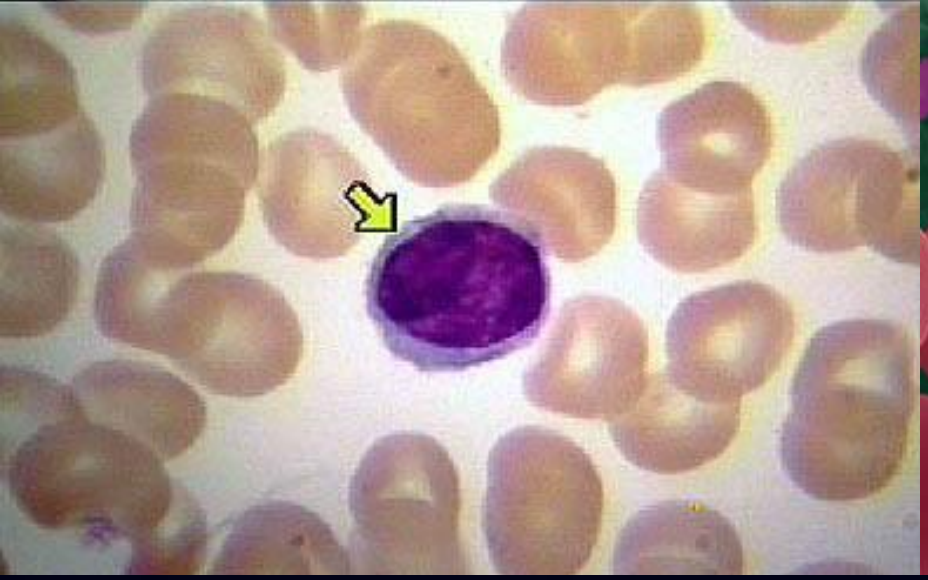
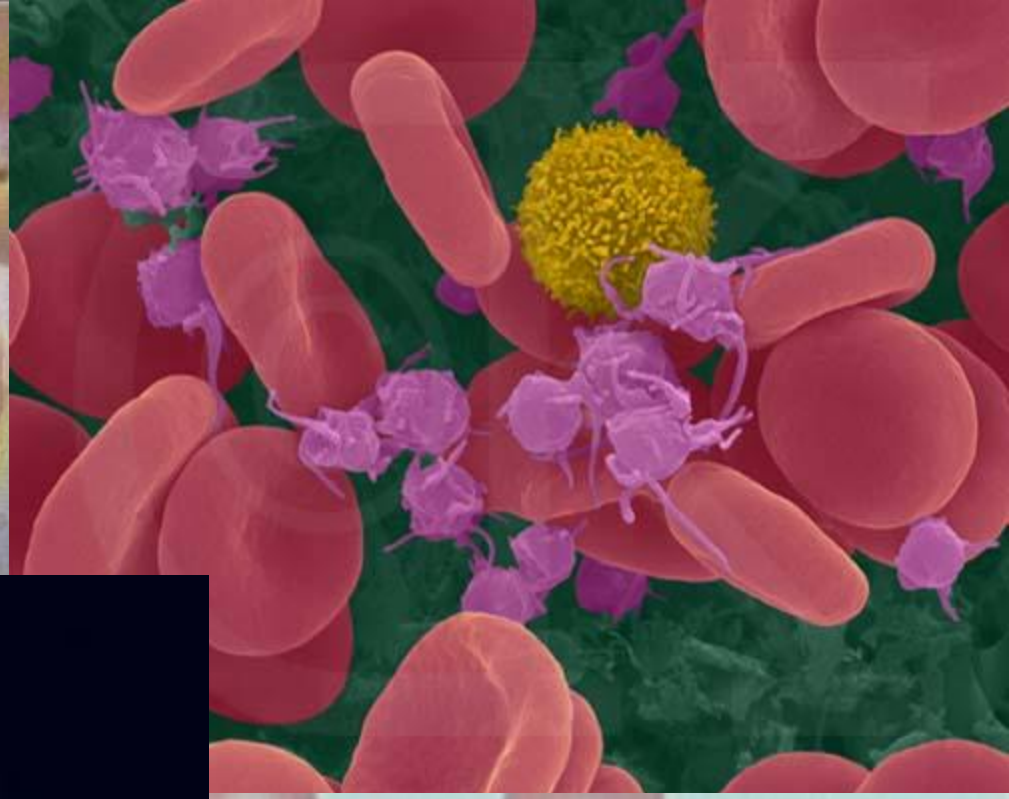
Волгоградский государственный медицинский университет

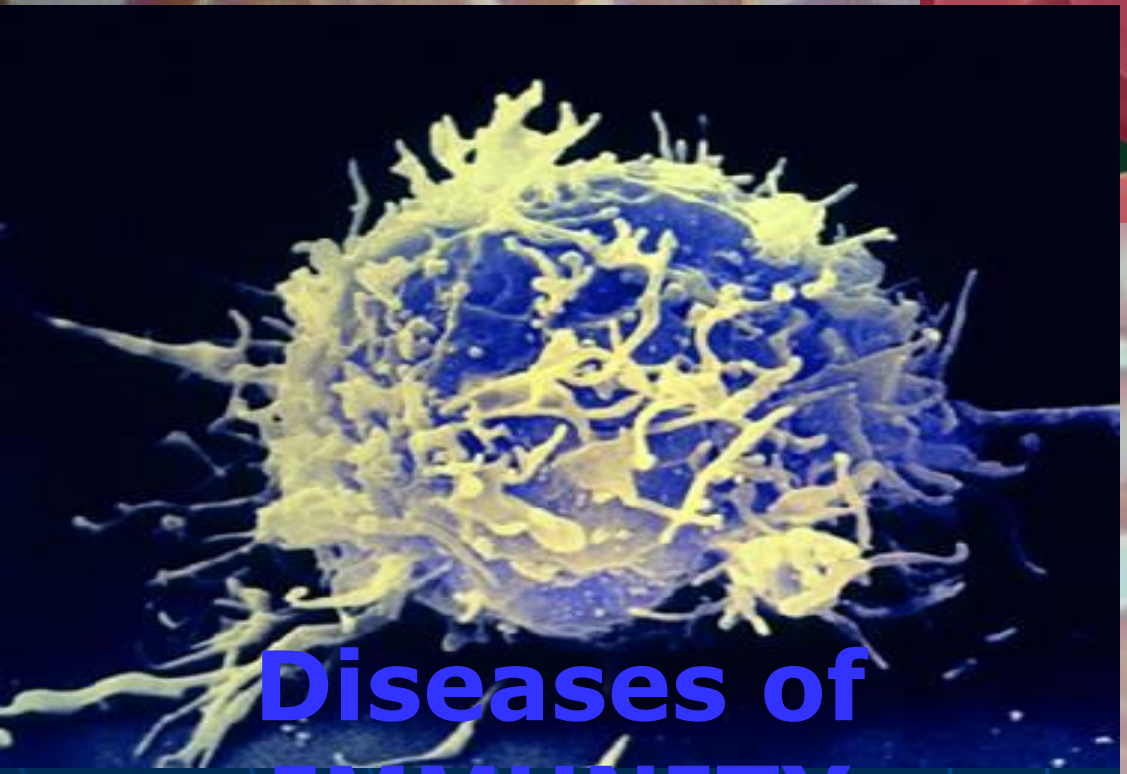
Кафедра патологической анатомии

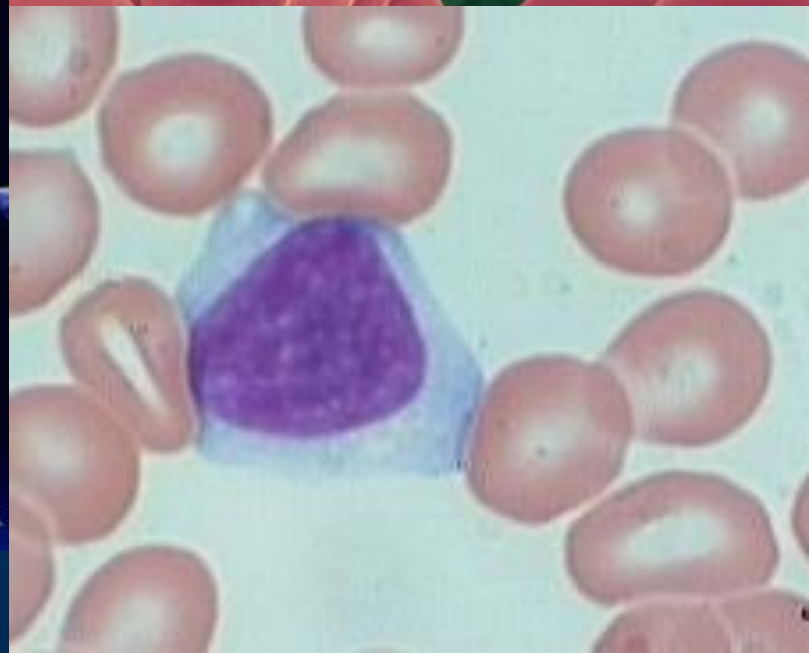
LECTURE.

Immune Disorders.









Diseases of IMMUNITY

Introduction:

- **Humoral Immunity**
  - B lymphocytes - Antibody
- **Cell mediated Immunity**
  - T lymphocytes – Macrophages
- **Non-Specific protective cells**
  - Neutrophils, Macrophages

IMMUNITY

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

MHC

Major Histocompatibility Complex

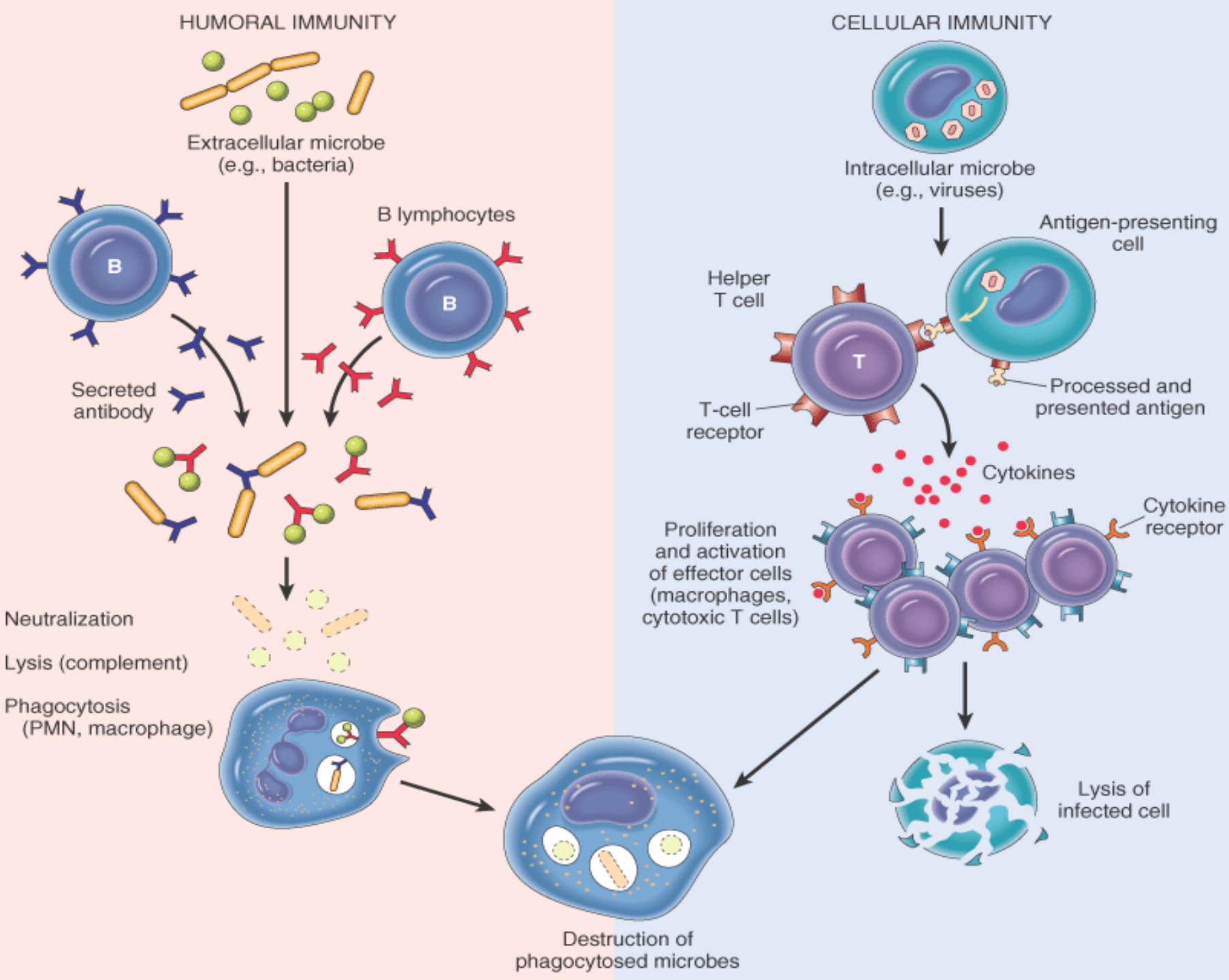
- A genetic "LOCUS" on Chromosome 6, which codes for cell surface compatibility
- Also called HLA (Human Leukocyte Antigens) in humans and H-2 in mice
- It's major job is to make sure all self cell antigens are recognized and "tolerated", because the general rule of the immune system is that all UN-recognized 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**

ADAPTIVE IMMUNITY

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

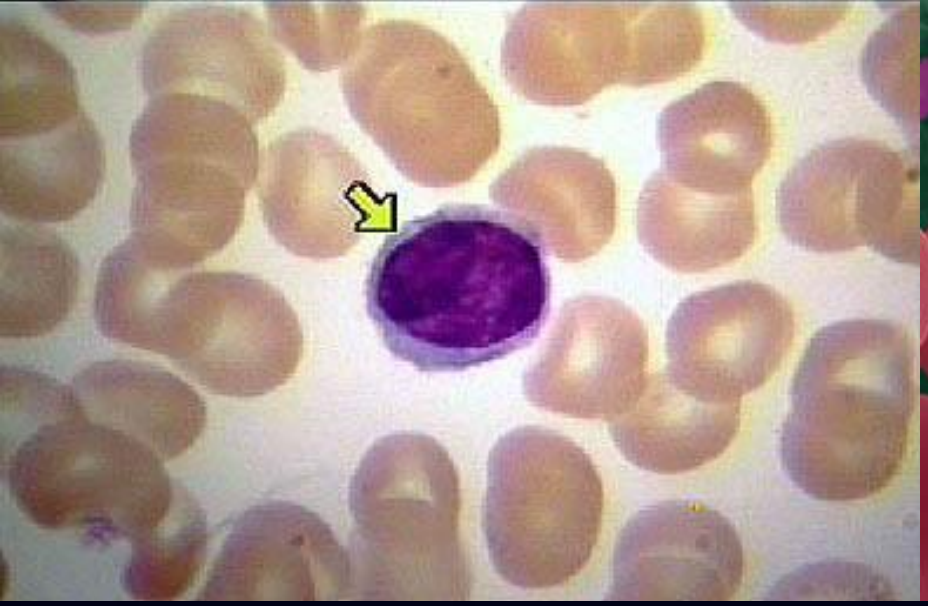

HUMORAL IMMUNITY
Extracellular microbe
(e.g., bacteria)
B lymphocytes
B
B
Secreted
antibody
Neutralization
Lysis (complement)
Phagocytosis
(PMN, macrophage)
CELLULAR IMMUNITY
Intracellular microbe
(e.g., viruses)
Antigen-presenting
cell
Helper
T cell
T
T-cell
receptor
Processed and
presented antigen
Cytokines
Cytokine
receptor
Proliferation
and activation
of effector cells
(macrophages,
cytotoxic T cells)
Lysis of
infected cell
Destruction of
phagocytosed microbes

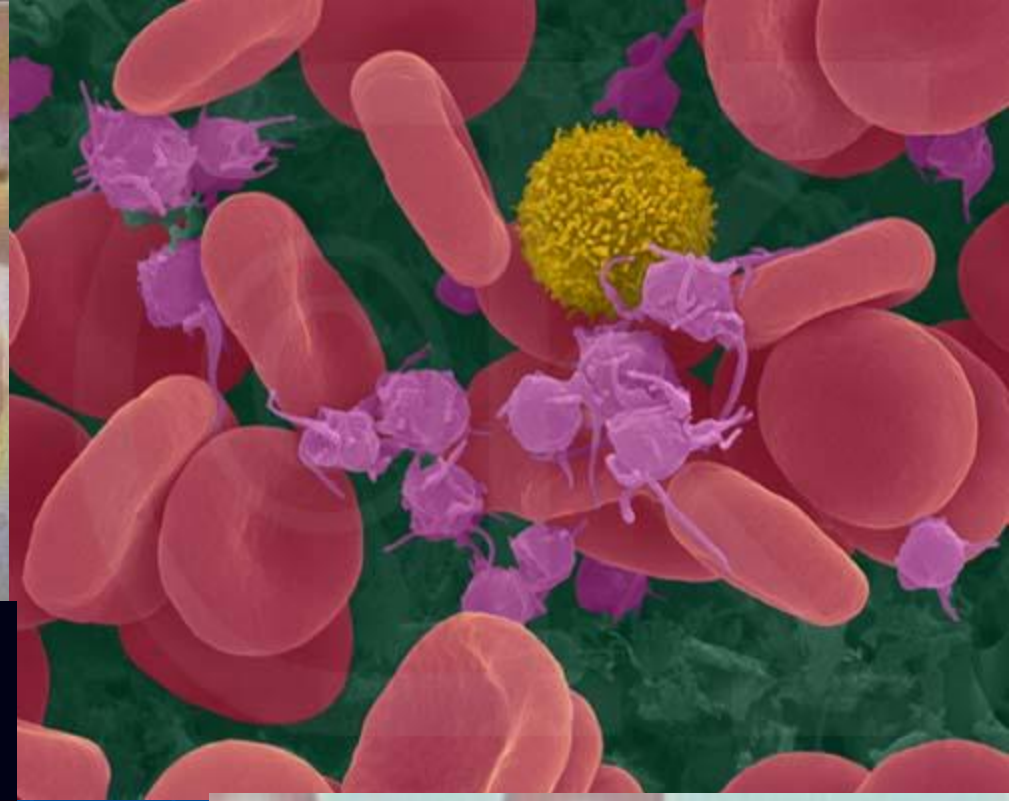
Introduction:

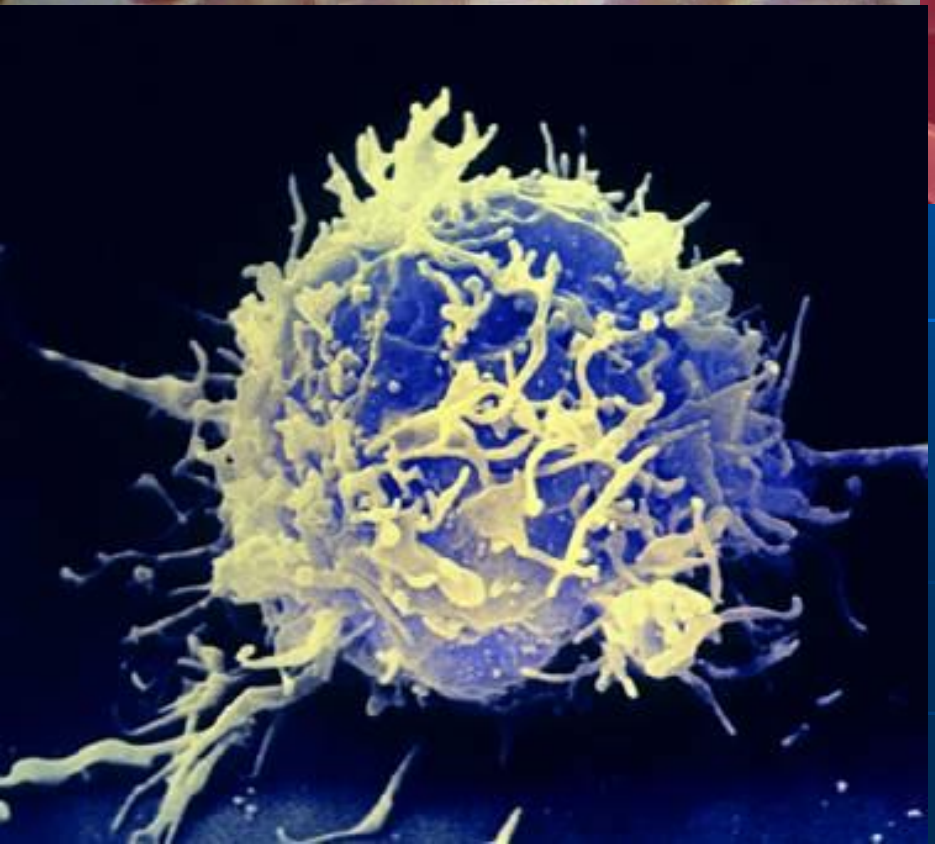
- **Immunity is not inherited.**
- **Antigen / Antibody**
- **Active / Passive immunity.**
- **Primary response – slow, weak.**
  - Learning period, memory cells.
- **Secondary response – rapid, strong**

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







L

Y

M

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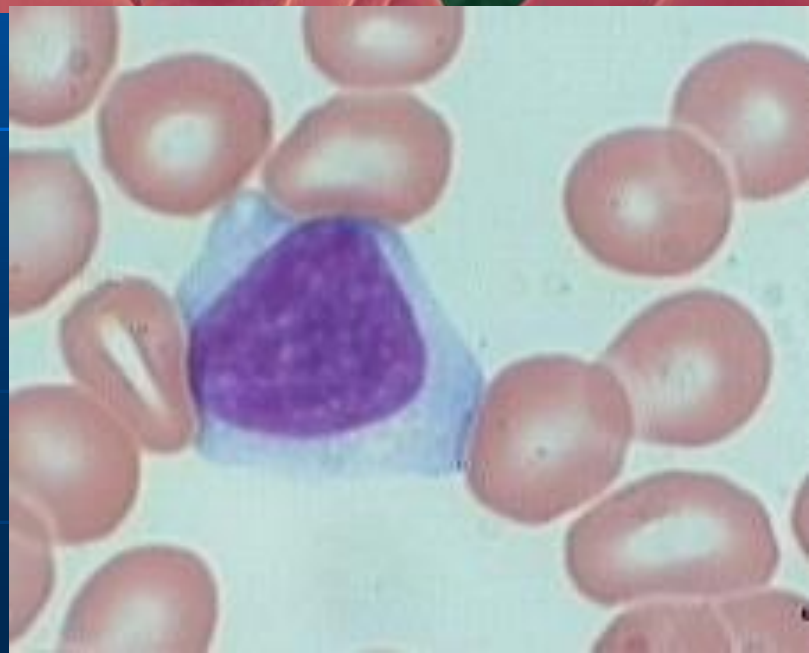
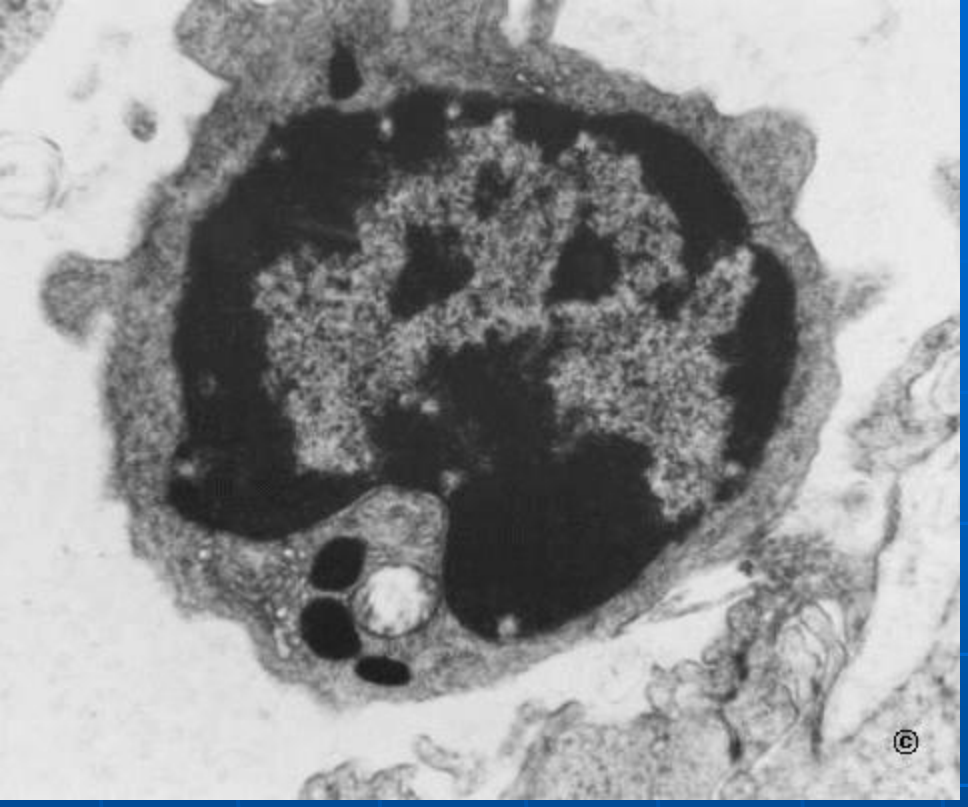
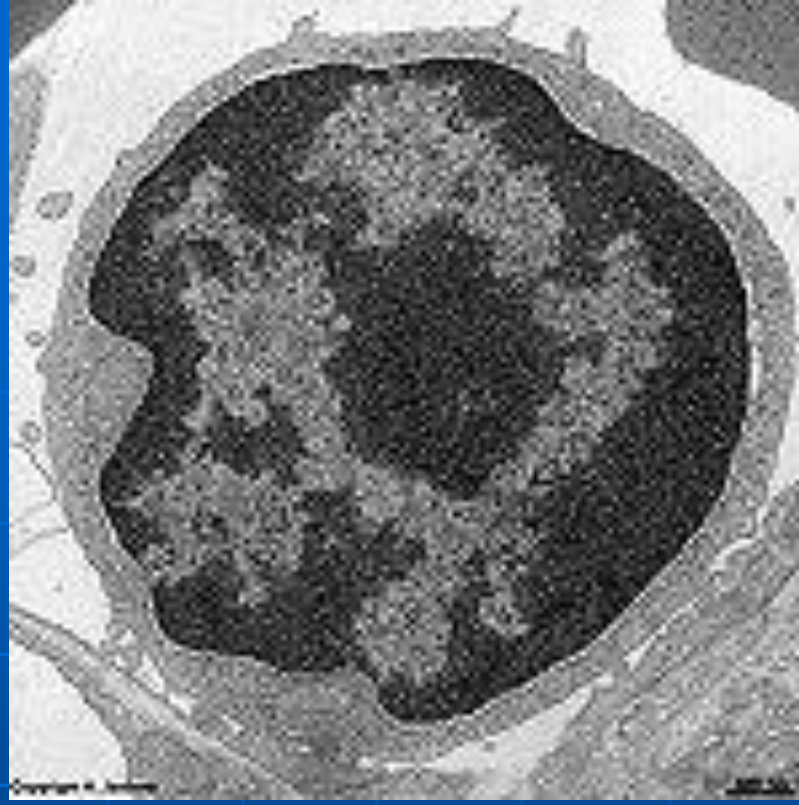
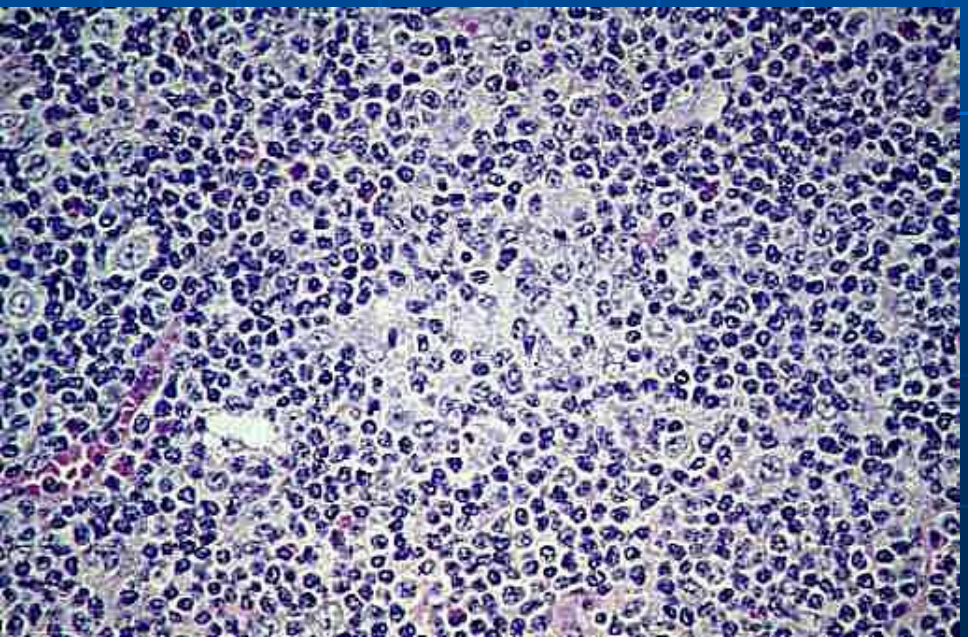
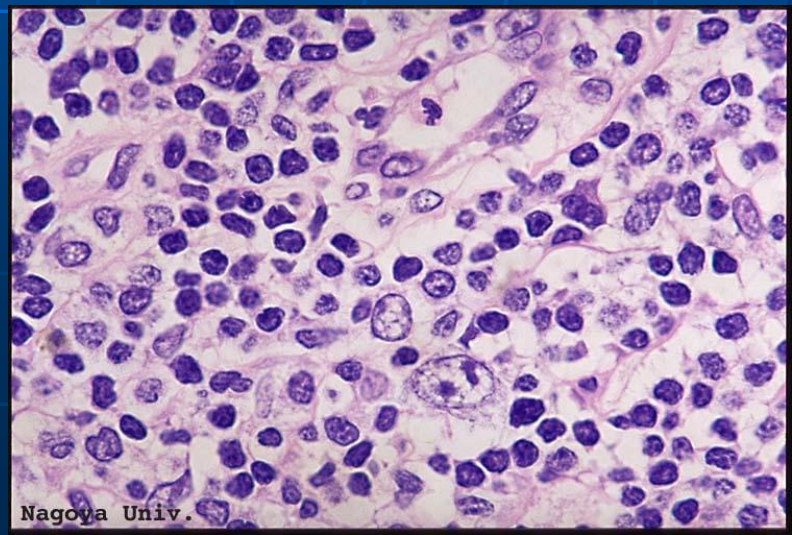








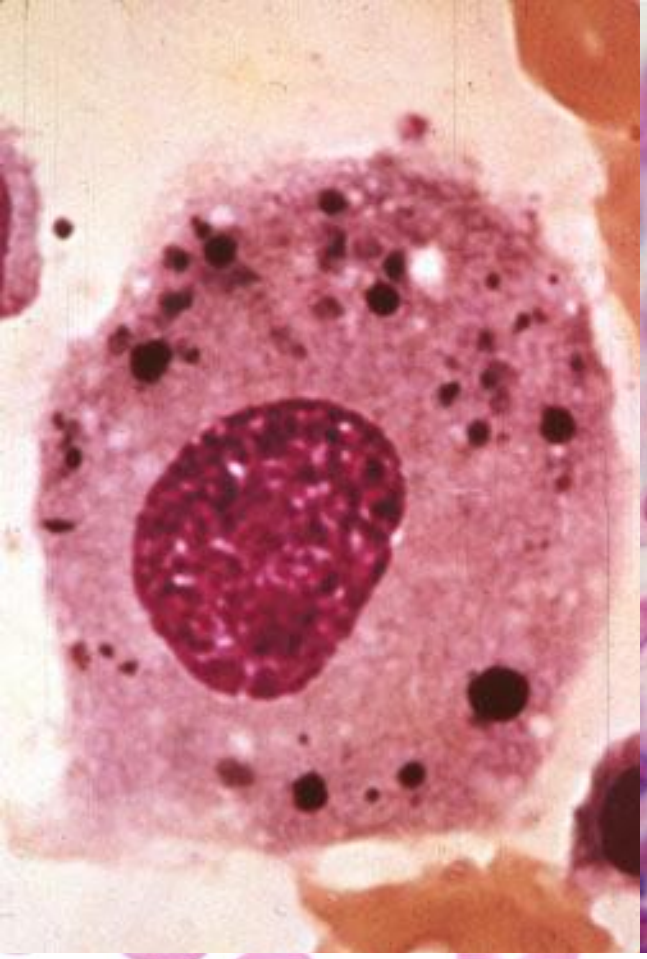

Nagoya Univ.

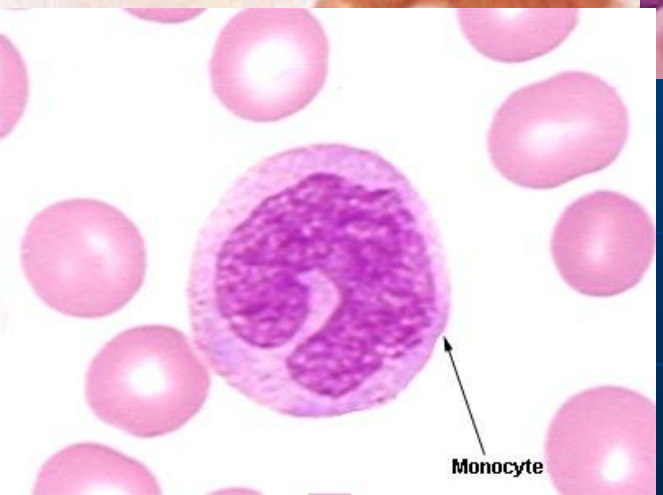
ANY ROUND CELL WITH RATHER DENSE STAINING NUCLEUS AND MINIMAL CYTOPLASM IN CONNECTIVE TISSUE, A BIT BIGGER THAN AN RBC, IS A

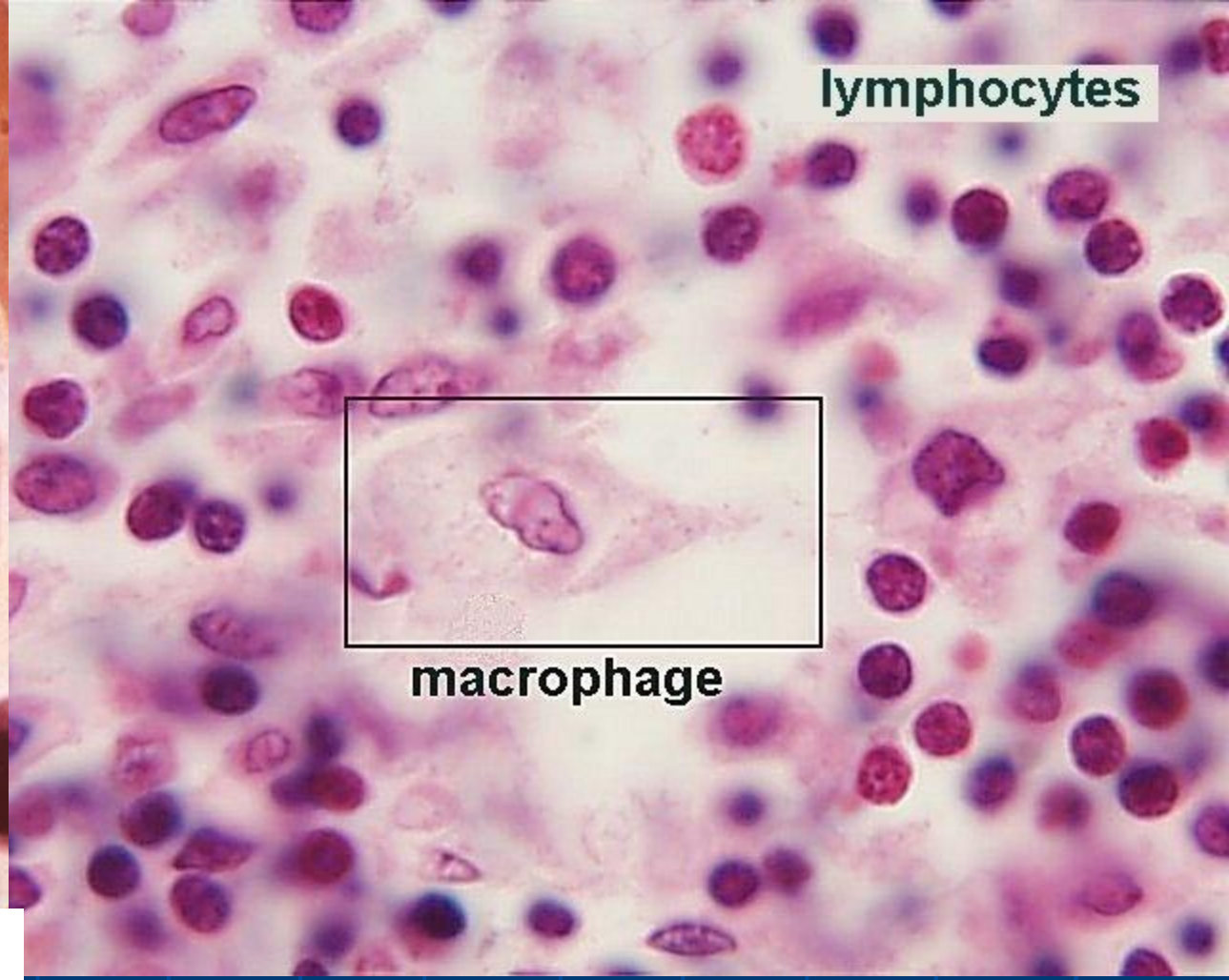
LYMPHOCYTE

…UNTIL PROVEN OTHERWISE

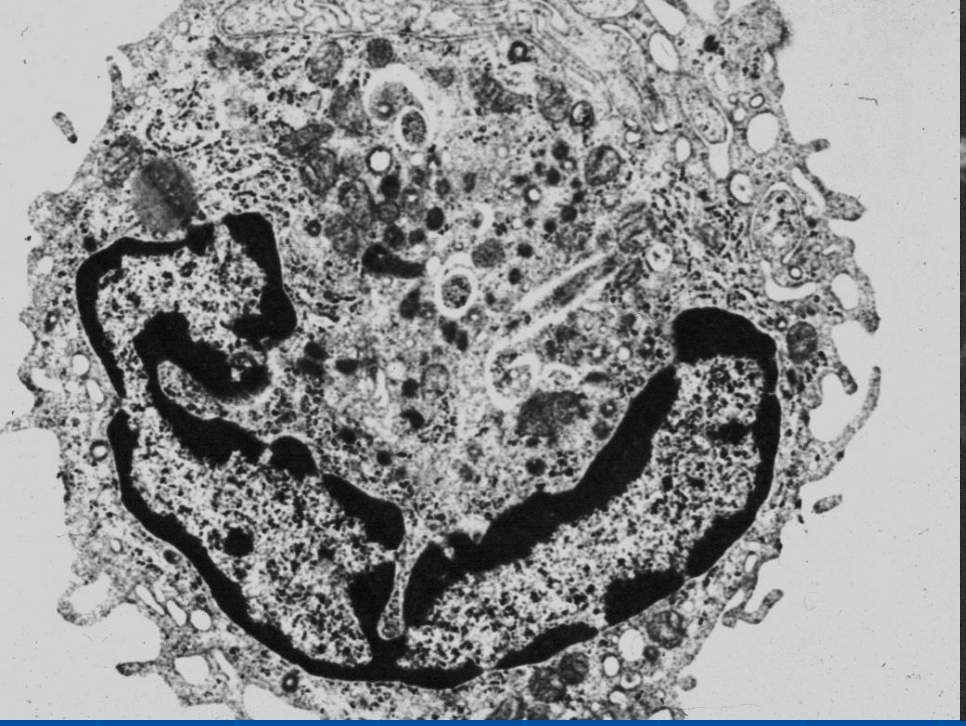

MACROPHAGE
aka
HISTIOCYTE

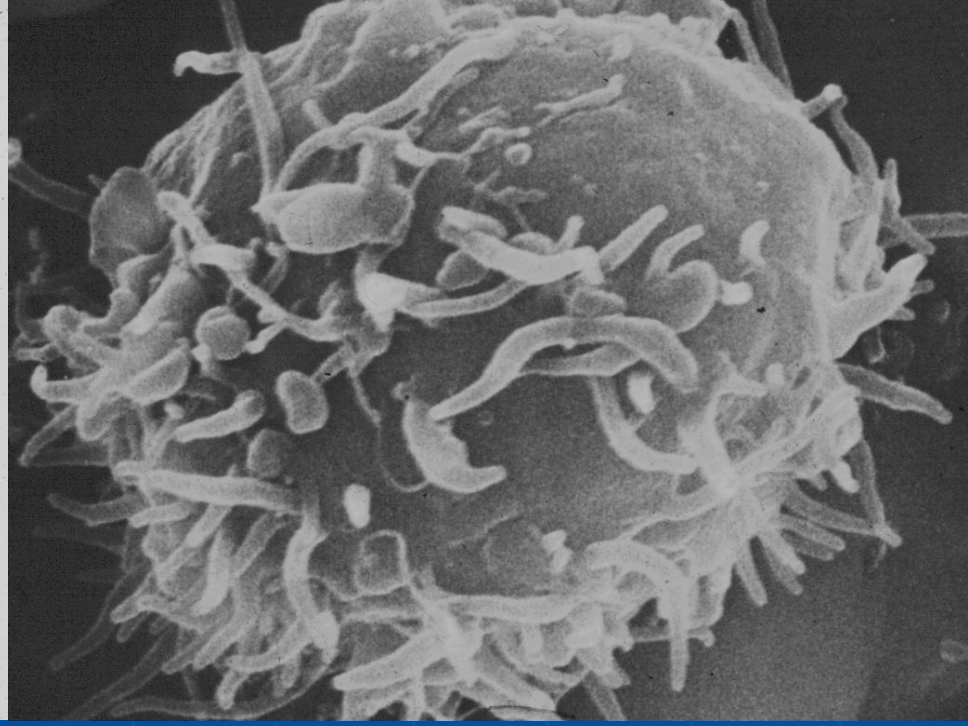






MACROPHAGES are MONOCYTES that have come out of circulation and have gone into tissue





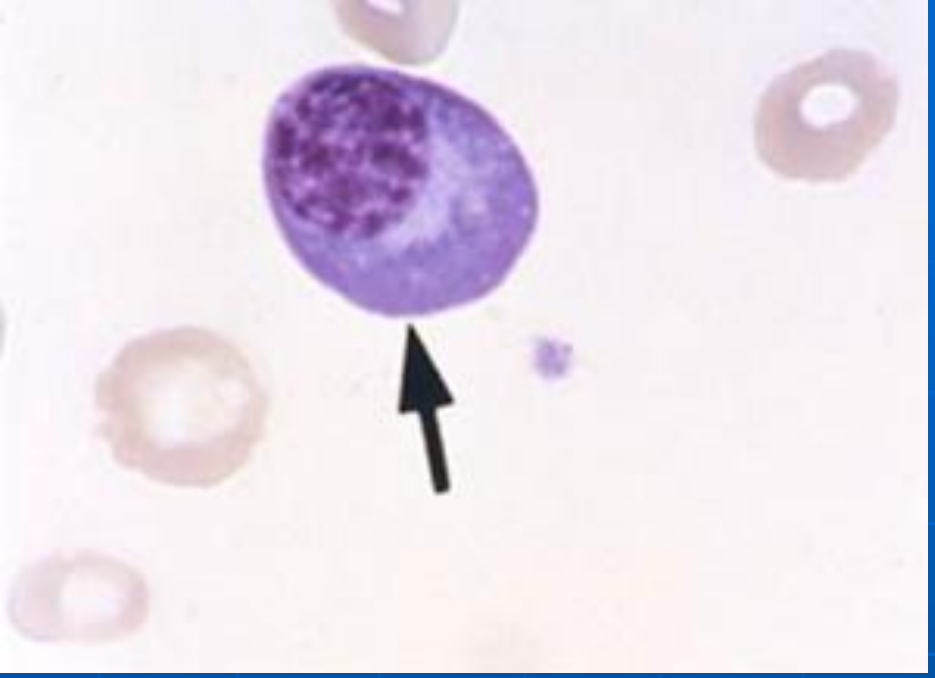
MACROPHAGES, TEM, SEM

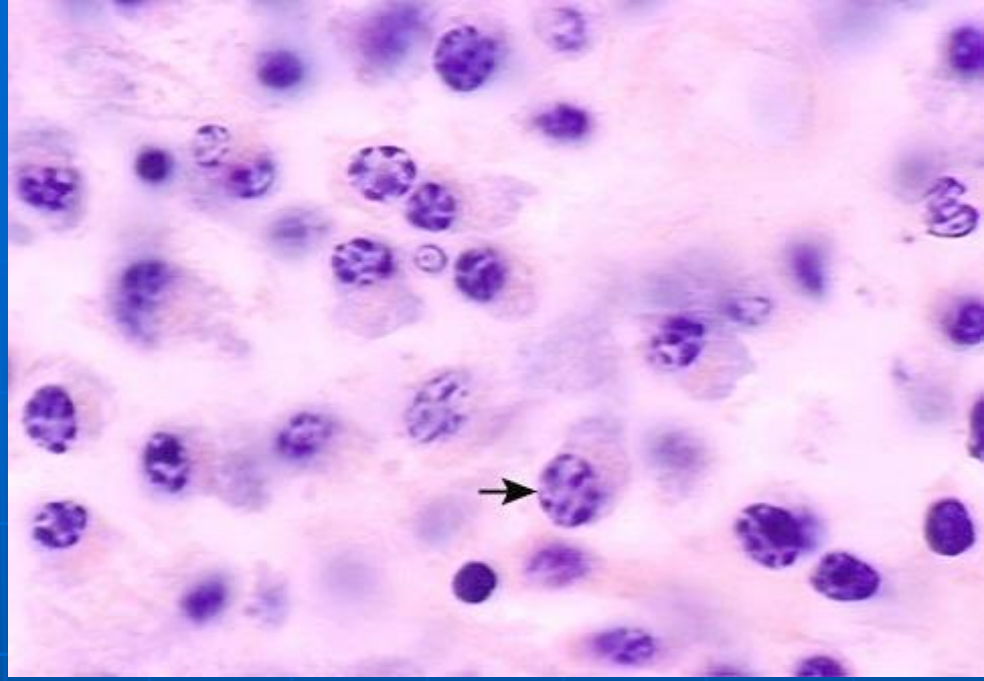
ANY CELL MIXED IN WITH LYMPHOCYTES BUT HAS A LARGER MORE "OPEN", LESS DENSE, LESS CIRCULAR NUCLEUS WITH MORE CYTOPLASM IS A

MACROPHAGE

...UNTIL PROVEN OTHERWISE

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





1) ROUND NUCLEUS

2) OVOID CYTOPLASM

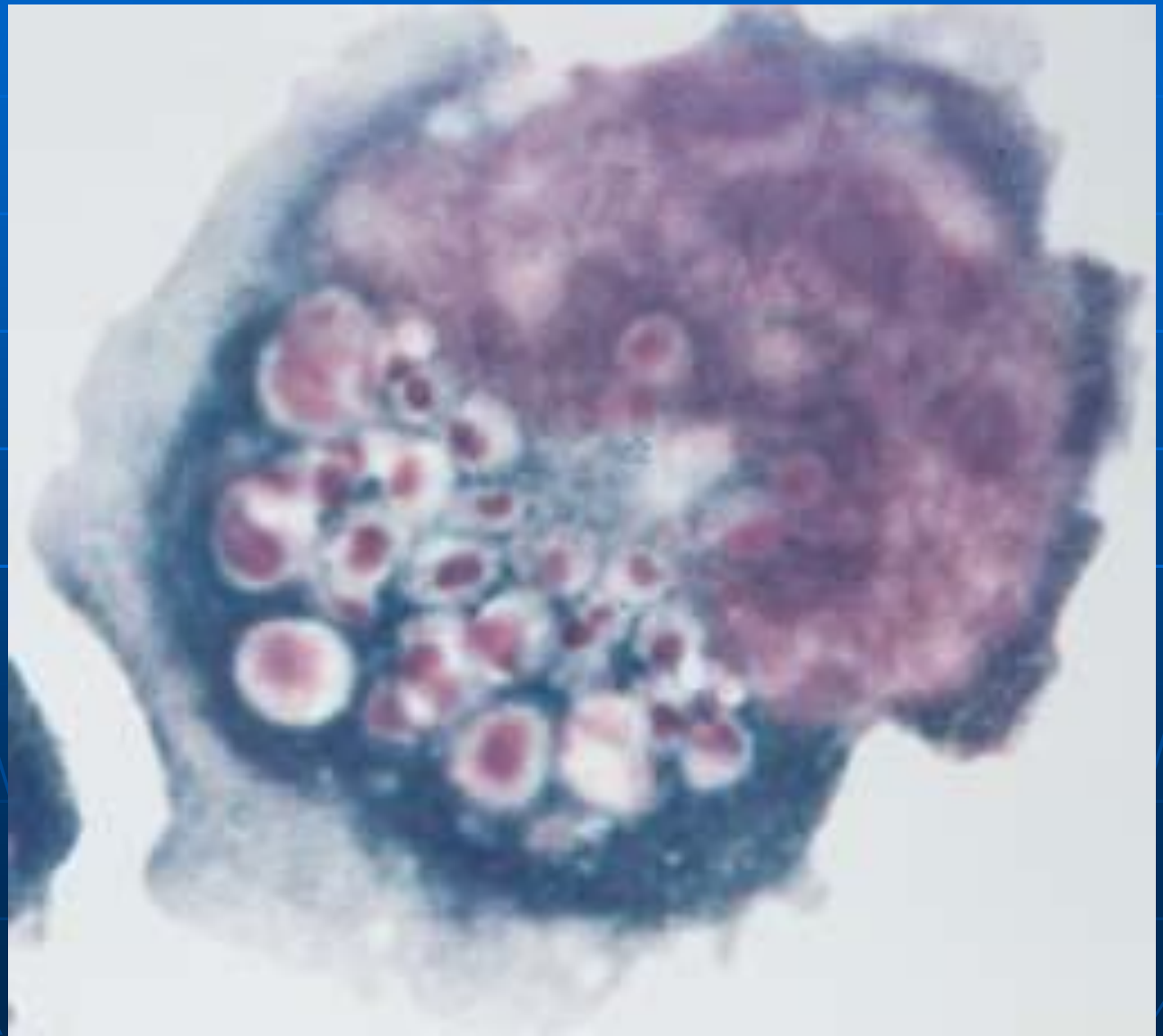
3) PERIPHERAL CHROMATIN

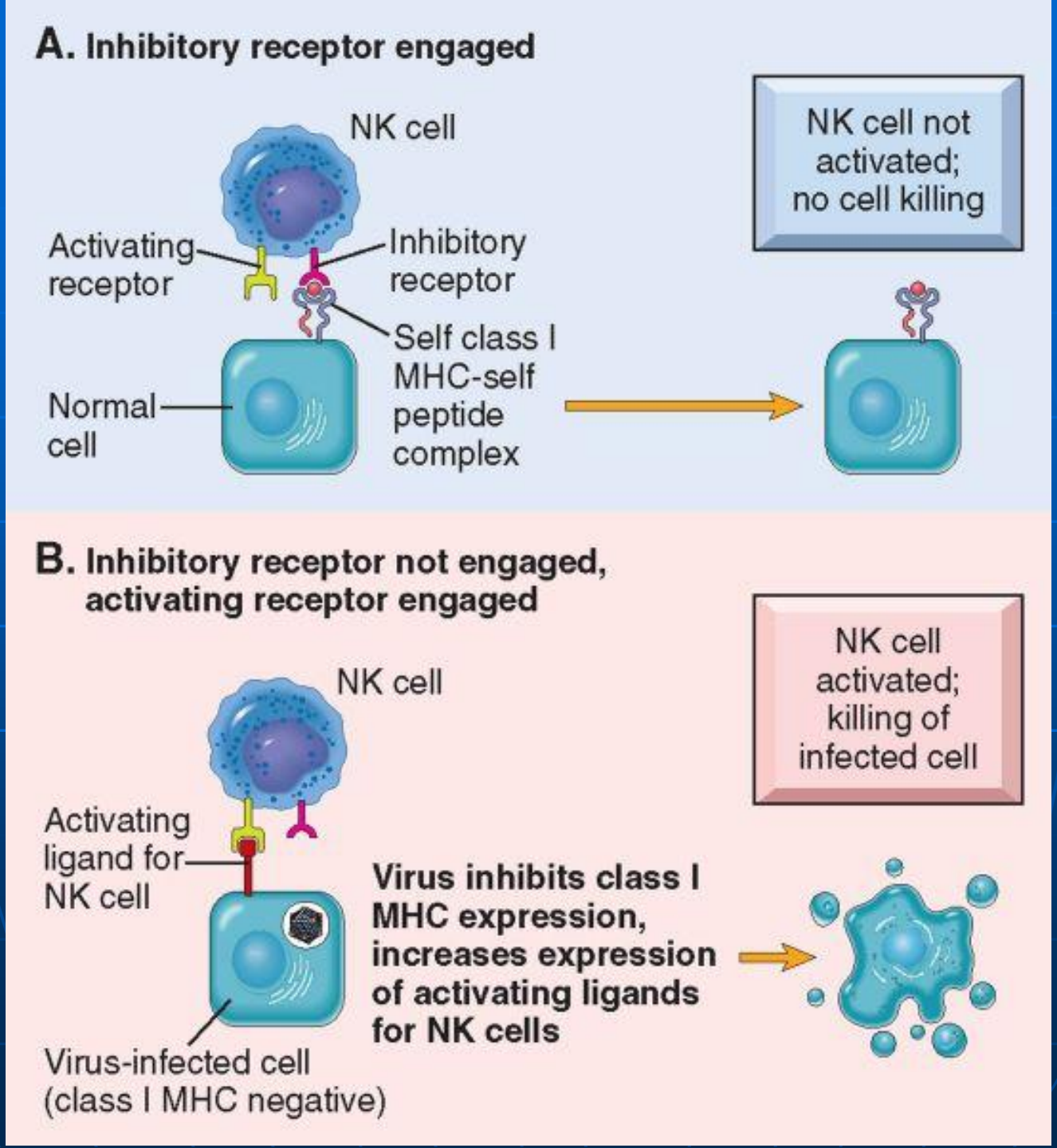
4) "CLEAR ZONE" BETWEEN NUCLEUS AND WIDER LIP OF CYTOPLASM

PLASMA CELLS


DENDRITIC CELL

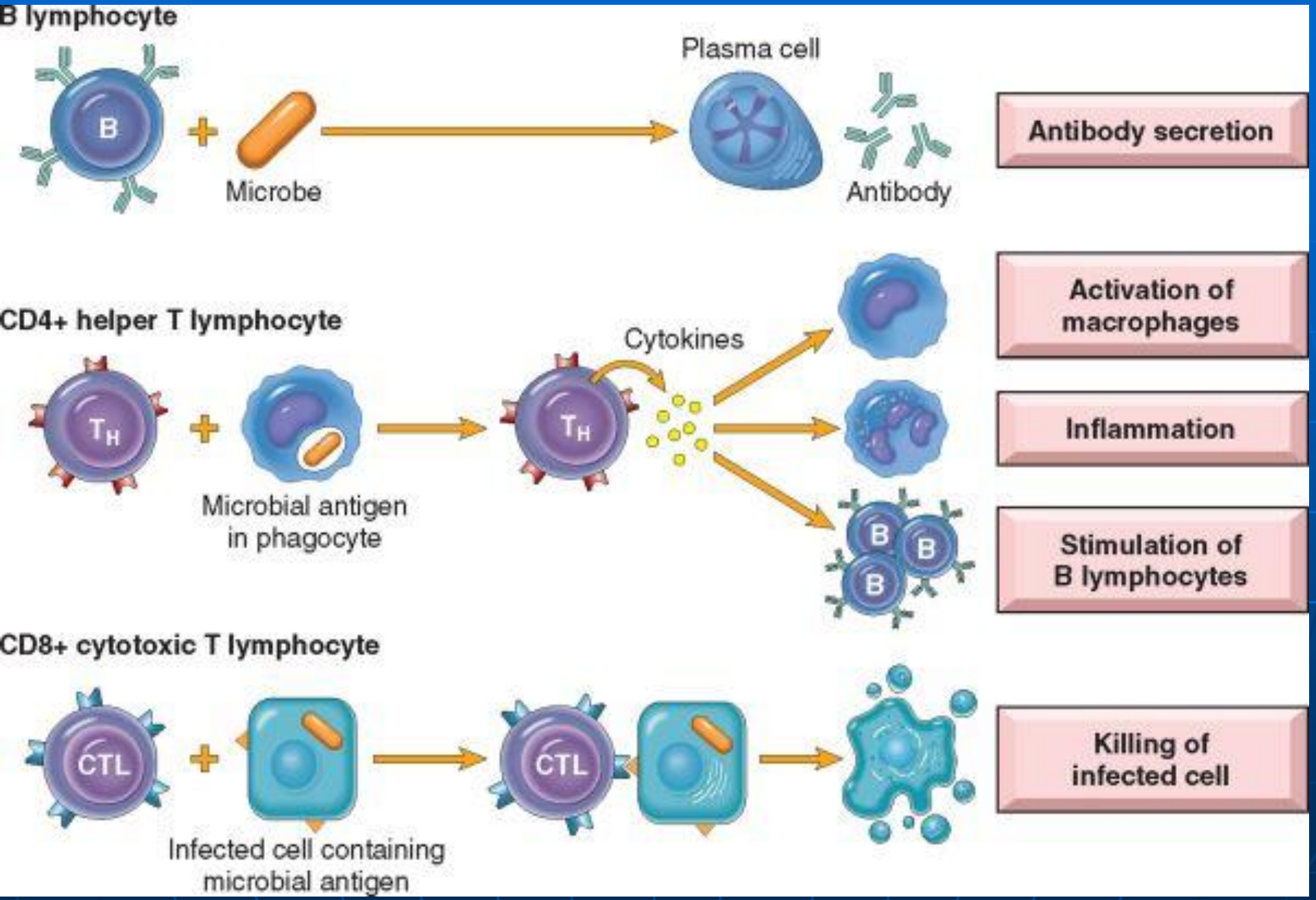
NK CELLS




A. Inhibitory receptor engaged
NK cell
NK cell not activated; no cell killing
Activating receptor
Inhibitory receptor
Self class I MHC-self peptide complex
Normal cell
B. Inhibitory receptor not engaged, activating receptor engaged
NK cell
NK cell activated; killing of infected 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)

GENERAL SCHEME of CELLULAR EVENTS

- **APCs (Macrophages, Dendritic Cells)→**
- **T-Cells→ (Control Everything)**
  - **CD4→ "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 Colony Stimulating Factors)**

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

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

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 Disorders:

- **Hypersensitivity Disorders (allergy)**
  - Type-I (IgE),
  - II-IgG,
  - III-Immunecomplex,
  - IV-Cell mediated.
- **Autoimmune disorders**
  - SLE, Rhematoid, Rheumatic fever.
- **Immunodeficiency disorders:**
  - PRIMARY (GENETIC)
  - SECONDARY (ACQUIRED) AIDS, antibody deficiency
- **Amyloidosis**

HYPERSENSITIVITY REACTIONS (4)

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

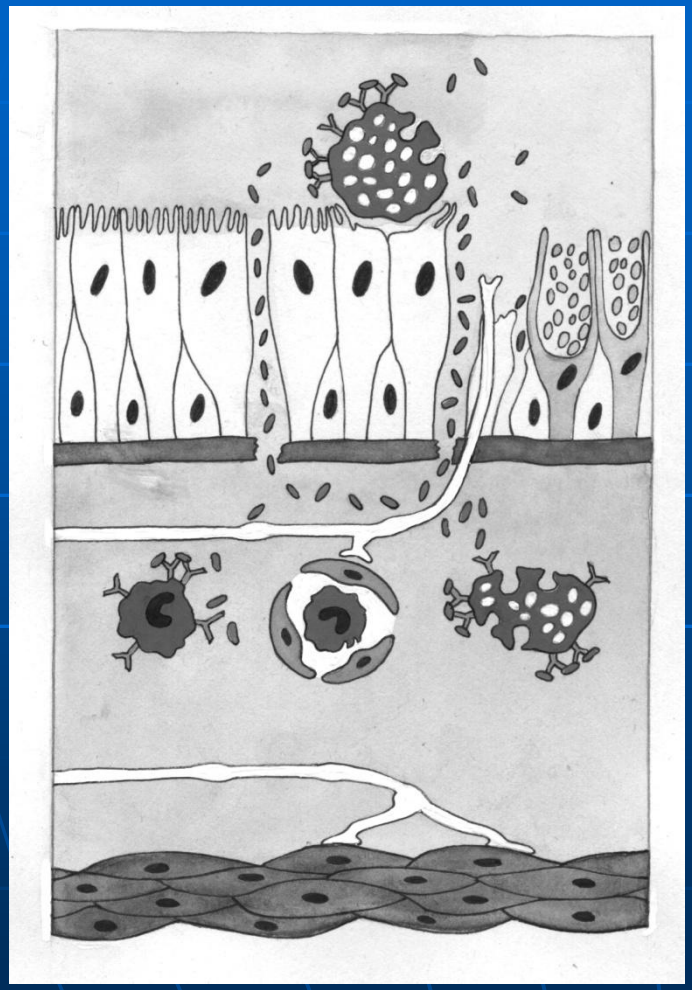
Type I
IMMEDIATE HYPERSENSITIVITY

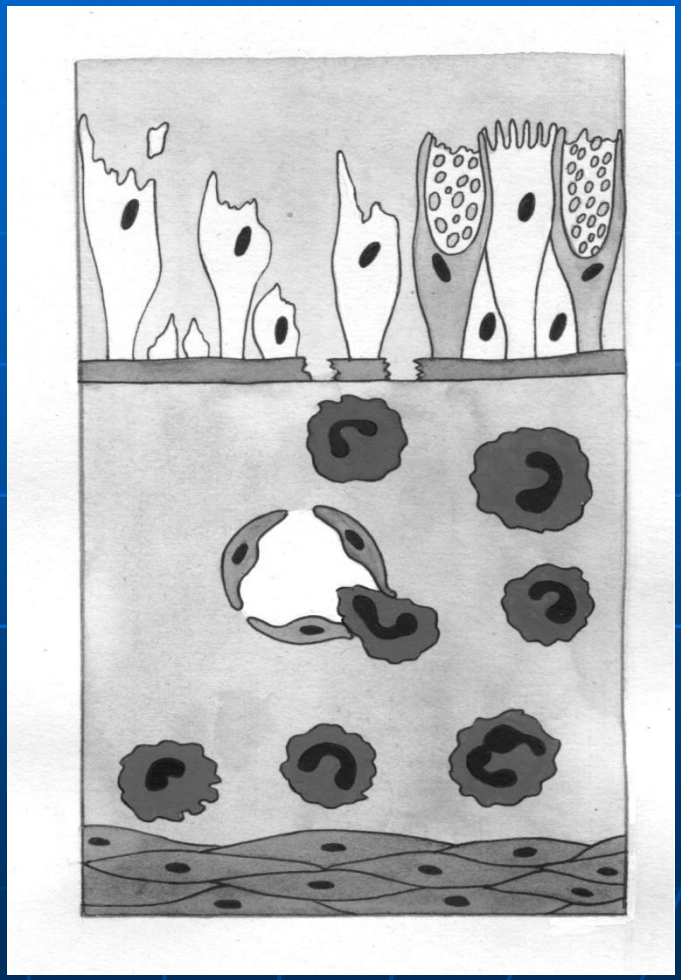
- "Immediate" means seconds to minutes
- "Immediate Allergic Reactions", which may lead to anaphylaxis, shock, edema, dyspnea death
  - 1) **Allergen exposure**
  - 2) **IMMEDIATE** phase: MAST cell DEgranulation, vasodilatation, vascular leakage, smooth muscle (broncho)-spasm
  - 3) **LATE** phase (hours,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

What is Asthma?

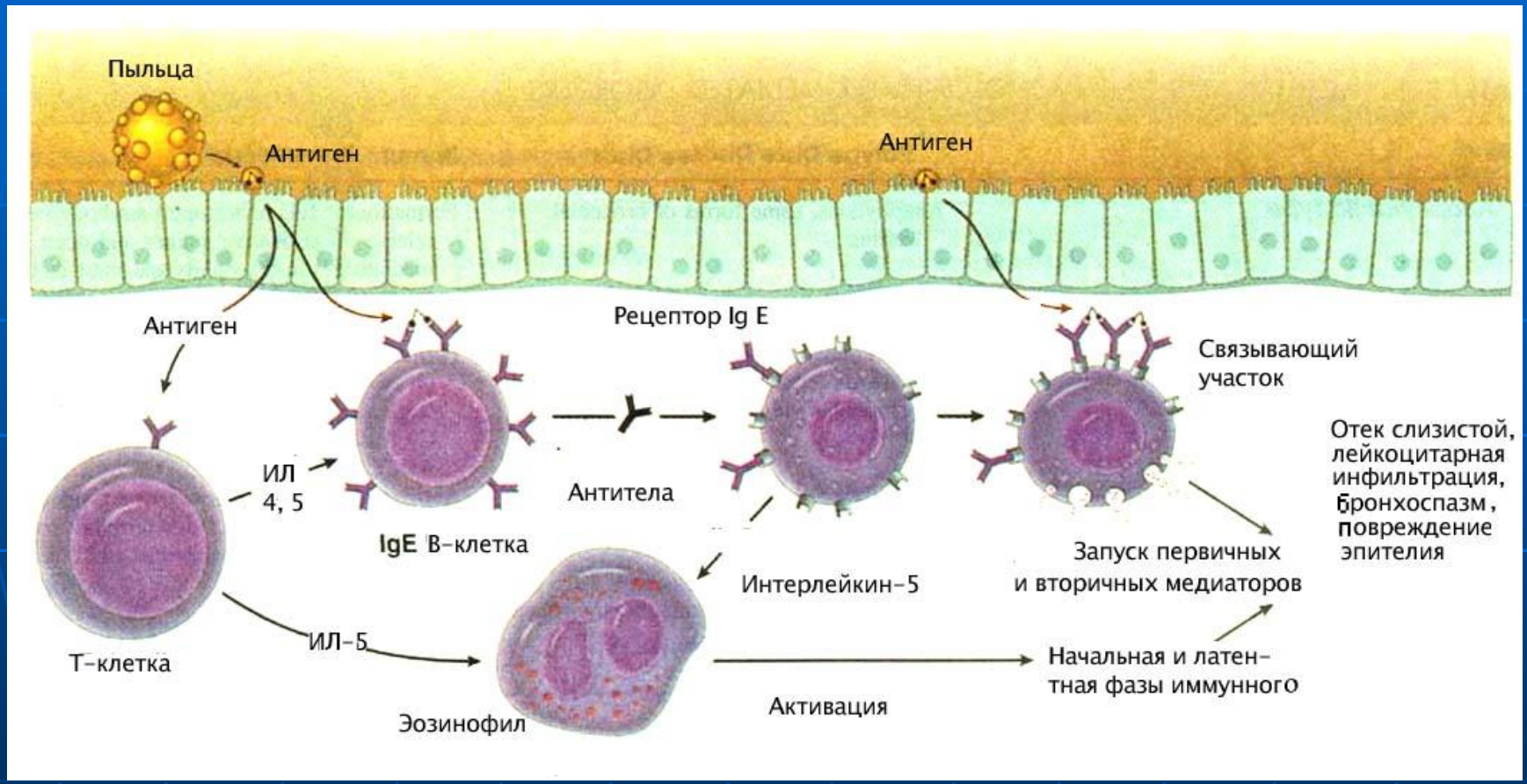
- **Hypersensitivity – Allergy , Type I**
- **of airways of lungs - Bronchi**
- **Allergens – in the air, mast cell - IgE ab.**
- **Inflammation of airways – Bronchitis.**
- **Genetic, Environmental, Race, Age.**
- **High in industrial cities 4-19%, Fiji < 1%**
- **Increasing incidence ...!**

Hypersensitivity Type-I

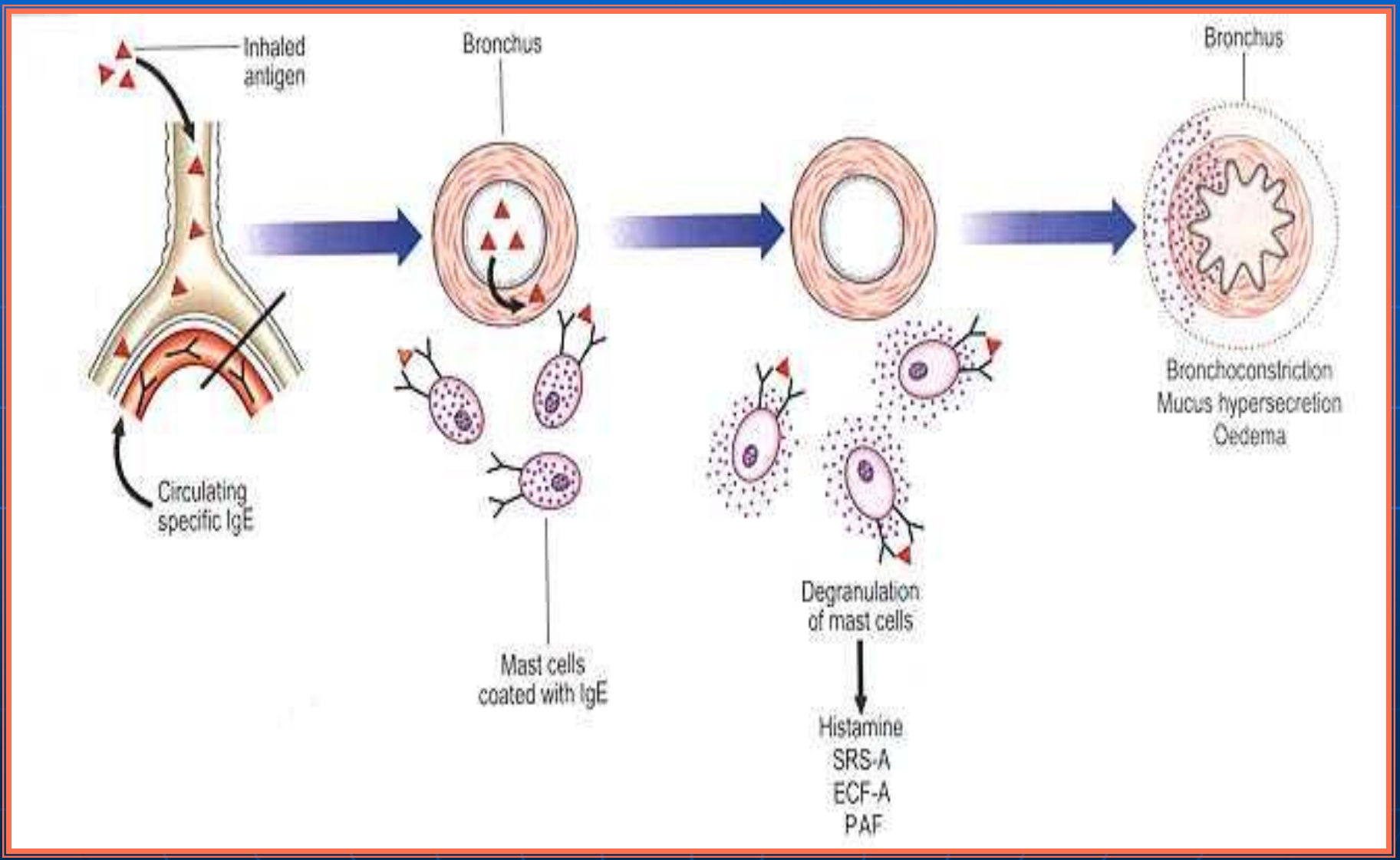




Hypersensitivity Type-I

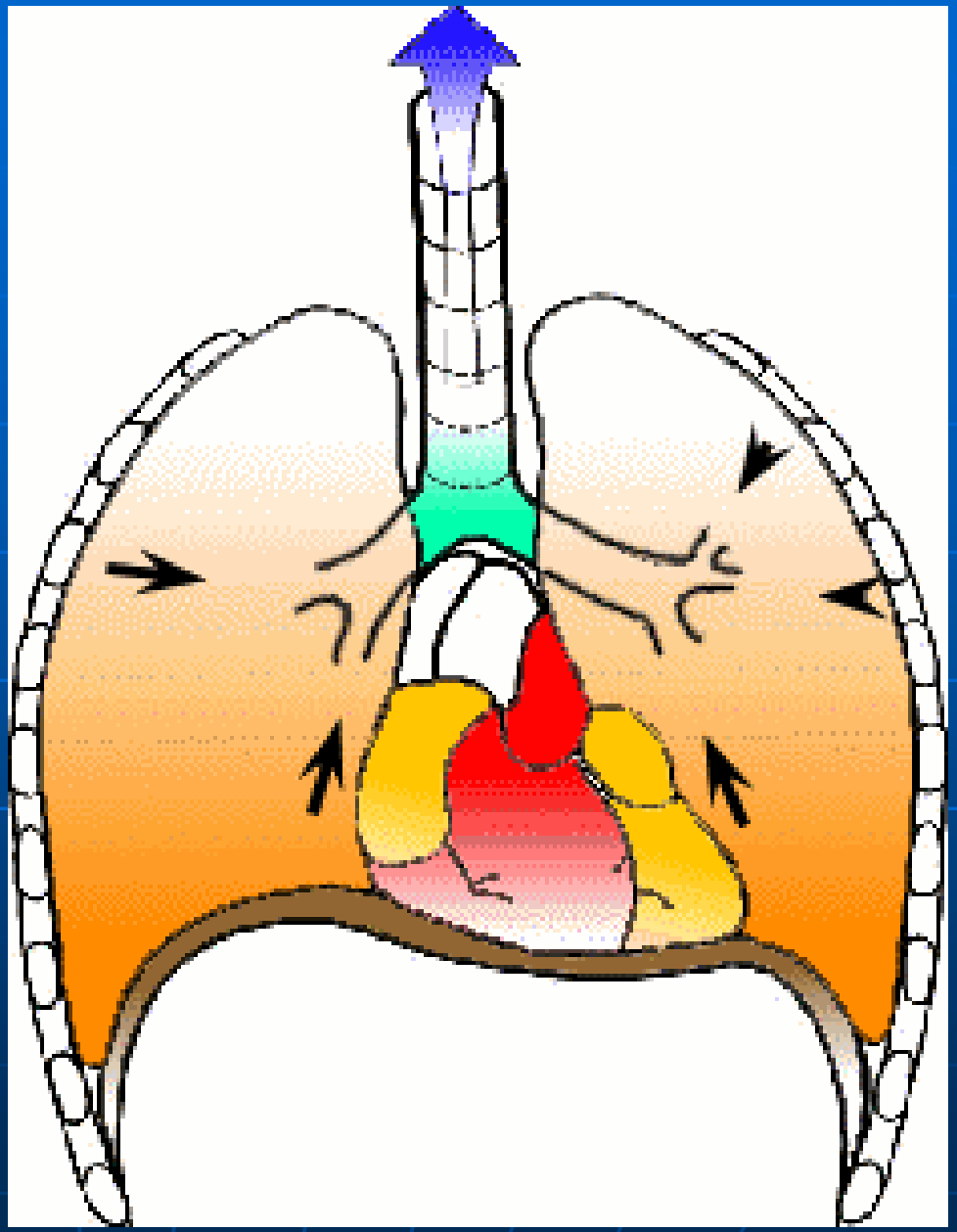


Pathogenesis - Atopic Asthma:



Asthma Mechanism:

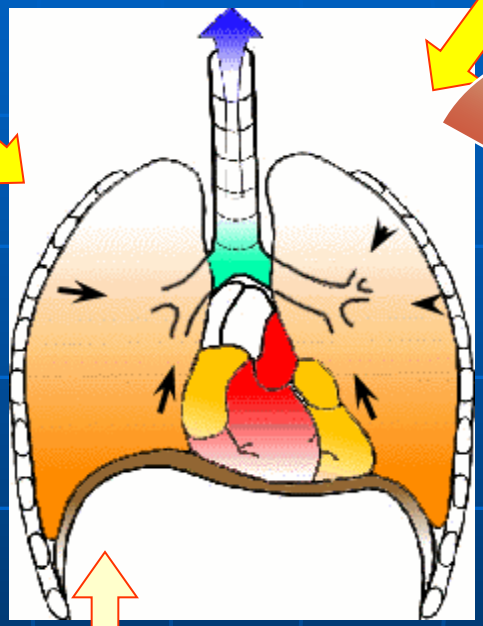
- **Allergy**
- **Inflammation Of Bronchi**
- **Obstruction**
- **Mucous Plugs**



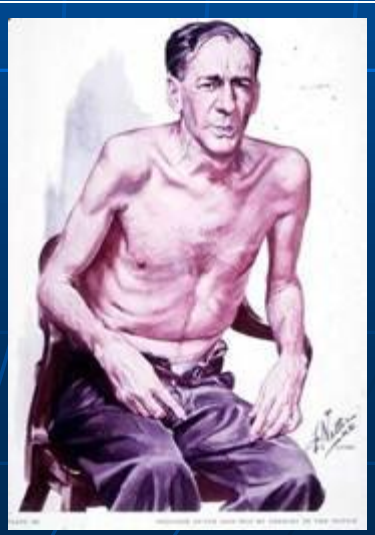
INFLAMMATION

Airway
Hyperresponsiveness
Genetic*

INDUCERS
Allergens,pollutants

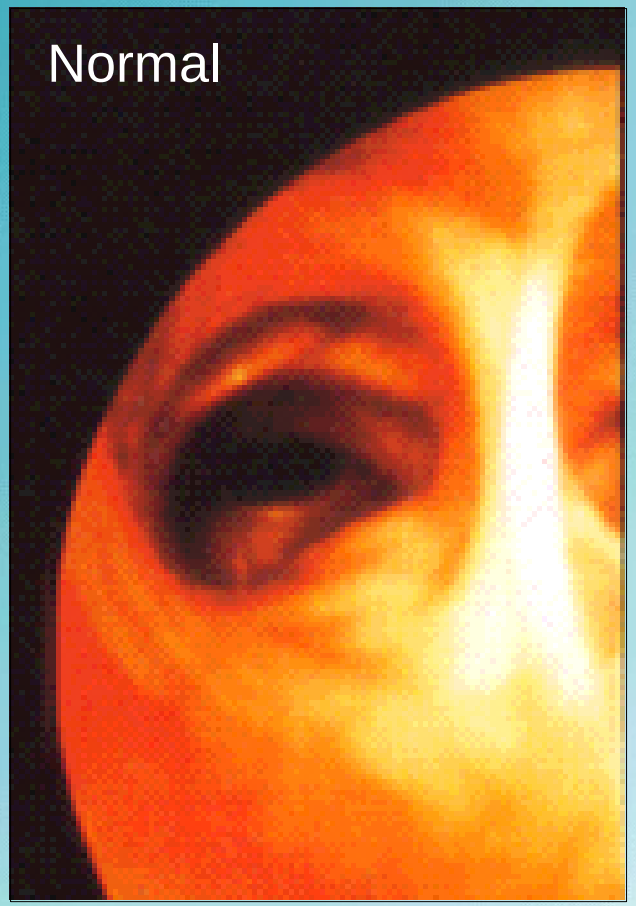


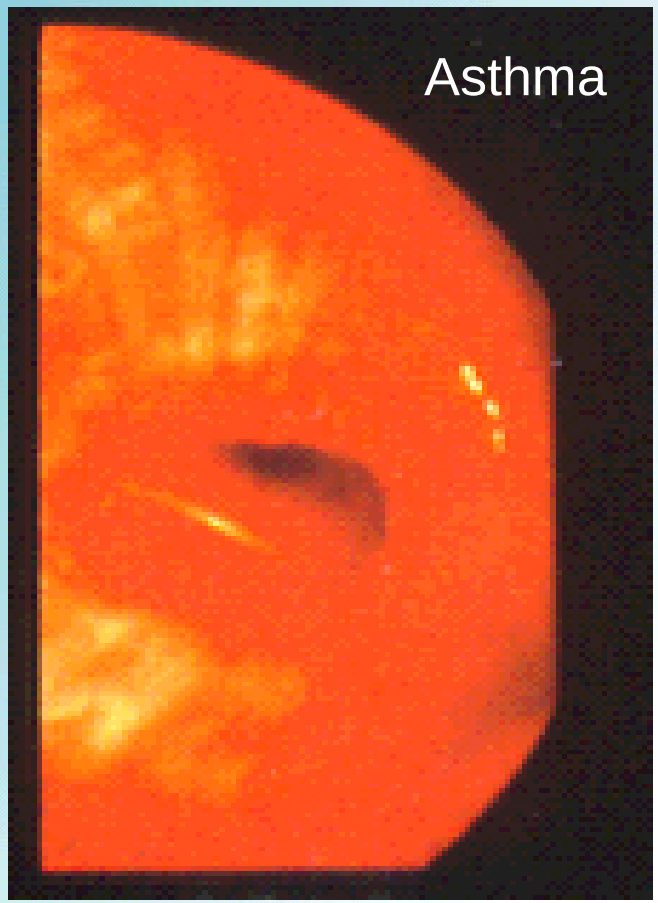
Airflow Limitation



TRIGGERS
Exercise
Cold Air, diseases,

Epidemiology/pathology



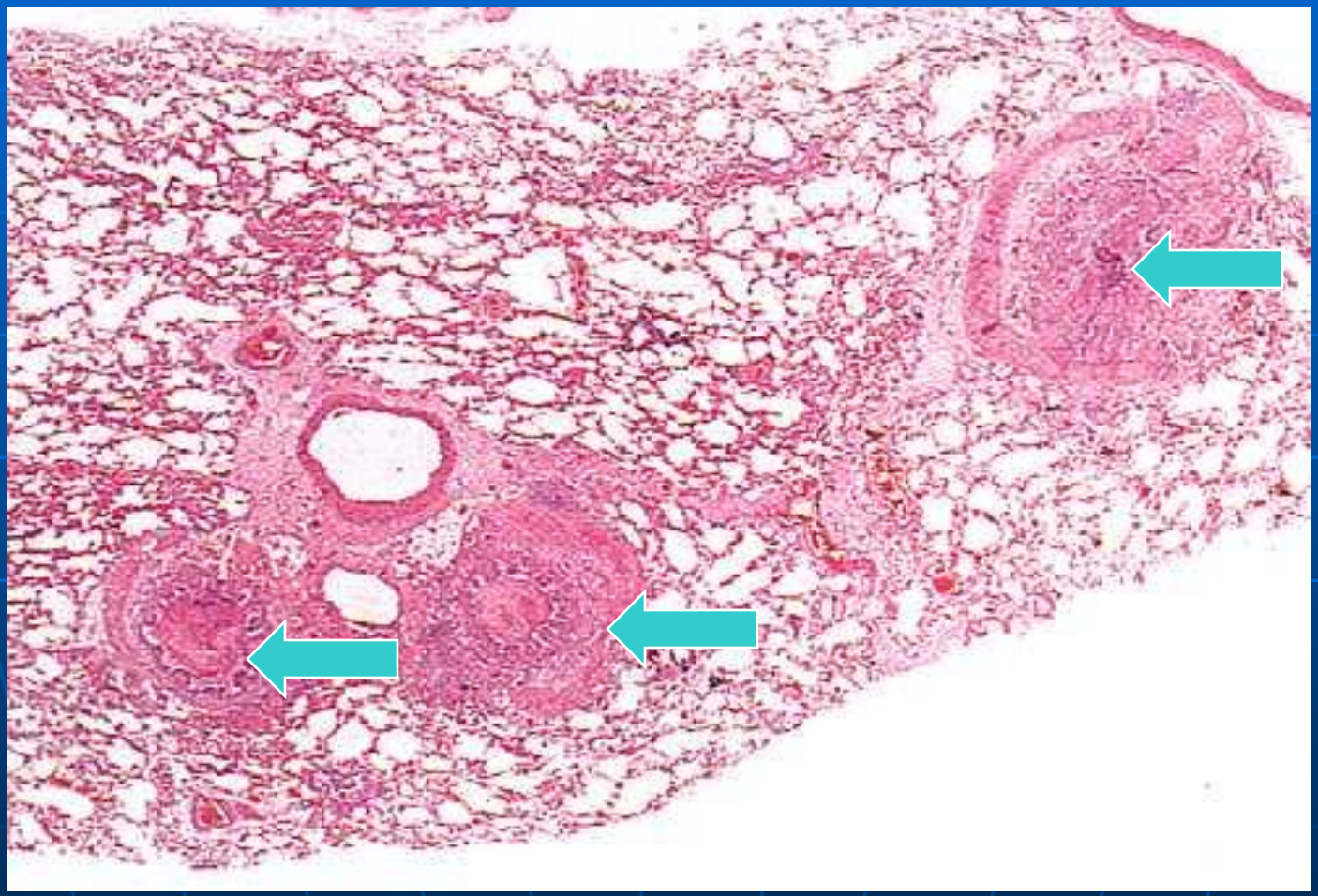


Barnes PJ

Lung in Asthma with Mucous plugs

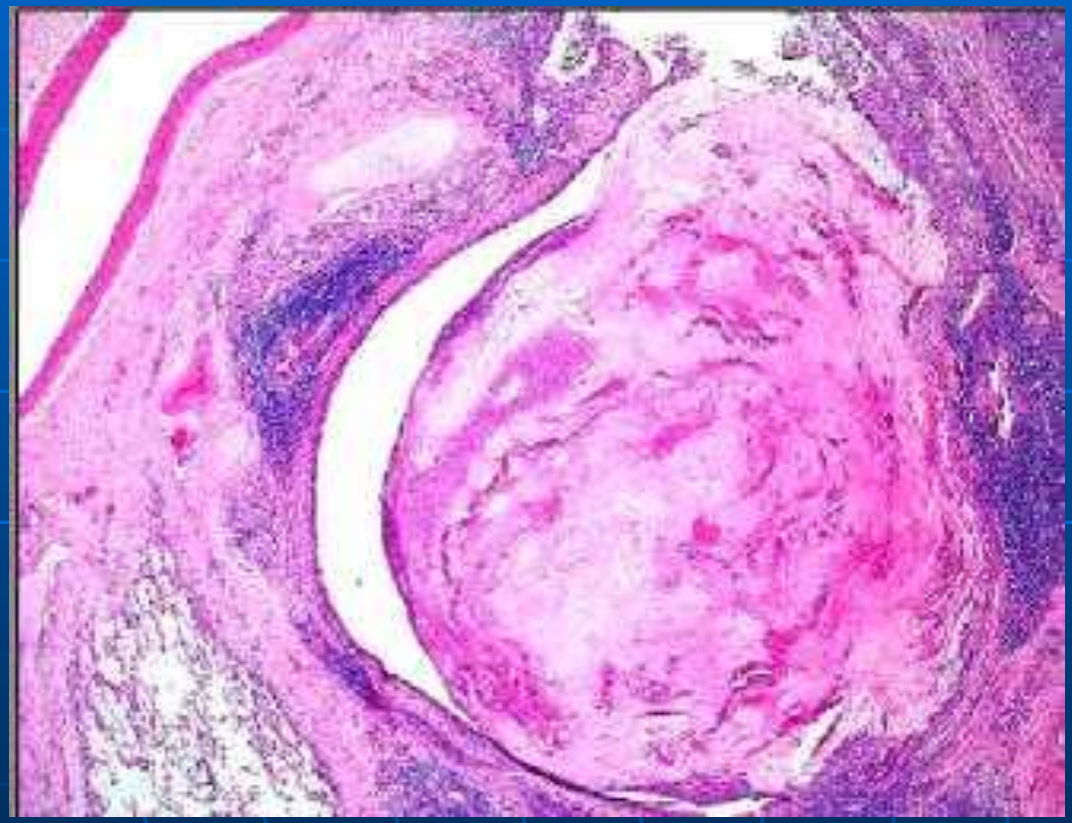
Mucous plug in asthma:

Asthma Microscopic Pathology



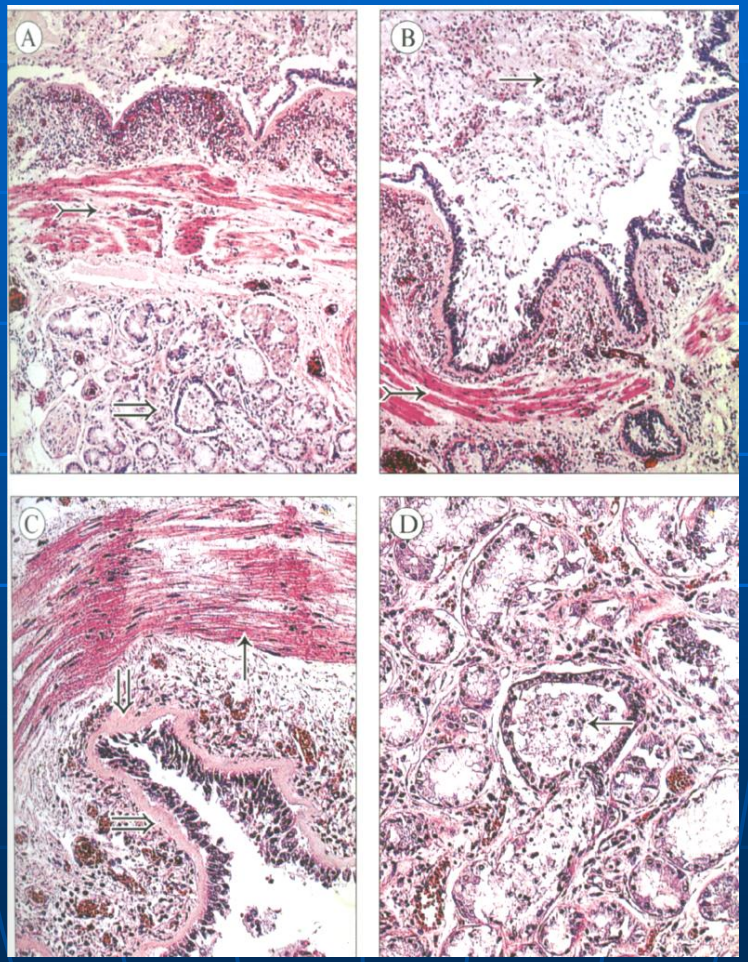
Obstructed Inflammed Bronchi

Asthma - Bronchial morphology



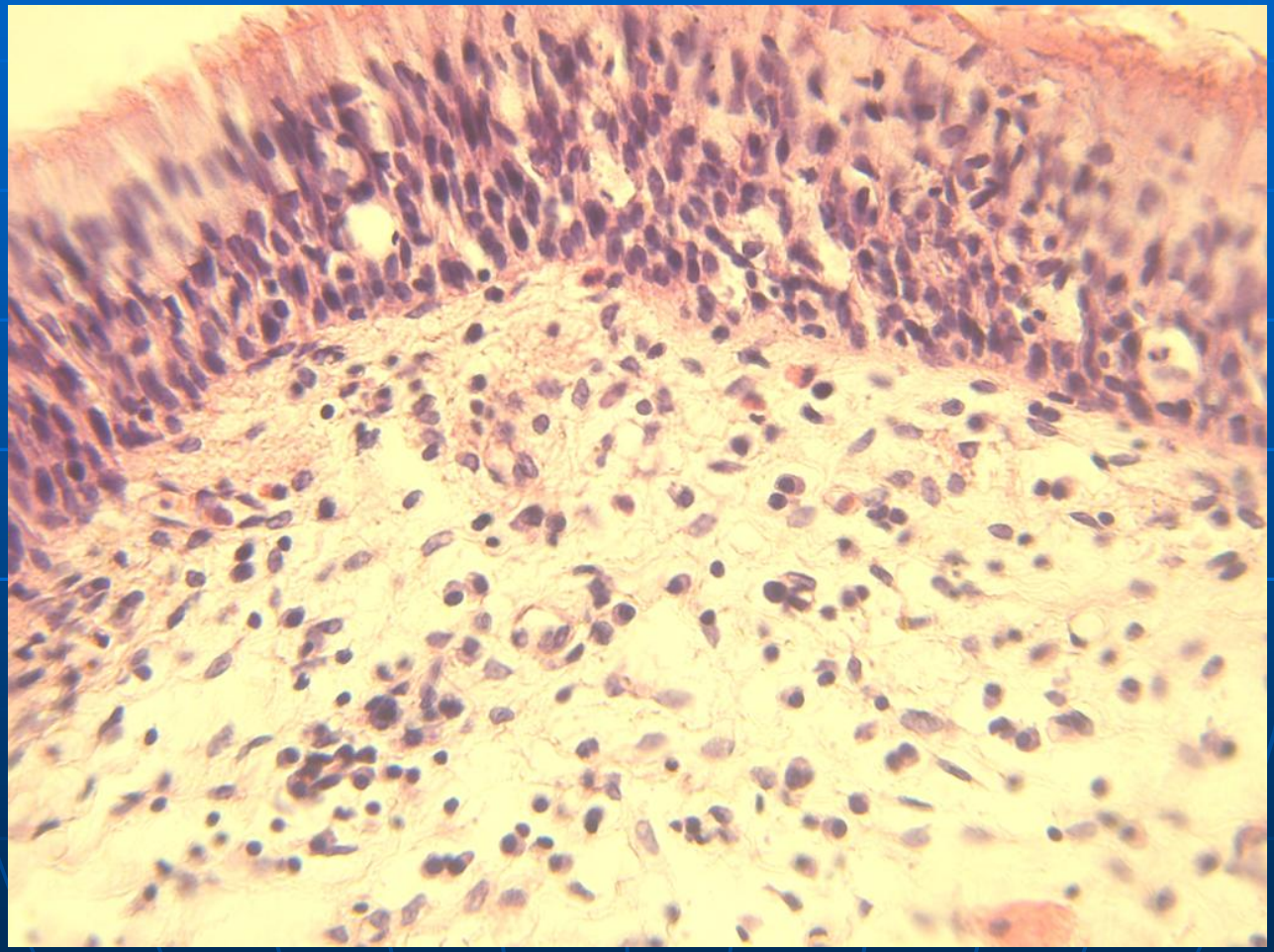
- inflammation
- Eosinophils
- Gland hyperplasia
- Mucous plug in lumen
- Hypertrophy of muscle layer

Asthma - Bronchial morphology



Hypersensitivity Type I.

Allergic rhinitis.



Hypersensitivity Type II

- IgM or IgG

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

Complement-Mediated Reactions

- cell lysis (direct)
- opsonization
  (IgM или IgG) hemolytic anemias.

Antibody-Dependent Cell-Mediated Cytotoxity

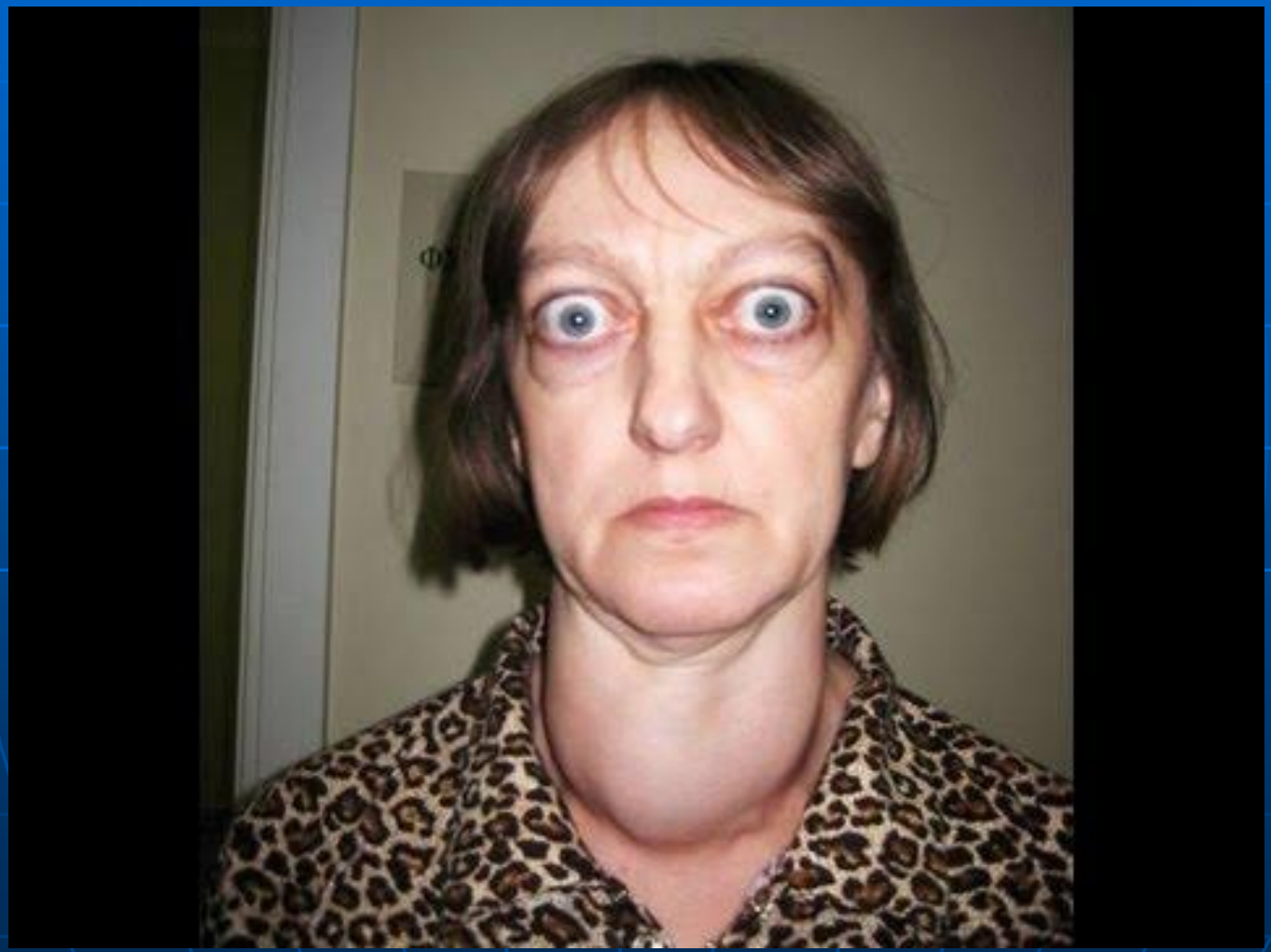
Target cells, coated IgG.

Cells bear receptors for Fc portion IgG (neutrophils, eosinophils, macrophages, NK cells) cause the lysis of target cells.

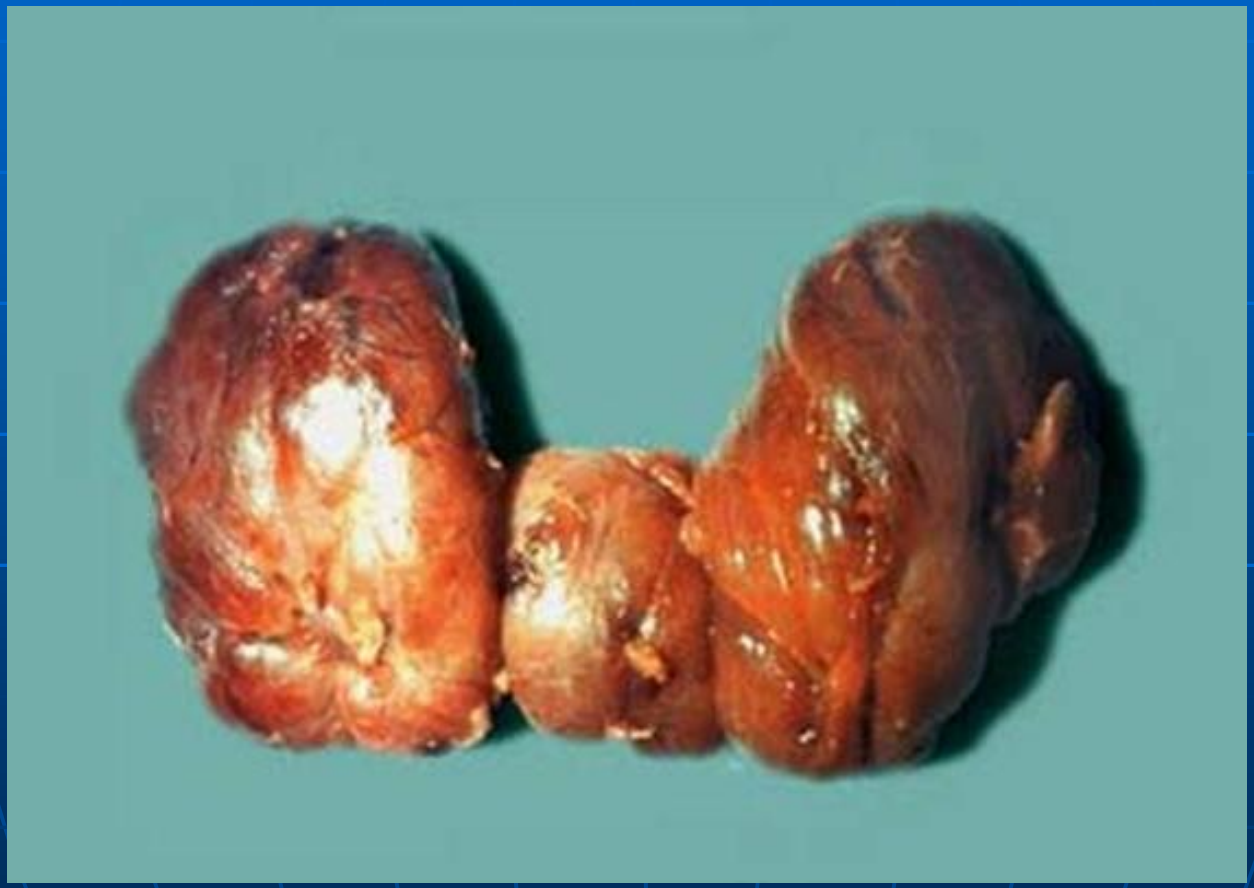
Antibody-Dependent Cellular Dysfunction

- Antibodies directed against cell surface receptors impair or dysregulate functions.

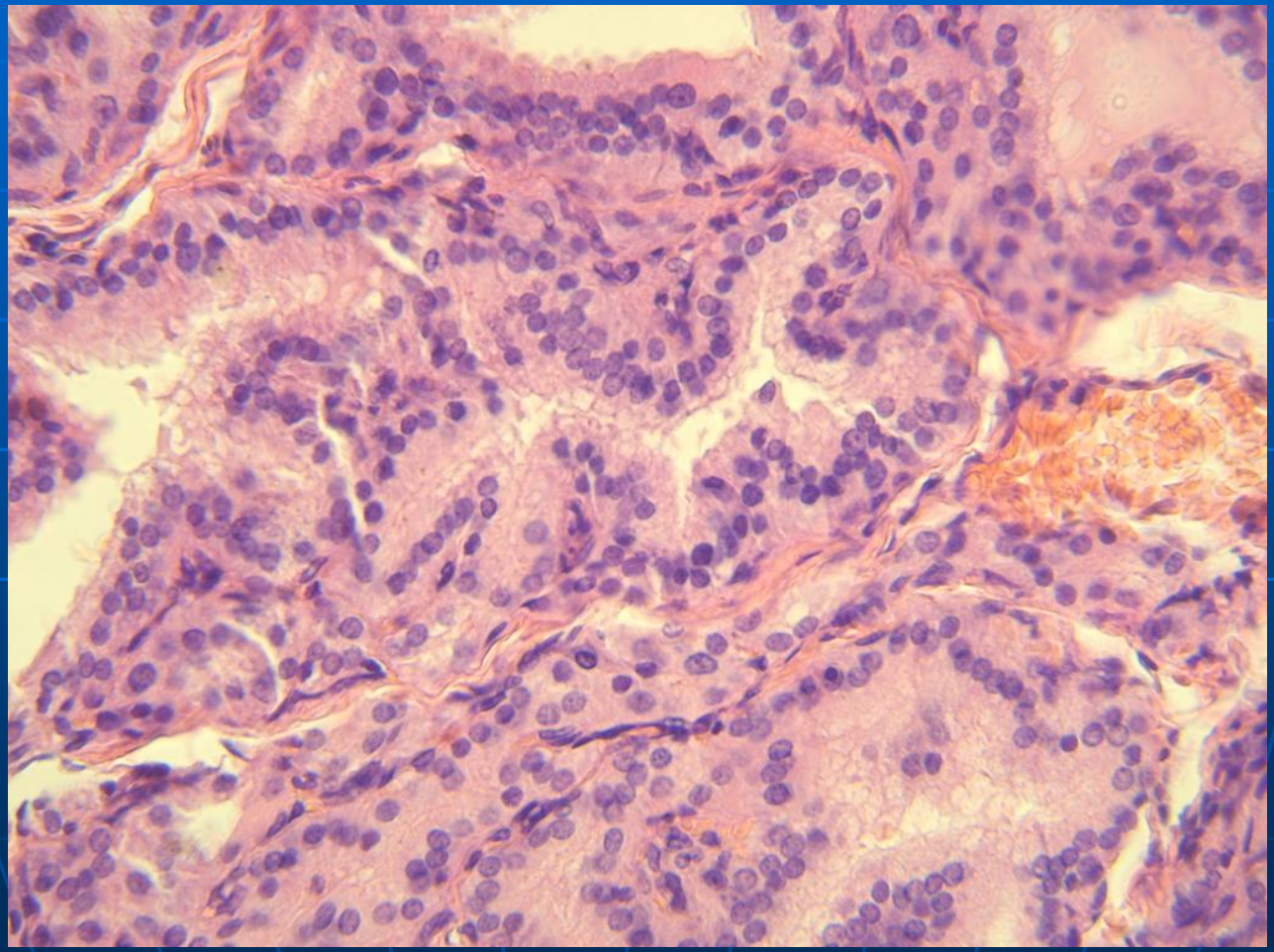
Grave’s disease.



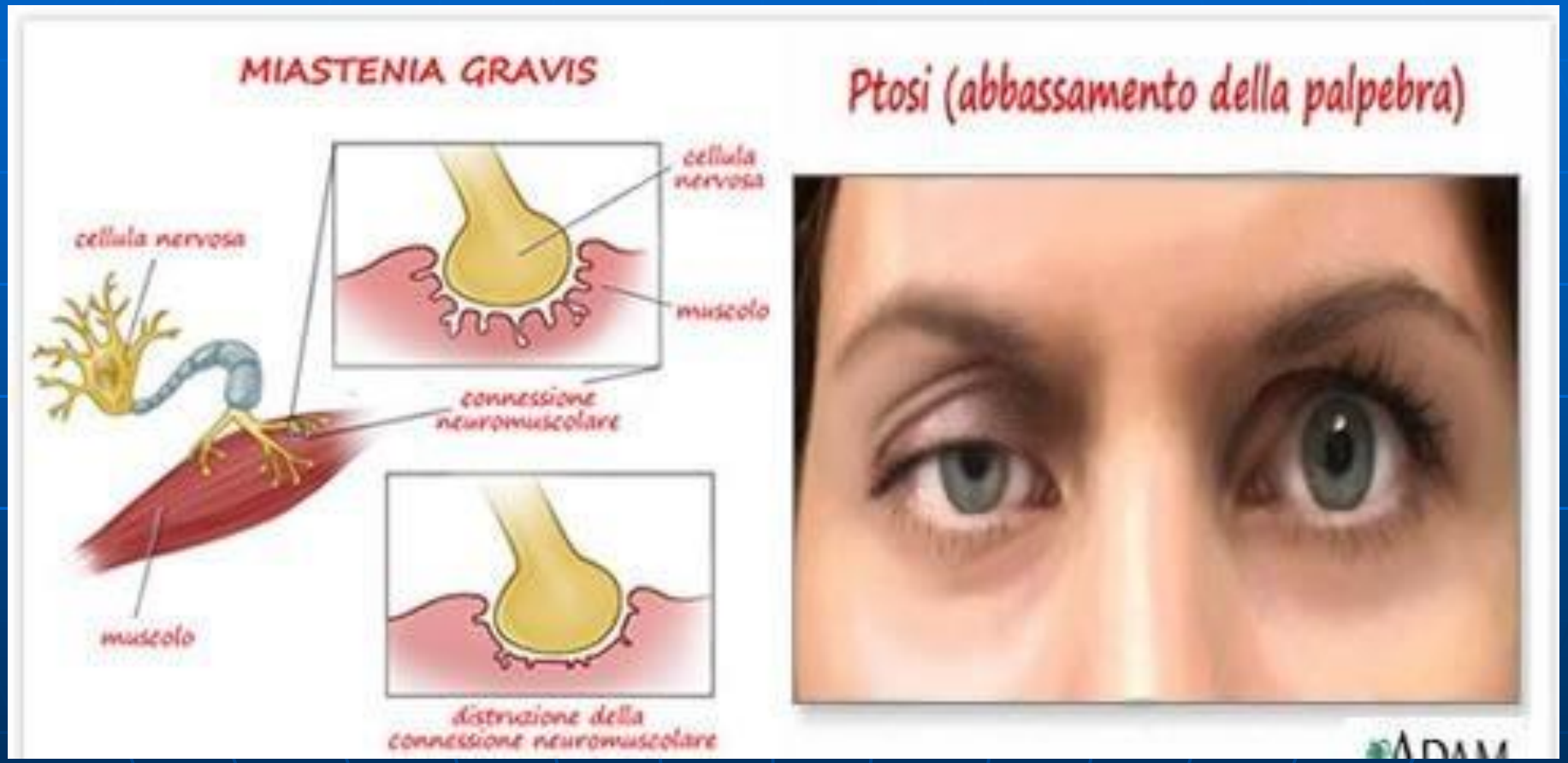
Grave’s disease.

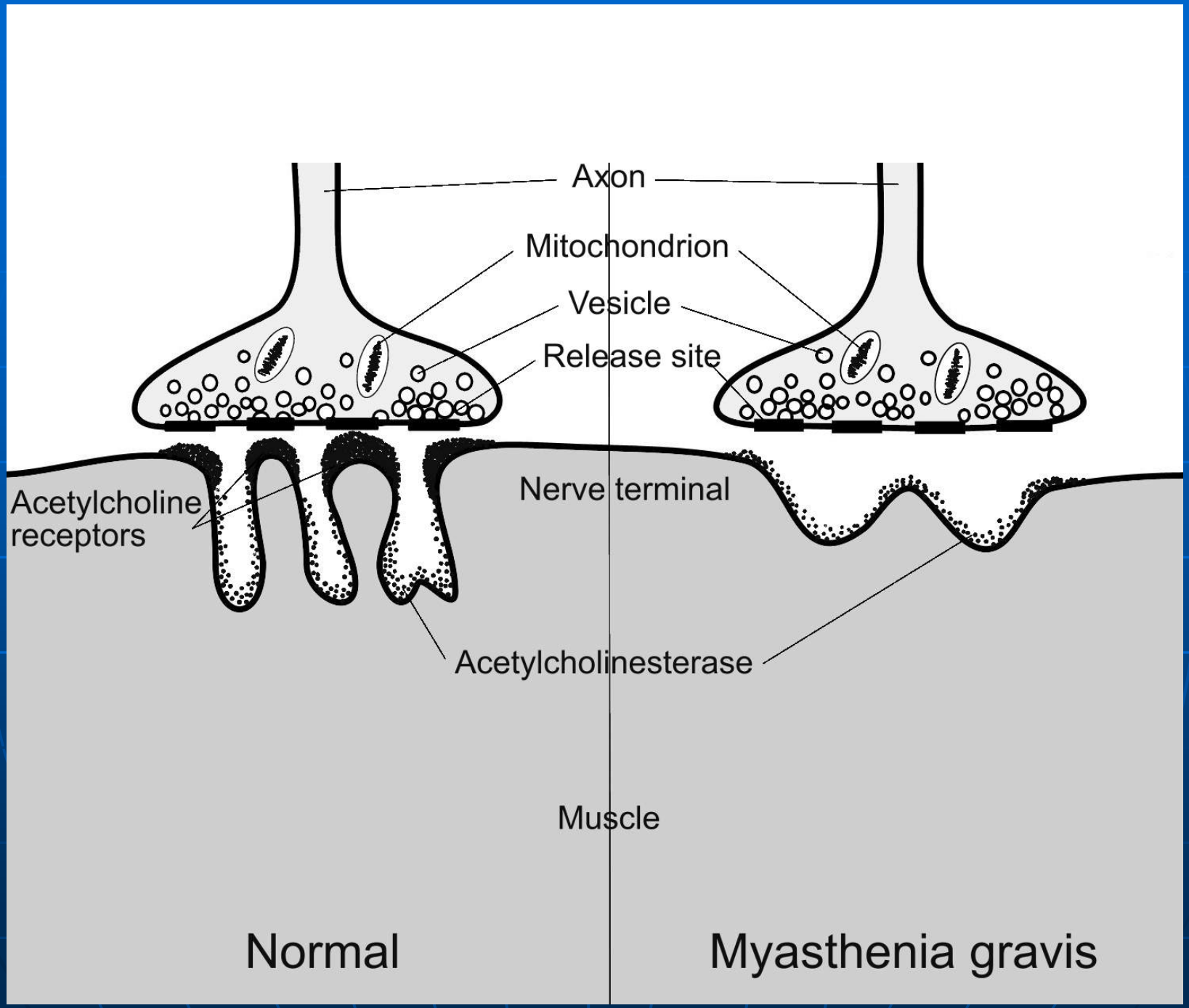


Grave’s disease.

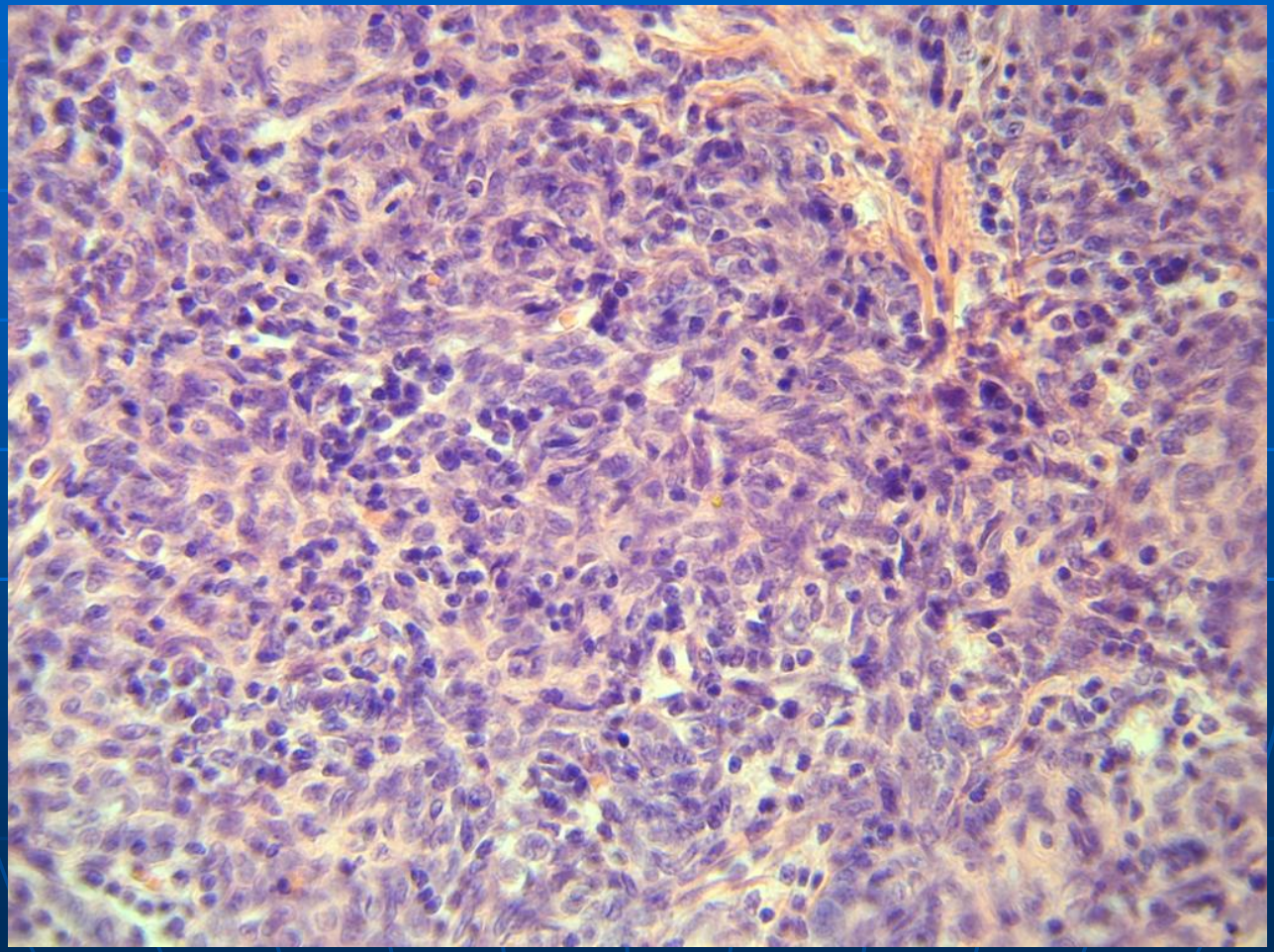


Myasthenia gravis.




Axon
Mitochondrion
Vesicle
Release site
Acetylcholine receptors
Nerve terminal
Acetylcholinesterase
Muscle
Normal
Myasthenia gravis

Myasthenia gravis.



Hypersensitivity Type III

(immune complex mediated)

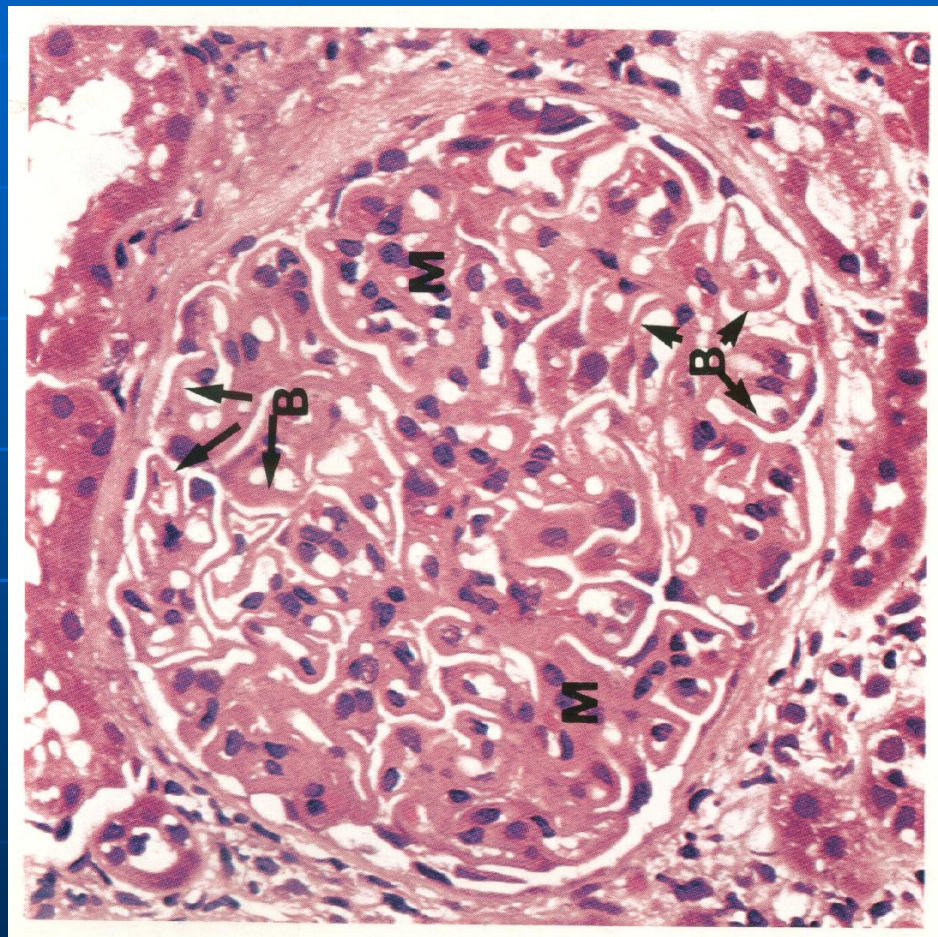
- Systemic immune complex disease

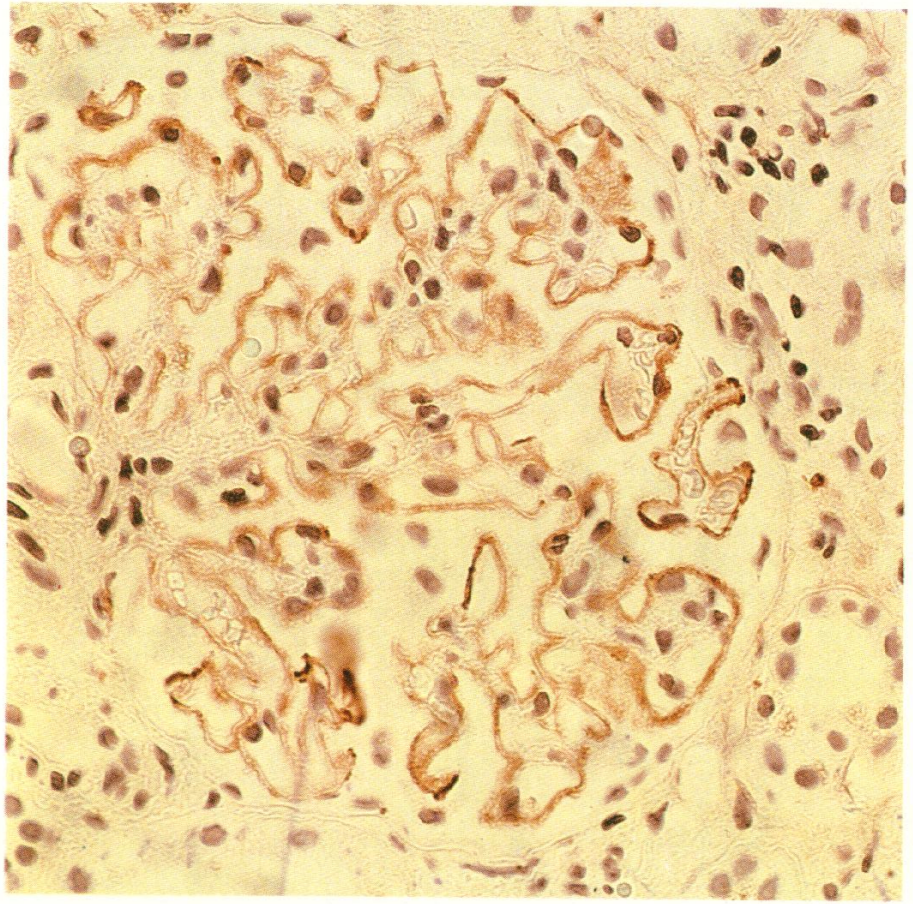
- Local immune complex disease (Arthus reaction)

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)

Membranous nephropathy.





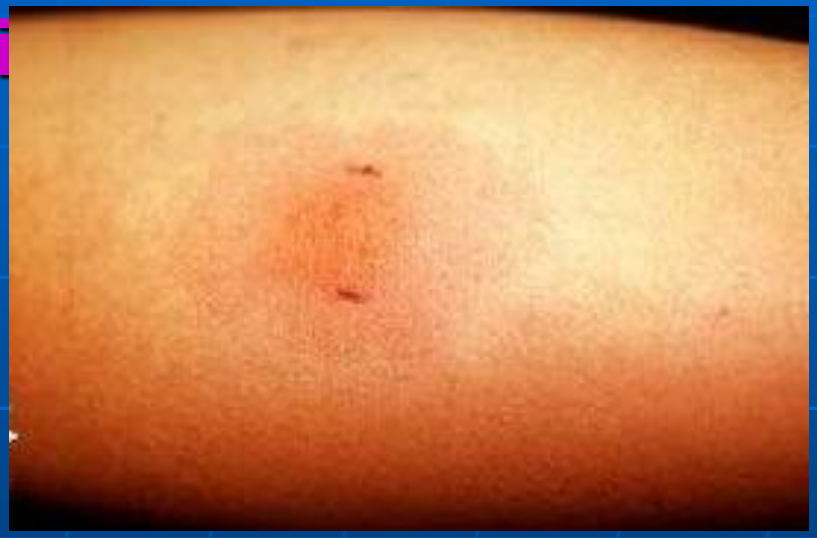
Hypersensitivity Type IV (Cell mediated).

- T-cells

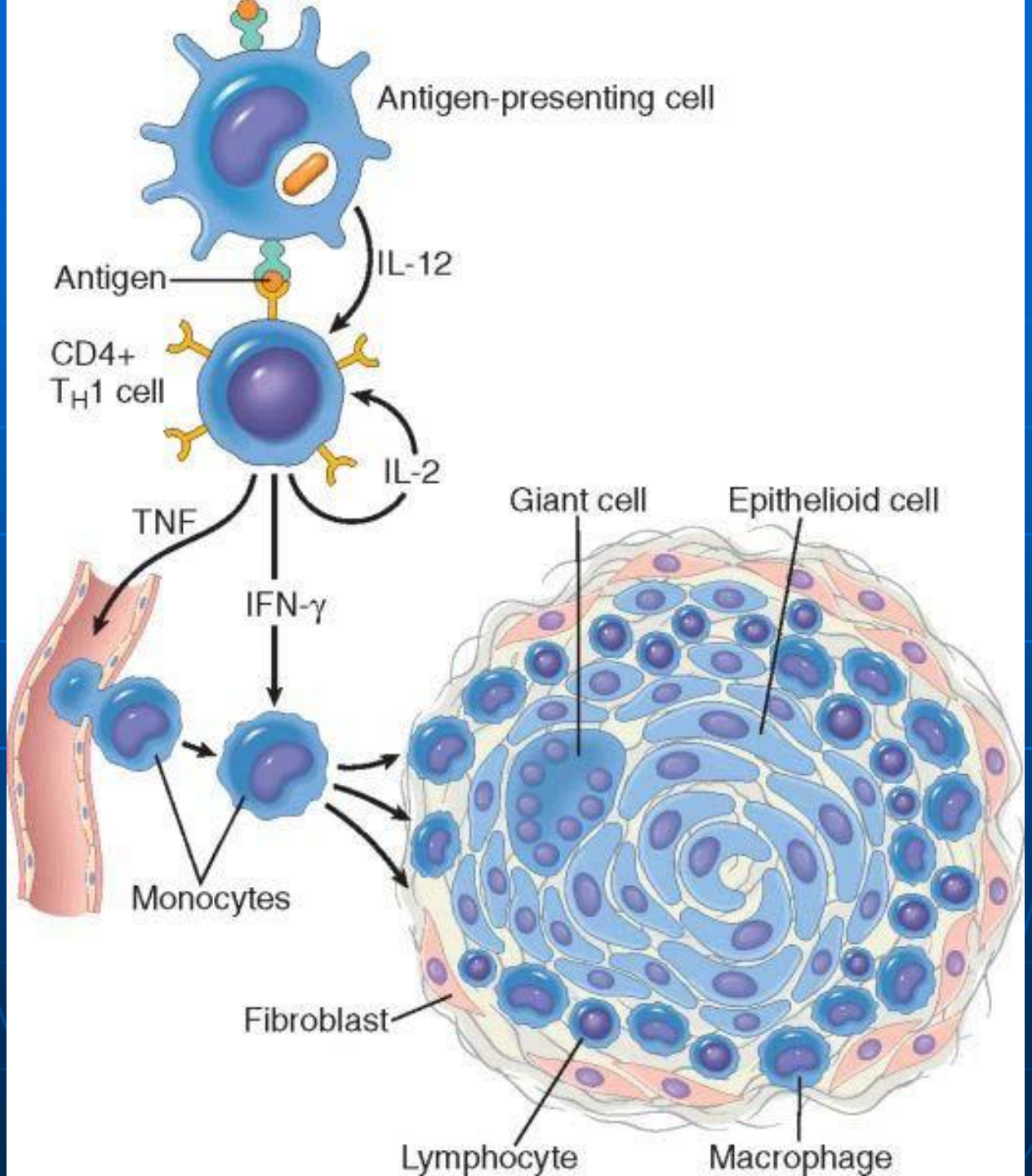
- Delayed Type of Hypersensitivity,
- T Cell-Mediated Cytotoxity

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

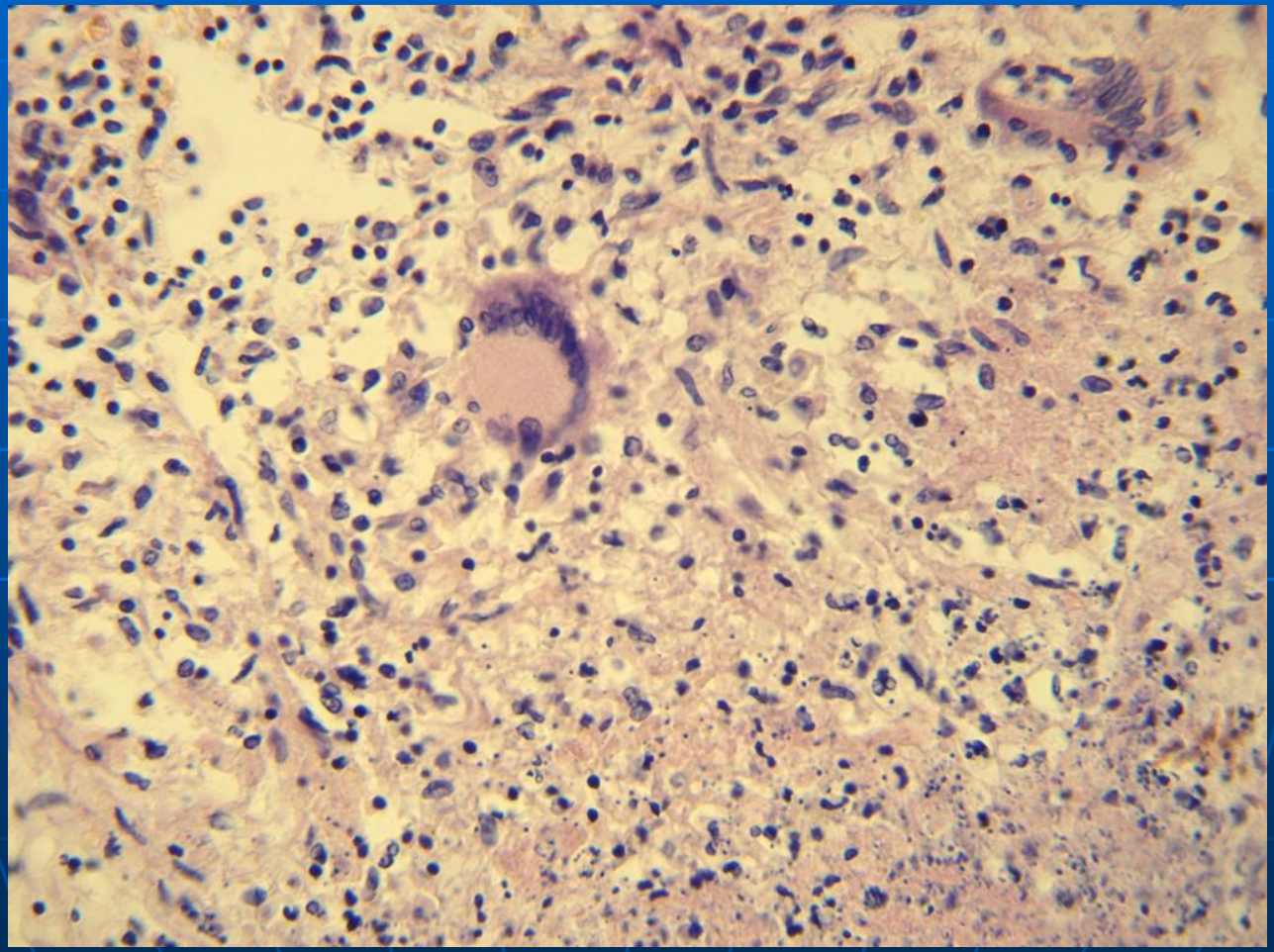
- Tuberculin Skin Reacti



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


Antigen-presenting cell
IL-12
Antigen
CD4+
T_H1 cell
IL-2
TNF
IFN-γ
Giant cell
Epithelioid cell
Monocytes
Fibroblast
Lymphocyte
Macrophage

Hypersensitivity Type IV



Hypersensitivity Type IV(Cell mediated).

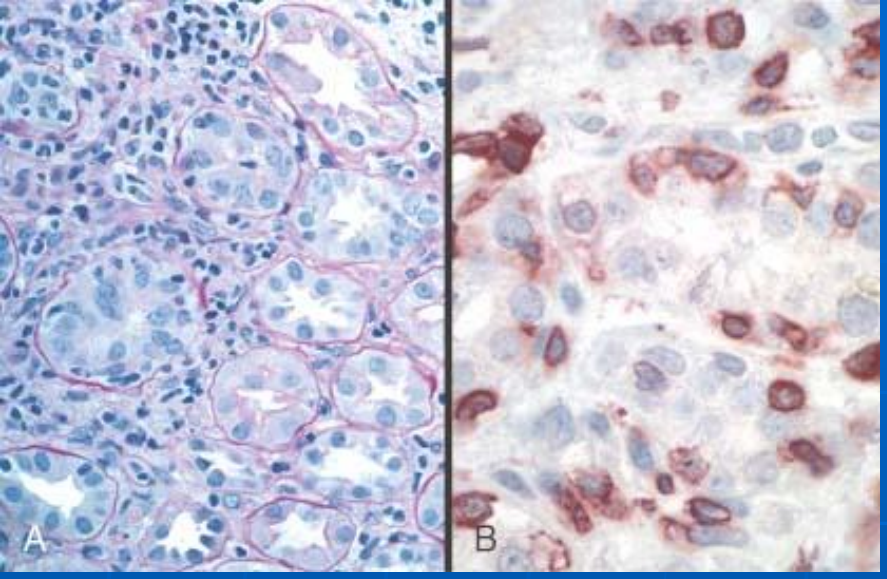
Электронограмма. Цитоплазматический мостик между активированным лимфоцитом и макрофагом. (В.В. Серов, 1986)

SUMMARY

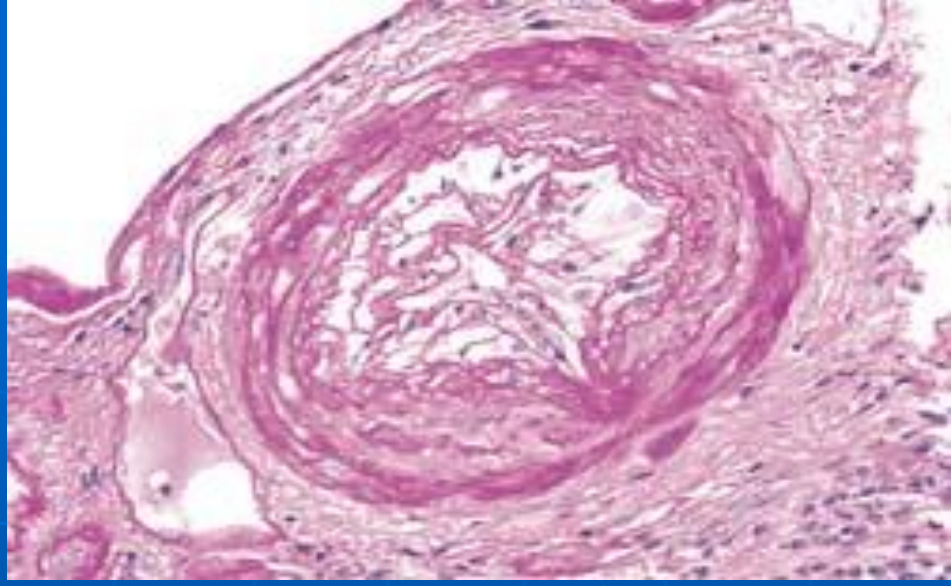
- **I** Acute allergic reaction
- **II** Antibodies directed against cell surfaces
- **III** Immune complexes
- **IV** Delayed Hypersensitivity, e.g., Tb skin test

RENAL TRANSPLANT REJECTION

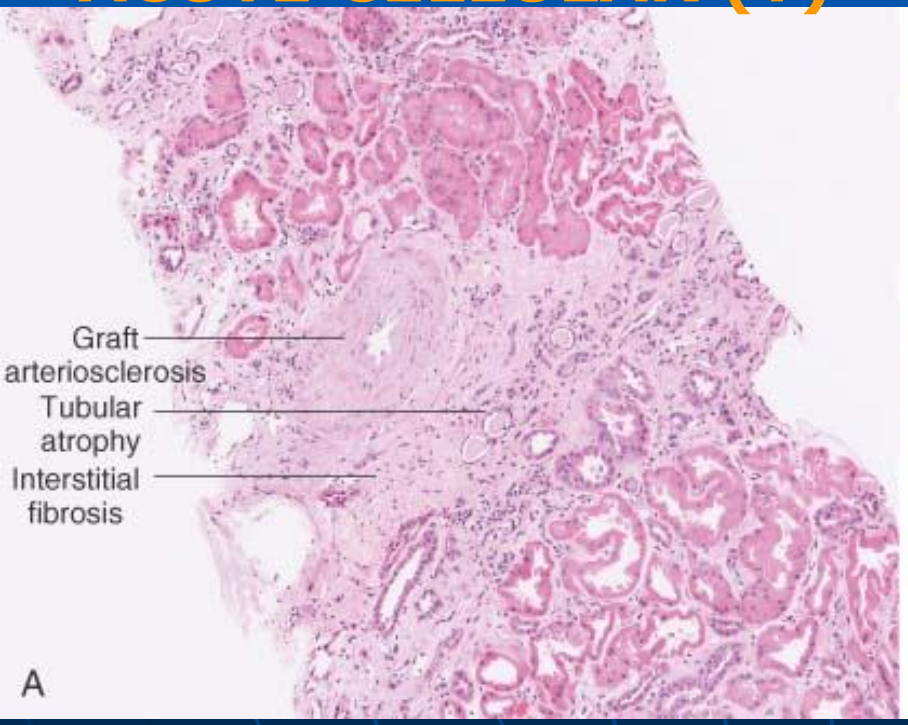
- **HYPERACUTE (minutes) :** AG/AB reaction of vascular endothelium
- **ACUTE (days→ months):** cellular (INTERSTITIAL infiltrate) and humoral (VASCULITIS)
- **CHRONIC (months):** slow vascular fibrosis

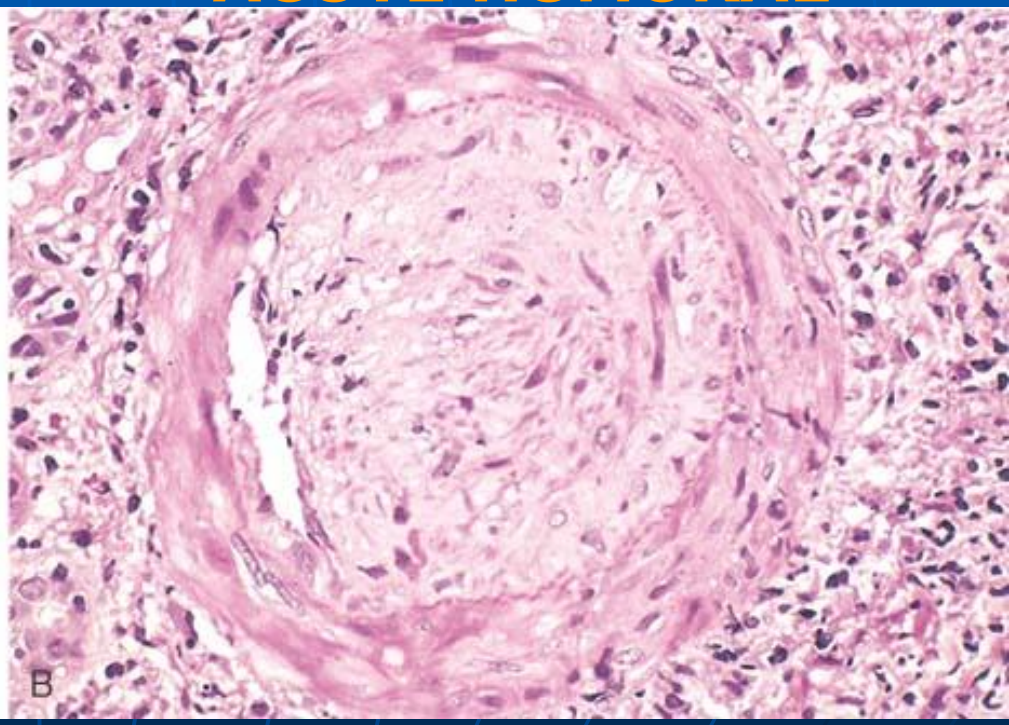


ACUTE CELLULAR (T)



ACUTE HUMORAL





CHRONIC

AUTOIMMUNE DISEASES

The evidence is now compelling that an immune reaction against "self-antigen" - autoimmunity - is the cause of certain diseases in humans. A growing number of diseases have been attributed to autoimmunity, but it must be confessed that in many the evidence is not firm.

Introduction

- Immune response against self antigen resulting in Tissue damage.
- Single organ or systemic multi organ.
- Common in females.
- Normally immune system is tolerant to self antigens (learns during fetal development).
- Autoimmune disorders result from Defective tolerance, cross reacting antibodies or antigenic mimicry.

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**

AUTOIMMUNE DISEASES

- 1. AUTOIMMUNE DISEASES OF NS
- 2. AUTOIMMUNE DISEASES OF ES
- 3. AUTOIMMUNE DISEASES OF BLOOD

AUTOIMMUNE DISEASES Nonspecific (SYSTEMIC)

- Systemic Lupus Erythematosus
- Rheumatoid artritis
- Polyarteritis nodosa

CLASSIC AUTOIMMUNE DISEASES (SYSTEMIC)

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

CLASSIC AUTOIMMUNE DISEASES (LOCAL)

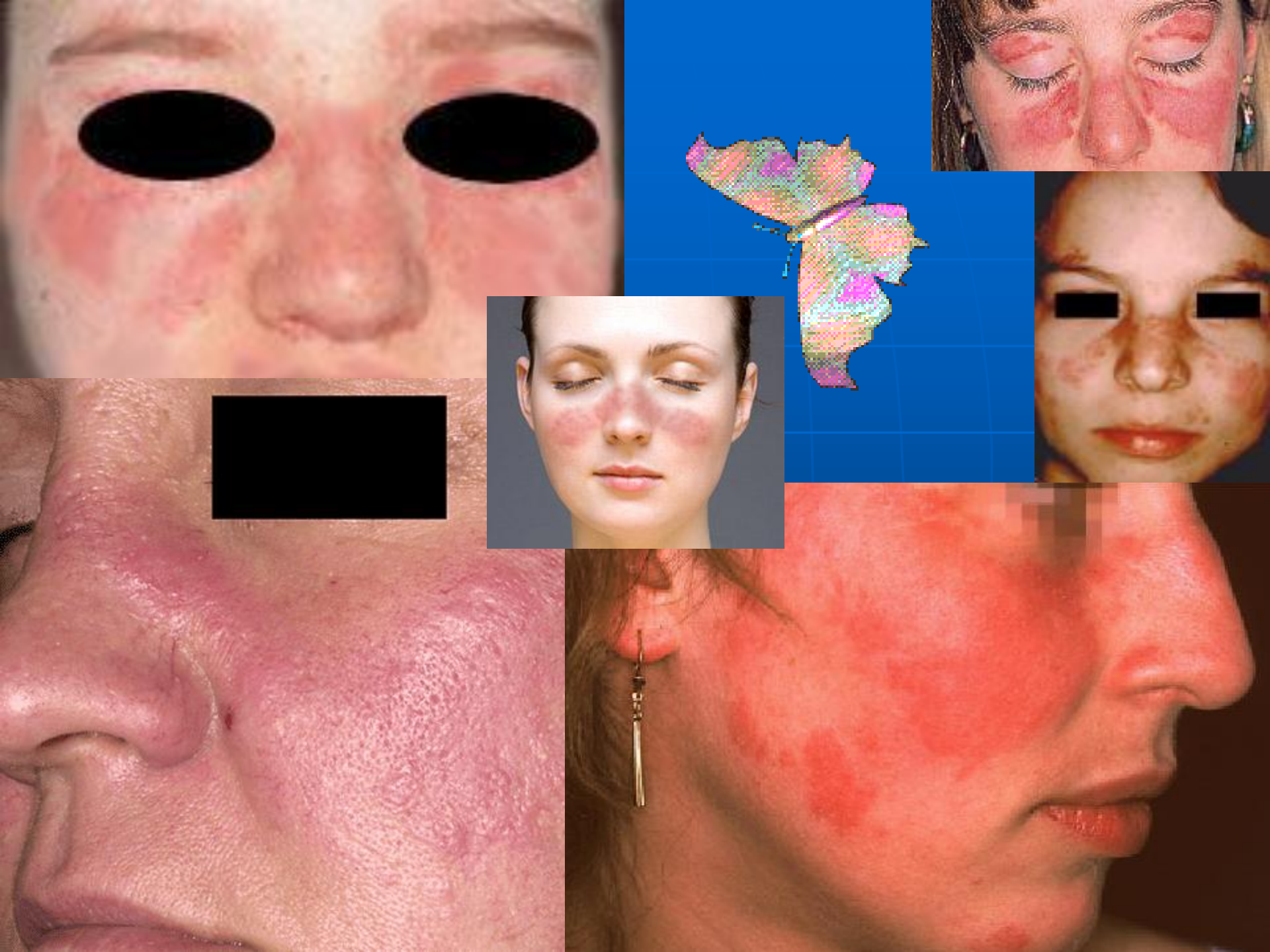
- HASHIMOTO THYROIDITIS
- AUTOIMMUNE HEMOLYTIC ANEMIA
- MULTIPLE SCLEROSIS
- AUTOIMMUNE ORCHITIS
- GOODPASTURE SYNDROME
- AUTOIMMUNE THROMBOCYTOPENIA
- "PERNICIOUS" ANEMIA
- INSULIN DEPENDENT DIABETES MELLITUS
- MYASTHENIA GRAVIS
- GRAVES DISEASE

N.B.

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

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.

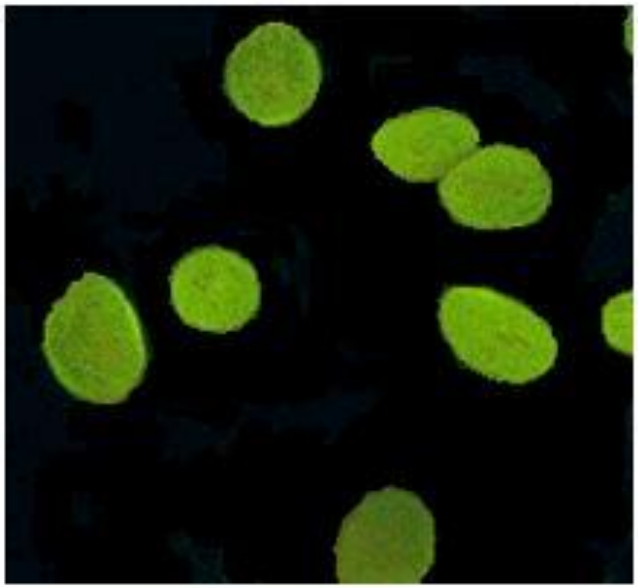


HOMO

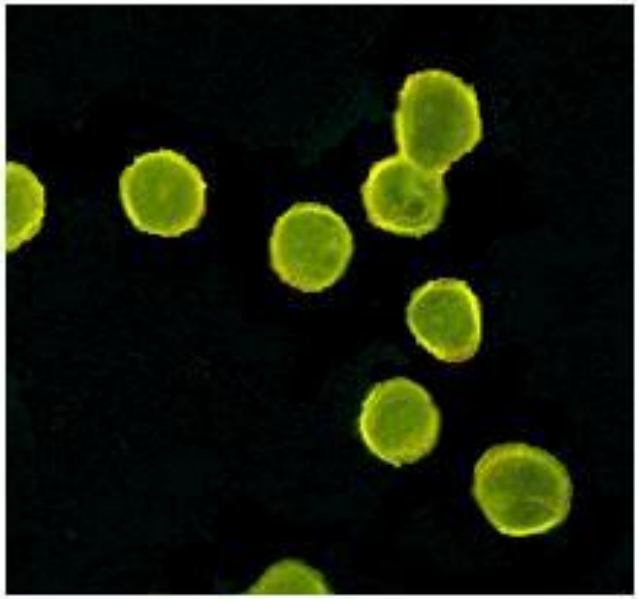
SPECK

RIM

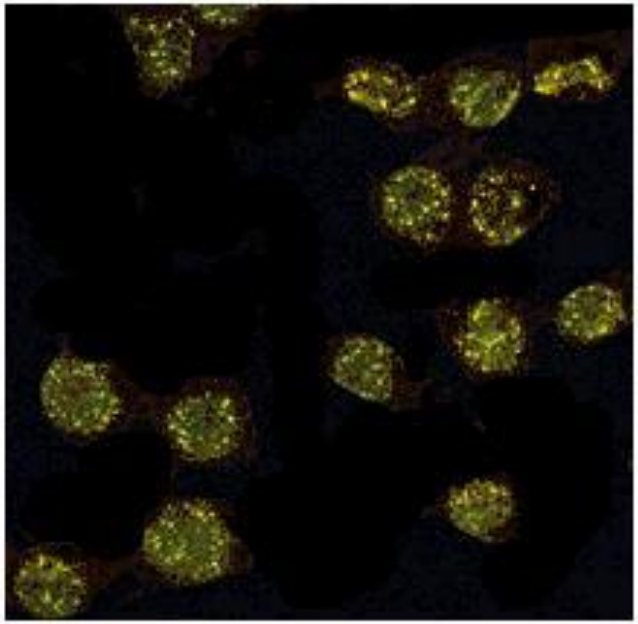
NUCLEOLAR



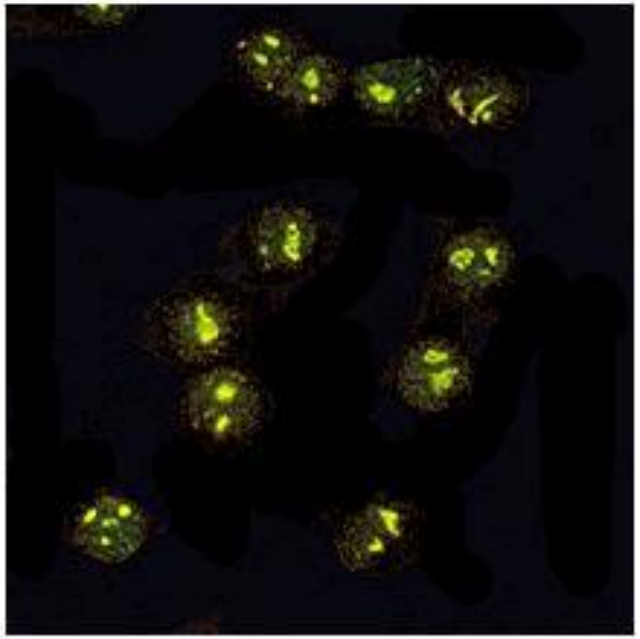
Homogenous pattern



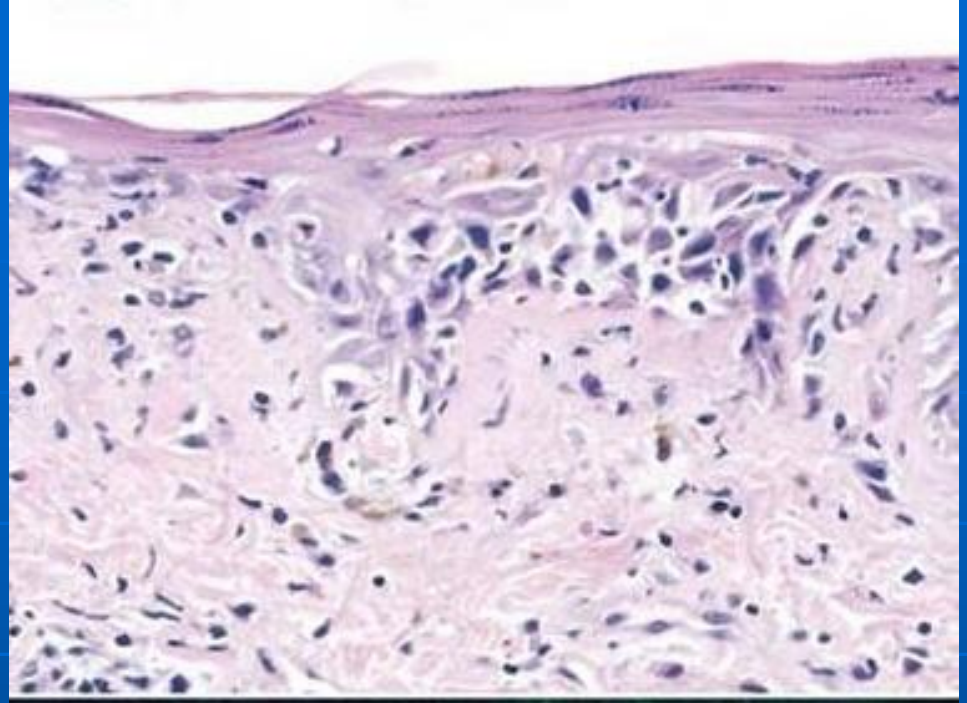
Rim pattern

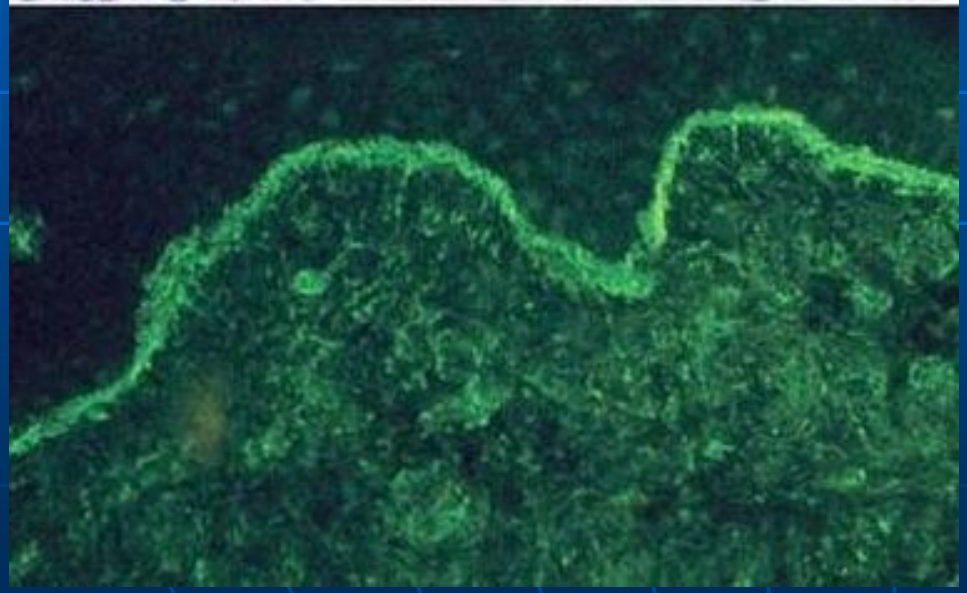


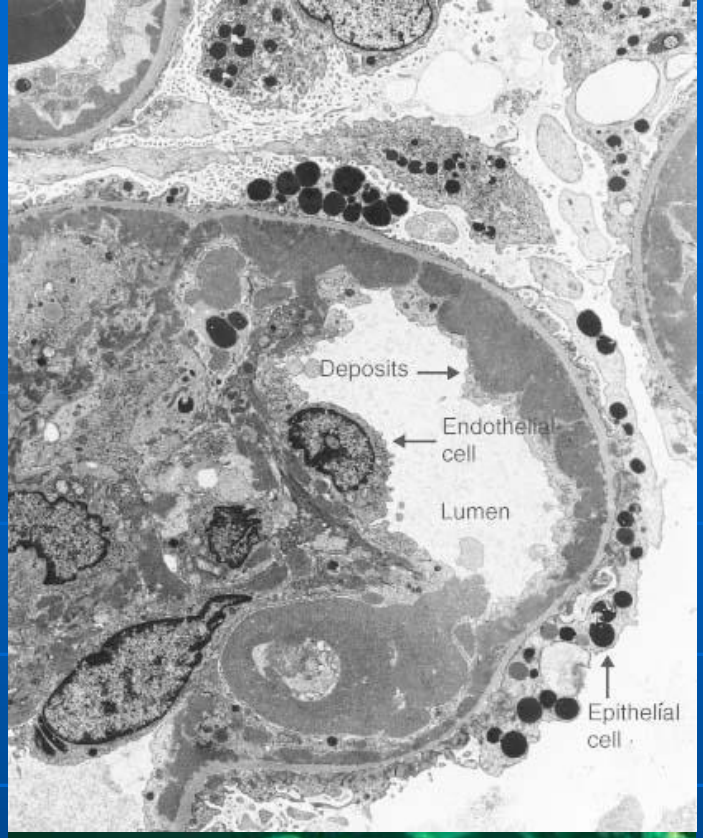
Speckled pattern

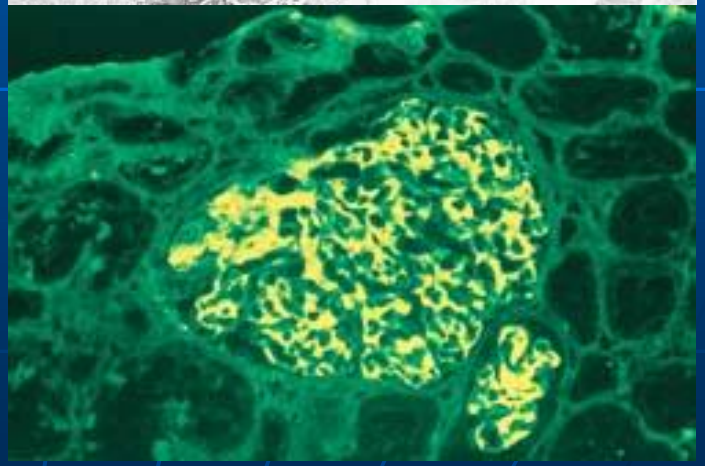


Nucleolar pattern



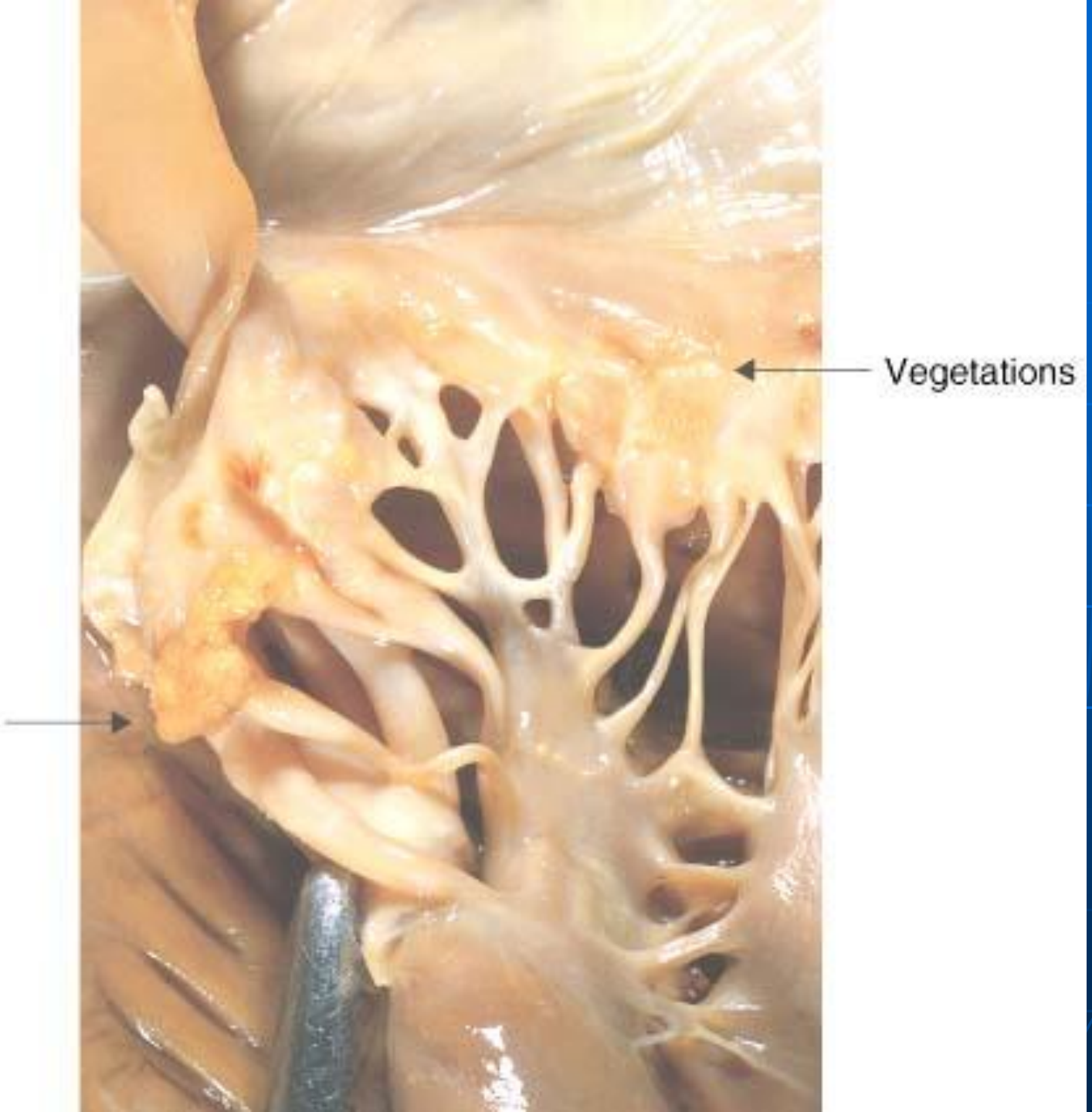






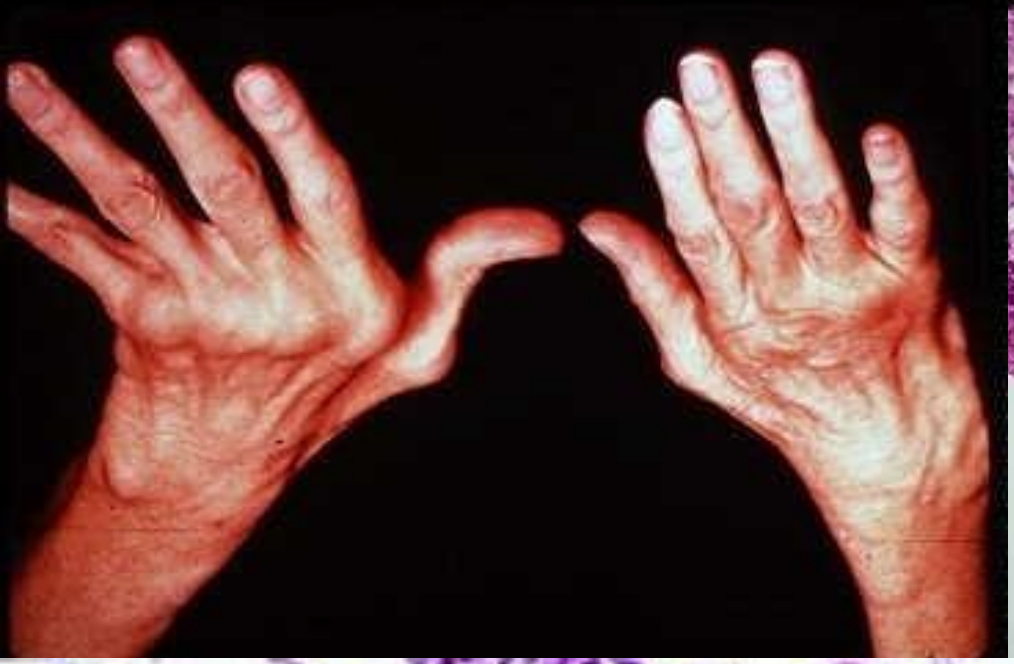
SLE, SKIN

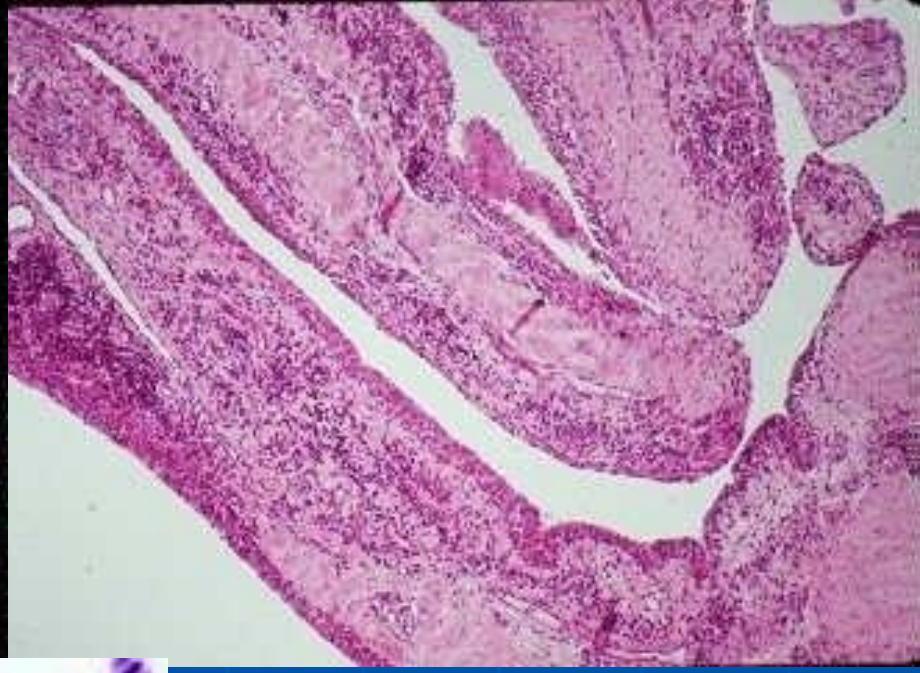
SLE,

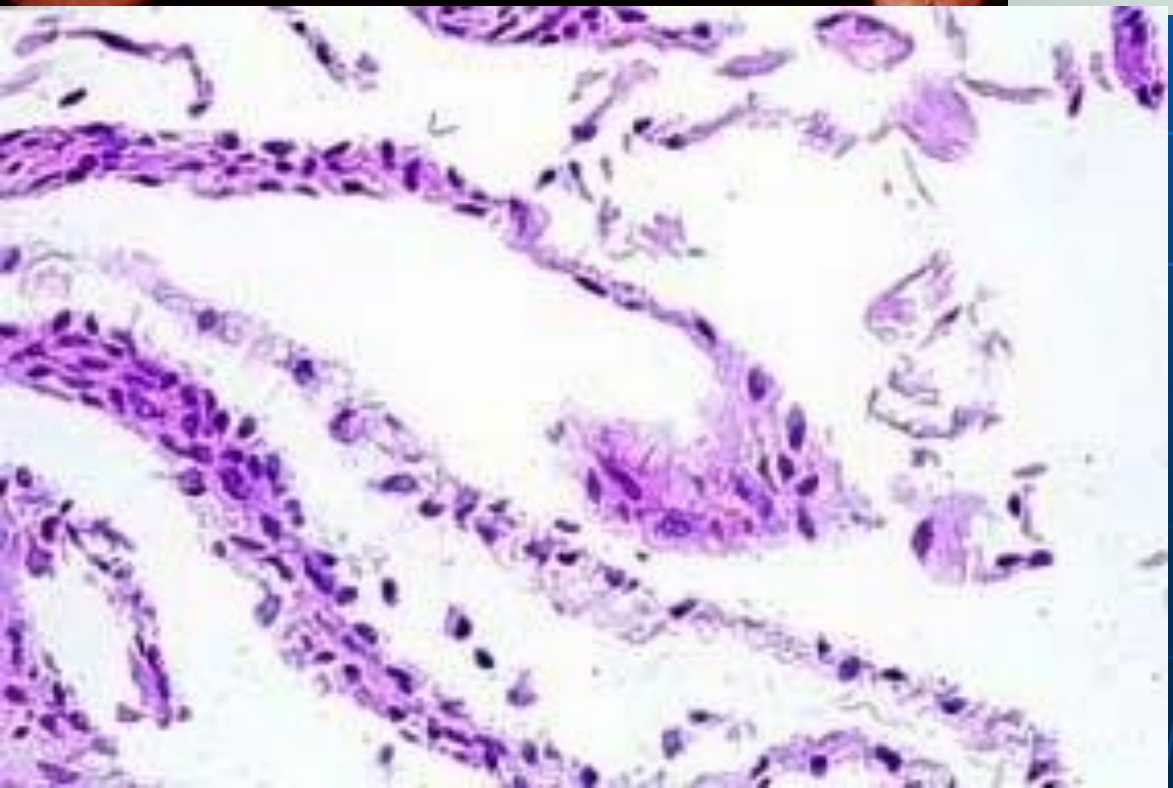

Vegetations

MORE SYSTEMIC AUTOIMMUNE DISEASES

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

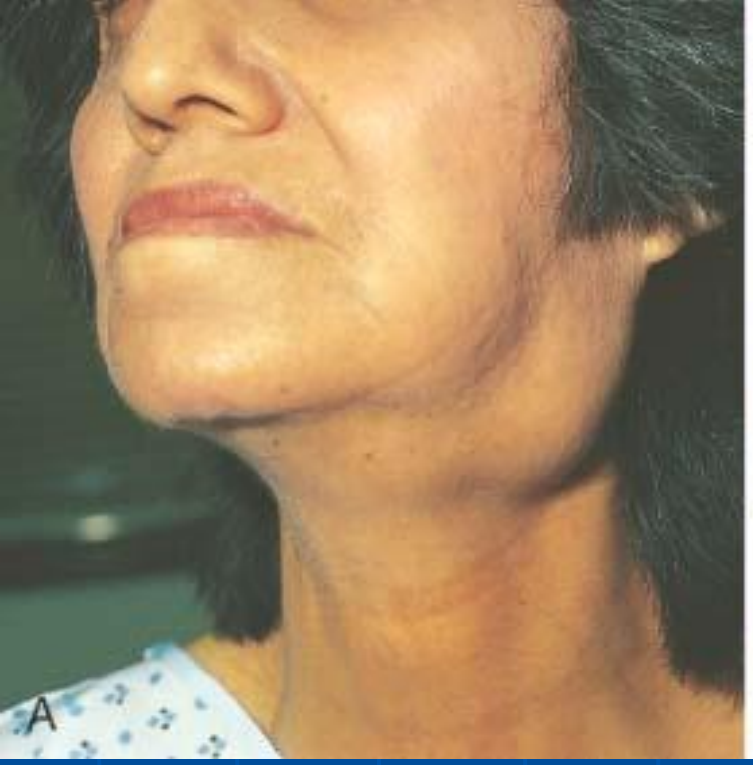


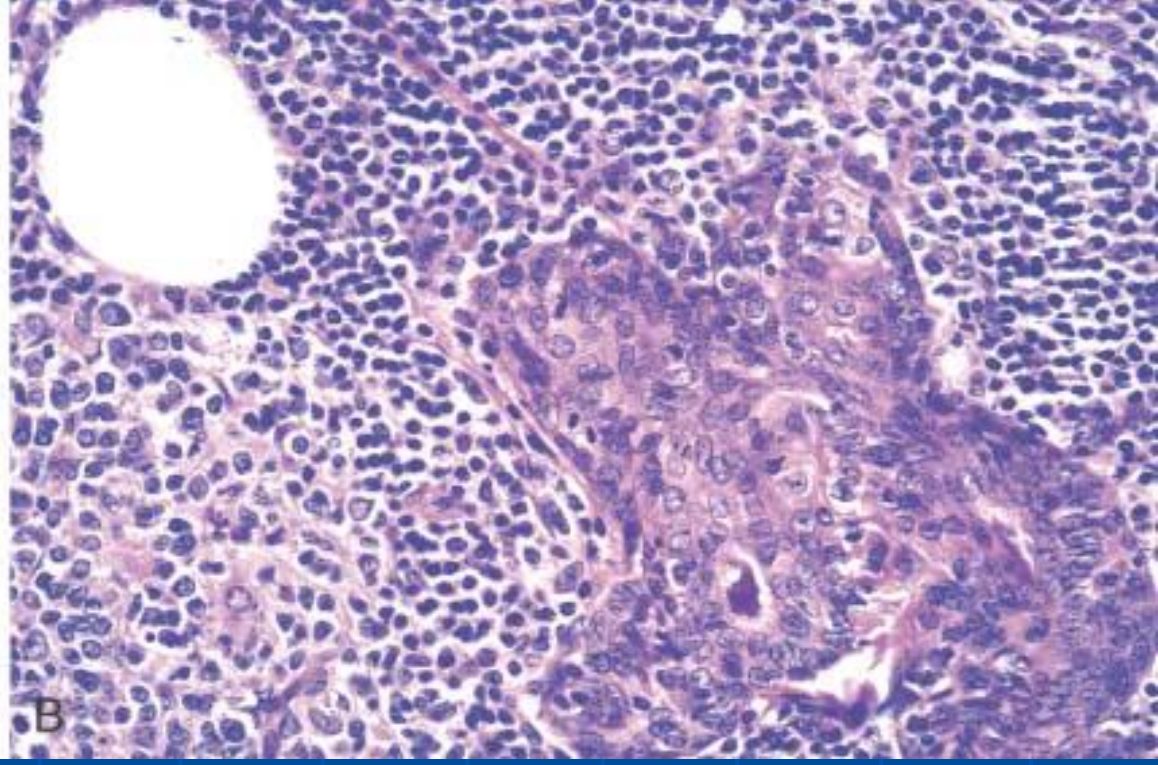




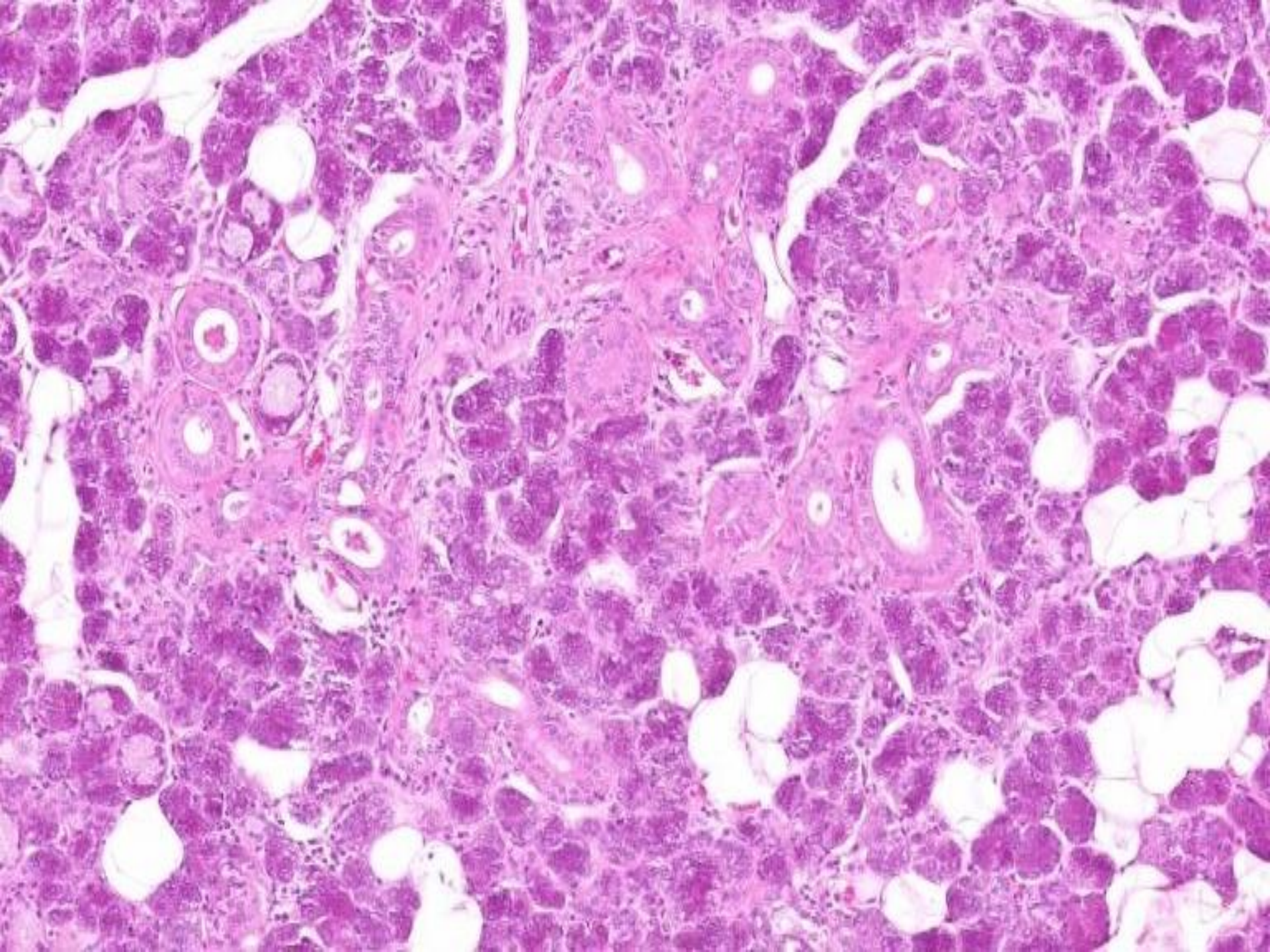
Destructive Rheumatoid Synovitis

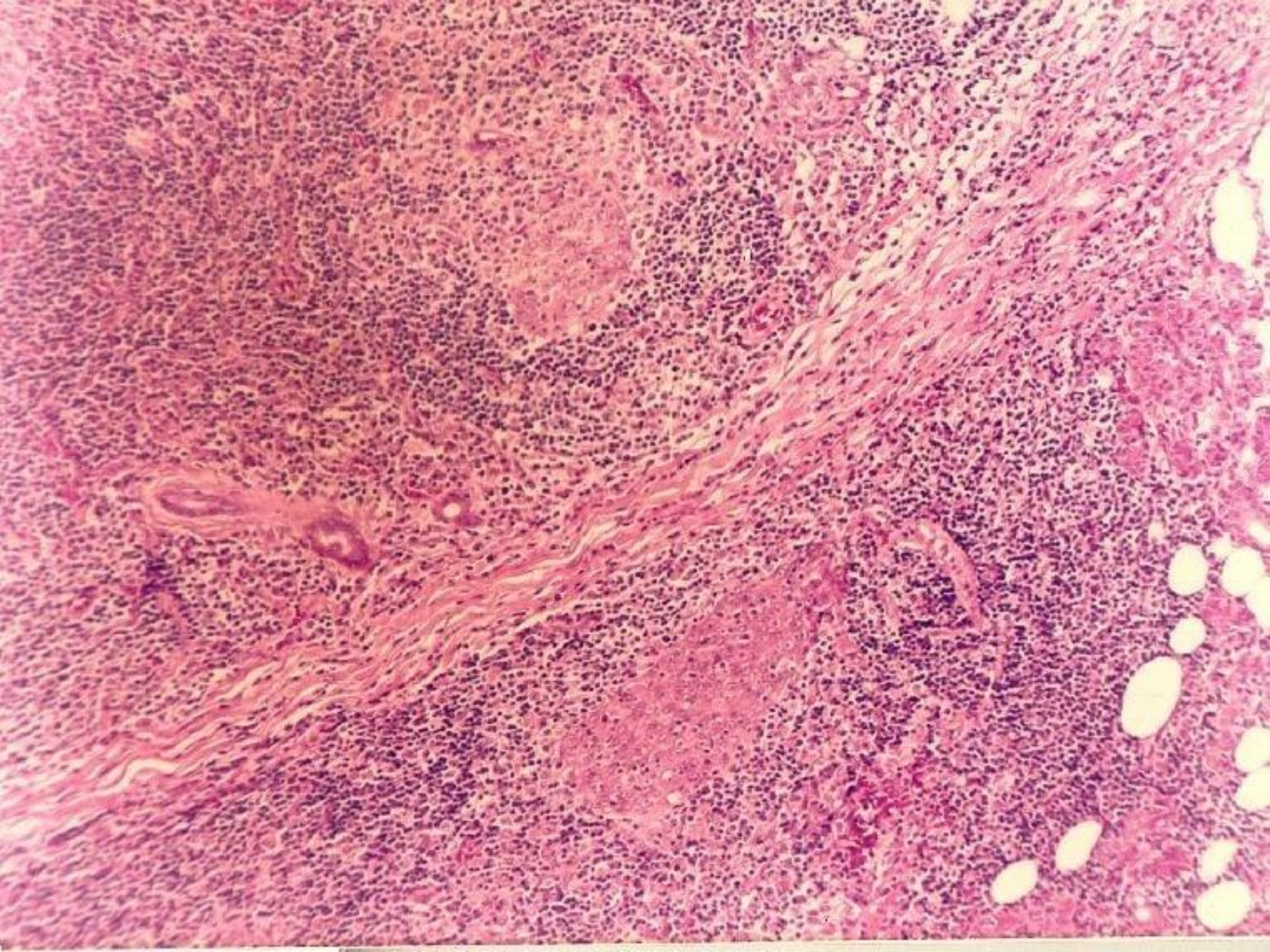
←**NORMAL** Bi-Layered Synovium

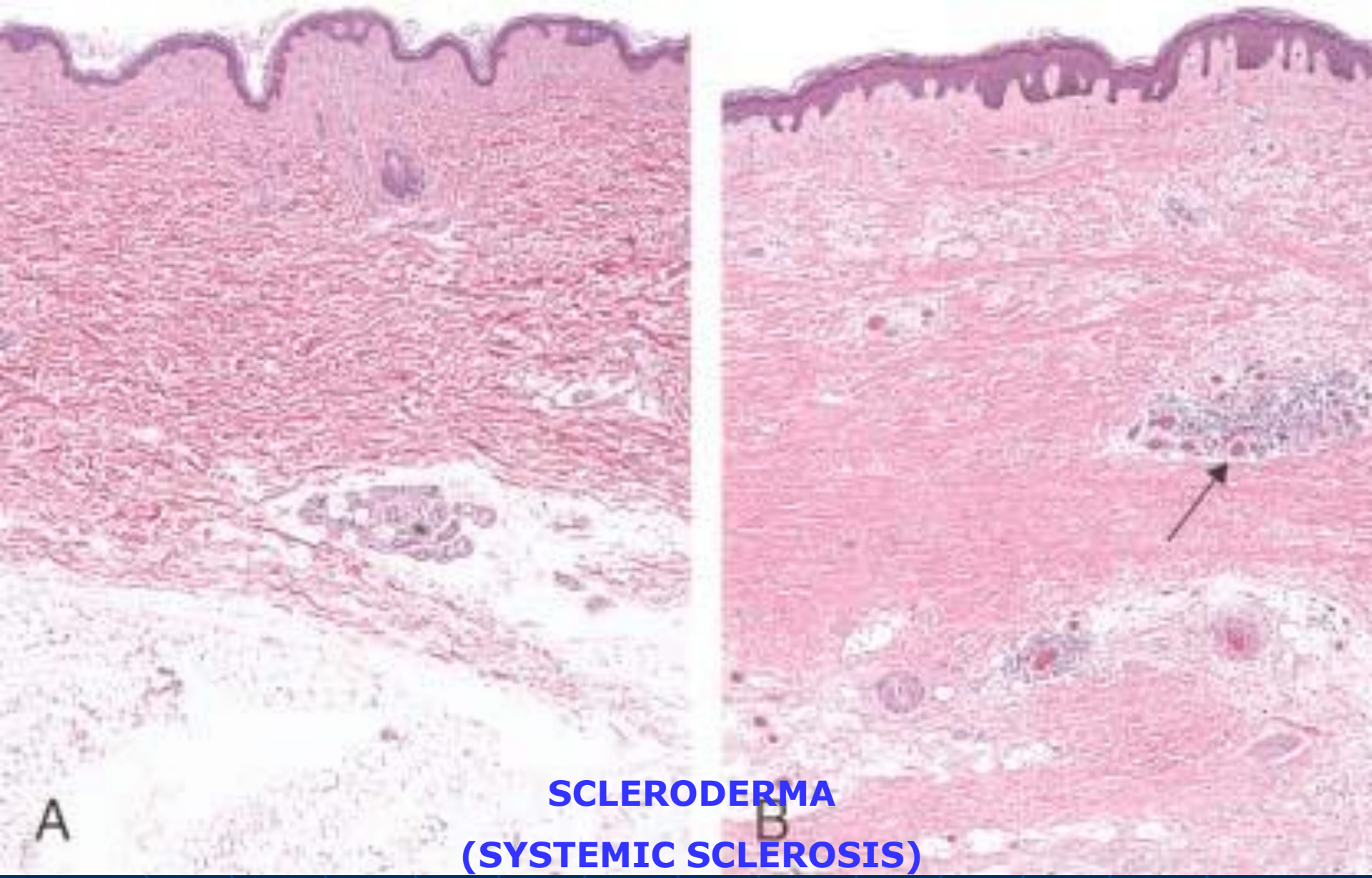




SJÖGREN SYNDROME







SCLERODERMA

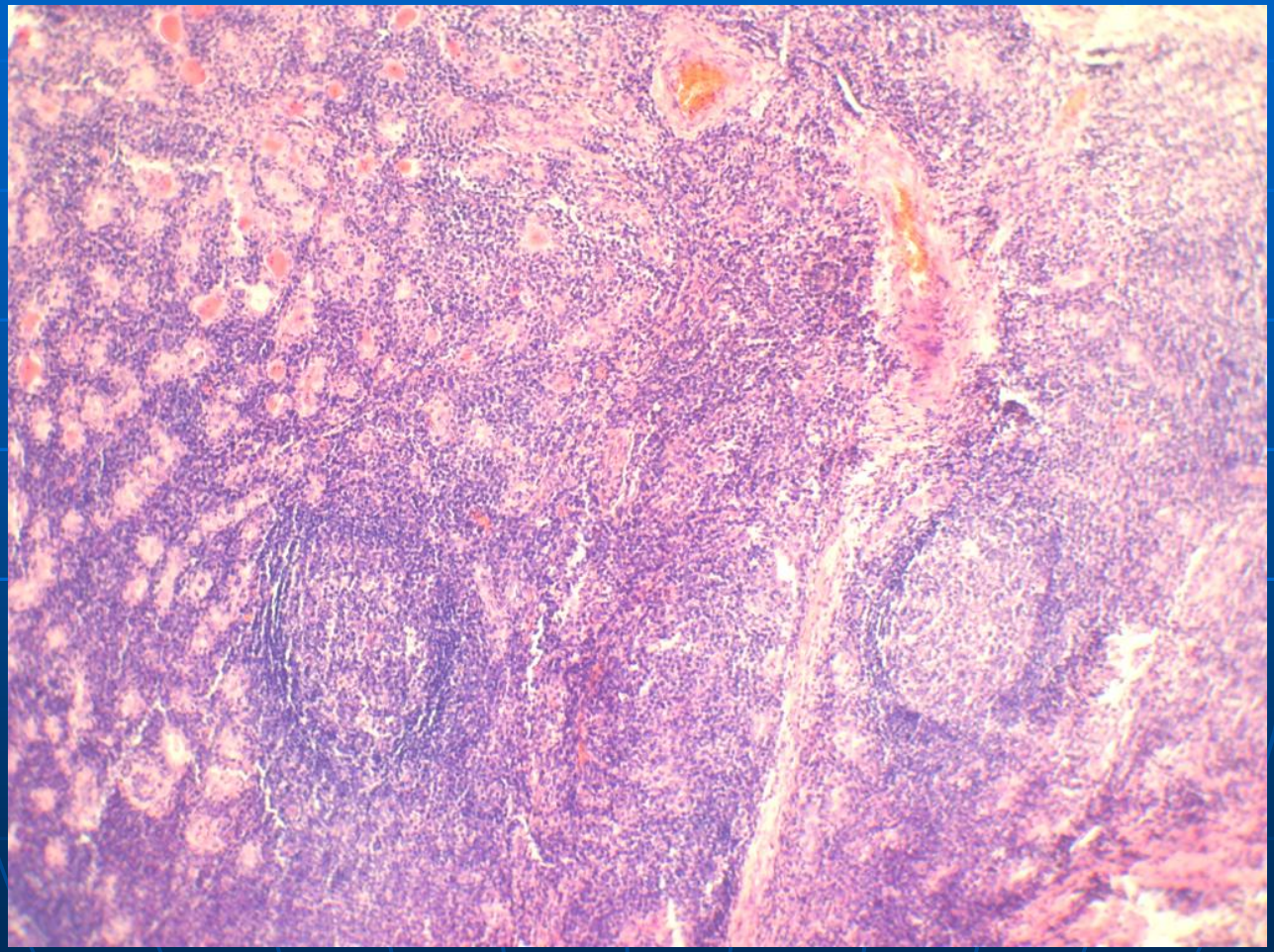
(SYSTEMIC SCLEROSIS)

SYSTEMIC SCLEROSIS
(SCLERODERMA)

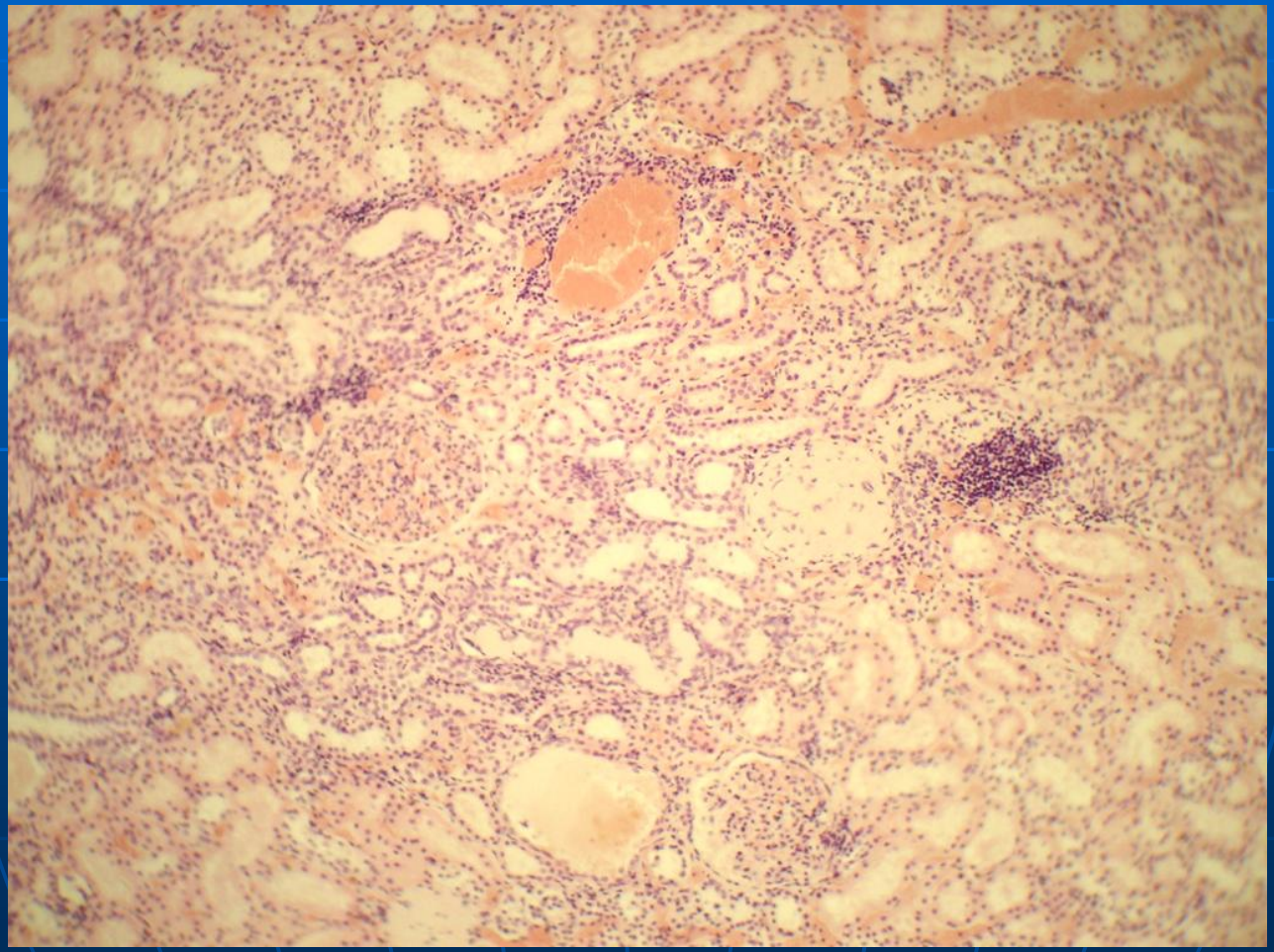
MORE AUTOIMMUNE DISEASES (LOCAL)

- 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

Hashimoto’s thyroiditis



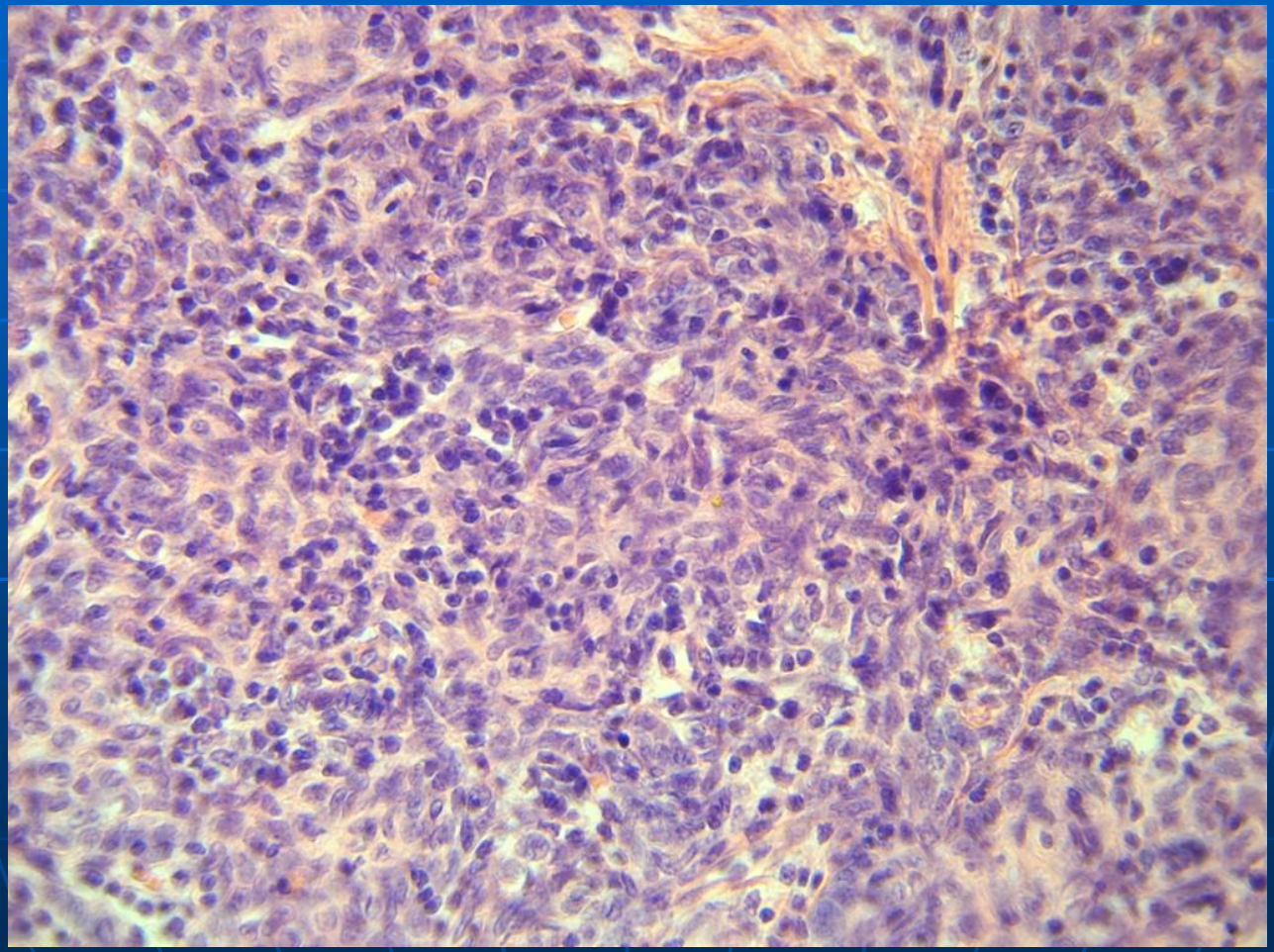
Polyarteritis nodosa



AUTOIMMUNE DISEASES
Intermediate

- Myasthenia gravis
- Goodpasture's syndrome

Myasthenia gravis



ImmunoDefiency Syndromes (-IDS)

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

Immunodeficiency

- **Serious, persistent, unusual, recurrent Opportunistic infections.**
- **Secondary causes more common.**
- **Antibody deficiency – Bacterial inf.**
- **Cell Mediated imm def. – viral / fungal**
- **AIDS – infection by HIV virus – destruction of T helper cells – deficiency of humoral & CM immunity.**

Classification:

- **Primary Deficiencies (Inherited)**
  - B cell defects – Ig def. Bacterial infections.
  - T cell defects – T cells. – Viral & fungal infect.
  - Combined defects – T & B
- **Secondary Deficiencies –(Acquired)** – T*
  - Malnutrition – Protein
  - Immunosuppressive therapy, drugs.
  - Infections – viral, chronic bacterial, malaria.
  - Chronic diseases – Diabetes*, Malignancy.

PRIMARY IMMUNODEFICIENCIES

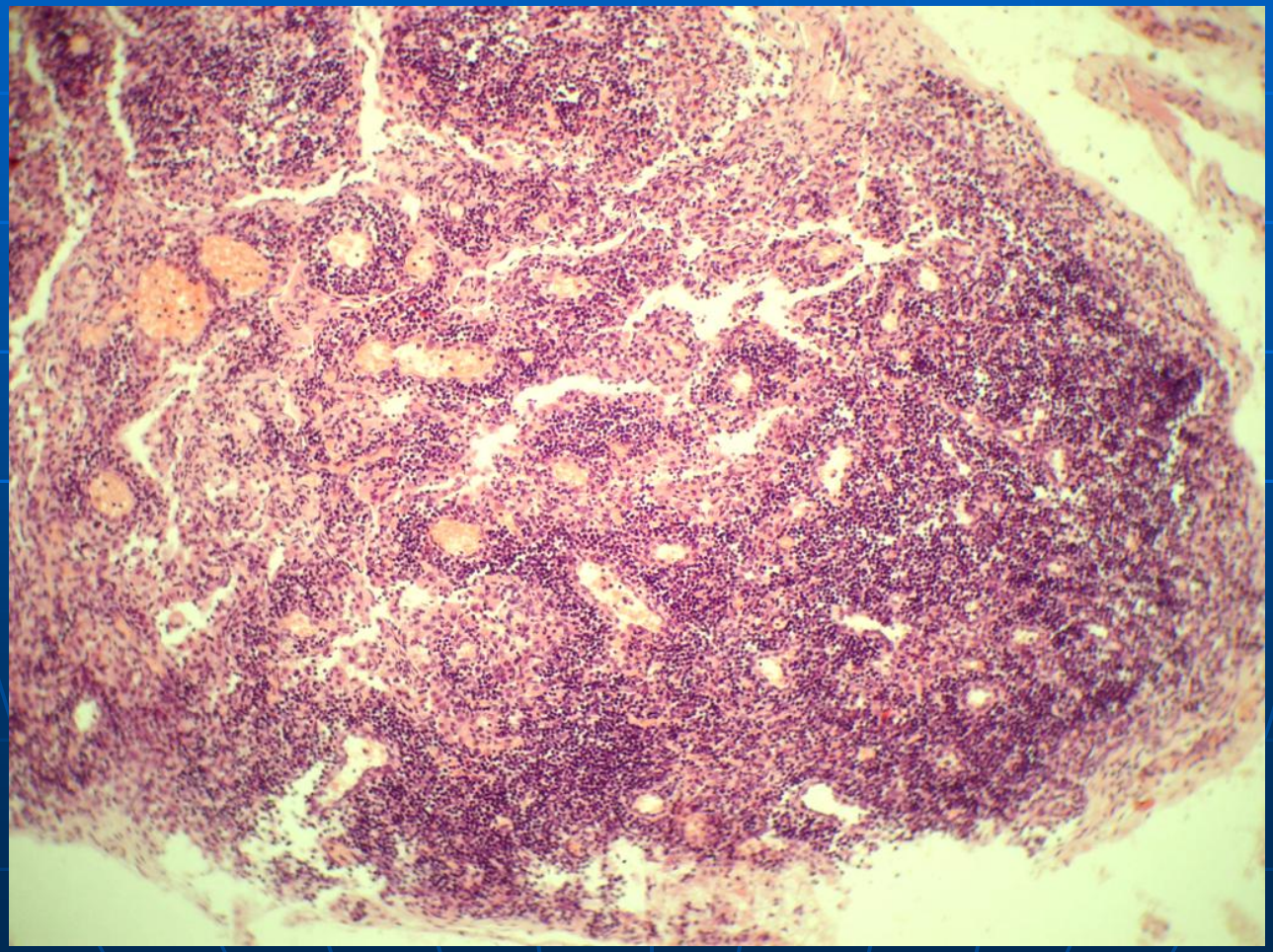
- Most primary immunodeficiency diseases are genetically determined and affect specific immunity (i.e. humoral and cellular) or nonspecific host defense mechanisms mediated by complement proteins and cells such as phagocytes or natural killer cells. Although originally thought to be quite rare, some forms, such as IgA deficiency, are common, and collectively they are a significant health problem, especially in children. Most primary immunodeficiencies manifest themselves in infancy, between six months and two years of life, and they are noted because of the susceptibility of infants to reccurent infections.

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

- There are some such diseases (X-linked Agammaglobulinemia of Braton, Common Variable Immunodeficiency (CVI), Isolated IgA Deficiency, Severe Combined Immunodeficiency Diseases (SCID), Immunodeficiency with Thrombocytopenia and Eczema (Wiscott-Aldrich Syndrome), Genetic Deficiencies of the Complement System, etc.), but only one of them is presented here.

BRUTON (X-linked agammaglobulinemia) lymph node



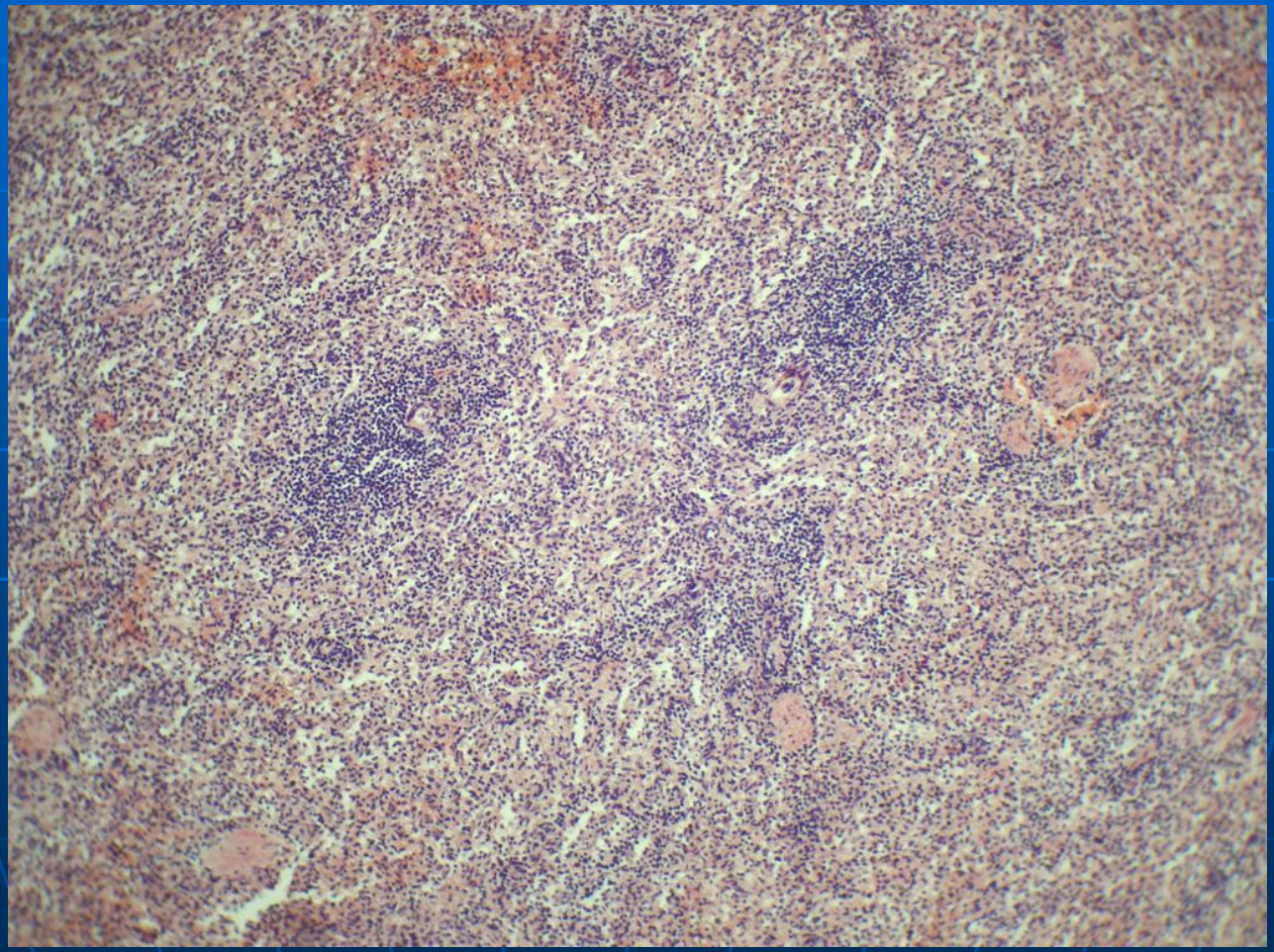
DiGeorge's Syndrome (Thymic Hypoplasia).

- This is the example of selective T-cell deficiency that derives from failure of development of the third and fourth pharingeal pouches. The latter give rise to the thymus, the parathyroids, some of the clear cells of the thyroid, and the umbilical body. Thus these patients have total absence of cell-mediated immune response (owing to hypoplasia or lack of the thymus), tetany (owing to lack of the parathyroids), and the congenital defects of the heart and great vessels. In addition, the appearance of the mouth, ears, and facies may be abnormal. Absence of cell-mediated immunity is reflected in low levels of circulating T-lymphocytes and a poor defense against certain fungal and viral infections. Plasma cells are present in normal numbers in lymphoid tissues, but the thymic-dependent paracortical areas of the lymph nodes and the periarteriolar sheaths of the spleen are depleted. Immunoglobulin levels tend to be normal.

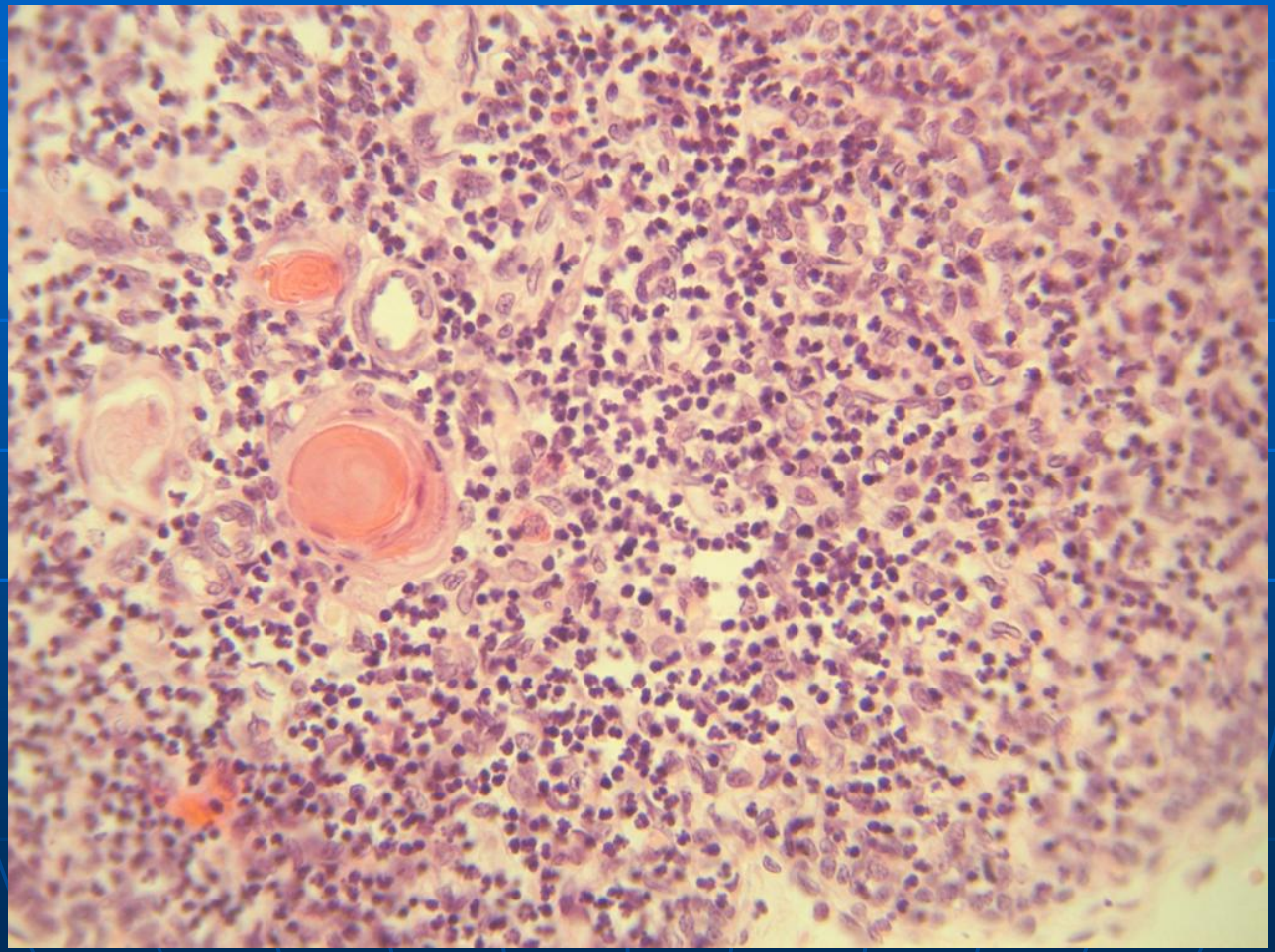
DiGeorge's syndrome

- DiGeorge's syndrome is not genetically determined but appears to be the result of intrauterine fetal damage around the eighth week of gestation. Patients with "partial" DiGeorge's syndrome, who have extremely small but histologically normal thymus, have also been recorded. T-cell function improves with age of these children, so by 5 years of age, many have no T-cell deficit. In those with a complete absence of thymus, transplantation of fetal thymus may be of benefit.

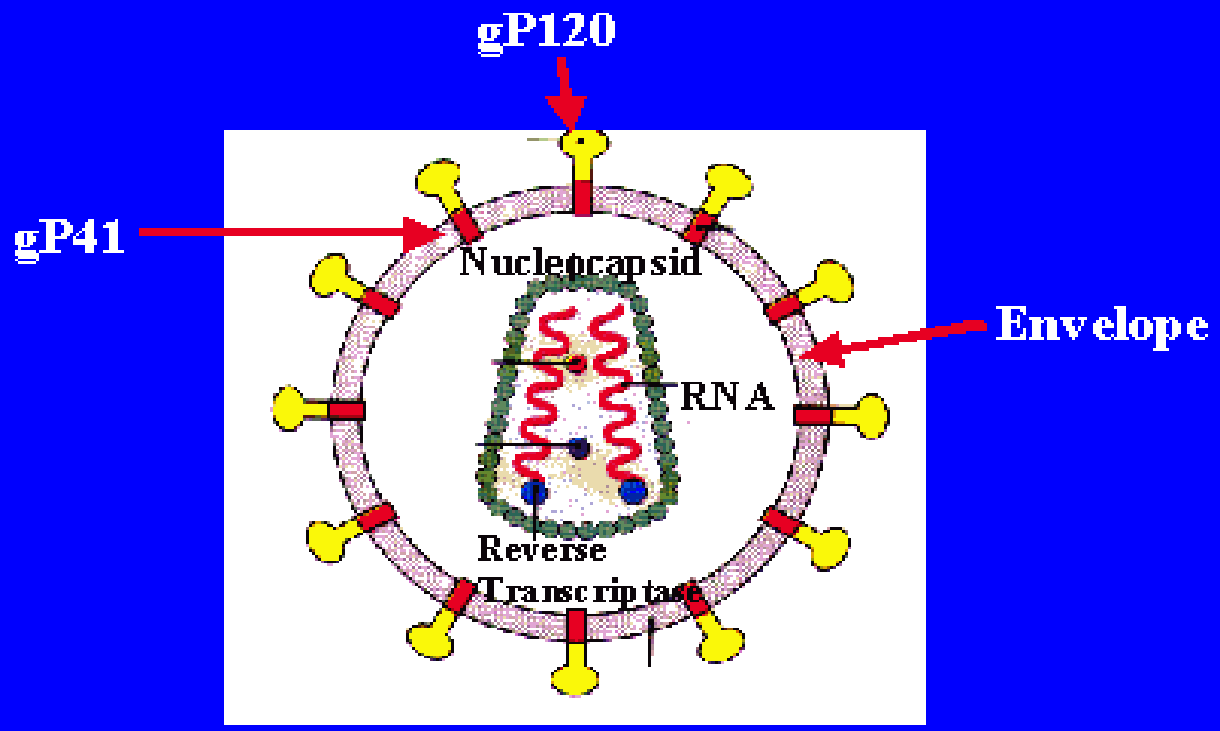
DiGeorge's syndrome



Thymus



HIV



gP120 = binding protein

gP41 = fusion protein

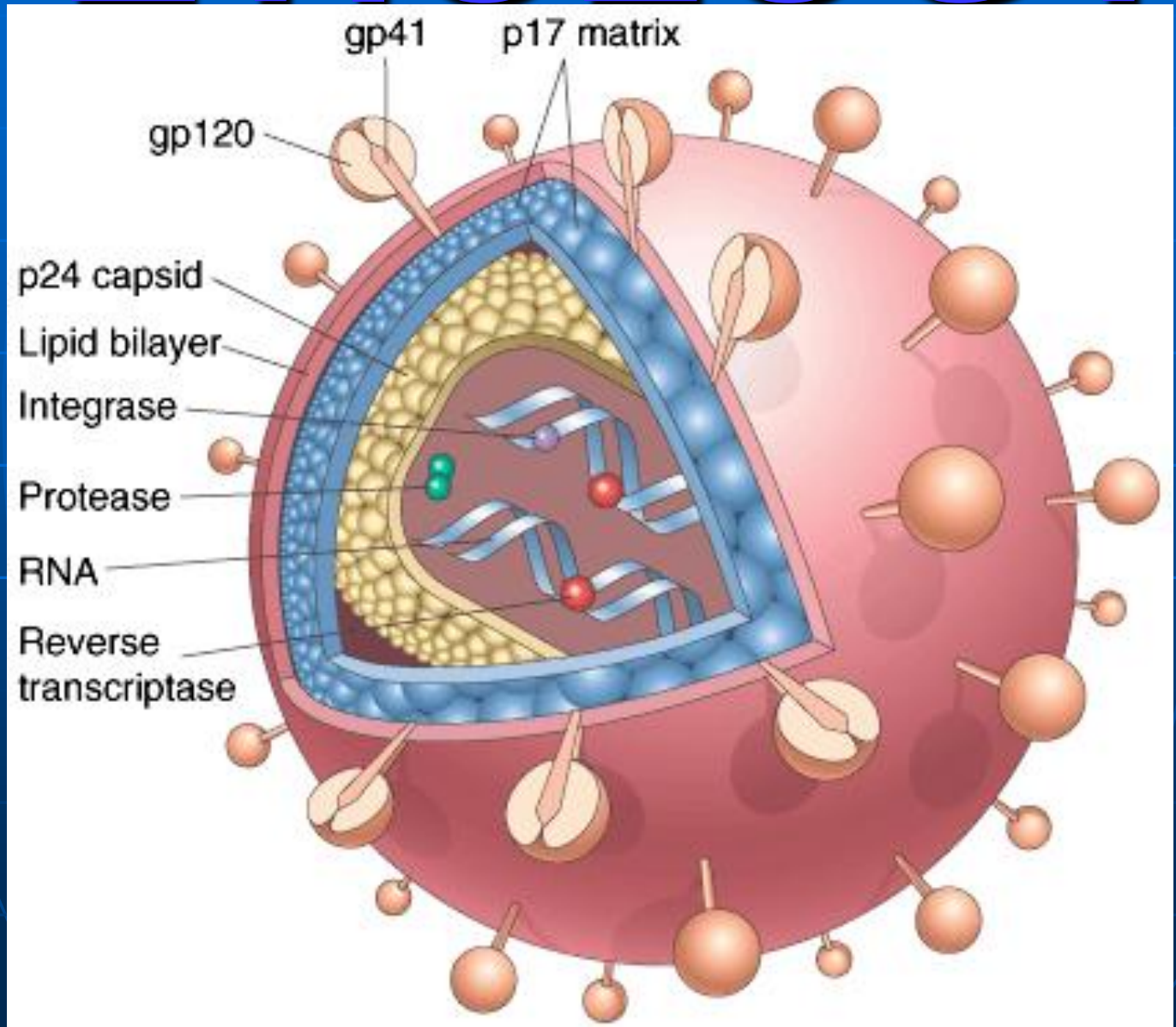
History

- 1979 – Increased Kaposi sarcoma and Pneumocystis carinii infections in homosexuals noted in Africa.
- 1981 – First case in California.
- > 30 million in world – 1999 – increasing
- 0.01% incidence in Australasia
- 67% in Sub-Saharan Africa...!

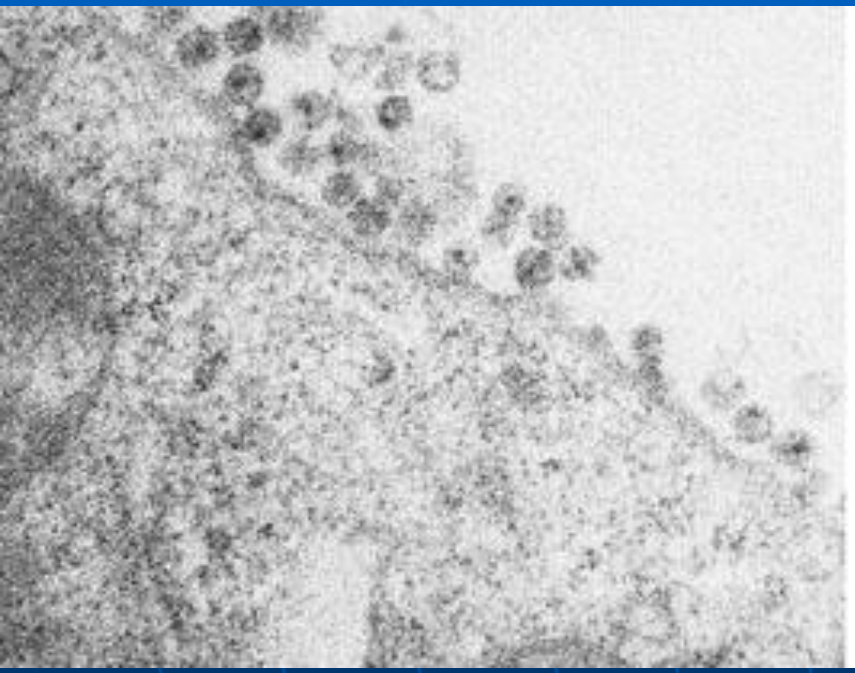
STRUCTURE OF THE VIRUS
COMPONENTS OF HIV

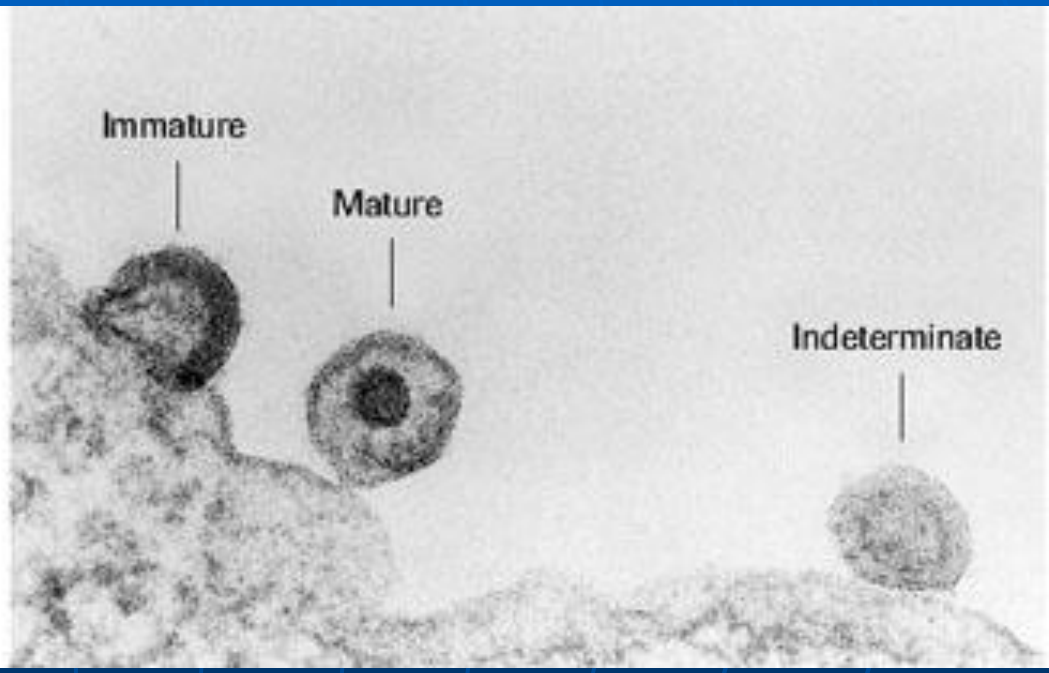
- HIV is a retrovirus with a similar structure to other retroviruses.
- SURFACE STRUCTURES
- Viral membrane
- The membrane is host-derived as a result of budding from the cell surface. Some host proteins become incorporated into the viral membrane. This lipid envelope make the virus susceptible to organic solvents.

ETIOLOGY


gp41
p17 matrix
gp120
p24 capsid
Lipid bilayer
Integrase
Protease
RNA
Reverse transcriptase

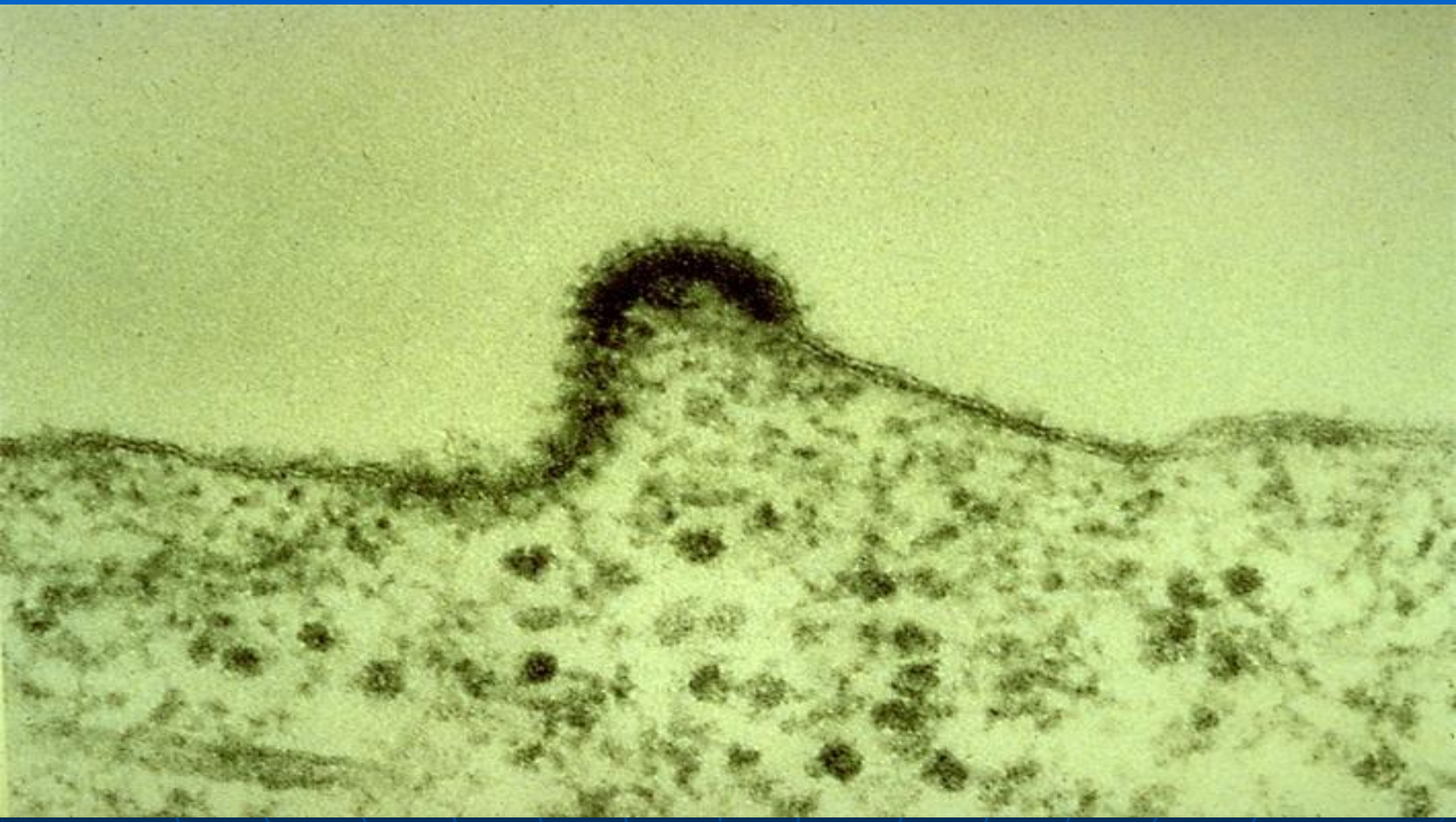
PATHOGENESIS





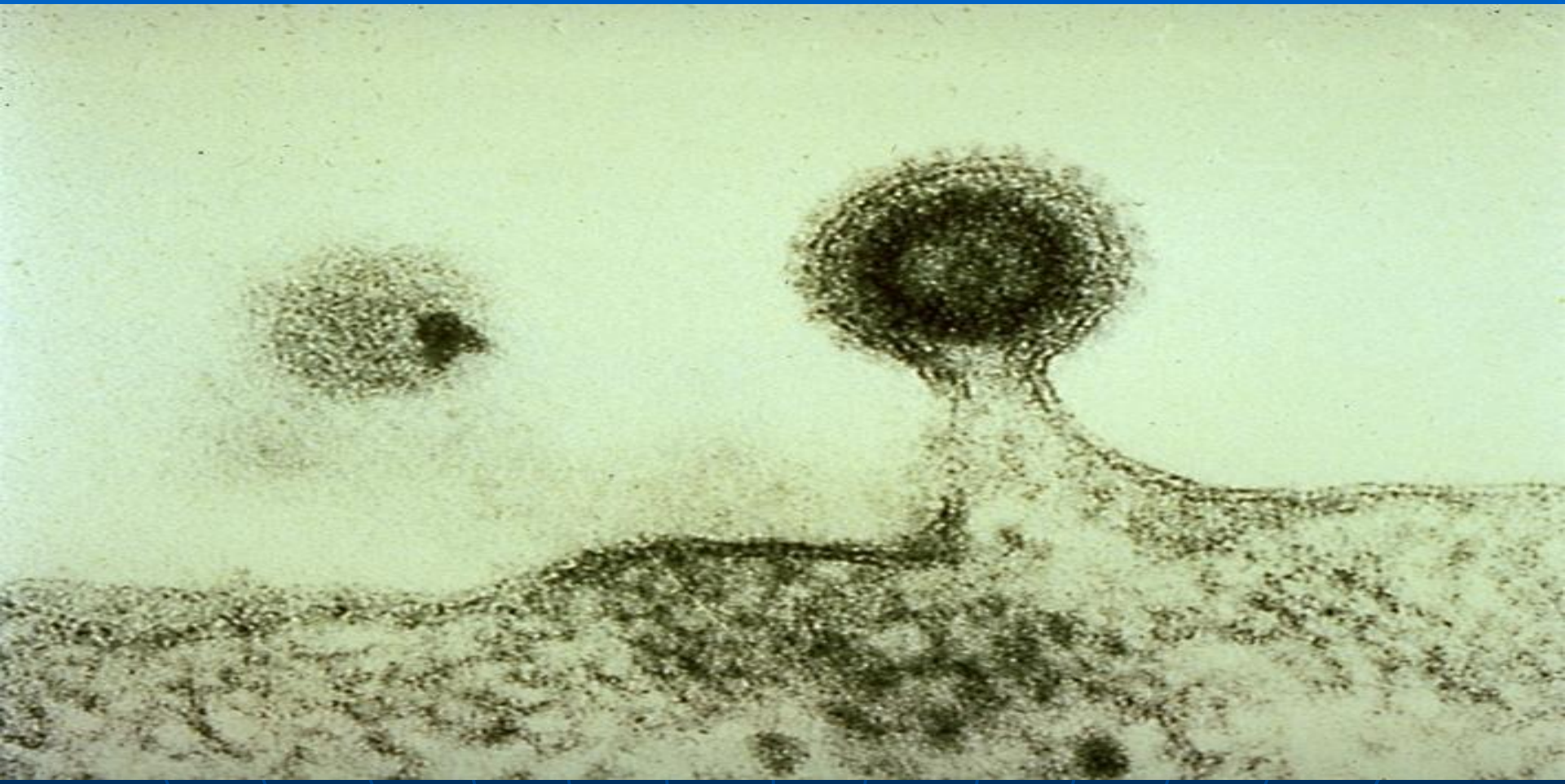
ATTACHING BUDDING

PATHOGENESIS



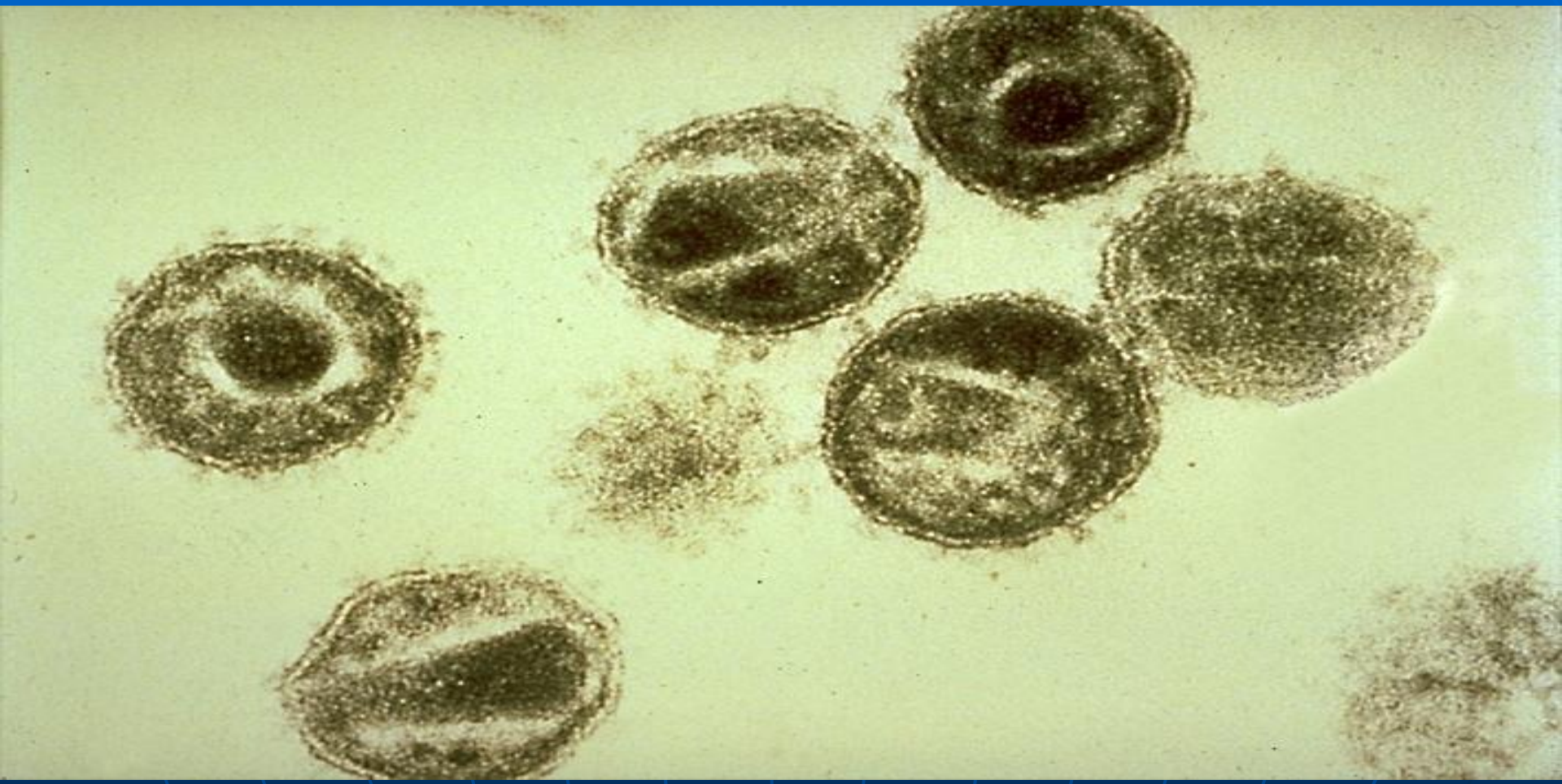
EARLY BUDDING

PATHOGENESIS



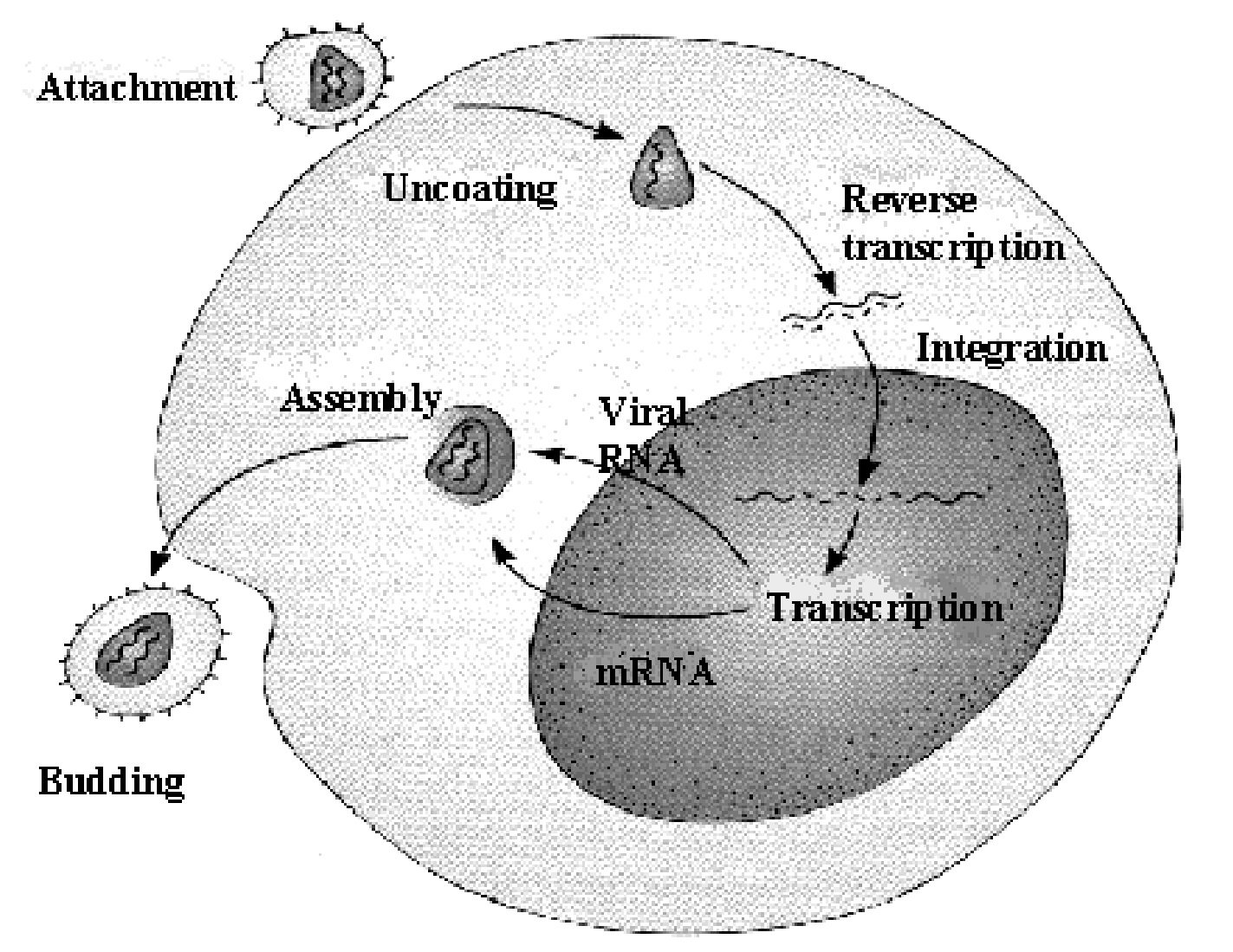
LATE BUDDING

PATHOGENESIS



MATURE NEW VIRIONS

Retrovirus Replication:



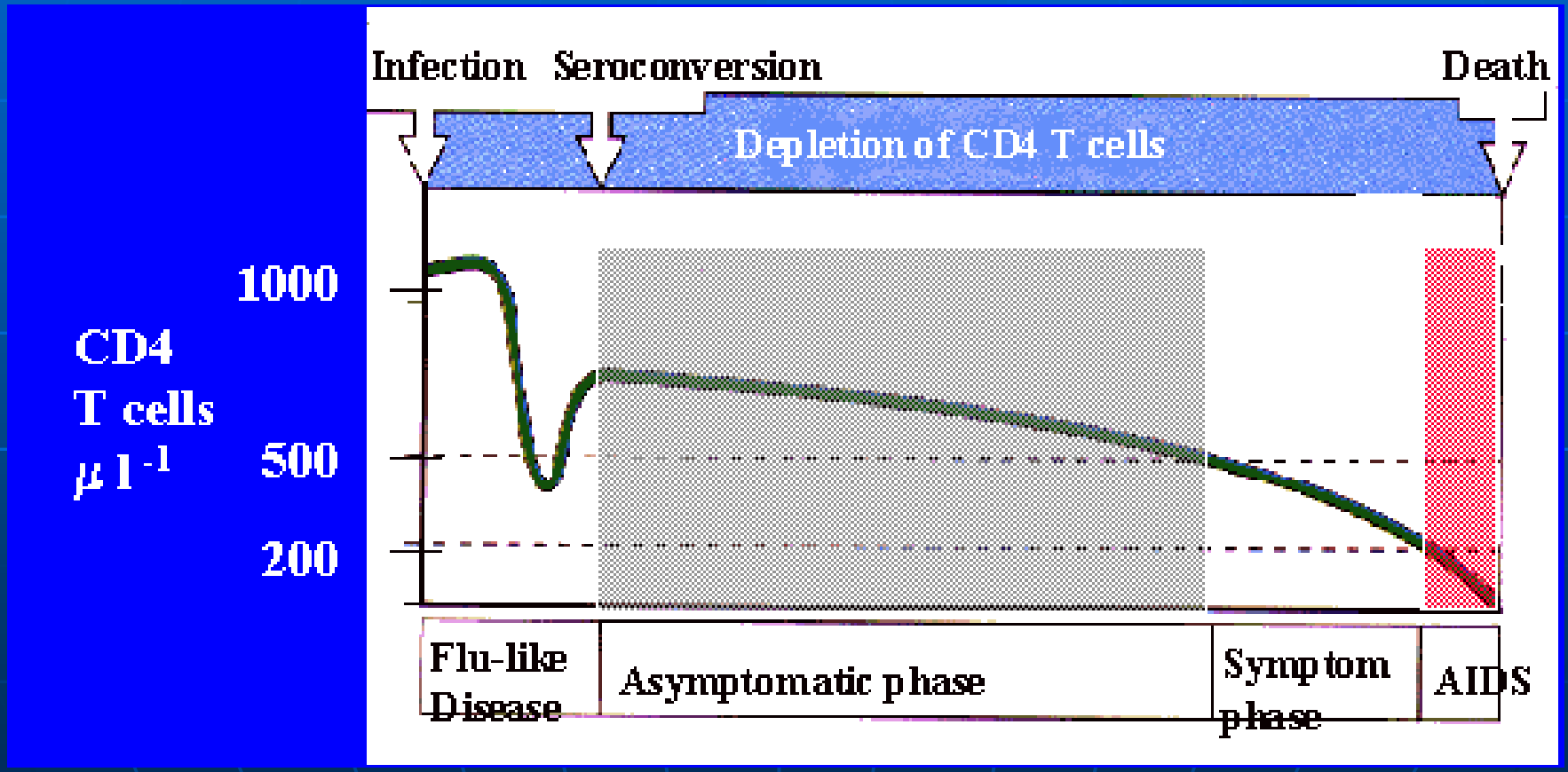
REVERSE TRANSCRIPTASE

- The enzyme reverse transcriptase (RT) is used by retroviruses to transcribe their single-stranded RNA genome into single-stranded DNA and to subsequently construct a complementary strand of DNA, providing a DNA double helix capable of integration into host cell chromosomes.

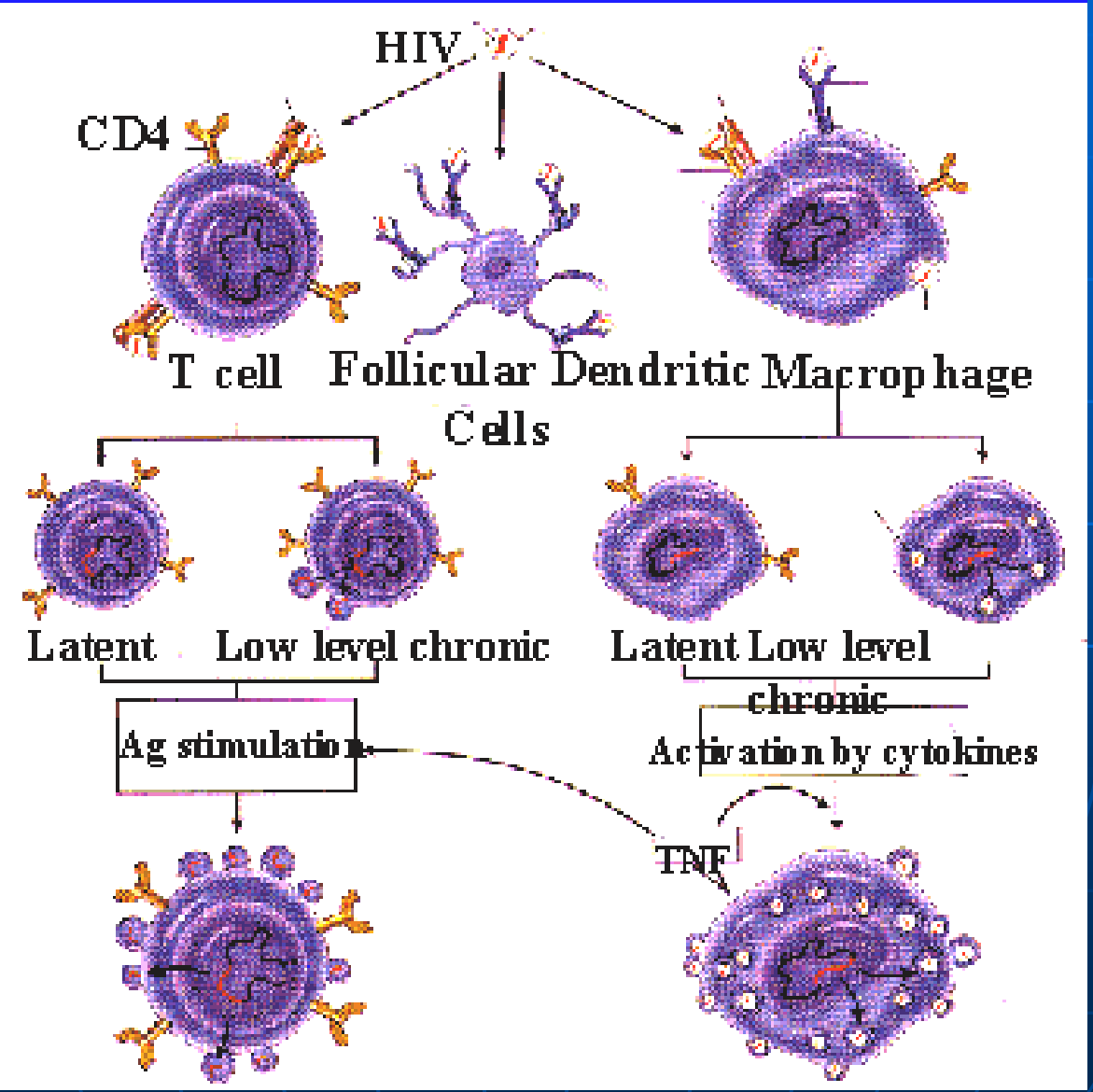
EPIDEMIOLOGY

- HOMOSEXUAL (40%, and declining)
- INTRAVENOUS DRUG USAGE (25%)
- HETEROSEXUAL SEX (10% and rising)

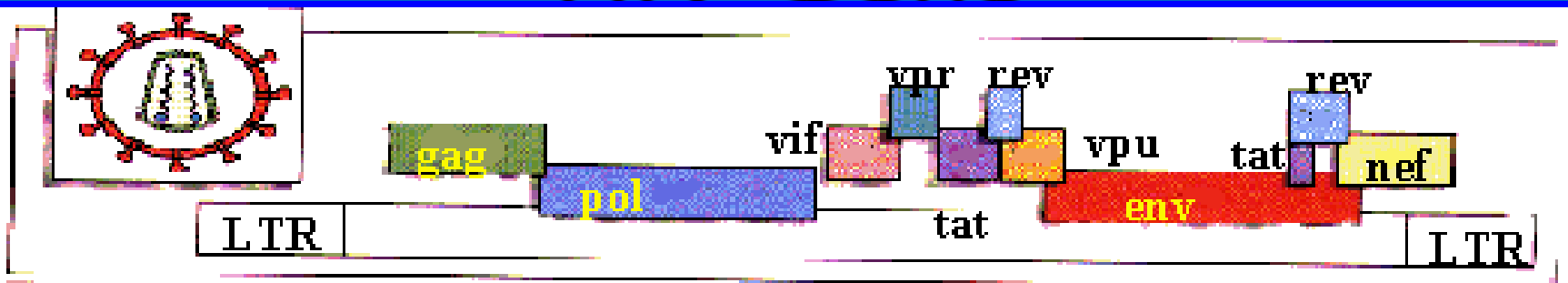
Clinical Course of AIDS



Pathogenesis



HIV-Gene



Gene		Gene product/function
gag	Group specific antigen	Core protein
pol	Polymerase	Rever transcriptase, protease & integ.
env	Envelope	Transmembr glycoprot, gp120 gp41
tat	Transactivator	Positive regulator of transcription
rev	Regulator of viral expression	Export of unspliced transcripts - nucleus
vif	Viral infectivity	Particle infectivity, assembly of virion
vpr	Viral protein R	Regulat transcription, aug. virion prod
vpu	Viral protein U	Down regulates CD4
nef	Negative-regulation factor	Augments viral repl.,down reg. CD4

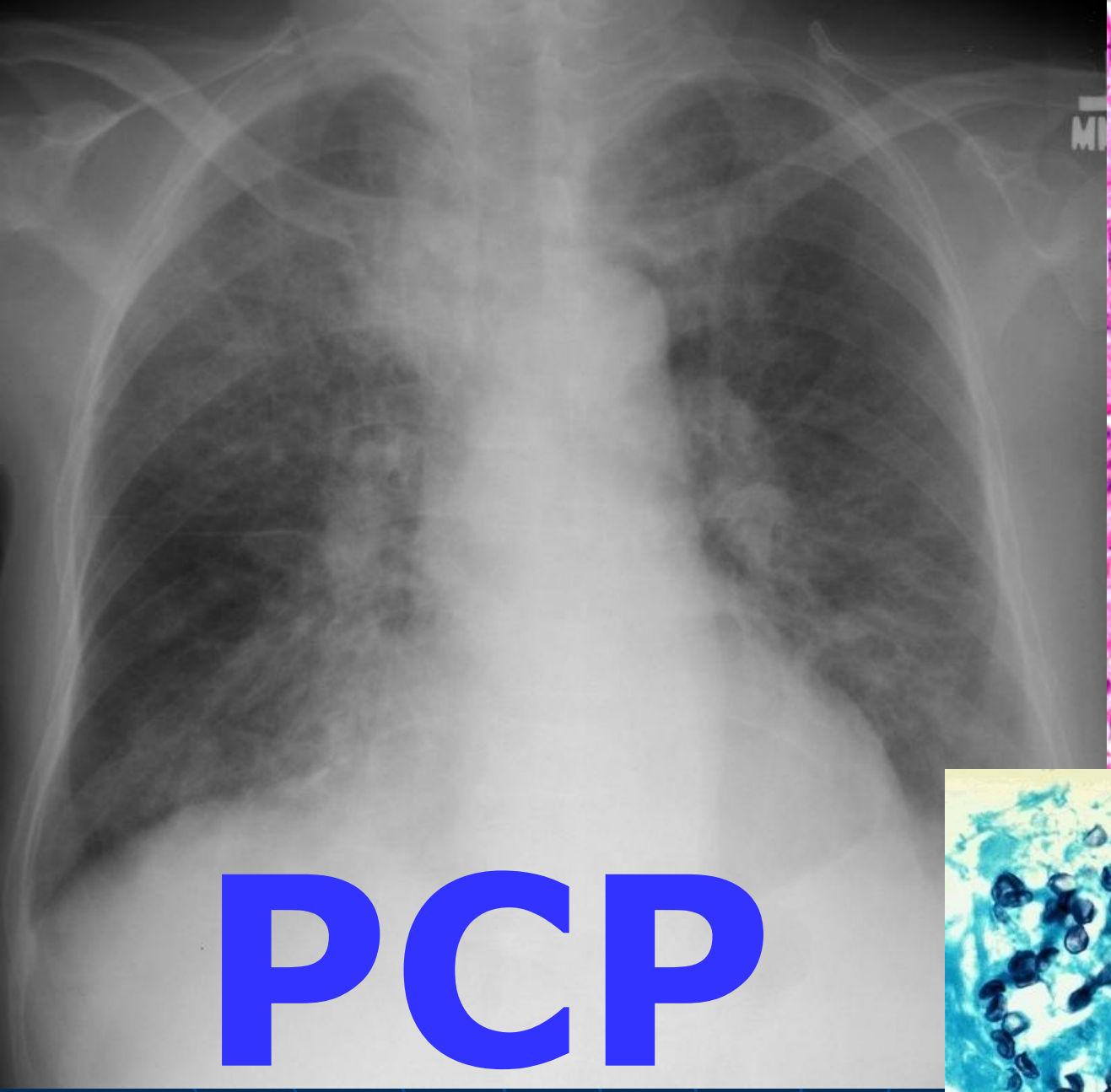
AIDS

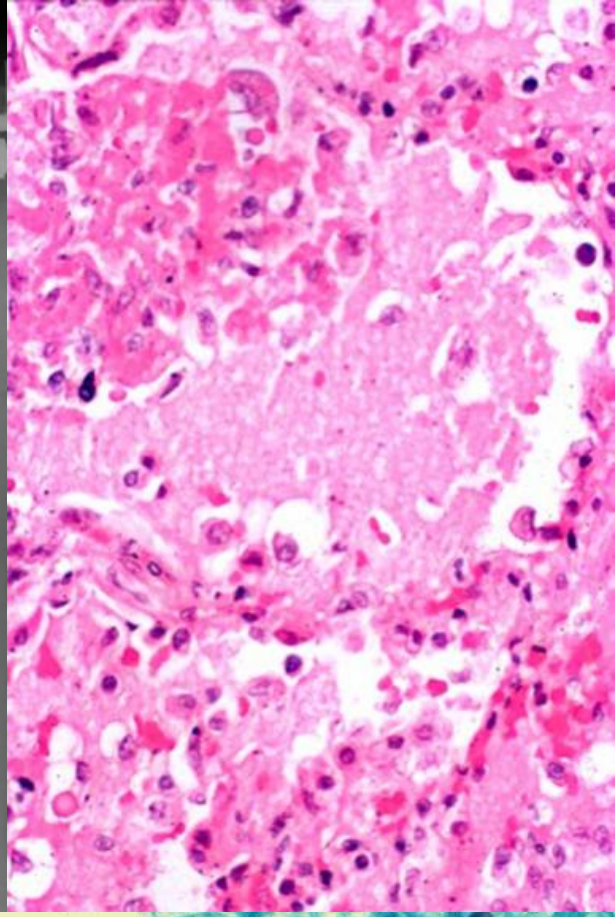
GENERAL IMMUNE ABNORMALITIES

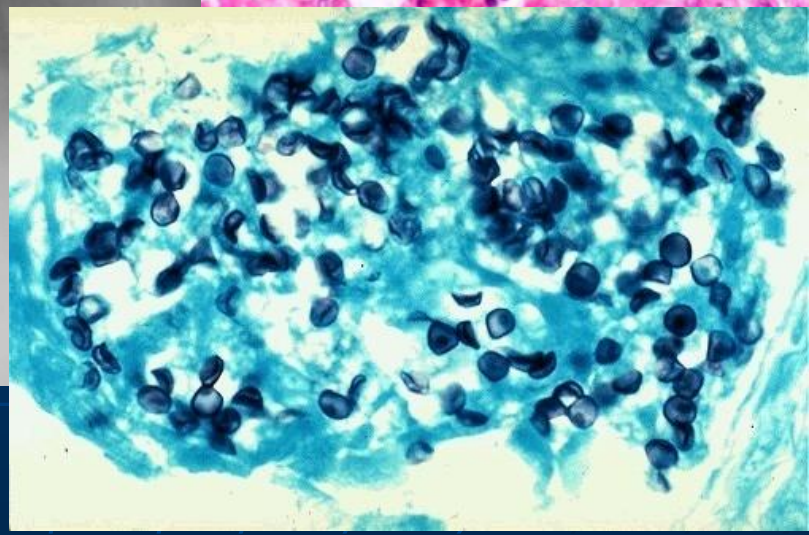
- LYMPHOPENIA
- DECREASED T-CELL FUNCTION
- B-CELL ACTIVATION, POLYCLONAL
- ALTERED MONOCYTE/MACROPHAGE FUNCTION

INFECTIONS

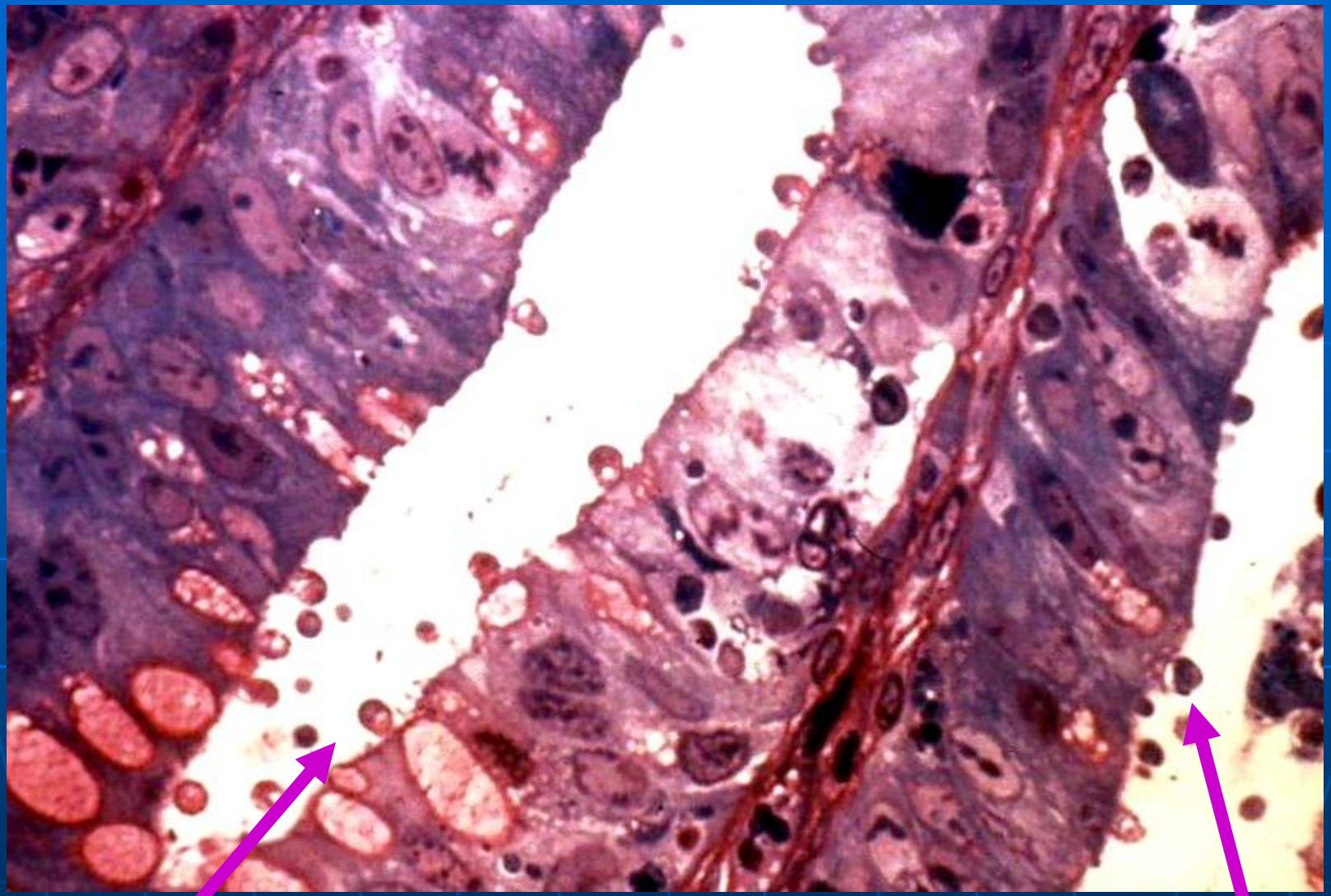
- Protozoal/Helminthic: Cryptosporidium, PCP (Pneumocystis Carinii Pneumonia), Toxoplasmosis
- Fungal: Candida, and the usual 3
- Bacterial: TB, Nocardia, Salmonella
- Viral: CMV, HSV, VZ (Herpes Family)



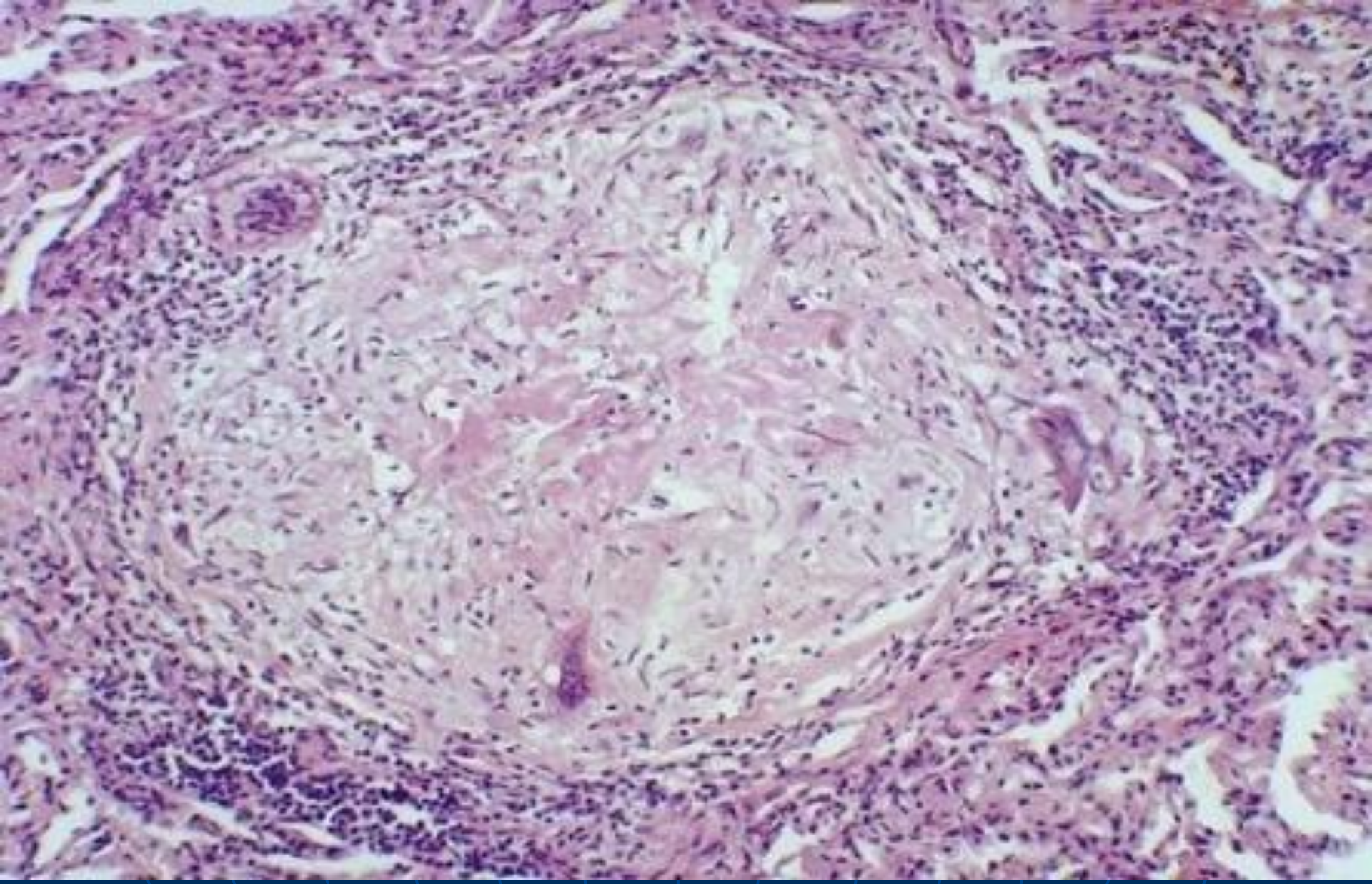




PCP

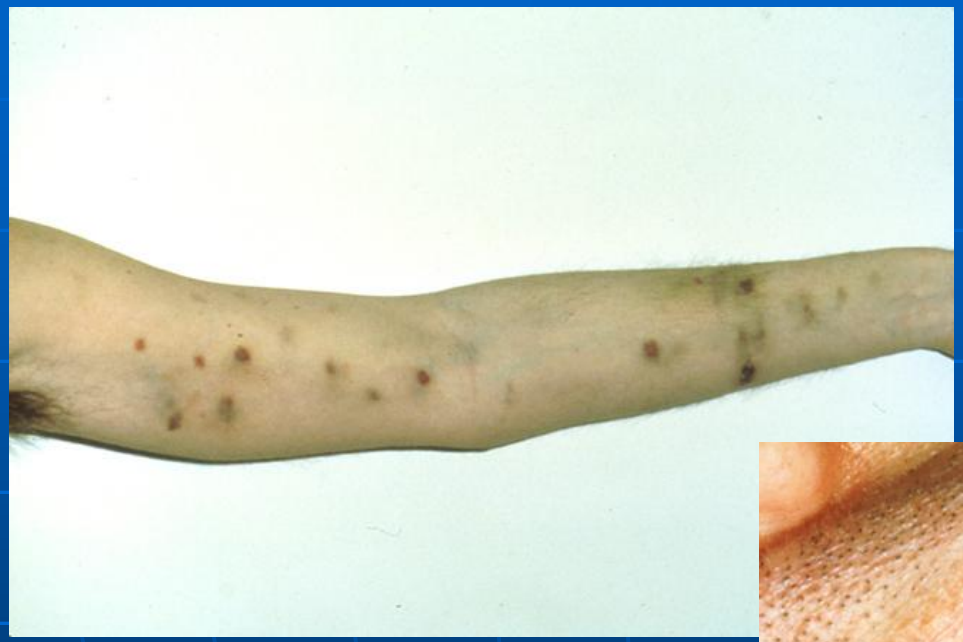


CRYPTOSPORIDIUM

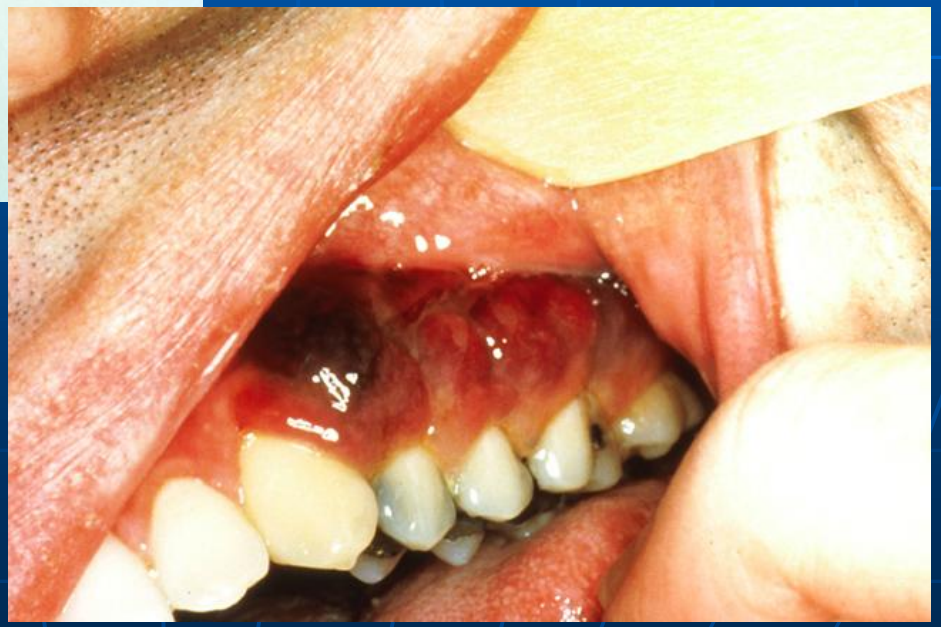


CASEATING GRANULOMA

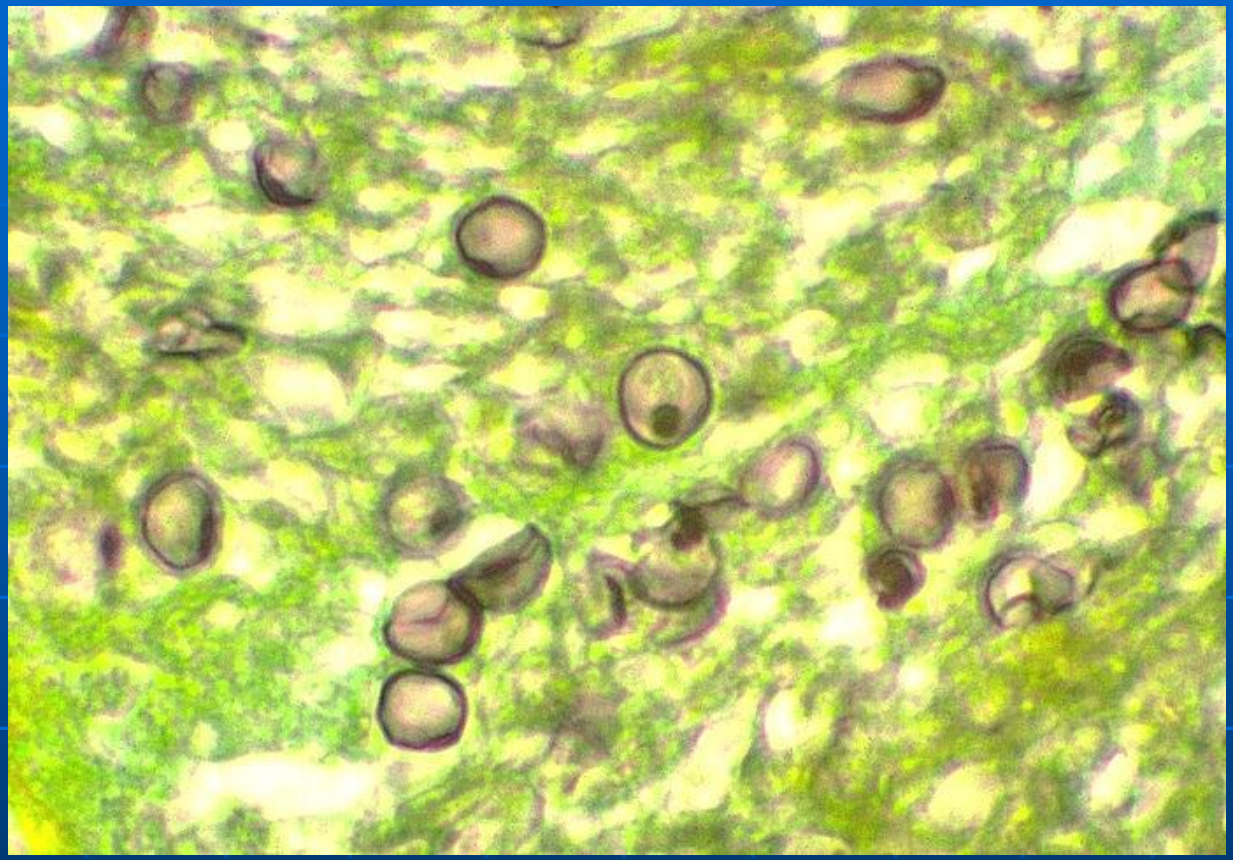
HIV



- Kaposi's sarcoma



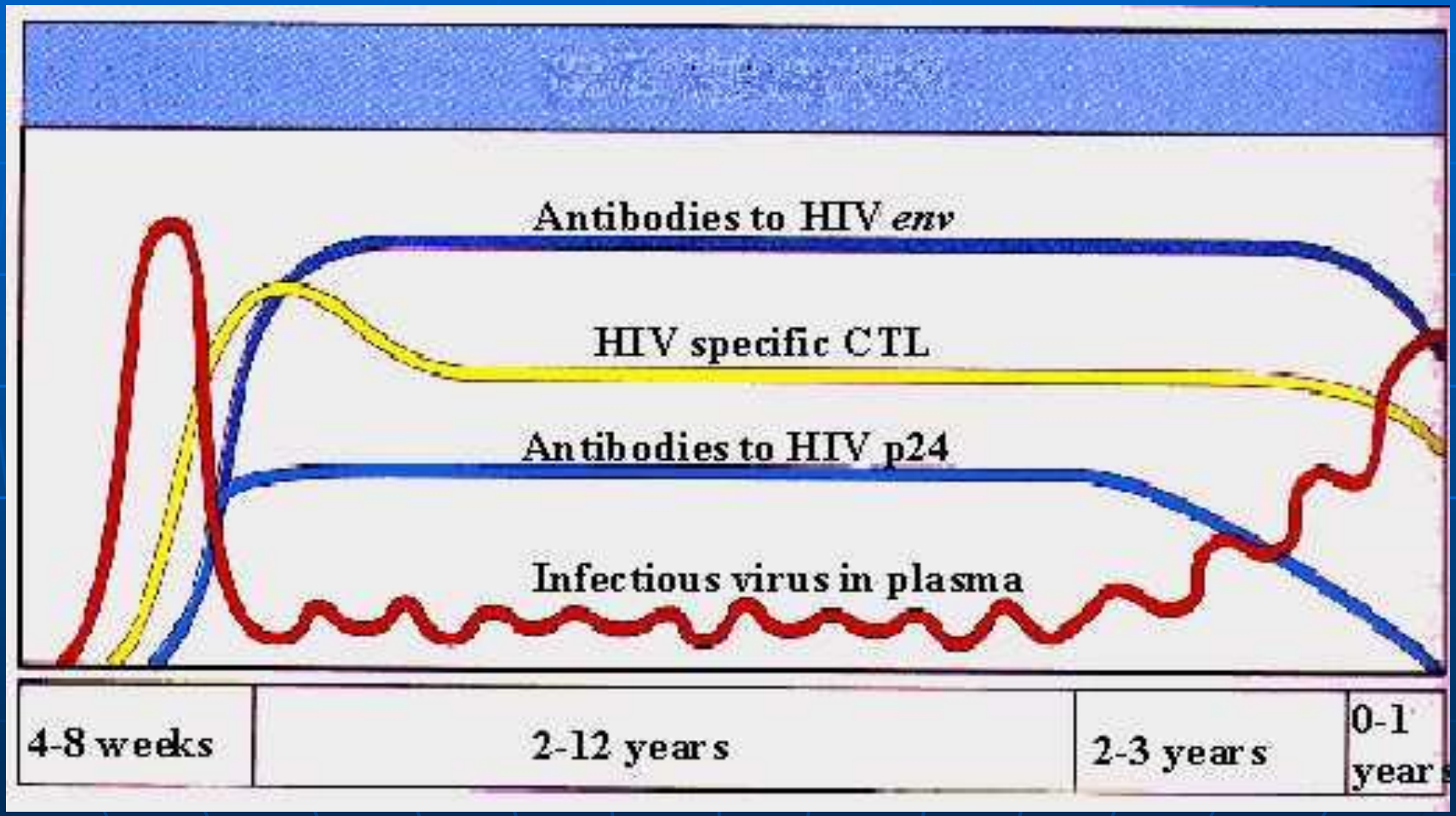
Cysts of Pneumocystis carinii in AIDS.



- Histopathology of lung shows characteristic cysts with cup forms and dot-like cyst wall thickenings.

  Methenamine silver stain. Dr. Edwin P. Ewing, Jr.

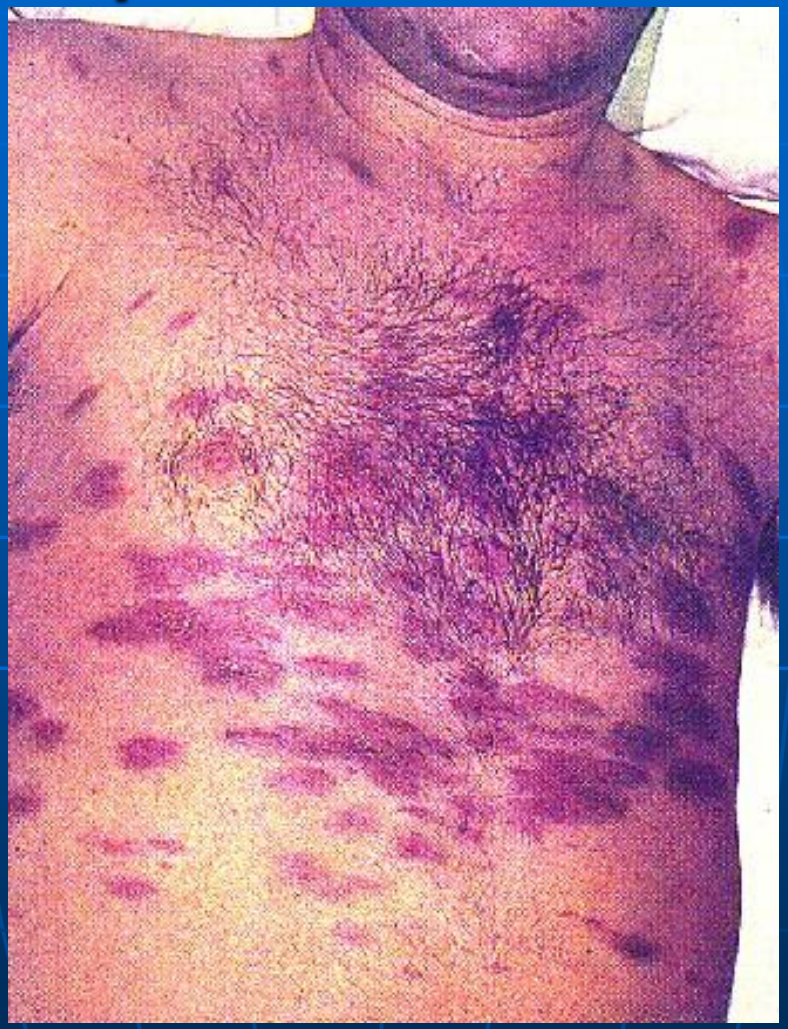
Immune Response to HIV



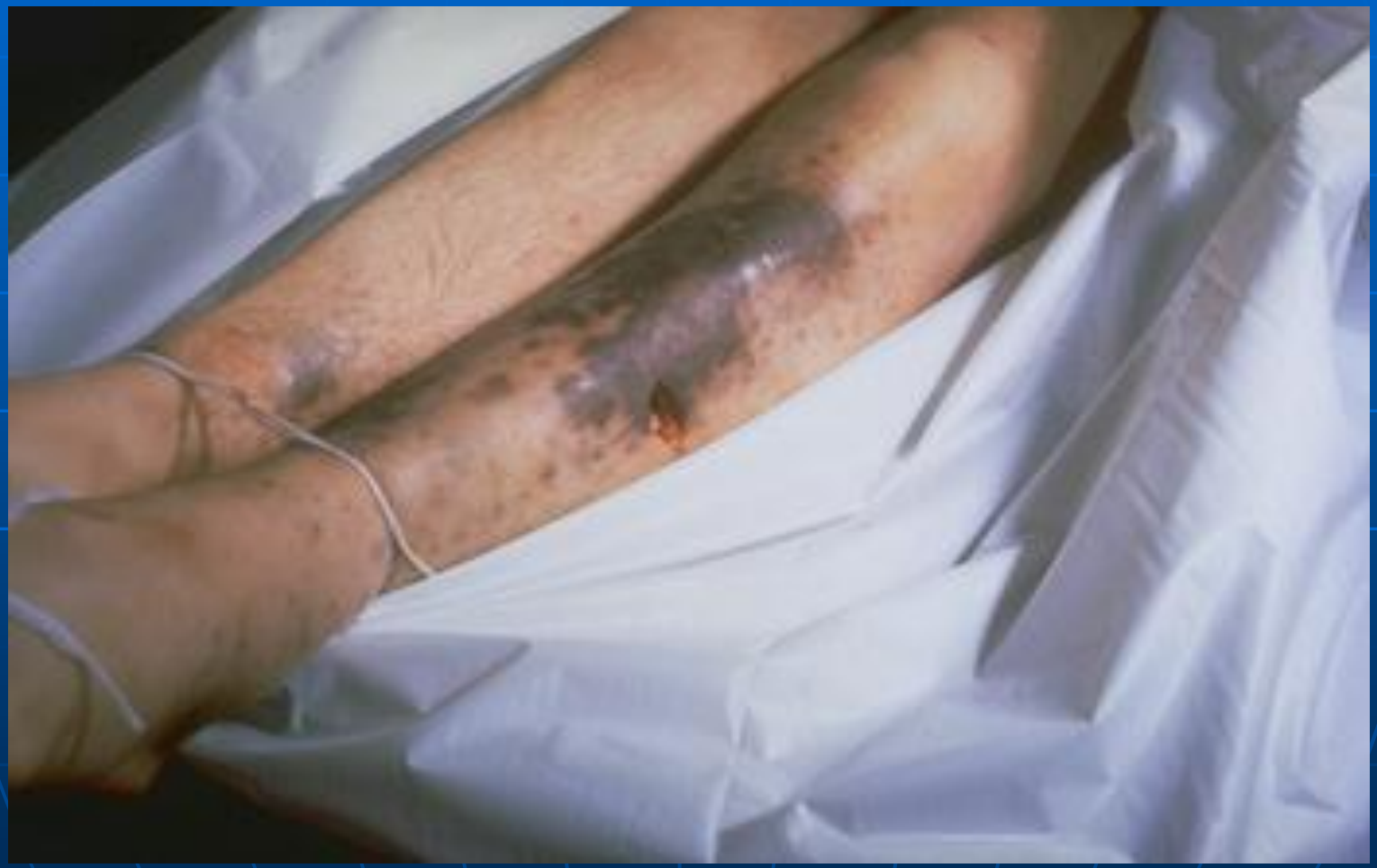
CANCERS of AIDS

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

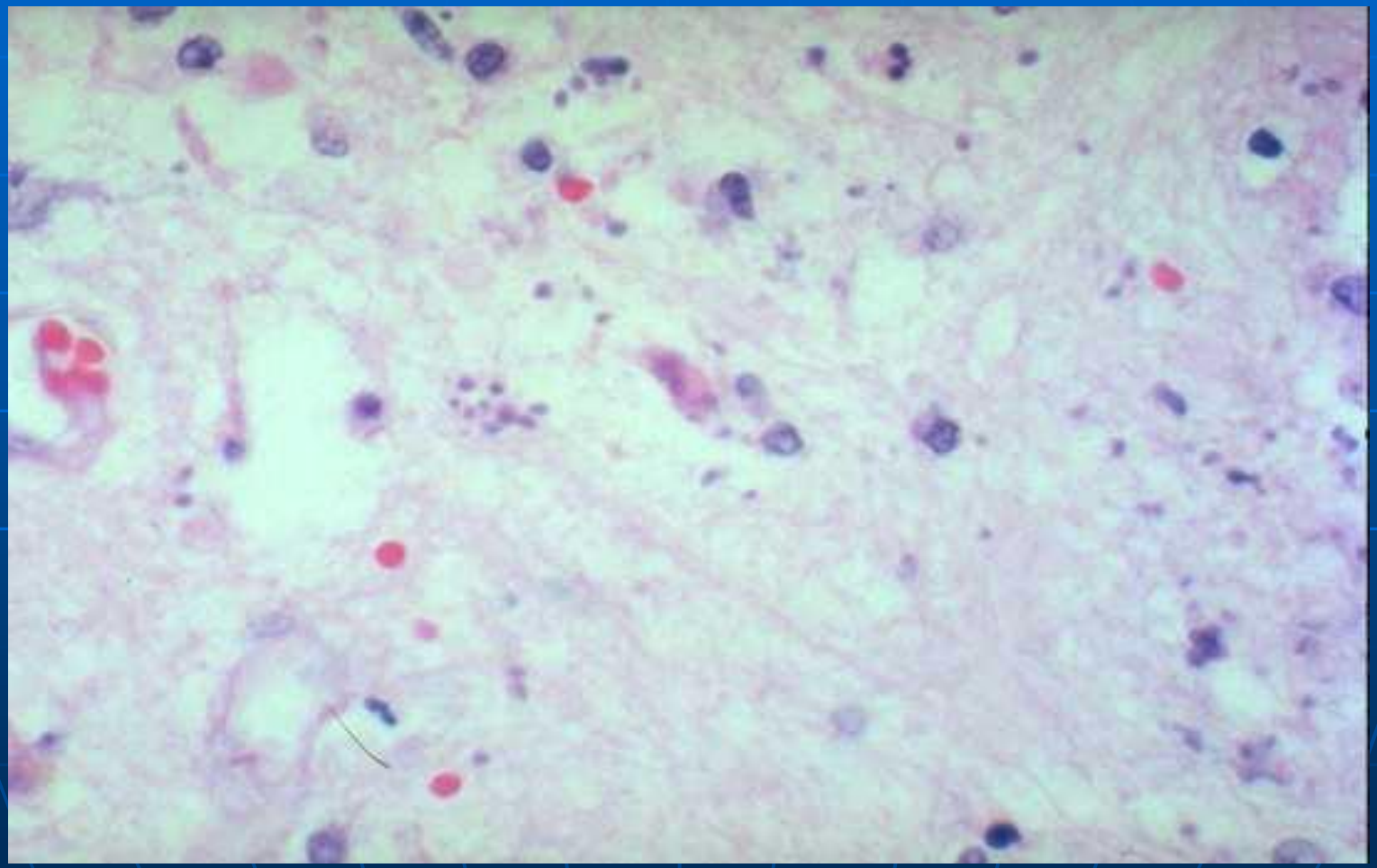
Kaposi Sarcoma



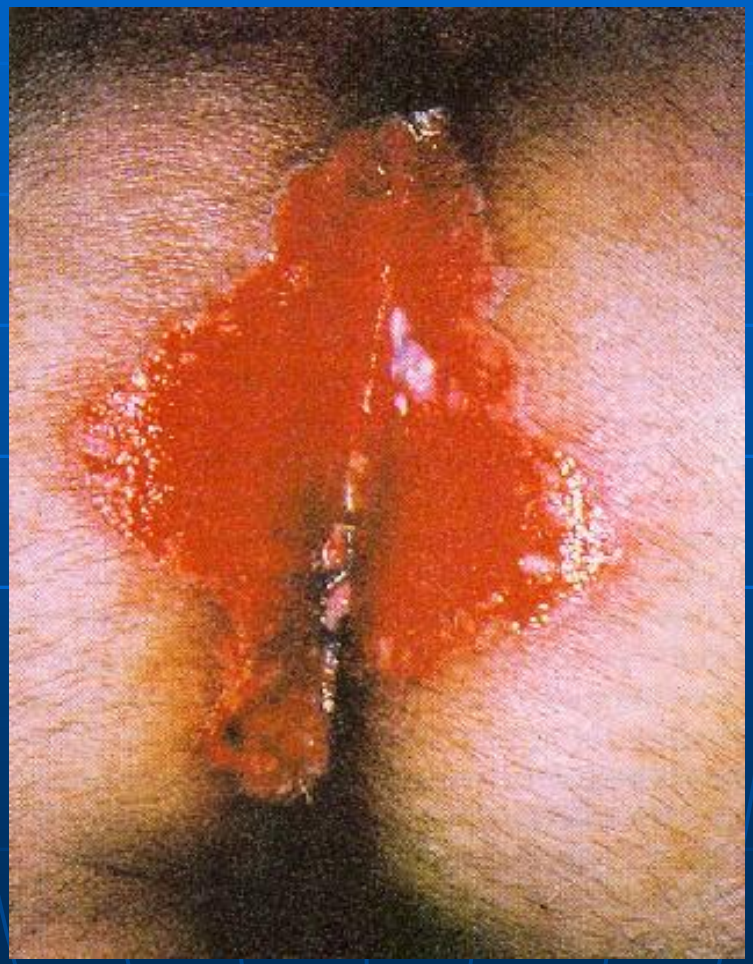
Kaposi Sarcoma



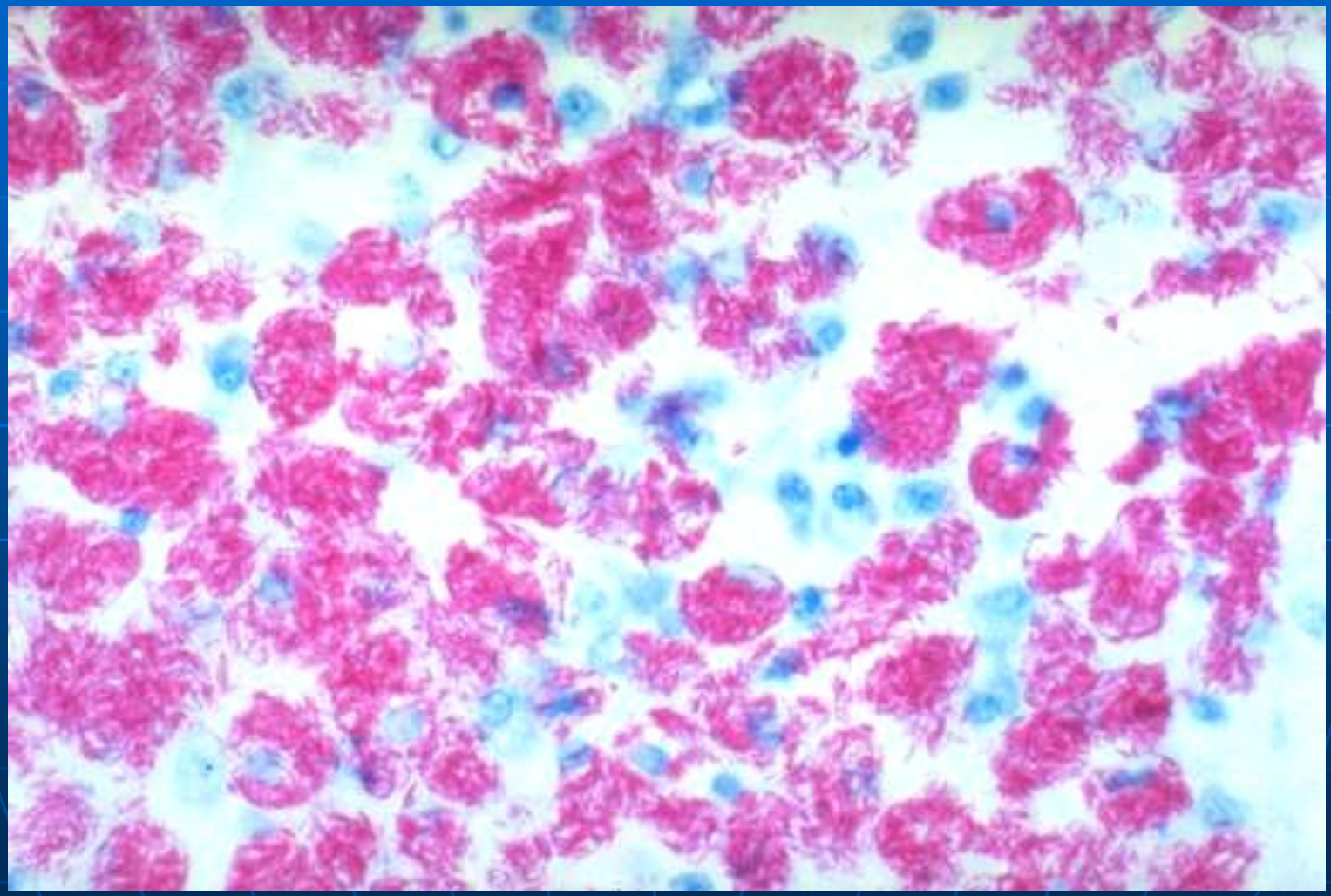
Toxoplasmosis - Brain



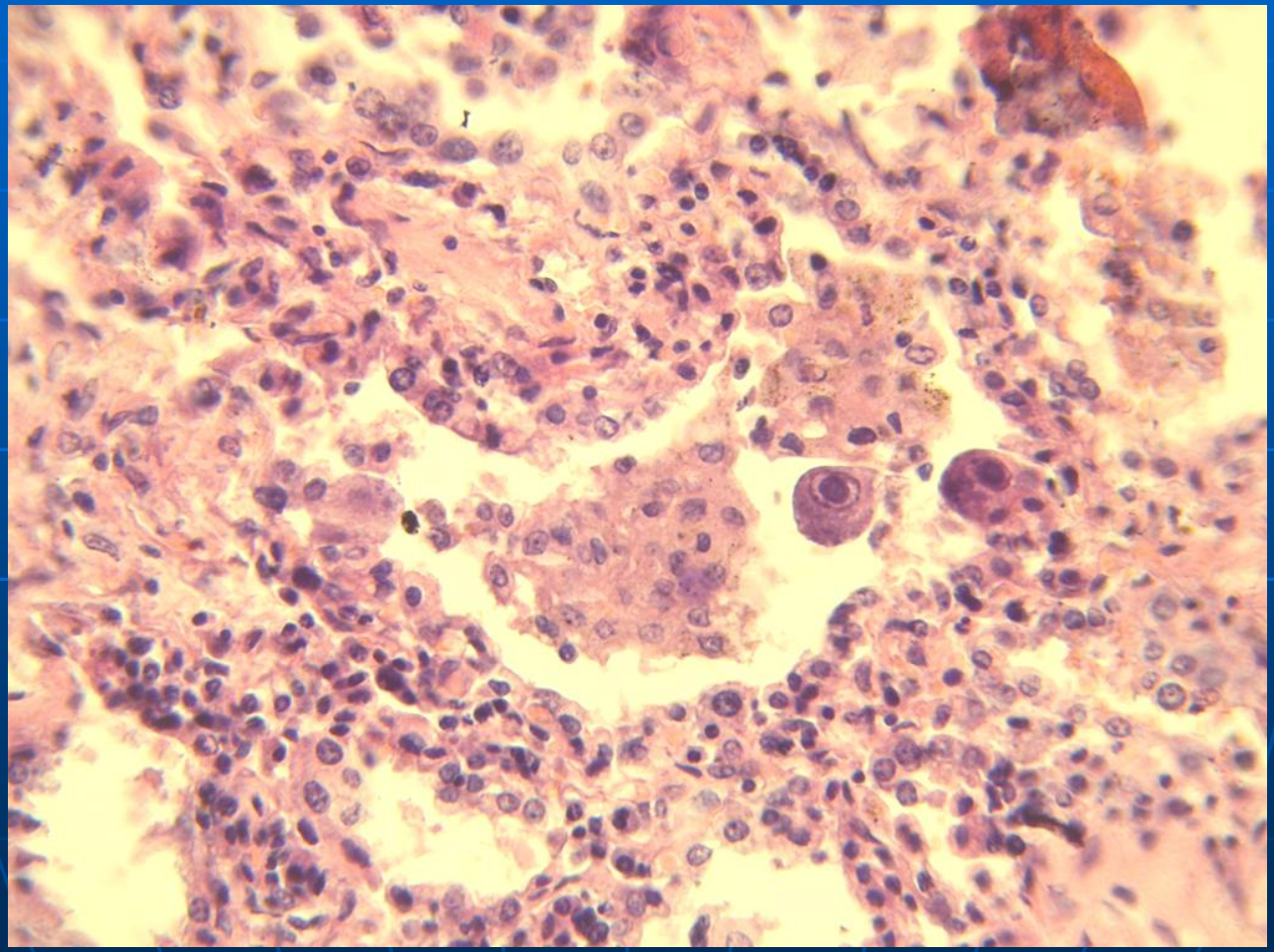
Anorectal Herpis simplex



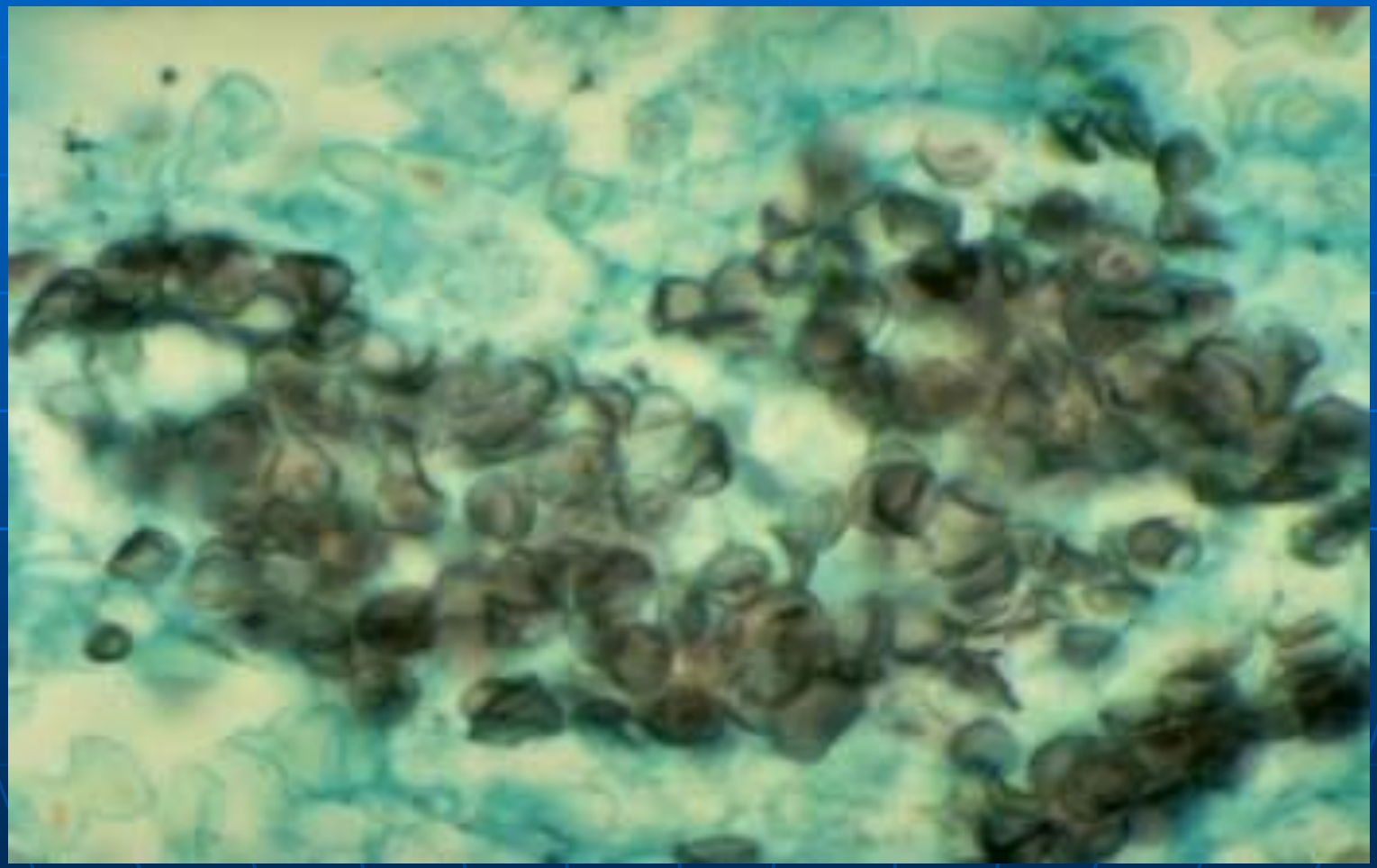
Atypical Mycobacteria



Pneumocystis Pneumonia

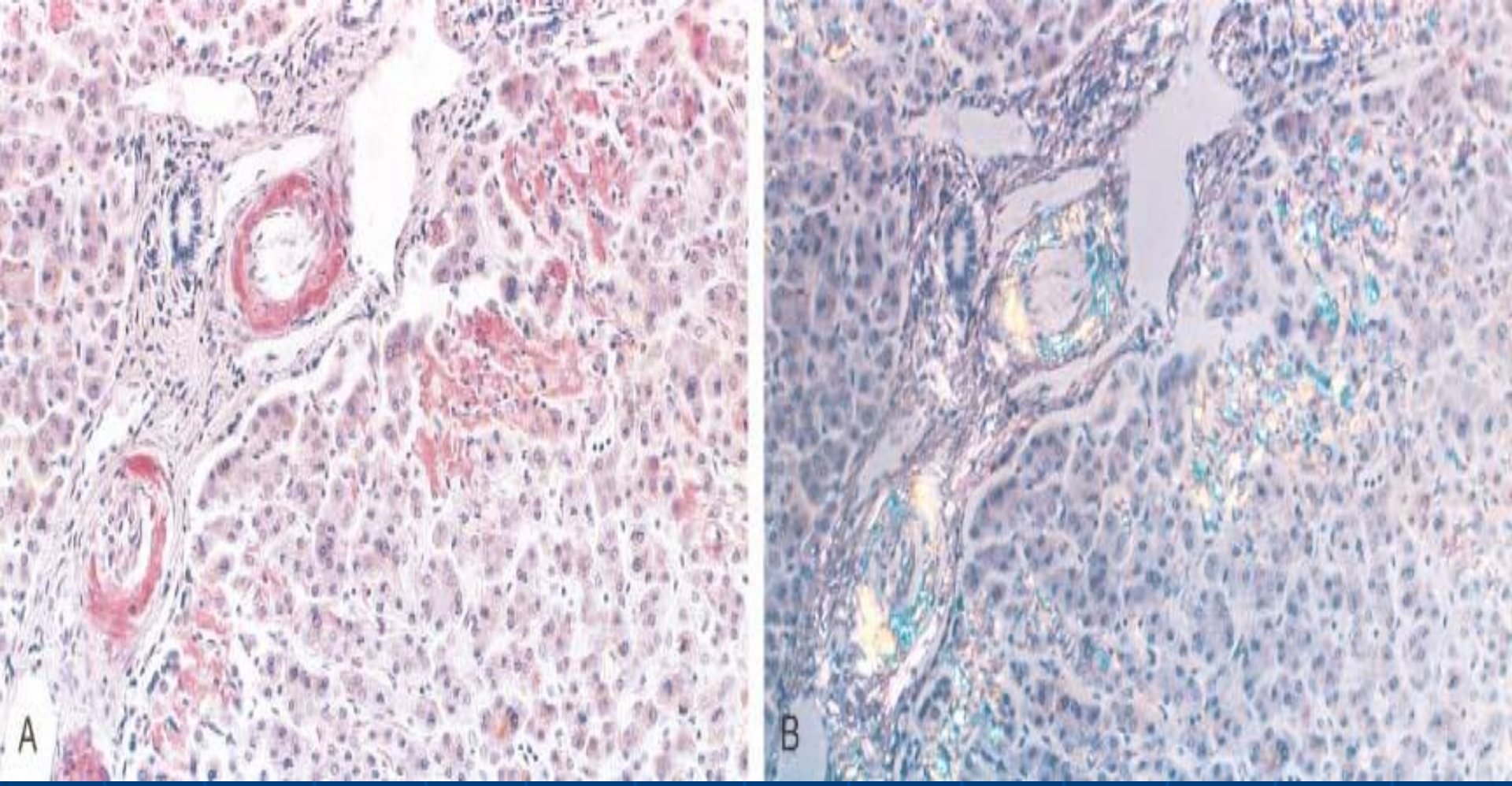


Pneumocystis carinii



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



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

- There are four main types of amyloidosis, each due to the deposition of a specific protein. The most common type is AL amyloidosis, caused by the deposition of light chain proteins produced by plasma cells in different disease states. The second most common is AA amyloidosis due to the accumulation of S amyloid A protein or SAA, which occurs in association with chronic infections - e.g. tuberculosis - or inflammatory illnesses such as rheumatoid arthritis. The third and the fourth type are due to the deposition of a genetically defective or normal form of a protein called transthyretin respectively. Other minor forms of amyloid are also known.

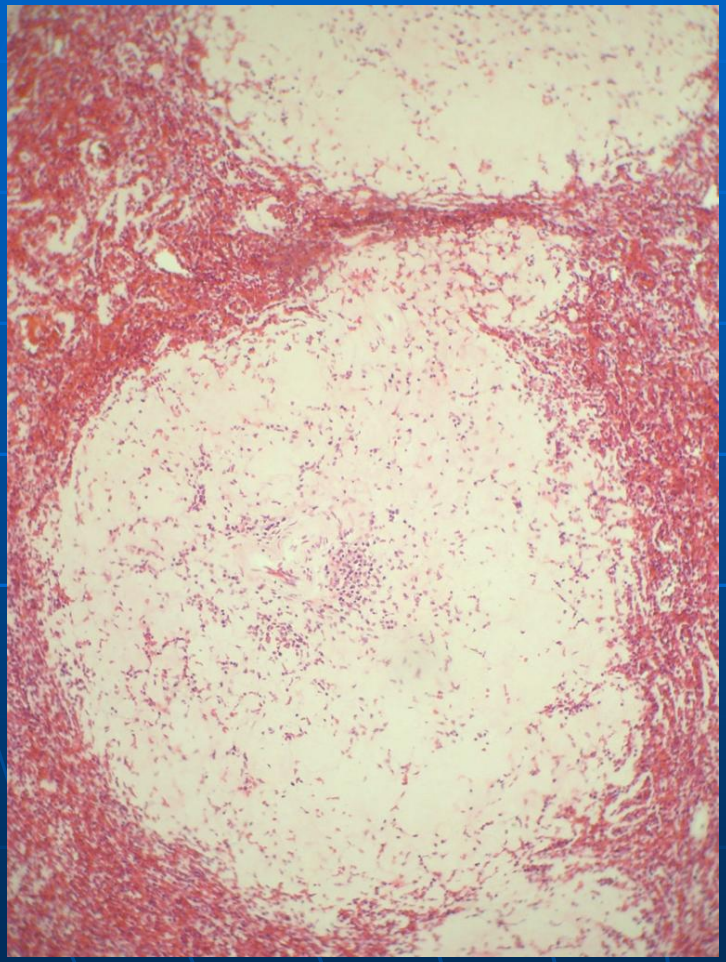
биохимические варианты амилоидного белка

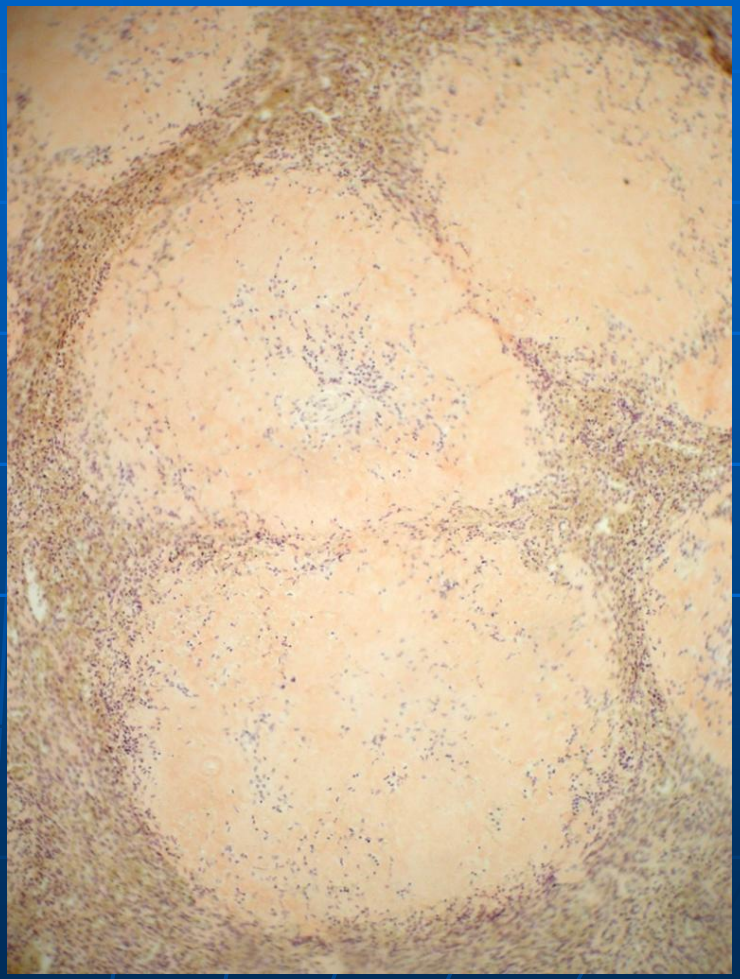
- *Транстиретин* — нормальный белок сыворотки, который связывает и транспортирует тироксин и ретинол. Мутантная форма транстиретина (ATTR) обнаруживается при семейной амилоидной полинейропатии.
- β2-амилоид — пептид, составляющий ядро мозговых бляшек при болезни Альцгеймера. Он образуется из наиболее крупных трансмембранных гликопротеидов. Встречаются также депозиты амилоида, образованные из разных предшественников, таких как гормоны (прокальцитонин) и кератин.
- Р-компонент отличается от амилоидных фибрилл, но тесно с ними связан при всех формах амилоидоза. Он обладает структурной гомологией с С-реактивным белком. Сывороточный Р-компонент обладает сродством к фибриллам амилоида и необходим для образования депозитов в тканях.

Classification

- The modern classification of amyloid disease tends to use an abbreviation of the protein that makes the majority of deposits, prefixed with the letter A. For example, amyloidosis caused by **transthyretin** is termed "ATTR". Deposition patterns vary between people but are almost always composed of just one amyloidogenic protein. Deposition can be systemic (affecting many different organ systems) or organ-specific. Many amyloidoses are inherited, due to mutations in the precursor protein.
- Other forms are due to different diseases causing overabundant or abnormal protein production - such as with overproduction of immunoglobulin light chains (termed AL amyloidosis), or with continuous overproduction of acute phase proteins in chronic inflammation (which can lead to AA amyloidosis).

AMYLOIDOSIS





AMYLOIDOSIS