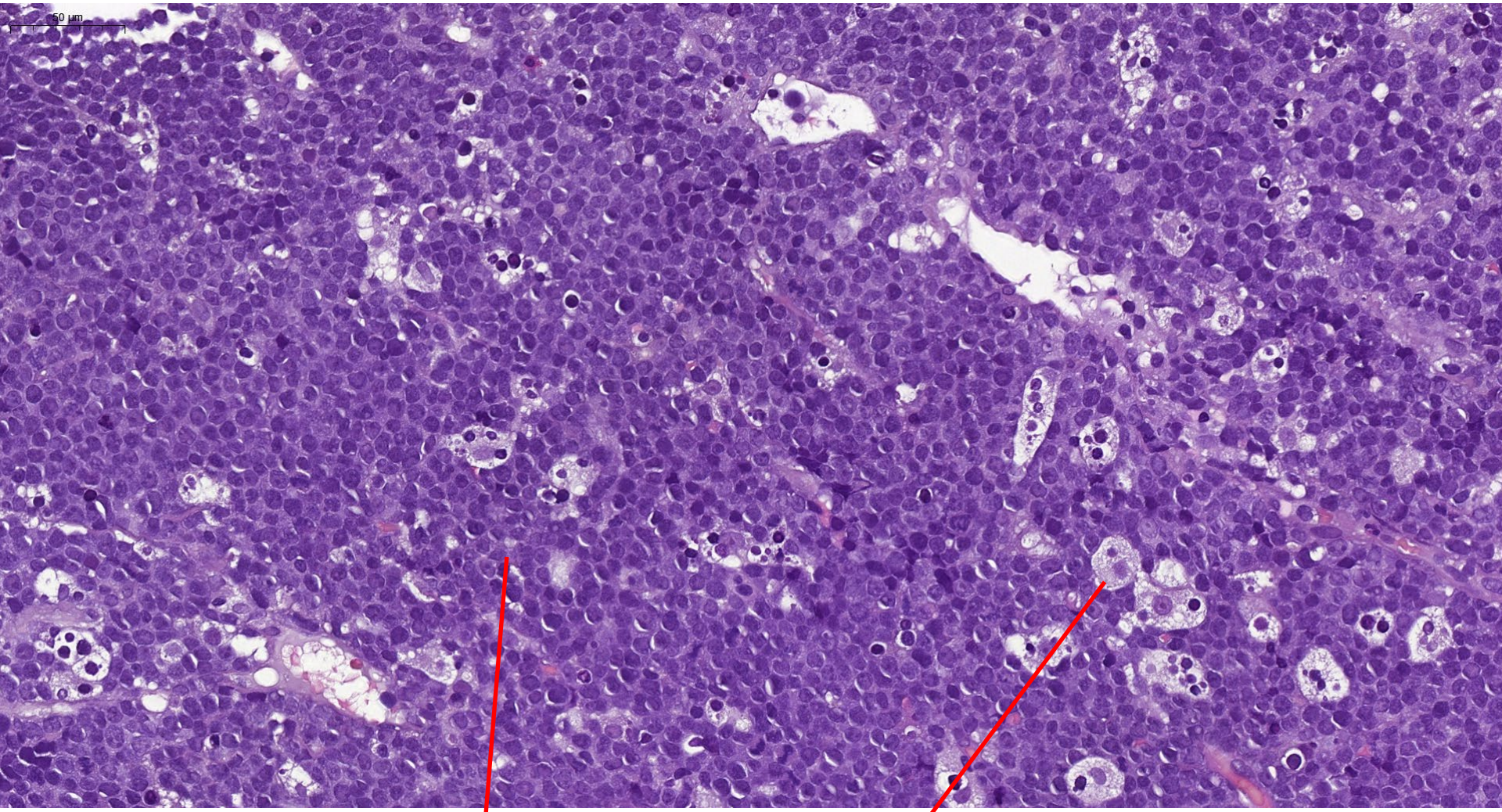
- **Patients with AIDS have a high incidence of certain tumors, notably Kaposi sarcoma, B cell lymphoma, cervical cancer in women, and anal cancer in men.**

Kaposi sarcoma herpesvirus – type 8 (HHV8)

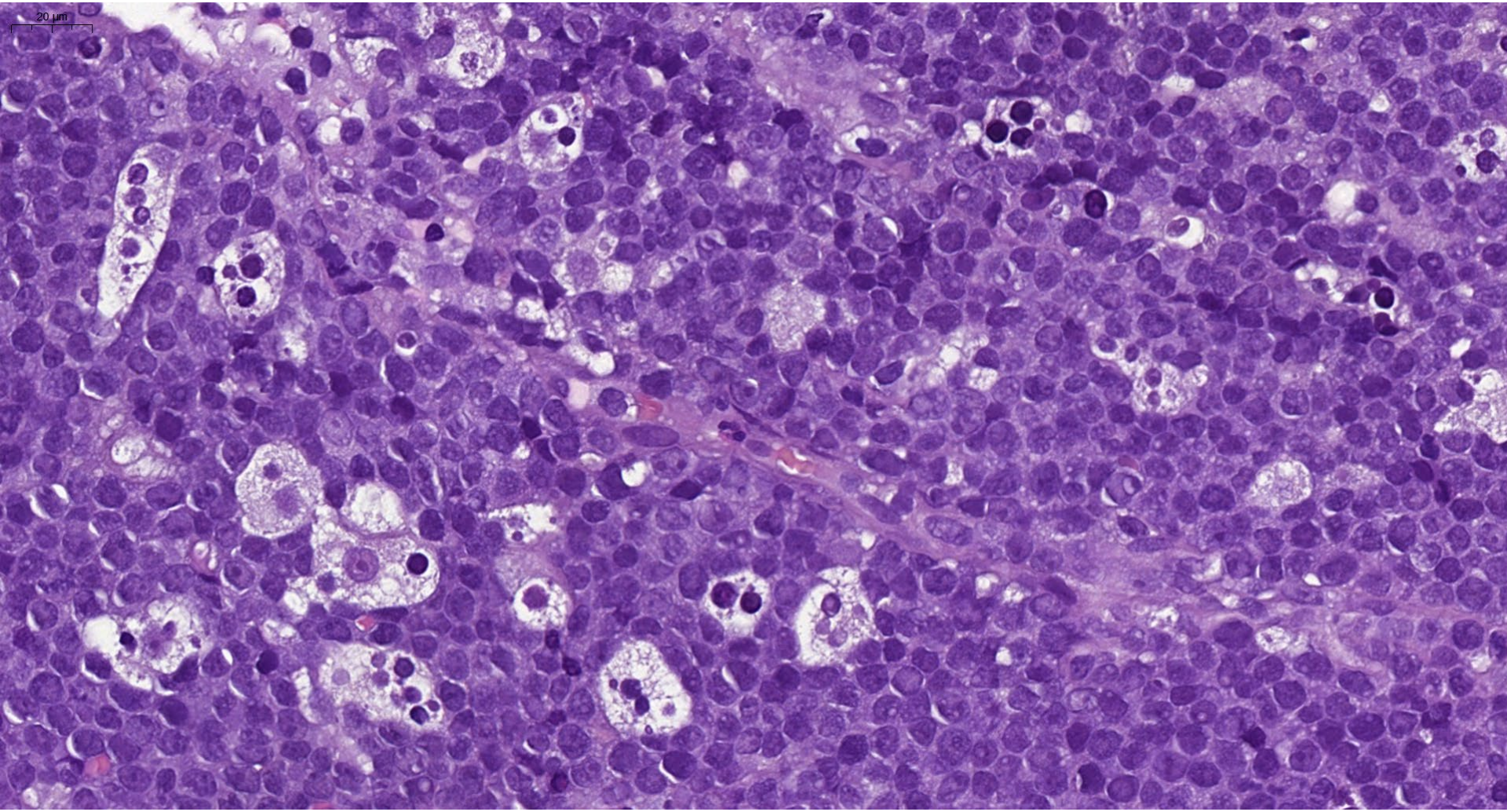
Epstein Barr Virus (B cell lymphoma)

Papillomavirus (HPV) - (cervical and anal carcinoma)

# Burkitt lymphoma



# "starry sky"



# AMYLOIDOSIS

**Amyloidosis is a condition associated with a number of disorders in which extracellular deposits of fibrillar proteins responsible for tissue damage and functional compromise.**

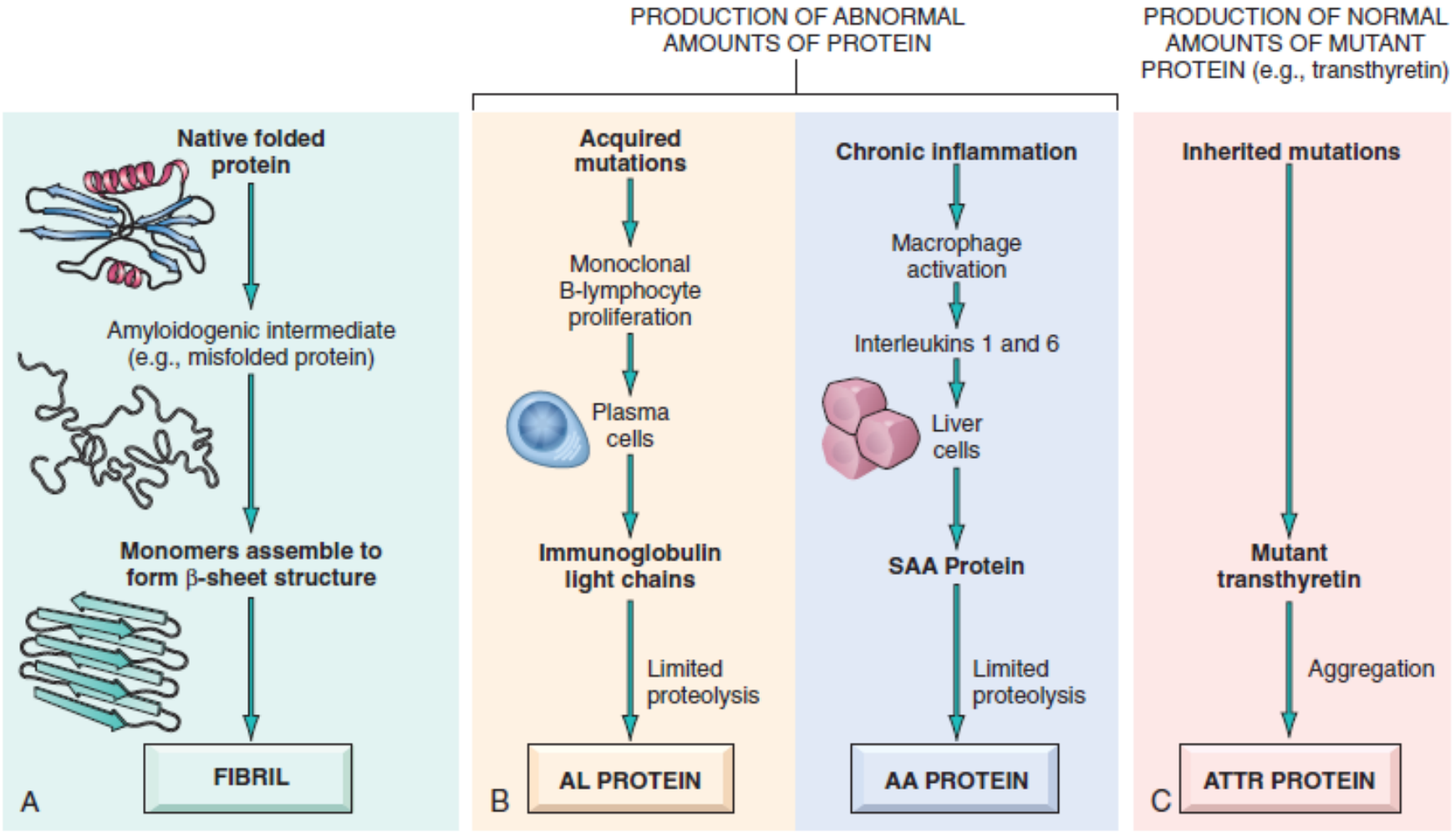
- Although amyloid always has the same morphologic appearance, it is biochemically heterogeneous. In fact, at least 30 different proteins can aggregate to form fibrils with the appearance of amyloid.

• ***AL (amyloid light chain) amyloid*** *is made up of complete* immunoglobulin light chains, the amino-terminal fragments of light chains, or both.

• ***AA (amyloid-associated) amyloid*** *is composed of an 8500-* dalton protein derived by proteolysis from a larger precursor in the blood called SAA (serum amyloidassociated) protein, which is synthesized in the liver.

• ***β-amyloid protein (Aβ)*** *is a 4000-dalton peptide that is* derived by proteolysis from a much larger transmembrane glycoprotein, called *amyloid precursor protein.*

# Classification of Amyloidosis and Mechanisms of Amyloid Formation




From: Kumar, V., Abbas, A. K., & Aster, J. C. (2017). Robbins Basic Pathology (10th ed.). Elsevier - Health Sciences Division.

# Clinicopathologic Category

| Clinicopathologic Category | Associated Diseases | Major Fibril Protein | Chemically Related Precursor Protein |
|---|---|---|---|
| **Systemic (Generalized) Amyloidosis** | | | |
| Plasma cell proliferations with amyloidosis (primary amyloidosis) | Multiple myeloma and other monoclonal plasma cell proliferations | AL | Immunoglobulin light chains, chiefly λ type |
| Reactive systemic amyloidosis (secondary amyloidosis) | Chronic inflammatory conditions | AA | SAA |
| Hemodialysis-associated amyloidosis | Chronic renal failure | $A\beta_2m$ | $\beta_2$-microglobulin |
| **Hereditary Amyloidosis** | | | |
| Familial Mediterranean fever | | AA | SAA |
| Familial amyloidotic neuropathies (several types) | | ATTR | Transthyretin |
| Systemic senile amyloidosis | | ATTR | Transthyretin |
| **Localized Amyloidosis** | | | |
| Senile cerebral | Alzheimer disease | Aβ | APP |
| Endocrine | Type 2 diabetes | | |
| Medullary carcinoma of thyroid | | A Cal | Calcitonin |
| Islets of Langerhans | | AIAPP | Islet amyloid peptide |
| Isolated atrial amyloidosis | | AANF | Atrial natriuretic factor |



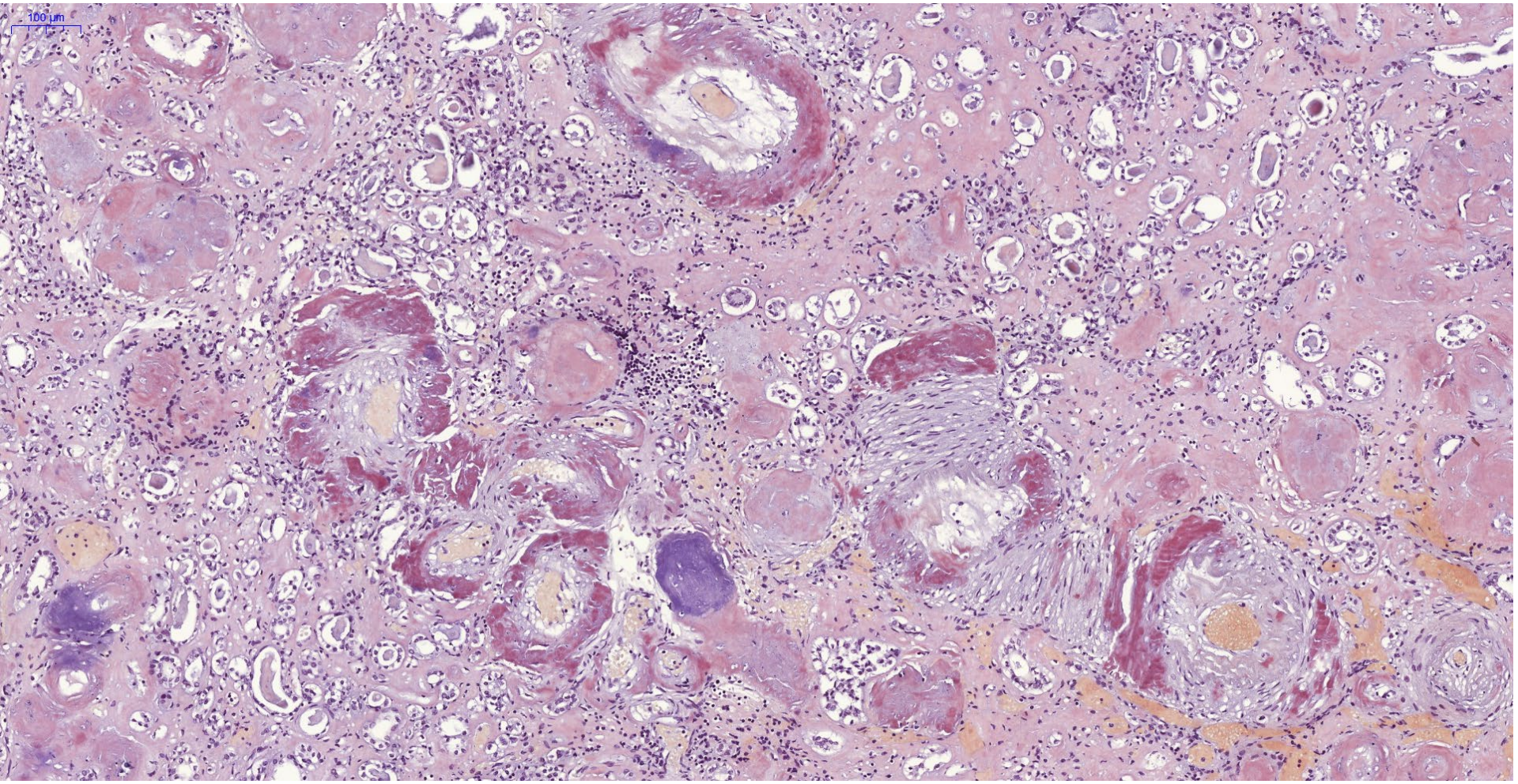
From: Kumar, V., Abbas, A. K., & Aster, J. C. (2017). Robbins Basic Pathology (10th ed.). Elsevier - Health Sciences Division.

# MORPHOLOGY

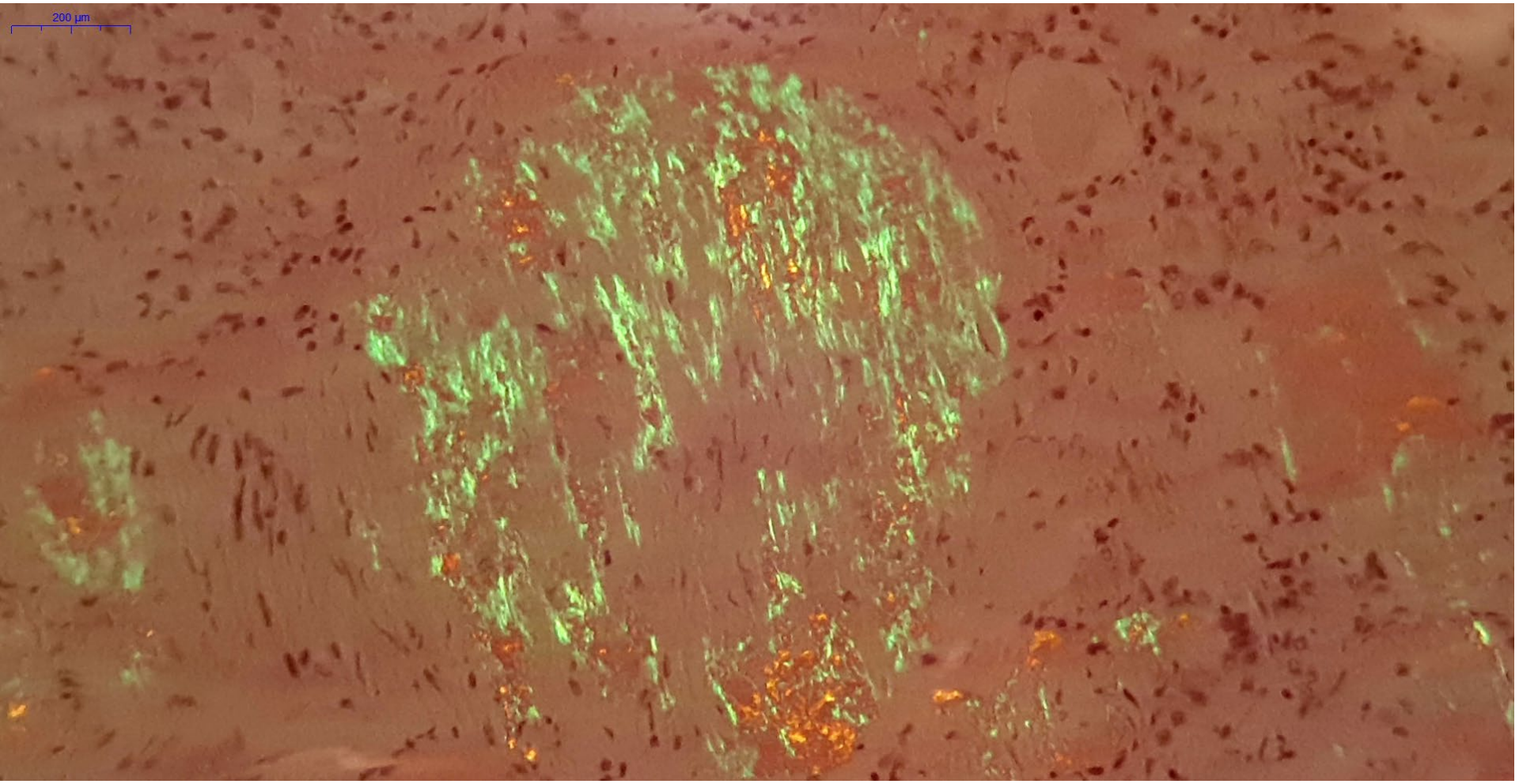
**Macroscopically**: the organ is frequently enlarged, and the tissue appears gray and has a waxy, firm consistency.

**Histologically** **always extracellular** and begins between cells, often closely adjacent to basement membranes. In the form associated with plasma cell proliferation, perivascular and vascular deposits are common.

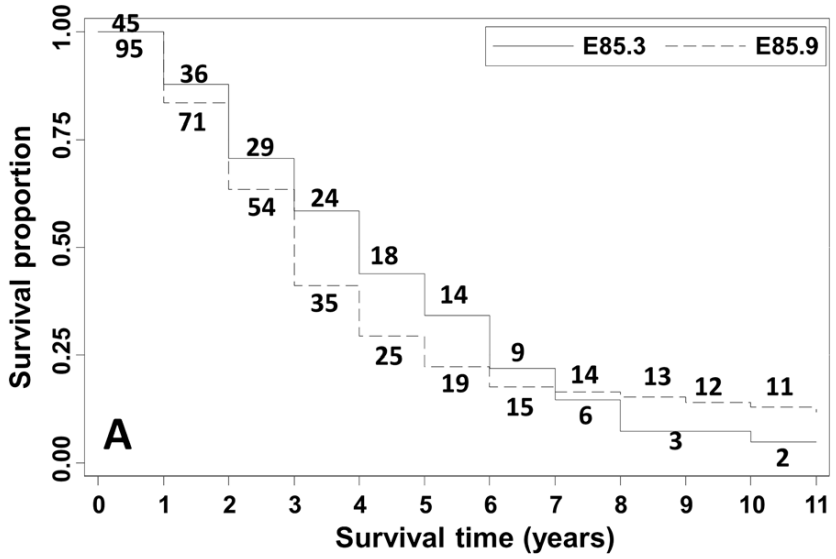
# The diagnosis of amyloidosis is based on histopathology

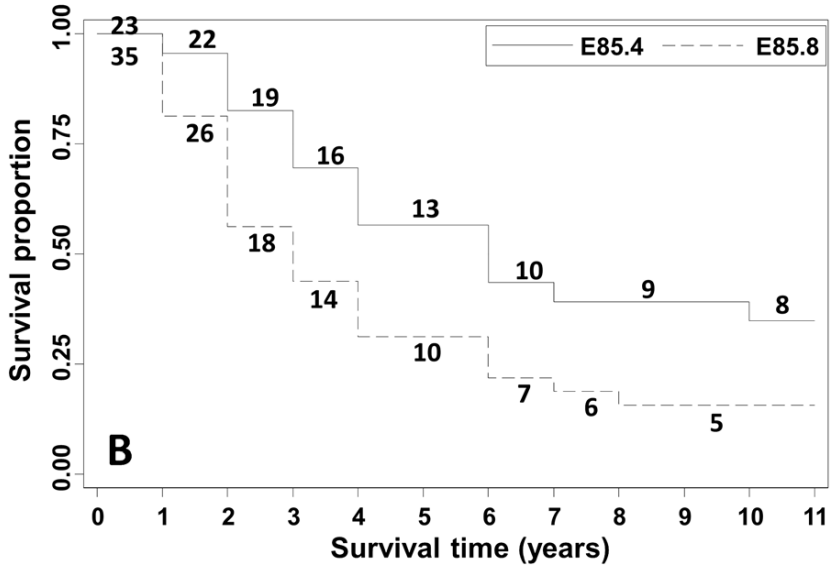



To differentiate amyloid from other hyaline materials (e.g., collagen, fibrin), a variety of histochemical stains are used. **The most widely used is the Congo red stain, which under ordinary light gives a pink or red color to tissue deposits**




specific green birefringence of the stained amyloid when observed by polarizing microscopy




**The prognosis** for individuals with generalized amyloidosis is poor.

Those with AL amyloidosis have a median survival of 2 years after diagnosis. Individuals with myeloma-associated amyloidosis have an even poorer prognosis.

Hemminki, K., Li, X., Försti, A. *et al.* Incidence and survival in non-hereditary amyloidosis in Sweden. *BMC Public Health* **12,** 974 (2012). https://doi.org/10.1186/1471-2458-12-974

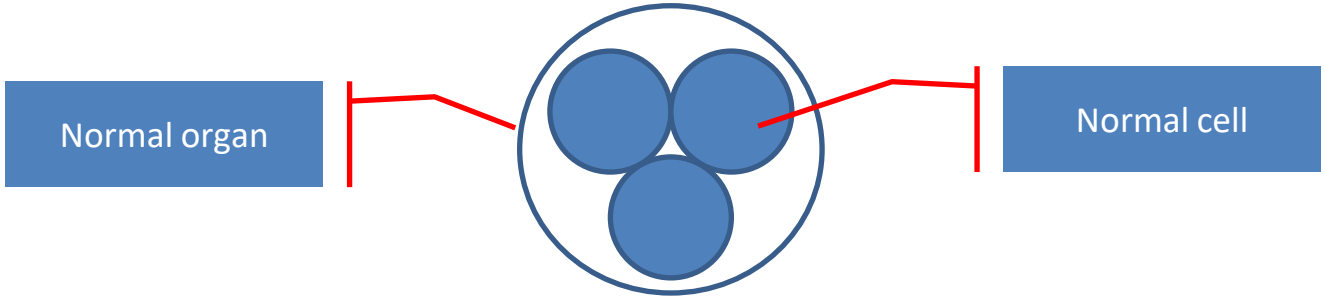
# ADAPTATIONS

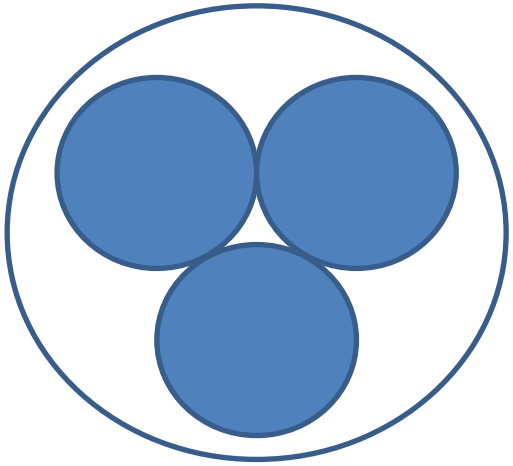
# Adaptations

| Physiologic adaptations | Pathologic adaptations |
| --- | --- |
| responses of cells to normal stimulation by hormones or endogenous chemical mediators or to the demands of mechanical stress. | responses to stress that allow cells to modulate their structure and function and thus escape injury, but at the expense of normal function |
| Example: hormone-induced enlargement of the breast and uterus during pregnancy | Example: squamous metaplasia of bronchial epithelium in smokers |

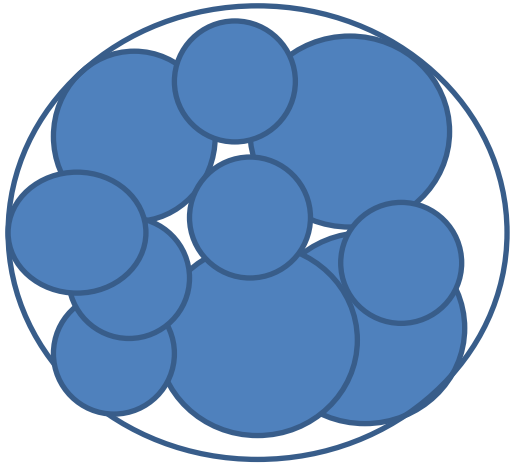
# Hypertrophy

- Hypertrophy is an increase in the size of cells resulting in an increase in the size of the organ.

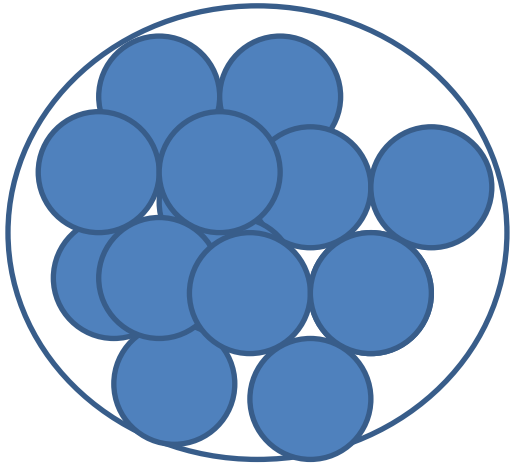


Hypertrophy



Hypertrophy + Hyperplasia



Hyperplasia

# Hypertrophy

| physiologic | pathologic |
| --- | --- |
| massive physiologic enlargement of the **uterus during pregnancy** occurs as a consequence of estrogen stimulated smooth muscle hypertrophy and smooth muscle hyperplasia | **Cardiac enlargement** that occurs with **hypertension** or aortic **valve disease.**<br><br>Myocardium subjected to a persistently increased workload, as in hypertension or with a narrowed (stenotic) valve, adapts by undergoing hypertrophy to generate the required higher contractile force. |
| in response to **increased workload** the **striated muscle cells** in both the skeletal muscle and the heart undergo only hypertrophy because adult muscle cells have a limited capacity to divide. | |

**An adaptation to stress such as hypertrophy can progress to functionally significant cell injury if the stress is not relieved.**

# Hyperplasia

- **Hyperplasia is an increase in the number of cells in an organ that stems from increased proliferation, either of differentiated cells or, in some instances, less differentiated progenitor cells.**

| physiologic | pathologic |
|---|---|
| **Hormonal hyperplasia**, exemplified by the proliferation of the glandular epithelium of the female breast at puberty and during pregnancy | **excessive hormonal or growth factor stimulation:** increased estrogenic stimulation causes endometrial hyperplasia |
| **compensatory hyperplasia**, in which residual tissue grows after removal or loss of part of an organ. | **Stimulation by growth factors** also is involved in the hyperplasia that is associated with certain viral infections |

**The hyperplastic process remains controlled; if the signals that initiate it abate, the hyperplasia disappears**

# Atrophy

- **Atrophy** is shrinkage in the size of cells by the loss of cell substance. When a sufficient number of cells are involved, the entire tissue or organ is reduced in size, or atrophic.

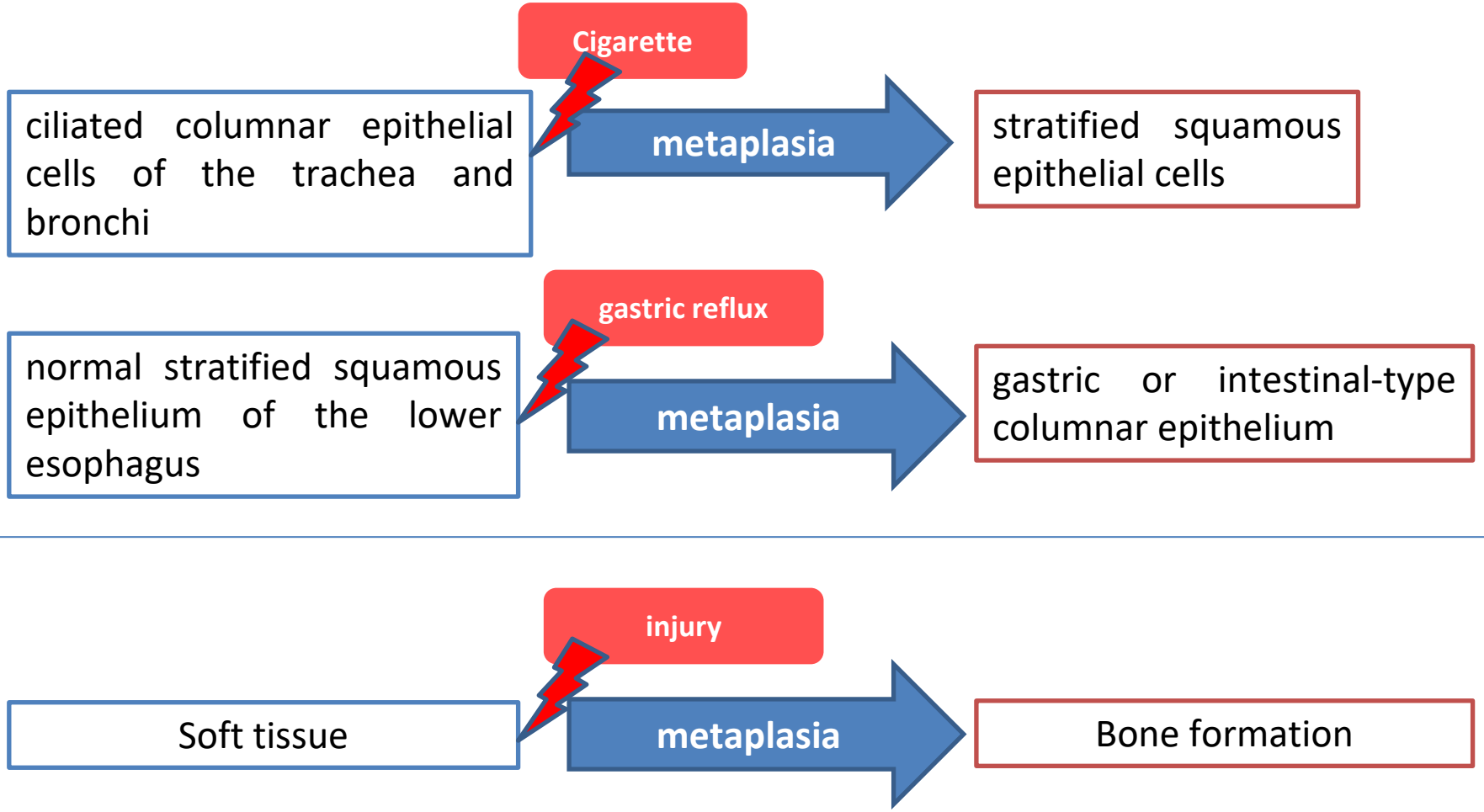
**Causes of atrophy :**

1. decreased workload,
2. loss of innervation,
3. diminished blood supply,
4. Inadequate nutrition,
5. loss of endocrine stimulation,
6. aging (senile atrophy).

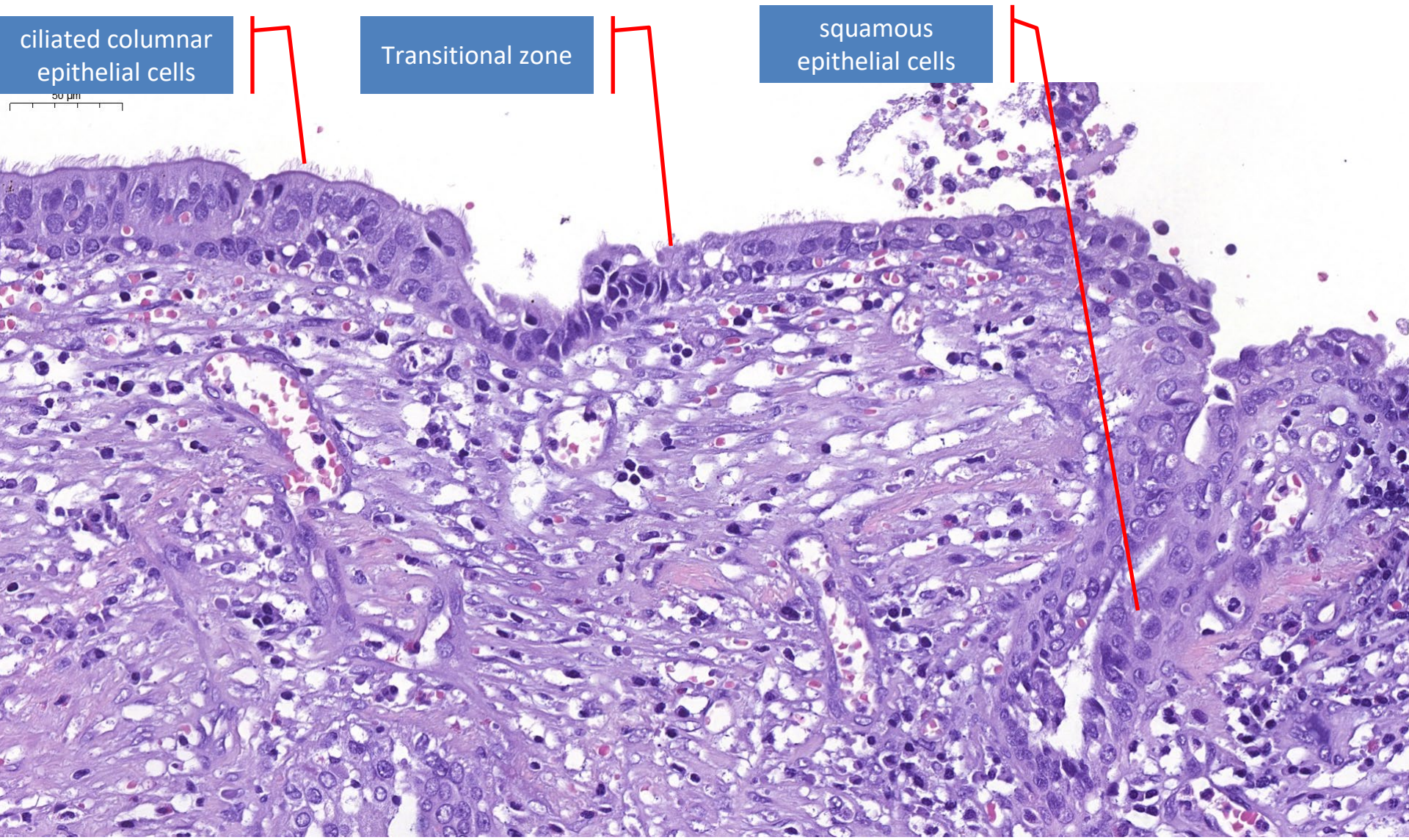
Although some of these stimuli are physiologic and others are pathologic, the fundamental cellular changes are similar.

# Metaplasia

- **Metaplasia** is a change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type.



# Squamous Metaplasia



# Dysplasia

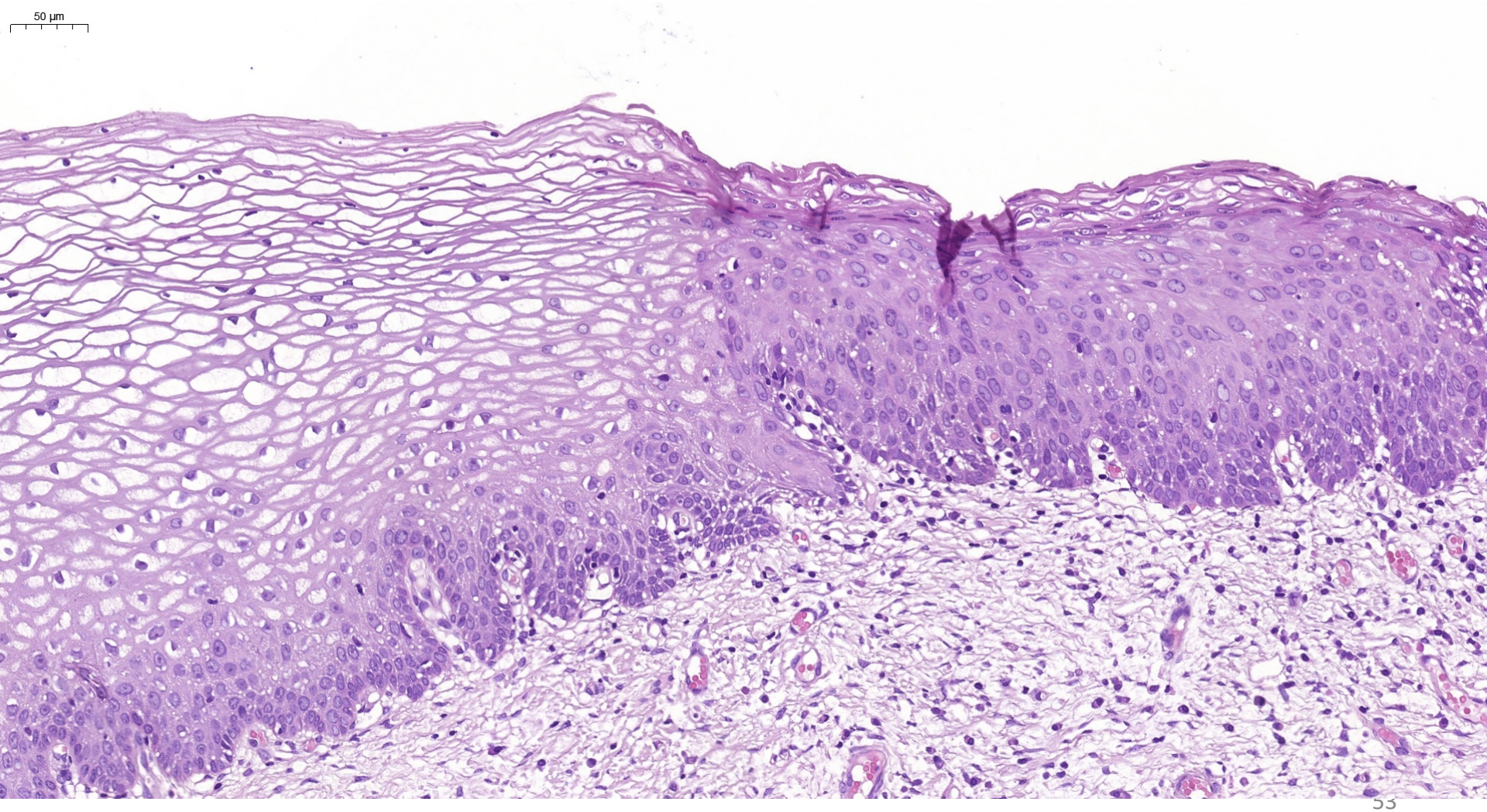
- *Dysplasia is the morphologic expression of a disturbance in growth regulation.*

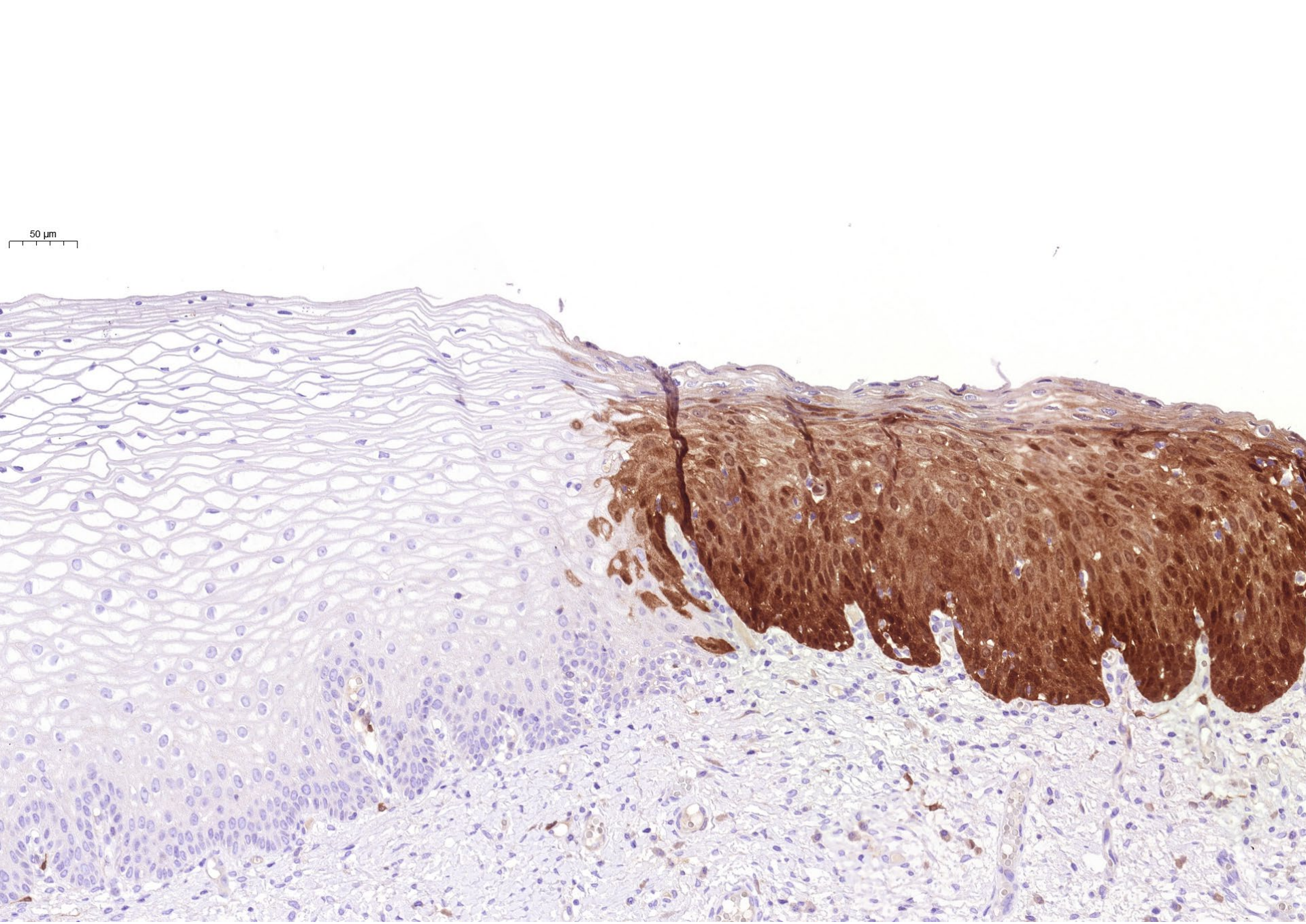
**Features of dysplasia**

(1) variation in cell size and shape;
(2) nuclear enlargement, irregularity and hyperchromatism;
(3) (3) disorderly arrangement of cells in the epithelium

**Dysplasia is a preneoplastic lesion**, in that it is a necessary stage in the multistep cellular evolution to cancer.

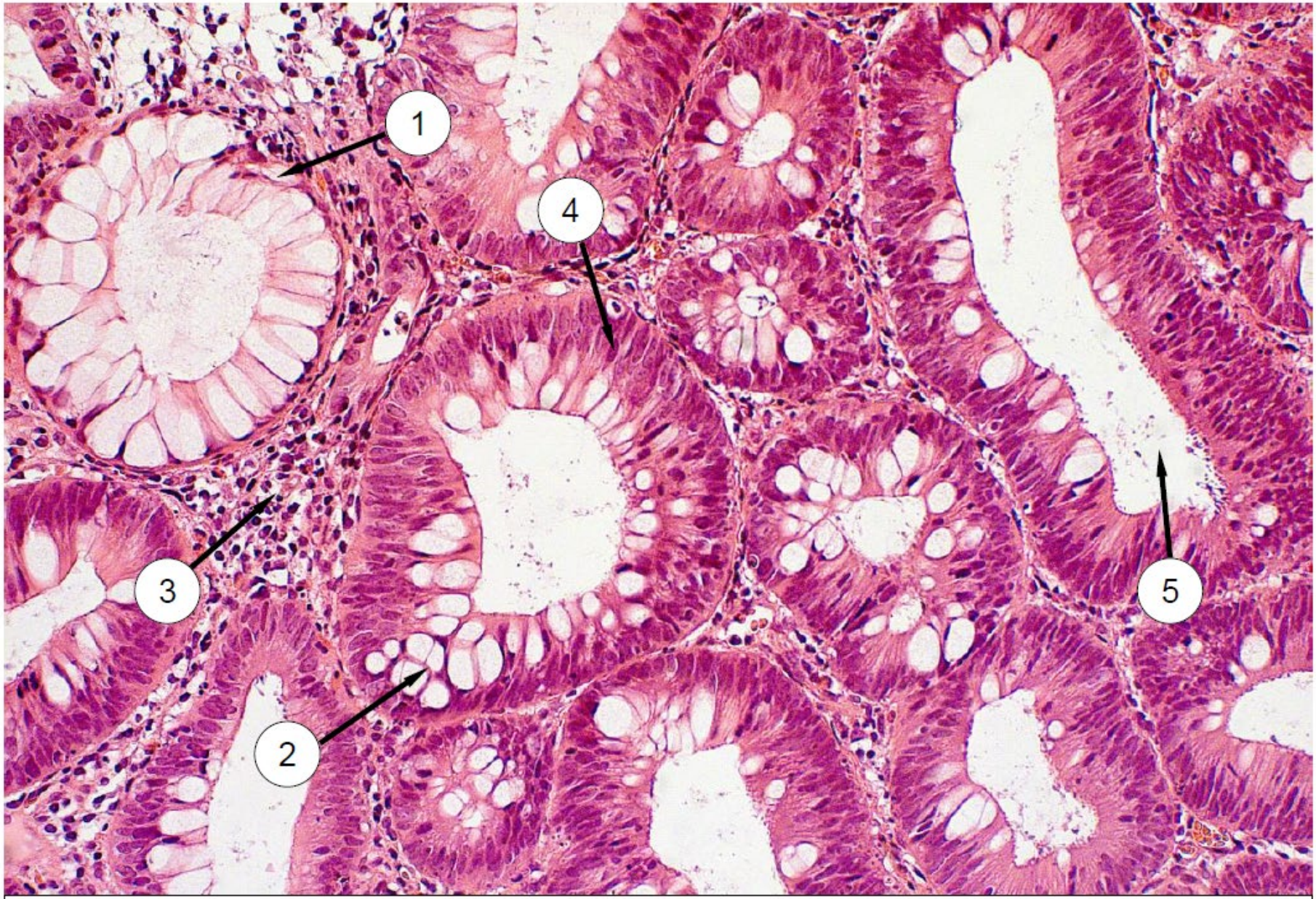
As in the development of cancer, dysplasia **results from sequential mutations in a proliferating cell population**.


50 µm

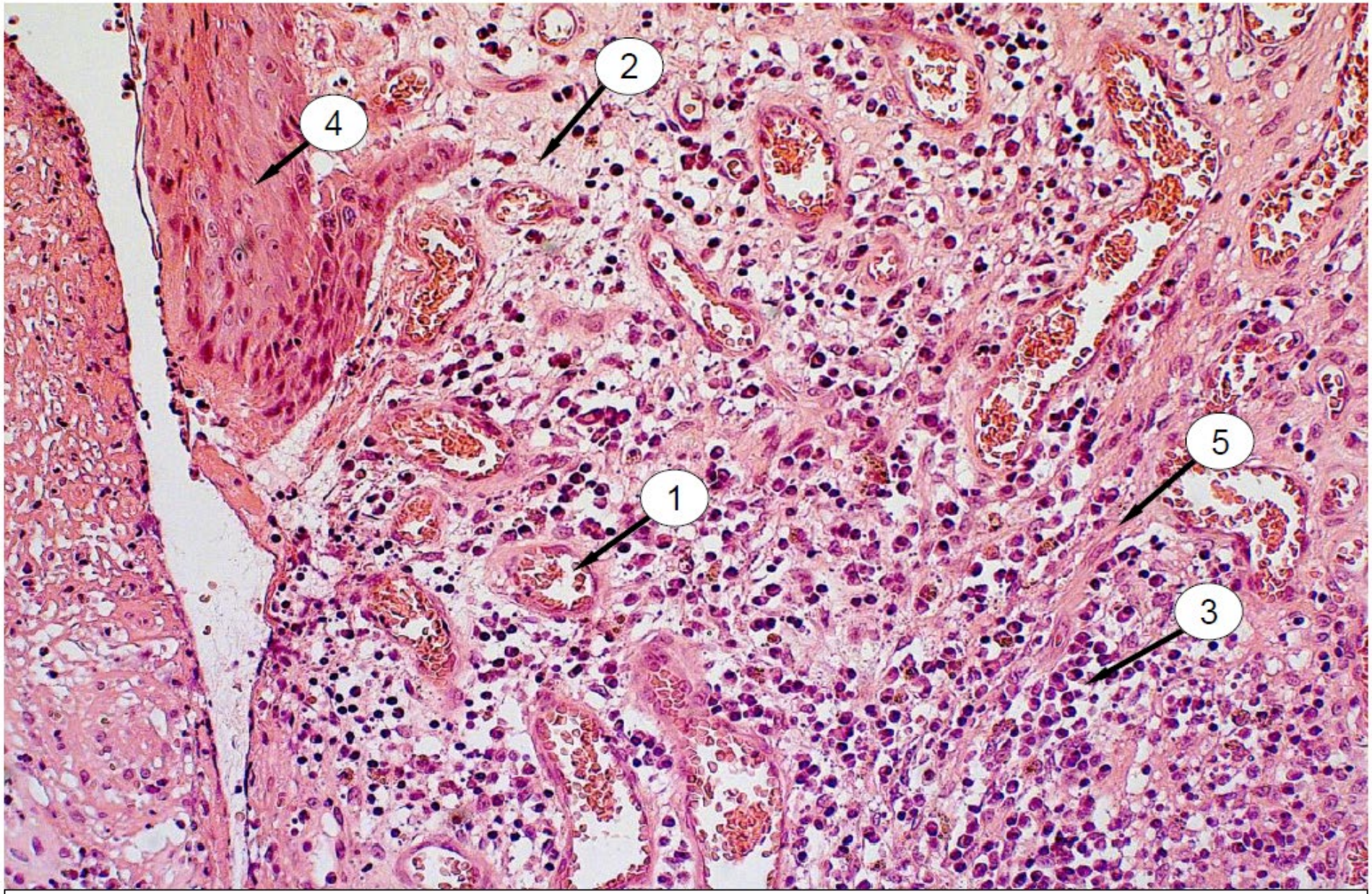

50 µm

# Histological slides for classroom work

# Dysplasia in gastric adenoma



# Granulation tissue



Thanks for attention!